激光功能医学及其应用
Laser Function Medicine and Its Applications

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内容提要

编者主要介绍激光功能医学在高脂血症、高黏血症、失眠症、孕妇分娩前血液处于高凝状态等方面的保健应用和轻度认知障碍、阿尔茨海默氏病、帕金森病、精神分裂症、镇痛、中风、抑郁症、炎症、冠心病、心肌梗死、小儿脑性瘫痪等方面的临床应用，为医务工作者提供了激光功能医学在高血压、血管性痴呆、癌症、糖尿病、衰老、发育、流感、嗅觉障碍、近似、戒断综合征、肾衰和健康促进等方面的基础知识和应用技能。本书内容权威，实用性强，可供医院及基层医务工作者、科研技术人员和对激光功能医学有兴趣的读者阅读参考。

Abstract

The authors present the science clearly and in sufficient detail to enable readers to make up their own minds about the plausibility of laser function medicine. The book mainly provide lay public and trainee experience on the present health care applications in hyperlipidemia, blood hyperviscosity, insomnia and high blood coagulation status in healthy pregnant women at term, and clinic applications in mild cognitive impairment, Alzheimer’s disease, Parkinson’s disease, schizophrenia, pain relief, stroke, depression, inflammation, coronary heart disease, myocardial infarction and cerebral palsy, and exports experience on its possible applications in hypertension, vascular dementia, cancer, diabetes, ageing, development, influenza, olfactory dysfunction, myopia, withdrawal symptoms, renal failure and health promotion. However, it doesn't offer a comparable level of technical detail when it comes to the clinic applications--and there is even less on the possible clinic applications, which can be found in the listed references. Nevertheless, readers won't have any difficulty evaluating the validity of the theory presented, because authors spell their ideas out clearly enough.

Laser Function Medicine and Its Applications

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序　言

Preface

光生物调节作用直接产生于单色光或激光（laser irradiation or monochromatic light, LI）对生物系统的化学效应而不是热效应（温度升高不超过 0.1-0.5°C），这种没有不可逆损伤的刺激或抑制作用获得了广泛的临床应用。LI 作用于人体的途径是多种多样的，体表有伤口或溃疡的直接照射、内脏器官的体表照射、穴位照射、鼻腔内照射等，体内有利用光纤实现的血管内照射、支气管内照射和肠内照射等。我国 1970 年代和 1990 年代先后流行用于内科疾病康复治疗的激光针刺疗法和低能量激光血管内照射疗法（intravascular low energy laser therapy, ILELT）。然而，ILELT 必须将光纤光针插入人体血管内，不仅给病人带来痛苦，如果操作不当，还可能引起医源性感染。1998 年开始探索低强度 LI（low intensity LI, LIL）血管外照射疗法，其中的鼻腔内 LIL 照射疗法（intranasal LIL therapy, ILILT）逐渐发展成为比较成熟的临床疗法。尽管俄罗斯早在 1998 年以前已经开始研究鼻腔内 LIL 照射，但主要处理的是鼻腔内局部炎症。ILILT 综合了激光针灸和 ILELT 的优势，可以说是唯一我国首创的一种用于内科疾病康复治疗的 LIL 疗法。我本人也一直使用 ILILT 进行保健，效果可佳。

Photobiomodulation (PBM) is a photochemical effect of laser irradiation or monochromatic light (LI) on biosystems with the temperature elevation less than 0.1 ~ 0.5℃, which stimulates or inhibits biological functions but does not result in irreducible damage and widely applied in clinic. There are many forms of LI-biosystem interaction such as cutaneous irradiation of wound, ulcer, viscera and acupoints, intranasal irradiation, intravascular irradiation, intrabronchial irradiation and intraintestine irradiation. In our country, 1970s and 1990s have seen the population of laser acupuncture and intravascular low energy laser therapy (ILELT) for rehabilitation therapy in internal medicine, respectively. However, the optical fiber should be introduced into vascular by invasive needle for ILELT, which makes patients feel pain and might be infective if the operation is not very careful. 1998 saw the many kinds of study of cutaneous irradiation of low intensity LI (LIL) on blood vessel among which intranasal LIL therapy (ILILT) has been widely applied in clinic. ILILT as an integration of ILELT and laser acupuncture for rehabilitation therapy of internal medicine is originally put forward in our country although it has been used for intranasal inflammation in Russian before 1998. I myself have used ILILT for health promotion and enjoyed its excellent rehabilitation effects.

早在 1980 年我就倡导并开展了激光生命科学研究，先后在 1989 年和 2005 年建成广东省和教育部的重点实验室。1989 年开始研究低水平 LI（low level LI, LLL）的在体效应。1993 年开始从细胞水平研究 LLL 治疗（LLL therapy, LLLT）的机理研究。1999 年我们邀请 LLLT 基础研究的国际权威、俄罗斯科学院的 Karu 院士组织了 LLLT 的国际会议。2000 年我们的研究成果获得美国激光医学会第

20 届年会的最佳生物刺激作用论文奖。2002 年分别成立了激光运动医学实验室和光子中医学实验室。我们对光生物调节作用及其中医基础与临床应用的深入研究包括了 LLL 细胞效应以及 ILELT、激光针灸和 ILILT 等的作用机理。

I have begun to study laser life science from as early as 1980, and established its key laboratory of Guangdong province in 1989 and then Ministry of Education in 2005. Our study on low level LI therapy (LLLT) was at in vivo level in 1989 and at cellular level in 1993. We have invited Prof. Tiina Karu, Academician of Russian Academy in Laser Science, who has been internationally famous in the science of LLLT to hold an international conference of LLLT in 1999 in Shunde, Guangdong. In 2000, one of our papers was chosen for its excellence in the speciality in biostimulation in the 20th annual meeting of American Society for Laser Medicine and Surgery. 2002 has seen our establishment of laboratories of laser sports medicine and photonic traditional Chinese medicine (TCM). From then on, our depth study in PBM and its foundation and applications in TCM has included the cellular effects of low level LI and the mechanism of ILELT, laser acupuncture and ILILT.

虽然我国光生物调节作用的基础研究已经进入国际前沿，但临床研究很不规范。尽管光生物调节作用的临床应用已经获得普遍，但很多临床医生或普通使用者对其作用机理了解甚少，存在不少临床上亟待解决的问题，有的医生或普通使用者甚至一直使用厂家建议的固定参数进行临床治疗，不但影响了疗效，也丧失了患者的信心。面临这种情况，这是一本非常及时的参考书。本书作者都是一直从事光生物调节作用的基础与临床应用研究的专家。本书从离体细胞实验和临床研究两个方面综述了 LLLT 作用机理和 ILILT 临床应用方面的大量研究，是相关领域的研究、教学和临床应用方面的重要的参考书。我相信，随着光生物调节作用基础研究与临床应用的普及和提高，无论是我国相应的学术地位，还是适应症的治疗效果，都将获得进一步提高。

Chinese therapeutic applications of LLLT, especially in ILELT and ILILT, were the most widely in the world, and its basic research was internationally progressive, but its randomized placebo-controlled trial need to be enforced. Although PBM has been widely applied in clinic, many physicians or persons interested in LLLT knew little on PBM mechanism, and many related clinic problems left unresolved. LLLT has been even used only according to the fixed parameters suggested by the instrument manufactory, which might not work and then increase the loss of patient belief. At this point, this book is very in time. The authors are very professional in the basic research of PBM and its clinic applications. It is very of use in studying, teaching and clinic in the mechanism research of LLLT and the clinic applications of ILILT because it has deeply reviewed the related topics. I believe our academic role will become bigger and the therapeutic effects will become more enhanced as our basic research of PBM and its clinic applications become wider and deeper in our country.

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Chapter 1 Important Stage of Phototherapy

At this time, when you mention laser, the first thing that comes into the mind is the laser that can cut through the body and be able to dissolve any naevi or tumors in the body parts. These are the hot lasers that are commonly being used in cosmetic surgery or in medicine to cure diseases such as cancers. And definitely, along with these comes the higher prices associated with procedures that involves laser. Though these are the common lasers that are known to most people, there is also one useful kind of laser irradiation or monochromatic light (LI) that is now being used. Did you ever hear of low level/intensity/energy LI therapy, soft LI or cold LI therapy and LI therapy based on the biostimulation or photobiomodulation (PBM)? All of these terms use the same principles. Among these terminologies, low level LI (LLL) therapy (LLLT) has been the dominant one in use internationally, and has now been adopted by many researchers, manufacturers and educators in this field of endeavor. This kind of LI therapy is being widely used in the whole world to cure a number of conditions. These photons come from the visible and infrared spectrum. Right now, this kind of LI is gaining its popularity in the market.

Just as traditional Chinese medicine (TCM) was a very old system of medicine being rediscovered, so is light therapy. Heliotherapy (light therapy) was practiced by physicians in ancient cultures in China, Egypt, Greece, and India to address many conditions. In TCM or psychology, color has been classified into the hot color such as red, orange and yellow, and the cold color such as green, blue and violet (Fig. 1.1), and the hot color and the cold color have been used to treat conditions in deficient *yang* and deficient *yin* which will be detailedly discussed in chapter 10.1, respectively. Archaeologists have found that as early as 1550 BC Egyptian papyri detailed the use of phototherapy as a treatment for everything from serious physical ailments to jewelry enhancement. The Greeks built solarium cities high in the mountains to harness the additional ultra-violet light or irradiation (UV) available at higher altitudes. They used these “cities of light” for healing tuberculosis and to treat and subdue the effects of the smallpox virus.

As early as in the 1660s, Isaac Newton separated light with a prism and discovered the visible spectrum. However, phototherapy, or the treatment of disease by light, has now, thanks to Prof. Finsen of Copenhagen, a recognized place in the domain of therapeutics. Finsen, Niels Ryberg (1860-1904), Danish physician and Nobel Prize winner who made important discoveries regarding the use of light in the treatment of disease. Finsen attended the University of Copenhagen in Denmark, receiving his medical degree in 1891. He then taught anatomy in the university's Department of Surgery, leaving in 1893 to devote himself full-time to studying "phototherapy," or the therapeutic effects of light. In 1896 he established the Light Institute in Copenhagen. For his groundbreaking contributions to the new field of phototherapy, Finsen received the 1903 Nobel Prize in physiology or medicine. Even as a child, Finsen had been fascinated by the effects of sunlight on living things, which will be discussed in chapter 4. His research as an undergraduate included experiments in which he observed how sunlight affected the tissue of insects, tadpoles, and other animals. Later Finsen decided to turn his efforts toward the treatment of human diseases. In 1893 he began to study the use of filtered sunlight in the treatment of skin lesions caused by smallpox, a viral disease. Red light—that is, light from the red end of the spectrum—with its harmful heat rays filtered out, proved successful in promoting the healing of smallpox lesions. After publishing key papers on phototherapy in 1893 and 1894, Finsen began research into the treatment of lupus vulgaris, a disfiguring skin disease caused by bacteria. Finsen

had noted the findings of previous researchers, who discovered that light could kill bacteria. Focusing an artificial light through a prism, Finsen exposed diseased tissue to high concentrations of UV. The method proved highly effective in treating lupus vulgaris. The Light Institute in Copenhagen was a landmark of phototherapy, where hundreds of lupus vulgaris patients were successfully treated over the next few years. The use of UV remained the central treatment for lupus vulgaris for decades.

The second famous scientist in phototherapy is Otto Warburg. His star was at its zenith seventy-eight years ago. The pioneering German biochemist delivered his Nobel address in December 1931. He described the ingenious experiments by which he had unmasked the enzyme responsible for the critical step of cell respiration, the process that turns the energy in chemical compounds into energy the cell can use. His work on respiration in the early 1930s nearly earned him a second Nobel, ultimately denied him by Hitler. Then his star began sinking. But now, Warburg's star is rising again. A new generation of researchers is returning to his ideas about respiration in cancer cells, and defines it as Warburg effect[1]. Recent findings suggest that the enzyme he identified, cytochrome oxidase, is a key player in a new understanding of how the cell's energy metabolism affects health and disease. And surprisingly they show that light has a profound effect on how the enzyme works — and could even be used to treat degenerative disease. Perhaps the most surprising aspect of the renaissance of Warburg's ideas is that the methods he used to make this discovery matter again. They exploit two chemical quirks: carbon monoxide (CO) can block respiration by binding to cytochrome oxidase in place of oxygen; and a flash of light can displace it, freeing up the site for oxygen to bind again. Any solution to excessive nitric oxide (NO) binding might lower the risk of both cancer and degenerative diseases, as it would make apoptosis more likely in cancer cells and less likely in normal cells. And the second essential feature of Warburg's experiments — light — might do just that (Lane 2006).

Albert Einstein (1879-1955) presented the first theory about laser in 1916. This paves the way for the other researches and the development of other studies for laser. In 1951, Dr. Charles H. Townes conceived the idea of the “MASER”, and a few months later he and his associates began working on a device using ammonia gas as the active medium. In early 1954, the first amplification and generation of electromagnetic waves by stimulated emission were obtained. Dr. Townes and his students coined the word "maser" for this device, which is an acronym for Microwave Amplification by Stimulated Emission of Radiation. In 1958, Dr. Townes and his brother-in-law, Dr. Arthur L. Schawlow showed theoretically that masers could be made to operate in the optical and infrared region and proposed how this could be accomplished in particular systems. Dr. Townes shared the Nobel Prize in physics in 1964 for his work leading to the development of the “MASER” and his research and ideas were instrumental in the development of the laser by Dr. Theodore Maiman. In 1960, Dr. Maiman constructed the first laser at Hughes Aircraft Research Laboratories in Malibu, California. Since then, laser has transformed world. The early 1960s saw the development of numerous lasers and numerous new applications in industry and medicine. Many of these new medical applications were in surgery and involved powerful instruments with outputs in the tens-to-hundreds of watts. Surgeons noticed faster healing times and less scarring when doing procedures with lasers than when using the standard scalpel. This was later found to be the result of biostimulation or PBM of the marginal

[1] The Warburg effect describes the enhanced conversion of glucose to lactate by tumor cells, even in the presence of adequate oxygen that would ordinarily be used for oxidative phosphorylation.

irradiation of laser beam in our laboratory (Liu TCY *et al*. 2009a).

In 1966, Endre Mester, a physician in Hungary, performed a series of experiments that showed the biostimulatory effect of visible red and infrared laser light at low intensity. He published his findings in an obscure Hungarian medical journal, which may explain why the benefits of LLL were appreciated in the Eastern bloc long before they were recognized in the West. They found out that this beam has a good effect in relieving pain, speeding up the healing process and producing less scar tissue.

Now, LLLT has been used extensively in Europe and Asia for many applications so that it has been scientifically well documented. There are more than 130 double-blind positive studies confirming the clinical effect of LLLT. More than 3400 research reports are published. LLLT may be an effective modality in battling many situations. However, more research is needed to establish ideal treatment parameters for specific conditions. The applications of LLLT in health management and internal medicine will be focused in this book.

Between 2002 and 2004, the Food and Drug Administration in USA (FDA) granted 510(k) approval to several companies to market lasers that provide LLLT. Recently, a laser company in the United States received approval of FDA for the treatment of carpal tunnel syndrome. No doubt, FDA will continue to approve the use of lasers for a variety of conditions. The FDA classifies LLL as class III B non-significant risk devices. There are FDA guidelines that govern the use of LLL as an investigational device, as well as state regulations. The applications of LLLT in health management and medicine will become wider as the basic research of LLLT become deeper.

Laser acupuncture (LA) such as interdigital low intensity laser therapy (DLILT) and intranasal low intensity laser therapy (ILILT) are two kinds of LLLT, and will be focused in this book.

Chapter 2 Therapeutic Light Source

The physical trail of light research is from phenomenology's describing how light behaves, Huygens' developing wave theory of light, Newton's developing particle theory of light, Maxwell's introducing electromagnetic wave theory of light, Einstein's putting forward the concept of photon, to quantum mechanics' culminating in the wave-particle duality. The light might be a wave when it propagates, and it might be a photon when it interacts with matter. For low level laser irradiation or monochromatic light therapy (LLLT), light interacts with biological systems so that the viewpoint of photon is preferred. Many kinds of light source have been used in LLLT. Their properties and safety will be discussed in this chapter.

2.1 Laser

A laser (light amplification by stimulated emission of radiation) is an amplifier of light. It is a specialized environment that will support and sustain stimulated emission. Laser emission is brought about by pumping a medium with energy, either as light or as electric current. The aim is to heave — or 'pump' — so many atoms or molecules within the medium up from their ground state into an excited state[1] that a population inversion is established, with more atoms in the higher-energy state than in the lower. The medium of a semiconductor laser is semiconductor. In this laser, each excitation boosts an atomic electron into a higher energy level, leaving behind a positively charged hole where the electron used to be. Electron and hole recombine after a short while, and stimulate others to follow suit. The result is the emission of amplified, coherent light of a single wavelength.

1 Laser light and incandescent light

There are 4 properties of laser light that separates it from incandescent light (such as that from a light bulb):

(1) Monochrome**.** A laser emits one kind of photons at a specific wavelength, but most light sources emit many kinds of photons over the wide spectral distribution, respectively. Laser light has a very narrow band width.

(2) Coherence**.** Laser light is extremely well organized and synchronous. The photons emitted from a laser have been compared to a troop of soldiers marching in precise order.

(3) Power. The power of laser light might be very higher.

(4) Directivity. The directivity of laser irradiation is better.

For LLLT, the monochrome is more important than the other three properties is. At the cellular level, there is no significant difference between laser irradiation and monochromatic light if the wavelength is the same (Karu 1998). Four parameters are important for clinicians to achieve the best possible therapeutic effects when using low level laser irradiation or monochromatic light (LLL): ①Selection of the correct beneficial **Wavelength**, ②the use of the correct **Intensity,** ③ the consistent application of the necessary amount of **Energy Density**, ④Another factor which has to be considered is **Pulsing Frequency**.

[1] An atom or molecule has many states. All the energy of states is lined from the lowest on to form energy levels. Among them, the state with the lowest energy is the ground state, and the other states are excited states.

2 Wavelength:

(1) Wavelength is measured in nanometers

(2) It is set in the probe and cannot be changed

(3) The wavelength of red or infrared light used in laser acupuncture (LA)，interdigital low intensity laser therapy (DLILT) and intranasal low intensity laser therapy (ILILT) are produced with wavelength of 632.8, 650, 670 or 810 nm

3 Red light

(1) Red light does not penetrate very effectively below the skin surface and into the tissue below

(2) Red light is the best for wound healing or superficial conditions but is not the most effective way to treat deeper injury

4 Dose

(1) Power [watts (W) or milliwatts (mW), 1 W = 1000 mW] is the strength of the probe, and is also the photons each second received by irradiated area. Intensity (W/cm^2 or mW/cm^2) is the quotient of power over laser speckle area. Clinicians need to know the power range of the probe they are choosing to use and also have the probes regularly checked to ensure that they are running to exact intensity on the irradiated area.

(2) Radiation time is the duration when light is irradiating.

(3) The amount of energy [Joules (J) or millijoules (mJ), 1 J = 1000 mJ], the product of power and radiation time, is the photons received by irradiated area. Energy density (J/cm^2 or mJ/cm^2) is the quotient of energy over laser speckle area.

(4) Energy which we as clinicians are providing in each treatment, is important, but the energy density is more important. However, the intensity is the most important:

$$\text{Energy} = \text{Power} \times \text{Radiation Time}$$

$$\text{Energy Density} = \text{Intensity} \times \text{Radiation Time}.$$

5 Pulse rate

Pulse rate equals the number of times per second light is emitted. Research has demonstrated there are pulse rate specific effects with LLLT.

2.2 Classification of Medical Lasers

Here are examples of lasers which can be used in medicine or surgery. The classification is in terms of the medium used to amplify light. The listed order is laser name, wavelength, pulsed (p) use in medicine or continuous (c), and medicine or surgery. There are many other types, but those mentioned above are the most common.

1. **Crystalline lasers:**

Ruby 694 nm p holograms, tattoo coagulation.
Nd:YAG 1064 nm p coagulation.
Ho:YAG 2130 nm p surgery, root canal.
Er:YAG 2940 nm p surgery, dental drill.
KTP/532 532 nm p/c dermatology.
Alexandrite 720-800 nm p bone cutting, cosmetic surgery.

2. **Semiconductor lasers:**

Gallium-Arsenide laser 904 nm p PBM.
Gallium Aluminum Arsenide (GaAlAs) laser 780-820-870 nm c PBM, surgery.
Aluminum-Gallium-Indium-Phosphorus (AlGaInP) laser 630-685 nm c PBM.

3. **Liquid laser:**

Dye laser (tuneable) p kidney stones.
Rhodamine: 560-650 nm c/p photodynamic therapy, dermatology.

4. **Gas lasers:**

Helium neon mixture (He-Ne) 632.8, 3390 nm c PBM.
Argon 350-514 nm c dermatology, eye.
CO_2 10600 nm c/p dermatology, surgery.
Excimer 193, 248, 308 nm p eye, vascular surgery.
Copper vapour 578 nm c/p dermatology.

2.3 Lasers in Low Level Laser Therapy

Two of the most common misconceptions about lasers is that 1) all lasers are high powered, and 2) their beams are always parallel. Conversely, lasers used in LLLT are most often designed with divergent beams as a safety precaution, and they operate at very low level energy or intensity.

Lasers used in LLLT include gas laser such as He-Ne lasers and diode lasers such as the gallium arsenide laser, GaAlAs laser, Aluminum-Gallium-Indium-Phosphorus (AlGaInP) laser and Gallium-Indium-Phosphorus/AlGaInP (GaInP/AlGaInP) laser. The longer the wavelength, the deeper the tissue penetration. The detailed properties are following

1. **Helium-Neon Laser (632.8 nm)** Helium-neon gas mixture (He-Ne). Visible red light. Relatively shallow depth of penetration. A He-Ne laser with a power output of 3.5 mW has a greatest active depth of 6-8 mm depending on the type of tissue involved. A He-Ne laser with an output of 7 mW has a greatest active depth of 8-10 mm. Very useful for LA, superficial applications, and wound healing. Absorbed by mitochondrial cytochromes. Large, fragile, and expensive instrument .
2. **Aluminum-Gallium-Indium-Phosphorus (AlGaInP) Laser (630-685 nm)** Now replacing He-Ne lasers. Visible red light, smaller and portable, inexpensive; higher power than the He-Ne, more durable. Same applications as He-Ne laser. Among them, 650 nm laser has been used in DLILT and ILILT of Hong Kong Bewell (Tab 2.1).

3. **Gallium-Indium-Phosphorus/Aluminum-Gallium-Indium-Phosphorus laser (650 nm)** Also replacing He-Ne lasers. Visible red light, smaller and portable, inexpensive; higher power than the He-Ne. The applications similar to He-Ne laser, especially in ILILT.

4. **Gallium-Aluminum-Arsenide (GaAlAs) Laser (780-890 nm)** Near infrared, invisible light. Deeper penetration. A GaAlAs probe of some strength has a penetration of 35 mm with a 55 mm lateral spread. Inexpensive. Many applications, very useful for the treatment of pain, but also effective in healing. Most popular therapeutic laser. Valuable to reach very deep acupuncture points or deep Ah Shi points

5. **Gallium-Arsenide Laser (904 nm)** Greatest depth of penetration, deeper than GaAlAs. This is due to a much longer wavelength and because they are pulsed, forcing the laser light deep into the tissues. Useful for reaching deep acupuncture points and for the treatment of pain. Continuous wave lasers are now also available.

Obviously, the depth of penetration of laser light depends on the light's wavelength, and on the power output. Moreover, the depth of penetration of laser light not only depends on whether the laser is super-pulsed, but also on the technical design of the apparatus and the treatment technique used. A laser designed for the treatment of naked skin is rarely suitable for treating animals with fur or the skin with hair. There are, in fact, lasers specially made for this purpose. The special design feature here is that the laser diode(s) obtrude from the treatment probe rather like the teeth on a comb. By delving between the animal's hair, the laser diode's glass surface comes in contact with the skin and all the light from the laser is "forced" into the tissue.

There is no exact limit with respect to the penetration of the light. The light gets weaker and weaker the further from the surface it penetrates. There is, however, a limit at which the light intensity is so low that no biological effect of the light can be registered. This limit, where the effect ceases, is called the greatest active depth. In addition to the factors mentioned above, this depth is also contingent on tissue type, pigmentation, and dirt on the skin. It is worth noting that laser light can even penetrate bone (as well as it can penetrate muscle tissue). Fat tissue is more transparent than muscle tissue.

A factor of importance here is the compressive removal of blood in the target tissue. When you press lightly with a laser probe against skin, the blood flows to the sides, so that the tissue right in front of the probe (and some distance into the tissue) is fairly empty of blood. As the haemoglobin in the blood is responsible for most of the absorption, this mechanical removal of blood greatly increases the depth of penetration of the laser light.

LLLT is completely safe. Food and Drug Administration in USA (FDA) has classified LLLT devices as "non-significant risk medical devices". It poses no health risk to the patient provided that the eyes are protected by protective eyewear or careful operation. THIS IS ESSENTIAL FOR THE SAFE USE OF THE DEVICES! Normal precautions should be followed like with any medical procedure. Please do not use ILILT when driving. Stop using ILILT when becoming unease. It can not be used by cognition-less child or adult. The patients with intranasal cancer, light-hypersensitivity, or heart rate which is slower than 60/min should be treated according to medical guidance.

2.4 Lasers in this book

As an approach to treat internal diseases, ILILT is put forward and popularized in China. The

lasers in ILILT were mainly produced in China. The various lasers in LA were produced in the world. As the pages are limited, only BeWell lasers (www.bewellglobal.com) will be introduced in this section as in Tab. 2.1, intranasal BeWell laser used in ILILT and interdigital BeWell laser used in DLILT. The other products might be referred in their websites. The BeWell lasers were produced in Germany. The low intensity AlGaInP diode laser irradiation at 650 nm is used in both the products.

Table 2.1 Technical Specification of BeWell lasers

	Intranasal BeWell laser	Interdigital BeWell laser
Size：	Ø86 x 30(T) mm	100(L) x 56(W) x 36(T) mm
Lasing medium：	AlGaInP	A1GaInP
Wavelength：	650 nm	650 nm
Power：	≤5 mW	≤5 mW
Irradiation time：	30 min	30 min
Battery：	3.7 V, DC , 850 mA	3.7 V, DC, 850 mA
Charger power：	Input 100 V – 240 V， AC 50/60 Hz Output 5.5V, DC, 1 A	Input 100 V – 240 V， AC 50/60 Hz Output 5.5V, DC, 1 A
Classification:	Class III B Laser	Class III B Laser
Work conditions:	temperature 5–40°C， humidity ≤ 80%， atmospheric pressure 860–1060 kPa	temperature 5–40°C， humidity ≤ 80%， atmospheric pressure 860–1060 kPa

2.5 Laser Safety

The low intensity laser irradiation or monochromatic light (LIL) are very safe; however, there is a potential for damage to the eye. The laser beam, if directed through the lens of the eye, could damage the retina. Yet in more than 40 years of research and clinical practice, an event of this type has never been reported. Protective goggles that filter out the specific wavelength of the laser light are suggested to be worn by the patient and acupuncturist/physician during a therapy session.

To safely operate a laser, the practitioner must thoroughly understand the nature of the equipment. Certain technical parameters exist that one must first comprehend. These parameters are the power (this is expressed in mW for LIL), wavelength, the characteristics of the laser beam (its optics; such as divergence, convergence, or parallel nature of the beam). All these influence the level of risk. Obviously, a high-power laser is riskier than a lower-power one. An infrared laser is riskier to use than a visible, red light laser with the same power and beam characteristics because the light is invisible and does not promote a blink response

The following factors are of importance regarding the eye risk of different lasers:

1 The divergence of the light beam. A parallel light beam with a small diameter is by far the most dangerous type of beam. It can enter the pupil, in its entirety, and be focused by the eye's lens to a spot with a diameter of hundredths of a millimeter. The entire light output is concentrated on this small area. With a 10 mW beam, the power density can be up to 12,000 mW/cm^2. It is fairly obvious that a powerful laser (many watts) is more hazardous to stare into than a weak laser.

The divergence is represented with divergence angle**,** 1 rad is 57°. There is less damage of light of larger divergence angle on eyes**.**

2 **The wavelength of the light**. Within the visible wavelength range, we respond to strong light with a quick blinking reflex. This reduces the exposure time and thereby the light energy which enters the eye. Light sources which emit invisible radiation, whether an infra-red laser or an infra-red light from light emitting diode array (LED), always entail a higher risk than the equivalent source of visible light. Radiation at wavelengths over 1400 nm is absorbed by the eye's lens, which might induce lens opacity**.** Radiation at wavelengths over 3,000 nm is absorbed by the cornea, which might induce cornea injury.

3 The distribution of the light source. If the light source is concentrated, which is often the case in the context of lasers, an image of the source is projected on the retina as a point, provided it lies within our accommodation range, i.e. the area in which we can see clearly. A widely spread light source is projected onto the retina in a correspondingly wide image, in which the light is spread over a larger area, i.e. with a lower power density as a consequence. For example: a clear light bulb (which is apprehended as a more concentrated light source) penetrates the eye more than a so-called "pearl" light bulb. A laser system with several light sources placed separately, such as a multiprobe (the probe is the part of the laser you hold and apply to the area to be treated: a single probe means there is only one laser diode in the probe, as opposed to a multiprobe, which has several laser diodes) with several laser diodes, can, seen as a whole, be very powerful but at the same time constitute a smaller hazard to the eye than if the entire power output was from one laser diode, because the diodes' separate placement means that they are reproduced in different places on the retina.

3 Laser Functional Medicine

Photobiomodulation (PBM) is a modulation of laser irradiation or monochromatic light (LI) on biosystems, which stimulates or inhibits biological functions but does not result in irreducible damage. The LI used in PBM is always low intensity LI (LIL), ~10 mW/cm^2. However, moderate intensity LI (MIL), $10^{2\sim3}$ mW/cm^2, is of PBM if the radiation time is not so long that it damages organelles or cells. The PBM of LIL and MIL are denoted as LPBM and MPBM, respectively. There are many kinds of PBM, such as cutaneous PBM, wound PBM, interdigital PBM, acupoint PBM, intravascular PBM, intranasal PBM, endobronchial PBM and so on. In this chapter, the principle of acupoint LPBM and intranasal LPBM will be discussed.

Acupuncture has been used in the treatment of a variety of illnesses in traditional Chinese medicine (TCM) for more than 2000 years. The practice of acupuncture is based on a theoretical system different from our understanding of human anatomy and physiology, and has developed through experience and observation. Stimulation of selective acupoints (situated along 'meridians' in the body) by inserting needles is believed to restore bodily functions by promoting the flow of 'vital energy', throughout the system. Because needles are inserted up to several centimetres beneath the skin, acupuncture may pose risks to patients. One of the most important complications is transmission of pathogenic micro-organisms, from environment to patient or from one patient to another. Other forms of stimulation which have been developed are heat, electrical stimulation, magnetism and, recently, laser. Laser acupuncture (LA) offers distinct advantages over the traditional method because the procedure is pain-free, infection-free and non-traumatic. Clinical applications include the control of pain in osteoarthritis, lumbago and migraine, and anaesthesia for certain surgical procedures, as well as other ailments of the cardiovascular, respiratory and nervous systems (Wang LQ *et al.* 1993, Chen TR *et al.* 1995). Interdigital low intensity laser therapy (DLILT) is one kind of LA. Laser irradiation in DLILT irradiates the interdigital acupoints of *pericardium* meridian of hand *jueyin*, *heart* meridian of hand *shaoyin*, *sanjiao* of hand *shaoyang* and other meridians.

From 1989 on, many Russian groups have studied the therapeutic effects of intranasal LPBM on the local inflammation in vasomotor rhinitis and acute and chronic maxillary sinusitis. In the mainland of China, intranasal LPBM has been studied to treat internal diseases and the special treatment was called intranasal low intensity laser therapy (ILILT). Nose-mediated therapeutics in TCM has been a very old system (Gao S 1994), but ILILT began in 1998. It has been applied to treat hyperlipidemia, the blood-stasis syndrome of coronary heart disease, myocardial infarction (MI) and brain diseases such as insomnia, intractable headache, Alzheimer's disease (AD), Parkinson's disease (PD), post-stroke depression(PSD), ache in head or face, migraine, cerebral thrombosis, diabetic peripheral neuropathy (DPN), cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, cerebral palsy (CP) and mild cognitive impairment. The studies indicated that serum amyloid β protein (Aβ), malformation rate of erythrocytes, plasma cholecystokinin-octapeptide (CCK-8), the level of viscosity at lower shear rates, hematocrit, and serum lipid decreased, respectively, and melanin production，red cell deformability (RCD), superoxidase dismutase (SOD) activity and β endorphin increased, respectively, circulation was improved, and immunity was regulated after ILILT.

There are four possible pathways mediating the ILILT, olfactory nerve, blood cells, meridians in TCM and autonomic nervous system (ANS). Its mechanism will be then discussed in view of

nose-mediated therapeutics in TCM (Gao S 1994). The therapeutic effects of acupoint LPBM are mediated by meridian. Its mechanism will be discussed in the related part in this chapter and will be detailedly discussed in Chapter 10.

3.1 Functional medicine

Functional medicine is personalized medicine that deals with primary prevention and underlying causes instead of symptoms for serious chronic disease (Jones 2006). It encompasses a dynamic approach to assessing, preventing, and treating complex, chronic disease. It helps clinicians identify and ameliorate dysfunctions in the physiology and biochemistry of the human body as a primary method of improving patient health. In this model of practice, it emphasizes that chronic disease is almost always preceded by a period of declining function in one or more of the body's systems. Returning patients to health requires reversing (or substantially improving) the specific dysfunctions that have contributed to the disease state. Those dysfunctions are, for each of us, the result of lifelong interactions among our environment, our lifestyle, and our genetic predispositions. Each patient, therefore, represents a unique, complex, and interwoven set of influences on intrinsic functionality that have set the stage for the development of disease or the maintenance of health. To manage the complexity inherent in this approach, functional medicine has adopted practical models for obtaining and evaluating clinical information that leads to individualized, patient-centered therapies.

Function medicine is a science-based field of health care that is grounded in the following 6 principles (Jones 2006).

1. Biochemical individuality describes the importance of individual variations in metabolic function that derive from genetic and environmental differences among individuals. Understanding inter-individual differences in stress response requires the explanation of genetic influences at multiple phenotypic levels, including complex behaviors and the metabolic responses of brain regions to emotional stimuli. Neuropeptide Y (NPY) is anxiolytic and its release is induced by stress. NPY is abundantly expressed in regions of the limbic system that are implicated in arousal and in the assignment of emotional valences to stimuli and memories. Zhou Z *et al.* (2008) have shown that haplotype-driven NPY expression predicts brain responses to emotional and stress challenges and also inversely correlates with trait anxiety, which helps to explain inter-individual variation in resiliency to stress, a risk factor for many diseases.

2. Patient-centered medicine emphasizes "patient care" rather than "disease care," following Sir William Osler's admonition that "It is more important to know what patient has the disease than to know what disease the patient has." Most directly tied to health care is a provision that focuses on comparative effectiveness research—evidence-based studies that compare the value of medical treatments, such as two different drugs, or a specific drug versus surgery. Proponents hope that these studies will improve the quality and lower the cost of health care by identifying the best treatments. The health care reform bill created an independent, nonprofit Patient-Centered Outcomes Research Institute to conduct this research (Kaiser 2010).

3. Dynamic balance of internal and external factors. Energy and glucose homeostasis are regulated by food intake and liver glucose production, respectively. The upper intestine has a critical role in nutrient digestion and absorption. Wang PY *et al.* (2008) found that upper intestinal lipids activate an intestine-brain-liver neural axis to inhibit glucose production. They found that

the reduction in liver glucose production in response to intestinal lipids ceases after only three days of feeding rats a high-fat diet. It suggested that such diets promote obesity and diabetes in part by impairing nutrient-sensing systems that are designed to restrict food intake and enhance insulin sensitivity.

4. Web-like interconnections of physiological factors – an abundance of research now supports the view that the human body functions as an orchestrated network of interconnected systems, rather than individual systems functioning autonomously and without effect on each other. For example, we now know that immunological dysfunctions can promote cardiovascular disease, that dietary imbalances can cause hormonal disturbances, and that environmental exposures can precipitate neurologic syndromes such as PD.

5. Health as a positive vitality due to homeostasis– not merely the absence of disease. The concept of homeostasis has been developed as function-specific homeostasis (FSH) in our Lab. (Liu TCY *et al.* 2009b) and will be detailedly discussed in the following sections.

6. Promotion of organ reserve as the means to enhance health span. If lifespan is related to aging, health span is related to successful aging. Successful aging is the balance of three components: absence of disease and disease-related disability, high functional capacity, and active engagement with life (Rowe *et al.* 1987).

Among the 6 principles, the first 4 principles are the same as the principles in traditional Chinese medicine (TCM). The 5th and 6th principles are similar to the healthcare principles in TCM, but they are more than the ones in TCM. TCM promotes the establishment of homeostasis, but function medicine enhances health span. Moreover, function medicine is based on the recent progress in modern science.

3.2 Function-specific homeostasis

Homeostasis is one of the most remarkable and most typical properties of a highly complex open biosystem (Cannon 1932). It is a negative feedback response of a biosystem to maintain constant conditions inside the biosystem. As illustrated in Fig. 3.1, a ball in the valley is in homeostasis. The ball will be automatically back in the valley if the ball is forced to be on a mountain slope. Seasonal variations in mood and behavior, termed seasonality, are commonly reported in the general population. Rintamäki *et al.* (2008) and Øyane *et al.* (2010) have investigated the relationship between seasonality, objective health measurements and health behaviors in terms of global seasonality score (GSS). Their data were illustrated in Tabs. 3.1&3.2. In Tab. 3.1, There are no effects of seasons on systolic blood pressure or body mass index (BMI) if the GSS of a person or a woman is smaller than 10, but there are modulation effects of seasons on systolic blood pressure or BMI if the GSS of a person or a woman is greater than 11. In this case, a person of GSS smaller than 10 is in homeostasis, and a person of GSS greater than 11 is far from homeostasis.

Homeostasis can be established by homeostatic engineering. Not so many years ago, adding a heterologous set of enzymes in order to augment the biosynthetic capacity of a microbe was acknowledged as a remarkable feat of rational design. Apart from the important technical concerns of efficiency and stability, attention then turned to the greater challenge of repairing metabolic dysfunction; the goal here was not only to restore the biochemical reactions but also to place them under endogenous regulation. Kemmer *et al.* (2010) demonstrate how this might be achieved in

mice suffering from excess uric acid, which in humans can lead to the condition commonly known as gout. Uric acid is the product of purine catabolism, and in mice, urate oxidase converts it to allantoin, which is excreted. Excess uric acid can precipitate as the sodium salt, and humans, who lack urate oxidase, cannot tolerate too much of it. Conversely, uric acid can scavenge free radicals, and a moderate amount is deemed to be beneficial. Stitching together a mini-circuit comprising a *Deinococcus* transcriptional repressor and promoter as well as *Aspergillus* urate oxidase enabled these authors to maintain serum uric acid concentration in urate oxidase–deficient mice at normal physiologic levels.

Homeostasis is a classic concept in physiology. However, oscillations are found at nearly every level of biology. From the dynamic instability of cytoskeletal elements in an individual cell to the circadian rhythms that regulate a multitude of operations at the organismal level, it is clear that periodicity is an essential characteristic of living systems. Gregor *et al.* (2010) have described how cell aggregation and development of the amoeba *Dictyostelium discoideum* is guided by emergent rhythmic behavior arising from the stochastic pulsing of individual cells with a chemical cue. By combining experimental and computational approaches, the authors presented the exciting story of the dynamical onset of collective behavior in this organism. The findings raise the question of whether biology uses oscillations to solve problems typically assumed to have static or unidirectional solutions.

At this point, homeostasis is too obscure to be studied so that it has been developed as FSH (Liu *et al.* 2009b). FSH is a negative-feedback response of a biosystem to maintain the function-specific fluctuations inside the biosystem so that the function is perfectly performed. A biosystem in a FSH means the function is in its FSH so that it is perfectly performed. A biosystem far from a FSH means the function is far from its FSH so that it is dysfunctional. For an athlete, the key function is a sport, and his key FSH is sport-specific homeostasis (SpSH). Fig. 3.2 illustrated variable dose-response relationship between exercise training and performance (Busso 2003). There are two kinds of exercise training, extraordinary training (ET) enhancing performance and ordinary training (OT) maintaining performance. Obviously, OT may be in SpSH, and ET may be in performance enhancement-specific homeostasis (PeSH) but far from SpSH.

The SpSH is independent of carbon dioxide (CO_2) content in the inhalation air. In order to examine the effect of acute respiratory acidosis induced by CO_2 inhalation prior to maximal exercise on blood lactate and physical performance, double determinations were carried out by Miyamura *et al.* (1989) for each subject on separate days; one day, after CO_2 inhalation and other day, after inhalation of room air. It was observed that in the untrained subjects the CO_2 inhalation prior to maximal treadmill exercise does not affect endurance time and maximum aerobic power, whereas blood lactate during recovery was lower in CO_2 breathing than that in room air. In addition, no significant difference of 200 m sprint time in the athletes was noticed between CO_2 and room air while blood lactate after 200 m sprint running was significantly lower in the CO_2 than that in room air. From these results, it was suggested that the effect of CO_2 inhalation prior to maximal exercise as applied here appeared to be mediate through metabolic rather than oxygen transport mechanism, but not related to physical performance.

Cells are able to maintain an earlier response to a signal. Gialitakis *et al.* (2010) studied such a mechanism in HeLa cells (an epithelial cell line derived from a human cancer). These cells respond to interferon (IFN) γ by increasing transcription of genes encoding major

histocompatibility complex (MHC) class II proteins. Cells that had been exposed to IFN-γ and then had the stimulus removed for 96 hours were more sensitive to a second treatment with IFN-γ than were unprimed cells. The cells previously exposed to IFN-γ showed faster and greater accumulation of messenger ribonucleic acid (mRNA) encoded by MHCII genes. The increased transcriptional responsiveness was associated with a persistent loss of histone H3, indicative of loss of nucleosomes, which may provide a more open conformation of the chromatin, and persistent dimethylation of histone H3. IFN-γ also caused increased production of the promyelocytic leukemia (PML) protein, which localizes in nuclear structures known as PML bodies that have been suggested to be sites of localized transcriptional activation. The MHCII locus was shown by immunostaining and fluorescence in situ hybridization to be more closely associated with PML bodies in cells responding to IFN-γ or in cells that had been primed by such a response. The mixed lineage leukemia methyltransferase complex also showed altered localization to the vicinity of PML bodies in primed cells or cells responding acutely to IFN-γ. Depletion of PML with small interfering ribonucleic acid (siRNA) decreased the IFN-γ–induced increase in dimethylation at the MHCII promoter and prevented the sustained priming effect. Transcriptional activation of the MHCII gene in response to IFN-γ was diminished in cells depleted of PML, as was the priming effect on a later response to IFN-γ. The results provide additional evidence for the importance of subnuclear localization not only for transcriptional regulation but also for the long-term memory effects that can be maintained over multiple generations in replicating cells. Gialitakis *et al.* (2010) proposed that such mechanisms could allow cells to maintain certain genes in a state poised for increased responsiveness to a subsequent signal for activation.

There are two kinds of regulation factors of a function of a biosystem, the homeostatic regulation factors which modulate the function so that there is no modulation on the function in its FSH and there is modulation on the function far from its FSH, and the developmental regulation factors which disrupt the FSH. Each FSH maintains its function. A developmental regulation factor can disrupt an FSH so that it can change the functions of a biosystem from one to another so that a developmental regulation factor can be also called as a non-homeostatic regulation factor. In Tab. 3.1 and Fig. 3.2, both seasons and OT are homeostatic regulation factors, but ET is a developmental regulation factor. For the HeLa cells discussed above, the first exposure to IFN-γ is a developmental regulation, but subsequent exposures to IFN-γ are homeostatic regulations. PBM can be then classified into two kinds, FSH-specific PBM (fPBM) in which LI is just a homeostatic regulation so that it is called low level LI (LLL) and its clinic applications is called LLL therapy (LLLT), and developmental PBM (dPBM) in which LI is just a developmental regulation. As chapter 8 will show, LPBM is a kind of fPBM so that LIL is a kind of LLL.

Acupoint LPBM is a kind of fPBM. With the randomized, double-blinded, placebo-controlled trial, Hübscher *et al.* (2007) have evaluated specific effects of LA at the Neiguan point (PC6) (Fig. 3.3) for sympathetic nerve (SN) and parasympathetic nerve (PSN) activity in healthy subjects, but they did not find any significant difference of heart rate variability (HRV). With a randomized, double-blinded, placebo-controlled trial, Banzer *et al.* (2006) have studied the effects of laser needle irradiation on the right forearm at acupuncture point PC6 (Fig. 3.3) on non-smoking males (averaged age, 27 years; averaged BMI, 24 kg/m^2), and found that laser needle stimulation may improve peripheral microcirculation under standardized conditions, whereas tissue oxygenation

remained unchanged. Zhang J *et al.* (2008a) have studied the effects of LA on blood pressure, body weight, and HRV by stimulating acupuncture points and meridians on college students and faculty members with mild hypertension (systolic blood pressure, 160-125 mm Hg; diastolic blood pressure, 110-81 mm Hg). This study was a randomized controlled pilot study with subjects divided into control and experimental groups. The control group received a sham LLLT treatment with no power output to the laser during their "treatment." The experimental group was treated with an activated laser. The acupuncture points used in this study were LI 4 and LI 11 (Fig. 3.4) for body weight and blood pressure. After using the laser treatment for 90 days (at least 12 treatments per subject), both the systolic and diastolic blood pressures decreased significantly. There were no significant changes in the HRV and body weight. In this case, the blood pressure was far from homeostasis, but the HRV and body weight were in homeostasis.

ILILT is an intranasal application of LIL, and is a kind of fPBM. The studies indicated that serum Aβ, malformation rate of erythrocytes, CCK-8, the level of viscosity at lower shear rates, hematocrit, and serum lipid decrease, respectively, and melanin production， SOD activity and β endorphin increase, respectively, after ILILT. However, there were no LPBM on serum lipid, Aβ, melanin production, plasma CCK-8 of health persons. Xu C *et al.* (2002b) have divided the objects into two groups, 47 patients of AD and 22 patients of gastric ulcer, and treated the patients with low intensity 632.8 nm He-Ne laser irradiation (LHNL) at 3.5~4.5 mW for 30 min each time, which was done once every morning for 30 days. They found that melatonin (Mel), score in Mini-Mental State Exam (MMSE) and score in Wechsler Memory Scale for Adult (WMS) increased in AD group, but there was no LPBM on gastric ulcer group. For the gastric ulcer group, AD-related systems are in FSH so that there is no LPBM. In terms of self-rating depression scale (SDS), Xu C *et al.* (2002c) divided 177 patients of stroke into two groups, 45 in pure stroke group (SDS < 40) and 132 in PSD group (SDS > 40), and then treated the two groups with LHNL at 3.5~4.5 mW for 30 min each time, which were done once a day in the afternoon for 30 days, and found serum Mel increased and SDS decreased only in PSD group, but there is no such changes in pure stroke group. For pure stroke group, the PSD-related systems are in FSH so that there is no LPBM. ILILT might improve the regional cerebral blood flow (rCBF) and brain blood flow function change rate (BFCR%) of the focus of cerebral infarction, but there is no PBM on the mirror healthy regions(Xiao X *et al.* 2005).

3.3 Homeostatic diversity

Keeney (2008), a decision analyst at Duke University's Fuqua School of Business, crunched data from the Centers for Disease Control to assess how many deaths in the United States are due to personal choices—things like smoking, overeating, or unsafe sex. The results: A remarkable 55 percent of deaths for people age 15 to 64 can be attributed to decisions with readily available alternatives. In other words, most people are the agents of their own demise. That's a vast difference from a century ago, when, Keeney estimates, a scant 5 percent of deaths were brought on by personal decisions (infectious diseases account for most of the rest).

Personal choices maintain personal homeostasis, but there are many kinds of homeostasis. A health person is in homeostasis so that all of his/her physiological functions are in their respective FSH, and we have physiological function-specific homeostasis (PhFSH) in which the

physiological function can completely perform. A pathological function which is defined as a disease-specific physiological function is far from the corresponding PhFSH, but may be in its pathological function-specific homeostasis (PaFSH). As discussed above on Tab. 3.1, a person of GSS smaller than 10 is in homeostasis, and a person of GSS greater than 11 is far from homeostasis. In Tab. 3.2, the GSS of a patient of metabolic syndrome may be smaller than 10 so that his/her metabolic function may be in PaFSH.

Addiction is a kind of PaFSH. Drug addicts' brain reward circuits often exhibit dulled responses, leading the addicts to seek more of the addictive substance to get their fix. Work in rats indicates that fatty foods may trigger similar responses (Johnson *et al.* 2010). Rather than try to avoid the shock when the light came on, as the rats with limited or no access to junk food did, "addicted" rats just kept on eating. We see the same thing in animals with extended access to cocaine.

A PaFSH should be maintained by pathological conditions such as unhealthy lifestyle as a PhFSH is maintained by physiology conditions such as healthy lifestyle. Misfolded proteins implicated in AD and prion disorders such as PD and Creutzfeldt–Jacob disease may interact, making each disease worse. Morales *et al.* (2010) introduced prions into normal mice and AD mice genetically predisposed to developing symptoms of AD, such as amyloid plaques in the brain. They found the onset of prion disease symptoms in AD mice appeared significantly faster than in normal mice. Obviously, the AD mice are in AD-specific homeostasis (ADSH), but the normal mice are far from ADSH.

The studies of stem cell niche indicated that individual microenvironment constituents can serve as regulators of tissue functions beyond that of stem cell support (Raaijmakers *et al.* 2010). Raaijmakers *et al.* (2010) found bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Their findings support the mechanism of malignancy resulting from the interaction of cell autonomous and microenvironmentally determined events, and point to the microenvironment as the site of the initiating event that leads to secondary genetic changes in other cells. It is therefore possible to envision a ‘niche-based’ model of oncogenesis in which a change in a specific microenvironmental cell can serve as the primary moment in a multi-step process towards malignancy of a supported, but distinct cell type. Signals from the microenvironment may select for subsequent transforming events and therefore such signals may represent candidate therapeutic targets in both treatment and prevention strategies.

There are no effects of LLL on a pathological function in its PaFSH, but there are effects of LLL on a pathological function if the pathological factors are transformed into the physiological factors. In the latter case, the pathological function will be far from its PaFSH, and LLLT may promote PhFSH establishment. For addiction, there are withdrawal symptoms if the unhealthy lifestyle is transformed into a healthy lifestyle, LLLT may promote the recovery from withdrawal symptoms as discussed in chapter 6.5.3.

3.4 Sirtuins

Exposure to a variety of mild stressors, including calorie restriction, thermal stress, or hyperbaric oxygen, induces an adaptive biological response that increases eukaryotic life span (Saunders *et al.* 2009). There are also a variety of mutations associated with both increased

resistance to stress and increased longevity. Adaptive responses to stressors are mediated by transcription factors that are regulated by the enzyme sirtuins (SIRTs) and then regulate both stress response and life span. SIRTs are a highly conserved family of nicotinamide adenine dinucleotide (NAD^+) -dependent histone deacetylases that regulate lifespan (Finkel *et al.* 2009, Saunders *et al.* 2009). The larger the ratio of NAD^+ and its reduced form NADH, NAD^+/NADH, is, the higher the SIRT activities, respectively. Fig. 3.5 illustrated examples of the organ-specific physiology of SIRT1, along with some of the direct or indirect targets of SIRT regulation. When a function is far from its FSH, LLL may increase NAD^+/NADH and then SIRT1 activity (Liu CY *et al.* 2009).

Maintenance of health depends on the ability to respond appropriately to environmental stressors via reciprocal interactions between the body and the brain. In this context, it is well recognized that the pineal hormone Mel plays an important role. Mel can enhance NAD^+ level (Bubis *et al.* 1998) and SIRT1 activity (Tajes *et al.* 2009). Mel synthesis in the pineal might be far from Mel synthesis specific homeostasis (MSH). The Mel synthesis far from its MSH can be promoted with ILILT. As mentioned above in section 3.1, the ILILT treatments of patients with AD (Xu C *et al.* 2002b) and PSD (Xu C *et al.* 2002c) may enhance serum Mel level, respectively. Xu C *et al.* (2001) have treated 38 patients with insomnia with LHNL at 3.5~4.5 mW for 30 min each time, which was done once a day and ten days each session for two sessions, and found serum Mel increase. Xu C *et al.* (2003) have treated 47 patients with PD with LHNL at 3.5~4.5 mW for 30 min each time, which was done once every morning for 20 days, and found the PD symptom improvement of 14 (29.8%), 27 (57.4%) and 6 (12.8%) patients were significant, mild and none, respectively, and SOD and Mel increased and malondialdehyde (MDA) decreased.

The effects of LA on Mel have not been studied, but the effects of acupuncture on Mel have been studied. Spence *et al.* (2004) have assessed the response to acupuncture of 18 anxious adult subjects who complained of insomnia in an open prepost clinical trial study. Five weeks of acupuncture treatment was associated with a significant nocturnal increase in endogenous melatonin secretion (as measured in urine) and significant improvements in polysomnographic measures of sleep onset latency, arousal index, total sleep time, and sleep efficiency. Significant reductions in stateand trait anxiety scores were also found. Chao DM *et al.* (2001) have established a rat seizure model by microinjecting benzylpenicillin into hippocampus to explore the alteration of Mel levels in pineal, hippocampus and serum during seizure crises and electroacupuncture anti-seizures. Mel level was elevated in pineal and hippocampus, and first had no change then significantly evaluated in serum during seizure crisis. The elevation of Mel level was greatly potentiated with 30 min electroacupuncture treatment. Meanwhile, the degree of seizures and the increases of electroencephalogram relative power induced by seizures were significantly reduced.

3.5 Olfactory functions

Prior studies have validated the bilateral olfactory bulbectomy causes a dysfunction of cortical-hippocampal-amygdala circuit underlying behavioral and other alterations. Theses changes seem to be dysfunctional in patients with major depression (Song C *et al.* 2005). The changes following bulbectomy are characterized by: (1) cell changes and a reduction in the number of synapses, dendritic spines and shafts in different brain areas such as the cortex, hippocampus, amygdale or cerebellum; (2) alterations in locomotor activity and behaviour; (3)

changes in the synthesis and release of neurotransmitters (noradrenaline, acetylcholine, serotonin, glutamate, γ-aminobutyric acid, etc.); (4) changes in immune system; (5) reduction in antioxidative systems; and (6) cell death, making the bulbectomized rat model a validity model for studying depression.

Tasset *et al.* (2010) have analyzed the effects of Mel (1 mg/kg) (intraperitoneal injection, ip) on behavioral changes of Male Wistar rats as well as cell and oxidative damage prompted by bilaterally olfactory bulbectomy. Olfactory bulbectomy caused an increase in lipid peroxidation products and caspase-3, whereas it prompted a decrease of reduced glutathione (GSH) content and antioxidative enzymes activities. Additionally, olfactory bulbectomy induced behavioral changes characterized by the enhancement of immobility time in the forced swim test and hyperactivity in the open field test. All these changes were normalized by treatment of Mel (14 days). Their data indicated that olfactory bulb mediated Mel has a beneficial neuropsychiatric action against oxidative stress, cell damage and behavior alterations.

The olfactory bulbs have been proposed as first portal for Venezuelan equine encephalomyelitis (VEE) virus entry into the central nervous system (CNS). In male albino mice infected with the VEE virus and exposed to bright light at 2500 lux with a 12 h light : 12 h dark photoperiod, Medina-Leendertz *et al.* (2001) have observed a significant increase in the levels of Mel in the olfactory bulb. In other words, bright light effects can promote MSH establishment as ILILT can. The increase in Mel content could represent one of the mechanisms of defense against the viral attack. This might hold for ILILT because ILILT can also increase Mel level. The possible applications of ILILT for prophylaxis or treatment on influenza will be detailedly discussed in chapter 6.4.

3.6 Laser Hemotherapies

Hemotherapy is the treatment of disease by the use of blood or blood derivatives, as in transfusion. Laser hemotherapy has been put forward in intracardiac LHNL therapy, extracorporeal LHNL therapy and intravascular low energy laser therapy (ILELT) in Russia from 1994 on. It will be discussed in this section as the blood cells in the internal diseases mentioned in the introduction of this chapter are always far from FSH so that there might be LPBM on their functions.

3.6.1 **Blood mediated intranasal low intensity laser therapy**

There is LPBM on erythrocytes, such as its protecting human erythrocytes from hypotonic hemolysis (Iijima *et al.* 1991), its improving the deformability of stored human erythrocytes(Iijima *et al.* 1993, Yokoyama *et al.* 2003), its producing acetylcholinesterase (AChEase) activity changes (Kujawa *et al.* 2003) and its inducing long-term conformational transitions of erythrocytic membrane which were related to the changes in the structural states of both erythrocyte membrane proteins and lipid bilayer and which manifested themselves as changes in fluorescent parameters of erythrocyte membranes and lipid bilayer fluidity so that there was the modulation of membrane functional properties: changes in the activity of membrane ion pumps and, thus, changes in membrane ion flows (Kujawa *et al.* 2004). PBM on erythrocyte deformability was found to be mediated by membrane aquaporin-1 and then G protein in our laboratory (Luo GY *et al.* 2007).

There were so many LPBM studies on erythrocytes, but a few of LPBM studies on platelets (Brill' *et al.* 2008), which provides the foundation for ILILT on the rheological properties of blood so that malformation rate of erythrocytes (Li Q *et al.* 1999a) and the level of viscosity at lower shear rates and hematocrit (Jie J *et al.* 1999) decreased, respectively, and RCD increased (Jin L *et al.* 2001b) after ILILT.

Litscher *et al.* (2005) have investigated a total of 34 volunteers (24 females, 10 males) and a 15-year-old intensive care patient after severe head injury. The mean age of volunteers was 25.2 years (range 20-35). Stimulation was performed using laser needle methods on the acupoints *Xiaguan* (ST 7)(Fig. 3.4) of *stomach* meridian of foot *yangming* and *erheliao* (SJ 22) (Fig. 3.6) of *sanjiao* meridian of hand *shaoyang*. They have evaluated the main parameter of mean blood flow velocity in the middle cerebral artery (left and right) as well as the pulsatility index. In addition, near infrared spectroscopy and blood pressure parameters were registered. They found that laser needle acupuncture partially led to significant changes in the main goal values.

Su WJ *et al.* (2009) have studied the therapeutic effects of ILILT on vascular diseases (Tabs. 3.3 and 3.4). 90 old patients of average age 76.1 years with coronary heart disease or cerebral infarction were randomly divided into two groups, 60 in the treatment group and 30 in the control group. The treatment group and the control group were intranasally treated with low intensity GaInP/AlGaInP diode laser irradiation at 650 nm (LGAL) at 3 and 0 mW for 30 minutes each time once a day ten days each session for two sessions, respectively. After the treatment, blood viscosity at high shear ($P < 0.05$), plasma viscosity ($P < 0.05$), red blood cell aggregation ($P < 0.01$), and total cholesterol ($P < 0.05$) decreased in the treatment group, respectively, high-density lipoprotein cholesterol increased in the treatment group ($P < 0.01$), but no significant differences occurred in the control group; low-density lipoprotein cholesterol, redox viscosity at low shear and high shear decreased in the treatment group ($P < 0.05$, 0.01 and 0,05), but increased in the control group ($P < 0.001$, 0.01 and 0.05), respectively; blood viscosity at low shear increased in the control group ($P < 0.05$), but no significant differences occurred in the treatment group. It was concluded that ILILT may improve blood lipid and hemorheologic behavior of patients with vascular diseases.

Table 3.3 Blood Viscosity Index (mean ± SEM)

Blood	Treatment Group(n)		Verified Statistics		Control Group(n)		Verified Statistics	
viscosity	Before	After	t	P	Before	After	t	P
BV(l)	8.34±1.91	8.15±1.91	0.545	>0.05	6.54±1.75	7.87±1.99	2.735	<0.05
BV(h)	4.23±0.82	3.94±0.74	2.020	<0.05	3.56±0.65	4.02±1.64	1.428	>0.05
PV	1.23±0.02	1.14±0.22	2.233	<0.05	1.23±0.18	1.23±0.01	--	--
RBCP	39.88±7.72	41.66±4.79	1.526	>0.05	37.92±6.04	38.55±6.52	0.388	>0.05
RV(l)	17.35±4.03	15.24±2.82	3.323	<0.01	14.09±3.26	16.88±4.04	2.944	<0.01
RV(h)	6.99±0.75	6.63±0.55	2.120	<0.05	6.27±1.17	7.21±1.54	2.662	<0.05
RBCA	2.15±0.41	1.95±0.24	3.263	<0.01	1.77±0.35	1.92±0.23	1.961	>0.05

WBV： Whole Blood Viscosity, PV: Plasma Viscosity
RV: Redox Viscosity, RBCA: Red Blood Cell Aggregation, RBCP: Red Blood Cell Pressure
h: high shear, l: low shear

Table 3.4 Blood Lipid Index (mean ± SEM)

Blood lipid	Treatment Group(n)		Verified Statistics		Control Group(n)		Verified Statistics	
	Before	After	t	P	Before	After	t	P
TC (mmol/l)	4.44±1.72	3.78±0.95	2.603	<0.05	4.10±1.15	4.07±1.26	0.096	>0.05
TG (mmol/l)	1.88±0.67	1.70±0.77	1.366	>0.05	1.85±0.71	1.87±0.70	0.110	>0.05
HDL-c(mmol/l)	1.07±0.27	1.20±0.24	2.790	<0.01	1.00±0.31	1.17±0.41	1.812	>0.05
LDL-c (mmol/l)	2.73±0.76	2.48±0.51	2.115	<0.05	1.39±0.70	2.33±0.93	4.424	<0.001
ApoA (g/l)	1.29±0.29	1.35±0.27	1.367	>0.05	1.24±0.26	1.22±0.34	0.256	>0.05
ApoB (g/l)	0.89±0.29	0.81±0.19	1.788	>0.05	0.81±0.29	0.86±0.33	0.125	>0.05
A/B	1.58±0.43	1.64±0.42	0.733	>0.05	1.54±0.44	1.55±0.49	0.083	>0.05

TC: Total Cholesterol, TG: Triglyceride,
HDL-c(LDL-c): High(Low)-Density Lipoprotein Cholesterol,
ApoA(ApoB): Apolipoprotein A(B), A/B: ApoA/ApoB,

Platelets not only save us from bleeding to death, but in recent years, platelets have also displayed powers no one imagined they had (Leslie 2010). They are healers that pour out growth factors and other soothing molecules that help damaged tissue rebuild. They are soldiers that spark the protective response known as inflammation, alert immune cells, and even attack microbial interlopers. They are long-haul truckers that pick up and deliver chemicals such as serotonin, which helps the liver regenerate after injury. They are even engineers, shaping the vascular system in newborns. Additional platelet functions continue to come to light, and biologists have just described a novel way that the body might make these multitalented cells—a finding that could one day ease the demand for donated blood. It has been found that the red LIL decreases adhesion and aggregation of blood platelets both at high and low rate of shift (Brill' *et al.* 2008). Obviously, more PBM on platelets will be found.

There is also LPBM on leukocytes, such as its stimulating lymphocytes to produce factor(s) that can modulate endothelial cell proliferation in vitro (Agaiby *et al.* 2000) and its modulating NO and cytokines production by leukocytes (Chichuk *et al.* 1999). There are two ways for polymorphonuclear neutrophils (PMNs) to kill bacteria, phagocytosis and neutrophil extracellular traps (NETs), both of which have been found to be induced or promoted with LIL in our laboratory (Duan R *et al.* 2001, Liu TCY *et al.* 2010a). Many cellular LPBM studies provide the foundation for ILILT on immunological functions so that the lymphocyte proliferation was promoted (Zhu J *et al.* 2008) and the CD3 and CD8 increased and CD4/CD8 decreased (Zhou Y *et al.* 2005) after ILILT.

Blood cells mediate the therapeutic effects of intranasal PBM on the local inflammation. Tulebaev *et al.* (1989) have found the LPBM treated patients with vasomotor rhinitis showed a significant increase of T-lymphocytes and a higher capacity of T-cells to form the migration inhibition factor. Kruchinina *et al.* (1991) have studied therapeutic effect of LHNL on microcirculation of nasal mucosa in children with acute and chronic maxillary sinusitis, and found that laser therapy produced a positive effect on microcirculation and reduced the potential of relapses. Shevrygin *et al.* (2000) have shown that LPBM is effective in correction of microcirculatory disorders and tissue mechanisms of homeostasis in children with neurovegetative vasomotor rhinitis.

3.6.2 Comparative Research of Two Laser Hemotherapies

The comparative research of ILILT with ILELT might support the blood role in ILILT.

ILELT was put forward for cardiocirculatory diseases in Russian in 1981 and then in USA in 1982, was popular in Russia in 1980s, and then in the mainland of China in 1990s. For ILELT, an optical needle was smoothly inserted into the vein, and the needle was connected to the laser transducer through an optical fiber (diameter, 0.2 mm). The order of the intensity at the tip of the optic fiber used in ILELT is about 10^3 mW/cm^2, a kind of MIL, but the blood velocity in vein is about 1-10 cm/s so that the order of the irradiation time of each blood cell is about 10 ms, and then the order of the dose of each blood cell is about 100 J/m^2, a kind of low energy. As the laser irradiation of ILELT is of moderate intensity but low energy, ILELT might be mediated by reactive oxygen species (ROS) (Dröge 2002) as it will be shown in chapter 8, and the level of ROS was so low that ILELT is a kind of fPBM. As Fig. 3.7 has indicated, different ROS levels activate different mitogen-activated protein kinase (MAPK) pathways, which will be detailedly discussed in chapter 7. Therefore, ILELT at different intensity might enhance ROS level and then rehabilitate immune functions and hemorheological functions, respectively.

The comparative research of ILILT with ILELT on cerebral infarction or/and traumatic brain injury have been done, but no significant difference has been found. Dou Z *et al.* (2003) randomly divided 60 patients of cerebral infarction and 36 patients of traumatic brain injury into two groups, 50 in ILILT group and 46 in ILELT group, and then treated ILILT group with LGAL at 2.4 mW for 30 min each time and ILELT group with He-Ne laser at 2.5 mW for 40 min each time, respectively, which were done once a day and five days each session for two sessions between which there were two days for rest. They found the cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), erythrocyte sedimentation rate and hematocrit were significantly reduced, Fugl Meyer movement scale and Barthel index scores were significantly increased and the brain damage area was reduced in both groups, but there was no statistical difference between the two groups. Xiao X *et al.* (2005) have treated 21 and 18 patients of cerebral infarction by ILILT with LGAL at 3.5~4.0 mW for 30 min and ILELT with LGAL at 2.5~3.0 mW for 30 min, respectively, and use single photon emission computed tomography (SPECT) in brain perfusion imaging to study the changes of rCBF and BFCR%, and found the ratio of local rCBF vs whole brain rCBF and BFCR% increased in the focus side of the brain after the treatment of either ILILT or ILELT, but no change in the mirror regions and no significant difference between ILILT and ILELT. Zhao R *et al.* (2005) randomly divided 99 patients of cerebral infarction into three groups, 30 in drugs-only group, 33 in ILILT+drugs group and 36 in ILELT+drugs group, and then treated ILILT+drugs with LHNL at 3.5~5.5 mW for 30 min each time and ILELT+drugs with He-Ne laser at 1.5 mW for 90 min each time, respectively, which have been done one time each day for days, respectively. They found both the leukocyte adhesion rate and the concentration of serum soluble intercellular adhesion molecule-1 decreased on the 10th day for drugs-only group, but decreased on the 5th day after the treatment of either ILILT or ILELT, and there is no significant difference between ILILT+drugs group and ILELT+drugs group.

There is LPBM on the blood cells flowing in nasal mucosa in ILILT. There is also MPBM on blood cells flowing in vein in ILELT. The similar therapeutic effects of ILILT and ILELT on

cerebral infarction or traumatic brain injury not only support blood dysfunction might be one of the main causes of the brain diseases, but also support ILILT might be mediated by blood cells. Jin L *et al.* (2001b) randomly divided 93 patients of cerebral infarction into three groups, 30 in drugs-only group, 32 in ILILT+drugs group and 31 in ILELT+drugs group, and then treated ILILT+drugs group with LIL at 670 nm and 7~10mW for 40 min each time and ILELT+drugs group with He-Ne laser at 1.5 mW for 90 min each time, respectively, which have been done one time each day for ten days. They found left parietal P300 event-related brain potential (P_3PL) decreased and erythrocyte deformability increased after the treatment of either ILILT or ILELT in comparison with drugs-only group.

3.7 Meridian functions

LA as a noninvasive, painless and cost-effective therapy can modulate meridian functions. It has been widely used for acute and chronic pain, nausea, circulatory dysfunction, mood-related behavioral disorders and so forth (Wang LQ *et al.* 1993, Tunér *et al.* 1999, Jiao JL *et al.* 2003). Its mechanism will be discussed in chapter 10. 2. In this section, the mechanism of ILILT was discussed according to meridian theory.

3.7.1 Hypothesis of Meridian Mediated Intranasal Low Intensity Laser Therapy

In TCM, meridians are channels that form a network in the body, through which *qi* (vital energy) flows. Blocked *qi* causes pain or illness. The flow of *qi* is restored by using pressure, needles, suction, or heat at hundreds of specific points, acupoints, along the meridians.

The meridian network links meridians with each other and connects all body structures—skin, tendons, bone and internal organs. Meridians also connect the interior with exterior and the upper body with the lower body. This interlinked, animating network through which *qi* flows freely makes the body an organic whole. In a longitudinal study (Eriksson *et al.* 2008), a history of atopic disorders such as asthma, eczema and rhinitis was positively associated with AD and dementia that is not mediated by vascular disease. There are six meridians inside/around nose, *stomach* meridian of foot *yang-ming*, *du* meridian, *yin-jiao* meridian, *yang-jiao* meridian, *large intestine* meridian of hand *yang-ming*, and *small intestine* meridian of hand *tai-yang*. These six meridians can be irradiated by intranasal LIL through intranasal multiple reflex. They are supposed to mediate some of the therapeutic effects of ILILT. This is called the meridian mediated ILILT hypothesis (MIH).

Because meridians respond to and carry stimulation as well as transmit information, they have the ability to bring healing energy to local, as well as distant, parts of the body. This can create physiological and other changes as *qi* circulates. It is this function that makes acupuncture and acupressure work at acupoints along the meridian so that the flow of *qi* can be enhanced or modified either with needles, LI or with the pressure of the finger or the hands. Therefore, if a meridian can be used by acupuncture to treat a disease, it might be also used by ILILT to treat the same disease if it can be irradiated by intranasal LIL. This is the foundation to verify MIH.

It has been found that cerebral infarction, insomnia, senile dementia such as AD and PD, and PSD might be effectively treated with acupuncture at acupoints along *du* meridian, respectively,

and acute MI, hyperlipidemia, child chronic cough and trigeminal neuralgia might also effectively treated with acupuncture at acupoints along *small intestine* meridian of hand *tai-yang*, *stomach* meridian of foot *yang-ming*, *large intestine* meridian of hand *yang-ming* and *stomach* meridian of foot *yang-ming* & *large intestine* meridian of hand *yang-ming*, respectively. All the mentioned diseases might be also effectively treated with ILILT, respectively. This comparison supported MIH.

3.7.2 Cerebral Diseases

According to MIH, *large intestine* meridian of hand *yang-ming*, *stomach* meridian of foot *yang-ming*, *du* meridian and *yin-jiao* meridian running through brain might mediate the therapeutic effects of ILILT on cerebral diseases.

Yang-ming meridian mediated treatment of cerebral diseases was most often studied. Zhang D *et al.* (1990) observed the effect of acupuncture at points of hand *yang-ming* meridian was bigger than that of foot *yang-ming* meridian on the facial temperature of the patients with facial nerve paralysis. Wu L *et al.* (1996) have adopted the principle of clearing *Yang-ming* and nourishing the *kidney* and *heart* in the treatment of 156 cases of Gilles de la Tourette's Syndrome with acupuncture. The total effective rate was 92.3%, and the cure rate in children aged 11-15 years was markedly higher than that in children 6-10 years of age. They found the pathological waves in 54 disappeared or ameliorated after the treatment among 84 cases with abnormal electroencephalogram. Zhang S *et al.* (1999) have found one of the mechanisms governing acupuncture treatment of apoplexy acupuncture at *Yang-ming* meridian points as main points was that acupuncture could produce therapeutic effects by adjusting the imbalance of important vaso-active substances, endothelin level in plasma, thromboxane B2 and 6-ketoprostaglandin F1α levels in urine. Wang L *et al.* (2005) found the acupuncture therapy of "*mother-son*" reinforcing-reducing method of the acupoints of the hand *yang-ming* and foot y*ang-ming* meridians can increase clinical therapeutic effect on stroke at restoration stage.

Du meridian mediated acupuncture effects on cerebral diseases were also studied. Xu N *et al.* (1996) found the brain contents of NO and endothalin increased when the rat bilateral common carotid arteries were occluded, and the levels of endothalin and NO in the brain and blood were returned significantly to normal after electroacupuncture of *du* meridian (GV 20, GV 14) point in rats, which suggested that electroacupuncture at *du* meridian have protective effect on neural damage induced by brain ischemia, and NO and endothalin are possibly involved in the regulative effect of electroacupuncture. Li Q *et al.* (2005) found electroacupuncture may inhibit epilepsy via upregulating the concentration of taurine transporter to increase the release of taurine on the acupoints of *du* 20, *bai hui*, and *du* 16, *feng fu*, along *du* meridian after epilepsy was induced by micro-injection of penicillin into hippocampus of Wistar rats. Seventy patients with heroinism were randomly divided into a treatment group (n= 35) and a control group (n=35). A 10-day decrescendo therapy of methadone and acupuncture at points of the *du* meridian were adopted in the treatment group, while the 10-day decrescendo therapy of methadone was simply performed in the control group. Zeng X *et al.* (2005) found the obvious difference in scores of abstinence symptoms on the first, second, fifth, sixth, seventh, eighth, ninth and tenth day in the treatment group was superior to those in the control group, particularly for such symptoms as perspiration,

anxiety and pain in the muscle and bone, which suggested acupuncture at points of the *du* meridian has an auxiliary therapeutic effect on abstinence symptoms of heroinism, which can effectively help alleviate the abstinence symptoms.

Therefore, there might be therapeutic effects of ILILT on brain diseases such as insomnia, intractable headache, AD, PD, PSD, ache in head or face, migraine, DPN, cerebral thrombosis, cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, CP and mild cognitive impairment.

3.8 Autonomic functions

The central ANS functions at maintaining cardiovascular hemodynamics. There is crosstalk between nasal ANS and central ANS (Ko JH *et al.* 2008). The central ANS activities significantly correlated with changes to the nasal airway during postural change. The central ANS, especially the sympathetic nervous system, may play a role in controlling nasal airway during postural change.

When ANS is in autonomic activity-specific homeostasis (AnSH), there are no PBM or Mel on ANS. With the randomized, double-blinded, placebo-controlled trial, Hübscher *et al.* (2007) have evaluated specific effects of laser needle acupuncture at the Neiguan point (PC6) (Fig. 3.3) on SN and PSN activity in healthy subjects using HRV analysis, but they did find any significant difference. Sletten *et al.* (2001) have investigated the potential contribution of bright light and melatonin to influence cardiac autonomic activity of 16 young healthy subjects in the evening. An initial baseline condition involved dim light exposure (< 10 lux), permitting the normal nocturnal rise in endogenous melatonin. In other sessions, subjects were exposed to bright light (> 3000 lux) to suppress Mel secretion and administered a placebo or Mel (5 mg) capsule at the estimated time of increase in endogenous Mel (wake time + 14 hours). Heart rate, pre-ejection period (a measure of cardiac sympathetic activity) and respiratory sinus arrhythmia (a measure of parasympathetic activity) were not significantly altered in response to the three Mel levels. Sakakibara *et al.* (2000) have investigated the effects of 5000 lux evening bright light on autonomic nervous function of 12 young health women (range: 20-21 years of age). Although a low frequency band (LF) increased in bright light conditions in comparison with controlled conditions, high frequency band (HF), LF:HF ratio and the coefficient of variance (CV R-R) were not significantly different between the two conditions.

The central ANS or intranasal ANS might be far from AnSH so that it might mediate LA and ILILT. ANS might be one of the pathways mediating acupuncture and LA (Jiao JL *et al.* 2003). Levels of affective disorders and stress are high in night shift workers. Wu JH *et al.* (2009) have applied laser energy to the Neiguan point (PC6) (Fig. 3.3) to examine the impact of LA on the ANS of 45 healthy young males who were night shift workers. They found LA stimulation increased vagal activity and suppression of cardiac sympathetic nerves and induce a new balance in the ANS, which is maintained for at least 40 minutes. With a randomized, double-blinded, placebo-controlled trial, Banzer *et al.* (2006) have studied the effects of LA on the right forearm at acupuncture point PC6 (Fig. 3.3) on non-smoking males (averaged age, 27 years; averaged BMI, 24 kg/m^2), and found that LA may improve peripheral microcirculation under standardized conditions, whereas tissue oxygenation remained unchanged. PC6 is one of the acupoints of

pericardium meridian of hand *jueyin* through interdigital. The above discussion indicated that DLILT may at least modulate ANS.

There is an extensive literature documenting a number of determinants of autonomic tone(Lauer 2009). Job strain was associated with a reduction in cardiac vagal control persisting throughout the 48 hr and elevations in sympathetic control during working hours so that the disturbed cardiovascular regulatory pattern associated with job strain increased risk of cardiovascular diseases linked with occupational exposure (Collins *et al.* 2005). Autonomic dysfunction is responsible for much of the morbidity associated with frequently encountered neurological disorders, such as PD, multiple sclerosis, cerebrovascular disease, and peripheral neuropathies, as well as with the rarer primary ANS degenerations (Freeman *et al.* 1993). On a patient level, decreased levels of parasympathetic tone or increased levels of sympathetic tone have been linked to obesity, insulin resistance, diabetes, hypertension, hypercholesterolemia, depression, anxiety, heart failure, and peripheral vascular disease (Lauer 2009).

Therefore, there might be therapeutic effects of LA and ILILT on brain diseases such as insomnia, intractable headache, AD, PD, PSD, ache in head or face, migraine, DPN, cerebral thrombosis, cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, CP and mild cognitive impairment. For example, melanin production can be improved in ILILT since the activation of sympathetic nervous subsystem can enhances melatonin production (Tang M *et al.* 2002).

3.9 Safety

LPBM is a safe modality for clinical use (Wolbarsht 1994, Logan *et al.* 1995). Complete laser hatching of human embryos using the Zona infrared laser optical system does not have an adverse effect on subsequent development(Wong BC *et al.* 2003). There is no cytotoxic and genotoxic potential of LIL (660 nm, 12 mW, 5 kHz, 2 and 20 J/cm^2) on mammalian cells (Logan *et al.* 1995). The induction of cell-cycle delay of visible-light irradiation at 660 nm is not initiated by deoxyribonucleic acid (DNA) strand breaks (Joyce *et al.* 1999). Following the doses of infrared A (IRA) (700-2000 nm) that induced ferritin levels, there was no alteration seen for nuclear DNA type damage, oxidative stress proteins or proteases involved in the degradation of skin (Applegate *et al.* 2000). The difference in the frequency of micronuclei between pre- and post-laser irradiation indicates that a LHNL at such energy densities 1, 2, 3 and 5 J/cm^2 does not induce micronucleus formation (El Batanouny *et al.* 2002).

Drug-induced liver injury (DILI) or drug-induced liver dysfunction might be one of the side effects of the use or chronic use of drugs. However, there are no side effects of LPBM on liver. DILI is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. According to the United States Acute Liver Failure Study Group, DILI accounts for more than 50% of acute liver failure, including hepatotoxicity caused by overdose of acetaminophen (39%) and idiosyncratic liver injury triggered by other drugs (13%). Because of the significant patient morbidity and mortality associated with DILI, Food and Drug Administration in USA (FDA) has removed several drugs from the market, including bromfenac, ebrotidine, and troglitazone. Other hepatotoxic drugs, such as risperidone, trovafloxacin, and nefazodone, have been assigned “black box” warnings. DILI is the most common cause for the withdrawal of drugs from the pharmaceutical market. DILI is initiated by direct hepatotoxic effects of a drug, or a reactive metabolite

of a drug (Holt *et al.* 2006).

Drug-induced kidney injury is a major side effect in clinical practice. However, there are no side effects of LPBM on kidney. Renal injury associated with drugs may involve several components of the kidney: glomerulus, tubules, interstitium and blood vessels. Acute renal failure may occur as a major reaction to many drugs. Moreover, therapeutic agents may induce an allergic reaction leading to interstitial inflammation and tubular damage (Karie *et al.* 2005). Although the exact incidence of drug-induced nephrotoxicity is not known, it is important for clinicians to be aware of the risks in certain patients and to know which drugs are the most commonly implicated. The latter include radiocontrast agents, aminoglycosides, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors. Other medications also have nephrotoxic potential when they are prescribed in specific patient populations. Renal injury may be transient and mild in many cases, but recognition of the patient at high risk and application of preventive measures are essential to avoid a severe and protracted course(Thatte et al 1996).

As LI photons have no rest mass, there are no metabolite problems in LPBM and then there are no side effects of LPBM on liver or kidney. LA and ILILT are just an acupoint LPBM and a nasal LPBM, respectively. There have not been any side effects found in its applications in health care, health promotion or disease treatment. Moreover, there are no effects of LIL on biosystem in FSH. Therefore, LA and ILILT should be a natural therapy. Moreover, Chi J *et al.* (2005) also found the aminotransferases level might decrease with ILILT, which indicates that ILILT might protect liver from injury. As chapter 6 will discussed, LA and ILILT may rehabilitate blood flow so that there might be rehabilitation on renal failure.

4 Sunlight Effects

The rotation of the earth results in regular changes in the light environment. Sunlight is crucial to life beginning ~3.5 billion years ago not only for its energy, but also for the evolutionary changes forced upon the biosphere due to variation in light. Conventional solar technologies produce electricity, but photosynthesis provides the energy-rich and structural molecules (as well as oxygen) on which most life on this planet depends by harnessing the Sun's energy. Moreover, organisms have evolved a molecular oscillator that allows them to anticipate sunlight changes. This daily molecular oscillator, known as the circadian clock, regulates a diverse array of physiologies across a wide variety of organisms. Because the photoperiod is equally long in autumn and spring, dormancy release in spring requires the information that winter has passed, obtained from the dose of low temperatures experienced by the plant. When this chilling requirement is fulfilled, plants become receptive to photoperiod signals. Once a critical photoperiod has passed, actual bud break is a matter of concurrent temperature (Körner *et al* 2010). On the other hands, interstitial fibre-optic solar surgery has been found to be used effectively to kill tissue in live animals, with highly concentrated sunlight producing the same rapid, localized and extensive damage that is achieved in laser surgery (Gordon *et al.* 2003). The sunlight effects are pervasive. As has been pointed out in chapter 1, Finsen, Niels Ryberg (1860-1904), Danish physician and Nobel Prize winner who made important discoveries regarding the use of light in the treatment of disease, have studied sunlight effects as early as in 1890s. The focus is on the latitude and season effects of sunlight, and their mimic, the bright light effects, in this chapter.

4.1 Season Effects

Seasonal variations in mood and behavior, termed seasonality, are commonly reported in the general population. As a part of a large cross-sectional health survey in Hordaland, Norway, Øyane *et al.* (2010) investigated the relationship between seasonality, objective health measurements and health behaviors. A total of 11,545 subjects between 40-44 years old participated, completing the Global Seasonality Score (GSS), measuring seasonality. Seasonality was positively associated with high waist-hip-ratio, body mass index (BMI), triglyceride (TG) levels, and in men high total cholesterol (TC). Seasonality was negatively associated with high-density lipoprotein cholesterol (HDL-C). In women seasonality was negatively associated with prevalence of exercise and positively associated with daily cigarette smoking.

Many factors contribute to the regulation of blood pressure. The role of climate has received relatively little attention. During a four-year period, Argilés *et al.* (1998) determined the influence of climate on blood pressure in 53 patients with end-stage renal disease treated with hemodialysis in Montpellier, France. In patients with end-stage renal disease treated with hemodialysis, blood pressure varies seasonally, with higher values in the winter and lower values in the summer (Argilés *et al.* 1998).

Lyckholm *et al.* (1996) have reported a case of the seasonality of lactate dehydrogenase (LDH). A 61-year-old roads inspector from Illinois presented in 1992 with hemolytic anemia and acrocyanosis and was found to have cold-agglutinin syndrome. He was treated with plasmapheresis, prednisone, and chlorambucil and then followed without therapy for two years. He continued to work, which involved spending the majority of time outdoors. The patient's

cold-agglutinin titer exceeded 1:524,288, with a thermal maximum (the temperature at which agglutination occurs in vitro) of 37°C. The severity of the hemolysis, reflected by the LDH concentration, was negatively related to the ambient temperature, as illustrated in Fig. 4.1. He was currently well and asymptomatic.

Seasonality is a driving force that has a major effect on the spatio-temporal dynamics of natural systems and their populations. This is especially true for the transmission of common infectious diseases (such as influenza, measles, chickenpox and pertussis), and is of great relevance for host-parasite relationships in general. Stone *et al.* (2007) have gained further insights into the nonlinear dynamics of recurrent diseases through the analysis of the classical seasonally forced SIR (susceptible, infectious or recovered) epidemic model. Their principles yielded forecasting tools that should have relevance for the study of newly emerging and re-emerging diseases controlled by seasonal vectors. The strong effect of seasonality on population dynamics is no better seen than in the historical long-term data sets of seasonally recurring childhood infectious diseases, such as measles, mumps and chickenpox. These diseases are driven by the seasonally changing contact rate between children which increases sharply at the beginning of each school year, and strongly controls the ensuing disease transmission. Fig. 4.2a&c displays two time series of reported cases of measles in New York (1928–64) and London (1948–68) in the pre-vaccination era. Major epidemics peak close to Spring each year, and on many occasions every second year if the dynamics are biennial and the outbreak 'skips' a year. Note there is also a strong erratic and possibly chaotic component, as seen in the variability of peak heights of the epidemics, as well as the intermittent jumps between periods of annual and biennial dynamics. Theoretical studies have shown that seasonal forcing can be responsible for inducing similar complex population dynamics such as higher-order cycles, resonances and deterministic chaos. These complex responses can easily mask any simple underlying mechanistic processes that might otherwise help in forecasting future epidemics (Fig. 4.2). The modelling framework used here helps uncover, and gives new insights into, these processes.

There has been seasonal difference in the incidence of many diseases. Soriano *et al.* (2007) have studied seasonal variations in mood and behavior in Romanian postgraduate students, and found winter seasonal affective disorder (SAD) and winter subsyndromal SAD (S-SAD) were significantly more prevalent than summer SAD and summer S-SAD, and those with access to air conditioners had a higher, rather than a lower, rate of summer SAD. Norovirus epidemic characteristics, and timing, are remarkably consistent from year to year, with a peak incidence during the wintertime (from October to April) and specific peaks in February and March. However, outbreaks of norovirus do occur during the summertime, typified by the persistence of norovirus gastroenteritis in the so-called off-season (May to September), although at a reduced rate and with an absence of epidemic spread to geographically remote areas (Rohayem 2009). Gluszak *et al.* (2009）have observed a marked, statistically confirmed relationship between atrial fibrillation episodes and effective sunshine in women, namely, most atrial fibrillation episodes were recorded from December to March, when sunshine levels were lowest. As in western countries, Bell's palsy does not have an infectious epidemiologic pattern in Spain, but its frequency decreases in warm weather (De Diego *et al.* 1999). Seasonal variations in the incidence of cardiovascular disease mainly characterized by a winter peak (Dentali *et al.* 2009). For example, a higher venous thromboembolism incidence during the winter months and a lower incidence in the summer months. Renal excretion of calcium in healthy subjects and in patients with renal stones increases

in the summer, as compared to the winter values (Głuszek *et al.* 1978).

4.2 Latitude Effects

There is extensive literature describing the effect of season on mortality rates, especially in cardiovascular and respiratory disease. Douglas *et al.* (1999) have compared latitude with the extent of seasonal variation of monthly deaths from all causes. In developed countries, there is a peak of deaths in winter and a trough in summer. Monthly numbers of deaths were established in 89 countries in the Northern and Southern Hemisphere. Using cosinor analysis, the extent of seasonal variation (amplitude) was established and correlated with latitude. The amplitude of seasonality was greatest in mid-latitude around 35 degrees, but low or absent near the equator and subpolar regions. The amplitude can differ at the same latitude. The weather in equatorial regions and in habitations near the Arctic Circle is very different, but death has a similar seasonal rhythm. Grivas *et al.* (2006) found age at menarche shows a decreasing trend as the geographic latitude approaches approximately the 25–30 degrees and then increases again toward 0 degrees (near the equator).

The global burden of influenza on morbidity and mortality is considerable, with an estimated 1 million annual deaths worldwide. In temperate regions, there are clear seasonal variations in the occurrence of influenza, with a marked peak in cold winter months. In contrast, seasonality is less defined in tropical regions—here, there is high background influenza activity throughout the year, on top of which epidemics occur at intermediate months between the influenza season in temperate countries of the Northern and Southern hemispheres. Influenza seasonal patterns in the Americas were summarized in Fig. 4.3 by Viboud *et al.* (2006), which illustrates the transition between the Northern and Southern hemispheres and the seasonality of influenza varies with latitude.

Brancaleoni *et al.* (2009) have studied two groups of students, 199 in Tromsø, Norway (69° N) and 188 in Ferrara, Italy (44° N), and found that GSS was significantly higher in Italian than in Norwegian students, in females and in students with sleeping-problems. Norwegian students had significantly higher SAD prevalence in winter and in spring. Karvonen *et al.* (1998) studied seasonal pattern for the clinical onset of insulin-dependent diabetes mellitus in Finland and Sardinia, Italy, and found a significant seasonal pattern during a calendar year for the sexes combined and for two age-groups (0-9 and 10-14 years), and also found the amplitude of the seasonality in Sardinia was more greater than the one in Finland.

Based on a large material of international and Soviet investigations as well as on the data of official statistics, Gundarov *et al.* (1991) have analyzed the main characteristics of the population morbidity and mortality depending on the geographic latitude. It has been demonstrated that with the moving away from the equator, the intensive growth of the general mortality is observable both in the Union of Soviet Socialist Republics (USSR) and in the countries of Europe and America as is of the lethality due to malignant neoplasms, circulatory diseases together with an increase of the lethality because of suicides. It has been revealed that the incidence of arterial hypertension, alcoholism and drug addiction associated with the geographic latitude.

We have also studied the latitude effects in the low latitude region of the investigated country or continent (Liu CY 1995). The lifespan in China and in Africa and long-distance runners in Africa decreased with latitude, respectively. The cancer mortality in China, Asian, Europe,

American, the cancer incidence in United States and South American and psoriasis incidence in China increased with latitude, respectively.

4.3 Sunlight Effects

There have been many theories explaining the latitude effects and the season effects.

One explanation viewpoint on seasonal influenza is from humidity. One sneeze and influenza is drifting through the air, plastered across palms of hands and around door handles, poised for its next victim. How long can the virus survive outside a living host? Shaman *et al.* (2009&2010) showed experimentally that low absolute humidity (grams of water per cubic meter of air), which tends to prevail during temperate winters, improves the airborne survival of influenza viruses within aerosolized drops and favors transmission. Shaman *et al.* (2009&2010) modeled how changes in absolute humidity have driven the seasonal peaks and troughs of influenza in the United States during a 30-year period. Epidemics were correlated with the onset of anomalously low absolute humidity, and variations in absolute humidity affected the occurrence of outbreaks during any one season. Thus, it may be just as feasible to forecast short-term influenza risk as it is the weather.

However, seasonal blood pressure was more correlated with temperature than with humidity. Argilés *et al.* (1998) have studied seasonal changes in blood pressure in patients with end-stage renal disease treated with hemodialysis. In Montpellier, France, the maximal monthly temperature varied from 10 degrees C in the winter to 31 degrees C in the summer, and the minimal monthly temperature from 1 degree to 20 degrees C. The mean (±SE) systolic and diastolic blood pressure was highest during the winter (153±3/82±2 mm Hg/mm Hg) and lowest during the summer (141 ±3/75±2 mm Hg/mm Hg). The seasonal pattern was evident throughout the four-year period. Blood pressure was correlated inversely with monthly maximal temperature ($r = -0.65$ and $P < 0.001$ for systolic pressure; $r = -0.71$ and $P < 0.001$ for diastolic pressure) and directly with minimal humidity ($r = 0.45$ and $P = 0.002$ for systolic pressure; $r = 0.43$ and $P = 0.003$ for diastolic pressure). Obviously, blood pressure was more correlated with temperature than with humidity. The long-term evolution of the Fall temperature disturbances in a 2.5 x 2.5 degrees area of the US North Pacific from 1945 to 2008 closely follows that of solar activity (Courtillot *et al.* 2010). Therefore, it is very reasonable to assume that blood pressure might be correlated inversely with sunlight.

Moreover, Mitsikostas *et al.* (1996) found humidity was not correlated to latitudial headache frequency. Mitsikostas *et al.* (1996) have carried out a questionnaire study on headaches, using a door-to-door survey, in a representative sample of the general Greek population, including 1737 men and 1764 women, from 15 to 75 years of age. They found humidity and atmospheric pressure were not correlated to headache frequency. However, in the northern areas of Greece, as well as in the regions with low mean temperature, more people suffered from daily headaches. These data may explain the lower 1-year prevalence of headaches in other Greece as compared to the prevalence of headaches in other northern European countries.

Although the exact cause of multiple sclerosis (MS) is unknown, a number of genetic and environmental factors are thought to influence MS susceptibility. One potential environmental factor is sunlight and the subsequent production of vitamin D. For example, there is a latitudinal variation in the prevalence rate of MS between the north and the south of Ireland so that Northern

Ireland has a high and rising prevalence rate of MS (McGuigan *et al*. 2004). A number of studies have correlated decreased exposure to ultraviolet irradiation (UV) and low serum 25-hydroxyvitamin D(3) [25(OH)D(3)] levels with an increased risk for developing MS. Furthermore, both UV and the active form of vitamin D, 1alpha,25-dihydroxyvitamin D(3), suppress disease in the experimental autoimmune encephalomyelitis (EAE) animal model of MS. These observations led to the hypothesis that UV likely suppresses disease through the increased production of vitamin D. However, UV can suppress the immune system independent of vitamin D. Therefore, it is unclear whether UV, vitamin D, or both are necessary for the putative decrease in MS susceptibility. Becklund *et al.* (2010) have probed the ability of UV to suppress disease in the EAE model of MS and assessed the effect of UV on serum 25(OH)D(3) and calcium levels. Their results indicate that continuous treatment with UV dramatically suppresses clinical signs of EAE. Interestingly, disease suppression occurs with only a modest, transient increase in serum 25(OH)D(3) levels. Further analysis demonstrated that the levels of 25(OH)D(3) obtained upon UV treatment were insufficient to suppress EAE independent of UV treatment. These results suggest that UV is likely suppressing disease independent of vitamin D production, and that vitamin D supplementation alone may not replace the ability of sunlight to reduce MS susceptibility.

As discussed in chapter 3.2 on Tabs. 3.1&3.2, a person or patient of GSS smaller than 10 is in homeostasis or pathological function-specific homeostasis (PaFSH), and a person or patient of GSS greater than 11 is far from homeostasis or PaFSH. In other words, there is no seasonability on a person in homeostasis or a patient in PaFSH, but there is seasonability on a person far from homeostasis or a patient far from PaFSH. Therefore, the season effects are a kind of homeostatic regulation according to chapter 3.1. As a reasonable extension, the latitude effects might be also assumed to be a kind of homeostatic regulation, and both of season effects and latitude effects are called sunlight effects. At this point, the roles of sunlight in photosynthesis and circadian clock can be excluded in sunlight effects.

It has been suggested that prolonged exposure to sunlight may induce systemic or local immune alterations, which may facilitate the development of skin cancer and, perhaps, non-Hodgkin's lymphona. Kanariou *et al*. (2001) have studied the effects of prolonged sunlight exposure on peripheral blood cells. Leukocytes and lymphocyte subpopulations of 12 volunteers aged 10-45 were investigated before and after a 3-week summer holiday in seaside resorts in Greece. There were no significant differences with respect to total numbers of T cells, T-helper/inducer, T-suppressor/cytotoxic, B cells or human leukocyte antigen (HLA) Dr^{+} cells. However, they have found evidence of lymphocyte stimulation, reflected in an increase in cells expressing the interleukin-2 receptor (IL-2R) and, more specifically, an increase in the T cells expressing IL-2R and HLA-Dr antigens. An increase in natural killer cells has also been noticed. Their findings suggested that prolonged intense exposure to sunlight may be associated with immunostimulation, rather than immunosuppression.

As the cold color light and hot color light of sunlight are antagonistic with each other because various biological objects have become adapted during evolution (Karu 1998), only the decayed light in the nasal cavities might play roles in sunlight effects, which are similar to ILILT so that the mechanism was called ILILT-like mechanism (ILILM). This ILILM is supported by the comparative studies of the wide applications of ILILT and sunlight effects or the following bright light effects.

4.4 Bright Light Effects

The sunlight effects in low latitude or in summer may be mimicked by bright light, which further supported the nose mediation. There were no effects of bright light effects on autonomic activity-specific homeostasis. Sletten *et al.* (2001) have investigated the potential contribution of bright light and melatonin to influence cardiac autonomic activity of 16 young healthy subjects in the evening. An initial baseline condition involved dim light exposure (< 10 lux), permitting the normal nocturnal rise in endogenous melatonin. In other sessions, subjects were exposed to bright light (> 3000 lux) to suppress melatonin secretion and administered a placebo or melatonin (5 mg) capsule at the estimated time of increase in endogenous melatonin (wake time + 14 hours). Heart rate, pre-ejection period (a measure of cardiac sympathetic activity) and respiratory sinus arrhythmia (a measure of parasympathetic activity) were not significantly altered in response to the three melatonin levels. Sakakibara *et al.* (2000) have investigated the effects of 5000 lux evening bright light on autonomic nervous function of 12 young health women (range: 20-21 years of age). Although a low frequency band (LF) increased in bright light conditions in comparison with controlled conditions, high frequency band (HF), LF:HF ratio and the coefficient of variance (CV R-R) were not significantly different between the two conditions. However, there were therapeutic effects of bright light. Bright light is a treatment of choice for SAD. Other indications for bright light therapy include non-seasonal depression, bipolar depression, chronic depressive disorder, ante- and postpartum depression, late luteal phase dysphoric disorder, circadian phase sleep disorders, jet lag, shift work problems, and behavioral disturbance and insomnia in organic dementia (Prasko 2008).

Zhang P *et al.* (1996) have studied the effect of two different light intensities (dim, 50 lux and bright, 5,000 lux) on handgrip exercise in a climatic chamber (26℃, 60% relative humidity) in eight female subjects, aged 20-24 years. The subjects were in either the dim or bright light from 10:00 to 18:00. They were then in 50 lux from 18:00 to 22:00 in complete darkness from 22:00 to 06:00 (sleep), and again in 50 lux from 06:00 to 08:00. They were instructed to perform handgrip exercise with a hand ergometer until the occurrence of exhaustion from 06:00. The main findings were firstly that the mean number of contractions was 766.63±43.28 in dim and 864.5 ±54.76 in bright intensities ($P < 0.01$), and secondly that rectal temperatures were slightly but significantly lower in the bright than in the dim intensities. Zhang P *et al.* (1999) then studied the effects after exposure to the two different light intensities on thermoregulatory responses during exercise in a climatic chamber (27℃, 60% relative humidity) in nine untrained female subjects, aged 19-22 years. The subjects were in either the dim or bright light intensities from 06:00 to 12:00. They were then instructed to exercise on a cycle ergometer at an intensity of 60% maximal oxygen uptake (VO2max) from 12:00 to 13:00 in a light intensity of 500 Iux. The main results can be summarized as follows. Firstly, exercise-induced increases of core temperature were significantly smaller, after exposure to the bright than after the dim light intensities, although both tests were performed in the same light intensity. Secondly, body mass loss after exercise was significantly greater after exposure to the bright light intensity. Thirdly, an increase in salivary lactic acid during exercise was significantly lower after the bright intensity. Fourthly although the salivary melatonin level was not different between the two light intensities both before and after the exercise, it increased significantly during exercise only after the bright intensity.

The bright light effects were further verified by Aizawa *et al.* (1998). They investigated the effect of exposure to differing light intensities for several hours during the daytime on the cutaneous vasodilatation and local forearm sweat rate induced by exercise. Seven healthy female subjects were exposed to bright light of 6000 lux (bright) or dim light of 100 lux (dim) during the daytime between 09:00 to 13:30, followed by exposure to 150 lux until the test was over at 16:00. They spent their time in neutral conditions (29℃, 40% relative humidity) from 09:00 to 1500, and then exercised on a cycle ergometer for 30 min at 50% maximal physical work capacity. Average tympanic temperatures were significantly lower in bright than in dim from 11:33 to 14:30. The onset of cutaneous vasodilatation and local forearm sweating occurred at significantly lower tympanic temperature (Tty) during exercise after bright than after dim. After exercise, the cessation of forearm sweating and the rapid change of skin blood flow occurred at significantly lower Tty after bright than after dim. They concluded that exposure to bright light over several hours during the daytime could reduce Tty and shift the threshold Tty for cutaneous vasodilatation and forearm sweating to a lower level.

4.5 Discussion

The Maunder minimum is connected to the Little Ice Age, a time of markedly lower temperatures, in particular in the Northern hemisphere. During the period, there were the Black Death and all the plagues of Europe (1347-1670) (Duncan *et al.* 2005), and the number of places in Europe reporting a plague epidemic increased (Duncan *et al.* 2005) when the sea surface temperature (SST) averaged over the North Atlantic ocean decreased (Feulner *et al.* 2010). The current exceptionally long minimum of solar activity has led to the suggestion that the Sun might experience a new grand minimum in the next decades, a prolonged period of low activity similar to the last Maunder minimum. Feulner *et al.* (2010) have used a coupled climate model to explore the effect of a 21st-century grand minimum on future global temperatures, finding a moderate temperature offset of no more than −0.3°C in the year 2100 relative to a scenario with solar activity similar to recent decades.

Visibility in the clear sky is reduced by the presence of aerosols, whose types and concentrations have a large impact on the amount of solar radiation that reaches Earth's surface. Wang K *et al.* (2007) have established a global climatology of inverse visibilities over land from 1973 to 2007 and interpreted it in terms of changes in aerosol optical depth and the consequent impacts on incident solar radiation. The aerosol contribution to "global dimming," first reported in terms of strong decreases in measured incident solar radiation up to the mid-1980s, has monotonically increased over the period analyzed. Since that time, visibility has increased over Europe, consistent with reported European "brightening," but has decreased substantially over south and east Asia, South America, Australia, and Africa, resulting in net global dimming over land.

The deployment of solar radiation for health management has been restricted to the visibility in the clear-sky periods in sun-belt climates, but conventional laser can be easily found. In view of wide effects of sunlight, the laser medical applications have been discussed in the previous chapter and will be deeply discussed in the next chapters.

5 Applications of laser function medicine

As has been discussed in the previous chapter, intranasal low intensity laser therapy (ILILT) is mediated by olfactory nerve, blood cells, meridians in traditional Chinese medicine (TCM) and autonomic nervous system (ANS). As will be discussed in chap. 10, the therapeutic effects of laser acupuncture (LA) are mediated by meridian. In this chapter, their health care and clinic applications will be discussed. Some of the related acupoints are illustrated in Figs. 3.3, 3.4, 3.6, 5.1-4. The other acupoints are referred in the related books.

5.1 Health Care

ILILT has been used to treat hyperlipidemia, blood hyperviscosity, insomnia and high blood coagulation status in healthy pregnant women at term. LA has been used to treat hyperlipidemia and blood hyperviscosity.

5.1.1 Hyperlipidemia

Hyperlipidemia is an elevation of lipids in the bloodstream. These lipids include cholesterol, cholesterol esters, estersphospholipids and triglycerides (TG). Numerous studies have suggested that hyperlipidemia is closely linked to cardiovascular disease. Lipid lowering has been shown to be effective in preventing primary and recurrent cardiovascular events and to save life. Statins almost exclusively used for this purpose meanwhile became one of the most widely prescribed families of drugs world-wide. Statins are possibly the most effective drugs for the prevention and treatment of hypercholesterolaemia and coronary heart disease (CHD). They are generally well tolerated, however, they do cause some unusual side-effects with potentially severe consequences, most prominently myopathy or rhabdomyolysis and polyneuropathy. More than 30,000 individuals in the United States suffer from severe life-threatening symptoms of statin-induced myopathy that may, in some cases, persist long after the cessation of therapy (Vladutiu 2008). Genes of interest include those involved in the pharmacokinetics of the statin response, muscle atrophy, exercise intolerance, pain perception, and mitochondrial energy metabolism. Genetic analysis for variants and disease-causing mutations relevant to statin myopathy will provide predisposition testing for this and other drug-induced disorders. This testing will become an integral part of personalized medicine that will contribute to the safe and informed use of selected drugs and improved compliance (Vladutiu 2008).

As a natural therapy as shown in chapter 3.9, ILILT has been used to rehabilitate hyperlipidemia. Zhang X *et al.* (2003) have treated 38 patients with hyperlipidemia with low intensity He-Ne laser irradiation (LHNL) at 1.5 mW for 30 min each time, which were done once a day and five days each session for two sessions, and found total cholesterol (TC), TG and low density lipoprotein cholesterol (LDL-C) levels deceased 23.7%, 36.2% and 20.2%, respectively.

Chi J *et al.* (2005) have randomly divided 30 patients with hyperlipidemia into two groups, 15 in drugs group, 15 in ILILT group, and then treated ILILT group with low intensity GaInP/AlGaInP diode laser irradiation at 650 nm (LGAL) at 5 mW for 45 min each time, which was done once a day and seven times each session for two sessions between which there was five

days for rest, and found ILILT induced significant decrease in TC, but the decrease was less than drugs induced one. Chi J *et al.* (2005) also found the aminotransferases level decreased.

It has been found that acupuncture induced blood lipid decrease was mainly mediated by *stomach* meridian of foot *yang-ming*. Nasal *stomach* meridian of foot *yang-ming* might also mediate ILILT induced decrease of blood lipid according to meridian mediated ILILT hypothesis (MIH) which was put forward in chapter 3.7.1. *Du* meridian and *liver* meridian of foot *jue-yin* are coupled with each other at *bai-hui* acupoint (GV 20) (Fig. 5.1) so that ILILT induced decrease of aminotransferases might be mediated by intranasal *du* meridian according to MIH.

In addition to ILILT, LA might be used to effectively treat hyperlipidemia. Li XW (2000) has treated 68 patients with hyperlipidemia with LHNL on acupoints for 5 min each acupoints each time, which were done once a day 30 days each session for 6 sessions between which there 3 days for rest, and found TG level deceased significantly, and the symptom improvement of 48(70.5%), 18 (28.1%) and 2(1.4%) patients were significant, mild and none, respectively, after only one session. In this treatment, the main acupoints are *sanyinjiao* (SP 6)(Fig. 3.4) and *zusanli*(ST 36)(Fig. 3.3), the adjunct acupoints are *neiguan* (PC 6)(Fig. 3.3), *taichong* (LR 3)(Fig. 3.3), *hegu* (LI 4)(Fig. 3.4) and *fenglong*(ST 40) (Fig. 3.3).

5.1.2 Blood hyperviscosity

Despite the methodological difficulties of evaluating the role of a single rheological component, some clinical situations characterized by an increase of blood viscosity can be identified. These are classified as 'blood hyperviscosity syndromes' and can be divided into 2 groups. The first includes pathophysiological conditions in which a primary blood abnormality causes a decrease of blood flow, as occurs in polycythaemic vera, sclerocythaemic and seric hyperviscosity syndromes, and may be referred to as 'primary blood hyperviscosity syndromes'. The second group includes pathological conditions in which a primary reduction of blood supply to tissue provokes tissue ischaemia, and an impairment of rheological properties of blood can be observed at microcirculatory level. Thus, these situations have been described as 'secondary blood hyperviscosity syndromes'. Patients with peripheral obliterative arterial disease, ischaemic cardiopathies and cerebrovascular insufficiencies show a diminution in blood fluidity during spontaneous or provoked ischaemic conditions which disappears after reperfusion of the tissue. The pathogenesis of this rheological damage is unclear, but may arise from the complex relationship among blood cells (red cells, leucocytes, platelets), endothelium and plasma components. In addition to these 2 groups of blood hyperviscosity syndromes, several pathological states such as diabetes, shock, surgery, and rheumatic disease have been described in which an increase of blood viscosity can be observed. For these situations, which require much further investigation, the term 'syndromes associated with blood hyperviscosity' could be proposed (Forconi *et al.* 1987).

Blood hyperviscosity may cause a variety of clinical manifestations including bleeding from mucosal membranes, congestive heart failure, retinopathy, and various neurologic deficits, but it might be treated with ILILT. Nie X *et al.* (2005) has treated 100 patients with hyperviscosity with LGAL at 5 mW for 30 min each time, which was done two times each day for five days, and found the blood viscosity, plasma viscosity, fibrinogen, erythrocyte aggregation index, erythrocyte

deformability index and erythrocyte sedimentation rate decreased, respectively. Blood cells flowing in nasal mucosa might mediate ILILT induced viscosity decrease.

Blood hyperviscosity might be also treated with LA. The patients with brain contusion were irradiated with LGAL at 10~15 mW on *futu* acupoint (LI 18) (Fig. 3.6) of both sides for 30 min (Cheng K *et al.* 2000). It has been found that low cut blood viscosity and hematocrit significantly decrease.

5.1.3 Insomnia

Sleep constitutes nearly one third of a person's life. As will be pointed out on well-being in chapter 11.1, sleep quality strongly influenced positive affect and enjoyment (Kahneman *et al.* 2004). However, many people are affected with difficulty in sleeping. Although there is wide variation in how insomnia is defined, it is clear that a number of persons suffer from the condition. In general, insomnia consists of a complaint of disturbed sleep, which presents as difficulty in sleep initiation or maintenance, and/or early awakenings. Insomnia also includes the presence of daytime impairments to normal functioning as a result of sleep insufficiency. These impairments are generally manifested as fatigue, irritability, a decrease in memory and concentration, and malaise. Given a lack of standardization for the term insomnia, and the infrequency of sleep problem assessment during patient histories, insomnia is often undiagnosed or untreated. Insomnia presents a challenge for managed care because it affects a large percentage of the population, particularly the elderly (Reeder *et al.* 2007).

Insomnia can be classified in 2 ways: by the duration of the insomnia or by its etiology. Classifications of insomnia based on etiology include primary and secondary insomnia. *Primary insomnia* is not caused by known physical or mental conditions. It is, however, characterized by consistent symptoms, a defined clinical course, and is responsive to treatment. *Secondary insomnia* (also referred to as *comorbid insomnia*) is a result of other medical and psychiatric illnesses, medications, or other sleep disorders. When classifying insomnia based on duration, 2 forms are generally considered. *Acute insomnia* (also known as transient insomnia) is typically the result of specific environmental or social events such as the death of a family member, working on a differential shift schedule, travel, or additional noise. Acute insomnia is typically managed by treating the episode directly; or in cases where insomnia is expected to occur (eg, travel, varying work schedule), it can be treated prophylactically. The second type of insomnia based on duration is *chronic insomnia*. Chronic insomnia does not have specific diagnostic criteria but generally lasts for more than 1 month, ranges from 1 to 6 months in duration, occurs 3 or more times per week, and results in some degree of daytime dysfunction. Chronic insomnia is often correlated with other intrinsic sleep disorders, primary insomnia, or other chronic medical conditions interfering with a patient's sleep pattern. Treatment for chronic insomnia typically requires a thorough examination of underlying conditions or disorders. According to the 2003 Sleep in America Poll conducted by the National Sleep Foundation, approximately one half (48%) of surveyed adults 55 to 84 years of age reported experiencing 1 or more symptoms of insomnia at least a few nights per week. Prevalence estimates reported in published studies for chronic insomnia range from 10% to 20%. The wide variation in estimates of insomnia reported in the literature is related to the lack of definition and consistency in diagnostic criteria for the disorder.

The elderly population is frequently affected by insomnia and should be of particular concern to managed care providers and payers (Reeder *et al.* 2007).

Insomnia treatment should reflect the etiology of the patient's insomnia. Primary insomnia generally responds well to pharmacologic therapy, while secondary insomnia may be treated with pharmacologic and/or psychologic treatments. Treatment should be geared toward the specific component of insomnia that is most problematic for the patient (*ie*, sleep onset, sleep maintenance, sleep quality, or next-day functioning). Pharmacologic options can be grouped into 4 main categories: benzodiazepines, nonbenzodiazepines, melatonin receptor agonists, and over-the-counter (OTC) medications. Currently, 5 benzodiazepines are approved for use in the United States for the short-term treatment of insomnia. However, use of these agents in certain populations, most notably the elderly and patients with a potential for abuse or addiction, is a concern. Moreover, Medicare Part D does not cover the use of benzodiazepines. The nonbenzodiazepine agents provide an alternative to benzodiazepines in the treatment of insomnia. However, a majority of the nonbenzodiazepine agents have a mechanism of action similar to the benzodiazepines in that both bind to a γ-aminobutyric acid receptor. The exception to this mechanism is ramelteon, which is a selective agonist for the melatonin MT1/MT2 receptors. Ramelteon has a reported advantage of no abuse potential compared with the benzodiazepines which are classified as C-IV controlled substances. Several OTC preparations are also available for insomnia treatment. These medications consist largely of antihistamines that are marketed as sleep aids because of their sedative side effects. These nonprescription agents have the advantage of being relatively inexpensive but are often associated with next-day sedation, anticholinergic side effects (dry mouth, blurred vision), and tolerance. Psychologic treatments for insomnia are also a consideration, particularly for patients suffering from secondary insomnia. Psychologic approaches to treatment include cognitive therapy, cognitive behavioral therapy, relaxation techniques, sleep restriction, and stimulus control (Reeder *et al.* 2007).

As a natural therapy, ILILT often used to treat insomnia. Wang F (2006) have treated 50 patients with insomnia with LGAL at 3 mW for 60 min each time, which was done once a day and 10~14 days each session for 1~2 sessions, and found the symptom improvement of 41(82.0%), 4 (8.0%) and 5(10.0%) patients were significant, mild and none, respectively. Xu C *et al.* (2001) have treated 38 patients with insomnia with LHNL at 3.5~4.5 mW for 30 min each time, which was done once a day and ten days each session for two sessions, and found serum melatonin increase. Xu C *et al.* (2002a) further treated 128 patients with insomnia with LHNL at 3.5~4.5 mW for 30 min each time, which was done once a day for ten days, and found the polysomnogram was improved. It has been found that acupuncture induced sleep rehabilitation was mainly mediated by *du* meridian. ILILT induced sleep rehabilitation might be mediated by nasal *du* meridian according to MIH.

ILILT can be integrated with LA. Chen YM *et al.* (2004) randomly divided 90 patients with insomnia into two groups, 40 in herb-only group, 50 in ILILT+LA+herb group. ILILT+LA+drugs group was treated with intranasal LHNL for 60 min each time and with LHNL on the acupoints such as *neiguan* (PC 6) and *shenmen* (HT 7)(Fig. 3.3) and so on for 20 min each time each acupoint, respectively, which was done once a day and seven days each session for 1~2 sessions. The LHNL works at power smaller than 5 mW. It has been found the symptoms were improved after treatment in these two groups, but ILILT+LA+herb group was more pronounced than

herb-only group. In the herb-only group, the symptom improvement of 16(40.0%), 15 (37.5%) and 9(22.5%) patients were significant, mild and none, respectively. In the ILILT+LA+herb group, the symptom improvement of 39(78.0%), 10 (20.0%) and 1(2.0%) patients were significant, mild and none, respectively.

5.1.4 High blood coagulation status in healthy pregnant women at term

Normal pregnancy is accompanied by a state of hypercoagulability, indicated by an increase in markers of coagulation activation. Extensive alterations of the coagulation system occur during pregnancy: Increasing levels of coagulation factors and continuous decrease of coagulation inhibitor proteins contribute to the increase of prothrombotic potential. The alterations in the coagulation system are one cause for the enhanced thromboembolic risk during pregnancy (Kemkes-Matthes 2001).

Gao X *et al.* (2008) have studied the effect of LGAL at 3 mW on blood coagulation status in 126 healthy pregnant women at term. It was found plasma prothrombin time, activated partial thromboplastin time, thrombin time levels were significantly lowered, whereas fibrinogen level significantly increased in the pregnant women before the treatment as compared with the control group of 123 healthy young unmarried women. The ILILT treatment has been done 20 min each time once a day for 7 days. After the treatment, these parameters were significantly improved in the pregnant women although there were still significant differences from those of the control group. This indicated that intranasal irradiation of LGAL might effectively improve high blood coagulation status in healthy pregnant women at term.

5.2 Clinic Applications

ILILT and LA have been studied to treat internal diseases. They have been applied to treat the blood-stasis syndrome of CHD, myocardial infarction (MI) and brain diseases such as intractable headache, Alzheimer's disease (AD), Parkinson's disease (PD), post-stroke depression (PSD), ache in head or face, migraine, cerebral thrombosis, diabetic peripheral neuropathy (DPN), cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, cerebral palsy (CP) and mild cognitive impairment (MCI). The clinic applications in MCI, AD, PD, schizophrenia, pain, stroke, depression, CP, inflammation, CHD and MI will be discussed in this chapter.

5.2.1 Mild cognitive impairment (MCI)

MCI refers to a transitional zone between normal ageing and dementia. Despite the uncertainty regarding the definition of MCI as a clinical entity, clinical trials have been conducted in the attempt to study the role of cholinesterase inhibitors currently approved for symptomatic treatment of mild to moderate AD, in preventing progression from MCI to AD. However, the use of cholinesterase inhibitors in MCI was not associated with any delay in the onset of AD or dementia. Moreover, the safety profile showed that the risks associated with cholinesterase inhibitors are not negligible. The uncertainty regarding MCI as a clinical entity raises the question

as to the scientific validity of these trials (Raschetti *et al.* 2007). At this point, ILILT is very potential. Jin L *et al.* (2000) have treated 25 persons of MCI with LIL at 670 nm and 7~10 mW for 40 min each time, which was done once a day for ten days, and found serum A β decreased.

Cognitive event-related potential (ERP) studies of memory and language impairments in amnesia and AD are very popular. Well-circumscribed lesions of the medial temporal lobe (MTL) or diencephalon causing an amnestic syndrome, an inability to encode and retrieve episodic memories beyond the brief duration of working memory, appear to produce altered plasticity of the late positive P600 component, but usually spare P300 and N400 components. The neuropathology of AD affects MTL and extends to neocortical association areas, causing deficits of episodic and semantic memory. In AD dementia, the P300, N400, and P600 all commonly show abnormalities. ERP studies of individuals with MCI may reveal neurophysiological changes prior to the emergence of clinical deficits, which could advance the early detection and diagnosis of AD (Taylor *et al.* 2007). Shi B *et al.* (2000) have investigated 141 women by using ERP, and found P300 peak latency (P_3PL) increase with aging. They have further treated the 60 women of memory loss among the 141 women with LIL at 670 nm and 7~10 mW for 40 min each time, which was done once a day for ten days, and found P_3PL decreased. Jin L *et al.* (2001a) have treated 60 patients with cerebral arteriosclerosis with LIL at 670 nm and 7~10 mW for 40 min each time, which was done once a day for ten days, and found P_3PL decreased and the electroencephalogram patterns were being become normal. Jin L *et al.* (2001b) randomly divided 93 patients with cerebral infarction into three groups, 30 in drugs-only group, 32 in ILILT+drugs group and 31 in ILELT(intravascular low energy laser therapy)+drugs group, and then treated ILILT+drugs group with LIL at 670 nm and 7~10 mW for 40 min each time and ILELT+drugs group with He-Ne laser at 1.5 mW for 90 min each time, respectively, which were done once a day for ten days, and found P_3PL decreased and erythrocyte deformity increased after the treatment of either ILILT or ILELT in comparison with drugs-only group.

Liu YZ *et al.* (2007) have treated 48 pupils with amnesia with herb and electric acupuncture on acupoints 40 min each acupoint once a day for ten days, and found the symptom improvement of 43(89.5%) and 5 (10.4%) patients were significant and mild, respectively. In this treatment, the main acupoints are *baihui* (GV 20) and two *shenchong*s (M-HN-1) (Fig. 5.1), the adjunct acupoints are *zusanli* (ST 36)(Fig. 3.3), *sanyinjiao* (SP 6) (Fig. 3.4), *xinyu* (BL 15) and *piyu*(BL 20)/*shenyu*(BL 23)(Fig. 5.2). For the 36 patients with deficient *xin* and *pi*, the *shenchongs* are left and right *shenchong*s, and the alternative adjunct acupoints is *piyu*. For the 12 patients with constant *xin* and *shen*, the *shenchongs* are before and back *shenchong*s, and the alternative adjunct acupoints is *shenyu*. In view of this electric acupuncture on amnesia, LA is also suggested to treat amnesia.

5.2.2 Alzheimer's disease (AD)

The number of people with dementia (currently 25 million worldwide) is expected to increase by 5 million each year. The risk of dementia, including AD, increases sharply with age: AD International estimates that 1.4% of people 65–69 have dementia, whereas almost a full quarter of those over the age of 85 years are affected. Almost all older dementia patients will experience, along with the cognitive and functional decline typical of the illness, some neuropsychiatric

symptoms. These symptoms can include agitation, aggression, and psychosis, and are often devastating for the older patient and his or her family and caregiver. Managing these symptoms is often a prime concern for health-care providers and families. Neuroleptics (sometimes called antipsychotics) are the class of drugs often used to manage or control neuropsychiatric problems, but there have been questions about their safety and appropriateness. Safety concerns involve risk of stroke, parkinsonism, sedation, edema, and chest infections but also include a worsening of cognitive decline with prolonged use of neuroleptics. For most patients with AD, withdrawal of neuroleptics had no overall detrimental effect on functional and cognitive status. Neuroleptics may have some value in the maintenance treatment of more severe neuropsychiatric symptoms, but this benefit must be weighed against the side effects of therapy (Ballard *et al.* 2008).

One hundred years ago a small group of psychiatrists described the abnormal protein deposits in the brain that define the most common neurodegenerative diseases, especially AD. Despite approval of several drugs for AD, the disease continues to rob millions of their memories and their lives. Fortunately, many new therapies directly targeting the mechanisms underlying AD are now in the pipeline. Among the investigative AD therapies in clinical trials are several strategies to block pathogenic A β and to rescue vulnerable neurons from degeneration. Complementary but less mature strategies aim to prevent the copathogenic effects of apolipoprotein E and the microtubule-associated protein tau. New insights into selective neuronal vulnerability and the link between aging and AD may provide additional entry points for therapeutic interventions. The predicted increase in AD cases over the next few decades makes the development of better treatments a matter of utmost importance and urgency. At this point, ILILT is very potential. Xu C *et al.* (2002b) have divided the objects into two groups, 47 patients with AD and 22 patients with gastric ulcer, and treated the patients with LHNL at 3.5~4.5 mW for 30 min each time, which was done once every morning for 30 days. They found that melatonin, score in mini-mental state exam (MMSE) and score in Wechsler memory scale for adult (WMS) increased in AD group, but there was no photobiomodulation (PBM) on gastric ulcer group.

An animal model of AD has been established with ibotenic acid infusion into the Sprague-Dawley rat nucleus basalis magnocellularis. Its acupoints, *baihui* (GV 20)(Fig. 5.1) and *dazhui* (GV 14)(Fig. 5.2), were irradiated with LHNL at 5.5 mW for 5 min each acupoint once a day ten days each session for two sessions between which there were 2 days for rest. It has been found that the positive response of microtubule associated protein 2, bcl-2 and 5-hydroxytryptamine significantly increases, respectively (Zhang Q *et al.* 2007, Li WQ *et al.* 2007). These results indicated that LA may be used to treat patients with AD.

5.2.3 Parkinson's disease (PD)

PD is a major neurodegenerative disorder characterized by progressive and substantial loss of dopaminergic neurons in the substantia nigra compacta, resulting in debilitating motor signs including tremors, bradykinesia, and rigidity. PD affects more than 1% of the population over the age of 60 in the United States, ranking it as the second most common neurodegenerative disorder. The development of treatment for the symptoms of PD has been one of the most notable successes of neurology. Dopaminergic therapies in the form of levodopa, dopamine agonists, or monoamine oxidase B inhibitors significantly improve the characteristic motor symptoms of bradykinesia and rigidity, with a beneficial effect upon tremor in a proportion of patients. Novel delivery of

dopaminergic drugs whether in the form of once a day sustained release preparations or transdermal applications ensures that they remain at the forefront of PD treatment. The development of drugs to slow the progression of PD has attracted considerable attention and there appears to be some measure of success although additional studies need to be performed. A range of nondopaminergic drugs including alpha 2-adrenergic antagonists, serotoninergics, and adenosine A2a antagonists are in late-stage development for PD and offer benefit for motor symptoms and motor complications (Schapira 2007).

Although the existing approaches to PD treatment alleviate the signs, they fail to prevent the progression of the neurodegenerative process. Currently, no available drugs prevent the progressive loss of nigral dopaminergic neurons. The mechanisms underlying the dopaminergic degenerative process observed in PD are not well understood, which has hampered development of successful neuroprotective drugs. Several clinical studies in post-mortem PD human brain tissues and experimental studies in animal PD models indicate that oxidative stress, mitochondrial and ubiquitin proteasomal dysfunction, and apoptosis all contribute to the dopaminergic degenerative process, primarily due to the higher vulnerability of nigral neurons to oxidative damage, compared with other brain regions (Zhang D *et al.* 2007). At this point, ILILT is very potential.

Li Q *et al.* (1999b) have treated 43 patients with PD with LHNL at 3.5~5.5 mW for 30 min each time, which was done once a day for ten days, and found serum cholecystokinin-octapeptide (CCK-8) decreased back to normal level. PD symptom improvement was thought to be significant when the Webster Scale scores (WSS) decease is larger than 50%, mild when the WSS decease is 10~50 % and none when the WSS decrease is smaller than 10%. Li Q *et al.* (1999b) found the PD symptom improvement of 11 (25.6%), 26 (60.4%) and 6 (14.0%) patients were significant, mild and none, respectively.

Xu C *et al.* (2003) have treated 47 patients with PD with LHNL at 3.5~4.5 mW for 30 min each time, which was done once every morning for 20 days, and found the PD symptom improvement of 14(29.8%), 27 (57.4%) and 6 (12.8%) patients were significant, mild and none, respectively, and superoxidase dismutase (SOD) and melatonin increased and malondialdehyde decreased.

Zhao G *et al.* (2003) have treated 36 patients with PD with LHNL at 3.5~5.5 mW for 30 min each time, which was done once a day for ten days, and found the PD symptom improvement of 10(27.8%), 21 (58.3%) and 5 (13.9%) patients were significant, mild and none, respectively.

The PD can be induced in C57BL/6J male mice by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. The electric acupuncture at 2~100 Hz and 2~4 V at its *siguan* acupoints: *hegu* (LI 4) (Fig. 3.4) and *taichong* (LR 3) (Fig. 3.3), has been done 20 min each acupoint once a day seven days each session for three sessions between which there a day for rest in a series of Chinese studies. It has been found that expression of dopamine transporter**,** brain-derived neurotrophic factor (BDNF), BDNF messenger ribonucleic acid (mRNA)**,** neural cell adhesion molecules might be significantly increased and synapstic plasticity might be significantly enhanced**.** In view of this electric acupuncture on the PD model, the acupuncture of LIL on the *siguan* acupoints, *hegu* and *taichong*, are also suggested to treat PD.

5.2.4 Schizophrenia

Schizophrenia is one of the most common psychiatric disorders listed by the World Health Organization (WHO) as being among the most debilitating illnesses in the developed world. It manifests early in adulthood and is associated with severe impairment as well as increased suicide risk. 7% of patients with schizophrenia would commit suicide. In addition, factors affecting disease severity, such as substance abuse, are often prevalent in the patient population. In the United States, the prevalence of schizophrenia is approximately 1% (Buckley 2008).

Schizophrenia is of multifactorial etiology. Schizophrenia is highly familial, with heritability estimates ranging from 59% to 87%. These estimates suggest that genes are overwhelmingly important. Obstetric complications had occurred in 20% of mothers of schizophrenia patients, with no particular complication specifically indicated. In addition, there is the curious finding that patients with schizophrenia are more likely to have been born from February through May, during the so-called "season of birth effect." There is also growing interest in the age of parents when they conceive, with several studies suggesting that children born to older fathers have a higher risk of schizophrenia (Buckley 2008).

Schizophrenia treatment typically includes the combination of an antipsychotic and psychosocial intervention, but medications are the bedrock of treatment. However, medications are only partially effective, and their mechanism of action is still poorly understood (Buckley 2008). The mechanisms of cholinergic, dopaminergic, and glutamatergic have been identified (Buchanan *et al.* 2007). Patients who are affected by the disorder also face the challenges of treatment nonadherence, which can be affected by substance abuse and can hinder symptom remission as well as spur unnecessary medication switches due to nonresponse(Buckley 2008). At this point, ILILT might be very potential. Liao Z *et al.* (2000) randomly divided 80 patients with schizophrenia into two groups, 40 in drugs-only group and 40 in ILILT+drugs group, and then treated ILILT+drugs group with LHNL at 2 mW for 60 min each time, which was done once a day for ten days, and found the significant improvement was achieved on the 26.2nd day in drugs-only group but on the 18.5th day in ILILT+drugs group.

The patients with schizophrenia have been also effectively treated with electric acupuncture on the acupoints *baihui* (GV 20) (Fig. 5.1) and *shenting* (GV 24)(Fig. 5.3). Therefore, the acupuncture of LIL on the two acupoints might used to treat schizophrenia.

5.2.5 Inflammation

Survival is impossible without vigilant defence against attack and injury. The innate immune system continuously surveys the body for the presence of invaders. When it encounters an attack, it involuntarily sets in motion a discrete, localized inflammatory response to thwart most pathogenic threats. The magnitude of the inflammatory response is crucial: insufficient responses result in immunodeficiency, which can lead to infection and cancer; excessive responses cause morbidity and mortality in diseases such as rheumatoid arthritis, Crohn's disease, atherosclerosis, diabetes, Alzheimer's disease, multiple sclerosis, and cerebral and myocardial ischaemia. If inflammation spreads into the bloodstream, as occurs in septic shock syndrome, sepsis, meningitis and severe trauma, the inflammatory responses can be more dangerous than the original inciting stimulus. Homeostasis and health are restored when inflammation is limited by anti-inflammatory responses that are redundant, rapid, reversible, localized, adaptive to changes in input and integrated by the nervous system (Tracey 2002).

An inflammatory response begins when cells of the immune system and/or cells involved in metabolic pathways sense pathogens, irritants and cellular damage, triggering the release of inflammatory substances, including cytokines, free radicals, hormones and other small molecules (Zhang K *et al.* 2008). These inflammatory substances further stimulate the cells that secreted them and target specialized cells in immune and metabolic pathways, thereby altering cellular physiology to contribute to wound healing and pathogen resistance. However, there is epidemiological, clinical and experimental evidence that cellular stress (that is, impaired biological processes within the cell) and excessive inflammation are causally linked to various metabolic conditions, such as obesity, type 1 and type 2 diabetes and atherosclerosis.

Antibiotic treatments are the most used treatments of bacterial infection induced inflammation, but antibiotic resistance is an increasing global problem. Bacterial multidrug tolerance (MDT) is an increasingly alarming phenomenon caused by the inability of antibiotics to eradicate infections completely. Most antibiotics target rapidly dividing cells. MDT is caused by a small population of bacterial cells, called persisters, which somehow become dormant but then switch back to growth phase after antibiotic removal and resume the infection. The biochemical basis for persistence is unknown, but the *Escherichia coli* HipA (High Persistence A) protein has been identified as a bona fide persistence factor. Schumacher *et al*. (2009) studied the structural mechanisms behind HipA function. HipA is a Ser/Thr kinase that phosphorylates the essential translation factor EF-Tu, potentially halting translation and leading to cell stasis. The DNA-binding protein HipB, which neutralizes HipA, was found to do so by locking HipA into an inactive state and by sequestering it away from its EF-Tu target.

Many diseases have been found to be of antibiotic resistance. Tuberculosis was one of the most well known ones. Eight million people develop tuberculosis each year and 5,000 of them will die from the disease every day throughout the world. Although treatable and curable, globally about 3% of all newly-diagnosed patients have multi-drug-resistant tuberculosis making their treatment complicated, expensive and uncertain (Raviglione *et al.* 2007). The worldwide rise in antibiotic resistance necessitates the development of novel antimicrobial strategies. However, traditional treatment paradigms combating antimicrobial resistance have been largely unsuccessful. It might be due to its aiming to bacteria themselves.

There are conflicting results in the literature regarding the association between the antibiotic exposure and breast cancer risk. Tamim *et al.* (2008) have assessed this association using a population-based approach. The source population was the dynamic cohort defined by membership in the Saskatchewan Prescription Drug Plan (Canada) between the years 1981 and 2000. Four matched controls were selected for each case identified by the Saskatchewan Cancer Agency, using incidence density sampling. Detailed drug exposure over a minimum of 15 years before diagnosis allowed studying the respective effects of dosage and timing of antibiotic use on breast cancer risk. A total of 3099 breast cancer cases and 12,396 matched controls were included. They found the incidence of breast cancer was higher in subjects who had more antibiotic prescriptions during the 1-15 years prior to the index date (RRs = 1.50, 1.63, 1.71 and 1.79 for the four quartiles, respectively, p-trend = 0.0001). Similar patterns of increased risk of breast cancer were detected for the specific antibiotic classes. They observed a dose-dependent increase in breast cancer risk in association with the antibiotic exposure up to 15 years in the past.

Tamim *et al.* (2008)'s study suggested the possible association between the antibiotic exposure and cancer risk. Moreover, the antibiotic resistance has been very popular. At this point, antibiotic should be used as less as possible. ILILT might be of use as it has been found to rehabilitate immunity in chapter 3. The bacteria in rapid proliferation might be killed by antibiotic, but the bacteria in rest or slow proliferation might be killed by ILILT-rehabilitated immunity.

Inflammation is a local, protective response to injury or microbial invasion. It must be fine-tuned and regulated precisely, because deficiencies or excesses of the inflammatory response cause morbidity and shorten lifespan. The discovery that cholinergic neurons inhibit acute inflammation has qualitatively expanded our understanding of how the ANS modulates immune responses. The ANS reflexively regulates the inflammatory response in real time, just as it controls heart rate and other vital functions. The opportunity now exists to apply this insight to the treatment of inflammation through selective and reversible 'hard-wired' neural systems(Tracey 2002). ILILT can modulate internal inflammation at least through ANS inflammatory reflex and blood cells flowing in nasal mucosa as discussed in chapter 3.

Many Russian studies on ILILT are on its effects on the local inflammation. Tulebaev *et al.* (1989) have used LHNL to treat 62 patients with vasomotor rhinitis. The patients were given 10 laser sessions. The efficacy of ILILT of vasomotor rhinitis became optimal on irradiation day 6 or 7 and reached a maximum on day 10.They found the ILILT treated patients showed a significant increase of T-lymphocytes and a higher capacity of T-cells to form the migration inhibition factor.

Kruchinina *et al.* (1991) have used LHNL to treat 65 patients, aged 6 to 15 years, with catarrhal and purulent forms of acute and chronic maxillary sinusitis. The results give evidence that ILILT produced a positive effect on microcirculation and reduced the potential of relapses. LHNL affected mostly vessel permeability (decrease of perivascular edema) and blood rheology (red blood cell aggregation). In terms of circulation changes, ILILT was more beneficial in the case of acute maxillary sinusitis.

Shevrygin *et al.* (2000) have used ILILT treat 46 children aged 6 to 15 years for neurovegetative vasomotor rhinitis. They found abnormal microcirculation recovered after 10 sessions of the radiation even in severe alterations of the microcirculatory bed and long history of the disease. They concluded that ILILT is effective in correction of microcirculatory disorders and tissue mechanisms of homeostasis in children with neurovegetative vasomotor rhinitis.

Cough is an important defensive reflex of the respiratory tract needed to clear and protect the upper airways; however, it may become exaggerated and interfere with quality of life. Although chronic cough may be successfully treated when associated with the common causes such as asthma and eosinophilic bronchitis, gastrooesophageal reflux disease and post-nasal drip syndrome or rhinosinusitis, increasingly, idiopathic cough or cough with no associated cause is recognized. Chronic cough is often associated with an increased response to tussive agents such as capsaicin, used as an index of the cough reflex. Some airway receptors mediate or influence cough through activation of vagal afferent pathways which converge on brain stem respiratory networks and of supramedullary centers. Plastic changes in intrinsic and synaptic excitability at the brain stem, spinal or ganglionic level may be the mechanism by which the cough reflex is enhanced in chronic cough. Subjective and objective measurements of cough in the clinic are now available but a major unmet need in chronic cough is the availability of effective antitussives. Future directions in chronic cough include the pathophysiological mechanisms of the enhanced cough reflex, and the discovery of effective antitussives that can successfully alleviate chronic cough.

(Chung KF 2007). ILILT might be very potential. Chen Q *et al.* (2005) randomly divided 48 child patients with chronic cough associated with post-nasal drip syndrome into two groups, 24 in drugs-only group and 24 in ILILT+drugs group, and then treated ILILT+drugs group with LHNL at 20 mW for 30 min each time, which was done once a day for 10 days, and found 19 patients were improved in ILILT+drugs group, but only 13 patients were improved in drugs-only group，and the difference was very significantly.

5.2.6 Pain Relief

Between 2002 and 2004, Food and Drug Administration in USA (FDA) granted 510(k) approval to several companies to market lasers that provide low level laser irradiation or monochromatic light therapy (LLLT). The LLLT lasers are classified under "lamp, non-heating, for adjunctive use in pain therapy". Usually, applying the low level laser irradiation or monochromatic light (LLL) on the site of the pain or injury carries out the treatment. Pain relief can be obtained after one or two sessions. But most of the time, the therapy needs to be carried out several sessions to get the best possible therapeutic effect. Yu LH *et al.* (1992) studied the abirritation of LA on rat *zusanli* acupoint (ST 36) (Fig. 3.3). They found that laser irradiation at 110 and 165 J/cm^2 have the abirritation by means of increasing the concentration of β-endorphin in the brain. The further research on the effects of LA on pain has generally shown that LA can improve the expression of β endorphin (Zalewska-Kaszubska *et al.* 2004), which has been also found for ILILT. LA and ILILT have been used for pain relief.

The burden associated with headache is a major public health problem, the true magnitude of which has not been fully acknowledged until now. Headache is one of the most frequent ailments of the human race. Headache prevalence is estimated at 11%–48% in children and 6%–71% in adults. A higher prevalence has been found in Europe and North America than in Asian and South American countries. Prevalence of migraine shows a clear sex difference, affecting about 15%–18% of women and 6% of men. Muscle contraction or tension accounts for most of the nonmigraine headaches encountered in population surveys (Jordan *et al.* 2007). Globally, the percentage of the adult population with an active headache disorder is 47% for headache in general, 10% for migraine, 38% for tension-type headache, and 3% for chronic headache that lasts for more than 15 days per month. The large costs of headache to society, which are mostly indirect through loss of work time, have been reported. On the individual level, headaches cause disability, suffering, and loss of quality of life that is on a par with other chronic disorders. Most of the burden of headache is carried by a minority who have substantial and complicating comorbidities (Jensen *et al.* 2008). Treatment for headaches includes medical and non-medical approaches. ILILT has succeeded in treating headache (Li Q *et al.* 1998a&b). Li Q *et al.* (1998a) have treated 39 patients with headache such as chronic headache, migraine and trigeminal neuralgia with LHNL at 3.5~4.5 mW for 30 min each time, which was done once a day and five days each session for two sessions between which there two days for rest, and found the symptom improvement of 26(66.7%), 9 (23.1%) and 4 (10.2%) patients were significant, mild and none, respectively, and blood β endorphin in blood of the 35 patients with symptom improvement increased (Li Q *et al.* 1998a&b).

Primary headaches such as migraine are among the most prevalent neurological disorders,

affecting up to one-fifth of the adult population (Link *et al.* 2008). Migraine is a chronic disorder with episodic attacks with a highly variable long-term prognosis. In many, migraine may have a very benign (complete remission) or relatively benign (partial remission) prognosis. In some, migraine persists and in others, it progresses. A recent population study showed that, over a 1-year period, 84% of the patients with migraine persisted with this diagnosis (migraine persistence); around 10% had 1-year complete clinical remission, and 3% had partial remission; the other 3% developed chronic migraine. Long-term studies support the concept that remission increases with age and also that risk factors for progression have been identified (e.g. medication overuse, obesity, etc.) (Bigal *et al.* 2008). The scientific work in the last decade has unraveled much of the pathophysiological background of migraine, which is now considered to be a neurovascular disorder. It has been discovered that the trigemino-cerebrovascular system plays a key role in migraine headache pathophysiology by releasing the potent vasodilator calcitonin gene-related peptide (CGRP). This neuropeptide is released in parallel with the pain and its concentration correlates well with the intensity of the headache. The development of drugs of the triptan class has provided relief for the acute attacks but at the cost of, mainly cardiovascular, side effects. Thus, the intention to improve treatment led to the development of small CGRP receptor antagonists such as olcegepant (BIBN4096BS) and MK-0974 that alleviate the acute migraine attack without acute side events. (Link *et al.* 2008). LA and ILILT are alternative therapeutic approaches of no side effects. Chen S (2003) have treated 30 patients with migraine by intranasal irradiating with LGAL at 3.5~4.5 mW for 60 min each time, respectively, which was done once a day and 7 ~ 10 days each session for 1 ~ 2 sessions between which there one week for rest. During the second session, the acupoints *lieque*(LU 7) (Fig. 3.3) and *fengchi* (GB 20) (Fig. 5.4) have been irradiated with LGAL for 5 min each acupoint once a day. Among the 30 patients, 18 and 12 patients have been treated for one session and for two sessions, respectively. It was found the symptom improvement of 28(93%) and 2 (7%) patients were significant and mild, respectively. Acupuncture such as LA is the most widely practised non-medicinal treatment for headaches. Chen S (2003)'s research indicated that the acupuncture of LIL might enhance the therapeutic effects of ILILT. Han HF *et al.* (1997) have studied the effects of LHNL acupuncture on the patients with migraine, and found the symptom improvement of 10(55.6%), 6 (33.3%) and 2 (11.1%) patients with typical migraine were completed, significant and mild, respectively, the symptom improvement of 8(53.3%), 3 (20.0%) and 4 (26.7%) patients with general migraine were completed, significant and mild, respectively, and the difference of 5-hydroxytryptamine (5-HT) level is significant after LHNL treatment. Of course, the skin-contact electric acupuncture of low frequency pulse might further promote the therapeutic effects.

DPN affects 5-50% of people with diabetes in the USA. DPN is most commonly characterized by tingling or burning sensations, particularly in the calves, ankles, and feet, with a loss of vibratory sense. Treatment of DPN, for the most part, has been unsatisfactory. Therapy has been directed toward either improving nerve function or alleviating symptoms of DPN, including pain and paresthesia. Hyperglycemia also is associated with decreased pain threshold in patients with diabetes mellitus. Glycemic control may slow the progression of DPN. The aldose reductase inhibitors, particularly tolrestat, have been shown to improve objective and subjective neurologic function. Pain or paresthesia has been treated effectively with antidepressants, lidocaine, mexiletine, and capsaicin. The anticonvulsants phenytoin and carbamazepine may be effective, but

are associated with a greater degree of adverse effects. Experimental treatments, such as gamma-linolenic acid, gangliosides, uridine, and the corticotropin4-9 analog ORG 2766, have been effective in improving neurologic function (Calissi *et al.* 1995). Li X *et al.* (2006) randomly divided 60 patients with DPN into two groups, 30 in drugs-only group, 30 in ILILT+drugs group, and then treated ILILT+drugs group with LGAL at 1.5~2.0 mW for 60 min each time, which was done once a day and ten days each session for two sessions between which there was three days for rest, and found the symptoms such as ache and feel, lipid, fibrinogen and electromyography were improved after treatment in these two groups, but ILILT+drugs group was more pronounced than drugs-only group.

Inflammation can make normally nonpainful stimuli cause pain (a phenomenon known as allodynia). Lorenzini *et al.* (2010) have studied the clinical efficacy of a LIL at 670 nm used to stimulate acupoints ST36 *zusanli* (Fig. 3.3) and TE5 *waiguan* (Fig. 3.4) on well-established experimental models of acute and persistent pain in the rat, e.g. acute inflammatory pain, muscle pain, visceral pain and neuropathic pain. They reported the anti-edema and anti-hyperalgesia effects of LA in models of acute inflammatory pain, e.g. complement-fixing antibody induced inflammation and myofascial pain. They also indicated that spontaneous pain and thermal hyperalgesia are reduced in a neuropathic pain model, e.g. axotomy. On the contrary, no effects due to LA were observed on disconfort indices in a model of visceral pain, e.g. cystitis due to cyclophosphamide. They thus provided evidences that acupoints stimulation using a LIL can control pain and edema in specific experimental conditions.

5.2.7 Stroke

Stroke is the second to third most common cause of death in adults, and more than a third of people who survive a stroke will have severe disability. Therapeutic options currently centre on fibrinolytic treatment, but its limitations restrict use to a small proportion of patients. Although a wide range of neuroprotective substances has been effective in experimental models, they have repeatedly failed in clinical trials because of toxicity or loss of effectiveness. Recent strategies based on neuroplasticity and cellular therapy have shown significant efficacy in improving functional recovery in experimental models, although further study is still necessary to clarify how the brain responds to ischemic damage and is able to reorganize itself in the long term (Rodríguez-González *et al.* 2007). As steps should still be taken to ensure the safety and feasibility of treatments based on neuroplasticity and cellular therapy, LLLT might be alternatively potential.

The NeuroThera Effectiveness and Safety Trial-1 (NEST-1) study evaluated the safety and preliminary effectiveness of the NeuroThera Laser System (NLS) in the ability to improve 90-day outcomes in ischemic stroke patients treated within 24 hours from stroke onset. The NLS therapeutic approach involves use of 808 nm infrared laser irradiating the shaved head of the patient at about 1 J/cm^2. This was a prospective, intention-to-treat, multicenter, international, double-blind, trial involving 120 ischemic stroke patients treated, randomized 2:1 ratio, with 79 patients in the active treatment group and 41 in the sham (placebo) control group. Only patients with baseline stroke severity measured by National Institutes of Health Stroke Scale (NIHSS) scores of 7 to 22 were included. Patients who received tissue plasminogen activator were excluded. Outcome measures were the patients' scores on the NIHSS, modified Rankin Scale, Barthel Index, and Glasgow Outcome Scale at 90 days after treatment. After this trial, Lampl *et al.* (2007)

concluded the NEST-1 study indicates that NLS therapy has shown initial safety and effectiveness for the treatment of ischemic stroke in humans when initiated within 24 hours of stroke onset. A larger confirmatory trial to demonstrate safety and effectiveness is warranted.

Cerebral infarction is just a kind of stroke. Qiao Y *et al.* (2004) have treated 68 patients with cerebral infarction with LHNL at 10~15 mW for 60 min each time, which was done once a day and ten days each session for given sessions how much of which depended the patient symptom but it was at best 3 sessions, and found the symptom improvement of 34(50.0%), 27 (39.7%) and 7(10.3%) patients were significant, mild and none, respectively. Xiao X *et al.* (2005) have treated 21 and 18 patients with cerebral infarction by ILILT with LGAL at 3.5~4.0 mW for 30 min and ILELT with GaInP/AlGaInP diode laser irradiation at 650 nm at 2.5~3.0 mW for 30 min, respectively, and the single photon emission computed tomography (SPECT) in brain perfusion imaging indicated the ratio of local regional cerebral blood flow (rCBF) vs whole brain rCBF and brain blood flow function change rate (BFCR%) increased in the focus side of the brain after the treatment of either ILILT or ILELT, but no change in the mirror regions and no significant difference between ILILT and ILELT.

Cerebral infarction is classified into cerebral embolism and cerebral thrombosis. Li Q *et al.* (1999a) have treated 40 patients with cerebral thrombosis with LHNL at 3.5~4.5 mW for 30 min each time, which was done once a day and five days each session for two sessions between which there were two days for rest, and found malformation rate of erythrocytes decreased.

Dou Z *et al.* (2003) randomly divided 60 patients with cerebral infarction and 36 patients with traumatic brain injury into two groups, 50 in ILILT group and 46 in ILELT group, and then treated ILILT group with LGAL at 2.4 mW for 30 min each time and ILELT group with He-Ne laser at 2.5 mW for 40 min each time, respectively, which were done once a day and five days each session for two sessions between which there were two days for rest, and found the cholesterol, TG, LDL-C, erythrocyte sedimentation rate and hematocrit were significantly reduced, Fugl Meyer movement scale and Barthel index scores were significantly increased and the brain damage area was reduced in both groups, but there was no statistical difference between the two groups.

The therapeutic effects of ILILT on cerebral infarction have also studied by the comparison of the integrated group of ILILT and ordinary drugs with drugs-only group. Chen L *et al.* (2004) divided 100 patients with cerebral infarction into two groups, 40 in drugs-only group, 60 in ILILT+drugs group, and then treated ILILT+drugs group with LGAL at 3~5 mW for 30 min each time, which was done once or twice (for patients with high blood viscosity) a day and two or three weeks each session for two or three sessions which depended on the symptom, and found the improvement of most of rheological parameters of blood in ILILT+drugs group were better than the one in drugs-only group. Jin L *et al.* (2001b) randomly divided 93 patients with cerebral infarction into three groups, 30 in drugs-only group, 32 in ILILT+drugs group and 31 in ILELT+drugs group, and then treated ILILT+drugs group with LIL at 670 nm and 7~10 mW for 40 min each time and ILELT+drugs group with He-Ne laser at 1.5 mW for 90 min each time, respectively, which were done once a day for ten days, and found P_3PL decreased and erythrocyte deformability increased after the treatment of either ILILT or ILELT in comparison with drugs-only group. Zhao R *et al.* (2005) randomly divided 99 patients with cerebral infarction into three groups, 30 in drugs-only group, 33 in ILILT+drugs group and 36 in ILELT+drugs group, and then treated ILILT+drugs with LHNL at 3.5~5.5 mW for 30 min each time and ILELT+drugs with

He-Ne laser at 1.5 mW for 90 min each time, respectively, which have been done one time each day for days, respectively. They found both the leukocyte adhesion rate and the concentration of serum soluble intercellular adhesion molecule-1 decreased on the 10^{th} day for drugs-only group, but decreased on the 5^{th} day after the treatment of either ILILT or ILELT, and there is no significant difference between ILILT+drugs group and ILELT+drugs group.

It is well-known that cerebral infarction treatment might improve blood rheology and lipid, which is verified by transcranial Doppler (TCD). It has is found that the level of viscosity at lower shear rates and hematocrit significantly decreased after the irradiation of LGAL at 10 mW on the acupoint *futu* (LI 18)(Fig. 3.6) of the patients with cerebral trauma in Medical School of Shanghai Jiao Tong University. This research suggested that LA might promote the rehabilitation of the patients with cerebral infarction.

5.2.8 Depression

As will be pointed out on well-being in chapter 11.1, depression strongly influenced positive affect and enjoyment (Kahneman *et al.* 2004). Everyone feels miserable occasionally. But for the people with depression these sad feelings last for months or years and interfere with daily life. Depression is a serious medical illness caused by imbalances in the brain chemicals that regulate mood. It affects one in six people at some time during their life, making them feel hopeless, worthless, unmotivated, even suicidal.

There has been considerable interest recently in the relationship between depression and the workplace. This interest is driven by the growing recognition that depressive disorders are highly prevalent in the workplace and have an enormously negative impact on performance, productivity, absenteeism, and disability costs. A variety of clinical research with occupational-related samples has helped to define those at risk for depression and has led to a better understanding of the overlap of the construct of clinical depression with more longstanding occupational health and organizational psychology models such as stress, burnout, and job satisfaction. From an employer perspective, depression's impact remains largely unmitigated due to stigma, uncertainty about treatment's cost effectiveness, and lack of effective interventions delivered in a workplace setting (Bender *et al.* 2008).

Medical school was not easy in USA. The students knew that they wanted to become doctors to help people, but they had given little thought to the process. They were poorly prepared for many things: the pressure to excel in ways that seemed so far from caring for people; rapidly mounting debts they signed off on every semester; a roller coaster existence from chronic lack of sleep; hazing from the more experienced students and residents; and the realities of patient suffering despite my best efforts. More recently, Dyrbye *et al.* (2008) analyzed survey responses from 2,248 medical students at seven medical schools across the country, and found approximately 50% of students experience burnout, 10% experience suicidal ideation during medical school, burnout seems to be associated with increased likelihood of subsequent suicidal ideation, whereas recovery from burnout is associated with less suicidal ideation..

Doctors measure the severity of depression using the “Hamilton Rating Scale of Depression” or self-rating depression scale (SDS). Mild depression is often treated with psychotherapy or talk therapy (for example, cognitive–behavioral therapy helps people to change negative ways of thinking and behaving). For more severe depression, current treatment is usually a combination of

psychotherapy and an antidepressant drug, which is hypothesized to normalize the brain chemicals that affect mood. Antidepressants include “tricyclics,” “monoamine oxidases,” and “selective serotonin reuptake inhibitors”. Before the advent of selective serotonin reuptake inhibitors — Lilly's prozac was the first to be approved by the FDA, in 1987, followed by zoloft from Pfizer, paxil from Glaxo Smith Kline, celexa from Forest Pharmaceuticals and others — existing antidepressants had many disabling side effects. Impaired memory and judgment, dizziness, drowsiness and other complications made them ill suited for troops in combat. The newer drugs have fewer side effects and, unlike earlier drugs, are generally not addictive or toxic, even when taken in large quantities. They work by keeping neural connections bathed in a brain chemical known as serotonin. That amplifies serotonin's mood-brightening effect, at least for some people. Selective serotonin reuptake inhibitors are the newest antidepressants and include fluoxetine, venlafaxine, nefazodone, and paroxetine. However, there have still been the side effects of these mental-health medications. Last year FDA urged the makers of antidepressants to expand a 2004 "black box" warning that the drugs may increase the risk of suicide in children and adolescents. The agency asked for — and got — an expanded warning that included young adults ages 18 to 24 (Kirsch *et al.* 2008).

Kirsch *et al.* (2008) found that drug–placebo differences in antidepressant efficacy increase as a function of baseline severity, but are relatively small even for severely depressed patients, and the relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication. These findings suggest that, compared with placebo, the new-generation antidepressants do not produce clinically significant improvements in depression in patients who initially have moderate or even very severe depression, but show significant effects only in the most severely depressed patients. The findings also show that the effect for these patients seems to be due to decreased responsiveness to placebo, rather than increased responsiveness to medication. Given these results, Kirsch *et al.* (2008) conclude that there is little reason to prescribe new-generation antidepressant medications to any but the most severely depressed patients unless alternative treatments have been ineffective. In addition, the finding that extremely depressed patients are less responsive to placebo than less severely depressed patients but have similar responses to antidepressants is a potentially important insight into how patients with depression respond to antidepressants and placebos that should be investigated further. At this point, LA and ILILT are suggested to be used to treat depression at least through intranasal *du* meridian according to MIH. Zhang JB *et al.* (2005) have found that acupuncture along *du* meridian at *baihui* (GV 20) (Fig. 5.1) and *shenting* (GV 24)(Fig. 5.3) can change the behavior abnormality induced by separation feeding, long term unpredictability and medium degree stimulation in depression model rats.

The effects of ILILT on depression have been supported by the bright light effects. Bright light therapy for seasonal affective disorder (SAD) has been investigated and applied for over 20 years. Physicians and clinicians are increasingly confident that bright light therapy is a potent, specifically active, nonpharmaceutical treatment modality (Terman *et al.* 2005). Indeed, the domain of light treatment is moving beyond SAD, to nonseasonal depression (unipolar and bipolar), seasonal flare-ups of bulimia nervosa, circadian sleep phase disorders, and more. Light therapy is simple to deliver to outpatients and inpatients alike, although the optimum dosing of light and treatment time of day requires individual adjustment. The side-effect profile is favorable

in comparison with medications, although the clinician must remain vigilant about emergent hypomania and autonomic hyperactivation, especially during the first few days of treatment. Importantly, light therapy provides a compatible adjunct to antidepressant medication, which can result in accelerated improvement and fewer residual symptoms. These results supported the effects of ILILT on depression according to chapter 4.

PSD is among the most common emotional disorders afflicting stroke sufferers. Approximately one third of stroke survivors experience an early or later onset of depression. PSD impedes the rehabilitation and recovery process, jeopardizes quality of life and increases mortality. Diagnosis of PSD is challenging in the acute and chronic aftermath. Therefore, it often remains unrecognized and/or undertreated. The interaction between depression and stroke is very complex and the pathophysiological mechanisms have not as yet been fully elucidated, although an interaction between anatomical and psychosocial factors may be important in PSD development. Neurochemical changes and clinical findings are similar to endogenous depression. PSD is potentially treatable, although no conclusive benefits of antidepressant agents and nonpharmacological interventions have been observed. The efficacy of preventive strategies in PSD remains essentially undetermined (Gaete *et al.* 2007). It should be pointed out that the rehabilitation of ILILT on PSD has been observed. In terms of SDS, Xu C *et al.* (2002c) divided 177 patients with stroke into two groups, 45 in pure stroke group (SDS < 40) and 132 in PSD group (SDS > 40), and then treated the two groups with LHNL at 3.5~4.5 mW for 30 min each time, which were done once a day in the afternoon for 30 days, and found serum melatonin increased and SDS decreased only in PSD group, but there is no such changes in pure stroke group.

Baihui (GV 20) (Fig. 5.1) and *shenting* (GV 24)(Fig. 5.3) have been often used in acupuncture on PSD. Therefore, LA might promote the therapeutic effects on the patients with PSD.

5.2.9 Coronary Heart Disease (CHD) and myocardial infarction (MI)

Inflammation and genetics play an important role in the pathogenesis of CHD. This is supported by epidemiological studies which have thoroughly investigated the association between CHD and gene polymorphisms of the inflammatory molecules. Moreover, efforts to find elective therapy have not been rewarding and, despite the increasing appreciation of the role of genetics in CHD and MI pathogenesis, pharmacogenomic approaches to uncover drug target have not been extensively explored. A critical search of published literature has suggested few inflammatory genes directly involved in the risk to develop CHD and MI. The selected genes are, the pro- and anti-inflammatory cytokines, toll-like receptor 4 (TLR4), CD14, chemokine (C-C motif) receptor 5 (CCR5), and lipoxygenases (COXs). The associations between candidate gene polymorphisms and CHD/MI are difficult and complex as a consequence of pleiotropy, variations with age, selection due to the lethality of the disease, and interactions with other genes and environmental factors. However, current data indicate that screening for interleukin (IL) 6, IL-10, TLR4, CCR5, COX and COX polymorphisms are likely to be a useful tool for CHD and MI risk assessment. What we believe is that dissecting out the influence of genetics polymorphism within the complex pathophysiology of CHD and MI will help to provide a more complete risk assessment and complement known classical cardiological risk factors. The detection of a risk profile will

potentially allow both the early identification of individuals susceptible to disease and the possible discovery of potential targets for drug of lifestyle modification (Candore *et al.* 2007).

According to TCM, *heart* and *small intestine*, and then *heart* meridian of hand *shao-yin* and *small intestine* meridian of hand *tai-yang* are coupled with each other so that CHD/MI might be treated through *small intestine* meridian of hand *tai-yang* in terms of *yin-yang* parallel principle in chapter 9. Therefore, ILILT can be used to treat CHD/MI at least through its acupuncture along nasal *small intestine* meridian of hand *tai-yang* according to MIH and its anti-inflammation discussed above. Xiong H *et al.* (2006) randomly divided 60 CHD patients with the TCM blood-stasis syndrome into two groups, 30 in drugs-only group and 30 in ILILT+drugs group, and then treated ILILT+drugs group with LGAL at 3~5 mW for 30 min each time according to the principle of random, imitated blind and parallel controlled trial, which was done once a day for 14 days, and found that angina and electrocardiogram in two groups were not significantly different from each other, but the mean total score of TCM syndrome in ILILT+drugs group was obviously higher than that of control group, and there was no toxic action and adverse effects in two groups during the treatment.

Acute MI is one condition included in the category of CHD. Jin F *et al.* (2008) have used SPECT to observe the therapeutic effects of ILILT with LGAL at 5 mW for 40 min on 5 patients with acute MI, and found myocardial blood flow was improved. Before treatment, the ventricular thickness, the ventricular wall motion and myocardial perfusion in patients were (4.79±2.85) mm, (23.31 ± 11.68)% and (57.92 ± 18.43)%, respectively. The above parameters significantly increased to (5.32±2.95) mm, (26.54±13.03)% and (59.92±18.30)% after laser treatment, respectively. The main target parameter of left ventricular ejection fraction increased from (41.00 ±5.77)% before treatment to (45.00±6.73) after treatment. The end-systolic volume decreased from (146.50 ± 18.19) ml before treatment to (141.75 ± 14.66) ml after treatment. The end-diastolic volume decreased from (86.75±16.19) ml before treatment to (77.75±13.18) ml after treatment. It had clearly showed that in all of 5 patients the region of poor myocardial blood flow perfusion was significantly improved after laser treatment in the myocardial perfusion map in the target area, the cardiac short axis, horizontal long axis and vertical long axis.

CHD is associated with ANS dysfunction. The population-based prospective study indicated that altered cardiac autonomic activity, especially lower parasympathetic activity, is associated with the risk of developing CHD (Liao D *et al.* 1997). The appraisal of alterations in the autonomic control mechanisms in the acute and post-acute phase of MI has not only confirmed the presence of an increased sympathetic and of a reduced vagal modulation in most of post-MI patients (Lombardi *et al.* 2001). As LA stimulation applied to the *neiguan* acupoint (PC 6) (Fig. 3.3) increased vagal activity and suppression of cardiac sympathetic nerves as pointed out in chapter 3.8, the acupuncture of LIL on the *neiguan* acupoint and interdigital low intensity laser therapy (DLILT) may be used to treat patients with CHD. Luo RH *et al.* (2005) found LHNL at *neiguan* can improve the cardiac function of senile patients with CHD. Forty senile patients (28 males and 12 females, 66-85 years old) with CHD hospitalized in the General Hospital of Henan People's Armed Police Force for rehabilitation from 2000 to 2001 were selected. The course of their CHD was from 2 years to 20 years. Among them, 15 and 7 were complicated with hypertention and hyperlipemia, respectively. LHNL was used to irradiated at *neiguan* once a day, 15 min each time, for 20 times. They found that LA improved cardiac load and myocardial oxygen consumption, increased the oxygen supple and the utilization rate of tissue, improved

relaxation-contraction function of coronary artery and promoted the blood supply and circulation of coronary artery.

He Z *et al.* (1989) have studied the effects of LHNL at *neiguan* (PC6) and *zusanli* (ST36) (Fig. 3.3) on the acute ischemic myocardial damage in rabbits, respectively. Thirty-six mongrel rabbits were made suffering from acute ischemic myocardial damage by applying the method of ligating the left anterior descending coronary artery. The potential changes of the ST values (II, avF) were used as the indexes. They found that LA at *neiguan* could help relieve acute ischemic myocardial damage. The therapeutic effects of LA along *pericardium* meridian of hand *jueyin* on acute ischemic myocardial damage have been confirmed by LA at *quze* (Chen D *et al.* 1997). These results indicated that DLILT may be sued to treat patients with acute ischemic myocardial damage.

5.2.10 Cerebral Palsy (CP)

CP is a disorder of movement and posture with additional potential to affect cognitive status. Extreme prematurity confers about a 100-fold increase in the risk of CP, relative to birth at term gestation. Although CP is primarily a disorder of movement, many children with this disorder have other impairments which may affect their quality of life and life expectancy (O'Shea 2008). The goals for management of the child with CP include the following: to promote optimal function; to maintain general health; to foster acquisition of new skills; to assist and educate parents and caregivers; and to anticipate, prevent, and treat the complications of this disorder. Pediatric management of the child with CP should begin at the time of diagnosis (Jones *et al.* 2007). A number of interventions to improve gait in individuals with CP have been reported in the literature. Types of interventions were mainly grouped into spasticity treatments, orthopedic (bony and soft tissue) surgery, lower extremity orthoses. Among them, each intervention had a statistically significant effect size. (Paul *et al.* 2007). ILILT might be very potential as ILILT has been found to improve cognitive dysfunction as discussed above.

There is dysfunctional microcirculation in CP. Liu Z *et al.* (2007) randomly divided 100 patients with CP into two groups, 50 in control group and 50 in ILILT group, after ordinary rehabilitation, and then treated ILILT group with LGAL at 5 mW for 45 min each time, which was done once a day and 7 days each session for two sessions between which there were 5 days for rest, and found the improvement of both erythrocyte aggregation and nailfold microcirculation in ILILT group was significantly in comparison with the control group.

After the regularity of coordination of acupoints to treat CP with acupuncture in 120 literatures has been analyzed referring to frequency analysis and cluster analysis, it has been found the common 3 acupoints in frequency analysis were *hegu* (LI 4) (Fig. 3.4), *quchi* (LI 11)(Fig. 3.4) and *zusanli* (ST 36)(Fig. 3.3). Therefore, LA may be used to treat the children with CP.

6 Potential Applications of Laser Function Medicine

Prospects for new drugs seem bleak. Only 17 new molecular entities were approved by Food and Drug Administration in USA (FDA) in 2007, a fall from 53 in 1996. Coincident trends worsen the situation: a decline in prescription drug sales, the flight of investors, corporate layoffs, and pricing inequities in advanced economies that fuse with demands from poorer countries to gain cheap and immediate access to new drugs.

On the other hands, reports of serious injuries and deaths that may have been caused by prescription drugs skyrocketed between 1998 and 2005. In 1998, the FDA received 34,966 reports of serious adverse events, including 5,519 reports of deaths, possibly related to the use of prescription drugs. By 2005, those figures more than doubled, to 89,842 events including 15,107 deaths. The rise can't be explained by an increase in the use of medicines. The number of serious adverse events reported rose four times as fast as prescriptions in the period. The increase was largely explained by reports from manufacturers. And those reports were mainly about side effects not already described on drugs' labels. Reports directly from doctors and pharmacists, as well as reports from drug companies of side effects already on drug labels, rose much more slowly. If side effects were skyrocketing in the real world, wouldn't reports from doctors to the FDA be shooting through the roof as well? The bigger issue is that the FDA's problem-ridden Adverse Event Reporting System isn't a systematic measure of how often drugs really cause side effects. Doctors aren't required to report drug side effects into the system, and it's been estimated as few as 10% of all adverse events get reported. So it's tough to draw any firm conclusions about what the data from the system mean.

Therefore, like star-crossed lovers, the health care faces both challenge and opportunity. At this point, low level laser irradiation or monochromatic light (LLL) should be a cheap and immediate choice. Our focus is on laser acupuncture (LA) and intranasal low intensity laser therapy (ILILT) in this book. As discussed in Chap. 3, LLL can increase the ratio of nicotinamide adenine dinucleotide (NAD^+) and its reduced form NADH, NAD^+/NADH, and then NAD^+ dependent sirtuin (SIRT) activities if the modulated functions far from their respective function-specific homeostasis (FSH), and melatonin (Mel) can also increase NAD^+/NADH and SIRT1. The deacetylation activity of SIRT1 can be stimulated by several polyphenolic compounds (Ullah *et al.* 2008). Polyphenols are a wide group of dietary compounds from plants, occurring in high amounts in fruits, vegetables, cereals, wine and tea. Epidemiological studies suggest that a diet rich in polyphenols may protect against cardiovascular diseases, and mechanistic studies in cells and animals have shown that polyphenols have a wide range of properties that also may play a role in the prevention of other diseases, such as cancer and neurodisfunctions (de Boer *et al.* 2006). As discussed in Chap. 4, the season effects and latitude effects of sunlight and bright light effects might be mediated by intranasal decayed light. In Chap. 5, we have discussed the present health care and clinic applications of LA and ILILT. In this chapter, we will discuss the possible applications of LA such as interdigital low intensity laser therapy (DLILT) and ILILT in chronic disease, ageing, development, influenza and miscellaneous diseases in view of the therapeutic effects of polyphenols, Mel, the effects of sunlight and bright light and the other kinds of LLL such as intravascular low energy laser therapy (ILELT) because they share the same SIRT1-mediated mechanism. The transmission efficiency of therapeutic information to the target will be also discussed.

6.1 Chronic Diseases

The Western lifestyle which is characterized by a highly caloric diet, rich in fat, refined carbohydrates and animal protein, combined with low physical activity, and resulted in an overall energy imbalance, is associated with a multitude of disease conditions, including obesity, diabetes, cardiovascular disease, arterial hypertension and cancer. Most of side effects of the Western lifestyle might be prevented or treated by LA and ILILT as discussed in chapters 3 and 5.

Currently, chronic diseases are by far the leading cause of death in the world and in Chinese and their impact is steadily growing. It has been projected that approximately 17 million people die prematurely each year as a result of the global epidemic of chronic disease such as dementia, coronary heart disease (CHD), stroke, cancer and diabetes. The therapeutic effects of ILILT on dementia, CHD and stroke have been reviewed in chapter 5. The possible applications of LA and ILILT on chronic diseases such as hypertension, vascular dementia (VaD), cancer and diabetes will be discussed in this chapter.

6.1.1 Hypertension

Hypertension is estimated to cause 4.5% of current global disease burden. Recent surveys estimate indicated one in three Americans has hypertension. Hypertension is already a highly prevalent cardiovascular risk factor worldwide because of increasing longevity and prevalence of contributing factors such as obesity. Hypertension is an underlying cause of heart attacks, strokes, kidney disease and heart failure. Blood pressure-induced cardiovascular risk rises continuously across the whole blood pressure range. Starting at a blood pressure of 115/80, research shows that the risk of a heart attack or stroke doubles with every 20-point increase of systolic pressure, the top number, or 10-point increase of diastolic pressure, the bottom number. Since publication of the WHO/ISH (World Health Organization /International Society of Hypertension) Guidelines for the Management of Hypertension in 1999, more evidence has become available to support a systolic blood pressure threshold of 140 mmHg for even 'low-risk' patients. Whereas the treatment of hypertension has been shown to prevent cardiovascular diseases and to extend and enhance life, hypertension remains inadequately managed everywhere. In high-risk patients there is evidence for lower thresholds. Lifestyle modification is recommended for all individuals. There is evidence that specific agents have benefits for patients with particular compelling indications, and that monotherapy is inadequate for the majority of patients. For patients without a compelling indication for a particular drug class, on the basis of comparative trial data, availability, and cost, a low dose of diuretic should be considered for initiation of therapy. In most places a thiazide diuretic is the cheapest option and thus most cost effective, but for compelling indications where other classes provide additional benefits, even if more expensive, they may be more cost effective. In high-risk patients who attain large benefits from treatment, expensive drugs may be cost effective, but in low-risk patients treatment may not be cost-effective unless the drugs are cheap (Whitworth *et al.* 2003).

High blood pressure is becoming increasingly resistant to drugs that lower it. The problem is not that the medications have stopped working. Instead, many blood-pressure patients are sicker to begin with and require more drugs, at greater dosages, to manage their conditions. Resistant

hypertension is defined as blood pressure that remains above clinical goals, even after a patient has been put on three or more different classes of medications. Additionally, patients whose blood pressure can be lowered to normal on four or more drugs should be considered resistant and should be closely monitored. It became more likely with advanced age, weight gain, a diet high in sodium, sleep apnea or chronic kidney disease. 20 to 30 percent could not control their blood pressure with three or more drugs, even when taking them exactly as prescribed. The 20 to 30 percent cohort appears to be growing. A large study in 2006 from Stanford found that the number of blood-pressure patients who were prescribed three or more drugs had increased over 12 years, to 24 percent from 14 percent. If patients need that many drugs, they are likely to be at greater risk for illness even if they lower their blood pressure to normal. These patients have usually had high blood pressure for some time and, as a result, have more organ damage.

Since drugs have side effects, patients might prefer physical therapy. It has been revealed that the incidence of arterial hypertension associated with the geographic latitude (Gundarov *et al.* 1991). When the global seasonality score (GSS) is greater than 11 so that the systolic blood pressure is far from its FSH in Tab. 3.1, the systolic blood pressure in summer is lower than that in spring or winter because the sunlight in summer is more intensive than the one in spring or winter. In patients with end-stage renal disease treated with hemodialysis, blood pressure varies seasonally, with higher values in the winter and lower values in the summer (Argilés *et al.* 1998). The sunlight effects on blood pressure or hypertension suggested that ILILT may be used to prevent from or improve prognosis of hypertension according to the ILILT-like mechanism of the sunlight effects (ILILM) in chapter 4.3.

In order to provide directions for LA application on hypertension, Zeng Z *et al.* (1997) have irradiated at *zusanli* (ST 36) (Fig. 3.3), *neiguan* (PC 6) (Fig. 3.3) and *heart* acupoint of ear (Fig. 3.7) with 810 nm diode laser, and studied the effects of the three groups on lowering blood pressure and improving cardiovascular function. They found the *neiguan* group has got the best effects on lowering systole pressure and blood viscosity, increasing heart output, heart systole ability and heart power to supply blood, enhancing heart index and blood ejection rate, releasing blood vessel resistance. This indicated that DLILT may be used to treat patients with hypertension.

Velizhanina *et al.* (2001a) have performed a randomized parallel study to compare the antihypertensive effect of normobaric hypoxia and low energetic laser irradiation in 57 patients with essential hypertension stage I using 24-hour blood pressure monitoring. High hypotensive efficacy of both methods is demonstrated. A course of normobaric hypoxia decreased mean 24-h and mean daytime systolic and diastolic blood pressure. Low energetic laser irradiation reduced mean 24-h, mean daytime and mean night systolic and diastolic blood pressure. Velizhanina *et al.* (2001b) also evaluated an antihypertensive activity of LIL in 52 males with essential hypertension stage I in a placebo-controlled study. The placebo group consisted of 14 matched patients. LIL was used as monotherapy of 10 daily procedures. This treatment significantly lowered systolic, diastolic and mean arterial pressure. Moreover, diastolic arterial pressure did not rise high at submaximal bicycle exercise. Total peripheral vascular resistance also decreased. A good hypotensive effect was achieved in 90.4% cases. Thus, LIL is a highly effective treatment in essential hypertension stage I.

Mokretsov *et al.*(1992) have presented data on the influence of LA on the central and peripheral hemodynamics in 76 agricultural machine operators facing transitory arterial

hypertension. Analysis revealed that LIL is more effective at the early stages of cardiovascular diseases. Therefore, LA on reflexogenic zones can be effectively used to correct hemodynamic disorders in subjects facing transitory arterial hypertension. Shuvalova *et al.* (1998) have studied the effectiveness of LIL on regulation of arterial blood pressure in 185 patients (51 men, 134 women). The above patients were prescribed four therapeutic complexes: group I was exposed to infra-red irradiation by zones; group II--to scanning He-Ne laser across the portal zone and paravertebrally CIII-Th5; group III--to He-Ne laser in the area of right sinocarotid zone; group IV underwent hydrolaser shower (in red and intra-red range). Complaints were studied as were data from laboratory investigations, the condition of different bodily systems, blood pressure level, the functional state of the cardiovascular system as per electrocardiography and rheography findings. A positive clinical effect was achieved in all the groups studied. Employment of low-intensity laser irradiation in the rehabilitation of patients with borderline hypertension during the sanatorium stage was noted to strikingly enhance the efficiency of the therapy administered. It can be prescribed to patients irrespective of their hemodynamic types. Irradiation of the right sinocarotid zone and hydrolaser therapy are indicated to patients presenting with hypo- and eukinetic types of hemodynamics and baseline sympatheticotonia.

6.1.2 Vascular dementia (VaD)

After Alzheimer's disease (AD), VaD is the second most common cause of dementia. In the vascular system, nitric oxide (NO) generated by endothelial NO synthase (NOS) plays an important role in maintenance of vascular tone. Hyperhomocysteinemia (Hhcy), or elevation of plasma total homocysteine, is an important risk factor for cardiovascular disease, stroke and VaD. Hhcy has been shown to induce endothelial dysfunction by decreasing the bioavailability of NO, and increasing vascular oxidative stress. The decreased NO level has been demonstrated to contribute to the pathogenesis of dementia (Koladiya *et al.* 2008) .

Increased levels of homocysteine have been documented to produce changes in structure and function of cerebral blood vessels along with oxidative stress, which play a key role in cerebral vascular dysfunction. Oxidative stress and vascular dysfunction are recognized as important contributing factors in the pathogenesis of AD and VaD. In AD and other neurodegenerative diseases, structural deformities in the cerebral capillaries lead to impairment of cerebral perfusion with subsequent neuronal dysfunction and death. The well established risk factors of endothelial dysfunction and subsequent VaD such as hypertension, history of stroke, diabetes mellitus and hypercholesterolemia are all associated with high risk of AD. The noted vascular dysfunction (vascular deformities) in AD and common risk factor of AD and VaD suggest a great overlap between AD and VaD. Moreover, Hhcy has been documented to increase cholesterol synthesis. Studies have revealed that in addition to elevated amyloid β protein (Aβ) and apolipoprotein E levels, high cholesterol level is another important risk factor for AD (Koladiya *et al.* 2008).

Only limited therapeutic interventions are available to reduce the incidence of VaD. Cholinesterase inhibitors, calcium channel blockers and glutamate antagonists are few classes of pharmacological agents which are being clinically explored to reduce symptomatically the impact of cognitive dysfunction associated with VaD. However, an agent that should improve both endothelial dysfunction and associated dementia still need to be explored. Very recently, the focus has been directed towards statins (HMG-CoA reductase inhibitors), which are most widely

prescribed drugs for dyslipidemias. Statins in additions to their cholesterol lowering action are known to possess many cholesterol independent actions including favorable effect on vascular endothelium. Moreover, there is an emerging data indicating that statins exert neuroprotective and antioxidant actions. Statins have been shown to reduce the risk of ischemic stroke and related memory impairment by a variety of mechanisms. Epidemiological studies have suggested that individuals above 50 years of age, who were receiving statins, had a substantially lowered risk of developing dementia, independent of the presence or absence of untreated hyperlipidemia, or exposure to non-statin lipid-lowering drugs. However, there are conflicting observations regarding the effect of statins on cognitive functions. Although, there are a few studies showing cognitive decline, some studies showing no effect on memory, yet few studies suggest improvement of cognitive functions with statin therapy. Therefore, implication of statins in endothelial dysfunction and related dementia deserves further investigation (Koladiya *et al.* 2008). As discussed in section 5.1.1, statins do cause some unusual side-effects with potentially severe consequences, most prominently myopathy or rhabdomyolysis and polyneuropathy. As there may be a great overlap between AD and VaD and LA and ILILT have therapeutic effects on AD, respectively, LA and ILILT are very potential for VaD, respectively.

Huang Y *et al.* (2007) have treated 33 patients of VaD with the traditional Chinese medicine (TCM) soup of fever relief and cognition enhancement and ILILT. The ILILT was done 60 min each time once a day five days each session for many sessions between which there are two days for rest. They found that the symptom improvement of 8(24.2%), 13 (39.4%), 7(21.2%) and 5(15.2%) patients were significant, effective, mild and none, respectively. This indicated that there might be the therapeutic effects of ILILT on VaD, which is supported by the direct therapeutic effects of ILILT on AD as discussed in the previous chapter.

Liu RH *et al.* (2008) have treated VaD with ILELT. They randomly divided 82 patients with VaD into two groups, 41 in drugs-only group, and 41 in ILELT+drugs group, and then treated ILELT+drugs group with He-Ne laser irradiation at 4.8 mW for 60 min each time once a day for 15 days, and found both mini-mental state exam (MMSE) and modified hasegawa dementia scale(MHDS)increased and plasma choline decreased after the treatment of ILELT in comparison with drugs-only group.

Unilateral middle cerebral artery (MCA) occlusion in Wistar rats produced a VaD model. Its acupoints, *baihui* (GV 20) (Fig. 5.1) and *dazhui* (GV 14) (Fig. 5.2), were irradiated with LHNL 30 min each acupoint once a day seven days each session for two sessions between which there were 3 days for rest. Cheng TZ *et al.* (2005) found that the learning and memory ability and the positive response of microtubule associated protein 2 in hippocampal CA1 region significantly increases, respectively.

As discussed above, LA and ILILT should be suggested to treat VaD. It is supported by many studies on the therapeutic effects of Mel and polyphenols.

6.1.3 Cancer

Cancer rates could further increase by 50% to 15 million new cases in the year 2020, according to the World Cancer Report, the most comprehensive global examination of the disease to date published by WHO in 2003. This report calls on governments, health practitioners and the general public to take urgent action. Action now can prevent one third of cancers, cure another

third, and provide good, palliative care to the remaining third who need it. At the core of this cancer control strategy, the essential package includes cost-effective interventions for the following components: tobacco control, infection control, healthy eating, a curable cancer program and palliative care. Epidemiological studies indicate that the frequent consumption of fruit and vegetables may reduce the risk of developing cancers of epithelial origin, including carcinomas of the pharynx, larynx, lung, oesophagus, stomach, colon and cervix. Recent data from the European Prospective Investigation into Cancer and Nutrition, suggests that a daily consumption of 500 grams of fruits and vegetables can decrease incidence of cancers of the digestive tract by up to 25 per cent.

The importance of the immune system at controlling and shaping developing tumors has been well established (El Hage *et al.* 2008). Malignancies might be caused by infectious agents, including hepatitis B and C virus (liver cancer), human papillomaviruses (cervical and ano-genital cancers), and Helicobacter pylori (stomach cancer). In the gastro-intestinal tract, any chronic tissue damage with necrosis and regeneration carries an in creased cancer risk, e.g. consumption of very hot beverages (squamous cell carcinoma of the esophagus), gastro-oesophageal reflux (adenocarcinoma of the esophagus), chronic gastritis induced by H. pylori infection (stomach cancer), Crohn's disease (cancer of the small intestines) and ulcerative colitis (colon cancer).

Resistance to challenges with aggressive mouse transplantable cancer cells, such as S180, L5178Y, or EL4, is rare for laboratory mice. Spontaneous regression/complete resistance (SR/CR) mice possess a unique autosomal dominant trait that allows them to survive challenges with aggressive mouse cancer cells at up to millions of times the lethal doses for wild type mice (Hicks *et al.* 2006). In SR/CR mice, cancer cells induce rapid infiltration of leukocytes that form rosettes around cancer cells, which then rapidly undergo cytolysis. Leukocytes from SR/CR mice also kill a wide array of mouse and human cancer cell lines *in vitro*. The cytolytic activity is specific to cancer cells, because SR/CR mice are cancer-free and disease-free for their lifetimes, with no detectable abnormality despite repeated challenges.

Animal might also have the ability of defence against tumour. It has been shown that oxidative burst of granulocytes is cytotoxic for melanoma B16F10 and for Walker 256 carcinoma (W256). Jaganjac *et al.* (2008) assumed that granulocytes could also be important mechanism of the host defence against tumour. They report massive granulocyte infiltration at the site of W256 transplanted in the hind limb of Sprague-Dawley rats associated with spontaneous tumour regression observed for 22/25 rats (87%). Peripheral blood granulocytes of these animals were highly cytotoxic for W256 cells cultured in vitro. After the tumour disappearance the inflammatory oxidative burst of the granulocytes ended. Distraction of granulocytes from the tumour by s.c. Sephadex injection decreased the incidence of the W256 regression to only 7/25 animals (30%). These results suggest that innate immunity based on immune competent granulocytes may be the cause of well known phenomenon of spontaneous regression of W256 carcinoma.

The link between inflammation and cancer is well documented. Several inflammatory diseases, including inflammatory bowel disease, increase the risk of cancer (Mantovani 2009). Conversely, in tumors that are epidemiologically unrelated to overt inflammatory conditions (such as breast cancer), the activation of oncogenes can orchestrate the production of inflammatory molecules and the recruitment of inflammatory cells. In the tumour microenvironment, inflammatory cells and molecules influence almost every aspect of cancer progress, including the

tumour cells' ability to metastasize. Thus, whereas there were previously six recognized hallmarks of cancer — unlimited replicative potential, self-sufficiency in growth signals, insensitivity to growth inhibitors, evasion of programmed cell death, ability to develop blood vessels, and tissue invasion and metastasis— cancer-related inflammation now emerges as number seven. Kim *et al*. (2009) shed light on the unexpected molecular pathways that link inflammation in the tumor microenvironment to metastasis.

Inflammation is an important factor in promoting cancer. So one idea is that CD95 aids tumour growth by inducing inflammation. For more than two decades, CD95 — also known as Fas and APO-1 — has been considered a killer, the *capo di tutti capi* of death receptors in the tumour-necrosis-factor (TNF) receptor family. Interaction of this cell-surface receptor with its ligand, CD95L, or with activating antibodies induces rapid apoptotic death in many cell types, and injection of such ligands or antibodies into animals results in liver destruction and death. Expression of CD95L in abnormal locations such as pancreatic islet cells or transplanted tissues can induce a dramatic infiltration of white blood cells — a hallmark of inflammation. Against this idea, however, Chen L *et al*. (2010) report that CD95L promotes tumour growth by mechanisms within the tumour, with no profound differences in inflammation between tumours expressing CD95 and those that do not express it. Furthermore, unlike membrane-bound CD95L, soluble CD95L does not promote inflammation.

Therefore, the risk of the related cancers and other cancers can be reduced by immune system in immunity-specific homeostasis. Dietary bioactive food components that interact with the immune response have considerable potential to reduce the risk of cancer. Reduction of chronic inflammation or its downstream consequences may represent a key mechanism that can be reduced through targeting signal transduction or through antioxidant effects (Ferguson *et al.* 2007). The immune regulation might be also achieved by ILILT at least through blood cells flowing in nasal mucosa and inflammatory reflex as discussed in the previous two chapters, respectively. ILILT has been successfully used to treat chronic cough associated with post-nasal drip syndrome (Chen Q *et al.* 2005). The semiconductor laser (630 nm, 10 mW) has been used to irradiate the *futu* acupoint (LI 18) (Fig. 3.6) just for 30 min, and natural killer cells in blood were then found to increase significantly. This research suggested that LA might be used to promote the immunity-specific homeostasis.

Sunlight effects may prevent from or improve prognosis of cancers. Porojnicu *et al.* (2008) found a 15-25% better survival for patients diagnosed for prostate cancer, breast cancer and colon cancer during summer in Norway. van der Rhee *et al.* (2006) have reviewed all published studies concerning sun exposure and cancer, excluding skin cancer. All selected studies on prostate (3 ecologic, 3 case-control and 2 cohort), breast (4 ecologic, 1 case-control and 2 cohort) and ovary cancer (2 ecologic and 1 case-control) showed a significantly inverse correlation between sunlight and mortality or incidence. Two ecologic, 1 case-control and 2 prospective studies showed an inverse relation between sunlight and colon cancer mortality; 1 case-control study found no such association. Ecologic studies on non-Hodgkin lymphoma (NHL) mortality and sunlight gave conflicting results: early studies showing mostly positive and later studies showing mostly negative correlations. Three case-control studies and 1 cohort study found a significant inverse association between the incidence of NHL and sunlight.

The rapid increase in mobile telephone use has generated concern about possible health risks related to radiofrequency electromagnetic fields from this technology. An interview-based

case–control study with 2708 glioma and 2409 meningioma cases and matched controls was conducted in 13 countries using a common protocol by International Agency for Research on Cancer of the World Health Organization (WHO) (Tab. 6.1) (The INTERPHONE Study Group 2010). It has been found that regular phone use seemed to actually decrease the risk of the cancers when the numbers were crunched. But the 10% of participants who reported the greatest amount of time spent on their mobile phones seemed to have a 40% increased risk of glioma. The brain cancer odds ratios (ORs) of 13 countries for regular use 1 year or more in the past were calculated from the authors' supplementary data in the last column in Tab. 6.1. Obviously, the lower the country latitude from 55°41'N on, the smaller the OR and the smaller the cancer risk in the Eurasian continent.

Tab. 6.1 Latitudinal distribution of brain cancer odds ratio (OR) for regular use 1 year or more in the past

Countries	Latitude	Brain Cancer OR*		
		Menigioma(M)	Glioma(G)	M+G
Israel	31°47'N	0.50	0.96	0.73
Australia	35°15'S	0.71	1.05	0.87
Japan	35°40'N	0.91	0.58	0.76
New Zealand	41°19'S	0.65	1.12	0.87
Italy	41°54'N	1.02	0.62	0.82
Canada	45°27'N	2.03	0.74	1.42
France	48°50'N	0.77	1.00	0.87
South UK	51°36'N	0.71	0.80	0.75
Germany	52°30'N	1.04	0.83	0.94
Denmark	55°41'N	1.10	0.80	0.96
North UK	55°57'N	0.67	0.66	0.67
Sweden	59°20'N	0.48	0.74	0.60
Norway	59°55'N	0.80	0.39	0.60
Finland	60°15'N	0.68	0.85	0.76

*ORs adjusted for sex, age, study centre, ethnicity in Israel, and education

Human breast cancer incidence has seasonal patterns that seem to vary among global populations. Oh *et al.* (2010) have collected and examined the aggregate monthly frequency of breast cancer diagnosis for 2,921,714 breast cancer cases diagnosed across 64 global regions over spans from 2 to 53 years. They found that breast cancer is consistently diagnosed more often in spring and fall, both in the Northern and Southern Hemispheres, regardless of presumable menopausal status (≤50, >50). This seasonality is increasingly more prominent as population distance from the equator increases and this latitude dependence is most pronounced among women living in rural areas. Moreover, the overall annual incidence (2005-2006), per 100,000 population, of breast cancer increased as the latitude of population residence increased. These data make it clear that human breast cancer discovery occurs non-randomly throughout each year with peaks near both equinoxes and valleys near both solstices.

The above sunlight effects on cancers suggested that ILILT may be used to prevent from or improve prognosis of cancers according to ILILM in chapter 4.3.

The effort to achieve pain relief in the palliative care of cancer deserves urgent attention. As it has discussed in previous chapter, ILILT has been successfully used to treat headache such as chronic headache, hemicranias and trigeminal neuralgia (Li Q *et al.* 1998a&b) and diabetic peripheral neuropathy (DPN)(Li X *et al.* 2006). It has been found that ILILT might elevate blood β endorphin (Li Q *et al.* 1998a&b) so that it might be also used for pain relief in the palliative care of cancer.

Cancer-related fatigue (CAF) is one of the most prevalent symptoms patients with cancer experience, both during and after treatment. CAF is pervasive and affects patients' quality of life considerably. It is important, therefore, to understand the underlying pathophysiology of CAF in order to develop useful strategies for prevention and treatment. At present, the etiology of CAF is poorly understood and the relative contributions of the neoplastic disease, various forms of cancer therapy, and comorbid conditions (e.g., anemia, cachexia, sleep disorders, depression) remain unclear. In any individual, the etiology of CAF probably involves the dysregulation of several physiological and biochemical systems. Mechanisms proposed as underlying CAF include 5-hydroxytryptamine neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and adenosine-5'-triphosphate (ATP) metabolism, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation. Currently, these hypotheses are largely based on evidence from other conditions in which fatigue is a characteristic, in particular chronic fatigue syndrome and exercise-induced fatigue (Ryan *et al.* 2007). Most symptoms of CAF could be treated with ILILT as discussed in the previous two chapters so that ILILT might be used to treat CAF.

Oral mucositis was always induced by chemotherapy and/or radiotherapy. LLL treatment has been suggested as an effective and safe method to prevent and/or treat (Genot-Klastersky *et al*. 2008). Genot-Klastersky *et al*. (2008) have conducted two clinical trials testing the LLL technique: firstly, as a secondary prevention in patients with various solid tumors treated with chemotherapy who all developed severe mucositis after a previous identical chemotherapy and, secondly, as therapeutic intervention (compared to sham illumination in a randomized way) in patients with hematological tumors receiving intensive chemotherapy and having developed low-grade oral mucositis. In both studies, the LLL treatment was performed with a scanning laser combining a visible 100 mW laser and an IR laser with power from 50, 250, and 500 mW (Traveller(s), made by Biophoton s.a., Toulouse, France) at 60 mW/cm^2 for 33 s per site (each session lasted approximately 6 min). They entered 26 eligible patients in the first study and 36 were randomized in the second study. The success rate was 81% (95%CI = 61-93%) when LLL was given as a preventive treatment. In the second study, in patients with existing lesions, the therapeutic success rate was 83% (95%CI = 59-96%), which was significantly different from the success rate reached in the sham-treated patients (11%; 95%CI = 1-35%); the time to development of grade 3 mucositis was also significantly shorter in the sham-treated patients ($p < 0.001$).Their results strongly support the already available literature, suggesting that LLL is an effective and safe approach to prevent or treat oral mucositis resulting from cancer chemotherapy.

Drizhak *et al.* (1997) have conducted ILELT in the early postoperative period in 32 patients with colorectal cancer with the use of semiconductor laser. It promoted the decrease of the purulent complications prevalence, the lowering of the thromboembolism occurrence risk, the diminution of the endogenic intoxication syndrome expression. Fast rehabilitation of patients was promoted by renewal of antitumoral resistance and immunity.

A recent study showed cancer patients undergoing chemotherapy are nearly 3 times more likely to have insomnia than the general population. In the general population, insomnia has many negative effects, including influencing cardiac and immune functions. Although the full impact of sleep deprivation on cancer patients is unknown at this time, the consequences of insomnia are expected to be similar to or worse than those in the general population. Cancer patients with insomnia might have less response to treatment, and the effect on their immune system might have an impact on disease progression and overall survival. At this point, ILILT might help cancer patients from the viewpoint of insomnia. Xu C *et al.* (2001) have treated 38 patients of insomnia with LHNL at 3.5~4.5 mW for 30 min each time, which was done once each day and ten days each session for two sessions, found serum melatonin increase. Xu C *et al.* (2002a) further treated 128 patients of insomnia with LHNL at 3.5~4.5 mW for 30 min each time, which was done once each day for ten days, and found the polysomnogram was improved.

Most cancer deaths occur when cells in a primary tumor metastasize, yet the mechanisms by which tumor cells acquire metastatic properties remain poorly understood. Ishikawa *et al.* (2008) explored the role of mitochondria in this process by taking mouse tumor cell lines with either a high or low propensity to metastasize and swapping their mitochondrial deoxyribonucleic acid (DNA). Interestingly, the recipient cells acquired the metastatic potential of the cells donating the mitochondrial DNA. In one tumor cell line examined in detail, the mitochondrial DNA conferring high metastatic potential was found to harbor mutations that led to overproduction of reactive oxygen species (ROS), and up-regulation of nuclear genes involved in metastasis. Pretreatment of tumor cells with ROS scavengers reduced their ability to metastasize in mouse models, suggesting a possible avenue for the development of therapies to suppress metastasis. As discussed in chapter 11, treatment with carotene, vitamin A, and vitamin E might increase mortality (Bjelakovic *et al.* 2007), ILILT might rehabilitate oxidant-antioxidant homeostasis (OAH) and then reduce ROS level so that ILILT might reduce tumor's ability to metastasize at least through blood cells flowing in nasal mucosa.

As discussed above, LA and ILILT should be suggested to prevent from cancers and treat cancer related complications. It is supported by many studies on the prophylaxis and therapeutic effects of Mel and polyphenols.

6.1.4 Diabetes

At present over 170 million people are living with diabetes, one of the most common metabolic disorders in humans, across the globe. The rate of new cases of diabetes soared by about 90 percent in the United States in the past decade, fueled by growing obesity and sedentary lifestyles. It was found there is no end in sight to the diabetes epidemic. Newly diagnosed cases of diabetes rose to 9.1 per 1,000 people annually between 2005 to 2007, up from 4.8 per 1,000 from 1995 to 1997. Among patients with diabetes, as much as 90% are living with diabetes type 2 while the remaining manage diabetes type 1 daily with insulin dosage. Recent research into the management of diabetes has found convincing evidence that diabetes type 2 can indeed be prevented and even delayed in high risk individuals through better diet, exercise and lifestyle choices. With a strong medical case for the prevention and control of diabetes, improving care for persons with diabetes as well as for those at high risk has increasingly become an important concern for decision-makers and health-care planners.

It was found that while doctors are using a wider array of newer, more costly drugs to treat diabetes, there is little long-term proof they work better than older, cheaper medications. Some common medications include metformin, which is available generically and also known by the Bristol-Myers Squibb brand name Glucophage. There are newer diabetes drugs in a class called glitazones, which include Takeda's Actos or pioglitazone, and GlaxoSmithKline Plc's Avandia, or rosiglitazone. Avandia has been under fire over safety concerns, and the U.S. advocacy group Public Citizen on Thursday called for it to be banned. GlaxoSmithKline defended its safety. At this point, ILILT might be of precautionary and therapeutic effects on diabetes.

Shen PF *et al.* (2007) randomly divided 100 patients of type 2 diabetes mellitus into two groups, 50 in the control group treated with oral administration of diaformin and 50 in the observation group treated with oral administration of diaformin combined with acupuncture along *du* meridian at the acupoints, *baihui* (GV 20) (Fig. 5.1) and *fengfu* (GV 16) (Fig. 5.4), and found the mood disorder improved and fasting blood glucose, blood glucose 2 h after meal, glycosylated hemoglobin levels decreased in the two groups, with the observation group being better than the control group. This study support ILILT, the acupuncture of LIL of ILILT and the skin-contact electric acupuncture of low frequency pulse on *baihui* and *fengfu* might improve the symptoms in type 2 diabetes patients at least through intranasal *du* meridian according to MIH.

Many groups have investigated the neural effect of acupuncture stimulation along *stomach* meridian of foot *yang-ming* at the *zusanli* acupoint (ST 36) (Fig. 3.3) in the streptozotocin-induced diabetic rats. Neuropeptide Y, a 36-amino-acid peptide, is known to increase appetite. Kim *et al.* (2002) found acupuncture increased cell proliferation and neuropeptide Y levels in the dentate gyrus. Lee JD *et al.* (2004) found neuropeptide Y expression decreased in both the arcuate nucleus and the paraventricular nucleus of the hypothalamus. Jang *et al.* (2003) found acupunctural treatment suppressed the diabetes-induced enhancement in the expression of NOS and neuronal NOS in the dorsolateral periaqueductal gray area. These investigations support ILILT and LA on the *zusanli* acupoint might be effective in improving diabetic conditions at least through intranasal foot *yang-ming* stomach meridian. Li X *et al.* (2006) divided 60 patients of DPN into two groups, 30 in drugs-only group, 30 in ILILT+drugs group, and then treated ILILT+drugs group with low intensity GaInP/AlGaInP diode laser irradiation at 650 nm (LGAL) at 1.5~2.0 mW for 60 min each time, and found the symptoms such as ache and feel, lipid, fibrinogen and electromyography were improved after treatment in these two groups, but ILILT+drugs group was more pronounced than drugs-only group.

Abnormal gastric slow-wave frequencies have been observed in diabetic gastroparesis and are associated with impaired antral motor activity. Fifteen patients with type II diabetes who had had dyspeptic symptoms for more than 3 months were enrolled. Two acupuncture needles were inserted into the subjects' legs along *stomach* meridian of foot *yang-ming* at *zusanli* (Fig. 3.3), and electrical stimulation (2-Hz pulses) was delivered for 30 min. Cutaneous electrogastrography was performed for 30 min at baseline, for 30 min during acupuncture, and for an additional 30 min after acupuncture. Chang *et al.* (2001) have found there was a significant increase in the percentages of normal frequency during and after acupuncture (baseline vs. acupuncture and after acupuncture), the percentage of tachygastric frequency was decreased significantly during and after acupuncture, the dominant frequency was also changed significantly, and there was an increase of serum human pancreatic polypeptide during acupuncture (baseline vs. acupuncture). These results revealed that electrical stimulation at the *zusanli* acupoints could increase the

percentage of normal electrogastrography frequency and decrease the percentage of tachygastric frequency in diabetic patients. The data suggested that LA on the *zusanli* acupoint might regulate of gastric myoelectrical activity in diabetic patients.

Because of both the scale of the problem and the current epidemic growth of diabetes, it is a priority to find new approaches to better understand and treat this disease. Gastrointestinal surgery may provide new opportunities in the fight against diabetes. Conventional gastrointestinal operations for morbid obesity have been shown to dramatically improve type 2 diabetes, resulting in normal blood glucose and glycosylated hemoglobin levels, with discontinuation of all diabetes-related medications. Return to euglycemia and normal insulin levels are observed within days after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes. Recent experimental studies point toward the rearrangement of gastrointestinal anatomy as a primary mediator of the surgical control of diabetes, suggesting a role of the small bowel in the pathophysiology of the disease. Rubino (2008) has further presented available evidence in support of the hypothesis that type 2 diabetes may be an operable disease characterized by a component of intestinal dysfunction, which might called Rubino hypothesis. By altering the gut's production of hormones, gastric bypass surgery may be able to eliminate type 2 diabetes according to Rubino hypothesis. However, scientists worry that this radical operation can also cause dangerously low blood sugar (Couzin 2008). At this point, ILILT might be very potential. According to Rubino hypothesis, type 2 diabetes might be characterized by dysfunctional small intestine, and then dysfunctional *small intestine* meridian of hand *tai-yang* along which there are acupoints around nose that can be irradiated by intranasal LIL. Therefore, ILILT and LA might has therapeutic effects on type 2 diabetes at least through *small intestine* meridian of hand *tai-yang* according to MIH as discussed in chapter 3.7.

The metabolic syndrome is a cluster of cardiovascular risk factors, and visceral adiposity is a central component that is also strongly associated with insulin resistance. Both visceral obesity and insulin resistance are important risk factors for the development of type 2 diabetes. It is likely that adipose tissue, particularly in the intra-abdominal depot, is part of a complex interplay involving several tissues and that dysregulated hormonal, metabolic and neural signalling within and between organs can trigger development of metabolic disease. Eriksson (2007) has put forward an attractive hypothesis that many factors leading to insulin resistance are mediated via the generation of abnormal amounts of ROS. There is much evidence supporting that detrimental effects of glucose, fatty acids, hormones and cytokines leading to insulin resistance can be exerted via such a common pathway. Eriksson (2007) mainly focused on metabolic and other 'stress' factors that affect insulin's target cells, in particular adipocytes, and highlighted oxidative stress as a potential unifying mechanism by which these stress factors promote insulin resistance and the development and progression of type 2 diabetes. At this point, ILILT might have precautionary and therapeutic effects on type 2 diabetes at least through its antioxidant action on blood cells flowing in nasal mucosa as discussed in chapter 10.

The therapeutic effect of antioxidant action on diabetes mellitus has been supported by a population-based, prospective cohort study (Harding *et al.* 2008). Epidemiologic studies suggest that greater consumption of fruit and vegetables may decrease the risk of diabetes mellitus, but the evidence is limited and inconclusive. Plasma vitamin C level is a good biomarker of fruit and vegetable intake. It has been found higher plasma vitamin C level and, to a lesser degree, fruit and vegetable intake were associated with a substantially decreased risk of diabetes. These findings

highlight a potentially important public health message on the benefits of a diet rich in fruit and vegetables for the prevention of diabetes.

As discussed above, LA and ILILT should be suggested to treat diabetes related complications.

6.2 Ageing

The world is ageing. With people living longer and fewer children being born, the absolute number of older people is increasing. Today, worldwide, there are some 600 million persons aged 60 and over; this total will double by 2025 and will reach virtually two billion by 2050 when there will be more people aged 60 and over than children under the age of 15. The vast majority of older persons will be living in developing countries which are often least prepared to meet the challenges of rapidly ageing societies. In our developing country, there are some 153 million persons aged 60 and over; this total will double by 2025 and will reach virtually 450 million by 2050.

Increased longevity is a triumph for public health and the result of social and economic development. Unfortunately however, the rapidity of population ageing is expected to continue to outpace social and economic development in developing countries. In other words, developing countries will become old before they become rich while industrialized countries became rich while they were growing old.

As we age, all too many aspects of our physique deteriorate--not just at the macroscopic scale of our limbs and organs, but also at the single-cell level. Nuclear pores allow for the transport of proteins and nucleic acids across the nuclear envelope, both from the cytoplasm to the nucleus and in the reverse direction, and are essential in normal trafficking processes involved in gene expression, cellular homeostasis, and growth. Nuclear pores are complexes of many individual protein components, some of which are extraordinarily long-lived. D'Angelo *et al.* (2009) have examined the characteristics of these complexes in aging postmitotic cells from *Caenorhabditis elegans* and from rodents, and find that as cells grow old, the lack of renewal of some nuclear pore components leads to the gradual deterioration of nuclear pore function. As a consequence, the nuclei of older cells become leaky, and proteins that would normally be excluded from the nucleus can be found within it.

There are various kinds of ageing. Among them, successful aging is defined as the balance of three components: absence of disease and disease-related disability, high functional capacity, and active engagement with life (Rowe *et al.* 1987). Rizzo *et al.* (2005) found that human longevity may protect toward an age-related decline. Splitting the whole study group into subgroups according to age, long-lived subjects had oxygen volume (VO_2) consumed in liters per minute, carbon dioxide volume (VCO_2) expired in liters per minute, Rq as the ratio of VCO_2 to VO_2 significantly higher than aged subjects but lower than adult subjects. In addition, long-lived subjects had total volume of expired air and resting metabolic rate greater than aged subjects but not different from ones found in adults. Ng TP *et al.* (2009) have examined whether a broad multidimensional definition of successful aging has good construct validity and identified a wider range of predictors that are relevant for multifaceted interventions. They found successful aging was significantly ($p < 0.05$) associated with age (OR = 0.90), female gender (OR = 1.37), ≧6 years of education (OR = 2.31), better housing (OR = 1.41), religious or spiritual beliefs (OR = 1.64),

physical activities and exercise (OR = 1.90), and low or no nutritional risk (OR = 2.16). The bigger the OR, the greater the contribution. Obviously, the contribution of the education to the successful aging is the greatest among the discussed interventions. In contrast to findings based on more restricted biomedical definitions of successful aging, a multidimensional definition of successful aging identified more variables including demographic status, psychosocial support, spirituality, and nutrition as salient determinants.

Obviously, the successful aging is in aging-specific homeostasis (AgSH). With ageing far from AgSH comes an increased risk of developing chronic diseases and disability. Older people with disabilities, such as the grandfather who suffers a stroke from uncontrolled hypertension, will need help just getting through their daily tasks – help that is most often provided by families already stretched for time and resources. In order to prepare for unprecedented population ageing now, it is of utmost importance that health systems in developing countries are prepared to address the consequences of these demographic trends. So does every family.

As discussed above, hypertension is a chronic condition that can be controlled and managed. Dealing with the increasing burden of chronic diseases requires opportunities for health promotion and disease prevention in the community as well as disease management within health care services, which addresses key concerns such as comprehensive and integrated care, continuum of care, and physical and social environment. Many chronic diseases and the associated disabilities that affect the later part of a person's life span along with their economic and human costs can be prevented. But prevention requires reaching the individual before the disease takes hold and that means intervening at earlier stages of life, i.e. taking a life course approach to active and healthy ageing which the WHO defines as *the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age.*

In addition to healthful lifestyle, drugs might be one of the choices. However, the side effects of drugs might prevent their long use. It has been shown the long-term use of ibuprofen and possibly other nonsteroidal anti-inflammatory drugs may help protect against AD (Van Dam *et al.* 2010), but it is still not clear if the risks outweigh the potential benefits. It has been shown the regular, long-term use of nonsteroidal anti-inflammatory drugs is associated with an increased risk of ulcers and potentially life-threatening stomach bleeding, especially in people over the age of 65.

Senescence is the age-related deterioration of the phenotype, explained by accumulation of mutations, antagonistic pleiotropy, free radicals or other mechanisms. Møller (2007) have investigated patterns of actuarial senescence in a sample of 169 species of birds in relation to latitude and migration, by analysing longevity records adjusted for sampling effort, survival rate and body mass. Senescence might decrease at low latitudes because of elevated adult survival rates and generally slow life histories (Wikelski *et al.* 2003). Alternatively, the rate of senescence might increase at low latitudes because of the greater impact of biological interactions such as parasitism, predation and competition on fitness through differential effects of age-specific mortality (e.g. because immunologically naïve young individuals and immuno-senescent old individuals might die more frequently than individuals belonging to intermediate age classes). Bird migration entails extensive exercise twice annually, with migrants spending more time in benign environments with little abiotic mortality than residents, migrants having higher adult survival rate and lower annual fecundity than residents, and migrants suffering more from the consequences of oxidative stress than residents. Finally, Møller (2007) found that the rate of senescence increased with latitude, and decreased with increasing migration distance. The sunlight

intensity decreases with latitude. One of the purposes of the annual second bird migration is for more intensive sunlight. In decaying sunlight, bird beak is similar to human nose so that the sunlight effects on birds are similar to the sunlight effects on human as discussed in chapter 4.3. We have found that the lifespan decreased with latitudinal increase in the low latitude region in China and in Africa (Liu CY 1995). Møller (2007)'s finding and ours suggested that sunlight may extend the longevity if the aging is far from AgSH. In other words, LLL can be used to inhibit aging far from AgSH.

LLL may extend the longevity if the aging is far from AgSH. Short exposure (3 or 4 h) to a broad-band light (wavelength > 500 nm) one to three times weekly enhances the proliferation rate of human diploid fibroblasts in culture. Parshad *et al.* (1977) further found the intermittent exposure to the same light extends lifespan of human diploid fibroblasts in culture. Litwin (1972) found an increased life span, but not enhanced proliferation rate in human embryonic lung fibroblasts, was established when the cells were irradiated with cool fluorescent light for 2 h daily over a period of 150 days: irradiated cells went through 70 divisions, while nonirradiated cells went through 53 divisions . Chernova *et al.* (2002) have studied the effect of the low-intensity impulse laser radiation (LIIL) on the life span of Drosophila melanogaster. The flies at various stages of their life (larvae and imago) were exposed to LIIL. The estimation of the effect of LIIL was carried out on the basis of the analysis of the basis parameters of aging. They found out increasing as well as shortening effects of the life span. The direction of the effect depends on parameters of radiation, stage of development of irradiated individuals and their sex.

As pointed out in chapter 3, LA and ILILT, two kinds of fPBM, might extend lifespan by rehabilitating biosystems far from AgSH. The free radical theory of aging assumes that oxidative stress is a major cause of aging. Free radicals damage the homeostatic mechanisms of an organism so that "the accumulation of changes in the cells and tissues that increase the risk of death" arises. Aging is the progressive destruction of functional elements in the cells of the organism caused by oxidative stress, which diminishes its homeostatic capacity (and increases the risk of death). (Novoseltsev *et al.* 2001). On the other hand, ILILT might have antioxidant effects at least through blood cells flowing in nasal mucosa as discussed in chapter 10 so that it might extend lifespan.

Senescence-accelerated mouse (SAM) strains are used as animal models for gerontological research. Male 8-month-old SAM prone 10 (SAMP10) and its homologous SAM resistance 1 (SAMRl) have been used to study the effects of acupuncture at the acupoints: *shanzhong* (CV17) (Fig. 6.1), *zhongwan* (CV12) (Fig. 6.1), *qihai* (CV6) (Fig. 6.1), *zusanli* (ST36) (Fig. 3.3) and *xuehai* (SP10) (Fig. 3.4). The cDNA arrays have provided data of 588 genes to define transcriptional patterns. It has been found that acupoints stimuli could completely or partly reverse some genes expression profiles in hippocampus with aging. Simultaneously, some genes not related with brain aging were affected by acupuncture as well. Meanwhile, non-acupoint had some effect on aging-unrelated genes expression and little or negative effect on aging-related genes. It has been concluded that the acupuncture could be a potential intervention to retard molecular events with aging in mammals (Ding X *et al.* 2006). This research suggested that LA on the acupoints, *shanzhong*, *zhongwan*, *qihai*, *zusanli* and *xuehai*, might retard molecular events with aging.

6.3 Development

There is development-specific homeostasis (DeSH). A development may be far from DeSH under pathological conditions. Early puberty onset is associated with hormone-related cancers (Günther *et al.* 2010). Moreover, the existence of a period of reduced learning coinciding with the onset of puberty in mice is well characterized (Shen H *et al.* 2010). Obviously, the earlier the puberty onset, the more difficult the learning.

Günther *et al.* (2010) have investigated the association of protein intake in early and mid-childhood with the ages at take-off of the pubertal growth spurt (ATO), peak height velocity (APHV), and menarche in girls and voice break in boys using data from the longitudinal Dortmund Nutritional and Anthropometric Longitudinally Designed Study. Among participants who provided 3-d weighed dietary records at 12 mo, 18-24 mo, 3-4 y, and 5-6 y, 112 had sufficient anthropometric measurements between 6 and 13 y to allow estimation of ATO. Life-course plots were used to identify critical periods of total, animal, and vegetable protein intake (percentage of total energy intake) for pubertal timing. At these ages, the association between tertiles of protein intake (T1-T3) and the outcomes was investigated using multiple linear regression analysis. A higher total and animal protein intake at 5-6 y was related to an earlier ATO. In the highest tertile of animal protein intake at 5-6 y, ATO occurred 0.6 y earlier than in the lowest [(mean, 95% CI) T1: 9.6, 9.4-9.9 vs. T2: 9.4, 9.1-9.7 vs. T3: 9.0, 8.7-9.3 y; P-trend = 0.003, adjusted for sex, total energy, breast-feeding, birth year, and paternal university degree]. Similar findings were seen for APHV (P-trend = 0.001) and the timing of menarche/voice break (P-trend = 0.02). Conversely, a higher vegetable protein intake at 3-4 and 5-6 y was related to later ATO, APHV, and menarche/voice break (P-trend = 0.02-0.04). These results suggest that animal and vegetable protein intake in mid-childhood might be differentially related to pubertal timing.

The light plays an important role in human reproductive development. Women with varying degrees of visual impairment appear to have altered reproductive function compared to sighted women. These differences have been attributed in part to differences in light exposure between the sighted and the blind. Flynn-Evans *et al.* (2009) have investigated whether differences exist in reproductive measures among blind women with at least light perception (LP) compared to women with no perception of light (NPL). They found NPL women reported an earlier menarche (mean age, 12.16±1.53 y) than LP women (mean age, 12.46±1.57 y). The adjusted odds ratio (OR) for each increasing year of menarche among NPL women compared to LP women, was 0.88 (95% confidence intervals [CI]: 0.81-0.96). When those women NPL from birth were compared to all others, the adjusted odds ratio was strengthened (OR: 0.80, 95% CI: 0.68-0.94). When they examined the association between age at onset of NPL and age at menarche, they found a significant positive association with earlier menarche being associated with an earlier age category of loss of light perception (test for trend $p < 0.01$). Obviously, lack of light perception may affect reproductive development in women.

Cons *et al.* (1975) have studied developmental patterns of follicle-stimulating hormone (FoSH) and luteinizing hormone (LH) in female rats deprived of light before puberty. Plasma FoSH and LH levels were examined in female rats reared in the dark at different ages from birth until sexual maturation to investigate whether, and to what extent, external factors such as light, influence gonadotropin levels during development. Control animals were raised in diurnal lighting consisting of 12 hours of light and 12 hours of dark. Light deprivation did not eliminate the characteristic peak of gonadotropins seen in early postnatal development but significantly

increased levels of FoSH and slightly decreased levels of LH (except for a transient rise at day 12). Constant darkness tended to lower whole body, ovarian and pituitary weights but to increase pineal weight. Whereas the time of eye-opening was the same in control and light-deprived animals, puberty (as judged by vaginal opening and first ovulation) was delayed in animals raised in the dark. The data suggest that environmental light has a mediating action on patterns of gonadotropin release, particularly on FoSH, during prepuberal development.

Grivas *et al.* (2006) found age at menarche shows a decreasing trend as the geographic latitude approaches approximately the 25–30 degrees and then increases again toward 0 degrees (near the equator). This indicated that solar radiation might promote DeSH establishment when the latitude is lower than 25–30 degrees. However, the exposure to direct solar radiation should be controlled. Salem *et al.* (1987) have studied the effect of exposure to direct solar radiation on the semen characteristics of the male rabbit. Three groups of cross-bred bucks (Baladi X standard breeds) were exposed to solar radiation for three hours per day during an 8-week experimental period in June and July and were compared with a control subgroup of the same age. Each subgroup (experimental and control) comprised 10 bucks, totalling 60 bucks. The effects were determined and assessed during the 28-week period following the experiment. The exposure to solar radiation at 5 or 12 weeks of age caused a delay in the onset of puberty. In all three groups, the concentration of sperms and the fructose content were decreased. There was a marked increase in the proportion of abnormal or dead sperms and in the methylene blue reduction time. The young animals were most affected by the exposure.

The above discussion indicated that there may be effects of LLL on development far from DeSH according to chapter 5. Mester *et al.* (1991) have studied the photochemical effect of LIL on the maturation and regeneration of olfactory-immature estrus day 15 (E15) and olfactory-mature estrus day 22 (E22) of rat fetuses. Neuritic outgrowths of olfactory bipolar receptor cells were quantified in olfactory neuroepithelial explants. Explants in the experimental groups were irradiated with a He-Ne laser. The parameters of neuritic outgrowth in E15 fetuses showed a significant increase of 30% to 50% vs. the control with a single laser irradiation at 0.5 J/cm^2. The rate of neuritic outgrowth observed in the E22 fetuses was less than in the E15 fetuses. The parameters of neuritic outgrowth in E22 fetuses showed a significant and substantially greater percentage increase than in the E15 fetuses with daily laser irradiations at 0.05 and 0.5 J/cm^2 when compared to the control.

6.4 Influenza

Influenza is an acute viral disease which mainly affects the respiratory tract and occurs in all age groups with yearly epidemics or influenza pandemic during the cold season. In the United States, seasonal influenza epidemics account for > 200,000 hospitalizations and > 30,000 deaths annually. More than 90% of the deaths are in the elderly. Three influenza pandemics occurred in the last century — A/H1N1 from 1918 through 1919, A/H2N2 from 1957 through 1963, and A/H3N2 from 1968 through 1970 (Miller *et al.* 2009). There has been a pandemic potential of a swine-origin influenza A (H1N1) virus characterized by a unique combination of gene segments that had not been identified among human or swine influenza A viruses (Garten *et al.* 2009) . A basic method of protecting the population against influenza, which is also the cheapest, is vaccination of as many people in the population as possible, especially those high-risk patients,

but it was susceptible to failure resulting from antigenic changes. Moreover, seemingly, from one influenza season to the next, the efficacy of the leading antiviral influenza drug has been lost because of resistance.

Human nasal mucosa, olfactory nerve and intranasal microvascular blood (MOB) in homeostasis can resist influenza, but MOB far from homeostasis is very susceptible to influenza (Liu TCY *et al.* 2010b). Acute cooling of feet might cause MOB far from homeostasis and then lead to the onset of common cold symptoms (Johnson *et al.* 2005). Chilling of the feet in cold water (12 ± 1°C) has been previously reported to cause an intense vasoconstriction of both the cutaneous and upper airway blood vessels (Drettner 1961) and the vasoconstriction of the upper airways has been proposed as a mechanism that reduces respiratory defence against infection (Mudd *et al.* 1919, Eccles 2002) due to stress-induced immunosuppression (Wheway *et al.* 2005). Chilling causes a pronounced constriction of the blood vessels in the nose and shuts off the warm blood that supplies the white cells that fight infection(Johnson *et al.* 2005). When common cold viruses are circulating in the community, a proportion of subjects will have sub-clinical infections, and chilling of these subjects may cause vasoconstriction in the upper airway epithelium and conversion of a sub-clinical to a clinical infection.

There are sunlight effects on influenza. Finkelman *et al.* (2005) have provided a descriptive analysis of laboratory-confirmed influenza surveillance data by type and subtype (A/H3N2, A/H1N1, and B) for 19 temperate countries in the Northern and Southern hemispheres with latitudes ranging between 67°N and 34°S from 1997 to 2005, compiled from a public database maintained by WHO (FluNet). For H3, H1 and B and in all countries, epidemics were primarily confined to the winter months. There was a positive correlation between increased distance from the equator, based on the absolute value of the latitude of the geographic center of the country, and later occurrence of epidemics for both H3 (regression between mean epidemic week and latitude, $r^2 = 0.49$, $P<0.001$) and H1 ($r^2 = 0.63$, $P<0.001$) ; however, no correlation was observed for B ($r^2 = 0.093$, $P = 0.10$).

The olfactory bulbs have been proposed as first portal for Venezuelan equine encephalomyelitis (VEE) virus entry into the central nervous system (CNS). In male albino mice infected with the VEE virus and exposed to bright light at 2500 lux with a 12 h light : 12 h dark photoperiod, Medina-Leendertz *et al.* (2001) have observed a significant increase in the levels of Mel in the olfactory bulb. The increase in Mel content could represent one of the mechanisms of defense against the viral attack.

The sunlight effects on influenza and the bright light effects on VEE virus suggested that there might be effects of LLL on influenza. Savtsova *et al.* (1990) have studied the influence of two schemes of LA on some cell-mediated and humoral immunity characteristics of mice, as well as on their nonspecific antiviral resistance, in acute experimental influenza infection. They found the use of both schemes considerably decreased the severity of infection, enhanced the activity of lymphocytes of infected mice in the graft versus host reaction, the O2-producing activity of alveolar macrophages and modulating the ratio of antihemagglutinins and nonspecific antiviral inhibitors in the blood serum.

As secreted factors, the type I interferons (IFNs) regulate a range of immune responses. All cells can respond to type I IFNs through the type I IFN receptor. IFN-α and –β increase expression of antiviral proteins through IFN receptor, thereby amplifying antiviral resistance, which leads to the generation of an "antiviral state" (García-Sastre *et al.* 2006) . LIL may promote

INF production. Marked induction was found at various He-Ne laser radiation power (1, 6-7, 20 mW) and at various radiation exposures: from 1 s to 1 min both for single (up to 512 units/ml) and repeated (up to 1024 units/ml) effects on leukocytes of the donor blood (Leonova *et al.* (1994). The major part of IFN was shown to be acid-labile and a lesser part was acid-stable IFN-α and -γ.

According to chapter 3 and the above discussion, LA and ILILT treatment might promote the homeostasis establishment of MOB so that LA and ILILT might be used for prophylaxis or treatment on influenza (Liu C *et al.* 2009, Liu TCY *et al.* 2010b).

6.5 Miscellaneous diseases

6.5.1 Olfactory dysfunction

Loss of smell sensation is a common finding associated with many diseases. The investigation of smell loss has long been neglected because the lack of olfaction has seldom been considered a major disability, and easy-to-use quantitative tests of olfactory function applicable to clinical assessment have not been generally available. However, olfactory deficits can produce significant impairment in the quality of life. Olfactory dysfunction generally is classified as either a peripheral conductive disorder caused by interference with the access of odonants to the olfactory receptors in the sinonasal tract or as a central sensonineural disorder resulting from injury to the olfactory receptors (within the olfactory mucosa); the olfactory bulb or tract; or related parts of the CNS such as the prefrontal lobe, septal nuclei, amygdala, and temporal lobe (Li C *et al.* 1994).

The olfactory bulbs have been proposed as first portal for VEE virus entry into the CNS. In male albino mice infected with the VEE virus and exposed to light at 2500 lux with a 12 h light : 12 h dark photoperiod, Medina-Leendertz *et al.* (2001) have observed a significant increase in the levels of melatonin in the olfactory bulb. The increase in melatonin content could represent one of the mechanisms of defense against the viral attack. This might hold for ILILT because ILILT can also increase MEL level.

Sinonasal tract disease is one of the common causes of olfactory disturbance. The cause of olfactory deficits among patients with nasal and pananasal sinus disease is most likely nasal airway obstruction. Any cause of bilateral obstruction can decrease smell sensations by limiting air flow to the olfactory receptors. Besides the obstructive effect, lesions in the upper nasal vault and/or cnibniform plate region can also directly damage the olfactory epithelium and olfactory neurons. The common peripheral sinonasal tract causes of olfactory deficits include infections, tumors, allergic rhinosinusitis, and congenital on developmental abnormalities (Li C *et al.* 1994). As it has been reviewed in chapter 4, many Russian have found the therapeutic effects of ILILT on the local inflammation. Therefore, there might be therapeutic effects of ILILT on sinonasal tract disease induced olfactory dysfunction. The acupoint *yingxiang* (LI 20)(Fig. 3.3), has been often used in acupuncture treatment of olfactory dysfunction. LA might promote the therapeutic effects of olfactory dysfunction.

Numerous CNS disorders may be associated with olfactory dysfunction. The most common types fall into the categories of degenerative neuropsychiatnic disorders, hereditary conditions, trauma, and neoplasms. These CNS disorders include AD, PD, Huntington's Disease, Korsakoff's psychosis, schizophrenia and congenital Anosmia. There are also reports of olfactory dysfunction

with major depression, hypochondniasis, and multiple sclerosis. Although the pathogenesis of olfactory dysfunction in these disorders is still unclear, it appears that a central mechanism rather than a peripheral one is operational (Li C *et al.* 1994). According to MIH in chapter 3.7.1, *large intestine* meridian of hand *yang-ming*, *stomach* meridian of foot *yang-ming*, *du* meridian and *yin-jiao* meridian running through brain might mediate the therapeutic effects of ILILT on cerebral diseases. There have been therapeutic effects of ILILT on brain diseases such as insomnia, intractable headache, AD, PD, PSD, ache in head or face, migraine, DPN, cerebral thrombosis, cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, CP and mild cognitive impairment. Therefore, there might be therapeutic effects of ILILT on CNS disease induced olfactory dysfunction.

6.5.2 Myopia

Myopia is a highly prevalent ocular condition, the major symptom of which is blurred distance vision. The primary structural cause of myopia is increased axial length of the eye, and a significant number of myopes (~15% of myopes or 3% of the general population) have high degrees of myopia and excessively long eyes (>25.5 mm). The outer coat of the eye, the sclera, becomes pathologically thin in highly myopic eyes, the resultant biomechanical instability in turn resulting in damage to the retina and choroid, causing irreversible loss of vision.

The mammalian sclera is a typical fibrous connective tissue, predominantly constructed of heterotypic collagen fibrils rich in type I collagen. Scleral biomechanical changes in pathological myopia are well documented both in humans and in animal models, with the sclera of myopic eyes demonstrating increased extensibility with increasing levels of myopia. It is now widely accepted that although the thinner sclera in high myopia contributes to increased extensibility, changes in the biochemical structure of the sclera make an independent contribution to this increased extensibility. Reduced extracellular matrix accumulation in the sclera of myopic eyes leads to increased ocular extensibility and is related to reduced levels of scleral transforming growth factor(TGF) β. Jobling *et al.* (2009) have shown that although reduced scleral TGF-β is a major contributor to the extracellular matrix remodeling in the myopic eye, it is the resulting increase in scleral stress that dominates the competing TGF-β effect, and, hence, producing a larger population of contractile cells in the myopic eye.

There were sunlight effects on myopia. Myopia in Israel was associated with birth during summer months (Mandel *et al.* 2008). A disproportionate number of UK high myopes were born in summer or autumn rather than in winter (McMahon *et al.* 2009). Myopia progression rates were slower during summer than during winter (Fulk *et al.* 2002). Ocular growth was also slower in the summer; but that trend, in most cases, was statistically significant only for changes in vitreous chamber depth and not for axial length(Fulk *et al.* 2002). Higher levels of total time spent outdoors, rather than sport per se, were associated with less myopia and a more hyperopic mean refraction, after adjusting for near work, parental myopia, and ethnicity (Rose *et al.* 2008). These Australian data were supported by Dirani *et al.* (2009) in Singapore teenage children.

In decaying sunlight, chick beak is similar to human nose so that the sunlight effects on chicken are similar to the sunlight effects on human as discussed in chapter 4.3. The sunlight effects on myopia were further supported with the sunlight effects on the chick model of deprivation myopia. It has been shown that sunlight or bright indoor light can inhibit the

development of deprivation myopia in chicks. Ashby *et al.* (2010) have tested how bright light interacts with compensation for imposed optical defocus. Chicks monocularly wore either -7 D or +7 D lenses for a period of five days, either under normal laboratory illuminance (500 lux) or high ambient illuminance (15,000 lux). They found high illuminance levels reduce the rate of compensation for negative lenses and enhance the rate for positive lenses, but does not change the set-point of emmetropisation. The retardation of myopia development by light is partially mediated by dopamine, at least in the case of deprivation myopia.

There is vision-specific homeostasis (VSH). Myopia in children is far from VSH. The sunlight or bright light effects on myopia indicated that LA or ILILT might be used to treat children with myopia to promote VSH establishment.

6.5.3 Withdrawal symptoms

Withdrawal symptoms are uncomfortable physical or mental changes that happen when the body is deprived of the alcohol, nicotine or drugs that it is accustomed to getting. Withdrawal symptoms only occur if a person has regular, heavy use of a drug, nicotine or alcohol. Withdrawal symptoms can last a few days to a few weeks and may include nausea or vomiting, sweating, shakiness, and anxiety. Withdrawal from all drugs of dependence appears to lead to mood disturbances although the extent to which these are due to the pharmacological actions of the drugs or to other physiological or psychological processes is unclear. Sleep disturbance is also common, although again direct links with the pharmacological actions of the withdrawn drug are yet to be established. Withdrawal from alcohol, benzodiazepines and opiates is often associated with somatic symptoms. In the former two cases, these can involve sweating, tremor and occasionally seizures. Perceptual disturbances have also been reported. In the case of opiates, flu-like symptoms are often reported, including muscle aches and gastric disturbances. In the case of nicotine, heightened irritability has been established as a direct pharmacological withdrawal effect. Characterization of stimulant withdrawal is still uncertain. There is little evidence of somatic symptoms but depression may occur as a result of a physiological rebound. There is also uncertainty over what role pharmacological withdrawal symptoms play in maintaining compulsive use (West *et al.* 1994).

Mirzaii-Dizgah *et al.* (2009) have studied the effects of LLLT on naloxone-induced withdrawal signs of morphine-dependent rats. A continuous GaAlAs laser irradiation at 830 nm and 227 mW/cm^2 was applied to the shaved skin of the animal skull at the cross-point between interaural line and midline of head for 55 s. They showed that the LLLT which applied immediately or 15 min prior to naloxone injection significantly decreased total withdrawal score. These results suggest that LLLT prior to naloxone injection attenuates the expression of withdrawal signs in morphine-dependent rats.

All withdrawal symptoms can be classified in two groups: CNS effects and autonomic dysfunction (Ista *et al.* 2007). ILILT might rehabilitate CNS through *large intestine* meridian of hand *yang-ming*, *stomach* meridian of foot *yang-ming*, *du* meridian and *yin-jiao* meridian according to MIH as has been pointed in the last section for olfactory dysfunction. Autonomic nervous system (ANS) is also a pathway mediating ILILT. Therefore, there might be therapeutic effects of ILILT on withdrawal symptoms.

For smoking cessation, therapeutic effects of LIL on the acupoints, *shenmen* (HT 7)(Fig. 3.3), *daling* (PC 7)(Fig. 3.3) and *hegu* (LI 4)(Fig. 3.4), have been found in a double blind, placebo controlled randomized trial and semi structured interviews (Kerr *et al.* 2008) .

Seventy patients with heroinism were randomly divided into a treatment group (n= 35) and a control group (n=35). A 10-day decrescendo therapy of methadone and acupuncture at the acupoints of the *du* meridian, *baihui*(GV 20)(Fig. 5.1), *dazhui* (GV 14) (Fig. 5.2), *shendao* (GV 11) (Fig. 5.2), *lingtai* (GV 10) (Fig. 5.2), *zhiyang* (GV 9) (Fig. 5.2) and *mingmen* (GV 4) (Fig. 5.2), were adopted in the treatment group, while the 10-day decrescendo therapy of methadone was simply performed in the control group. Zeng X *et al.* (2005) found the obvious difference in scores of abstinence symptoms on the first, second, fifth, sixth, seventh, eighth, ninth and tenth day in the treatment group was superior to those in the control group, particularly for such symptoms as perspiration, anxiety and pain in the muscle and bone, which suggested acupuncture at points of the *du* meridian has an auxiliary therapeutic effect on abstinence symptoms of heroinism, which can effectively help alleviate the abstinence symptoms.

The above discussion supports that LA or ILILT might improve withdrawal symptoms. It is supported by many studies on the therapeutic effects of Mel and polyphenols.

6.5.4 Renal failure

Renal failure is the sudden or progressive loss of kidney function. When the kidneys cannot function normally, waste products and excess water accumulate throughout the body. Causes of renal failure include vascular problems as well as trauma, infection, or exposure to chemicals or medications. The kidneys, two small bean-shaped organs, are located on both sides the spine, below the ribcage. Blood flow through the kidney normally allows the kidney to excrete wastes, concentrate urine, and conserve electrolytes (mineral salts). Any condition that significantly interferes with blood flow to the kidney can result in renal failure. There are three stages of renal failure: acute renal failure, chronic renal failure; and end-stage renal failure. The kidney cannot filter the waste and water adequately in any of these stages, but the severity of the condition varies widely. End-stage renal failure is the last stage of chronic renal failure and often requires dialysis or kidney transplantation as life-saving measures. In general, renal failure results when weak blood flow prevents the kidneys from filtering the blood properly.

Oxidative stress has emerged as a constant feature of chronic renal failure (CRF) (Vaziri 2004). The presence of oxidative stress in CRF is evidenced by an overabundance of lipid, carbohydrate, and protein oxidation products in the plasma and tissues of uremic patients and animals. We recently have shown that oxidative stress in CRF animals is associated with and, in part, owing to up-regulation of superoxide-producing enzyme, nicotinamide-adenine dinucleotide phosphate (NAD(P)H) oxidase, and down-regulation of superoxide dismutase (SOD). The functional significance of these findings was confirmed by favorable response to administration of the cell-permeable SOD-mimetic agent, tempol, in CRF rats. Oxidative stress in CRF plays an important role in the pathogenesis of the associated hypertension (oxidation of NO and arachidonic acid and vascular remodeling), cardiovascular disease (oxidation of lipoproteins, atherogenesis), neurologic disorders (nitration of brain proteins, oxidation of myelin), anemia (reduction of erythrocyte lifespan), inflammation (nuclear factor kappa B activation), fibrosis, apoptosis, and accelerated aging. The CRF-induced oxidative stress is aggravated by diabetes,

uncontrolled hypertension, and autoimmune diseases, which independently increase production of reactive oxygen intermediates, and frequently are associated with CRF. In addition, dialysis treatment (blood interaction with dialyzer membrane and dialysate impurities), acute and chronic infections (blood access infection, hepatitis, and so forth), and excessive parenteral iron administration intensify CRF-associated oxidative stress and its adverse consequences in patients with end-stage renal disease. The problem is compounded by limited intake of fresh fruits and vegetables (K(+) restriction), which contain numerous natural phytochemicals and antioxidant vitamins.

There are sunlight effects on CRF. Uraemic patients with CRF on regular haemodialysis have a mean serum 25-hydroxyvitamin D [25(OH)D(3)] concentration comparable to controls and that they also exhibit a seasonal variation with a significant reduction during the winter months (Cook *et al.* 1977). de Castro *et al.*(1998) have studied seasonal variation of blood pressure in maintenance hemodialysis of sixteen patients with CRF, and found that the blood pressure has a seasonal variation with higher pressures in fall and winter than in summer. Argilés *et al.* (1998) determined the influence of climate on blood pressure in 53 patients with end-stage renal disease treated with hemodialysis in Montpellier, France. In patients with end-stage renal disease treated with hemodialysis, blood pressure varies seasonally, with higher values in the winter and lower values in the summer (Argilés *et al.* 1998).

According to chapter 4.3, the sunlight effects on CRF suggested that ILILT and LA might have therapeutic effects on renal failure.

6.6 Transmission Efficiency of Therapeutic Information to the Target

There is very small part of oral drug diffused to the target so that the target dose might not be enough to have therapeutic effect but the non-target dose might produce side effects. At this point, the concept of controlled drug delivery has been put forward and developed to obtain specific release rates or spatial targeting of active ingredients at the target. Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs and increased patient comfort and compliance. Polymeric microspheres are ideal vehicles for many controlled delivery applications due to their ability to encapsulate a variety of drugs, biocompatibility, high bioavailability and sustained drug release characteristics (Varde *et al.* 2004). Bioadhesive polymers as platforms for oral controlled drug delivery has been studied extensively in the last decade and applied to improve the performance of these drug delivery systems. Recent advances in polymer science and drug carrier technologies have promulgated the development of novel drug carriers such as bioadhesive microspheres that have boosted the use of "bioadhesion" in drug delivery. The spectrum of potential applications of bioadhesive microspheres in controlled drug delivery ranged from the small molecules, to peptides, and to the macromolecular drugs such as proteins, oligonucleotides and even DNA. The development of mucus or cell-specific bioadhesive polymers and the concepts of cytoadhesion and bioinvasion provide unprecedented opportunities for targeting drugs to specific cells or intracellular compartments (Vasir *et al.* 2003).

As has been discussed in chapter 3, the therapeutic information of ILILT might be transmitted

directly to intranasal dysfunctional ANS or blood cells or from intranasal acupoints to the target through meridian, and LA might be transmitted from intranasal acupoints to the target through meridian. The transmission efficiency of therapeutic information of ILILT or LA to the target is obviously more effective than the one of oral drugs. Moreover, it might even be more effective than the one of the controlled drug delivery.

Moreover, the production of drugs or bioadhesive microspheres is high energy-dependent, but the energy consumption of ILILT or LA is very low. ILILT or LA is an ideal precautionary/therapeutic approach to treat chronic diseases.

7 Cell Basic of Photobiomodulation

Cells having their chromosomes located in a nucleus and separated from the rest of the cell, so called eukaryotic cells, appeared on earth about two billion years ago. Organisms consisting of such cells can either be unicellular, such as yeasts and amoebas, or multi-cellular such as plants and animals. The human body consists of a huge number of cells, on the average about one billion cells per gram tissue. Each cell nucleus contains our entire hereditary material, deoxyribonucleic acid (DNA), located in 46 chromosomes (23 pairs of chromosomes). Cells constitute human body. As pointed out in next chapter, photobiomodulation (PBM) is a cellular rehabilitation so that cytology is also the foundation of PBM. In this chapter, cytological basis will be outlined.

7.1 Cell Structure

A cell is enclosed by a plasma membrane and contains a membrane-bound nucleus and organelles such as mitochondrion (MIT), ribosome, endoplasmic reticulum (ER) and lysosome:

1. Cell Membrane It is composed of protein and lipid (fat) molecules (Fig. 7.1). It acts as a boundary layer to contain the cytoplasm (fluid in cell) and interlocks surfaces bind cells together. It is selectively permeable to select chemicals that pass in and out of cells. There are many kinds of proteins in the membrane. Each protein has its cellular function and its function-specific homeostasis (FSH). The interaction of protein with laser irradiation or monochromatic light (LI) is extraordinarily weak. The number of each kind of protein is from a few thousands to a few ten thousands. The identical protein molecules randomly distribute in the membrane when the related function is in its FSH so that the ultraweak LI-protein interaction can not affect protein conformation and there is no PBM, but they cooperate with one another to form coherent states when the related function is far from its FSH so that the ultraweak LI-protein interaction can be amplified and affect protein conformation and there is PBM.

2. Nucleus The nucleus consists of the nuclear envelope, nucleolus, chromatin, and nucleoplasm.

(1) **Nuclear Envelope** It consists of two unit membranes with a fluid-filled space. Nuclear pores present. Outer membrane may be continuous with ER. It contains nuclear contents. It is selectively permeable to control movement in or out.

(2) **Chromatin** It is composed of long thin strands of DNA. It contains instructions that control cell metabolism and heredity

(3) **Nucleolus** It consists of non-membraneous matrix of ribonucleic acid (RNA) and protein. The instructions in DNA are copied here. It works with ribosomes in the synthesis of protein.

3. **Mitochondrion** It is composed of modified double unit membrane (protein, lipid), and its inner membrane is infolded to form cristae. It is the site of cellular respiration i.e. the release of chemical energy from food:

Glucose + Oxygen →Carbon Dioxide + Water + Energy [Adenosine-5'-triphosphate (ATP)]

4. **Ribosome** It consists of non-membraneous, spherical bodies composed of ribonucleic acid (RNA) and protein enzymes. It is the site of protein synthesis.

5. **Endoplasmic Reticulum (ER)** It consists of sheets of unit membrane with ribosomes on the outside, and forms a tubular network throughout the cell. It transports chemicals between cells

and within cells, and provides a large surface area for the organization of chemical reactions and synthesis.

6. **Lysosome** It is just membrane bound bag containing hydrolytic enzyme (water split biological catalyst using water to split chemical bonds). It breaks large molecules into small molecules by inserting a molecule of water into the chemical bond

7.2 Signal Transduction

Cell surface receptors convert extracellular cues into receptor activation, thereby triggering intracellular signaling networks and controlling cellular decisions. A cell decides whether to proliferate, differentiate, remain in a resting state, or die depending on the output from signaling networks that are characterized by pathway redundancies and crosstalk. Signal transduction is an important mechanism of PBM. Membrane receptors form coherent state and mediate phototransduction when the related function is far from its FSH. Endogenous photosensitizers produce reactive oxygen species (ROS) and then activate signal transductions. In this section, the fundamental knowledge of signal transduction will be introduced.

Signal transduction is a series of specific actions in a cell in which a signal is passed from one molecule to the next in the series from outside the cell to inside. It can be simple, like that associated with receptor molecules of the acetylcholine class: receptors that constitute channels which, upon ligand interaction, allow signals to be passed in the form of small ion movement, either into or out of the cell. These ion movements result in changes in the electrical potential of the cells that, in turn, propagates the signal along the cell. More complex signal transduction involves the coupling of ligand-receptor interactions to many intracellular events. These events include phosphorylations by tyrosine kinases and/or serine/threonine kinases. Protein phosphorylations change enzyme activities and protein conformations. The eventual outcome is an alteration in cellular activity and changes in the program of genes expressed within the responding cells.

Signal transducing receptors are of three general classes: (1) Receptors that penetrate the plasma membrane and have intrinsic enzymatic activity. Receptors that have intrinsic enzymatic activities include those that are tyrosine kinases, tyrosine phosphatases, guanylate cyclases and serine/threonine kinases. Receptors with intrinsic tyrosine kinase activity are capable of autophosphorylation as well as phosphorylation of other substrates. Additionally, several families of receptors lack intrinsic enzyme activity, yet are coupled to intracellular tyrosine kinases by direct protein-protein interactions. (2) Receptors that are coupled, inside the cell, to guanosine triphosphate (GTP)-binding and hydrolyzing proteins (termed G-proteins). Receptors of the class that interact with G-proteins all have a structure that is characterized by 7 transmembrane spanning domains. (3) Receptors that are found intracellularly and upon ligand binding migrate to the nucleus where the ligand-receptor complex directly affects gene transcription. The mail signal transduction pathways will be introduced as following.

1. **Receptor Tyrosine Kinases (RTKs)** The proteins encoding RTKs contain four major domains: an extracellular ligand binding domain, an intracellular tyrosine kinase domain, an intracellular regulatory domain and a transmembrane domain.

The amino acid sequences of the tyrosine kinase domains of RTKs are highly conserved with those of 3'-5'-cyclic adenosine monophosphate (cAMP)-dependent protein kinase (PKA) within

the ATP binding and substrate binding regions. Some RTKs have an insertion of non-kinase domain amino acids into the kinase domain termed the kinase insert. RTK proteins are classified into families based upon structural features in their extracellular portions (as well as the presence or absence of a kinase insert) which include the cysteine rich domains, immunoglobulin-like domains, leucine-rich domains, Kringle domains, cadherin domains, fibronectin type III repeats, acidic domains, and epidermal growth factor (EGF)-like domains. Based upon the presence of these various extracellular domains the RTKs have been sub-divided into at least 14 different families.

2. Non-Receptor Protein Tyrosine Kinases (PTKs) There are numerous intracellular PTKs that are responsible for phosphorylating a variety of intracellular proteins on tyrosine residues following activation of cellular growth and proliferation signals. There are now recognized two distinct families of non-receptor PTKs. The archetypal PTK family is related to the steroid receptor coactivator (Src) protein. The Src protein is a tyrosine kinase first identified as the transforming protein in Rous sarcoma virus. Subsequently, a cellular homolog was identified as c-Src. Numerous proto-oncogenes were identified as the transforming proteins carried by retroviruses. The second family is related to the Janus kinase (Jak).

3. **Receptor Serine/Threonine Kinases** The receptors for the transforming growth factor (TGF) β superfamily of ligands have intrinsic serine/threonine kinase activity. There are more than 30 multifunctional proteins of the TGF-β superfamily which also includes the activins, inhibins and the bone morphogenetic proteins (BMPs). This superfamily of proteins can induce and/or inhibit cellular proliferation or differentiation and regulate migration and adhesion of various cell types. The signaling pathways utilized by the TGF-β, activin and BMP receptors are different from those for receptors with intrinsic tyrosine kinase activity or that associate with intracellular tyrosine kinases.

4. Non-Receptor Serine/Threonine Kinases There are several serine/threonine kinases that function in signal transduction pathways. The two more commonly known are PKA and protein kinase C (PKC). Additional serine/threonine kinases important for signal transduction are the mitogen activated protein kinases .

(1) Protein Kinase C PKC was originally identified as a serine/threonine kinase that was maximally active in the presence of diacylglycerols (DAG) and calcium ion. It is now known that there are at least ten proteins of the PKC family. Each of these enzymes exhibits specific patterns of tissue expression and activation by lipid and calcium. PKCs are involved in the signal transduction pathways initiated by certain hormones, growth factors and neurotransmitters. The phosphorylation of various proteins, by PKC, can lead to either increased or decreased activity. Of particular importance is the phosphorylation of the EGF receptor by PKC which down-regulates the tyrosine kinase activity of the receptor. This effectively limits the length of the cellular responses initiated through the EGF receptor.

(2) Mitogen Activated Protein Kinases (MAPK) MAPK were identified by virtue of their activation in response to growth factor stimulation of cells in culture, hence the name mitogen activated protein kinases. MAPK are also called ERKs for extracellular-signal regulated kinases. On the basis of *in vitro* substrates the MAPK have been variously called microtubule associated protein-2 kinase, myelin basic protein kinase, ribosomal S6 protein kinase and EGF receptor threonine kinase. All of these proteins have similar biochemical properties, immuno-crossreactivities, amino acid sequence and ability to *in vitro* phosphorylate similar

substrates.

Maximal MAPK activity requires that both tyrosine and threonine residues are phosphorylated. This indicates that MAPK act as switch kinases that transmits information of increased intracellular tyrosine phosphorylation to that of serine/threonine phosphorylation. Although MAPK activation was first observed in response to activation of the EGF, insulin receptors, other cellular stimuli such as T cell activation, phorbol esters (that function through activation of PKC), thrombin, bombesin and bradykinin (that function through G-proteins) as well as electrical stimulation rapidly induce tyrosine phosphorylation of MAPK.

(3) Protein Kinase B (PKB) PKB is also known as Akt. This kinase serves as a major molecular node to control the function of many cell survival and death proteins through phosphorylation-mediated protein modification. The end result of the activation of Akt is enhanced cell survival and proliferation, pre-requisites for malignant transformation.

5 Phospholipases and Phospholipids in Signal Transduction Phospholipases and phospholipids are involved in the processes of transmitting ligand-receptor induced signals from the plasma membrane to intracellular proteins. The primary protein affected by the activation of phospholipases is PKC which is maximally active in the presence of calcium ion and DAG. The generation of DAG occurs in response to agonist activation of various phospholipases. The principal mediators of PKC activity are receptors coupled to activation of phospholipase C(PLC)-γ. PLC- γ contains SH2 domains that allow it to interact with tyrosine phosphorylated RTKs. This allows PLC- γ to be intimately associated with the signal transduction complexes of the membrane as well as membrane phospholipids that are its substrates. Activation of PLC- γ leads primarily to the hydrolysis of membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) leading to an increase in intracellular DAG and inositol 1,4,5-trisphosphate (IP_3). The released IP_3 interacts with intracellular membrane receptors leading to an increased release of stored calcium ions. Together, the increased DAG and intracellular free calcium ion concentrations lead to increased activity of PKC.

6. G-Protein Coupled Receptors For the signal transduction mediated by G proteins, the membrane receptor activation leads to the activation of the α subunit of G protein and mediates the concentration change of intracellular messengers. There many kinds of G proteins such as Gs protein, Gi protein and Gq protein. The activation of Gs protein and Gi protein lead to the elevation of cAMP and cyclic guanosine monophosphate (cGMP), respectively. Gq protein activation leads to the elevation of DAG and IP_3.

There are several different classifications of receptors that couple signal transduction to G-proteins. These classes of receptor are termed G-protein coupled receptors (GPCRs). Well over 1000 different GPCRs have been cloned, most being orphan receptors having no as yet identified ligand. Three different classes of GPCR are reviewed:

(1) GPCRs that modulate adenylate cyclase activity. One class of adenylate cyclase modulating receptors activate the enzyme leading to the production of cAMP as the second messenger. Receptors of this class include the β-adrenergic, glucagon and odorant molecule receptors. Increases in the production of cAMP leads to an increase in the activity of PKA in the case of β-adrenergic and glucagon receptors. In the case of odorant molecule receptors the increase in cAMP leads to the activation of ion channels. In contrast to increased adenylate cyclase activity, the α-type adrenergic receptors are coupled to inhibitory G-proteins that repress adenylate cyclase activity upon receptor activation.

(2) GPCRs that activate PLC-γ leading to hydrolysis of polyphosphoinositides (e.g. PIP_2) generating the second messengers, DAG and IP_3. This class of receptors includes the angiotensin, bradykinin and vasopressin receptors.

(3) A novel class of GPCRs is the photoreceptors. This class is coupled to a G-protein termed transducin that activates a phosphodiesterase which leads to a decrease in the level of cGMP. The drop in cGMP then results in the closing of a Na^+/Ca^{2+} channel leading to hyperpolarization of the cell.

Recent evidence indicates that phospholipases D and A_2 (PLD and PLA_2) also are involved in the sustained activation of PKC through their hydrolysis of membrane phosphatidylcholine (PC). PLD action on PC leads to the release of phosphatidic acid which in turn is converted to DAG by a specific phosphatidic acid phosphomonoesterase. PLA_2 hydrolyzes PC to yield free fatty acids and lysoPC both of which have been shown to potentiate the DAG mediated activation of PKC. Of medical significance is the ability of phorbol ester tumor promoters to activate PKC directly. This leads to elevated and unregulated activation of PKC and the consequent disruption in normal cellular growth and proliferation control leading ultimately to neoplasia.

Phosphatidylinositol-3-Kinase (PI-3K) is tyrosine phosphorylated, and subsequently activated, by various RTKs and receptor-associated PTKs. PI-3K phosphorylates various phosphatidylinositols at the 3 position of the inositol ring. This activity generates additional substrates for PLC-γ allowing a cascade of DAG and IP_3 to be generated by a single activated RTK or other protein tyrosine kinases.

7. G-Protein Regulators The activity of G-proteins with respect to GTP hydrolysis is regulated by a family of proteins termed GTPase activating proteins (GAPs). The proto-oncogenic protein, Ras, is a G-protein involved in the genesis of numerous forms of cancer (when the protein sustains specific mutations). Of particular clinical significance is the fact that oncogenic activation of Ras occurs with higher frequency than any other gene in the development of colo-rectal cancers. Regulation of Ras GTPase activity is controlled by rasGAP.

8. Intracellular Hormone Receptors Hormone receptors are proteins that effectively bypass all of the signal transduction pathways described thus far by residing within the cytoplasm. Additionally, all of the hormone receptors are bi-functional. They are capable of binding hormone as well as directly activating gene transcription.

The steroid/thyroid hormone receptor superfamily (e.g. glucocorticoid, vitamin D, retinoic acid and thyroid hormone receptors) is a class of proteins that reside in the cytoplasm and bind the lipophilic steroid/thyroid hormones. These hormones are capable of freely penetrating the hydrophobic plasma membrane. Upon binding ligand the hormone-receptor complex translocates to the nucleus and bind to specific DNA sequences termed hormone response elements (HREs). The binding of the complex to an HRE results in altered transcription rates of the associated gene.

9. Phosphatases in Signal Transduction Substantial evidence links both tyrosine and serine/threonine phosphorylation with increased cellular growth, proliferation and differentiation. Removal of the incorporated phosphates must be a necessary event in order to turn off the proliferative signals. This suggests that phosphatases may function as anti-oncogenes or growth suppressor genes. The loss of a functional phosphatase involved in regulating growth promoting signals could lead to neoplasia. However, examples are known where dephosphorylation is required for promotion of cell growth. This is particularly true of specialized kinases that are directly involved in regulating cell cycle progression. Therefore, it is difficult to envision all

phosphatases as being tumor suppressor genes.

7.3 Cell Cycle

It has been known for over one hundred years that cells multiply through division. It is however only during the last two decades that it has become possible to identify the molecular mechanisms that regulate the cell cycle and thereby cell division. These fundamental mechanisms are highly conserved through evolution and operate in the same manner in all eukaryotic organisms.

The cell cycle consists of several phases (see Fig. 7.2). In the first phase (G1) the cell grows and becomes larger. When it has reached a certain size it enters the next phase (S), in which DNA-synthesis takes place. The cell duplicates its hereditary material (DNA-replication) and a copy of each chromosome is formed. During the next phase (G2) the cell checks that DNA-replication is completed and prepares for cell division. The chromosomes are separated (mitosis, M) and the cell divides into two daughter cells. Through this mechanism the daughter cells receive identical chromosome set ups. After division, the cells are back in G1 and the cell cycle is completed. Different phases of the cell cycle are regulated by cyclin and cyclin dependent kinase (Cdk). Cell proliferation is an increase in the number of cells as a result of cell growth and cell division.

The cellular proliferation is maintained by intracellular protein fluctuations (López-Avilés *et al*. 2009) (Fig. 7.3). In Fig. 7.3, the fluctuation proteins are anaphase promoting complex (APC), the Cdk inhibitor Sic1, mitotic cyclin Clb2 and APC activator Cdh1, and MCM1 denotes the active form of the Clb2 transcription factor complex Fkh2/Ndd1/Mcm1. The right part maintains proliferation-specific homeostasis (PSH), but the left part is far from PSH. Generally, the cellular proliferation in 10% fetal calf serum (FCS) is in PSH, but the one in the FCS at the concentration extremely lower or higher than 10% is far from the PSH.

The duration of the cell cycle varies between different cell types. In most mammalian cells it lasts between 10 and 30 hours. Cells in the first cell cycle phase (G1) do not always continue through the cycle. Instead they can exit from the cell cycle and enter a resting stage (G0).

The cell cycle can be halted during one of the normal phases (G1, S, G2, M). The process is called cell cycle arrest. For example, dexamethasone (DEX) might induce G1 cell cycle arrest (Funakoshi *et al*. 2005). Cellular senescence is the state of permanent cell cycle arrest.

7.4 Cell Functions

An abundance of scientific literature exists demonstrating that oxidative stress influences MAPK signaling pathways (Fig. 3.7) (Dröge 2002, McCubrey *et al*. 2006). It has been shown that different ROS levels activate different MAPK pathways, that is, low level ROS activates ERK mediated MAPK, a signal for proliferation, differentiation and survival, moderate level ROS activates the stress signals c-Jun N-terminal kinase (JNK) or p38 mediated MAPK, which leads to cell survival or apoptosis[1], and high level ROS leads to cellular apoptosis or necrosis (Bladier *et al*. 1997, Owuor *et al*. 2002). ROS also increased phosphorylation of Akt kinase in a dose-dependent

[1] Apoptosis, also called programmed cell death, is a type of cell death in which a series of molecular steps in a cell leads to its death. This is the body's normal way of getting rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells..

and promoted rapid activation of PI3K(Zhuang S *et al.* 2003, Venkatesan *et al.* 2007)， and activated nuclear factor κB (NFκB)(Dröge 2002)

Polymorphonuclear neutrophils (PMNs) are one of the main types of effector cell in the innate immune system and were first shown to effectively kill microorganisms by respiration burst more than 100 years ago (Nathan 2006). The signal transduction mechanism involved in superoxide anion generation during respiration burst, in response to chemical substances, has been extensively studied, and some of the key signaling proteins and their associated pathways are summarized in Fig. 7.4, which are based on the work from a number of groups (Duan R *et al.* 2001). As is shown in Fig. 7.4, the process is a complicated network with crosstalk among different pathways. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase at the end of the signal transduction pathway of respiratory burst is responsible for the generation of superoxide anions. There are currently seven proteins reported to be associated with the NADPH oxidase assembly. In resting PMNs, these NADPH oxidase protein components are segregated into cytoplasmic and plasma membrane compartments. Upon activation of the NADPH oxidase, the cytosolic protein components translocate to the plasma membrane or phagosomal membrane where they assemble around a central membrane-bound protein known as flavocytochrome b, forming a functionally active complex which catalyzes the reduction of O_2 to O_2^- using NADPH as the electron donor. Our experiments showed that PTKs, PLC and PKC are required for low intensity He-Ne laser irradiation (LHNL) induced respiratory burst of PMNs. As PTKs can activate PLC-γ, our results suggested that one of these pathways mediating LHNL-induced respiration burst of PMNs is that PTKs—PLC-γ—PKC—NADPH oxidase which are marked in red in Fig. 7.4.

Alzheimer's Disease (AD) is the most common neurodegenerative disorder known as "dementias" with the main features being a progressive cognitive deterioration. The pathological hallmark of AD includes widespread neuronal degeneration, neuritic plaques containing β-amyloid protein (Aβ), and neurofibrillary tangles enriched region in the disease-damaged brain. Aβ induced neuron apoptosis was one of the cellular model of AD. Various strategies have been developed to prevent neuron apoptosis. Their signal transduction pathways are illustrated in Fig. 7.5 (Zhu L *et al.* 2009a).

7.5 Protein acetylation

Like protein phosphorylation in signal transduction, the posttranslational addition of acetyl groups (ACs) to lysine residues of eukaryotic and prokaryotic proteins has been known for decades. Dynamic changes in lysine acetylation may provide an important regulatory switch in complex cellular processes. Among the deacetylases, sirtuins (SIRTs) are the most popular ones (Finkel *et al.* 2009, Saunders *et al.* 2009). To date, seven mammalian homologues have been identified. Cell biological studies have demonstrated different subcellular compartments for each family member, with SIRT6 and SIRT7 being nuclear proteins, SIRT3, SIRT4 and SIRT5 mitochondrial proteins, and SIRT1 and SIRT2 being found both in the nucleus and the cytoplasm, in a cell- and tissue-dependent context.

SIRT1, a mammalian ortholog of the yeast transcriptional regulator Sir2, is a stress-activated nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase that regulates cell survival, replicative senescence, inflammation, and metabolism through the deacetylation of

histones (the major protein components of chromatin) and other cellular factors including the transcription factors p53, NF-κB, heat shock factor (HSF) 1, and forkhead box class O (FOXO)1, 3, and 4, and the transcriptional regulator peroxisome proliferator-activated receptor-γ coactivator (PGC) 1α (Fig. 7.6) (Saunders *et al.* 2009). Calorie restriction extends life span in part by increasing SIRT1 expression, and in yeast, worms, and fruit flies, the lack of Sir2 abrogates the effects of calorie restriction on life span. Similarly, mice lacking SIRT1 do not show some of the beneficial effects of calorie restriction related to longevity. The enzymatic activity of SIRT1 is activated by resveratrol, a polyphenol produced by plants under stress. Resveratrol extends the lifespan of yeast, worms, and flies only when Sir2 is present.

SIRT1 is activated by various stresses. As a reasonable development, the SIRT1 activity in FSH, FSH-specific SIRT1 activity (FSSA1), should be at local minimum so that there might a SIRT1 activity potential well (SAP1) as is illustrated in Fig. 7.7, which is called SAP1 hypothesis (SAP1H). This SAP1H has been supported in our recent cellular experiment. Mouse C3H muscle myoblasts (C2C12) were cultured in Dulbecco's modified Eagle medium (DMEM) at 4.5, 22.5, 45, 67.5 and 90 mM glucose. It was found that the proliferation peak is at 22.5 mM glucose at which NAD^+/NADH and SIRT1 expression arrive at their minimum, respectively.

Different cellular functions have different FSSA1, respectively. There are different acetylomes of the three different cell types, epithelial cell line(A549), human acute myeloid leukemia cell line (MV4-11) and lymphoid origin cell line (Jurkat) (Choudhary *et al.* 2009). Moreover, the spectrum of acetylated proteins is highly conserved in the liver between mouse and human, but is very different between liver and leukemia cells (Zhao S *et al.* 2010). Analysis indicated messenger ribonucleic acid (mRNA) of SIRT1 was widely expressed in the heart, liver, lung, kidney, spleen, muscle, subcutaneous and visceral adipose of piglets and adult pigs (Bai L *et al.* 2007). For piglets, SIRT1 mRNA was most abundant in lung, kidney and spleen tissue and least abundant in skeletal muscle and subcutaneous adipose. For adult pigs, SIRT1 mRNA was highly expressed in kidney and spleen tissue, and least expressed in heart tissue. Furthermore, SIRT1 mRNA expression was significantly different between subcutaneous adipose and visceral adipose. This suggested that SIRT1 is not only existed in pig but also widely expressed in various tissues from pigs of different developmental stages, speculating that SIRT1 may be involved in multiple activities in pig and exerts different effects in various tissues. After systematical summarization, the different kinds of FSSA1 of different cellular functions were illustrated in Fig. 7.8 (Liu CY *et al.* 2009).

Laser acupuncture (LA), intranasal low intensity laser therapy (ILILT) and bright light may enhance melatonin (Mel) level and then NAD^+ level and SIRT1 activity as discussed in chapter 3.4&3.5. Low intensity laser irradiation or monochromatic light (LIL) might directly enhance the ratio of NAD^+ and its reduced form (NADH) and SIRT activities. There is a stress-specific homeostasis (StSH) such as development-specific homeostasis (DeSH) in chapter 6.3 and aging-specific homeostasis (AgSH) in chapter 6.2. A stress inducing a function far from its FSH may far from its StSH, and its increasing SIRT activities may be very weak. If a stress far from its StSH induce a function far from its FSH, LIL can promote StSH establishment to increase NAD^+/NADH and then SIRT activities to promote FSH upgradation or degradation. Development is a kind of stress, and DeSH results in FSH upgradation, which promotion has been discussed in chapter 6.3. Aging is also a kind of stress, and AgSH results in FSH degradation, which promotion has been discussed in chapter 6.2. We have studied the inhibition of red light (640±15 nm) from

light emitting diode array (RLED640) on hydrogen peroxide (H_2O_2) induced apoptosis of differentiated PC12 cells (a cell line derived from a pheochromocytoma of the rat adrenal medulla), and found the promotion of RLED640 on the expression of tyrosine hydroxylase and brain-derived neurotrophic factor might be mediated by SIRT1 (Zhu L *et al.* 2009b). There are two kinds of antimicrobial activities of neutrophils: respiration burst and neutrophil extracellular traps (NETs) consisting of chromatin and granular proteins. We have studied the rehabilitation of RLED640 on dexamethasone induced inhibition of NET formation, and found the rehabilitation was mediated by SIRT2 (Liu TCY *et al.* 2010b).

8 Cellular Rehabilitation of Photobiomodulation

Biology is one of the dominant sciences of the 21st century. It will transform many aspects of society in fundamental ways, and function medicine or traditional Chinese medicine (TCM) in particular will impact other sciences such as engineering. Function-specific homeostasis (FSH) is one of the key concepts in function medicine or TCM. In this chapter, photobiomodulation (PBM) is deeply discussed from homeostatic viewpoint.

8.1 Function-specific homeostasis

FSH is one of the most remarkable and most typical properties of highly complex open systems. Such a system reacts to every change in the environment, or to every random disturbance, through a series of modifications of equal size and opposite direction to those that created the disturbance. The goal of these modifications is to maintain the function. There is a proliferation-specific homeostasis (PSH) for human fetal lung fibroblasts (WI-38) so that androgens (testosterone, dihydrotestosterone, and dehydroepiandrosterone), estrogen (17 beta-estradiol), and progesterone had no effect on cell density at concentrations lower than 0.5 micrograms/ml although they caused a decrease in cell density at higher concentrations (5 micrograms/ml, or more) (Kondo *et al.* 1983). Without therapy, most people infected with human immunodeficiency virus (HIV) ultimately progress to acquired immunodeficiency syndrome (AIDS). Rare individuals (‘elite controllers’) maintain very low levels of HIV ribonucleic acid (RNA) without therapy, thereby making disease progression and transmission unlikely(Košmrlj *et al.* 2010). Certain human leukocyte antigen (HLA) class I alleles are markedly enriched in elite controllers, with the highest association observed for *HLA-B57*. Compared to other HLA-restricted T cells, a larger fraction of the naive repertoire of B57-restricted clones recognizes a viral epitope, and these T cells imposes strong immune pressure on immunodominant HIV epitopes and emergent mutants, thereby promoting efficient control of the virus.

There are many conditions to maintain a FSH, but FSH-essential conditions might be very sparse. There are many typical examples such as sparse coding, working memory, the “brainless” worker and Blind luck archer. Several theoretical, computational, and experimental studies suggest that neurons encode sensory information using a small number of active neurons at any given point in time (Olshausen *et al.*2004). Recent physiological recordings from sensory neurons have indicated that the sparse coding could be a ubiquitous strategy employed in several different modalities across different organisms (Olshausen *et al.* 2004). For example, Vinje *et al.* (2000)’s experiments have provided direct experimental evidence that primary visual cortex uses a sparse code matched to the underlying sparse structure of natural scenes. Recently, Huber *et al.* (2008) have studied sparse optical microstimulation in barrel cortex in freely moving mice. Their data induicated that mechanisms exist to read out extremely sparse codes from primary sensory areas. Houweling *et al.* (2008) have studied behavioral report of single neuron stimulation in somatosensory cortex. Their results demonstrate that single neuron activity can cause a change in the animal's detection behaviour, suggesting a much sparser cortical code for sensations than previously anticipated.

Limits on the storage capacity of working memory significantly affect cognitive abilities in a wide range of domains. Some researchers have proposed that working memory stores a limited set

of discrete, fixed-resolution representations, whereas others have proposed that working memory consists of a pool of resources that can be allocated flexibly to provide either a small number of high-resolution representations or a large number of low-resolution representations. Zhang W *et al.* (2008) have shown that memory resolution varied over a narrow range that cannot be explained in terms of a general resource pool but can be well explained by a small set of discrete, fixed-resolution representations.

Feuillet *et al.* (2007) reported the “brainless” white-collar worker. The 44-year-old worker presented with a 2-week history of mild left leg weakness. At the age of 6 months, he had undergone a ventriculoatrial shunt, because of postnatal hydrocephalus of unknown cause. When he was 14 years old, he developed ataxia and paresis of the left leg, which resolved entirely after shunt revision. His neurological development and medical history were otherwise normal. He was a married father of two children, and worked as a civil servant. On neuropsychological testing, he proved to have an intelligence quotient (IQ) of 75: his verbal IQ was 84, and his performance IQ 70. Computer tomography (CT) showed severe dilatation of the lateral ventricles; Magnetic resonance imaging revealed massive enlargement of the lateral, third, and fourth ventricles, a very thin cortical mantle and a posterior fossa cyst. Feuillet *et al.* (2007) diagnosed a non-communicating hydrocephalus, with probable stenosis of Magendie's foramen. The leg weakness improved partly after neuroendoscopic ventriculocisternostomy, but soon recurred; however, after a ventriculoperitoneal shunt was inserted, the findings on neurological examination became normal within a few weeks. The findings on neuropsychological testing and CT did not change.

Blind luck helped archer make one-in-a-million Robin Hood shot (Blind 2008). Mrs Trotter, a 74-year-old grandmother from Uffculme, North Devon, has achieved a one-in-a-million feat of marksmanship after splitting one arrow with another. She pulled off the shot, known among archers as a "Robin Hood", at a practice session of the Wellington Bowmen in Somerset. She lost most of her sight following a head injury 17 years ago. Her husband, Tony, is crucial to her success, telling her how near her shots are to the target each time she shoots. "He isn't allowed to tell me to aim left or right before I let loose an arrow," Mrs Trotter said. "I can only make my own adjustments to my aim before I shoot." She may dismiss the shot as a fluke, but she also won a gold medal at the British Blind Sports National Championship last year.

The main FSH of an athlete is the sport-specific homeostasis (SSH). The sparse FSH-essential condition phenomena are also enriched by our metabonomic studies[1] of SSH. First void urine samples of 18 Chinese male athletes, who were training for the swimming competition at Doha Asian games in 2006, were collected once a week for 3 consecutive weeks in a month before the games. Samples were analyzed by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. 409 data were from each urine sample after data reduction from ^{1}H NMR spectra. After principal component analysis[2] (Ringnér 2008), we found finalists can be distinguished from non-finalists

[1] Metabonomics broadly aims to measure the global, dynamic metabolic response of living systems to biological stimuli or genetic manipulation. The focus is on understanding systemic change through time in complex multicellular systems.

[2] Principal component analysis is a mathematical algorithm that reduces the dimensionality of the data while retaining most of the variation in the data set. It accomplishes this reduction by identifying directions, called principal components, along which the variation in the data is maximal. By using a few components, each sample can be represented by relatively few numbers instead of by values for thousands of variables. Samples can then be plotted, making it possible to visually assess similarities and differences between samples and determine whether samples can be grouped.

by only two principal components (PCs), PC3 and PC25, which are the most stable PCs among all the PCs (Li J *et al.* 2008).

8.2 Function Modulation

Western mainstream medicine studied body mainly from anatomical viewpoint, but function medicine and TCM studied body mainly from functional viewpoint. The function modulation was discussed from the TCM viewpoint.

Drug therapy is one of the main therapeutic approaches of function medicine and TCM. TCM follows the tenet that a formula should have four major ingredients, each playing its unique role while working together synergistically, to achieve the optimum therapy. The four major ingredients have been described in ancient texts as 'emperor', 'minister', 'assistant' and 'delivering servant'. Wang L *et al.* (2008) have taken one well-known and clinically tested TCM formula for leukaemia therapy as a model and unveiled the biochemical roles of each ingredient. The formula, known as realgar–Indigo naturalis formula, contains realgar and indigo minerals, as well as the herb red sage root. Through molecular analyses, they showed that arsenic in realgar works as 'emperor' by directly attacking the receptor oncoprotein in leukaemia cells. Indirubin, the active ingredient in indigo, works as 'assistant' by antagonizing the toxicity of arsenic and slowing leukaemia cell growth. Tanshinone, the active ingredient in red sage root, acts as 'minister' by partially restoring those pathways that stop leukaemia spreading. Lastly, indurbin and tanshinone work as 'delivering servants'; these ingredients can enhance the cellular uptake of arsenic by increasing the gene-expression level and therefore the synthesis of carrier pore proteins in the cell membrane.

As discussed in chapter 3, there are two kinds of regulation factors of a function of a biosystem, the homeostatic regulation factors and the developmental regulation factors. Generally, the TCM formulae consist of several types of medicinal herbs or minerals, in which one represents the principal component, and others serve as adjuvant ones to assist the effects or facilitate the delivery of the principal component so that the multiple components could hit multiple targets and exert synergistic therapeutic efficacies. Obviously, the 'emperor' is the principal component, and it is the developmental regulation in the leukaemia therapy; and the 'minister', 'assistant' and 'delivering servant' are the adjuvant ones, and they are the homeostatic regulations in the leukaemia therapy. PBM might be the principal one or the adjuvant ones. PBM can be then classified into two kinds, FSH-specific PBM (fPBM) in which laser irradiation or monochromatic light (LI) is just a homeostatic regulation, and developmental PBM (dPBM) in which LI is just a developmental regulation. These phenomena will be reviewed in the following two sections.

8.3 Photobiomodulation of Low Intensity Laser Irradiation or Monochromatic Light

PBM of low intensity LI (LIL) is an fPBM. As it will be discussed in the next chapter, LIL PBM (LPBM) is so weak that it can not disrupt the FSH and there is no LPBM on the function of a biosystem in FSH. As Karu (1998) has pointed out, there is no effects of LIL on the cell which redox potential is so that the cell normally functions, and the lower the redox potential of a cell comparing with the normal redox potential, the stronger the LPBM. The cell which normally

functions is in FSH. Fig. 8.1 illustrated cellular LPBM from the viewpoint of redox potential. As Tunér *et al.* (1999) have summarized, the light energy is thought to reap the greatest benefit where it is most needed.

There is no LPBM on the proliferation of cells in proliferation-specific homeostasis (PSH). The chondrocytes in 0, 2.5, 5, and 10 % fetal calf serum (FCS) have been irradiated by low intensity He-Ne laser irradiation (LHNL) at 5.74 mW/cm^2 for 2, 8, 16, 30 and 45 min in our laboratories (Yang X *et al.* 2006). There was significant PBM on chondrocyte proliferation in 0, 2.5 and 5% FCS, but there was no PBM on the proliferation in 10% FCS. The chondrocyte proliferation in 10% FCS has been in PSH so that there was no PBM on the proliferation. As discussed in chapter 7.3, dexamethasone (DEX) might induce G1 cell cycle arrest (Funakoshi *et al.* 2005) which is in G1 cell cycle arrest-specific homeostasis so that no proliferation differences of the myoblasts in combination with 100 nmol/L DEX were observed between red light at 640±15nm of light emitting diode array (RLED 640), simvastatin treatment and the control (Chen XY 2008). After analyzed many experiments, Karu (1998) pointed out, only the proliferation of slowly growing subpopulations can be stimulated by LIL, and it is not possible to activate a process which is activated already or occurring at speed near maximal so that the cells are in PSH. The results of Mognato's group (Mognato *et al.* 2004) are a confirmation of previous observations carried out on human cells, where only the proliferation of slowly growing cell populations appeared to be stimulated by laser light.

There is no LPBM on the protein production of cells in protein-production-specific homeostasis. Bouma *et al.* (1996) have investigated the effects of LIL on cytokine release by human peripheral blood monocytes in vitro. There is no significant difference for the interleukin (IL)-6 production of the cells stimulated by two concentrations of lipopolysaccharides (LPS). In other words, the IL-6 production has been fully stimulated by LPS so that the cells were in IL-6 production-specific homeostasis and LIL fails to modulate the IL-6 production. The chondrocytes used in Lin YS *et al.* (2004)'s experiment were cultured in 10% FCS, but the cells have been separated from arthritic cartilage and the studied function was stress protein production. Lin YS *et al.* (2004) have found LHNL promoted the stress protein production of the chondrocytes, which indicates that the stress protein production of the arthritic chondrocytes in 10% FCS might not be in stress protein production-specific homeostasis.

There is no LPBM on the deformability of red blood cell (RBC) in deformability-specific homeostasis. Iijima *et al.* (1993) have investigated the effect of LHNL on human RBC deformability. RBC solution samples obtained from hematologically normal adult donors by venipuncture were assigned to three groups. Group 1 were irradiated for 0 (control), 1, 3, 5, 10, 15, and 30 min within 2 hr after sampling, but Group 2 and Group 3 were stored at 5℃ for 24 and 36 hr, respectively, and received similar irradiations after 12 hr (in both groups), 24 hr (in Group 2), and 36 hr (in Group 3) from sampling. The deformability shown as the filter filtration rate was unchanged in Group 1 (fresh cell group) from the control value, but improved significantly in Groups 2 and 3 (damaged cell groups) after the irradiation. In this case, RBC in Group 1 is in deformability-specific homeostasis.

Although there is no LPBM on the function of cells in FSH, LIL can inhibit the disruption of a developmental factor. Our laboratory has studied of the effect of statins on proliferation of C2C12 myoblast and its PBM (Chen XY 2008). C2C12[3] myoblasts in 10% FCS is in PSH so that

[3] C2C12 cell line from mouse C3H muscle myoblast can be differentiated into C2C12 myotubes.

simvastatin at 2.0×10^{-6}, 2.0×10^{-7} and 2.0×10^{-8} mol/L had no effects on the myoblast proliferation, and no PBM on the proliferation has been found. However, simvastatin at 2×10^{-5} mol/L inhibited the myoblast proliferation so that only 37.2% of the myoblasts remained to survive, and the inhibited proliferation was promoted with RLED 640 at 0.848 mW/cm^2 and 15 min. Our laboratory has studied LPBM on the amyloid β protein (Aβ) 25-35 induced apoptosis of PC12[4] cell in vitro, and found RLED 640 at 0.09 mW/cm^2 and 60 min inhibited the apoptosis (Duan R *et al*. 2003). Eells *et al*. (2003) have studied red light at 670 nm from LED (RLED 670) on methanol induced mitochondrial dysfunction of cone cells and rod cells in vivo, and found RLED 670 at 28 mW/cm^2 and 144 min inhibited the retinal toxicity. Low level LI (LLL) therapy (LLLT) is a known anti-inflammatory therapy. After irradiating the rats or mice on the skin over the upper bronchus at the site of tracheotomy after LPS, Aimbire *et al*. (2008) found LLLT reduced the rat lung permeability by a mechanism in which the IL-1β seems to have an important role and reduced the levels of anti-apoptotic factors in mice lung polymorphonuclear neutrophils (PMNs) by an action mechanism in which the NF-κB seems to be involved.

LIL can also promote the disruption of a developmental factor. Spleen cells at rest might be in rest-specific homeostasis. An object of phagocytosis *Candida albicans* can disrupt the rest-specific homeostasis and activate their respiration burst which might be evaluated by the luminol-amplified chemiluminescence (LDC). Karu *et al.* (1989) have studied the respiration burst in murine spleen cells after treatment with an object of phagocytosis *Candida albicans* and LHNL, and found the irradiation effect was detectable only in these cases when the cells were treated first with a low concentration of *Candida albicans* (5×10^7 particles/ml), and no additional activation by LHNL was possible at the concentration of 1×10^8 particles/ml at which the chemiluminescence was maximally activated so that the cells were in respiration burst-specific homeostasis. Aimbire *et al.* (2006) have studied PBM on trachea muscle relaxation response in rats with tumor necrosis factor (TNF) α-mediated smooth airway muscle dysfunction, and found LIL promoted TNF-α induced 3'-5'-cyclic adenosine monophosphate (cAMP) accumulation. Karu *et al.* (2001a) have studied donors of nitric oxide (NO) and LPBM on cell attachment to extracellular matrices, and found LIL promoted the inhibition of sodium nitroprusside on the cell attachment.

We have studied the individual difference of LPBM (Wu M *et al.* 2008). The PMNs were isolated from peripheral blood of 13 volunteers (10 ordinary persons, 3 athletes) and treated by RLED 640 at 50, 100, 300, 500 and1000 J/m^2 for fixed 100 s duration. Blood samples of athletes were extracted at different time in the 10 km non-interrupted long-distance running, before running, 1 hour after running beginning, just finishing the running, resting for 1 hour and 2 hours after running. We found that there were three types of modulation of RLED 640 on the respiratory burst of three types of PMNs, respectively, promotion for the one of subactivated PMNs, inhibition for the one of overactivated PMNs and none for the PMNs in respiration burst-specific homeostasis.

8.4 Photobiomodulation of Moderate Intensity Laser Irradiation or Monochromatic Light

PBM of moderate intensity LI (MIL) is mainly mediated by reactive oxygen species (ROS) (Liu TCY *et al.* 2005&2007). The modulation of MIL PBM (MPBM) on FSH is just the one of ROS on FSH.

[4] PC12 cell line is a cell line from rat adrenal pheochromocytoma

ROS, also termed "oxygen-derived species" or "oxidants," are produced as intermediates in reduction-oxidation (redox) reactions leading from O_2 to H_2O (Dröge 2002). ROS are reactive chemical entities comprising two major groups: free radicals (e.g., superoxide [$\cdot O_2^-$], hydroxyl [OH·], nitric oxide [NO·]) and nonradical derivatives of O_2 such as hydrogen peroxide (H_2O_2), $ONOO^-$. A free radical is any species capable of independent existence (thus the term "free") that contains one or more unpaired electron. The unpaired electron imparts high reactivity and renders the radical unstable. Nonradical derivatives are less reactive and more stable with a longer half-life than free radicals. The sequential univalent reduction of O_2 is as follows:

Of the ROS generated in cardiovascular cells, $\cdot O_2^-$ and H_2O_2 appear to be particularly important (Paravicini *et al.* 2008).

In biosystems, $\cdot O_2^-$ is short-lived owing to its rapid reduction to H_2O_2 by superoxidase dismutase (SOD) (Dröge 2002). The charge on the superoxide anion makes it unable to cross cellular membranes, except possibly through ion channels. In contrast, H_2O_2 has a longer biological lifespan than $\cdot O_2^-$, is relatively stable, and is easily diffusible within and between cells. The main source of H_2O_2 in vascular tissue is the dismutation of $\cdot O_2^-$: $2 \cdot O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$. This reaction can be spontaneous or it can be catalyzed by SOD, of which there are three mammalian isoforms: copper/zinc SOD (SOD1), mitochondrial SOD (Mn SOD, SOD2), and extracellular SOD (ecSOD, SOD3). The major vascular SOD is erythrocyte SOD(eSOD) (Paravicini *et al.* 2008).

8.4.1 Developmental photobiomodulation

MPBM might be an fPBM or dPBM, which depends on ROS level and cell sensitivity. The PBM of MIL of higher intensity may be dPBM. The PMNs from 20 healthy male volunteers is normal in respiration burst-specific homeostasis, but can be attenuated by the infrared diode laser (GaAlAs), 830-nm continuous wave at 150 mW/cm^2 (Fujimaki *et al.* 2003). For the NCTC 2544 keratinocytes in 10% FCS, mitogen-activated protein kinase/extracellular signaling regulated kinase (MAPK/ERK) was strongly activated, but can be further activated by ultraviolet A (320-400 nm) (UVA) (4 mW/cm^2, 75 min) (Djavaheri-Mergny *et al.* 2001). DEX might induce G1 cell cycle arrest (function 1) (Funakoshi *et al.* 2005), but MIL(GaAlAs diode 780 nm laser, 250 mW/cm^2, 12 s) acts as a proliferative stimulus (function 2) on osteoblast-like cells, even under the influence of DEX (Fujihara *et al.* 2006). Agkistrodon contortrix laticinctus myotoxin might induce muscle injury, which regeneration can not be promoted by fPBM of LIL(GaAs diode 904 nm laser, 7.5 mW/cm^2, 2.2 or 8 min) (Oliveira *et al.* 1999), but can be promoted by dPBM of moderate intensity He-Ne laser irradiation (MHNL)(371mW/cm^2, 7s) (Amaral *et al.* 2001). The chondrocyes have been cultured in 10% normal goat serum so that they were in PSH, but the ROS level induced by pulsed GaAlAs diode 780 nm laser irradiation (300 J, 1 W, 10 min) (MIL) is high enough to destroy the PSH and further promote chondrocyte proliferation in an Italian group (Morrone *et al.* 2000). As the lack of vascularity in cartilage in vivo leads to the relative hypocellularity, Italian group's cellular model might not be a best cellular model of cartilage regeneration. Apoptosis and proliferation are two kinds of cellular functions, and their transformation

into each other can only be realized by dPBM. MPBM induced anti-apoptosis has been observed for serum-free induced apoptosis of myofibers and their adjacent cells, as well as cultured myogenic cells with MHNL(177 mW/cm^2, 3 s) (Shefer *et al.* 2002), and nutritional deficiency induced Cho K-1 cell apoptosis with a GaAlAs semiconductor laser irradiation (810 nm, 1990 mW/cm^2, 1 s) (Carnevalli *et al.* 2003). Both Shefer *et al.* (2002) and Carnevalli *et al.* (2003) have found MIL induced proliferation (function 1) of the cells in serum-deprivation-induced apoptosis (function 2), but it was mediated by MIL induced ROS and its MAPK activation (Shefer *et al.* 2002). In above cases, MPBM can change functions from one into another so that it is not a homeostatic regulation.

Human osteoblasts were kept under standard conditions (37°C, humidified incubators, with 5% CO_2) in phenol-red-free Dulbecco's Modified Medium supplemented with 10% FCS so that they were in PSH. They did not alter their alkaline phosphatase (ALP) activity under 690 nm laser irradiance of 51 mW/cm^2. However, the irradiance at 102 mW/cm^2 and 204 mW/cm^2 resulted in a significant ($P < 0.005$) increase, respectively (Haxsen *et al.* 2008). In this case, the MIL at 102 mW/cm^2 and 204 mW/cm^2 disrupted the PSH and increases the intracellular sirtuin 1 (SIRT1) activity so that the cells were nearer to differentiation-specific homeostasis (Fig. 7.8).

8.4.2 Function-specific homeostasis specific photobiomodulation

Intravascular low energy laser therapy (ILELT) is an intravascular application of MIL. MPBM might promote ROS generation, but the concentration of endogenous photosensitizers is so low and the radiation time is so short that the generated ROS can not disrupt the FSH in ILELT. Therefore, ILELT is just a clinical application of fPBM. Mi XQ *et al.* (2004) have studied the effects of 632.8 nm (150 mW/cm^2, 540 J/cm^2) and 532 nm (150 mW/cm^2, 90 or 180 J/cm^2) laser irradiation on some rheological factors in human blood in vitro, and found no PBM on the rheological factors in blood from health persons. Wang TD *et al.* (1992) have studied MHNL of extracorporeally circulatory blood on ATP phosphohydrolase (ATPase) activities of erythrocyte membrane in 13 cases of patients with insulin dependent diabetes mellitus. The results showed that ATPase were significantly lower in insulin dependent diabetes mellitus than that in control healthy subjects in FSH ($P<0.01$), MPBM could markedly activate the Na^+/K^+-ATPase, Ca^{2+}, Ma^{2+}-ATPase of the patients with insulin dependent diabetes mellitus ($P<0.05$ or 0.01), but could not significantly affect the ones of the control ($P>0.05$). ROS generation in whole blood can be registered with LDC. Acute pneumonia and asthmatics (Farkhutdinov *et al.* 2001), or bronchial asthma (Farkhutdinov *et al.* 2007) patients with intensive LDC exposed to ILELT retained free radical oxidation defects and the disease symptoms because the reduced enzymic and non-enzymic antioxidant activities in acute pneumonia (Cemek *et al.* 2006) and the reduced activities of antioxidant enzymes in asthmatics (Mitsunobu *et al.* 2003), but ILELT activated ROS generation and raised treatment effectiveness in low intensity of blood LDC.

Xiao XC *et al.* (2005) have treated 21 and 18 patients of cerebral infarction by ILILT with LGAL at 3.5~4.0 mW for 30 min and ILELT with GaInP/AlGaInP diode laser irradiation at 650 nm at 2.5~3.0 mW for 30 min, respectively, and then use single photon emission computed tomography (SPECT) of brain perfusion imaging to study the changes of regional cerebral blood flow (rCBF) and brain blood flow function change rate (BFCR%), and found the ratio of local rCBF vs whole brain rCBF and BFCR% increased in the focus side of the brain after the treatment

of either ILILT or ILELT, but no change in the mirror health regions.

8.5 Cellular Rehabilitation

Physicians have long recognized that a therapeutic drug eliciting the desired response in one patient (maximal efficacy for the disorder being treated, with minimal side effects) may achieve only a suboptimal response in another patient. Phenomenology of PBM indicated that PBM is cell-specific. Kipshidze *et al.* (1996) have determined the effect of LIL on growth of rabbit and human aortic endothelial cells (ECs) and smooth muscle cells (SMCs) in vitro. All cell cultures were irradiated with single dose LIL using LHNL with different energy densities. Both human and rabbit ECs revealed enhanced growth rate and reached confluence faster following LHNL with 0.54 J/cm^2 than control non-irradiated cells. Higher doses of LHNL, however, decreased cell growth. In contrast, the experiments on SMCs revealed that nontoxic doses of the LHNL did not enhance growth rate and there was no difference in comparison with control cultures. Higher doses of LI were cytotoxic for both ECs and SMCs and decreased their growth. In this case, the cell-specific LHNL at 0.54 J/cm^2 promoted EC proliferation, but it has no PBM on SMC proliferation. Kipshidze *et al.* (1998) further showed that endoluminal irradiation with LHNL prevents restenosis after balloon angioplasty in an atherosclerotic rabbit model.

As discussed in chapter 1, all of low level/intensity/energy LI therapy, soft LI or cold LI therapy and LI therapy based on the biostimulation or PBM used the same principles. The same principle should be fPBM from the above discussion, and all the therapeutic approaches should be the clinic applications of fPBM so that they are unified to be denoted as LLLT. Of course, LLLT included ILILT and ILELT.

Cell rehabilitation rate has once been used to assay the cytotoxicity of radiation (Korogodin *et al.* 1997) or drugs (Wang XL *et al.* 2007). It represents the function recover of the cells cultured in fresh media for 72 hours after they are irradiated at the given dose or cultured in the media with a drug for 24 hours. LLLT is a clinic application of cell-specific fPBM. It may promote the cellular function recovery and elevate the cell rehabilitation rate so that it is of cellular rehabilitation. LLLT might be the first therapeutic approach which is found to be of cellular rehabilitation.

We have studied RLED 640 promotion on the recovery of differentiated PC12 (dPC12) cells from H_2O_2 cytotoxicity (Liu TCY *et al.* 2010c). {[t(HM)],[t(FM)]} meant dPC12 cells were cultured with the medium of hydrogen peroxide (H_2O_2) at 150 umol/L for t(HM) hrs and then with fresh medium for t(FM) hrs. There were the non-radiant groups{[0.5, 1, 3, 6, 12], [0, 3, 6, 12, 24]}, the radiant groups {[0.5], [0, 1, 3, 6, 9, 12]} which were irradiated with RLED640 at 0.06mW/cm^2 for 10, 20, 40 and 60 min and 72 mJ/cm^2 for 5, 10, 20 and 40 mins, respectively. It was found that the dPC12 cell viability decreased with t(HM), but there were no significant differences between different t(FM). Among the radiant groups {[0.5], [6]} at 0.06mW/cm^2 or 72 mJ/cm^2, 10 and 20 mins irradiation was the most effective in promoting cellular rehabilitation, respectively. RLED640 may promote the recovery of dPC12 from H_2O_2.

There are almost equal numbers of positive and negative results on fPBM or LLLT. In our opinion, there was something wrong with the negative results. For example, the negative results might be due to its trying to modulate the function in FSH or its inattentive research on dose

relationship which will be discussed in the next chapter. At this point, we only discuss positive results.

9 Photobiomodulation Process

Photobiomodulation (PBM) is a modulation of laser irradiation or monochromatic light (LI) on biosystems. As chapter 1 has pointed out, phototherapy was as old as traditional Chinese medicine (TCM) was. However, low level LI (LLL) effects was deeply studied just after laser was discovered and biostimulation as their mechanism was put forward in 1970. As its research became deeper, bio-inhibition was also found, and PBM was put forward to describe the mechanism of LLL effects in 1996 (Kipshidze *et al.* 1996). PBM is now more popularly used than biostimulation is.

Since its introduction in the early 1960s, laser has transformed phototherapy. Now in its developing years, the PBM field is still experiencing growing pains especially in dose relationship. The dose relationship of PBM is very important topic which has been often underestimated. A paper of excellent results could not been referred because there has been no clear dose relationship. Some international groups always reported negative results of PBM since their inattentive research on dose relationship, which have left other researchers or physicians confused. Many Chinese groups have done the same things so that there almost was no laser acupuncture in clinic, and intravascular low energy laser therapy (ILELT) was forbidden by Chinese health ministry.

At the same time, there are signs that the field is maturing especially in extraocular phototransduction (EPT), as researchers confront the limitations of PBM research. As early as 1996, we have put forward quasi-hormone model of laser biostimulation from the viewpoint of EPT (Liu TCY *et al.* 1996, Liu TC *et al.* 1997), which was developed as the biological information model of PBM (BIMP) (Liu TCY *et al.* 2003). The possibility of circadian EPT was put forward by Campbell *et al.* (1998) in explaining their investigation that LIL exposure to the area behind the knee caused phase shifts of the human circadian rhythms. The first EPT phenomenon was observed in low intensity 632.8 nm He-Ne laser irradiation (LHNL) induced respiratory burst of polymorphonuclear neutrophils (PMNs) in our laboratory in 2001 (Duan R *et al.* 2001). Since then, many low intensity LI (LIL) induced EPT phenomena have been observed. Moreover, BIMP has held for the EPT phenomena.

In this chapter, we study the dose relationship of PBM from dynamic viewpoint, and discuss EPT mediated LIL PBM (LPBM) and reactive oxygen species (ROS) mediated PBM of moderate intensity LI (MIL) from phototransduction.

9.1 Dynamic Photobiomodulation

The first law of photochemistry (and photophysics) states that light must be absorbed for photochemistry (or photophysics) to occur. This is a simple concept, but it is the basis for performing photobiological experiments correctly. Since photobiological and phototherapeutic effects are initiated by photochemistry (or photophysics), unless light of a particular wavelength is absorbed by a system, no photochemistry (or photophysics) will occur, and no photobiological effects will be observed, no matter how long one irradiates with that light.

There are many processes of PBM from LI absorption to the observed biomedical effect among which one process is called the key process[1] which is very critical for PBM, and its rate

[1] A complicated process consists of many subprocesses each of which has its rate. The key subprocess is one of

determines PBM rate. The dynamics of PBM tries to find the key process, and discuss further the dose relationship of PBM. There is little research on the dynamics of PBM although its phenomena and mechanism have been widely studied, which is in the way of the deep research of PBM mechanism, especially the urgent research on the dose relationship in clinic applications.

The biosystem is very complicated, but it can be studied at cellular level. The primary process of cellular PBM of LI is the interaction of LI with cellular molecules. The key process of cellular PBM was studied by means of comparison of the transition rate of its primary process with its dose relationship after reviewing cellular PBM in this section.

9.1.1 Primary Process

LLL therapy (LLLT) works provided us with sufficient empirical evidence of the value of light in medicine. The scientific evidence for this rests in quantum physics, the photoelectric effect first discovered by Hertz, and the theory of light elucidated by Albert Einstein. According to the photoelectric effect, when light strikes any material substance, electrons are discharged, creating a current. Simply, light interacts with matter as the energy of the light is transferred to the electrons. In 1905, Einstein offered an explanation for this phenomenon with his corpuscular theory of light, for which he was awarded a Nobel Prize.

Einstein proposed that light is composed of corpuscular units called photons. He further claimed that a photon is the smallest unit of light and has a dual nature, being both a particle and a wave at the same time. A photon travels at the rate of light and its energy is related to the frequency of radiation. The energy of the photon is transferred to the electrons when it collides with any material substance. The shorter the wavelength of light, the greater the energy transferred to the electron. The intensity of the light determines how many photons strike given surface and how many electrons are, thus, affected. The higher the intensity, the greater the number of photons and therefore, the greater the amount of energy transferred to the electrons. Hence the physics of lasers were first imagined by Einstein.

For cellular PBM, the material substance is a cellular molecule. The primary process of PBM is a molecule-LI interaction. A molecule in the ground state $|n\rangle$ with energy E_n has been irradiated with LI at angular frequency ω and intensity I for radiation time t. According to quantum mechanics, the coefficient, $\langle k|n\rangle$, of the ground state $|n\rangle$ in the expansion of the wavefunction of the excited state $|k\rangle$ with energy E_k at the time t is denoted by the following equation under the electric-dipole approximation

$$\langle k|n\rangle = \frac{1}{2\hbar}\sqrt{I}D_{kn}\frac{1-\exp[i(\omega_{kn}-\omega)t]}{\omega_{kn}-\omega} \tag{1}$$

where $\hbar$ is the reduced Plank constant, D_{kn} is the matrix element, and $\omega_{kn} = (E_k - E_n)/\hbar$. We then have the transition rate of the molecule (Liu TCY *et al.* 2003&2005)

$$r = \frac{d}{dt}\left|\langle k|n\rangle\right|^2 = \frac{1}{2\hbar^2}\left|D_{kn}\right|^2 I\frac{\sin(\omega_{kn}-\omega)t}{\omega_{kn}-\omega} \tag{2}$$

If the identical protein molecules interacting with LI are in the membrane of the cell or their organelles(Fig. 7.1), the identical molecules might cooperate with each other to form coherent states when the related function is far from its function-specific homeostasis (FSH), and the

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the subprocesses and its rate is the smallest among the subprocesses.

transition rate of a cell should be (Liu TCY *et al.* 2003)

$$R = \frac{1}{2\hbar^2} C_k N^2 \left|D_{kn}\right|^2 I \frac{\sin(\omega_{kn} - \omega)t}{\omega_{kn} - \omega} \tag{3a}$$

where N and C_k are the number of the identical molecules and the quantum constant of the excited $|k\rangle$. For the resonant transition, $\omega_{kn} = \omega$, we have from Eq. 2

$$r_r = \frac{1}{2\hbar^2} \left|D_{kn}\right|^2 It \tag{4a}$$

We then have the reciprocity rule (Bunsen-Roscoe law) (Karu 1998), the photochemical response is independent of the intensity I and the radiation time t when the dose It is kept constant.

According to whether the primary process is resonant or non-resonant, the pathways mediating cellular PBM are classified into two kinds, the specific pathway which is mediated by the resonant interaction of LI with endogenous photosensitizers such as hemoglobin, flavin and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases which consist of the membrane-bound cytochrome b558 (Lubart *et al.* 2005), the non-specific pathway which is mediated by the non-resonant interaction of LI with the proteins in the membrane of cells or organelles (Liu TCY *et al.* 2003&2005). Eqs. 3a and 4a hold for non-specific pathways and specific pathways, respectively.

Obviously, the non-resonant transition rate (Eq. 2) is extraordinarily small in comparison with resonant transition rate (Eq. 4a) ($r << r_r$) so that the non-specific pathway may be impossible. However, the non-specific pathway may be nonlinearly amplified according to our identical particle model within the frame work of quantum mechanics (Liu TCY *et al.* 2003). There are $10^{3\sim4}$ membrane protein molecules (Fig. 7.1) mediating the non-specific pathway. All the membrane molecules mediating the non-specific pathway are identical. They cooperate with one another to form the coherent states when the related cellular function is far from its FSH. The coherent states can be classified into two kinds, the superradiant state which transition rate is a nonlinear function of the molecular numbers N so that the ultra-weak non-resonant interaction can be amplified according to Eq. 3a, and the subradiant state which transition rate is zero. It has been shown that the function of cells which molecules mediating the non-specific pathway are in superradiant states is not optimal and the cells are far from FSH. Therefore, the PBM mediated by non-specific pathway should be FSH-specific PBM (fPBM). As discussed in the previous chapter, LPBM is mainly mediated by the non-specific pathway (Liu TCY *et al.* 2005) and then might be fPBM. This is in agreement with the conclusion in the previous chapter.

9.1.2 Key Process

The key process is the rate-limiting process. As photodegradation is a key process in governing the residence time and fate of many agrochemicals in top soils (Ciani *et al.* 2005), the primary process of cellular PBM might be supposed to be the key process of cellular PBM so that the dose relationship of cellular PBM should be decided by transition rate of the primary process, Eqs. 3a & 4a, which was called the key process hypothesis of cellular PBM (KPHCP) for convenience. According to KHPH, Eq. 3a should hold for the non-specific pathway mediated response (NSPR),

$$NSPR \propto I \frac{\sin(\omega_{kn} - \omega)t}{\omega_{kn} - \omega} \tag{3b}$$

and the reciprocity rule, Eq. 4a, should hold for the specific pathway mediated response (SPR),

$$SPR \propto It \tag{4b}$$

Therefore, Eqs. 3 &4 might be the dose relationship of LPBM and MPBM because LPBM and MPBM may be mainly mediated by non-specific pathways and specific pathways (Liu TCY *et al.* 2005), respectively. KPHCP was supported by its applications.

MPBM or photodynamic effects is mainly mediated by SPR so that the reciprocity rule, Eq. 4, should hold according to KPHCP. Ben-Dov *et al.* (1999) have studied MPBM on satellite cell proliferation in vitro, and found that there is a linear relationship of PBM and irradiation time when the intensity was kept constant. Stadler *et al.* (2000) have studied the MIL of whole blood on the lymphocyte proliferation, and also found a linear relationship of the PBM and irradiation time when the intensity was kept constant. Obviously, Eq. 3 holds for MPBM. Wang Y *et al.* (1996) have used ILELT to treat New Zealand rabbits with Alloxan-diabetes, and observed the variations of their erythrocyte filtration index (EFI). Their data have been linearized as following

$$\text{First day after treatment,}\quad y_1 = -0.00490x_1 + 0.288\,,\quad R_1 = 0.9130 \tag{5}$$

$$\text{Third day after treatment,}\quad y_3 = -0.0492x_3 + 0.386\,,\quad R_3 = 0.9300 \tag{6}$$

where x , y and R are the intensity, EFI and the correlation coefficient.

LPBM is mainly mediated by NSPR (Liu TCY *et al.* 2005) so that Eq. 3 should hold according to KPHCP. In this case, the reciprocity rule, Eq. 4, should not hold, and LPBM depends intensity or radiation time if the dose is kept constant. From the observations of different research groups and their own observations, Sommer *et al.* (2001) concluded that the threshold parameters dose and intensity are biologically independent from each other. The analysis of intensity and radiation time dependences for the same biological response indicates that the reciprocity rule does not hold when HeLa cells are irradiated with LHNL (Karu *et al.* 1982). Although few studies have addressed the validity of the reciprocity rule in experimental and applied photobiology to date, most of these data point to the fact that the rule of reciprocity is invalid or of limited validity for many photobiological reactions, and it has been shown that at a constant total dose, the intensity of the source is a major factor that determines quality and quantity of the response for the effects of LLL (Schindl *et al.* 2001). van Breugel *et al.* (1992) have found LHNL at 1.24 mW/145 s can significantly promote the preliferation of human diploid skin fibroblasts in vitro but the irradiation at 0.55 mW/330 s or 5.98 mW/30 s can not although their doses are almost the same. Lubart *et al.* (1993) have investigated the effect of LIL on mammalian cells. They found that the induction of fibroblast proliferation at a constant dose depends on the applied intensity in a non-linear manner. In the research of Li YL *et al.* (2004), PMNs were irradiated by LHNL at doses of 800, 1,000, 1,800, and 2,000 J/m^2, respectively, and the intensity was changed at each dose. They found that the NADPH oxidase activity was different at different intensity for each dose of LHNL. Lanzafame *et al.* (2007) have studied the effects of red light at 670nm from light emitting diode array (RLED 670) on pressure ulcers of C57/BL mice, and found varying irradiance and exposure time to achieve a specified energy density affects phototherapy outcomes.

When the dose of LIL is constant, the reciprocity rule might not hold so that there might be a maximum PBM according to Eq. 3. Let T be defined as following

$$T = (\omega_{kn} - \omega)t \tag{7}$$

From Eq. 3a, we have

$$R = \frac{1}{2\hbar^2} C_k N^2 \left| D_{kn} \right|^2 It \sin T / T \tag{8}$$

and then

$$dR/dt = \frac{1}{2\hbar^2} IC_k N^2 \left| D_{kn} \right|^2 \left(\cos T - \sin T / T \right) \tag{9}$$

Therefore, the transition rate of the primary process and then LPBM arrives at their maximum value, respectively, at $T = T_0$

$$T_0 \cos T_0 = \sin T_0 \tag{10}$$

Karu (1989) have measured DNA synthesis in exponentially growing HeLa cells and proliferation after constant low doses of 632.8 nm (0.01 J/cm²) and 454 nm (0.3 J/cm²) laser irradiation applied within different exposure times (i.e. with different intensities), respectively. Her findings pointed to the non-validity of the reciprocity rule as the biological response varied clearly with different intensities peaking between 1 mW/cm² and 20 mW/cm². Karu *et al.* (2005) also observed dependence of stimulation of DNA synthesis rate on light intensity or irradiation time at a constant dose measured 1.5 h after irradiation of log-phase HeLa cells with a continuous wave dye laser pumped by an argon laser (633 nm, 8 mW/cm^2) at 100 J/m^2, and found the maximum PBM at about 10s.

Obviously, the optimum T_0 and then the optimum radiation time t_0 is dose-independent according to Eqs. 7 and 10. We also observed the maximum PBM of low intensity 810 nm GaAlAs laser irradiation at the constant dose 528 and 2130 mJ/cm^2, respectively, on NIH 3T3 fibroblasts (Cheng L 2007). Moreover, the optimum irradiation time 40 s at the maximum PBM has been found dose-independent (Cheng L 2007). This is a direct support to KPHCP.

KPHCP was also supported by the dose relationship when the intensity or the radiation time is kept constant. There are many works on the dose relationship when the intensity is kept constant (Karu 1998). In this case, the LPBM should be the SIN function of radiation time according to KPHCP and Eq. 3, which is supported by Al-Watban *et al.* (2001), Brill *et al.* (2000), Karu(1998), Karu *et al.* (1981, 2001, 2003 & 2004), Yang XH *et al.* (2006), Zhang Y *et al.* (2003) and Zharov *et al.* (1987).

There are few works on the dose relationship when the radiation time is kept constant. In this case, the LPBM should be the linear function of intensity according to KPHCP and Eq. 3, which is supported by Cheng L *et al.* (2006), Duan R *et al.* (2001), Karu(1998), Liang J *et al.* (2008) and Xu XY *et al.* (2008).

We have studied red light at 640±15nm from light-emitting diode array (RLED 640) promotion on the recovery of differentiated PC12 (dPC12) cells from H_2O_2 cytotoxicity (Liu TCY *et al.* 2010c). dPC12 cells were cultured with the medium of H_2O_2 at 150 μmol/L for 30 min and then with fresh medium for 6 hrs, and were then irradiated with RLED640 at 0.06 mW/cm^2 for 10, 20, 40 and 60 min and 72 mJ/cm^2 for 5, 10, 20 and 40 min, respectively. It was found among the irradiation at 0.06mW/cm^2 or 72 mJ/cm^2, 10 and 20 min irradiation was the most effective in promoting cellular rehabilitation, respectively. Obviously, Eq. 3 may hold.

9.2 Phototransduction

Phototransduction is the process by which a photon of light captured by a molecule of visual pigment generates an electrical response in a photoreceptor cell (Arshavsky *et al.* 2002). In this pathway, the photoreceptor-specific G protein, transducin, mediates between the membrane visual pigment, rhodopsin, and the effector enzyme, cGMP phosphodiesterase. The possibility of circadian EPT was put forward by Campbell *et al.* (1998) in their report that 3 h of bright light exposure to the area behind the knee caused phase shifts of the circadian rhythms of both body temperature and saliva melatonin in humans. However, Yamazaki *et al.* (1999) found no evidence for extraocular photoreceptors in the circadian system of the Syrian hamster, and Wright *et al.* (2002) found the absence of circadian phase resetting in response to bright light behind the knees. The first cellular EPT phenomenon was observed in LHNL induced respiratory burst of PMNs in our laboratory in 2001 (Duan R *et al.* 2001). Duan R *et al.* (2001) found that PTKs—PLC-γ—PKC —NADPH oxidase might mediate the respiratory burst. Since then, many EPT phenomena (Zhang Y *et al.* 2003, Luo GY *et al.* 2007, Gao X *et al.* 2006, Huang P *et al.* 2008) have been observed. According to BIMP, the signal transduction pathways can be classified into two kinds so that the Gs protein mediated pathways belong to pathway 1, and the other pathways mediated by Gi protein, Gq protein, PTKs, PLC, PKCs, PI-3K or MAPK belong to pathway 2. Most of the present pathways found to mediate PBM (Duan R *et al.* 2001, Shefer *et al.* 2001 & 2003, Zhang Y *et al.* 2003, Luo GY *et al.* 2007, Huang P *et al.* 2008) belong to pathway 2. These would be reviewed in this section (Zhu L *et al.* 2009a).

9.2.1 Non-Specific Pathway Mediated Phototransduction

LPBM is mainly mediated by the non-specific pathways (Liu TCY *et al.* 2005). In other words, the non-specific pathways mediated EPT might be observed in LPBM. It should be pointed out that all the EPT phenomena were found by Chinese researchers.

The first EPT phenomenon was observed in our laboratory (Duan R *et al.* 2001). We have probed signal transduction pathways of respiratory burst of bovine PMNs which were induced by LHNL at a dose of 300 J/m^2 for 100 s by using the PTK inhibitor, genistein, the PLC inhibitor, U-73122, and the PKC inhibitor, calphostin C, respectively, and found the inhibitor of PTKs can completely inhibit LHNL-induced PMN respiratory burst, and PLC and PKC inhibitors can obviously reduce it, but not fully inhibit it. These results suggested that PTKs play a key role in LHNL-induced PMN respiratory burst and [PTK-PLC-PKC-NADPH oxidase] signal transduction pathways might be involved in this process (Fig. 7.4).

The second research was done by the cDNA microarray technique in Hong Kong (Zhang Y *et al.* 2003). The gene expression profiles revealed that 111 genes of human fibroblasts were regulated by LIL of red light at 628 nm and can be grouped into 10 functional categories. Two kinds of signaling pathways, the p38 MAPK signaling pathways and the platelet-derived growth factor signaling pathways, were found to be involved in cell growth promoted by LIL.

The third research was done by fluorescence resonance energy transfer (FRET) imaging in MOE Key Laboratory of Laser Life Science & Institute of Laser Life Science. The human lung adenocarcinoma cells, ASTC-a-1 cells, were irradiated with LHNL at 0.8 J/cm^2 in the dark after 24 hours of serum deprivation. Its FRET imaging indicated the PBM was mediated by PKCs (Gao X *et al.* 2006). Serum withdrawal to a 1% level was used as a positive apoptosis control for human cells from

the anulus in vitro (Gruber *et al.* 2000). In Gao X *et al*'s experiments on effects of LHNL at different doses on serum-starved ASTC-a-1 cells, ASTC-a-1 cells were cultured in Dulbcco's modifed Eagle medium (DMEM) supplemented with 1% fetal calf serum (FCS) so that there should be FCS withdraw induced ASTC-a-1 cell apoptosis. Therefore, the PBM phenomena observed by Gao X *et al.* (2006) should be PKCs mediated anti-apoptosis (Wu M *et al.* 2007). A series of FRET papers after the first paper by Gao X *et al.* (2006). They found the roles of PI3K/Akt (Zhang L *et al.* 2009&2010) and H-Ras and PI3K(Gao X *et al.* 2009) in LPBM

LHNL at 0.15 mW/cm^2 has been used to irradiate human umbilical vein endothelial cells and was found to increase endothelial cell proliferation, migration and nitric oxid (NO) secretion in Taiwan (Chen CH *et al.* 2008). The induced endothelial NO synthase (eNOS) expression was inhibited by the PI-3K inhibitor, LY294002, indicating that the effect of LHNL on human umbilical vein endothelial cells could be attributed to the up-regulation of eNOS expression through PI-3K pathway at the cellular and molecular levels (Chen CH *et al.* 2008).

DEX induced C2C12 myotube atrophy was studied as a cellular model of steroid myopathy in our laboratory. The effects of RLED 640 on the cellular model was studied as a cellular model of PBM on steroid myopathy by using the PI-3K activity inhibitor, Wortmannin at 1μmol/L, and MAPK and ERK kinase (MEK) activity inhibitor, PD98059 at 50 μmol/L, and it was found PI-3K might mediate the inhibition of RLED 640 at 3.5 mW/cm^2 for 300 s on MEK mediated C2C12 myotube atrophy induced by DEX at 1 μmol/L (Huang P *et al.* 2008).

LHNL on RBC deformability was found to be mediated by G protein and membrane aquaporin-1 in our laboratory(Luo GY *et al.* 2007). The deformability of chinocytes is dysfunctional. Human echinocytes were cultured with G protein inhibitor, GDP-β-S, at 200 μmol/L for 15 mins, and then were irradiated by LHNL at 5 mW and 5 mins. The deformability of echinocytes was improved by LHNL, but no modulation of LHNL on RBC deformability has been found when the echinocytes were cultured with GDP-β-S. Human echinocytes were irradiated with LHNL at 1-5 mW for 5-30 min, respectively, and aquaporin-1 inhibitor, $HgCl_2$, was used to study the role of aquaporin-1 in mediating PBM at LHNL optimum dose. It was found the LHNL optimum dose promoting echinocyte deformability is 1.3 J/cm^2 at 4.4 mW/cm^2, but it is significantly inhibited by 0.2 μM $HgCl_2$.

Aβ25-35 induced PC12 cell apoptosis is a cellular model of AD (Fig. 7.5). In our laboratory, Duan R *et al.* (2003) has found RLED 640 at 0.09 mW/cm^2 for 60 min inhibited Aβ25-35 induced PC12 cell apoptosis, Zhu L *et al.* (2008) further found that Aβ25-35 enhanced intracellular cAMP level, and RLED 640 promoted further the enhancement but induced the secretion of the anti-apoptosis factors. Zhang L *et al.* (2008) found LHNL at 0.52 mW/cm^2 for 5~40 minalso inhibited Aβ25-35 induced PC12 cell apoptosis, and its FRET imaging indicated that the inhibition was mediated by PKC.

9.2.2 Reactive Oxygen Species Mediated Phototransduction

Although excess ROS are toxic, physiological concentrations of ROS may function as signaling molecules to mediate various responses, including cell migration and growth (Dröge 2002). The ROS family comprises many molecules that have divergent effects on cellular function, such as regulation of cell growth and differentiation, modulation of extracellular matrix production

and breakdown, inactivation of NO, and stimulation of many kinases and proinflammatory genes. For example, increased $\cdot O_2^-$ levels inactivate the vasodilator NO leading to endothelial dysfunction and vasoconstriction, characteristic of many vascular diseases. On the other hand, H_2O_2 acts as a vasodilator in some vascular beds, including cerebral, coronary, and mesenteric arteries (Paravicini *et al.* 2008).

The distinct properties between $\cdot O_2^-$ and H_2O_2 and their different sites of distribution mean that different species of ROS can activate different signaling pathways, which lead to divergent, and potentially opposing, functional responses (Dröge 2002). An abundance of scientific literature exists demonstrating that oxidative stress influences the MAPK signaling pathways (McCubrey *et al.* 2006). It has been shown that different ROS levels activate different MAPK pathways (Fig. 3.7), that is, low level ROS activates ERK mediated MAPK, a signal for proliferation, differentiation or survival, moderate level ROS activates the stress signals JNK or p38 mediated MAPK, which leads to cell survival or apoptosis, and high level ROS leads to cellular apoptosis or necrosis (Bladier *et al.* 1997, Owuor *et al.* 2002). ROS also increased phosphorylation of Akt in a dose-dependent and promoted rapid activation of PI-3K(Zhuang *et al.* 2003, Venkatesan *et al.* 2007), and activated NFκB (Dröge 2002).

ROS may be produced in response to receptor activation. However, given that ROS are diffusible and short-lived, localizing the ROS signal at the precise subcellular compartment is essential for stimulation of specific redox signaling. As a kind of localized ROS signal, MIL induced ROS production has been directly found in PBM. Wu S *et al.*(2007) have studied the apoptotic effect of moderate intensity He-Ne laser irradiation (MHNL) (200 mW/cm^2) on ASTC-a-1 cells, and found immediate generation of mitochondrial ROS following MHNL, reaching a maximum level 60 min after irradiation. Zhang J *et al.*(2008b) use FRET to visualize the dynamic Src activation in HeLa cells immediately after irradiated with MHNL (64.4 mW/cm^2), and found that it was ROS that mediated MHNL induced Src activation.

An Israel group has studied the effects of MHNL at 177 mW/cm^2 on mouse skeletal muscle satellite cells, pmi28 (Ben-Dov *et al.* 1999) or i28 (Shefer *et al.* 2001&2003). The MHNL affected pmi28 proliferation in 5% horse serum in a bell-shaped manner[2], with a peak at 3 s of irradiation (Ben-Dov *et al.* 1999). The 3 s-MHNL drives quiescent i28 cells after 36 h FCS deprivation into the cell cycle and enhances their proliferation via the PI3K/Akt and Ras/Raf/ERK pathways (Shefer *et al.* 2001&2003). The ROS mediated mechanism of the MHNL effects is supported by the phenomenon the thymidine incorporation of the group irradiated for 10 s in 5% horse serum was significantly lower than the one of the control (Ben-Dov *et al.* 1999), which shows the 10 s-MHNL might induce pmi28 apoptosis.

Schieke *et al.* (2002) have found 60 min exposure of cultured human dermal fibroblasts to infrared A (IRA) (760-1400 nm) at 333 mW/cm^2 (MIL) induced the expression of matrix metalloproteinase 1 at the mRNA and protein level via activation of MAPK/ERK1/2. p38 MAKP was also activated but did not mediated expression of matrix metalloproteinase 1 (Schieke *et al.* 2002), which might be due to the long radiation time so that the ROS activates the stress signals. Miyata *et al.* (2006) have studied the effects of a GaAlAs semiconductor 810 nm laser 90 s-irradiation at 231 mW/cm^2 (MIL) on human dental pulp-derived fibroblast-like cells (dental pulp

[2] Bell-shaped manner: Eq. 3 holds. PBM linearly increases and decreases with radiation time before and after the peak, respectively

cells) obtained by primary culture of human dental pulp tissues from extracted third molar teeth, and found the MIL activated MAPK/ERK, but did not activate the stress signals p38 MAPK and JNK in human dental pulp cells.

UVA exposure is associated with increased production of ROS and MAPK activation (Bode *et al.* 2003). Low-dose MIL and high-dose MIL activated MAPK/ERK (Yanase *et al.* 2001, Djavaheri-Mergny *et al.* 2001) and p38/JNK MAPK (Klotz *et al.* 1999), respectively. The effects of UVA (360–400 nm) at 40–44 mW/cm^2 and ≈12 min and singlet oxygen $^1O_2$ [3] are similar in their activation of MAPKs in HSFbs (Klotz *et al.* 1999). In this study, the UVA induced a rapid transient activation of p38 kinase and JNKs, but had little effect on ERKs. The UVA-induced phosphorylation of p38 kinase was diminished in the presence of $^1O_2$ scavengers, sodium azide, or imidazol, but not in the presence of hydroxyl radical scavengers, mannitol, or dimethylsulfoxide, indicating that $^1O_2$ may be a mediator of UVA-induced effects in these cells (Klotz *et al.* 1999). In melanocytes pretreated with *N*-acetyl-L-cysteine, a thiol-containing compound and a general free radical scavenger, UVA (365 nm, 0.2 mW/cm^2, 500 s)-induced activation of ERKs was inhibited (Yanase *et al.* 2001). In the UVA irradiated melanocytes, no DNA damage products were detected, suggesting that the activation of ERKs occurred by upstream signals originating from ROS or from activated tyrosine kinase receptors, but not by signals originating from damaged DNA (Yanase *et al.* 2001). In NCTC 2544 keratinocytes, experimental quenching or enhancing of singlet oxygen levels also indicated an involvement of ROS and MAPK/ERK activation in UVA (4 mW/cm^2, 25, 50, 75 and 100 min)-induced activation of activator protein 1 (Djavaheri-Mergny *et al.* 2001).

9.2.3 Biological Information Model of Photobiomodulation

The different photonic signals in different dose zones have been related with the signal transduction pathways by our BIMP （Liu TCY *et al.* 2003&2005）.

There might be dose zone effect for PBM so that the dose zones are named dose 1, 2, …, from the lowest dose on, respectively. In our laboratory, Cheng L *et al.* (2006) have studied the effects of LHNL on the proliferation and collagen synthesis of cultured HSFs for the constant radiation time, and found that HSF proliferation was inhibited in dose 1 (16, 24 mJ/cm^2), and promoted in dose 2 (298, 503, 597mJ/cm^2), and the collagen synthesis was inhibited in dose 2 (401，526 mJ/cm^2), and promoted in dose 3 (714, 926，1539, 1727mJ/cm^2) .

Color is frequency within the visible spectrum of light. It is composed of a small band of the total electromagnetic spectrum, from violet at 400 nm (higher-energy photon) through red at 700 nm (lower-energy photon). Beyond violet, in increasingly shorter wavelengths, are ultraviolet light, x-rays, and γ radiation which contain tremendous amounts of energy. Infrared and radio waves are longer wavelengths outside the red end and less energetics. Each color of the spectrum is composed of a band of frequencies (Fig. 1.1). Therapeutic applications of LI to the body are accomplished by applying a single monochromatic wavelength within that band. According to BIMP, the color has been extended to include UVA and IRA so that hot color and cold color include IRA and UVA, respectively.

According to BIMP, LI is the input, and the LI induced/modulated cellular functions are the

[3] The ground state of oxygen is a triplet state with two unpaired and parallel electron spins. The singlet oxygen is its excited stated and a kind of ROS.

observed output. As the LI-induced cellular functions are mediated by pathway 1 or 2, BIMP have found the correspondence relationship of LI and the signal transduction pathways for fPBM on the cells far from FSH and developmental PBM (dPBM) on cells. The LI at the same wavelength but at different doses in the same dose zone has the PBM similar to one another, but the one in different dose zones has the PBM different from one another. The correspondence relationship of LI at different wavelength in the n^{th} dose zone and signal transduction pathways was then called BIMP n. In the $(2n-1)^{th}$ (n = 1, 2, …) dose zone, the cold LI and hot LI activates pathway 2 and 1, respectively, according to BIMP (2n-1). In the $2n^{th}$ (n = 1, 2, …) dose zone, the cold LI and hot LI activates pathway 1 and 2, respectively, according to BIMP 2n.

For most of non-specific pathway mediated phototransduction (9.2.1), BIMP 2 holds for the PBM of LHNL (hot color) on PMNs (Duan R *et al.* 2001) and human umbilical vein endothelial cells (Chen CH *et al.* 2008), ASTC-a-1 cells (Gao X *et al.* 2006, Zhang L *et al.* 2010) and African green monkey SV40-transformed kidney fibroblast cells (COS-7) (Gao X *et al.* 2009, Zhang L *et al.* 2009), the PBM of 628 nm light (hot color) on fibroblasts (Zhang Y *et al.* 2003), and PBM of RLED 640 (hot color) on DEX induced C2C12 myotube atrophy (Huang P *et al.* 2008). For the inhibition of Aβ25-35 induced PC12 cell apoptosis (Fig. 7.5), Zhu L *et al.* (2008) found the PBM of RLED 640 at 0.09 mW/cm^2 for 60 min (Dose 1) was mediated by cAMP (BIMP 1 holds), but Zhang L *et al.* (2008) found the PBM of LHNL at 0.52 mW/cm^2 for 5~40 min(dose 2) was mediated by PKC (BIMP 2 holds).

For ROS mediated phototransduction (9.2.2), BIMPs 1-3 hold for MAPK mediated PBM of UVA (cold color) on fibroblasts (Bode *et al.* 2003). BIMP 4 holds for the PBM of MHNL (hot color) on skeletal muscle satellite cells (Shefer *et al.* 2001) and skeletal muscle myoblasts (Shefer *et al.* 2003), and the PBM of IRA (hot color) on fibroblasts (Schieke *et al.* 2002). Src activation belongs to pathway 2. For MHNL induced Src activation (Zhang J *et al.* 2008b), BIMP 2 holds.

Almost all the found pathways of EPT belong to pathway 2. Although there were a few studies on EPT, there have been much more PBM phenomena which support BIMP (Liu TCY *et al.* 2003). Of course, the already done studies on EPT were rather primary, and the further work should be done.

EPT may be a linear signaling cascades which has been discussed above and depicted in Fig. 9.1A. However, it may be actually a network organization of cellular signaling depicted in Fig. 9.1B. Living cells are complex systems that are constantly making decisions in response to internal or external signals. Among the most notable carriers of information are protein kinases and phosphatases, enzymes that receive inputs from cell surface or internal receptors and determine what actions should be taken in response, by phosphorylating or dephosphorylating substrates. Breitkreutz *et al.* (2010) have revealed the kinase-phosphatase interaction network (Fig. 9.1B) describing how protein kinases and phosphatases in budding yeast are associated with other proteins and, most notably, with each other. In Fig. 9.1B, the high degree of connections among kinases and phosphatases suggests a "board of directors" type of organization, whereby many proteins outside of the canonical pathway (in red) can influence its output. Such cooperative organization might allow the network to integrate several inputs and output complex responses. A certain degree of noise is expected to emanate from such a network.

9.3 Discussion

Almost all the previous clinical applications of ILILT have adopted only one LIL dose, and have not studied the LIL dosage yet. This did not indicate there should be one dose for one disease since the negative results did not be published. As cellular BIMP has pointed out, there should be a dose zone for the PBM on a cellular function far from its FSH. The clinic applications of PBM are based on the cellular studies so that there should be a dose zone for a specific disease. Of course, the dose zone should include the used dose, but the optimum dose in the dose zone should be found in terms of dosage studies according to one of the three ways as discussed in section 9.1, the fixed radiation time, the fixed intensity and the fixed dose.

The dosage, intensity or dose, discussed above should be the effective dosage at which LI exactly interacts with the target cells. The LI gets weaker and weaker the further from the surface it penetrates so that there may be a difference between the LI dosage and its effective dosage especially for the clinical applications. The dosage for PBM should be location-specific in order to get the same effective dosage. This LI penetration is on tissue type, pigmentation, and dirt on the skin or membrane. LI can even penetrate bone (as well as it can penetrate muscle tissue). Fat tissue is more transparent than muscle tissue.

As discussed in chapter 3, almost every pathway mediated ILILT is in or under the nasal mucosa. The LIL penetration and then the LIL dose in ILILT is person-dependent because the thickness of the nasal mucosa is person-specific. It is necessary to increase LIL doses in ILILT to penetrate thicker nasal mucosa. It should be pointed out the dosage used in the previous clinical applications as discussed in chapter 5 is just for reference for the further clinical applications.

10 Photonic Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is an integral part of the glorious culture of the Chinese nation. In the past several thousand years, it has made outstanding contributions to the flourishing and prosperity of the Chinese nation, and with remarkable efficacy, striking national characteristics, unique diagnostic methods, systematic theoretical system and abundant historical literature materials, it stands as an indispensable part of the medical sciences of the world, constituting a common wealth of the medical treasure house of the mankind. The fact that it has not been declining during the past several thousands of years indicates the vitality of itself. Accompanying the development of reform and opening to the outside world, and with the progress in TCM work, international exchange and cooperation in the field of TCM is increasing, and thereby the international influence and status of TCM are continuously elevated. However, the progress of sciences depends on the one of technology. As TCM technology did not made any revolutionary progress, TCM is just an alternative medicine even in China.

In recent year, photonics has made marvelous progress. There are many definitions of photonics. According to Poldervaat's definition, a photon of laser irradiation or monochromatic light (LI) is not only a carrier of energy but also a carrier of information. Recently, the biological information function of photons has been used in TCM diagnosis and treatment. At this point, Liu SH, academician of Chinese Academy of Sciences in optics in our university, South China Normal University, and Deng TT, famous TCM professor in TCM university of Guangzhou, have put forward an inter-discipline of photonics and TCM, photonic TCM. It studies TCM, such as the diagnostics, therapeutics, indistinct disease theory, rehabilitation, health care and so forth, by using photonics. In this chapter, we will review its progress in modern basis of *yin-yang* principle, cellular photobiomodulation (PBM) and laser acupuncture (LA).

10.1 *Yin-Yang* Model

The role of process or function in TCM is the same as the one of state or structure in modern sciences so that TCM might be called process medicine. As process philosophy become more popular, TCM become more important. *Yin-yang* is one of the basic models of TCM to establish a system of physiology, pathology, diagnosis and therapy of diseases (Shuai 1992).

It should be pointed out that the *yin-yang* model is only used to discuss TCM objects such as whole body, five *zang*s, six *fu*s or meridians. However, the *yin-yang* concept is widely used in the cellular level for modern sciences (Tan YH 1993, Hunter 1995, Akam 1998, La Thangue 2003, Ou BX *et al.* 2003). For example, Ou BX *et al.* (2003) propose that *yin-yang* balance is antioxidation-oxidation balance with *yin* representing anti-oxidation and *yang* as oxidation. At this point, the *yin-yang* model of TCM should be extended to discuss cellular processes.

A process might be represented by the process-specific time t_p (Liu TCY *et al.* 2003). For example, the time spending in 100 m running track is the process-specific time of 100 m running track, $t_p(100m)$. Obviously, the shorter the $t_p(100m)$, the more excellent the runner and the more difficult the running process. At this point, the degree of difficulty (DD) of a process has been defined in terms of the process-specific time t_p (Liu TCY *et al.* 2003) so that the shorter the

process-specific time, the higher the DD:

$$t_p \downarrow, \text{DD} \uparrow \tag{1}$$

After comparative research with the TCM *yin-yang* model (Shuai 1992), we redefine *yin* and *yang* in terms of DD: the process of low DD is defined to be *yang* and the process of high DD is defined to be *yin* for the two nonlinearly coupled processes of a system, which is called the DD *yin-yang* model. As Tab. 10.1 has shown, TCM *yin-yang* model and DD *yin-yang* model are agreed with each other.

Table 10.1 DD and TCM *Yin-Yang*

Physiological system or process	DD(process-specific time)		TCM *Yin-Yang*	
	Low(long)	High(short)	*Yang*	*Yin*
Five *zang*-organs	(Heart, brain) lungs	Liver, kidneys (spleen, pancreas)	Heart, lungs	Liver, kidneys, spleen
Autonomic nervous system	sympathetic nervous subsystem	parasympathetic nervous subsystem	sympathetic nervous subsystem	parasympathetic nervous subsystem
Color(vision)	hot	cold	Hot	cold
Cell signal transduction	Pathway 2	Pathway 1	Pathway 2	Pathway 1
LI dose 1	Cold	Hot	Cold	Hot
LI dose 2	Hot	Cold	Hot	Cold
LI dose 3	Cold	Hot	Cold	Hot
LI dose 4	Hot	Cold	Hot	Cold

Note：1 pathway 1: Gs pathway: cAMP↑; pathway 2：Gq, Gi or non-G protein mediated pathways: cAMP↓.
2 Cold-color : green, blue, violet, UVA; Hot-color : red, orange, yellow, IR (Fig. 1.1).

As a typical example, we discuss the cellular membrane receptor mediated signal transduction pathways. They can be classified into two classes, the one mediated by the G proteins, and the non-G protein pathways mediated by the kinases such as PTKs, PI-3K or MAPK. The receptor of the former pathway strides membrane seven times. However, the receptor of the latter pathway strides membrane less than seven times. Obviously, the activation of the former receptors is more difficult than the latter receptors is. In terms of Eq. 1, we have

$$t_p(\text{non-G protein pathways}) > t_p(\text{G protein}) \tag{2}$$

G protein consists of α, β and γ subunits. In the pathway mediated by G protein, the migration of the α subunit is the key elementary process that is of the shortest process-specific time. The larger the molecular mass of α subunit, the more difficult the migration. As molecular mass (α_s) > molecular mass (α_q) > molecular mass (α_i), we have from Eq. 1

$$t_p(\text{G}_i) > t_p(\text{G}_q) > t_p(\text{G}_s) \tag{3}$$

In chapter 8, the signal transduction pathways have been classified into two kinds, pathway 1 which is Gs protein mediated pathway: cAMP↑, and pathway 2 which is G_i protein mediated pathway, G_q protein mediated pathway, or one of non-G protein mediated pathways: cAMP↓, according to our biological information model of photobiomodulation (BIMP) (Liu TCY *et al.* 2003). We then have from Eqs. 2 and 3

$$t_p(\text{pathway 2}) > t_p(\text{pathway 1}) \tag{4}$$

According to the DD *yin-yang* model, we have cellular *yin* and *yang* from Eq. 4 since the protein kinases of two kinds of pathways might phosphorylate the same protein bands:

Pathway 1 belongs to *yin*, and pathway 2 belongs to *yang* (5)

As Tab. 9.1 has shown, TCM *yin-yang* model and DD *yin-yang* model are agreed with each other.

10.1.1 *Yin-Yang* Parallel Principle

According to the time parallel principle (Liu TCY *et al.* 2003), the changes of the process-specific times of two weakly nonlinearly coupled processes are parallel to each other:

$$t_{p1} \uparrow,\ t_{p2} \uparrow \tag{6}$$

This is in agreement with the TCM *yin-yang* parallel principle for TCM objects (Shuai 1992) according to the DD *yin-yang* model so that it is called the DD *yin-yang* parallel principle: the *yin* process of one system is related with the *yin* process of the other system and the *yang* process of one system is related with the *yang* process of the other system between the processes of two weakly nonlinearly coupled systems, which is supported by the modern research of TCM herb done by Ou BX *et al.* (2003) and Ko KM *et al.* (2004) in Hong Kong. As Ou BX *et al.* (2003) have stated, the *yin*-tonic traditional Chinese herbs have, on average, about six times more antioxidant activity (*yin*) and polyphenolic contents than the *yang*-tonic herbs. As Ko KM *et al.* (2004) have pointed out, although *yang*-tonic herbs tend to boost body function possibly through enhancing the mitochondrial oxidative processes (*yang*), the *yin* property (i.e. antioxidant potential) of these herbs can also play a role in safeguarding mitochondrial adenosine-5'-triphosphate (ATP) generation.

10.1.2 *Yin Ping Yang Mi*

There are two kinds of modern viewpoints on *yin ping yang mi* of the TCM *yin-yang* model, *yin-yang* balance (Shuai 1992) and function-specific homeostasis (FSH) in which both *yin* and *yang* works in optimum. Only the latter viewpoint was supported within the framework of the DD *yin-yang* model so that we call it the DD *yin ping yang mi*. As discussed in the previous two chapters, there is no FSH-specific photobiomodulation (fPBM) on a function in FSH, but fPBM can modulate a function far from the FSH; and developmental PBM (dPBM) can disrupt FSH so that it can change the cellular functions from one to another. In other words, PBM can modulate cellular functions from the viewpoint of *yin-yang*, which would be detailedly discussed in the following three sections.

Yoon *et al.* (2003) found that treatment of chondrocytes in protein-synthesis-specific homeostasis with indomethacin alone did not affect the accumulation of sulfated proteoglycan or type II collagen expression although pretreatment of chondrocytes with indomethacin blocked the NO-induced dedifferentiation

Paik *et al.* (2000) found that treatment of RAW 264.7 cells in NFκB-specific homeostasis with flufenamic acid alone does not affect the basal promoter activity of NFκB although pretreatment with flufenamic acid leads to a dose-dependent inhibition of LPS-stimulated

transcriptional activity of NFκB reporter genes.

10.1.3 *Yin-Yang* Inter-Transformation

Yin and *yang* will transform into each other under some condition according to TCM (Shuai 1992), which can be extended to other systems such as cells according to the DD *yin-yang* model so that it is called the DD *Yin-Yang* inter-transformation. This is supported by the cellular research done by Paik *et al.* (2000) and Lee SP *et al.* (2004). Paik *et al.* (2000) have found flufenamic acid induces cyclooxygenase (COX)-2 expression (*yang*) but it inhibits lipopolysaccharides (LPS)-induced COX-2 expression (*yin*). Lee SP *et al.* (2004) have found, in cells that coexpress D1 and D2 dopamine receptors, application of a D1 or a D2 dopamine agonist alone leads to receptor-mediated effects on adenylyl cyclase activity, with the D1 receptor activating adenylyl cyclase through $G_{s/olf}$ (*yin*) and the D2 receptor inhibiting adenylyl cyclase through $G_{i/o}$ (*yang*). After coactivation of D1 and D2 receptors, the D1-D2 receptor complex leads to the activation of PLC through G_q (*yang*).

The DD *Yin-Yang* inter-transformation holds for BIMP. The *yin* and *yang* of LI depend on its dose. According to BIMP, the dose zones were called dose 1, dose 2, …, dose n, …, from the lowest dose on so that there is different qualitative PBM in different dose zones and there is the same qualitative PBM in the same dose zone。 In dose 1, the lowest dose for PBM, we have the *yin-yang* of LI according to Tab. 10.1

Hot color belongs to *yin*, and cold color belongs to *yang* (7)

We then have BIMP 1 from Eqs. 5 and 7 and the DD *yin-yang* parallel principle

Hot color activates pathway 1, cold color activates pathway 2 (8)

If the dose is in dose 2 which is larger than the threshold of dose 1, the *yin-yang* properties of LI will transform into each other according to the DD *Yin-Yang* inter-transformation so that we have,

Hot color belongs to *yang*, and cold color belongs to *yin* (9)

We then have BIMP 2 from Eqs. 5 and 9 and the DD *yin-yang* parallel principle

Cold color activates pathway 1, Hot color activates pathway 2 (10)

Generally, we have Eq. 10 according to the DD *yin-yang* inter-transformation if the dose is in dose 2n (n = 1, 2, 3, …) which is larger than the threshold of dose 2n-1 if it does not damage membrane or cell compartments so that Eq. 10 is called BIMP 2n, and we have Eq. 8 according to the DD *yin-yang* inter-transformation if the dose is in dose 2n+1 (n = 1, 2, 3, …) which is larger than the threshold of dose 2n if it does not damage membrane or cell compartments so that Eq. 8 is called BIMP 2n+1. Of course, it should be noted that BIMP only holds for fPBM on the cells far from the FSH and dPBM.

10.1.4 *Yin-Yang* Antagonism

Yin and *yang* will antagonistic with each other according to TCM (Shuai 1992), which can be extended to other systems such as cells according to the DD *yin-yang* model so that it is called the DD *yin-yang* antagonism. Cellular *yin* and *yang*, pathways 1 and 2, are antagonized with each other. For example, Gs-mediated pathway and Gi-mediated pathway are antagonized with each other (Spät *et al.* 2004).

Yova *et al.* (1994) have shown that the effects of low intensity He-Ne laser irradiation

(LHNL) in dose 2 and adrenalin on erythrocyte deformability are antagonistic. Adrenalin can elevate the intracellular cAMP level, and belongs to DD *yin*. However, LHNL in dose 2 can lower the intracellular cAMP level according to BIMP2, and belongs to DD *yang*. The observed result is due to the DD *yin-yang* antagonism.

One has the same results when the HeLa cells were simultaneously irradiated with narrow-band red light in dose 2 and a wide-band cold light in dose 2 (Fig. 10.1). In this cases, the red light belongs to DD *yang*, and the cold light belongs to DD *yin* according to BIMP 2, and the DNA synthesis rate was near control level due to the DD *yin-yang* antagonism.

10.1.5 *Yin-Yang* Interdependence

Yin and *yang* depend on each other according to TCM (Shuai 1992), which can be extended to other systems such as cells according to the DD *yin-yang* model so that it is called the DD *yin-yang* interdependence. Cellular DD *yin* and DD *yang* depend on each other since the protein kinases of two kinds of pathways might phosphorylate the same protein bands.

Karu (1998) has studied the stimulation of DNA synthesis in HeLa cells after consecutive irradiation with blue and red light in dose 2 (Fig. 10.2), and she found, the sequence 633 nm followed by 404 nm had no effect on DNA synthesis, but the sequence 404 nm followed by 633 nm stimulated it. DNA synthesis mediated by pathway 2 in HeLa cells belongs to DD *yang* according to Eq. 5, and the stimulation of DNA synthesis in HeLa cells is to reinforce DD *yang*. Karu's results (Karu 1998) shows that the sequence reinforcing DD *yang* followed by replenishing *yin* can not reinforce DD *yang* due to the DD *yin-yang* antagonism, only the sequence replenishing DD *yin* followed by reinforcing DD *yang* can reinforce *yang* due to DD *yin-yang* interdependence.

10.2 Laser Acupuncture

It has been known that acupuncture has various effects such as analgesia, promotion of FSH establishment, improvements in circulation, and rectification of internal disorders (Lee JD *et al.* 2004). Acupuncture has been used in the treatment of a variety of illnesses for more than 2000 years. The practice of acupuncture is based on a theoretical system different from our understanding of human anatomy and physiology, and has developed through experience and observation. Stimulation of selective acupoints (situated along 'meridians' in the body) by inserting needles is believed to restore bodily functions by promoting the flow of 'vital energy', throughout the system. Other forms of stimulation which have been developed are heat, electrical stimulation, magnetism and, recently, laser from 1970s on. LA offers distinct advantages over the traditional method because the procedure is pain-free and non-traumatic. Clinical applications include the control of pain in osteoarthritis, lumbago and migraine, and anaesthesia for certain surgical procedures, as well as other ailments of the cardiovascular, respiratory and nervous systems (Wang LQ *et al.* 1993, Chen TR *et al.* 1995, Tunér *et al.* 1999, Jiao JL *et al.* 2003). Among them, LA devices were cleared for marketing by Food and Drug Administration in USA (FDA) through the Premarket Notification/510(k) process as adjunctive devices for the temporary relief of pain. In this section, the mechanism of LA will be discussed.

There are many pathways mediating LA. One of the pathways is from PBM on acupuncture point cells to autonomic nervous system (ANS) which includes sympathetic nervous subsystem

(SN) and parasympathetic nervous subsystem (PSN) through meridian. Wu JH *et al.* (2008) applied laser energy to the *neiguan* acupoint (PC6) (Fig. 3.3) to examine the impact of LA on the ANS of 45 healthy young males who were night shift workers and evaluated their heart-rate variability (HRV). The laser group (n = 15) received LA (9.7 J/cm^2, 830 nm) for 10 min, and the placebo group (n = 15) received sham laser treatment. After treatment and after the 30-min rest period, the independent-sample t-test showed that both groups exhibited statistically significant differences in high-frequency band (HF), low-frequency band (LF), and the LF/HF. Compared with the placebo group, the paired-samples t-test showed that after laser treatment the treatment group had a statistically significant improvement in HF, LF, and the LF/HF. They concluded LA stimulation applied to the *neiguan* acupoint increased vagal activity and suppression of cardiac sympathetic nerves. This effect was positive and could be used to help patients who have circadian rhythm disorders.

LI can be nonlinearly coupled with ANS through meridian. LI used for LA is often hot color such as red or infrared A (IRA). As the *yin-yang* of LI is dependent on its dosage in Tab. 10.1, we have the following model in terms of the 3rd line and 5-8th lines of Tab 10.1 and DD *yin-yang* parallel principle:

at dose 1($10^{0\sim3}$ J/m^2), the LI activates *yin* process such as PSN;
at dose 2($10^{3\sim5}$ J/m^2), the LI activates *yang* process such as SN;
at dose 3($10^{1\sim2}$ J/cm^2), the LI activates *yin* process such as PSN;
at dose 4($10^{3\sim4}$ J/cm^2), the LI activates *yang* process such as SN.

In this section, we apply the above model to discuss the clinic basic research of LA.

Zheng ZP (1981) irradiated ear acupoints with LHNL at 3.8 mW, twice a day, 15 min each time (~10^5 J/m^2, dose 2). He found that it suppressed the increase of the salivary secretion which was induced by the medicine of anti-mental disorders. When SN is activated , the function of the salivary secretion is suppressed (Wang ZD *et al.* 1994, Gao L *et al.* 1997). Hence, the hot color laser irradiation of dose 2 can reinforce *yang* and promote the SN activity.

Chen HM *et al.* (1983) found that when they simulated the *dannang* acupoint (EX-LE 6) (Fig. 3.4) with LHNL at 6 mW, 10 min each acupoint, the gall-bladder contracts, which reinforced *yin*(~10 J/cm^2, dose 3). Zhang YJ *et al.* (1980) found that when the *dannang* acupoint was simulated with LHNL, the gall-bladder was in either dilation or contraction. The SN makes gall-bladder dilation and the PSN makes gall-bladder contraction(Guyton 1981).

Yu LH *et al.* (1992) studied the abirritation of LA on rat *zusanli* acupoint (ST 36) (Fig. 3.3). They found that laser irradiation at 55 J/cm^2 and 165 J/cm^2 have the abirritation by means of increasing the concentration of β-endorphin in the brain. But it has no significant effect on dynorphin in the spinal cord. According to the neurobiology, the endorphin of 31 amino acid residues will not be released until the information is transmitted to hypothalamus. However the dynorphin of 17 amino acid residues in the spinal cord will be released as soon as the information is transmitted to parabrachial nuclei which is located in the same level with cerebellum. According to DD *yin-yang* model as stated in previous section，we know that the release of endorphin belongs to *yin* process and the release of dynorphin belongs to *yang* process since the release of endorphin is more complex than the one of dynorphin. Hence the abirritation of laser irradiation at 110 J/cm^2 and 165 J/cm^2 is achieved by reinforcing *yin*（dose 3）.

Tang M *et al.* (1998) found that local cerebral blood flow of rats brain decreased when *fu tu* acupoints (LI 18) (Fig. 3.6) of rats were stimulated with low intensity GaInP/AlGaInP diode laser

irradiation at 650 nm (LGAL) acupuncture at 10 mW for 10 min (10^2 J/cm^2, dose 3). In this case, the laser irradiation reinforced the *yin* process which have the PSN activated and reduce the cerebral blood flow.

Dose 3 of the hot color LA are often used in the clinic study in order to reinforce *yin* process (Wang LQ *et al.* 1993). The arithmetic product of the laser irradiation power (mW) and irradiation time (min) is under 100. For example, the hypertension patients whose symptoms belong to the insufficiency of *yin* and relative excessiveness of *yang* were stimulated with LHNL at 3-5 mW for 5 min each points. The therapeutic effect was significant.

Dose 4 of the hot color LA are also used in the clinic study in order to reinforce *yang* process (Wang LQ *et al.* 1993). The arithmetic product of the laser irradiation power (mW) and irradiation time (min) is over 100. For example, the hyperthyroidism patients whose symptoms belong to the deficiency of *yin* and relative excessiveness of asthenic fire were stimulated with LHNL at 25 mW for 5-7 min each points. The therapeutic effect was significant.

According to our model, even lower dose of the LA also can make good effect. Certainly it needs to study in the future.

11 Health Promotion of Laser Function Medicine

Health has been defined as the state of an organism with undisturbed functional dynamic homeostasis providing optimum performance of organism functions to the extent necessary for productive relations of the organism with the environment. Health promotion is the process of enabling people to increase control over, and to improve, their health. Biosystems are characterized by the quality of function-specific homeostasis (FSH), the ability to self-stabilize from internal and external disturbances. In this chapter, we show that FSH not only determines our health, but also determines our performance in our activities. The health promotion is just the elevation of the quality of FSH. In other words, the health promotion is just a transition from the FSH of low quality to the one of high quality. FSH-specific photobiomodulation (fPBM) can be used to promote the establishment of human FSH, and laser acupuncture(LA) such as interdigital low intensity laser therapy (DLILT), and intranasal low intensity laser therapy (ILILT), two kinds of fPBM, can be then used to promote health.

11.1 Well-being

Sociological surveys usually try to measure well-being by asking people to assess their current level of happiness. Such questions are a regular feature of surveys of the public, such as the 2005 Pew Research Center survey, which asked 3,014 adult Americans: "How happy are you these days in your life?" Half reported being "pretty happy", 34% "very happy" and 15% "not too happy" (Reichhardt 2006).

Daniel Kahneman, a Princeton University psychologist who won the 2002 Nobel Prize for Economics for applying psychology to decision-making in the face of uncertainty, wants to develop surveys that ask more sophisticated questions. His group has investigated how a person's sense of overall life satisfaction diverges from their everyday ups and downs by using the day reconstruction method (DRM) (Kahneman *et al.* 2004). His group found that positive affect and enjoyment are strongly influenced by aspects of temperament and character (e.g., depression and sleep quality) and by features of the current situation. In contrast, general circumstances (e.g., income, education, marriage, religion and a risk of being laid off) have little impact on the enjoyment of a regular day. In comparison of survey reports of happiness with other factors, ranging from income to pet ownership, Kahneman *et al.* (2006) concluded that people with more money report being happier, but only up to a point. Beyond a certain level (for Americans in 2004, an annual household income of $50,000 to $90,000), more money doesn't bring more happiness.

In several countries where median income has risen — including China, America and Japan — happiness levels remain stubbornly constant (Reichhardt 2006). These surveys rely on questions about subjective well-being, and it is reasonable to ask how reliable survey answers are as measures of the quality of life as people experience it. Oswald *et al.* (2010) have carried out an interesting test of this. First they measure subjective well-being in each U.S. state, and then compare it with the average objectively measured wage in the same U.S. state (both variables being controlled for personal factors). The negative correlation of the two variables is remarkably high—as it should be if higher wages are compensating for a lower experienced quality of life (and vice versa):

$$\text{Adjusted Life Satisfaction} = -0.0035 - 0.0012\,(\text{Objective Rank}),$$

$$r = 0.598, \quad P < 0.001$$

Where the objective quality of life so ranked that 1 is the highest and 50 is the lowest.

As Kahneman *et al.* (2004) have pointed out, life circumstances don't have much affect on long-term happiness. Surveys show that happiness increases after marriage, but only temporarily. An oft-cited 1978 study found that, a year after their life-changing event, both lottery winners and paralysis victims had reverted to close to their former level of happiness (Reichhardt 2006). This contributed to the notion of a 'hedonic setpoint' to which people return no matter what life throws their way. Well-being researchers are also going beyond questionnaires to borrow tools from medicine, neuroscience and genetics. Based on studies showing similar levels of reported happiness in twins, the hedonic setpoint appeared to be genetically determined (Reichhardt 2006). However, different kinds of happiness change over time. For example, older people report declines in both positive and negative moods (Reichhardt 2006). Obviously, hedonic setpoint is a typical phenomenon of homeostasis. The well-being is discussed from FSH viewpoint in this chapter.

The quality of a FSH includes function complexity and performance stability. An elite athlete has a sport-specific homeostasis (SpSH) to maintain sport performance. For a 100 m sprint runner, the 100 m sprint time represents the function complexity. The less the running time, the more complicated the run. The coefficient of variation (CV) of the sprint time represents the performance stability. The higher the CV, the lower the performance stability.

A person has many kinds of functions and then may have many kinds of FSH. An elite part-time athlete might have at least two kinds of FSH, one part-time SpSH for competition and one full-time FSH for living. A record breaker of a Guinness World Record might have at least two kinds of FSH, one part-time FSH for breaking the record and one full-time FSH for living. If the two or more SpSH-specific systems were so similar that they can be integrated into a system in homeostasis, the corresponding sports might be integrated into a sports group, and the corresponding homeostasis might be called sports-group-specific homeostasis (SGSH). The athlete in the SGSH might be simultaneously elite in two or more sports, which is defined as the concurrent sports.

We have studied the phenomena of concurrent sports of swimming sports of male swimmers by means of the concurrent rate defined as the number of the concurrent sports which each swimmer kept in the world records (Li J *et al.* 2010). The mean concurrent rate of Americans or Australians was statistically higher than the one of Russians or the other countries. There were three stages of the concurrent rate increase: 1993-1998（1.20±0.06), 1999-2002(1.33±0.05) and 2003-2007(1.49±0.07). 92% swimmers succeeded in the concurrent sports differing in distance but in the same stroke. For the same stroke, the higher the concurrent rate, the smaller the distance difference. For different strokes, the mean concurrent rate of backstroke, freestyle，breaststroke, individual medley and butterfly was 1.67±0.86, 1.44±0.12, 1.4±0.51, 1.17±0.24 and 1.17± 0.36, respectively. For example, Ian Thorpe has been champions in swimming both in 200 and 400m, and Michael Fred Phelps has been swimming champions in 100, 200 and 400m.

Let **Q** be the quality of a FSH. A person might simultaneously have many kinds of FSH, $\{FSH_i, i = 1, 2, \ldots, n\}$, and then has $\{\mathbf{Q}_i, i = 1, 2, \ldots, n\}$. Let $\mathbf{Q}max=max\{\mathbf{Q}_i, i = 1, 2, \ldots, n\}$. Obviously, **Q**max represents the health level or the quality of life. The aging process is of course under genetic control, but it can also be considered a result of the failure of homeostasis due to the accumulation of damage (Petropoulou *et al.* 2000, Novoseltsev *et al.* 2001). Aging is defined as

the progressive decline of homeostasis that occurs after the reproductive phase of life is complete, leading to an increasing risk of disease or death, which results from a failure of organs to repair DNA damage by oxidative stress (nonprogrammed aging) and from telomere shortening as a result of repeated cell division (programmed aging) (Ito *et al.* 2009). Therefore, **Q**max is becoming higher in developing and lower in ageing. The age when Qmax is of highest value is defined as optimum age, *h*. Crimmins *et al.* (2006) have shown that increasing longevity and declining mortality in the elderly occurred among the same birth cohorts that experienced a reduction in mortality at younger ages. In other words, the developing and the ageing might be symmetric. The most possible life-span, *y*, of a person might be $y = 2h + 1$ if the developing and the ageing are supposed to be symmetric (Liu CY 1995). The life-span is a normal distribution around the most possible life-span (Liu CY 1995). In other words, the higher the **Q**max at the optimum age, the longer the life-span. It has been observed that the life-span of the persons of life-long job might be longer than the one of other jobs (Liu CY 1995), and the world class male athletes have increased life expectancy (Sarna *et al.* 1993). It has been found that higher levels of physical activity are associated with decreased risks of coronary heart disease (CHD), cerebrovascular disease, hypertension, non-insulin-dependent diabetes mellitus, colon and, possibly, breast cancer, as well as osteoporosis (Lee IM *et al.* 1997). Lee IM *et al.* (1997) further found that physical activity is also effective in postponing mortality and enhancing longevity.

A system in FSH reacts to every change in the environment, or to every random disturbance, through a series of modifications of equal size and opposite direction to those that created the disturbance. The higher the quality of the FSH is, the stronger the disturbance resistance. Therefore, the longer the life-span is, the stronger the disturbance resistance, and then the stronger the capacity of the chronic disease prevention. It has been observed that elite athletes from most sports disciplines have lower overall morbidity risk and enjoy better self-rated health in later years compared with the general population and matched controls who were healthy at young age chronic disease prevention (Kujala *et al.* 2003, Lynch *et al.* 2007). Pinkston *et al.* (2006) have studied the link between organismal aging and cancer in a worm model of aging and tumor development and find that different signaling pathways implicated in the aging process also control tumorigenesis. Mutant worms with long life spans appear immune to the life-shortening effects of tumors because of enhanced defense mechanisms, including increased apoptosis and decreased cell proliferation within the tumors.

7-year study found fitness is a key element in determining male diabetic's longevity (Kokkinos *et al.* 2009). The researchers used 2,690 male diabetic veterans, most of whom were overweight or obese based on their body mass index, a measure of body fat using height and weight. The veterans were categorized as having low, moderate or high fitness level, depending on their performance on a standard treadmill exercise tolerance test. The researchers found that the higher the man's level of fitness, the lower his risk of dying during the study period. For example, those in the high fitness level -- whether at normal body weight or overweight -- reduced their risk of death by 40 percent. The findings were even more dramatic for those classified as obese but in reasonable good shape: a cut in death risk of 52 percent, when compared to peers not physically fit, the study found during its seven-year follow-up period. In this case, the fitness is a kind of FSH. The higher the man's level of fitness, the higher his FSH quality and then the longer his longevity.

11.2 Training Ladder

As treadmill used in exercise science, the concept of hedonic treadmill was used in well-being studies such as DRM (Kahneman *et al.* 2004). The well-being upgrading was discussed in this section.

There are many subsystems to maintain a FSH, FSH-essential subsystems (FESs) and FSH-non-essential subsystems (FNSs). As discussed in chapter 8.1, FESs might be very sparse. This sparse characteristic is also supported by the theoretical study of the steady-state fluctuation. Fluctuations in the abundance of molecules in the living cell may affect its growth and well being. For regulatory molecules (e.g., signaling proteins or transcription factors), fluctuations in their expression can affect the levels of downstream targets in a metabolic network. Levine *et al.* (2007) have developed an analytic framework to investigate the phenomenon of noise correlation in molecular networks, and they found the steady-state fluctuation in different nodes of the pathways to be effectively uncorrelated for all but one case examined. Consequently, fluctuations in enzyme levels only affect local properties and do not propagate elsewhere into metabolic networks, and intermediate metabolites can be freely shared by different reactions. Therefore, a person has many kinds of functions and then may have many kinds of FSHs. As a reasonable extension, we suppose there may be FES-specific homeostasis (FESH) and FNS-specific homeostasis (FNSH) for a FSH.

There are two kinds of training upgrading the present FSH, extraordinary training (ET) and ordinary training (OT). ET establishes the FESHs of higher quality by destroying the present FSH of lower quality. OT maintaining FESHs has two phases, OTA during which FNSHs and then the new FSH are established, and OTB during which the new FSH is maintained. For SpSH upgrading, ET results in delayed-onset muscle soreness (DOMS), OT includes tapering or reduced training, ET induced fatigue is recovered during OTA, and athletes enjoy OT during OTB (Liu CY *et al.* 2008). During DOMS, there is three subsequent phases: Z-line streaming, proteolysis of damaged proteins and protein synthesis (Liu TCY *et al.* 2006). The last two phases is just protein metabolism. The DOMS normally recovers in seven days if the protein metabolism is in its protein metabolism-specific homeostasis (PmSH), but it takes more than a week or weeks if the protein metabolism is far from its PmSH, which can be promoted by laser irradiation or monochromatic light (LI) at low intensity (Liu XG *et al.* 2009) .

FSH should hold for students. Learning is often considered complete when a student can produce the correct answer to a question. In Karpicke *et al.* (2008)'s research, students in one condition learned foreign language vocabulary words in the standard paradigm of repeated study-test trials. In three other conditions, once a student had correctly produced the vocabulary item, it was repeatedly tested but dropped from further study, repeatedly studied but dropped from further testing, or dropped from both study and test. They found that repeated studying after learning had no effect on delayed recall, but repeated testing produced a large positive effect. In this case, learning is a kind of ET, the second studying is a kind of OT so that the students can produce the correct answer to a question. The further study-test is a kind of OTB-Testing (OBT). The repeating study-test is a kind of OBT1-OBT2-….

Karpicke *et al.* (2008)'s research indicated repeated testing is of critical importance to the performance. A training period might be ET-OTA-OBT1-OBT2-…-Testing (EOT). The performance of the last testing should represent the training level. The training ladder should be

EOT1-EOT2-….

This holds in sport performance (Liu CY *et al.* 2008). Performance-enhanced competition might be of critical importance after OT induced recovery from ET induced fatigue. Obviously, the competition should be during OTB. Performance-enhanced competition should be OTB-Competition (OBC). A training period might be ET-OTA-OBC1-OBC2-…-Competition (EOC). The performance of the last competition should represent the training level. The training ladder should be EOC1-EOC2-….

11.3 Oxidant-Antioxidant Homeostasis

The function of oxidant-antioxidant homeostasis (OAH) is redox. The quality of OAH is represented by the reactive oxygen species (ROS) level it maintains, OAH-essential ROS level (oROS). Obviously, the lower oROS is, the higher the quality of OAH.

Antioxidants are defined as substances that, when present at low concentrations relative to an oxidizable substrate, significantly delay or prevent oxidation of that substrate. Living organisms have evolved a number of antioxidant defenses to maintain their survival against oxidative stress (Dröge 2002, Paravicini *et al.* 2008). These mechanisms are different in the intracellular and extracellular compartments and comprise enzymatic and nonenzymatic types. The major vascular enzymatic antioxidants are superoxidase dismutase (SOD), catalase, and glutathione peroxidase. SOD catalyzes the dismutation of $\cdot O_2^-$ into H_2O_2 and O_2. Of the three SOD isoforms, extracellular SOD is the main vascular SOD. It is produced and secreted by vascular smooth muscle cells and binds to glycosaminoglycans in the vascular extracellular matrix on the endothelial cell surface and plays an important role in the regulation of the oxidant status in the vascular interstitium. Reduced glutathione plays a major role in the regulation of the intracellular redox state of vascular cells by providing reducing equivalents[1] for many biochemical pathways. Glutathione peroxidase reduces H_2O_2 and lipid peroxides to water and lipid alcohols, respectively, and in turn oxidizes glutathione to glutathione disulfide. The glutathione peroxidase/glutathione system may be important in low-level ROS. Catalase is an intracellular antioxidant enzyme that is mainly located in cellular peroxisomes and to some extent in the cytosol, which catalyzes the reaction of H_2O_2 to water and molecular oxygen. Catalase is very effective in high-level ROS and protects cells from H_2O_2 produced within the cell. The enzyme is especially important in the case of limited glutathione content or reduced glutathione peroxidase activity. Thioredoxin reductase is an antioxidant enzyme that participates in thiol-dependent cellular reductive processes. Numerous nonspecific antioxidants, such as α-tocopherol (vitamin E) and ascorbic acid (vitamin C), scavenge $OH\cdot$ as well as other radicals..

Contraction-induced production of ROS has been shown to cause oxidative stress to skeletal muscle (Ji LL *et al.* 2007). Activation of nuclear factor κB (NFκB) and mitogen-activated protein kinase (MAPK) pathways in skeletal muscle has been shown to enhance the gene expression of several enzymes such as mitochondrial SOD (MnSOD) and inducible NO synthase (iNOS). As an adaptive response, muscle antioxidant defense systems are upregulated in response to training, especially ET, so that oROS is reduced and the quality of OAH is enhanced. While an acute bout of exercise activates NFκB and MAPK signaling and upregulates MnSOD and iNOS,

[1] The term reducing equivalent refers to any of a number of chemical species which transfer the equivalent of one electron in redox reaction. http://en.wikipedia.org/wiki/Reducing_equivalent

administration of chemical agents that suppress ROS production can cause attenuation of exercise-induced MnSOD and iNOS expression, and attenuate oROS reduction.

ROS play an important role in the development of many diseases such as cancer, hypertension, atherosclerosis, diabetes, cardiac hypertrophy, heart failure, ischemia-reperfusion injury, and stroke(Dröge 2002). Antioxidant supplements have been used for prevention of several diseases. However, Bjelakovic *et al.* (2007) have shown that treatment with β carotene, vitamin A, and vitamin E may increase mortality. Overall results of clinical studies investigating antioxidant effects have been disappointing given the consistent and promising findings from experimental investigations, clinical observations, and epidemiological data (Paravicini *et al.* 2008). In these cases, antioxidant supplements might reduce ROS level to so low that they might disrupt OAH. OAH can automatically maintain ROS level at oROS, but antioxidant supplements can only work when their local concentration is high enough.

On the other hand, as one kind of fPBM, LA and ILILT might rehabilitate a system far from OAH. It has been found that the inactivated SOD can be photoreactivated by low intensity 632.8 nm He-Ne laser irradiation (LHNL) (Vladimirov *et al.* 1988) and SOD activity in erythrocytes was significantly higher in the irradiated samples with low intensity LI (LIL) at 660 nm (Stadler *et al.* 2000). The metabolic modifications induced in rat brain tissues by LHNL included a marked increase of total SOD (Rossetti *et al.* 1991). Zhang Y *et al.* (2003) have investigated the gene expression profiles of human fibroblasts irradiated by LIL at 628nm, and found it regulated 111 genes, such as up-regulating antioxidative related genes and up-regulating anti-apoptosis related genes. It was found that the mitochondria membrane potential (MTP) of leukocytes declined during daily, repetitive aerobic exercise at an intensity of 60% and 85% maximum oxygen consumption (VO_2max) although similar changes were not found during a more moderate aerobic exercise (35% VO_2max) (Hsu *et al.* 2002). On the other hand, it was found the declined MTP of Hep-2 cells can become high by photobiomodulation (PBM) (Bortoletto *et al.* 2004). Ischemic injury in skeletal muscle is initiated during hypoxia and is aggravated by reoxygenation during blood reperfusion and accumulation of cytotoxic reactive oxygen superoxides. Avni *et al.* (2005) found the low level LI (LLL) protection of rat skeletal muscles from ischemic injury induced in the gastrocnemius muscles by complete occlusion of the blood supply for 3 h and then by reperfusion was mediated by increasing antioxidant activity. We used the electrical stimulation of C2C12 myotubes as the cellular model of exercise, and study the LIL PBM (LPBM) on the cellular model in our laboratory. We found that electrical stimulation at 20 ms, 5 Hz, and 45 V for 75 min can induce ROS increase in cultured C2C12 myotubes, and LIL at doses of 0.33-8.22 J/cm^2 can rehabilitate the ROS level (Xu XY *et al.* 2008). We studied the LPBM of red light at 640±15nm from light emitting diode array (RLED 640) on H_2O_2 induced differentiated PC12 apoptosis, and found the inhibition of the LPBM on the apoptosis might be mediated by the up-regulation of tyrosine hydroxylase gene expression (Zhu L *et al.* 2009b).

11.4 Health promotion

The sunlight plays an important role in well-being. In terms of state rank using regression-adjusted life satisfaction in the data of the U.S. Behavioral Risk Factor Surveillance System (BRFSS) (www.cdc.gov/BRFSS) (Oswald *et al.* 2010), Fig. 11.1 illustrated the well-being distribution It indicated that the lower the latitude in the low latitude states, the higher the subjective well-being

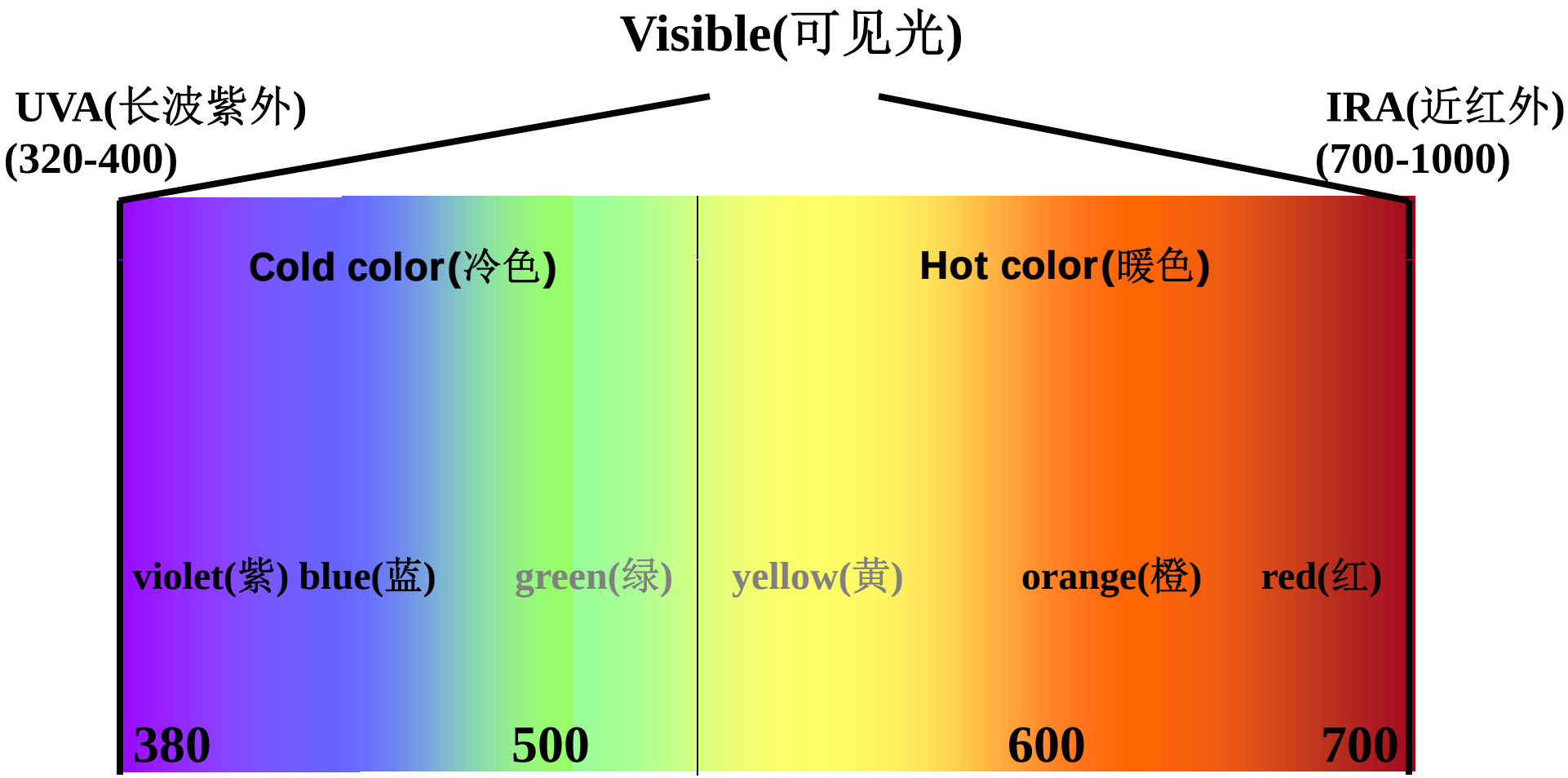
which so ranked that 1 is the highest and 50 is the lowest. On the other hand, Davis *et al.* (2002) found there is a positive linear relation between the variation in suicide rate and geographic latitude in terms of raw suicide rates from the Organization for Economic Cooperation and Development (OECD) database from 1960 through 1997. A Spring peak for 52,533 completed suicides in 1930-1938 was found in Hungary, stronger in rural regions than in urban regions (Lester *et al.* 2007). According to chapter 4, these sunlight effects suggested that LA or ILILT may be used to enhance well-being. This is supported by the possible effects of LA or ILILT on aging as discussed in chapter 6.2.

From an evolutionary perspective, we humans have good reason to be wary of things that seem to be 'unnatural'. Anything out of the ordinary can be dangerous. But the evolutionary origin of that response also guarantees that it will be guided more by emotion than by reason. Any performance-enhancing drug, either ergogenic agents in athletic competition or cognition-enhancing drugs, makes accomplishments somehow less worthy because they aren't natural. However, performance-enhancing FSH discussed above is natural. As an fPBM, ILILT can be used to promote the establishment of a FSH. There might be training-induced fatigue/chronic fatigue syndrome during ET and OTA. During ET, ILILT can be used to promote the establishment of PmSH and FESH so that the period can be shortened. During OTA, ILILT can be used to promote the establishment of FNSH and then FSH so that the period can be also shortened. The training ladder is just a healthy promotion. Any modulations promoting training ladder will promote health. ILILT can promote the establishment of PmSH, FESHs, FNSHs and FSH so that it can shorten the delayed ET or OTA period and then promote health. Therefore, ILILT can be used to promote health.

Today there are several drugs on the market that improve memory, concentration, planning and reduce impulsive behaviour and risky decision-making, and many more are being developed. Doctors already prescribe these drugs to treat cognitive disabilities and improve quality of life for patients with neuropsychiatric disorders and brain injury. The prescription use of such drugs is being extended to other conditions, including shift-workers. Meanwhile, off-label and non-prescription use by the general public is becoming increasingly commonplace. A rise in the use of these drugs and other neuroenhancing products and procedures might be as they become available. Like the rise in cosmetic surgery, use of cognitive enhancers is likely to increase as bioethical and psychological concerns are overcome and as the products gain cultural acceptance. One difference is that use of cognitive enhancers doesn't rely on training of medical specialists such as surgeons. Internet availability will also greatly accelerate use. Although the appeal of pharmaceutical cognitive enhancers — to help one study longer, work more effectively or better manage everyday stresses — is understandable, potential users, both healthy and diseased, must consider the pros and cons of their choices (Sahakian *et al.* 2007). In view of the side effects of these drugs such as headaches, jitteriness, anxiety and sleeplessness, LA and ILILT is very potential. Among the six meridians inside/around nose, *stomach* meridian of foot *yang-ming*, *du* meridian and *yin-jiao* meridian pass through brain and then might mediate the rehabilitation of ILILT on cognitive dysfunctions and diseases. This is supported by the therapeutic effects of ILILT on mild cognitive impairment (MCI) as discussed in chapter 5.2.1.

Fig. 1.1 Yin-Yang of Light： Wavelength (nm).

图1.1 光的阴阳： 波长（纳米）



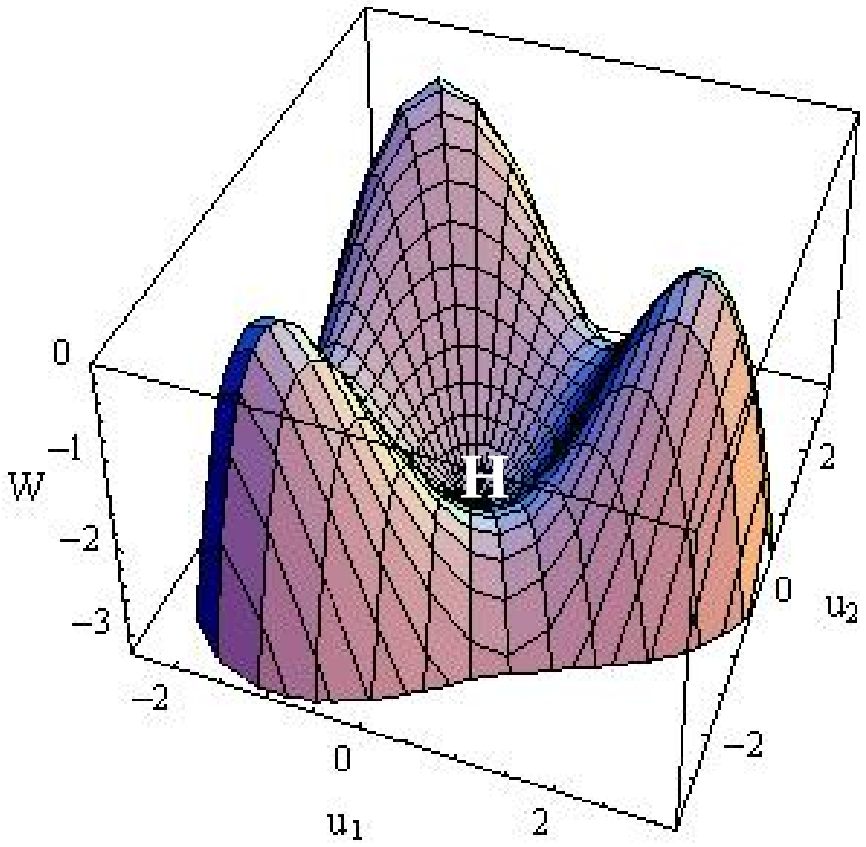


Fig. 3.1 Homeostasis(H) illustration

图3.1 内稳态（H）的示意图

Tab. 3.1 Effect of season on the associations between high seasonality and objective health risk factors (Øyane *et al.* 2010)

Health measurement	Seasonality group	Season				Statistics for seasonality group*season	
		Winter	Spring	Summer	Fall	Anova F(6)	P
Men							
Systolic blood pressure (mm Hg)	GSS<8	132 (13)	131 (14)	130 (13)	131 (15)	2.60	.016
	GSS 8–10	133 (13)	130 (13)	129 (14)	132 (13)		
	GSS≥11	134 (15)	131 (12)	123 (20)	129 (17)		
Women							
BMI	GSS<8	24.6 (4.0)	24.6 (4.1)	24.2 (3.7)	24.3 (3.8)	2.34	.030
	GSS 8–10	24.4 (3.8)	24.7 (3.8)	25.0 (4.1)	24.8 (4.1)		
	GSS≥11	25.5 (4.5)	25.3 (4.2)	24.8 (3.8)	25.6 (4.4)		
Systolic blood pressure (mm Hg)	GSS<8	124 (14)	123 (14)	122 (15)	123 (14)	2.21	.039
	GSS 8–10	123 (13)	123 (13)	123 (14)	123 (14)		
	GSS≥11	123 (12)	124 (15)	119 (12)	123 (13)		

表3.1 生理参数的季节敏感性性 (Øyane *et al.* 2010)

季节敏感性性分组						分组与季节二维统计差异	
生理参数 **Health measurement**	**Seasonality group**	季节 **Season**				**Statistics for seasonality group*season**	
		Winter	**Spring**	**Summer**	**Fall**	**Anova F(6)**	**P**
Men 男		冬	春	夏	秋		
Systolic blood pressure (mm Hg) 收缩压	GSS<8	132 (13)	131 (14)	130 (13)	131 (15)	2.60	.016
	GSS 8–10	133 (13)	130 (13)	129 (14)	132 (13)		
	GSS≥11	134 (15)	131 (12)	123 (20)	129 (17)		
Women 女							
BMI	GSS<8	24.6 (4.0)	24.6 (4.1)	24.2 (3.7)	24.3 (3.8)	2.34	.030
	GSS 8–10	24.4 (3.8)	24.7 (3.8)	25.0 (4.1)	24.8 (4.1)		
	GSS≥11	25.5 (4.5)	25.3 (4.2)	24.8 (3.8)	25.6 (4.4)		
Systolic blood pressure (mm Hg) 收缩压	GSS<8	124 (14)	123 (14)	122 (15)	123 (14)	2.21	.039
	GSS 8–10	123 (13)	123 (13)	123 (14)	123 (14)		
	GSS≥11	123 (12)	124 (15)	119 (12)	123 (13)		

Tab. 3.2 Number of individuals w/o metabolic syndrome among the participants and their number being representative of the Finnish population aged over 30 years表3 30岁以上芬兰人代谢综合征的数目 (Rintamäki et al. 2008)

	Study participants		Nationwide population	
	Metabolic syndrome	Metabolic syndrome	Metabolic syndrome	Metabolic syndrome
	No	Yes	No	Yes
GSS				
0	290	135	157,806	73,694
1	236	109	128,519	59,117
2	377	151	205,076	82,037
3	482	170	262,428	92,268
4	569	209	309,467	113,674
5	490	197	266,419	107,398
6	622	244	338,539	133,030
7	337	160	183,096	87,089
8	266	152	144,515	82,916
9	194	106	105,309	57,866
10	134	60	72,940	32,519
11	72	40	39,376	21,701
12	58	38	31,660	20,899
13	25	16	13,420	8725
14	14	8	7354	4559
15	8	3	4535	1701
16	2	1	1058	517
17	2	0	1176	0
18	2	2	1103	1174
GSS				
0 to 7	3403	1375	1,851,349	748,308
8 to 18	776	427	422,447	232,577

	研究样本		全国人口普查	
	Study participants		Nationwide population	
	代谢综合征 Metabolic syndrome 否 No	代谢综合征 Metabolic syndrome 是 Yes	代谢综合征 Metabolic syndrome 否 No	代谢综合征 Metabolic syndrome 是 Yes
GSS				
0	290	135	157,806	73,694
1	236	109	128,519	59,117
2	377	151	205,076	82,037
3	482	170	262,428	92,268
4	569	209	309,467	113,674
5	490	197	266,419	107,398
6	622	244	338,539	133,030
7	337	160	183,096	87,089
8	266	152	144,515	82,916
9	194	106	105,309	57,866
10	134	60	72,940	32,519
11	72	40	39,376	21,701
12	58	38	31,660	20,899
13	25	16	13,420	8725
14	14	8	7354	4559
15	8	3	4535	1701
16	2	1	1058	517
17	2	0	1176	0
18	2	2	1103	1174
GSS				
0 to 7	3403	1375	1,851,349	748,308
8 to 18	776	427	422,447	232,577

表3.2 30岁以上芬兰人代谢综合征的数目 表3.2 (Rintamäki et al. 2008)

Fig. 3.2 Training program plateau 图3.2 训练平台(Busso 2003)

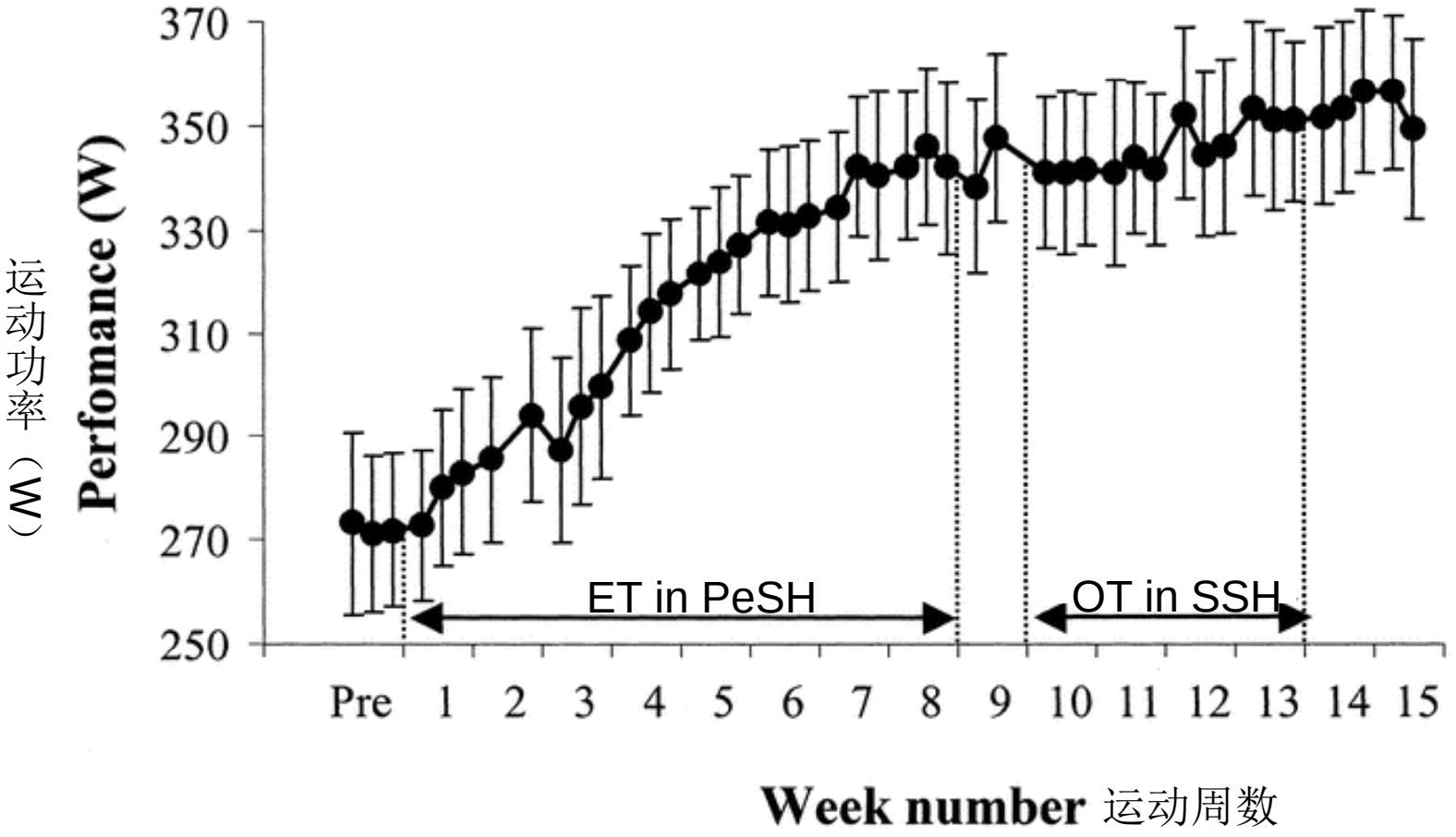


Fig.3.3 Acupoints: *taichong*, fenglong,zusanli, shenmen, daling, leque, *neiguan* and *yingxiang*

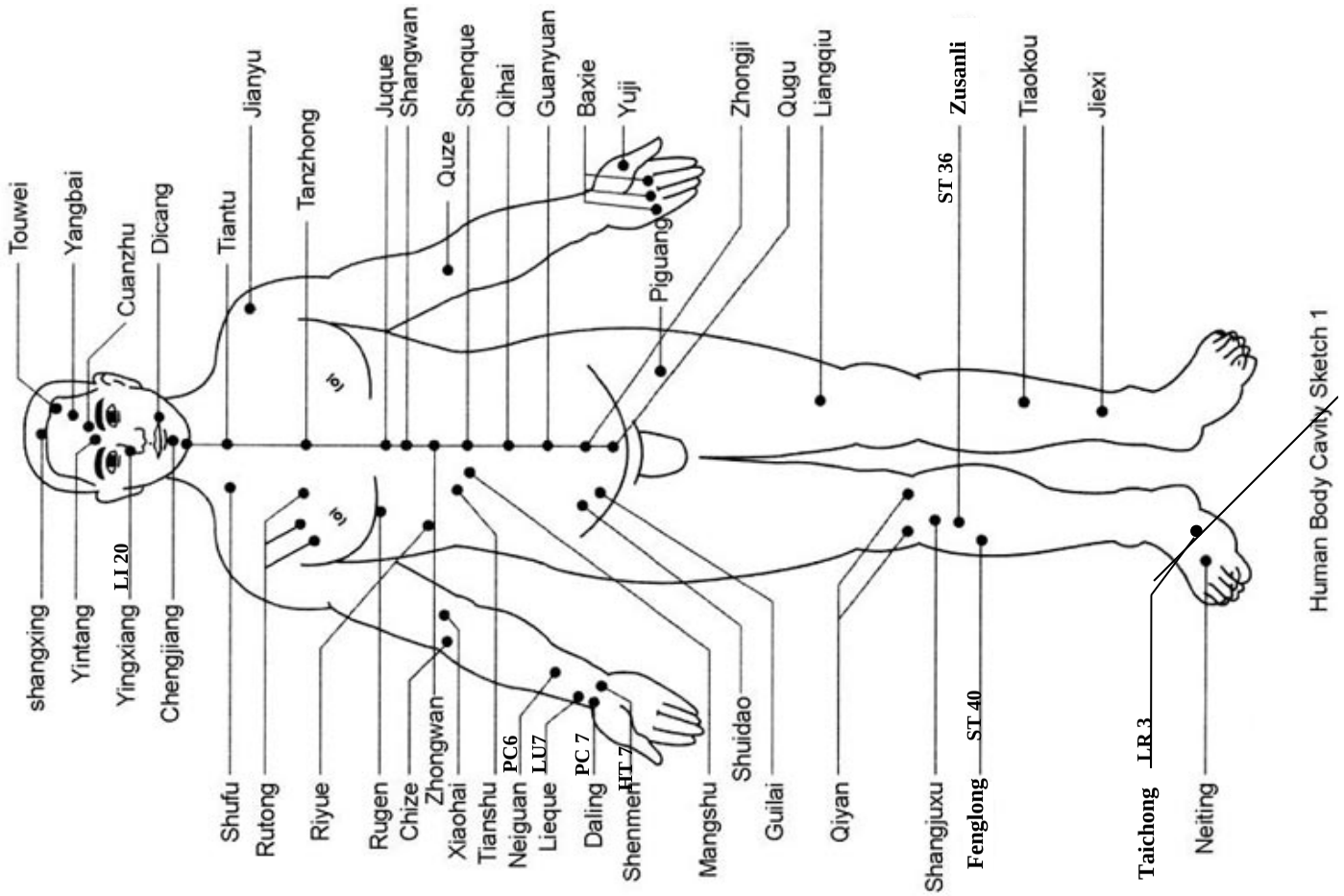


图3.3 穴位¨ 太冲（LR 3）´ 丰隆（ST40）´ 足三里（ST 36）´ 神门（HT 7）´ 大陵（PC 7）´ 列缺（LU 7）´ 内关（PC 6）和迎香（LI 20）

Fig. 3.4 Acupoints: *quchi,waiguan, hegu, dannang, xiaguan, renying, xuehai* and *sanyinjiao*.

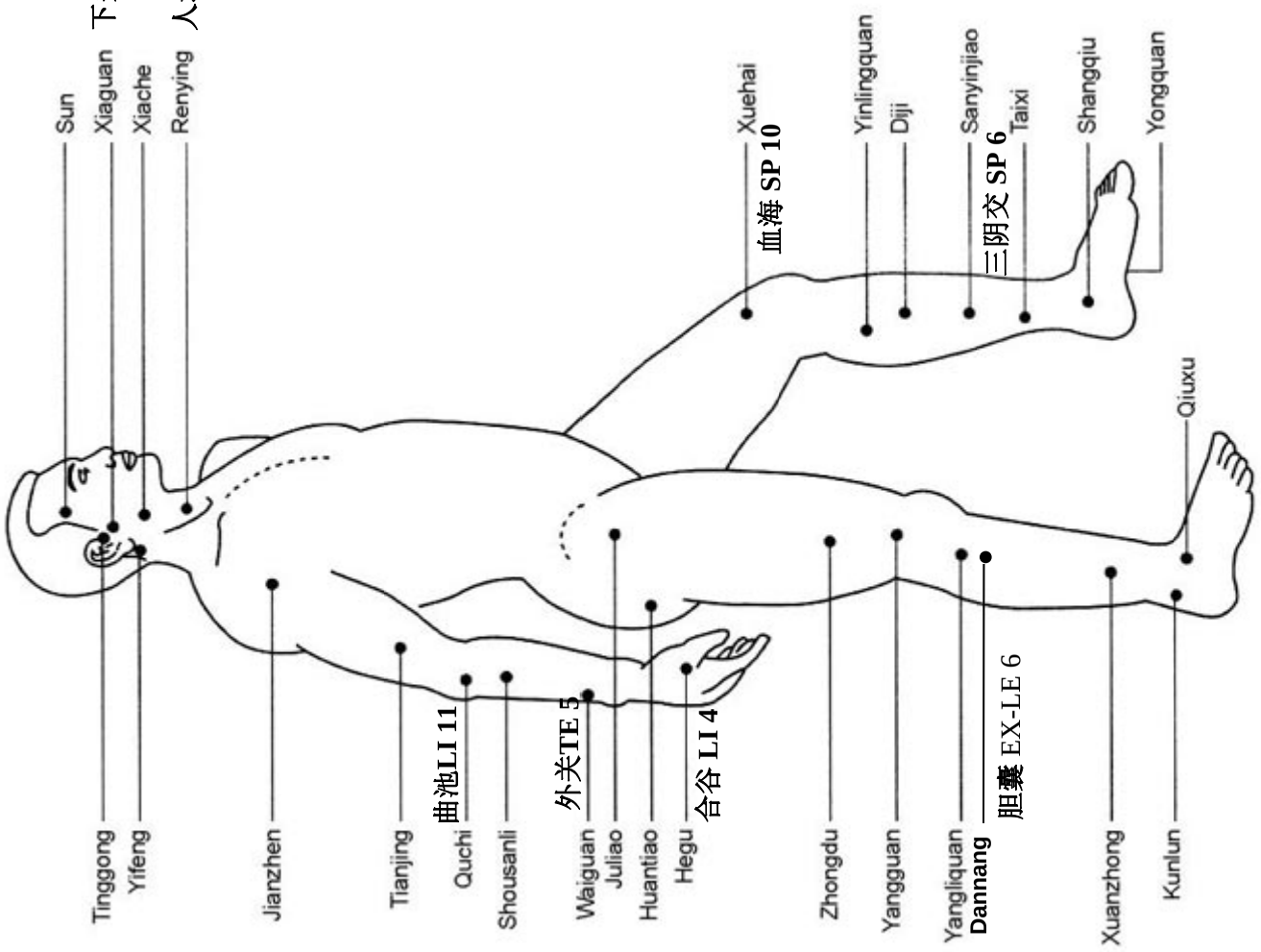


图3.4 穴位：曲池、外关、合谷、胆囊、下关、人迎、血海、和三阴交

Fig. 3.5 Physiological roles of the SIRT1

图 3.5 SIRT1的生理功能(Finke *et al.* 2009**)**

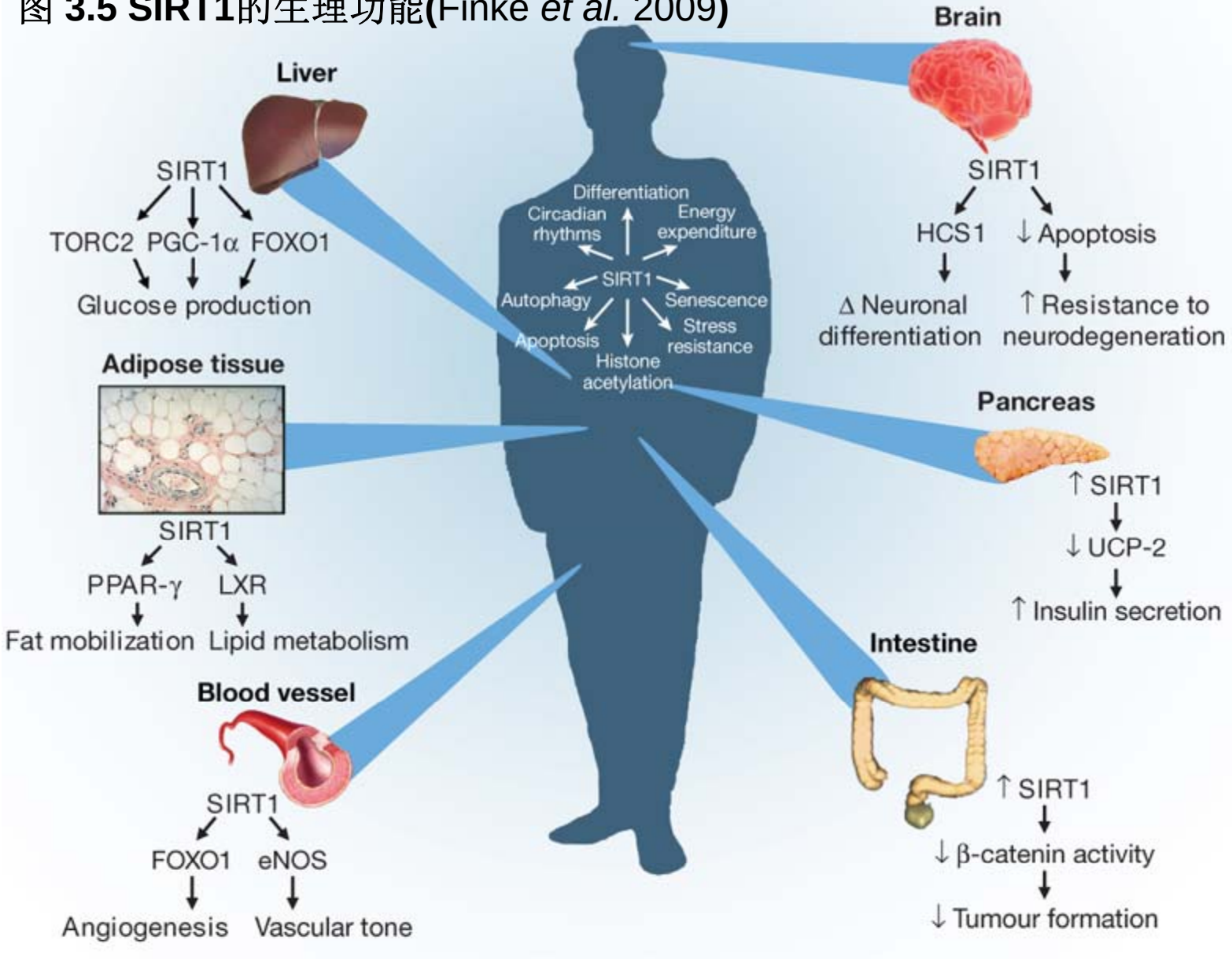


Fig.3.6 Acupoints of erheliao(TE22), *futu* (LI 18) and renying (ST 9)

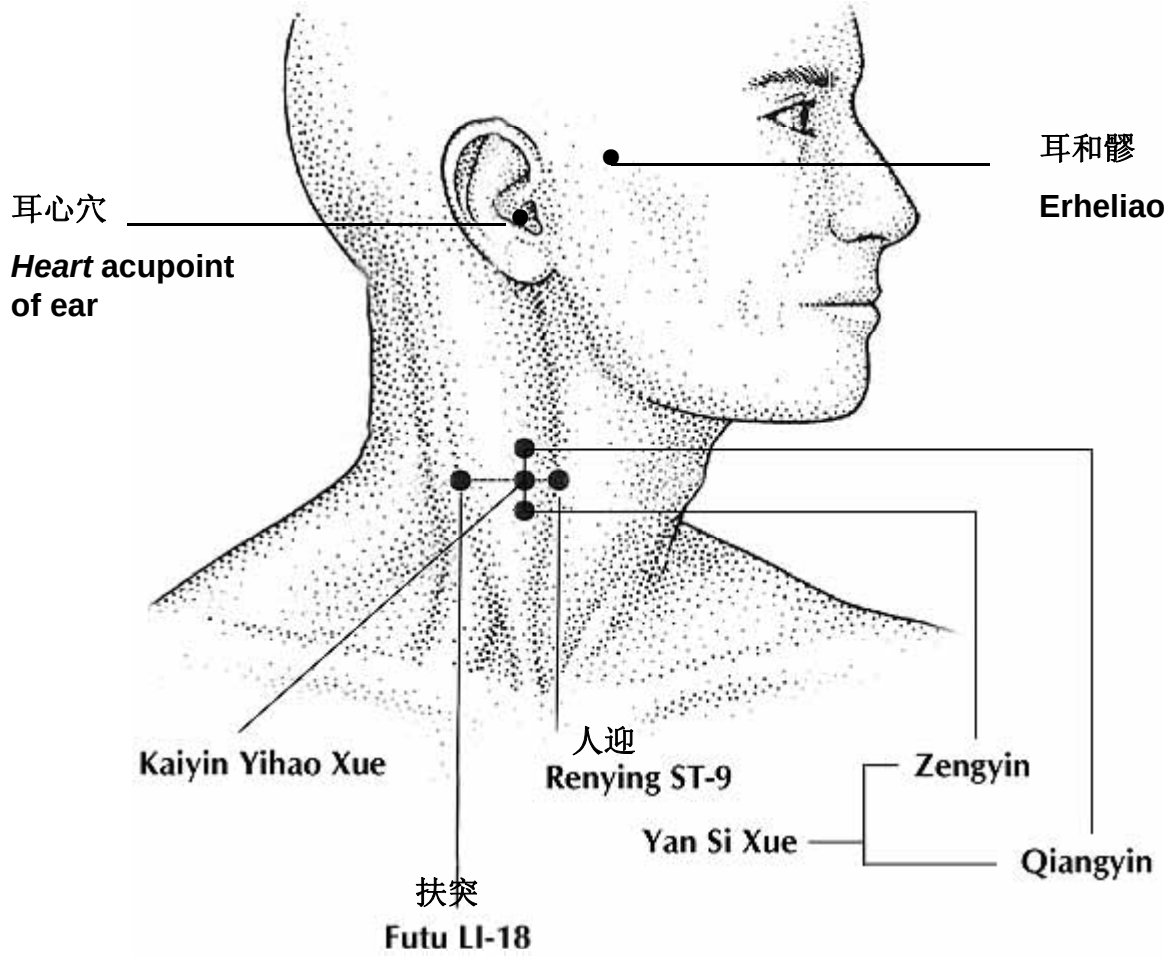


图3.6 穴位：耳和髎、扶突和人迎

Fig. 3.7 ROS modulation on cells

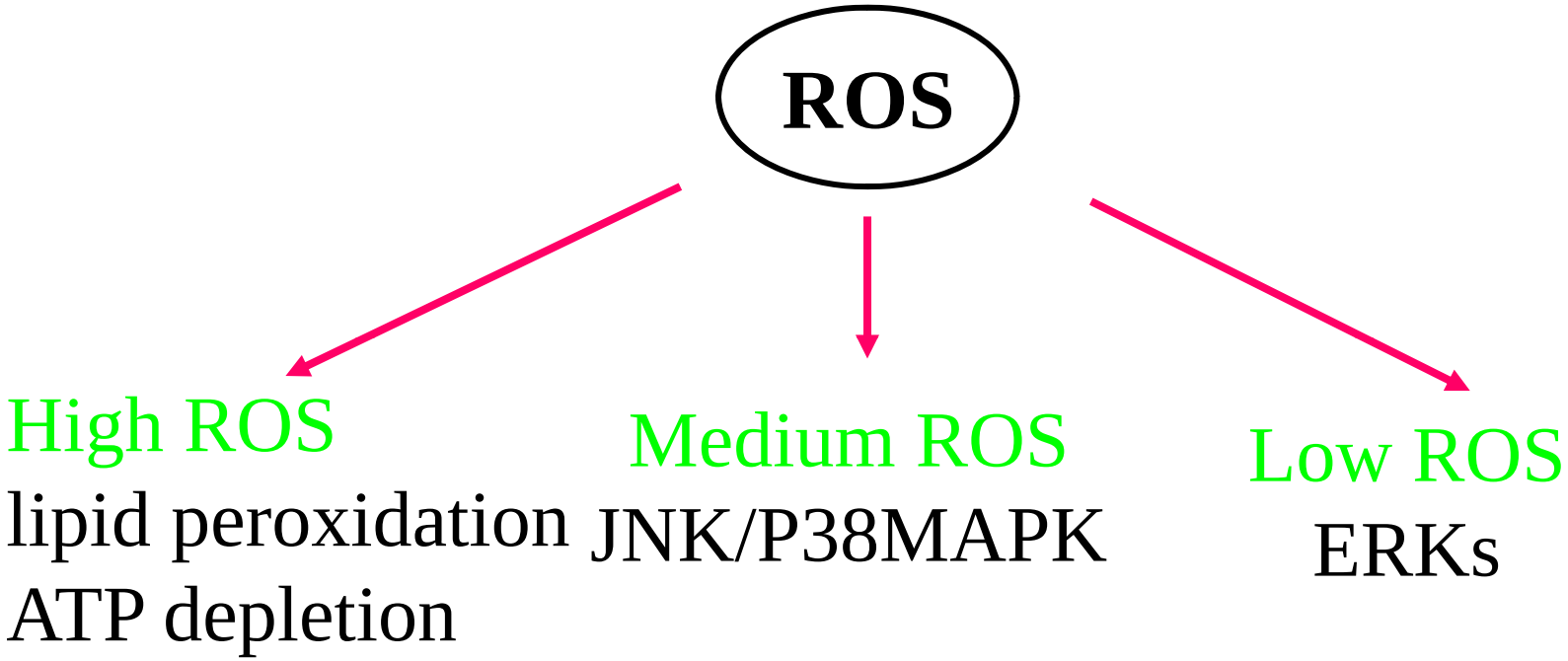


图3.7 ROS的细胞调节作用

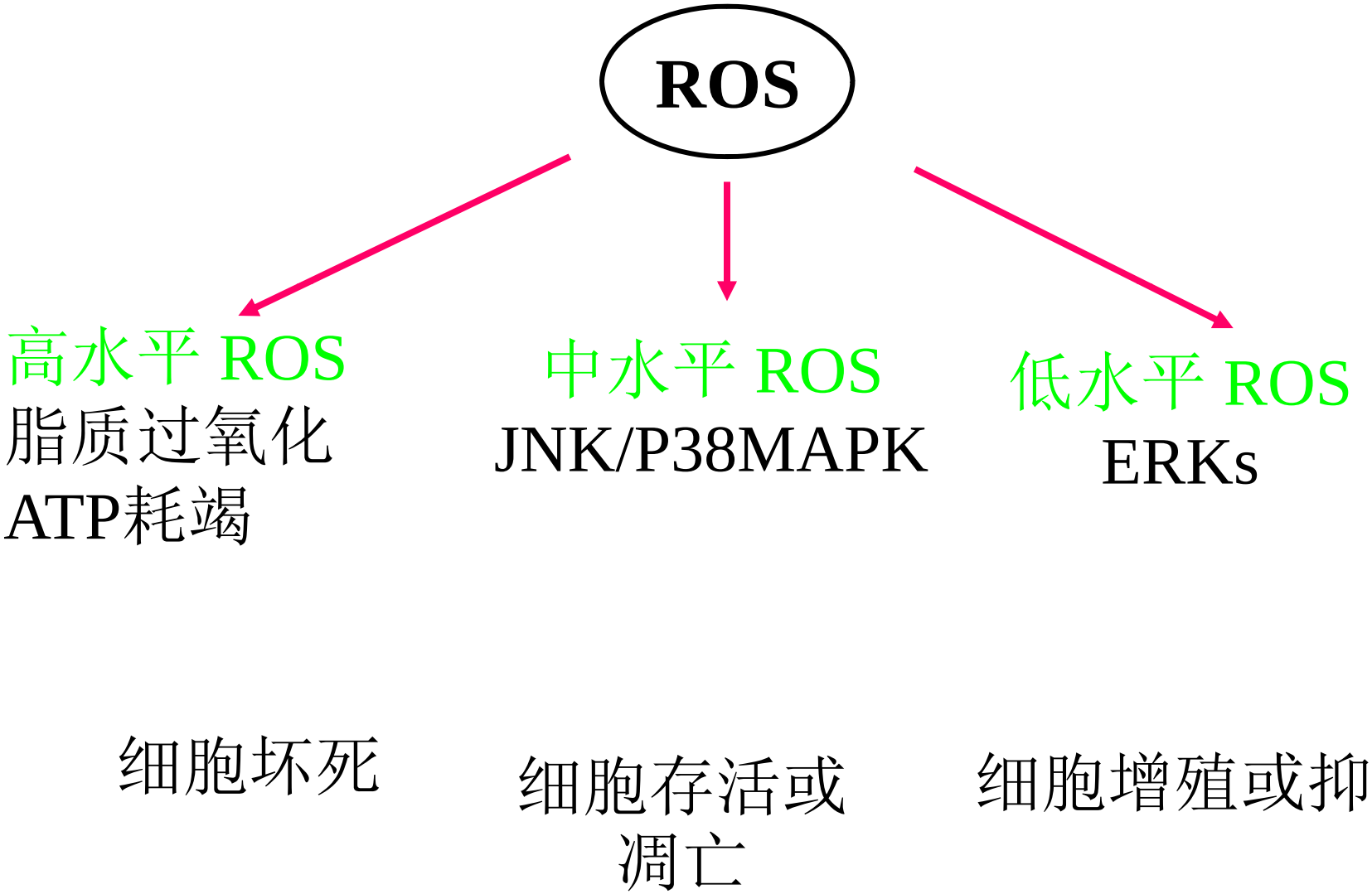


Fig. 4.1 Monthly patient lactate dehydrogenase 图4.1 患者乳酸脱氢酶月变化(Lyckholm *et al.* 1996)

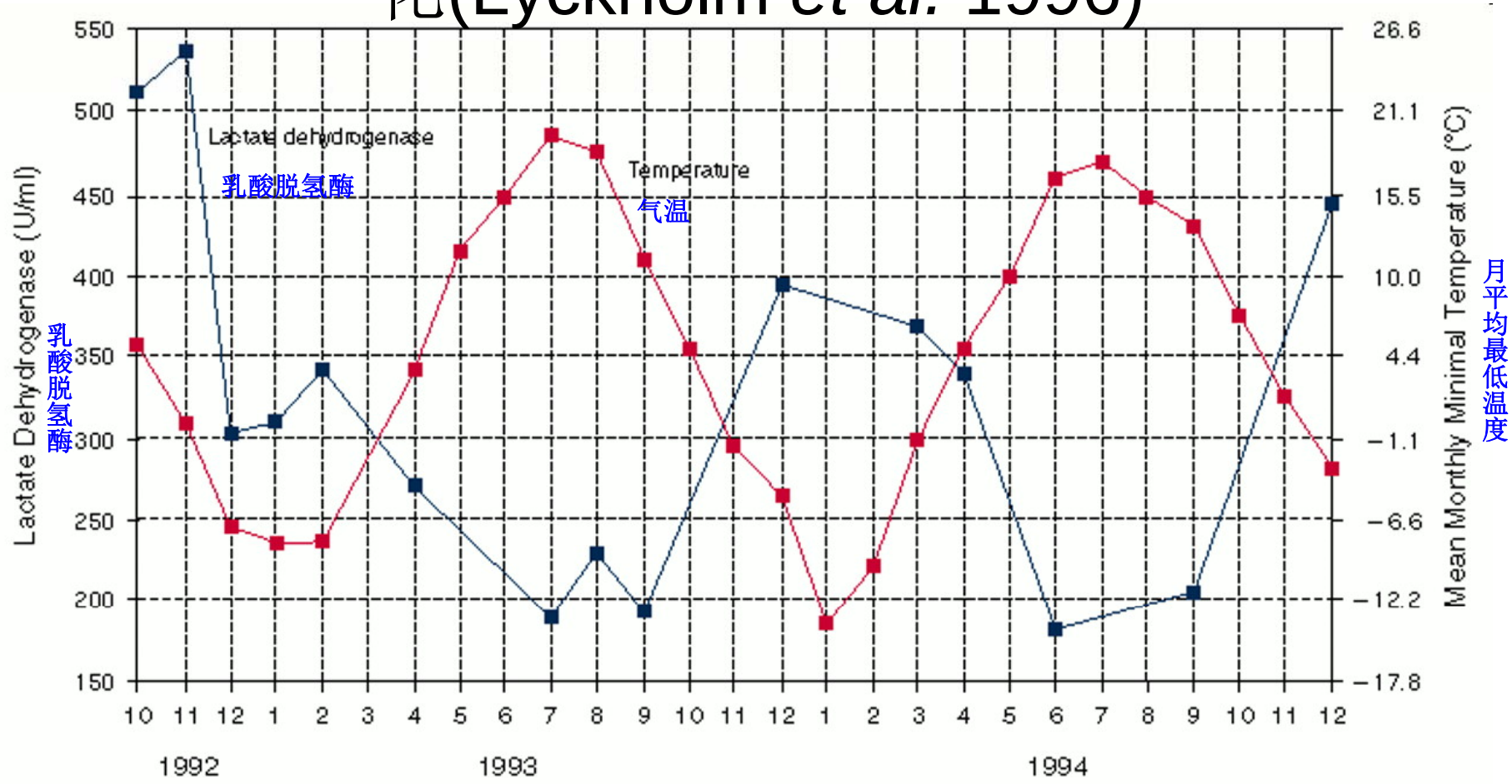


Fig. 4.2 Reported measles infective cases in two cities图5.2双城报道的麻疹感染病例 (Stone *et al.* 2007)

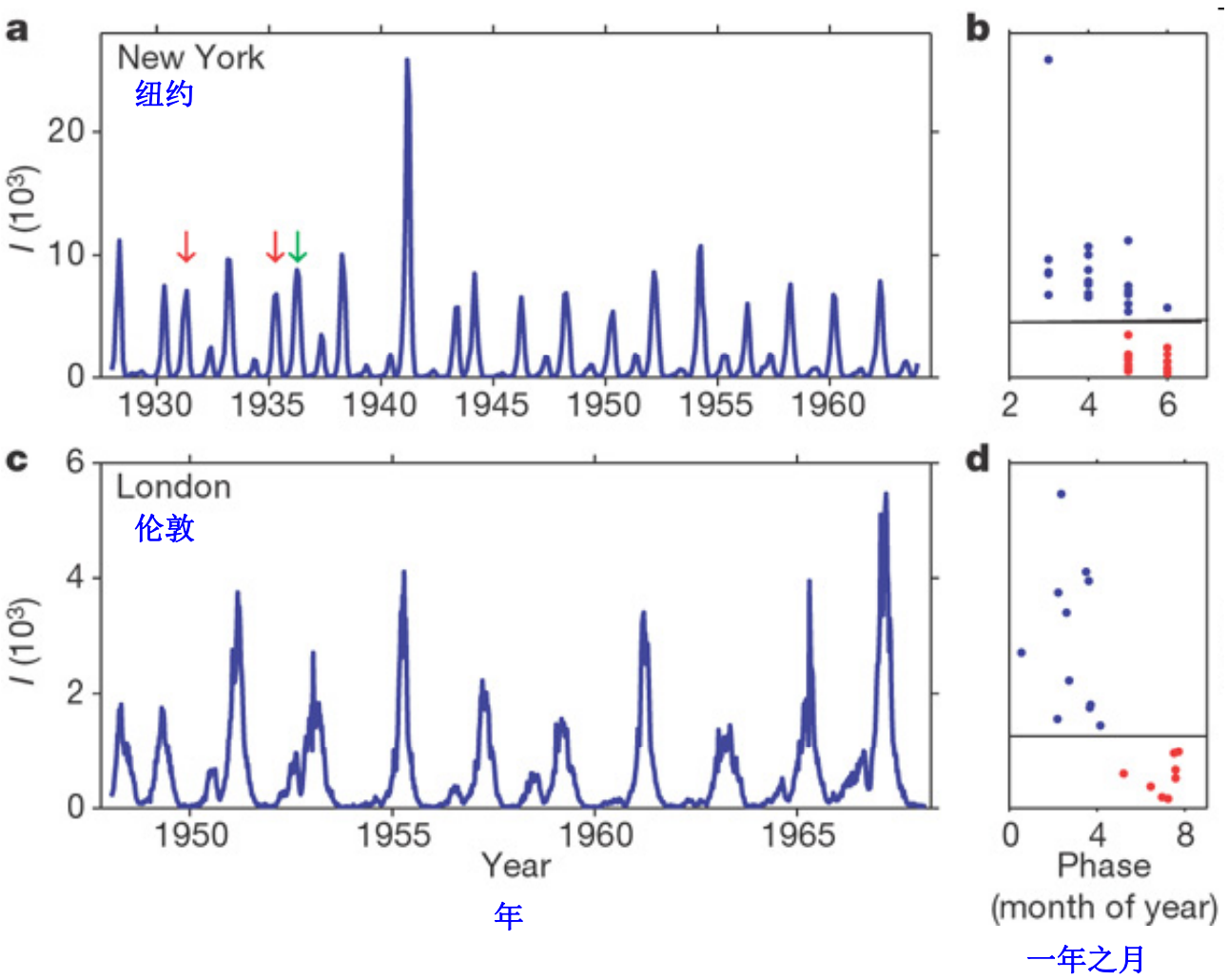
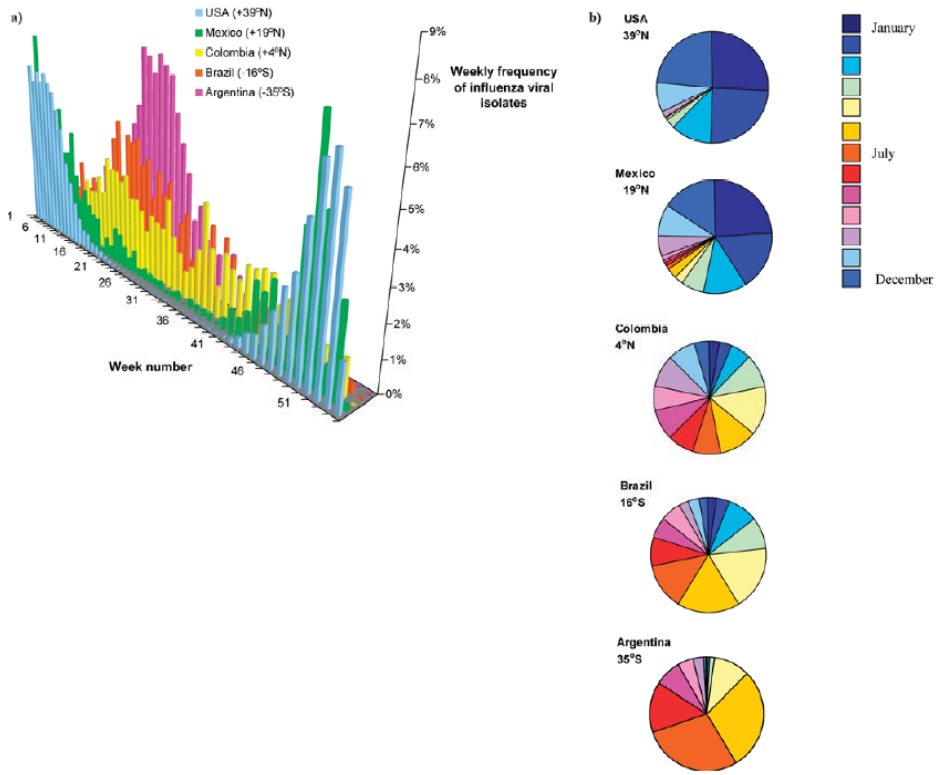
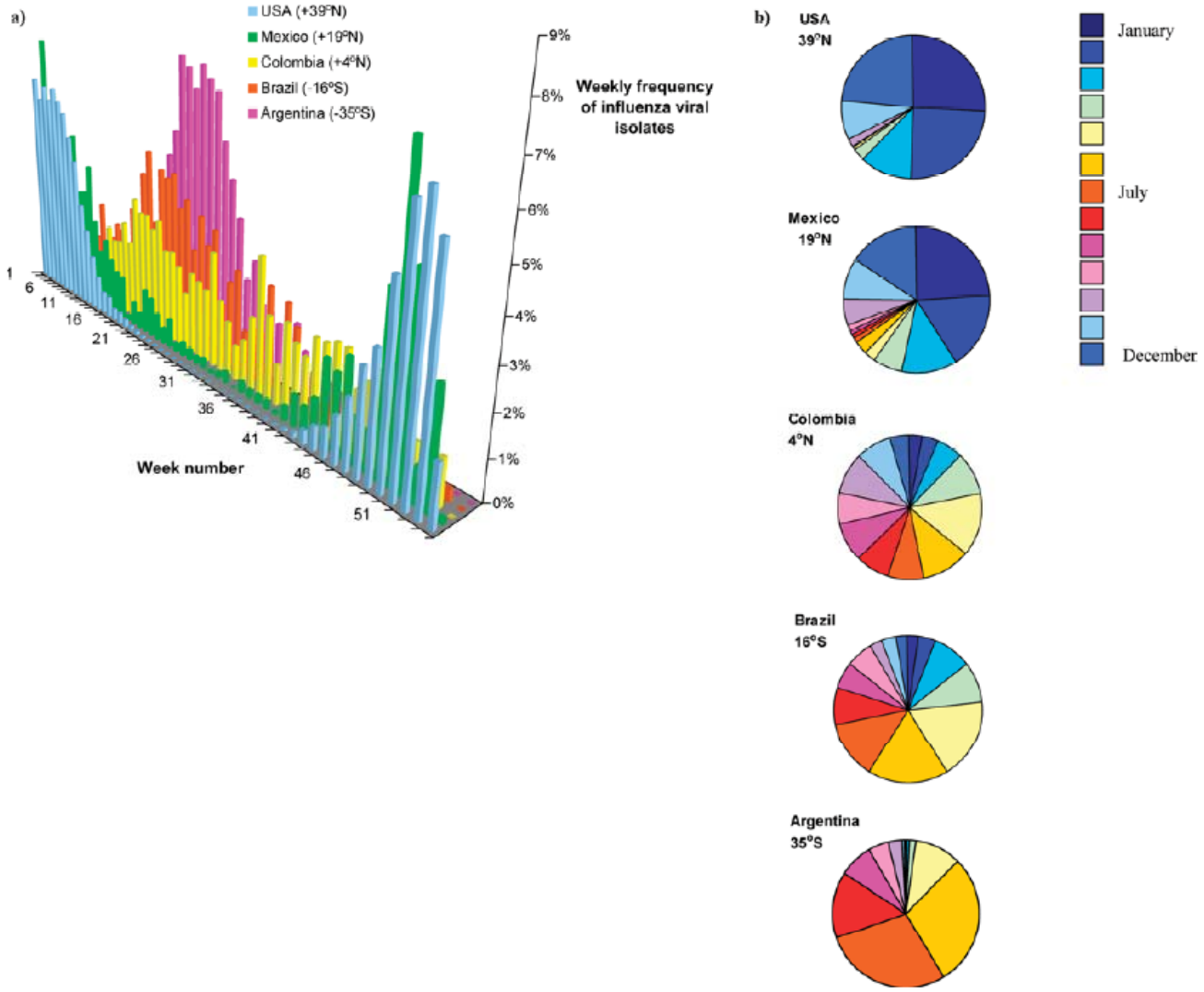


Fig. 4.3 Influenza Seasonal & Latitudial Patterns



(a) Weekly distribution of influenza laboratory isolates (from week 1 to week 52; weekly frequency (*y*-axis) is calculated as the weekly number of isolates divided by the annual number of isolates).
(b) Weekly numbers of isolates were aggregated over four-week periods to show a (nearly) monthly distribution of influenza circulation. Each color represents a different month (color bar on the right). Note the transition in seasonal patterns from north to south, ranging from marked seasonal winter activity centered around January in the US, to uniform circulation throughout the year in Columbia and again, strong winter epidemics center around July in Argentina. (Viboud et al 2006)

图4.3 流感的季节和纬度分布



美国和墨西哥、哥伦比亚‘巴西和阿根廷四个南美国家一年各周(a)和各月(b)实验室确诊的流感分布(Viboud et al 2006)

Fig. 5.1 Acupoints: *baihui and 4 shencongs(before, back, left and right)*

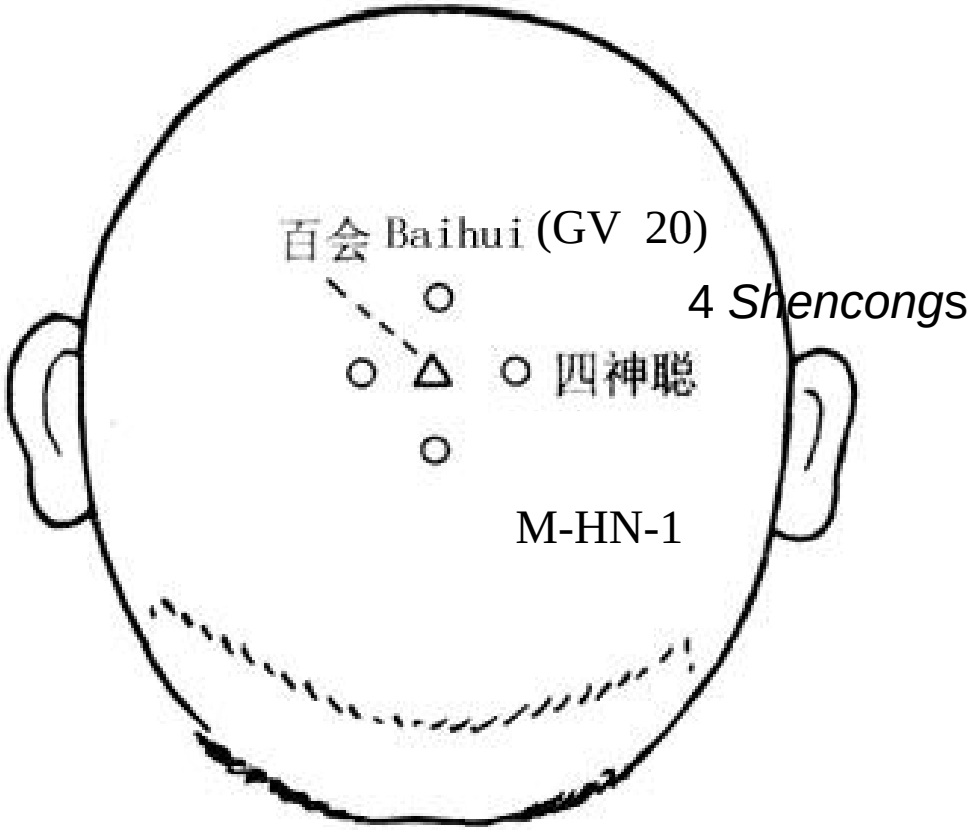


图5.1 穴位：百会和四神冲（前、后、左和右）

Fig. 5.2 Acupoints: *dazhui*, *shendao*(GV 11), *lingtai*(GV 10), *zhiyang*(GV 9), *mingmen*(GV 4), *changqiang*, *xinyu*, *piyu*, *weiyu*, and *shenyu*

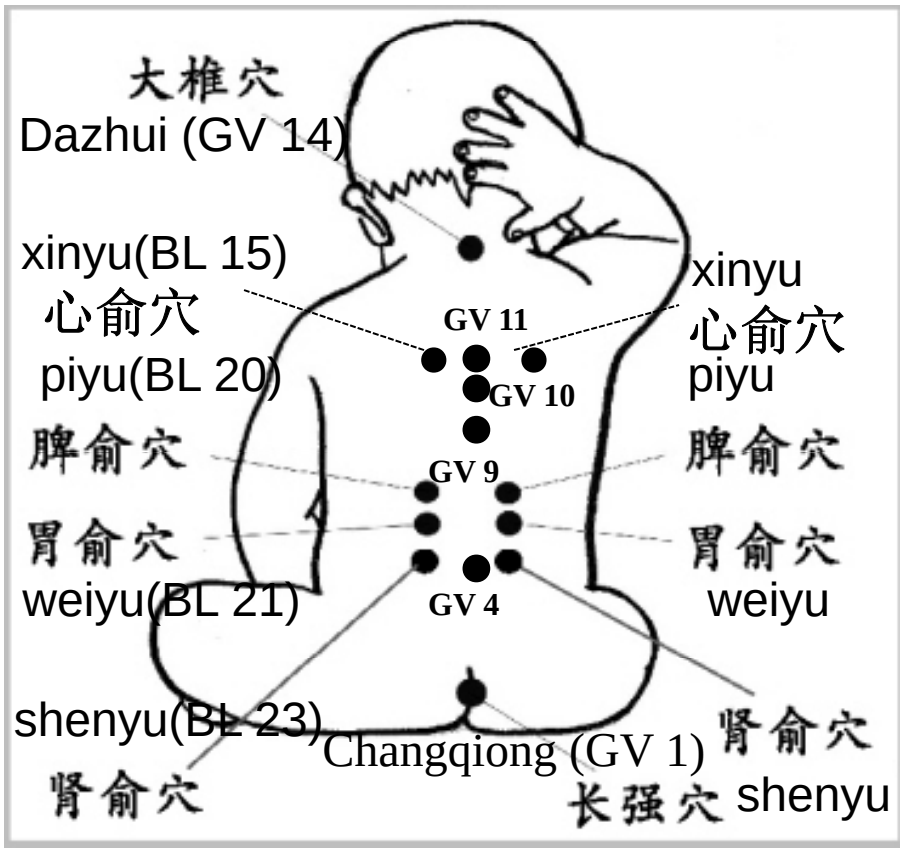


图5.2 穴位：大椎、神道(GV 11)、灵台(GV 10)、至阳(GV 9)、命门(GV 4)、长强、心俞、脾俞、胃俞和肾俞

Fig. 5.3 *Shenting* acupoint

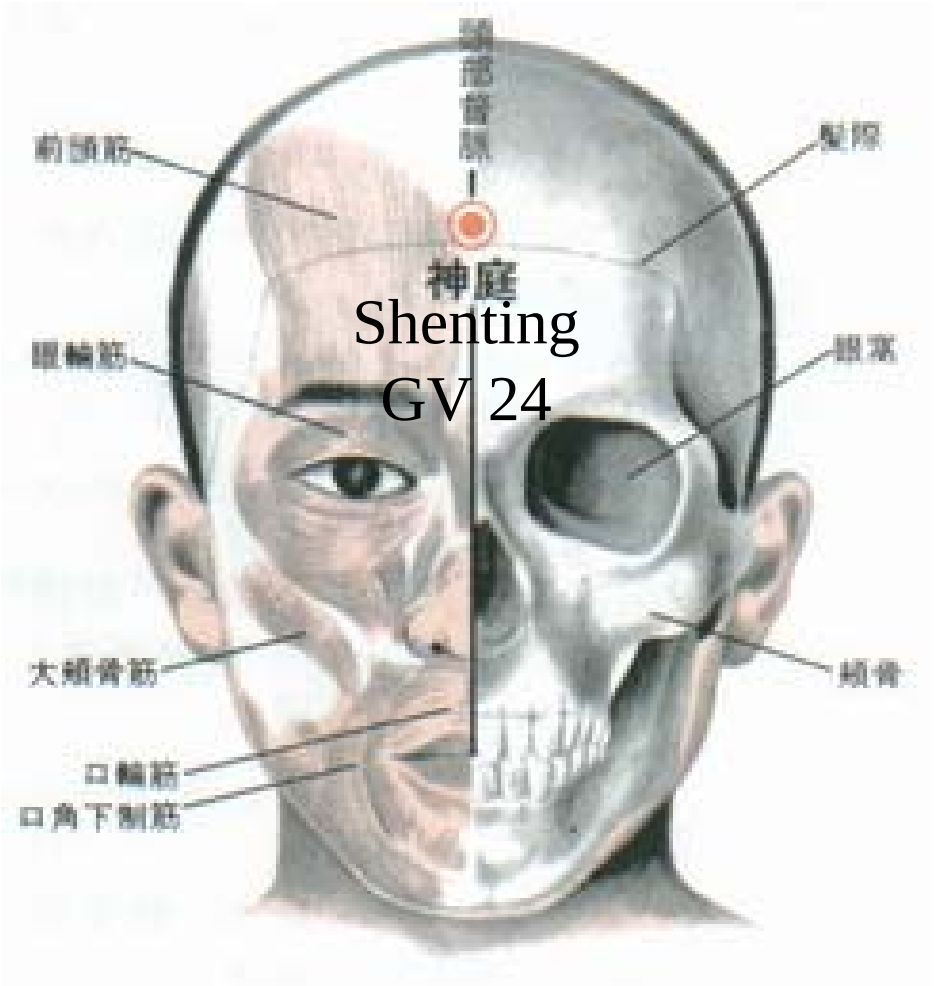


图5.3 神庭穴

Fig. 5.4 Acupoints: *fengchi*, and *fengfu*

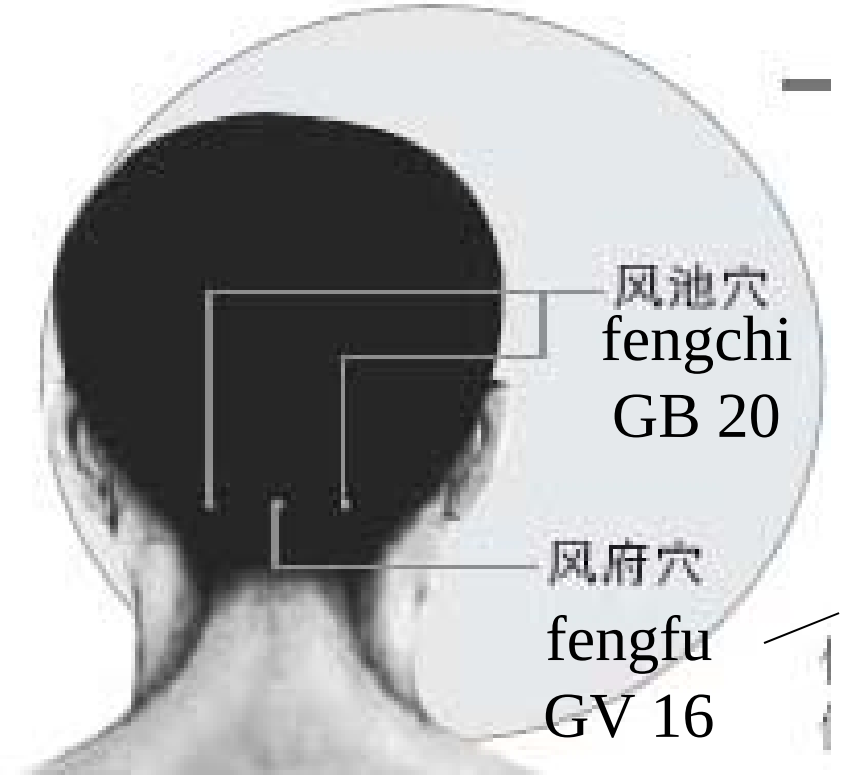


图5.4 穴位：风池和风府

Fig. 6.1 Acupoints: *shanzhong, zhongwan* and *qihai*

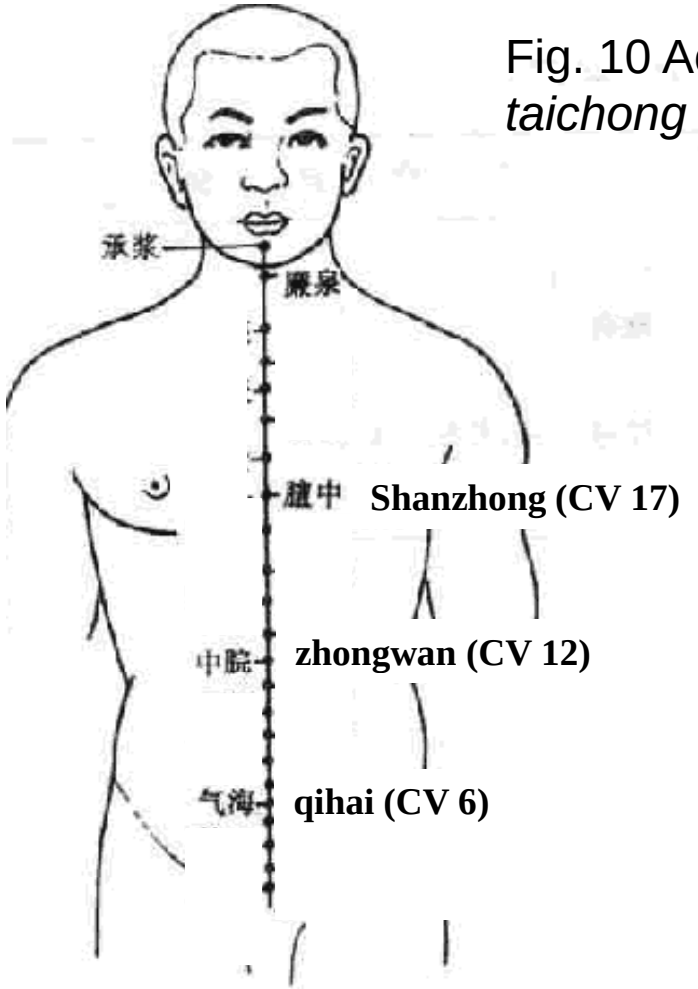


Fig. 10 Acupoints: *fengchi, fengfu* and *taichong*

图6.1 穴位：膻中、中脘和气海

Fig. 7.1 cellular membrane

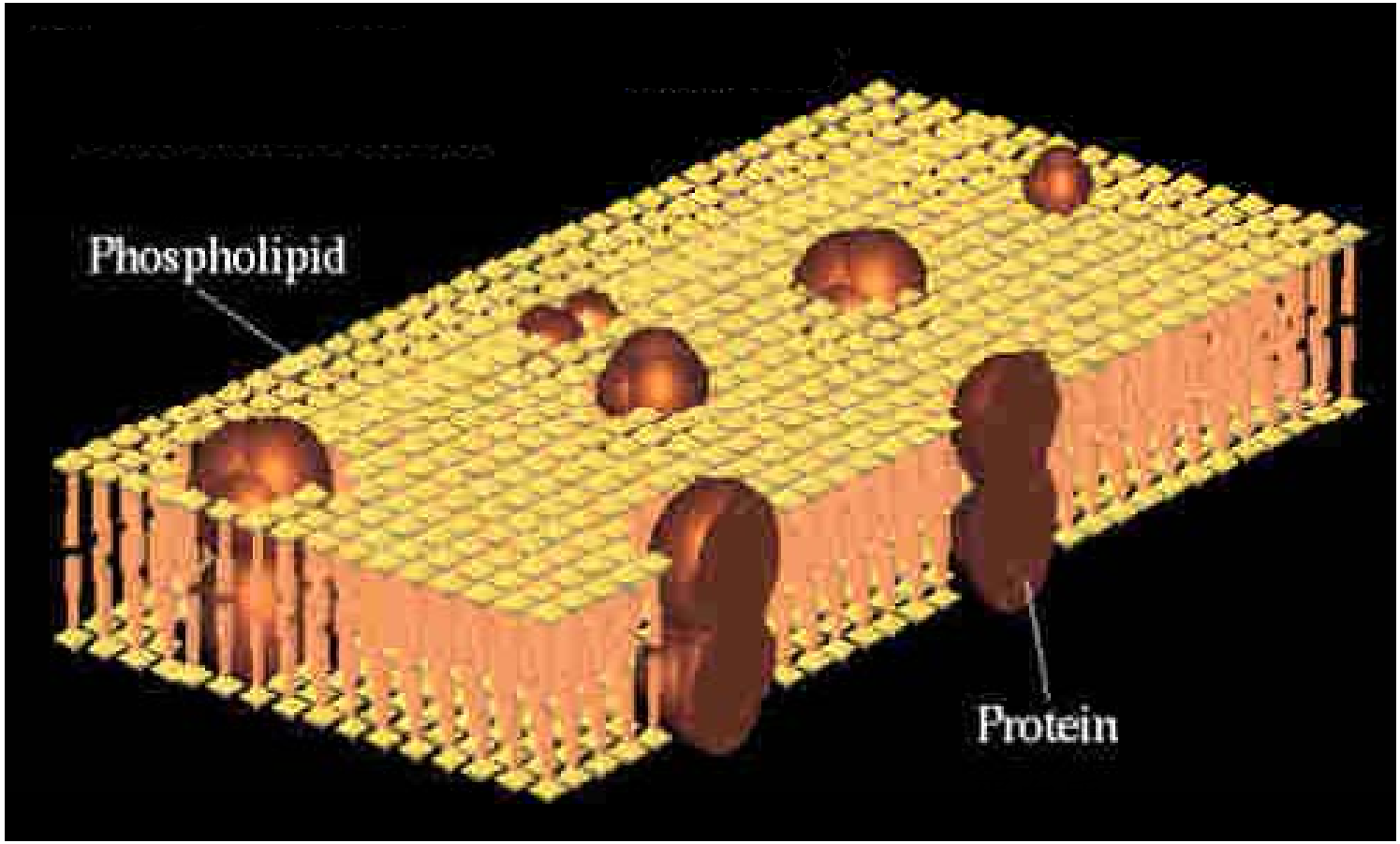


图7.1 细胞膜

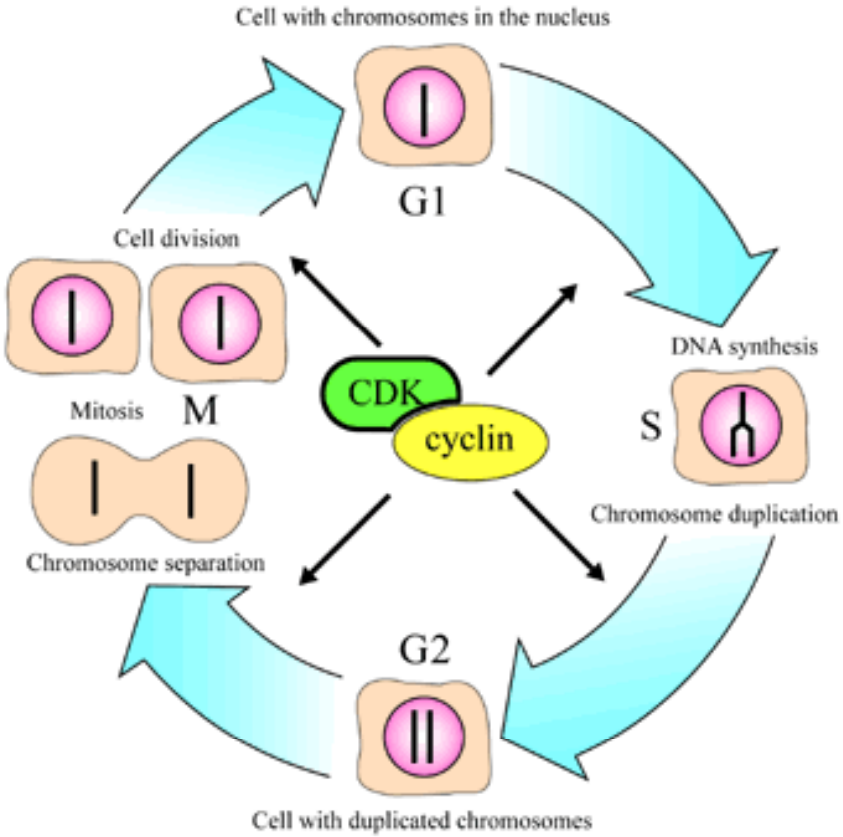


Fig. 7.2 Cell cycle
图7.2 细胞周期

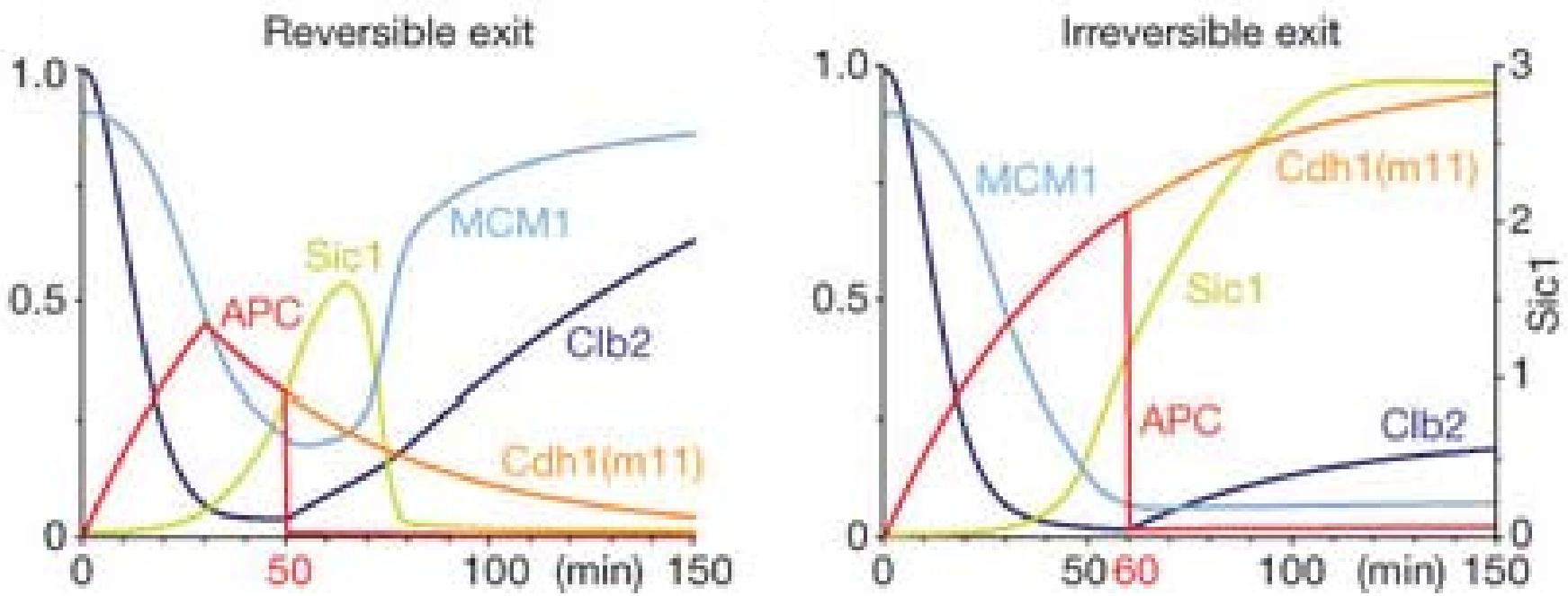


Fig. 7.3 Protein fluctuations in prolerfation

图7.3 细胞增殖过程中蛋白质的变化（López-Avilés *et al.* 2009）

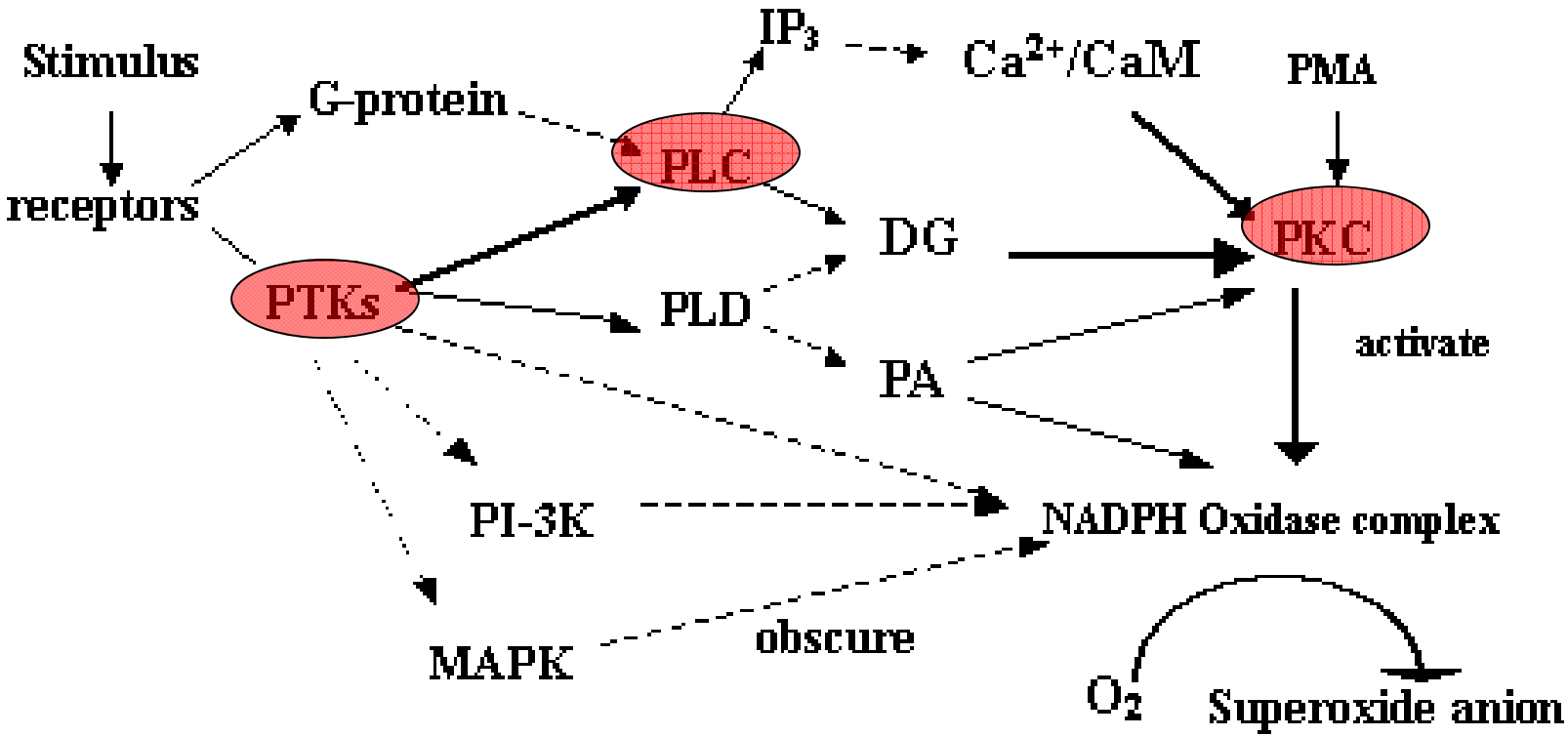


Fig. 7.4 Signal Transduction Pathways of He-Ne Laser Irradiation Induced PMN respiratory burst

图7.4 He-Ne激光诱导PMN呼吸爆发的信号转导通路 （Duan R *et al.* 2001）

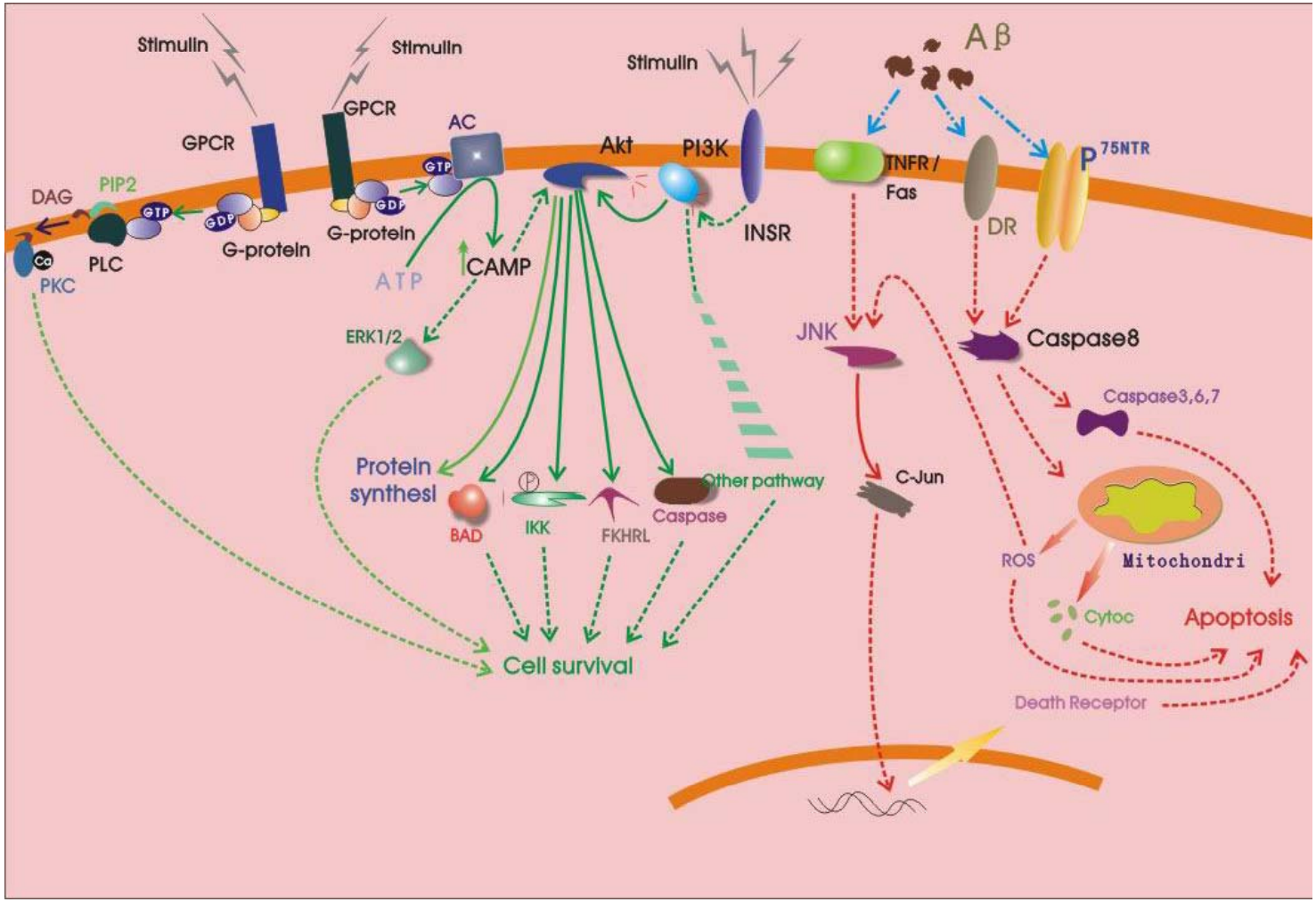


Fig. 7.5 signal transduction pathways of Aβ induced neurons apoptosis and its inhibition

图7.5 Aβ诱导的神经元凋亡及其抑制作用的信号通路(Zhu L *et al.* 2009a)

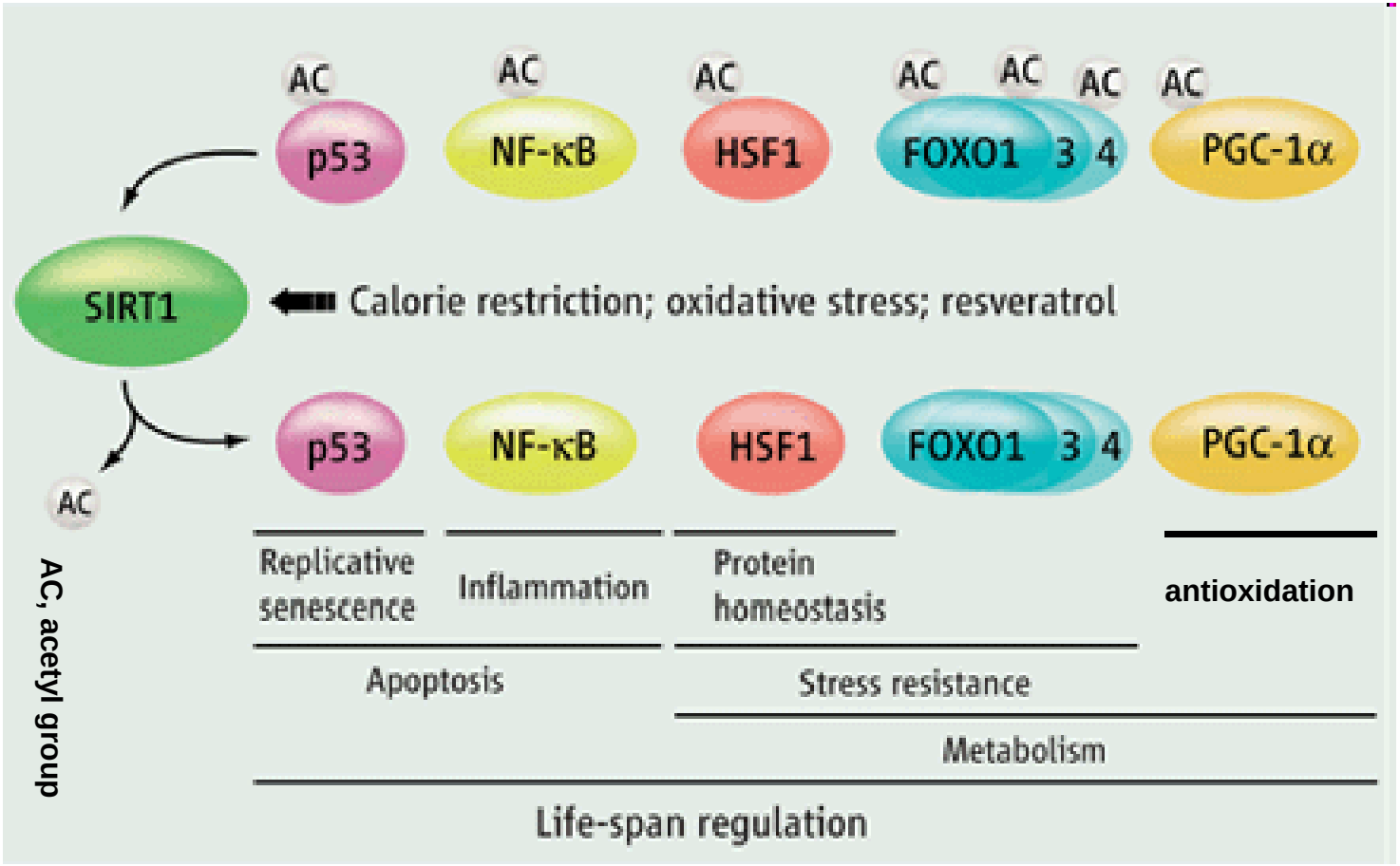


Fig. 7.6 SIRT1 mediated handing **stress** (Saunders *et al.* 2009)

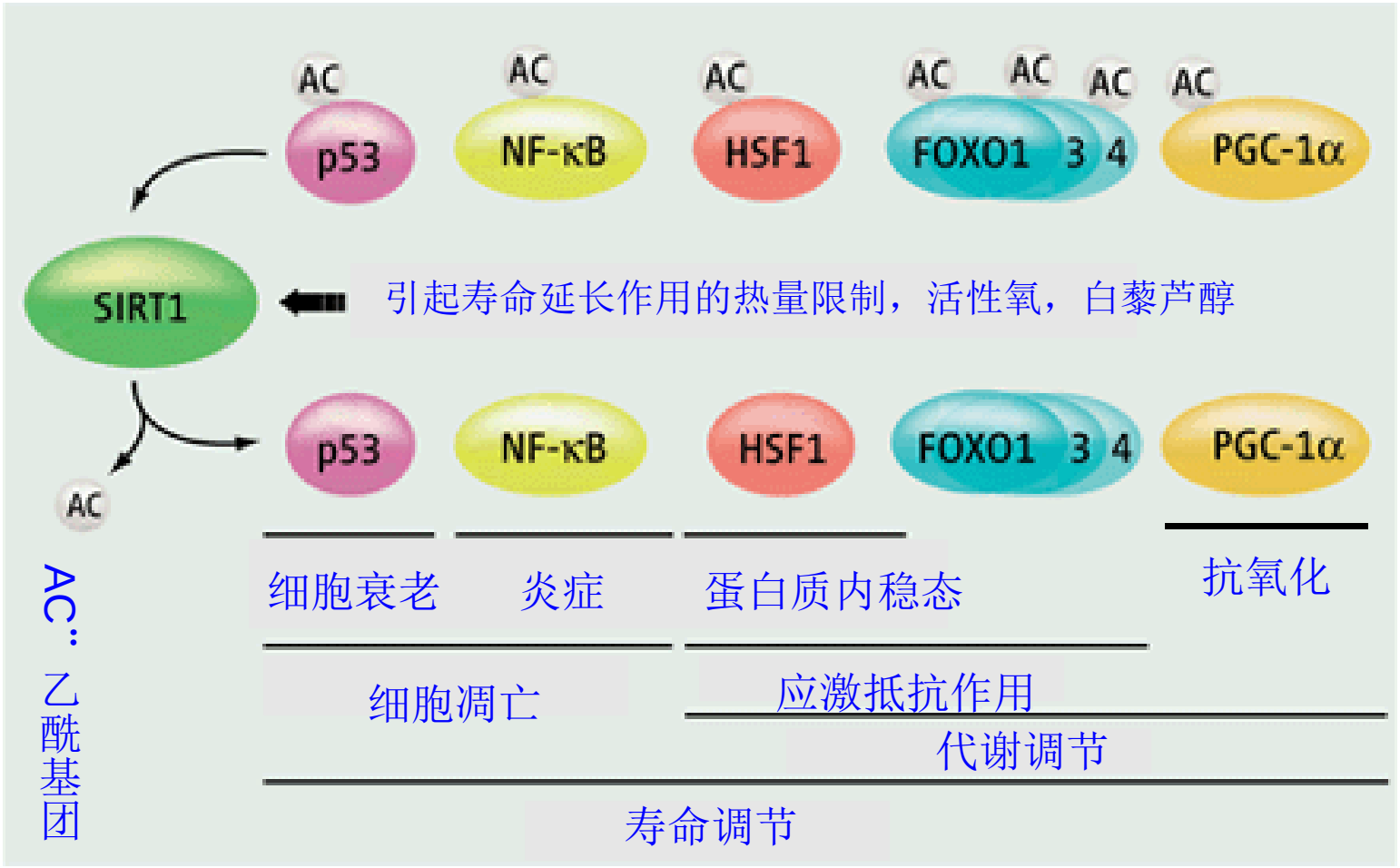


图7.6 SIRT1的应激处理 【修改自Saunders *et al.*（2009）】

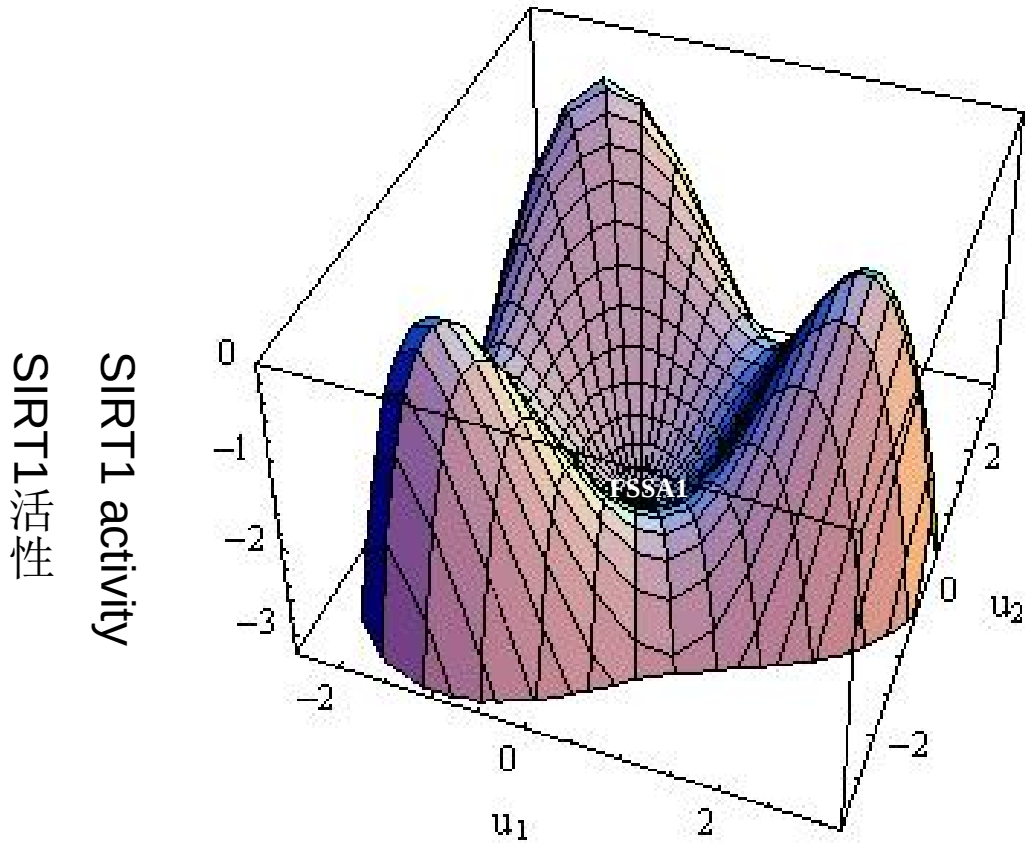


Fig. 7.7 Sirtuin 1 (SIRT1) activity potential well. FSSA1 denotes function-specific homeostasis specific SIRT1 activity

图7.7 组蛋白去乙酰化酶1(sirtuin 1, SIRT1)活性势阱. FSSA1表示功能内稳态特异的SIRT1活性

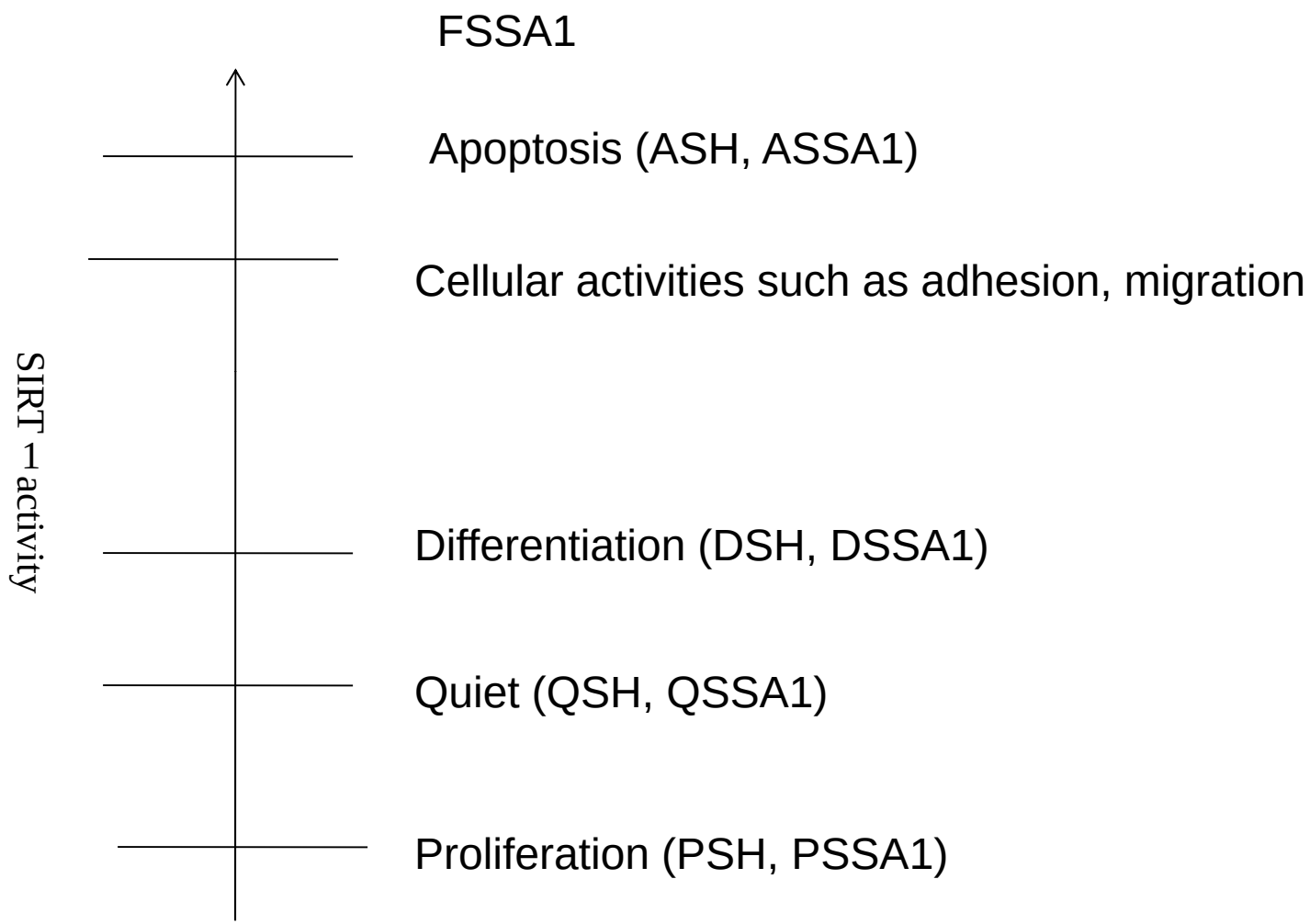


Fig. 7.8 FSH-specific SIRT1 activity (FSSA1)（Liu CY *et al.* 2009）

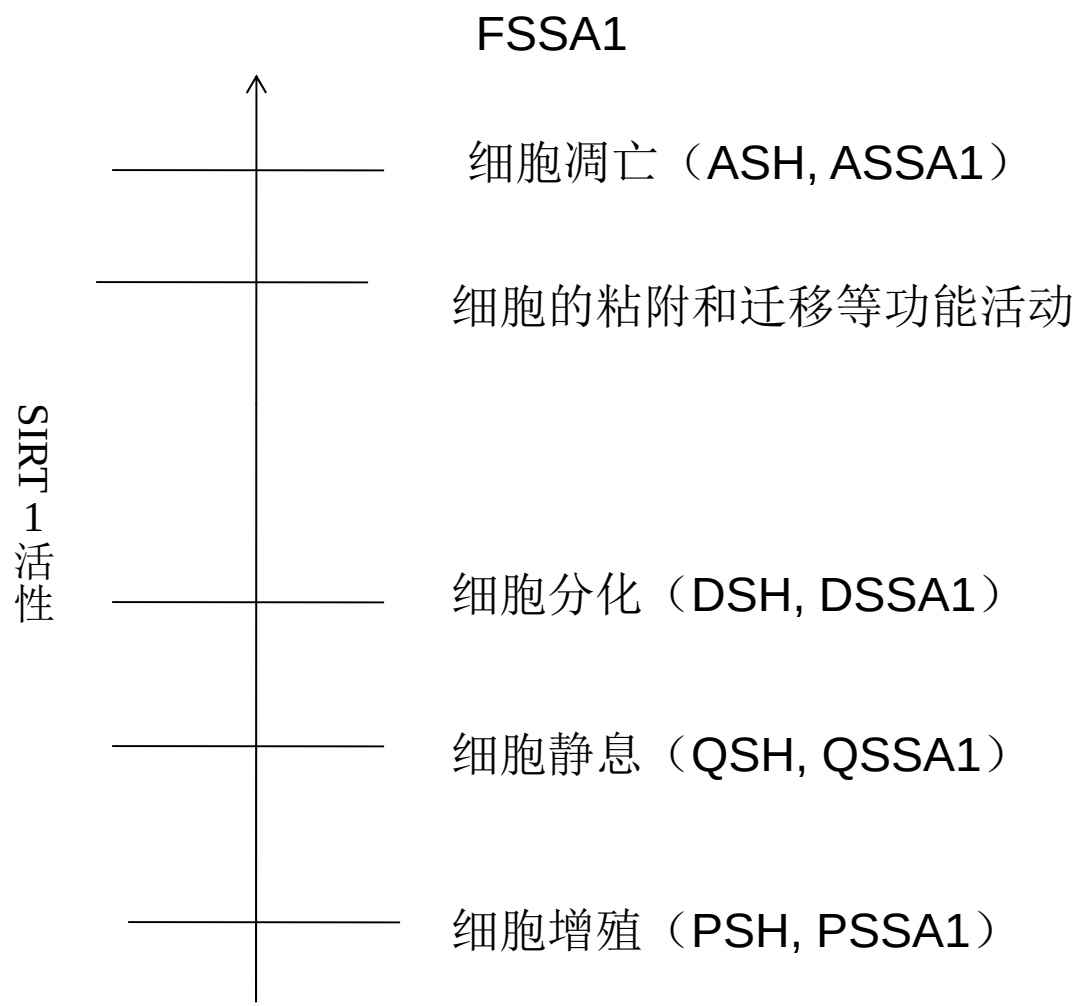


图7.8 细胞功能内稳态特异的SIRT1活性(FSSA1)（ Liu CY *et al.* 2009 ）

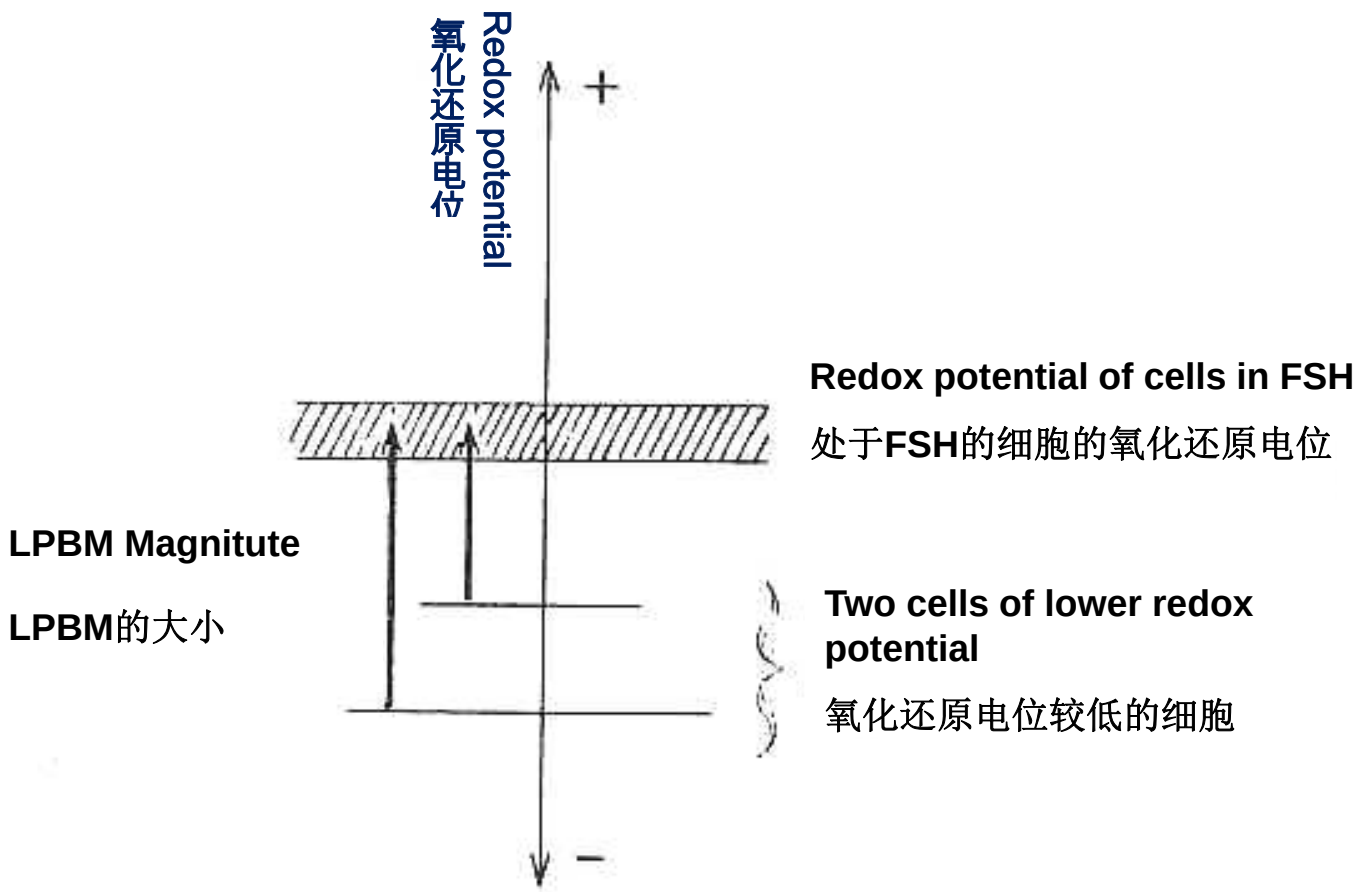
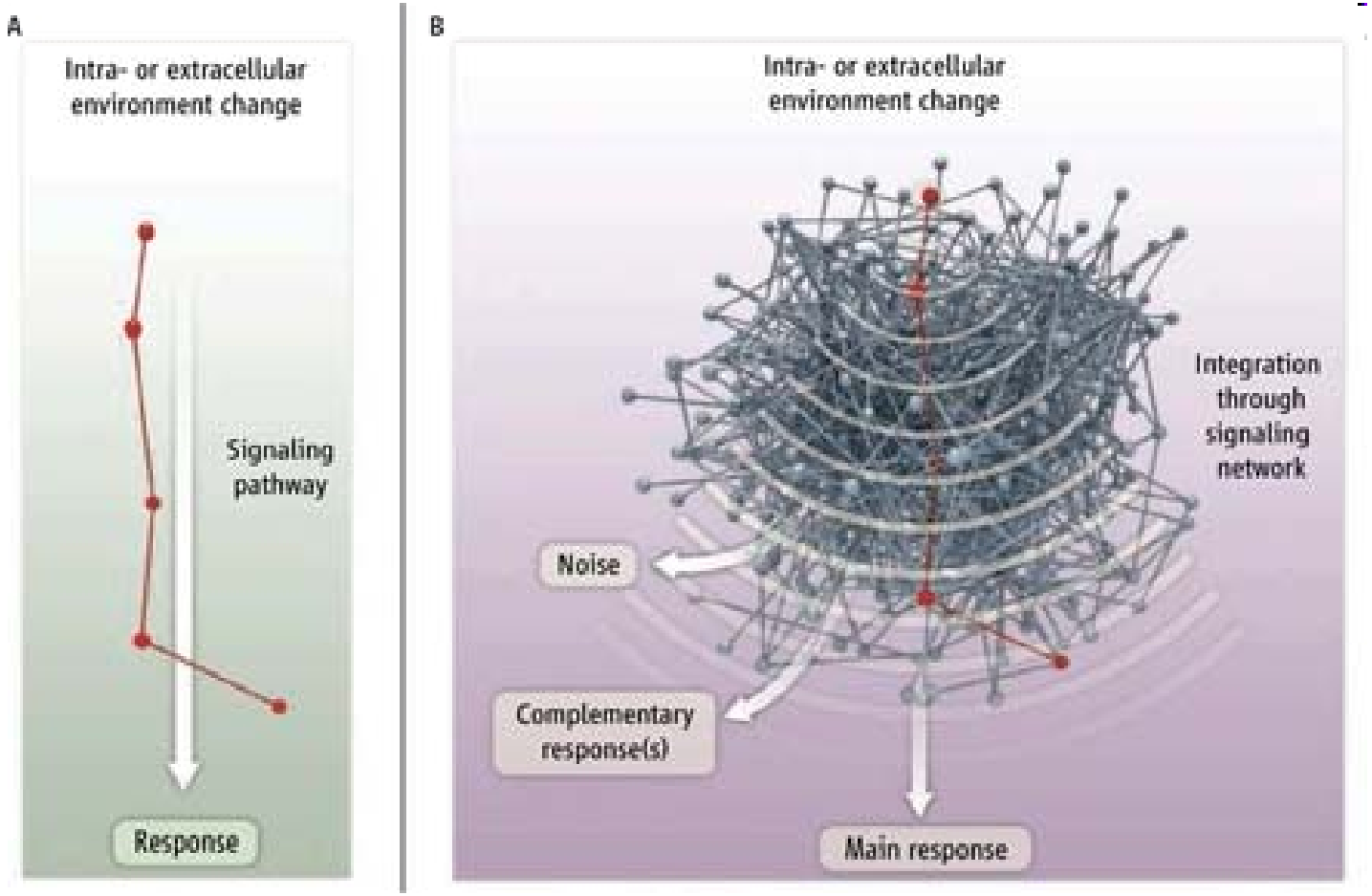


Fig.8.1 Cellular LPBM: The magnitute of LPBM is determined by redox potential of the cell at the moment (edited from Karu 1998)

图8.1 细胞LPBM: LPBM的大小决定于当时的细胞氧化还原电位

Fig. 9.1 **Cellular signaling: canonical pathway (A)** & network(B) (Levy *et al.* 2010) 图9.1 细胞信号：正则通路（A）与网络（B）



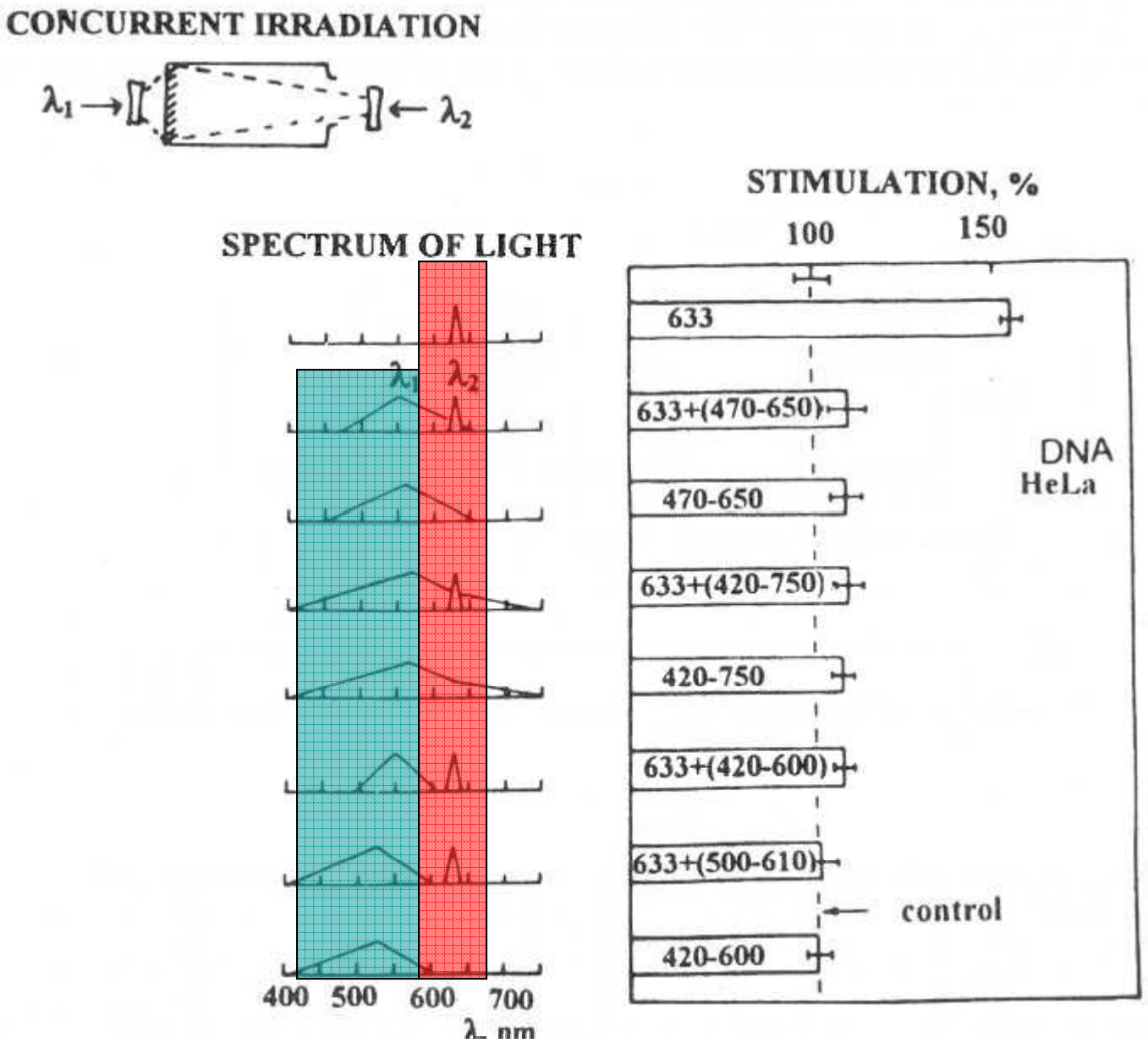


Fig. 10.1 The effects of concurrent irradiation of two LI beams on HeLa DNA synthesis rate (Karu 1998)

图10.1 两束光同时照射对HeLa细胞DNA合成的影响(Karu 1998)

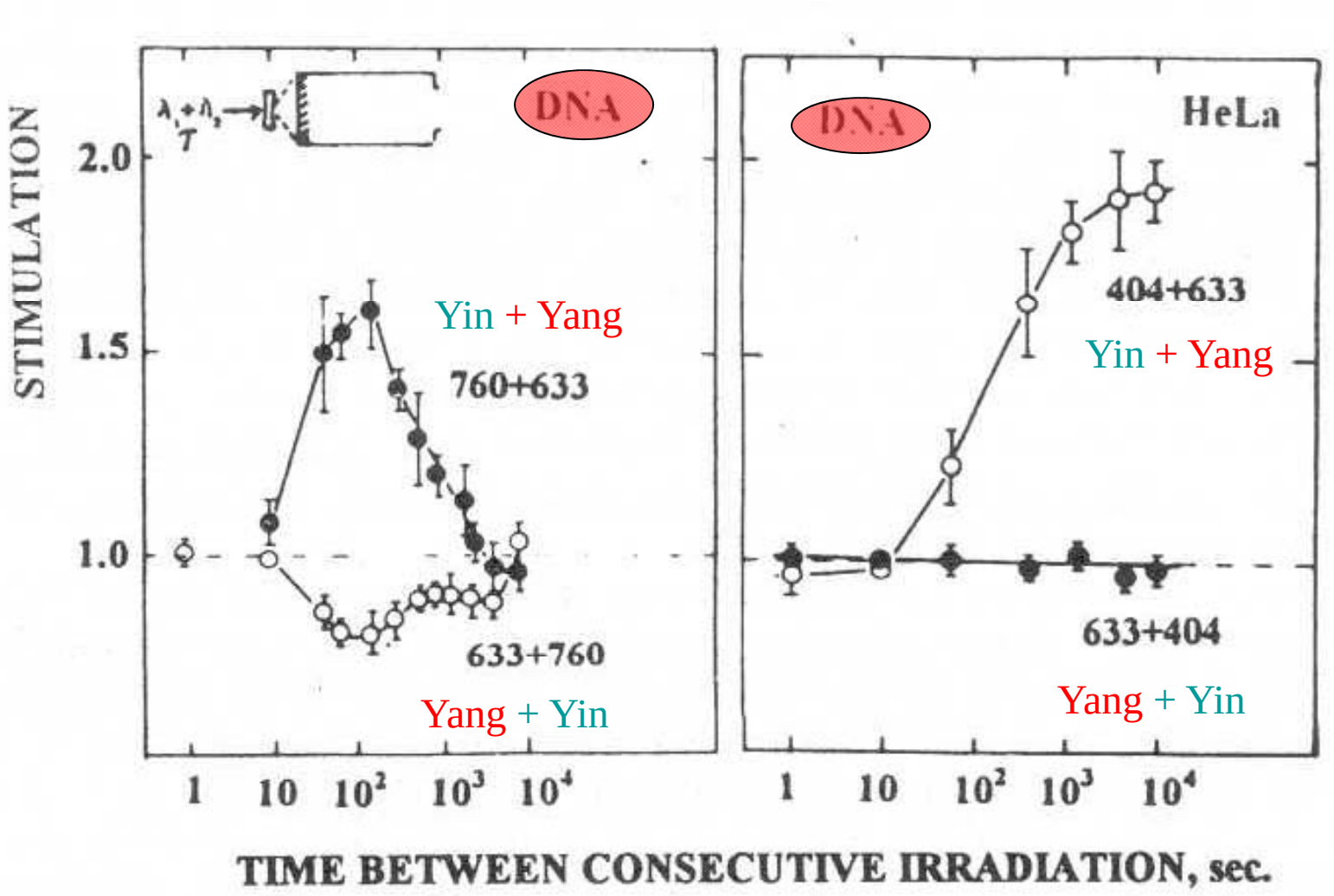


Fig. 10.2 The effect s of consecutive irradiation of two LI beams on HeLa DNA synthesis rate (Karu 1998)

图10.2 两束光相继照射对HeLa细胞DNA合成的影响(Karu 1998)

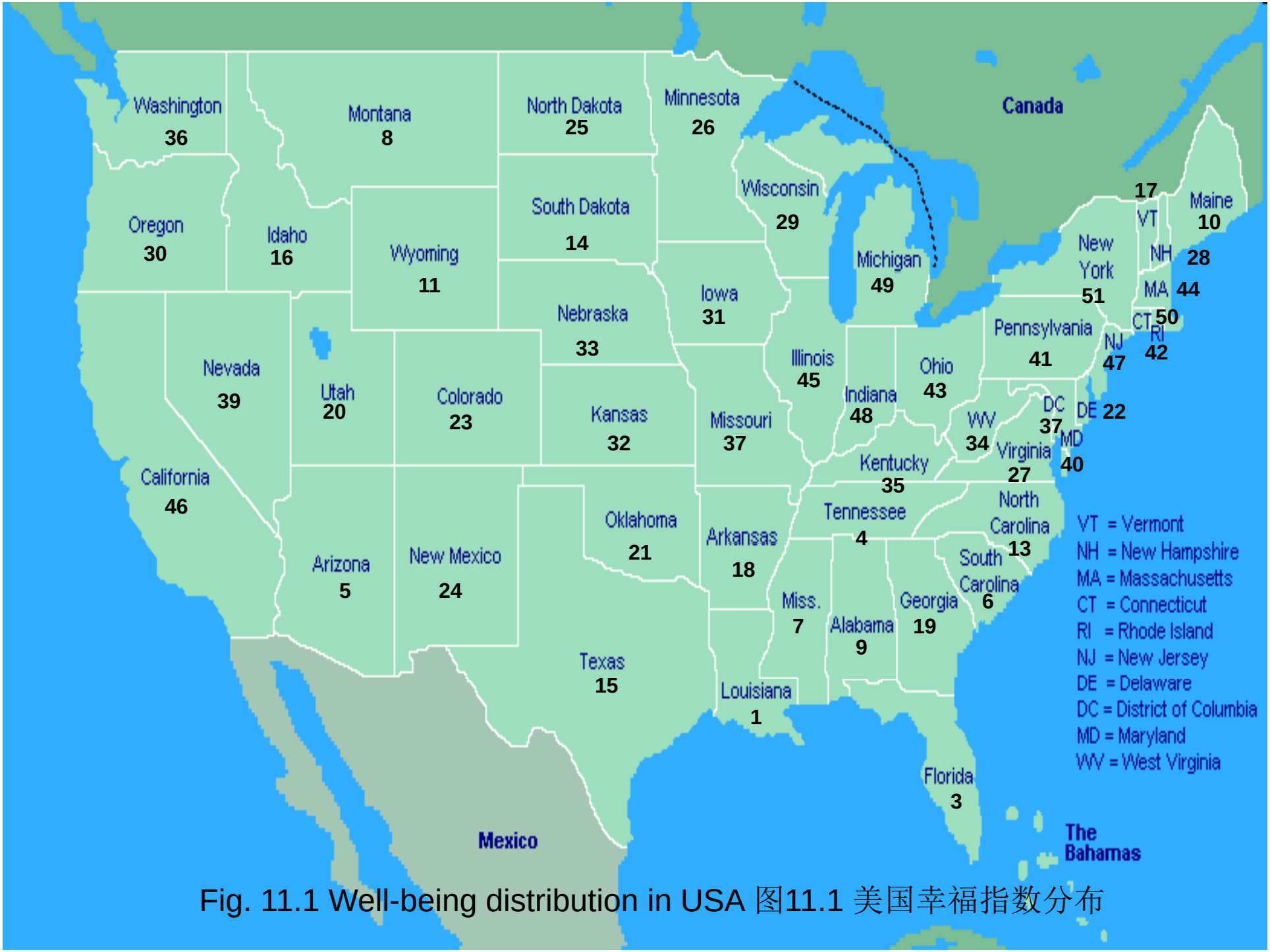


Fig. 11.1 Well-being distribution in USA 图11.1 美国幸福指数分布

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Acronym（缩写）

°αβγ

25(OH)D(3): 25-hydroxyvitamin D(3), 25-羟维生素 D(3) , Chap. 4（第 4 章）

5-HT: 5-hydroxytryptamine, 5-羟色胺, Chap. 5（第 5 章）

Aβ: amyloid β protein, β 淀粉样蛋白, Chap. 3（第 3 章）

AC: acetyl group, 乙酰基,Chap. 7（第 7 章）

AD: Alzheimer's disease, 阿尔茨海默氏病, Chap. 3（第 3 章）

ADSH: AD-specific homeostasis, AD 特异的内稳态, Chap. 3（第 3 章）

AgSH: aging-specific homeostasis, 衰老内稳态, Chap. 6（第 6 章）

AIDS: acquired immunodeficiency syndrome, 艾滋病, Chap. 8（第 8 章）

Akt: The other name of PKB, PKB 的别名, Chap. 7（第 7 章）

AlGaInP: Aluminum-Gallium-Indium-Phosphorus, the medium of diode laser, 铝镓铟磷, 半导体激光的介质 Chap. 2（第 2 章）

ALP: alkaline phosphatase, 碱性磷酸酶, Chap. 8（第 8 章）

ANS: autonomic nervous system, 植物神经, Chap. 3（第 3 章）

AnSH: autonomic activity-specific homeostasis, 植物神经内稳态, Chap. 3（第 3 章）

APC: anaphase promoting complex, 多亚基泛素连接酶后期促进复合体, Chap. 7（第 7 章）

ATO: ages at take-off of the pubertal growth spurt, 青春生长迸发期开始的年龄, Chap. 6（第 6 章）

APHV: ages at peak height velocity, 生长速度高峰年龄, Chap. 6（第 6 章）

ATP: adenosine-5'-triphosphate, 三磷酸腺苷, Chap. 6（第 6 章）

BDNF: brain-derived neurotrophic factor, 脑源神经营养因子, Chap. 5（第 5 章）

BFCR%: brain blood flow function change rate, 脑血流功能变化率, Chap. 3（第 3 章）

BIMP: biological information model of photobiomodulation, 光生物调节作用的生物信息模型, Chap. 9（第 9 章）

BMI: body mass index,体重指数, Chap. 3（第 3 章）

BMP: bone morphogenetic protein, 骨形态发生蛋白, Chap. 7（第 7 章）

BRFSS: behavioral risk factor surveillance system, 行为危险因子监视系统, Chap. 11（第 11 章）

C2C12: Mouse C3H muscle , 小鼠 C3H 骨骼, Chap. 7（第 7 章）

CAF: cancer-related fatigue, 癌因性疲乏, Chap. 6（第 6 章）

cAMP, 3'-5'-cyclic adenosine monophosphate, 环腺苷酸, Chap. 7（第 7 章）

CCK-8: cholecystokinin-octapeptide, 八肽胆囊收缩素, Chap. 3（第 3 章）

CCR5: chemokine (C-C motif) receptor 5, 趋化因子(C-C 基元)受体 5, Chap. 5（第 5 章）

CD95L: CD95 ligand, CD95 配体, Chap. 6（第 6 章）

Cdk: cyclin dependent kinase, 细胞周期蛋白依赖性激酶, Chap. 7（第 7 章）

cGMP: cyclic guanosine monophosphate, 环鸟苷酸, Chap. 7（第 7 章）

CGRP: calcitonin gene-related peptide, 降钙素基因相关肽, Chap. 5（第 5 章）

CHD: coronary heart disease, 冠心病, Chap. 5（第 5 章）

CI: 95% confidence intervals, 置信区间, Chap. 6（第 6 章）

CNS: central nervous system, 中枢神经系统, Chap. 3（第 3 章）

COX: cyclooxygenase, 环氧合酶, Chap. 5（第 5 章）

CP: cerebral palsy, 小儿脑性瘫痪（简称脑瘫）, Chap. 3（第 3 章）

CRF: chronic renal failure, 慢性肾衰, Chap. 6（第 6 章）

CT: computer tomography, 计算机 X 射线断层术, Chap. 8（第 8 章）

CV: the coefficient of variance, 变异系数, Chap. 3（第 3 章）
DAG: diacylglycerols, 甘油二酯, Chap. 7（第 7 章）
DD: degree of difficulty, 难度, Chap. 10（第 10 章）
DeSH: development-specific homeostasis, 发育内稳态, Chap. 6（第 6 章）
DEX: dexamethasone, 地塞米松, Chap. 7（第 7 章）
DILI: drug-induced liver injury, 药物性肝损害, Chap. 3（第 3 章）
DLILT: interdigital low intensity laser therapy, 手指间低强度激光照射治疗, Chap. 1（第 1 章）
DMEM: Dulbecco's modified Eagle medium, Dulbecco 改进的 Eagle 培养基, Chap. 7（第 7 章）
DNA: deoxyribonucleic acid, 脱氧核糖核酸, Chap. 3（第 3 章）
DOMS: delayed-onset muscle soreness, 延迟性肌肉酸痛, Chap. 11（第 11 章）
dPBM: developmental PBM, 发展性光生物调节作用, Chap. 3（第 3 章）
dPC12: differentiated PC12, 化成熟的 PC12, Chap. 8（第 8 章）
DPN: diabetic peripheral neuropathy, 糖尿病周围神经病变, Chap. 3（第 3 章）
DRM: Day Reconstruction Method，日重现法, Chap. 11（第 11 章）
EAE: encephalomyelitis, 脑脊髓炎，Chap. 4（第 4 章）
EC: endothelial cell, 内皮细胞, Chap. 8（第 8 章）
EFG: epidermal growth factor, 表皮生长因子, Chap. 7（第 7 章）
EFI: erythrocyte filtration index, 红细胞滤过指数, Chap. 9（第 9 章）
EOC: ET-OTA-OBC1-OBC2-…-Competition, ET-OTA-OBC1-OBC2-…-比赛, Chap. 11（第 11 章）
EOT: ET-OTA-OBT1-OBT2-…-Testing, ET-OTA-OBT1-OBT2-…-测试, Chap. 11（第 11 章）
eNOS: endothelial NO synthase, 内皮 NO 合酶，Chap. 9（第 9 章）
EPT: extraocular phototransduction, 眼睛外光信号转导, Chap. 9（第 9 章）
ER: endoplasmic reticulum, 内质网, Chap. 7（第 7 章）
ERK: extracellular signaling regulated kinase, 细胞外信号调节蛋白激酶, Chap. 7（第 7 章）
ERP: event-related potential, 事件相关电位， Chap. 5（第 5 章）
ET: extraordinary training, 超常训练, Chap. 3（第 3 章）
FCS: fetal calf serum, 小牛血清, Chap. 7（第 7 章）
FDA: Food and Drug Administration in USA, 美国食品和药物管理局, Chap. 1（第 1 章）
FES: FSH-essential subsystem, FSH 必需子系统, Chap. 11（第 11 章）
FESH: FES-specific homeostasis, FES 特异的内稳态, Chap. 11（第 11 章）
FNS: FSH-non-essential subsystem, FSH 非必需子系统, Chap. 11（第 11 章）
FNSH: FNS-specific homeostasis, FNS 特异的内稳态, Chap. 11（第 11 章）
FoSH: follicle-stimulating hormone, 促卵泡激素, Chap. 6（第 6 章）
FOXO: forkhead box class O, 叉头框蛋白, Chap. 7（第 7 章）
fPBM: FSH-specific PBM, 功能内稳态特异的光生物调节作用, Chap. 3（第 3 章）
FRET: fluorescence resonance energy transfer, 荧光共振能量转移技术, Chap. 9（第 9 章）
FSH: function-specific homeostasis, 功能内稳态. Chap. 3（第 3 章）
FSSA1: FSH-specific SIRT1 activity, FSH 特异的 SIRT1 活性, Chap. 7（第 7 章）
GaAlAs: gallium aluminum arsenide , the medium of diode laser (780-890 nm) 镓铝砷，780-890 nm 的半导体激光的介质, Chap. 2（第 2 章）
GaInP/AlGaInP: Gallium-Indium-Phosphorus/AlGaInP, the medium of diode laser (650 nm)，镓铟磷/镓铟铝磷, 650 nm 半导体激光的介质 Chap. 2（第 2 章）
GAPs: GTPase activating proteins, GTP 酶激活蛋白, Chap. 7（第 7 章）

GPCRs: G-protein coupled receptors, G 蛋白偶联跨膜受体, Chap. 7（第 7 章）
GSH: glutathione, 谷胱甘肽, Chap. 3（第 3 章）
GSS: global seasonality score, 整体季节敏感性评分, Chap. 3（第 3 章）
GTP: guanosine triphosphate, 三磷酸鸟苷, Chap. 7（第 7 章）
G-proteins（G 蛋白）: GTP-binding and hydrolyzing proteins, GTP 结合与水解蛋白, Chap. 7（第 7 章）
HDL-C: high-density lipoprotein cholesterol, 高密度胆固醇, Chap. 4（第 4 章）
He-Ne: helium neon mixture, the medium of gas laser (632.8nm)，氦氖混合气体，632.8nm 气体激光的介质, Chap. 2（第 2 章）.
HF: high frequency band, 高频, Chap. 3（第 3 章）
Hhcy: hyperhomocysteinemia, 高同型半胱氨酸血症, Chap. 6（第 6 章）
HIV: human immunodeficiency virus, 人类免疫缺陷病毒, Chap. 8（第 8 章）
HLA: human leukocyte antigen, 人白细胞抗原, Chap. 4（第 4 章）
HRE: hormone response element, 激素效应元件, Chap. 7（第 7 章）
HRV: heart rate variability, 心率变异性, Chap. 3（第 3 章）
HSF: heat shock factor, 热休克因子, Chap. 7（第 7 章）
Hsp: heat shock protein, 热休克蛋白, Chap. 7（第 7 章）
HSFb: human skin fibroblast, 人的皮肤成纤维细胞, Chap. 9（第 9 章）
IL: interleukin，白细胞介素, Chap. 5（第 5 章）
IL-2R: interleukin-2 receptor, 白介素 2 受体, Chap. 4（第 4 章）
ILELT: intravascular low energy laser therapy, 血管内低能量激光照射疗法，Chap. 3（第 3 章）
ILILM: ILILT-like mechanism, 类 ILILT 机理, Chap. 4（第 4 章）
ILILT: intranasal low intensity laser therapy, 鼻腔内低强度激光治疗，Chap. 1（第 1 章）
IFN: interferon, 干扰素, Chap. 3（第 6 章）
iNOS: inducible nitric oxide synthase, 诱导型一氧化氮合酶, Chap. 11（第 11 章）
IP_3: inositol 1,4,5-trisphosphate, 肌醇 1，4，5-三磷酸, Chap. 7（第 7 章）
IQ: intelligence quotient, 智商, Chap. 8（第 8 章）
IRA: infrared A (700-2000 nm), 短波红外（700-2000 nm）, Chap. 3（第 3 章）
Jak: Janus kinase, Janus 家族酪氨酸激酶, Chap. 7（第 7 章）
JNK: c-Jun N-terminal kinase, c-Jun 氨基末端激酶, Chap. 7（第 7 章）
KPHCP: key process hypothesis of cellular PBM, 细胞光生物调节作用的关键过程假定，Chap. 9（第 9 章）.
LA: laser acupuncture, 激光针刺, Chap. 1（第 1 章）
LDC: luminol-dependent chemiluminescence, 鲁米诺增强的化学发光, Chap. 8（第 8 章）
LDH: lactate dehydrogenase, 乳酸脱氢酶, Chap. 4（第 4 章）
LDL-C: Low density lipoprotein cholesterol, 低密度胆固醇, Chap. 3（第 3 章）
LED: light-emitting diode array, 发光二极管阵列 Chap. 2（第 2 章）
LF: low frequency band, 低频, Chap. 3（第 3 章）
LGAL: low intensity GaInP/AlGaInP diode laser irradiation at 650 nm, 低强度 GaInP/AlGaInP 半导体激光, 波长 650 nm, Chap. 3（第 3 章）
LH: luteinizing hormone, 黄体生成素, Chap. 6（第 6 章）
LHNL: low intensity He-Ne laser irradiation, 低强度氦氖激光, Chap. 3（第 3 章）
LI: laser irradiation or monochromatic light,激光或单色光, Chap. 1（第 1 章）
LIIL: low-intensity impulse laser radiation, 低强度脉冲激光, Chap. 6（第 6 章）

LIL: low intensity LI （~10 mW/cm^2），低强度激光或单色光, Chap. 2（第 2 章）
LLL: low level LI, 低水平激光或单色光, Chap.1 （第 1 章）
LLLT: low level LI therapy, 低水平激光或单色光治疗，Chap. 1（第 1 章）
LP: light perception, 光感, Chap. 6（第 6 章）
LPBM: PBM of LIL, 低强度激光或单色光的光生物调节作用, Chap. 3（第 3 章）
LPS: lipopolysaccharides, 脂多糖, Chap. 8（第 8 章）
MAPK: mitogen-activated protein kinase, 丝裂原活化蛋白激酶, Chap. 3（第 3 章）
MCI: mild cognitive impairment, 轻度认知障碍, Chap. 5（第 5 章）
MDA: malondialdehyde, 丙二醛, Chap. 3（第 3 章）
MEK: MAPK and ERK kinase, MAPK 和 ERK 激酶, Chap. 9（第 9 章）
Mel: melatonin, 褪黑素, Chap. 3（第 3 章）
MHC: major histocompatibility complex, 主要组织相容性复合体, Chap. 3（第 3 章）
MHDS: modified hasegawa dementia scale, 长谷川痴呆修改量表, Chap. 6（第 6 章）
MHNL: moderate intensity He-Ne laser irradiation, 中等强度氦氖激光, Chap. 8（第 8 章）
MI: myocardial infarction, 心肌梗死, Chap. 3（第 3 章）
MIH: meridian mediated ILILT hypothesis, ILILT 的经络介导假设, Chap. 3（第 3 章）
MIL: moderate intensity LI（$10^{2\sim4}$ mW/cm^2），中等强度激光或单色光, Chap. 3（第 3 章）
MIT: mitochondrion, 线粒体, Chap. 7（第 7 章）
MMSE: mini-mental state exam, 简易精神状态量表, Chap. 3（第 3 章）
MOB: nasal mucosa, olfactory nerve and intranasal microvascular blood, 鼻黏膜、嗅觉神经和鼻内微血管中的血液, Chap. 6（第 6 章）
MPBM: PBM of MIL, 中等强度激光或单色光的光生物调节作用, Chap. 3（第 3 章）
mRNA: messenger ribonucleic acid, 信使核糖核酸, Chap. 3（第 5 章）
miRNA: micro ribonucleic acid, 微核糖核酸, Chap. 3（第 3 章）
MS: multiple sclerosis, 多发性硬化症, Chap. 4（第 4 章）
MSH: Melatonin synthesis specific homeostasis, 褪黑素合成特异的内稳态, Chap. 3（第 3 章）
MTL: medial temporal lobe, 内侧颞叶, Chap. 5（第 5 章）
MTP: mitochondria membrane potential, 线粒体膜电位, Chap. 11（第 11 章）
NAD^+: nicotinamide adenine dinucleotide，烟酰胺腺嘌呤二核苷酸辅酶, Chap. 3（第 3 章）
NADH: reduced form of NAD^+, NAD^+的还原型, Chap. 3（第 3 章）
NADPH: nicotinamide adenine dinucleotide phosphate, 烟酰胺腺嘌呤二核苷酸磷酸, Chap. 6（第 7 章）
NEST-1: NeuroThera Effectiveness and Safety Trial-1, 神经治疗有效性和安全性试验 1, Chap. 5（第 5 章）
NETs: neutrophil extracellular traps, 中性粒细胞胞外菌阱, Chap. 3（第 3 章）
NF-κB: nuclear factor-κB, 核因子 κB, Chap. 7（第 7 章）
NHL: non-Hodgkin lymphoma,非霍奇金淋巴瘤, Chap. 6（第 6 章）
NIHSS: National Institutes of Health Stroke Scale, 国立卫生研究院中风量表, Chap. 5（第 5 章）
NLS: NeuroThera Laser System, 神经治疗激光系统, Chap. 5（第 5 章）
NMR: nuclear magnetic resonance, 核磁共振, Chap. 8（第 8 章）
NO: nitric oxide, 一氧化氮, Chap. 1（第 1 章）
NOS: nitric oxide synthase, 一氧化氮合酶, Chap. 6（第 6 章）
NPL: no perception of light, 无光感, Chap. 6（第 6 章）
NPY: neuropeptide Y, 神经肽-Y" , Chap. 3（第 3 章）

NSPR: non-specific pathway mediated response, 非特异性通路介导的响应，Chap. 9（第 9 章）
OAH: oxidant-antioxidant homeostasis, 氧化还原内稳态, Chap. 6（第 6 章）
OBC: OTB-Competition, OTB-比赛, Chap. 11（第 11 章）
OBT : OTB-Testing, OTB 和考试, Chap. 11（第 11 章）
OECD: Organization for Economic Cooperation and Development, 经济合作及发展组织, Chap. 11（第 11 章）
OR: odds ratio, 效应量比数, Chap. 6（第 6 章）
oROS: OAH-essential ROS level, 氧化还原内稳态所维持的 ROS 水平, Chap. 11（第 11 章）
OT: ordinary training, 常规训练, Chap. 3（第 3 章）
OTA: FNSHs and then the new FSH are established, 建立 FNSH 和新的 FSH, Chap. 11（第 11 章）
OTB: the new FSH is maintained, 维持新的 FSH, Chap. 11（第 11 章）
OTC: over-the-counter, 非处方, Chap 5（第 5 章）
P_3PL: P300 event-related brain potential peak latency, 事件相关电位 P300 峰潜伏期, Chap. 3（第 3 章）
PaFSH: pathological function-specific homeostasis, 病理功能特异内稳态, Chap. 3（第 3 章）
PBM: photobiomodultion, 光生物调节作用, Chap. 1（第 1 章）
PC: phosphatidylcholine, 磷脂酰胆碱（旧称卵磷脂）, Chap. 7（第 7 章）
PC12: a cell line derived from a pheochromocytoma of the rat adrenal medulla, 大鼠肾上腺髓质嗜铬细胞瘤的克隆细胞系, Chap. 7（第 7 章）
PD: Parkinson's disease, 帕金森病, Chap. 3（第 3 章）
PeSH: performance enhancement-specific homeostasis, 成绩提高内稳态, Chap. 3（第 3 章）
PGC: peroxisome proliferator-activated receptor-γ coactivator, 过氧化物酶体增殖物激活受体 γ 辅激活子, Chap. 7（第 7 章）
PhFSH: physiological function-specific homeostasis, 生理功能特异内稳态, Chap. 3（第 3 章）
PI-3K: phosphatidylinositol-3-kinase, 磷脂酰肌醇 3 激酶, Chap. 7（第 7 章）
PIP2: phosphatidylinositol 4,5-bisphosphate, 磷脂酰肌醇-4,5-二磷酸, Chap. 7（第 7 章）
PKA: cAMP-dependent protein kinase, 环磷酸腺苷依赖性蛋白激酶 A, Chap. 7（第 7 章）
PKB: protein kinase B, 蛋白激酶 B, Chap. 7（第 7 章）
PKC: protein kinase C, 蛋白激酶 C, Chap. 7（第 7 章）
PLA_2: phospholipases A_2, 磷脂酶- A_2, Chap. 7（第 7 章）
PLC: phospholipase C, 磷脂酶 C, Chap. 7（第 7 章）
PLD: phospholipases D, 磷脂酶 D, Chap. 7（第 7 章）
PML: promyelocytic leukemia, 早幼粒细胞白血病, Chap. 3（第 3 章）
PMN: polymorphonuclear neutrophil, 中性粒细胞, Chap. 3（第 3 章）
PmSH: protein metabolism-specific homeostasis, 蛋白质代谢特异的内稳态, Chap. 11（第 11 章）
PSD: post-stroke depression, 卒中后抑郁症, Chap. 3（第 3 章）
PSH: proliferation-specific homeostasis, 增殖内稳态, Chap. 7（第 7 章）
PSN: parasympathetic nervous subsystem, 副交感神经, Chap. 3（第 3 章）
PTKs: non-receptor protein tyrosine kinases, 非受体型酪氨酸蛋白激酶, Chap. 7（第 7 章）
RBC: red blood cell, 红细胞, Chap. 8（第 8 章）
rCBF: regional cerebral blood flow, 局部脑血流量, Chap. 3（第 3 章）
RCD: red cell deformability, 红细胞变形能 力, Chap. 3（第 3 章）

RLED 640: red light at 640±15nm of LED, 来自 LED 的 640 nm 红光, Chap. 7（第 7 章）
RLED 670: red light at 670nm from LED, 来自 LED 的 670 nm 红光, Chap. 8（第 8 章）
RNA: ribonucleic acid, 核糖核酸, Chap. 7（第 7 章）
ROS: reactive oxygen species, 活性氧, Chap. 3（第 3 章）
RTKs: receptor tyrosine kinases, 受体酪氨酸激酶, Chap. 7（第 7 章）
SAD: seasonal affective disorder, 季节性情感障碍症, Chap. 4（第 4 章）
SAM: senescence-accelerated mouse, 快速老化小鼠, Chap. 6（第 6 章）
SAMP10: SAM prone 10, SAM 亚系 10, Chap. 6（第 6 章）
SAMRl: SAM resistance 1, 抗快速老化小鼠亚系 1, Chap. 6（第 6 章）
SAP1: SIRT1 activity potential well, SIRT1 活性势阱, Chap. 7（第 7 章）
SAP1H : SAP1 hypothesis, SAP1 假设, Chap. 7（第 7 章）
SDS: self-rating depression scale, 抑郁自评量表, Chap. 3（第 3 章）
SGSH: sports-group-specific homeostasis, 项群内稳态, Chap. 11（第 11 章）
SIRT: sirtuin, NAD 依赖的组蛋白去乙酰化酶, Chap. 3（第 3 章）
SMC: smooth muscle cell, 平滑肌细胞, Chap. 8（第 8 章）
SN: sympathetic nervous subsystem, 交感神经, Chap. 3（第 3 章）
SOD: superoxidase dismutase , 超氧化物歧化酶, Chap. 3（第 3 章）
SPECT: single photon emission computed tomography, 单光子发射型计算机断层仪, Chap. 3（第 3 章）
SPR: specific pathway mediated response, 特异性通路介导的响应, Chap. 9（第 9 章）
SR/CR: Spontaneous regression/complete resistance,自愈/完全抗性, Chap. 6（第 6 章）
Src: steroid receptor coactivator, 类固醇激素受体协同激活因子, Chap. 7（第 7 章）
S-SAD: subsyndromal SAD, 亚综合征 SAD, Chap. 4（第 4 章）
SpSH: sport-specific homeostasis, 项目内稳态, Chap. 3（第 3 章）
SST: sea surface temperature, 海表温度, Chap. 4（第 4 章）
StSH: stress-specific homeostasis, 应激特异的内稳态, Chap. 7（第 7 章）
TC: total cholesterol, 总胆固醇, Chap. 4（第 4 章）
TCD: transcranial Doppler, 经颅多普勒超声, Chap. 5（第 5 章）
TCM: traditional Chinese medicine, 中医 Chap. 1（第 1 章）
TG: triglycerides, 甘油三酯, Chap. 3（第 3 章）
TGF: transforming growth factor, 转化生长因子, Chap. 6（第 6 章）
TLR4: toll-like receptor 4, Toll 样蛋白受体 4, Chap. 5（第 5 章）
TNF: tumor necrosis factor, 肿瘤坏死因子, Chap. 6（第 8 章）
Tty: tympanic temperature, 鼓室温度, Chap. 4（第 4 章）
UV: ultraviolet irradiation, 紫外辐射, Chap. 1（第 1 章）
UVA: ultraviolet A (320-400 nm), 长波紫外（320-400 纳米）, Chap. 8（第 8 章）
VaD: vascular dementia, 血管性痴呆, Chap. 6（第 6 章）
VEE: Venezuelan equine encephalomyelitis, 委内瑞拉马脑脊髓炎, Chap. 3（第 3 章）
VCO_2: carbon dioxide volume expired in liters per minute, 呼出二氧化碳体积, Chap. 6(第 6 章)
VO_2: oxygen volume consumed in liters per minute, 吸氧量, Chap. 6（第 6 章）
VO_2max: maximum oxygen consumption, 最大摄氧量, Chap. 4（第 4 章）
VSH: vision-specific homeostasis, 视力内稳态, Chap. 6（第 6 章）
W256: Walker 256 carcinoma, Walker2 5 6 癌荷瘤, Chap. 6（第 6 章）
WHO: World Health Organization, 世界卫生组织, Chap. 5（第 5 章）

WMS: Wechsler memory scale for adult, 韦克斯勒记忆量表, Chap. 3（第 3 章）
WSS: Webster scale scores, Webster 记分, Chap. 5（第 5 章）

作者简介－刘承宜

刘承宜 博士 教授 博士生导师 美国激光医学会（ASLMS）会士，Photomedicine and Laser Surgeryza 杂志编委，华南师范大学（SCNU）激光运动医学实验室（LLSM）主任。1963 年生于四川。作为物理化学学士、量子化学硕士和激光技术博士分别毕业于南京大学（1983）、吉林大学（1986）和华中科技大学（HUST）（1993）。曾任 HUST 物理化学助教（1986-1988）、SCNU 生物光子学博士后（1993-1995）、SCNU 生物系（1995-1997）和传输光学实验室（LLTO）（1998-1999）生物化学副教授、LLTO（1999-2002）和 LLSM（2003-）生物物理学教授、香港教育学院科学系访问教授（2002-2003）。主要研究光生物调节作用（PBM）和功能内稳态（FSH）的机制及其在激光医学、生物医学和体育科学中的应用。1996 年提出 PBM 的生物信息模型。2001 年发现视觉外细胞光信号转导现象。2008 年将生理学内稳态发展为 FSH。2000 年所指导的硕士研究生段锐获得美国激光医学会年会最佳生物刺激作用论文奖（图 1）。2010 在美国凤凰城参加 ASLMS 年会期间与查尔斯·汤斯（Charles H. Townes）博士合影（图 2）

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Curriculum Vitae—Timon Cheng-Yi Liu

Timon Cheng-Yi Liu, Ph. D., Professor, Supervisor of Ph D candidates, Fellow of American Society for Lasers in Surgery and Medicine (ASLMS), editorial board member of Photomedicine and Laser Surgery, head of Laboratory of Laser Sports Medicine (LLSM), South China Normal University (SCNU)(Guangzhou, China). Born in 1963 in Sichuan. Graduated as a BS in physical chemistry in Nanjing University in 1983, as a MS in quantum chemistry in Jilin University in 1986, as a Ph D in laser technology in Huazhong University of Science and Technology (HUST) in 1993. Worked as an assistant in physical chemistry in HUST (1986-1988), as a postdoctoral in biophotonics in SCNU (1993-1995), as an associate professor in biochemistry in biological department in SCNU (1995-1997) and then in light propagation in laboratory of light transmission optics (LLTO) in SCNU (1998-1999), as a professor in light propagation in LLTO in SCNU (1999-2002) and then in laser sports medicine in LLSM (2003-), as a visiting professor in physical education in department of science in Hong Kong Institute of Education (2002-2003). Main interests in the mechanisms of photobiomodulation (PBM) and function-specific homeostasis (FSH) and their applications in laser medicine, biomedicine and sports science. We have put forward the biological information model of PBM in 1996, observed the first phenomenon of extraocular phototransduction in 2001 and developed the concept of FSH from physiological homeostasis in 2008. In 2000, the paper of my MS candidate, Rui Duan, was awarded for its excellence in biostimulation by annual meeting of ASLMS (Fig. 1). In 2010, have a photo with Dr. Charles H. Townes in Phoenix when attending the annual meeting of ASLMS (Fig. 2)

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图 1 美国激光医学会 2000 年会生物刺激作用优秀论文奖

Fig1 The paper excellent in biostimulation awarded by American Society for Lasers in Surgery and Medicine in 2000

图 2 与查尔斯·汤斯（Charles H. Townes）博士在美国凤凰城合影

Fig. 2 A photo with Dr. Charles H. Townes in Phoenix