Review Article

Photobiomodulation on Stress

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Photobiomodulation (PBM) is a nondamaged modulation of laser irradiation or monochromatic light (LI) on a biosystem function. It depends on whether the function is in its function-specific homeostasis (FSH). An FSH is a negative-feedback response of a biosystem to maintain the function-specific conditions inside the biosystem so that the function is perfectly performed. A function in its FSH is called a normal function. A function far from its FSH is called a dysfunctional function. The process of a function from dysfunctional to normal is called a functional normalization. For a normal function in its FSH, there are FSH-essential subfunctions (FESs), FSH-nonessential subfunctions (FNSs), and an FES/FNS-specific homeostasis (FESH/FNSH). A FSH can resist internal/external disturbances under the threshold, but can be disrupted by an FSH-specific stress (FSS). A normal/dysfunctional FSS is called a successful/chronic stress. An FESH/FNSH-specific stress was called an extraordinary/ordinary stress. A low level LI (LLL) cannot directly affect a normal function, but can modulate a chronic stress. A normal function may have a chronic ordinary stress, and an LLL may modulate the chronic ordinary stress so that it promotes the normalization of the dysfunctional FNS and then upgrades the normal function. A high level LI can modulate a normal function and may be a successful stress.

1. Introduction

The human mind and body respond to stress [1, 2], a state of perceived threat to homeostasis, by activating the sympathetic nervous system and secreting the catecholamines adrenaline and noradrenaline in the “fight-or-flight” response. The stress response is generally transient because its accompanying effects (e.g., immunosuppression, growth inhibition, and enhanced catabolism) can be harmful in the long term. When chronic, the stress response can be associated with disease symptoms such as peptic ulcers or cardiovascular disorders and leads to DNA damage [3]. Stress is also broadly defined as a noxious factor (physical, chemical, or biological), which triggers a series of cellular and systemic events, resulting in restoration of cellular and organismal homeostasis [4, 5]. It was re-defined from the viewpoint of our function-specific homeostasis (FSH) [6–8] and its photobiomodulation (PBM) was discussed in this paper.

2. Function-Specific Homeostasis

Negative feedback is common in biological processes and can increase a system's stability to internal and external perturbations [9]. An FSH is a negative-feedback response of a biosystem to maintain the function-specific conditions inside the biosystem so that the function is perfectly performed [6–8]. A function in its FSH is called a normal function. A function far from its FSH is called dysfunctional function. The process of a function from dysfunctional to normal is called functional normalization. A normal function is better performed than all the dysfunctional functions so that the normal function is locally the best performed one. A biosystem in an FSH means its normal function is in its FSH. A biosystem far from an FSH means its dysfunctional function is far from its FSH. Youk et al. have studied log-phase growth rates of single-HXT2 (hexose transporter 2) strain of yeasts at varying [glucose] but constant [doxycycline] (2.5 $\mu\text{g/mL}$) and

found the growth rate peaked in glucose between 0.06% and 0.20%, which corresponded to the normal growth that resists the concentration change of glucose between 0.06% and 0.20% [10]. We also have found that these are the best concentrations of glucose, normal glucose, in which C2C12 cells proliferated in their optimal rate and between which there was no significant difference of the proliferation rate, and the low/high glucose whose concentration was lower/higher than the one of normal glucose, and in which the C2C12 cells proliferated in a rate lower than the optimal rate [11–13]. In other words, the C2C12 cell proliferation in normal glucose was a normal proliferation which resisted the concentration change in the normal glucose.

The quality of an FSH, the functional fitness of a normal function, includes function complexity and function stability. At the molecular level, control loops always involve signalling steps with finite rates for random births and deaths of individual molecules. Lestas et al. have shown that seemingly mild constraints on these rates place severe limits on the ability to suppress molecular fluctuations [9]. Specifically, the minimum standard deviation in abundances decreases with the quartic root of the number of signalling events. In other words, the higher the function complexity, the higher the function stability. Let Q be the functional fitness of a normal function. A biosystem might simultaneously have many kinds of normal functions, $\{FSH_i, i = 1, 2, \dots, n\}$, and then have functional fitness set, $\{Q_i, i = 1, 2, \dots, n\}$. Let $Q_{\max} = \max\{Q_i, i = 1, 2, \dots, n\}$, and $F_{\max}$ and $F_{\max SH}$ denote the corresponding normal function and its homeostasis, respectively. For proliferative cells in 10% fetal calf serum (FCS), proliferation and its PLSH may be generally $F_{\max}$ and $F_{\max SH}$, respectively.

3. Stress

The response of a biosystem in an FSH to internal/external disturbances depends on the disturbance level. A normal function in its FSH can resist a low level disturbance, but cannot resist a high level disturbance. The high level disturbance is defined as a stressor, an FSH-specific stressor (FSSor), in this paper. In other words, a FSSor is so defined that it disrupts its corresponding FSH. A psychological/physiological/cellular stressor disrupts its corresponding psychological/physiological/cellular-function-specific homeostasis. An oxidative stressor disrupts a redox-specific homeostasis. The FSSor dose depends on its intensity and its action time. A strong FSSor can disrupt its corresponding FSH in a short time, but a weak FSSor can also disrupt its corresponding FSH in a long time. Burd et al. found that low-load high volume resistance exercise is more effective in inducing acute muscle anabolism than high-load low volume or work-matched resistance exercise modes [14].

3.1. FSH-Specific Stress. The response of a biosystem in a FSH to internal/external disturbance is FSH-specific. Fibroblasts from long-lived mutant mice are resistant to many forms of lethal injury as well as to the metabolic effects of rotenone and low-glucose medium. Salmon et al. have evaluated fibroblasts from young adult naked mole-rats (NMR)

FIGURE 1: Successful stress and chronic stress. After the existing FSH is disrupted, many possible kinds of wFSH would be established. Among them, the wFSH of the highest functional fitness, mFSH, would be established by the FSS in its FSSH so that the normal FSS is called a successful stress; the other kinds of wFSH, wFSHa, wFSHb, wFSHc, ..., or wFSHz would be established by the FSS far from FSSH so that the dysfunctional FSS is called a chronic stress.

[15], a rodent species in which maximal longevity exceeds 28 years. Compared to mouse cells, NMR cells were resistant to cadmium, methyl methanesulfonate, paraquat, heat, and low-glucose medium, consistent with the idea that cellular resistance to stress may contribute to disease resistance and longevity. Surprisingly, NMR cells were more sensitive than mouse cells to H_2O_2 , ultraviolet (UV) light, and rotenone. NMR cells, like cells from Snell dwarf mice, were more sensitive to tunicamycin and thapsigargin, which interfere with the function of the endoplasmic reticulum (ER). The sensitivity of both Snell dwarf and NMR cells to ER stress suggests that alterations in the unfolded protein response might modulate cell survival and aging rate.

3.2. Successful Stress and Chronic Stress. An FSH-specific stress (FSS) is defined as a response of a biosystem in its FSH to an FSSor. It is also a function of a biosystem and there is an FSS-specific homeostasis (FSSH). After the existing FSH is disrupted by a FSS, many possible kinds of would-be FSH (wFSH) would be established (Figure 1). Among them, the wFSH of the highest functional fitness, mFSH, would be established by the FSS in its FSSH so that the normal FSS is called a successful stress such as self-limiting/limited conditions [16, 17]; the other kinds of wFSH, wFSHa, wFSHb, wFSHc, ..., or wFSHz would be established by the FSS far from FSSH so that the dysfunctional FSS is called a chronic stress such as the delayed self-limiting/limited conditions. In protein folding and secretion disorders, successful activation of ER stress signaling protects cells, alleviating stress that would otherwise trigger apoptosis. Studies in chondrocytes, which abundantly secrete collagens, have shown that dedifferentiation away from a secretory cell

phenotype may play a role in adaptation to chronic ER stress [18]. This suggests that the pathogenic features of chronic ER stress may be played out not only at the level of cell death but also at the level of altered cell function.

Self-limited/limiting conditions [16, 17] are examples of successful stress unless they are compromised. In immunocompetent hosts, the infection is self-limiting [19]. Inflammation involves a coordinated, sequential, and self-limiting sequence of events controlled by positive and negative regulatory mechanisms [20]. Bazzoni et al. found Toll/interleukin (IL)-1 receptor activated nuclear factor (NF) kappaB rapidly increases the expression of miR-9 that operates a negative feedback control of the NF-kappaB-dependent responses by fine tuning the expression of a key member of the NF-kappaB family [20]. Photoparoxysmal responses (PPRs) are generalized epileptiform abnormalities occurring during photic stimulation. Prolonged PPRs, which outlast the stimulus, can be distinguished from self-limited PPRs, which cease spontaneously or when the flashes stop. Comparing PPR groups, Puglia et al. found that a prolonged PPR was associated with a higher incidence of seizures than a self-limited response, and patients with a prolonged PPR more often had other epileptiform abnormalities than the self-limited group [21]. Kumar et al. infected mice with sublethal influenza A virus [22]. Despite early damage to lungs after infection, they had essentially returned to normal 3 months later. Repair was initiated by stem cells that proliferated in the bronchiolar epithelium and migrated to sites of damage, where they formed clusters around bronchioles and differentiated into alveolar structures destroyed by the infection. This is a typical self-limited condition. Its delayed cases can cause extensive, life-threatening lung pathology in humans.

Generally, the functional fitness of a normal function is higher than the one of a successful stress. A successful stress is easily disrupted by other stressors. The training program plateau [23] corresponded to the sport-specific homeostasis (SpSH). Exercise stress can disrupt SpSH1, which induces delayed onset muscle soreness (DOMS) [24]. A successful exercise stress such as a bout of eccentric exercise or high intensity exercise can further establish SpSH2, and its DOMS is self-limited [25]. However, the DOMS might be delayed due to exhaustive eccentric exercise, insulin resistance, or aging.

3.3. Extraordinary Stress and Ordinary Stress. A complicated biosystem is just a network of functions [9]. There are many subfunctions to maintain a normal function/Fmax, FSH/FmaxSH-essential subfunctions (FESs/FmaxESs) and FSH/FmaxSH-nonessential subfunction (FNSs/FmaxNSs). FESs/FmaxESs might be very sparse [6]. 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 their 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. 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 [26]. 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 [26].

For a normal function/Fmax, all the FESs/FmaxESs should be in their respective FES/FmaxES-specific homeostasis (FESH/FmaxESH), but some FNSs/FmaxNSs may be allowed far from their respective FNS/FmaxNS-specific homeostasis (FNSH/FmaxNSH). Obviously, the more the FNSs/FmaxNSs in their FNSH/FmaxNSH, the higher their functional fitness. The response of a biosystem to a FSSor disrupting a FESH/FmaxESH or FNSH/FmaxNSH is defined as an extraordinary or ordinary stress of the function in this paper.

Inhibitors of epidermal growth factor receptor (EGFR) signaling might induced an extraordinary stress of tumor cells in their respective PISH. Chemotherapeutic agents that induce the DNA damage response (DDR) are typically used to kill tumor cells; however, the effects of aberrant growth factor signaling, for example, can lead to resistance. Lee et al. took a systems-level approach to examine the interplay between growth factor signaling and the DDR in triple-negative breast cancer (TNBC) cells [27], which respond poorly to standard therapies. The greatest extent of apoptosis was caused by pretreatment with inhibitors of EGFR signaling before treatment with the DNA-damaging agent doxorubicin; simultaneous treatment with these compounds was not as potent. Prolonged (6 hours) EGFR inhibition led to changes in the expression of many genes, which suggested that the oncogenic potential of some TNBC cells is dependent on EGFR signaling. The staggered application of EGFR inhibitor and doxorubicin induced cell death in lung cancer cell lines in a caspase 8—dependent manner. It was found that the timed application of signaling inhibitors causes the rewiring of signaling pathways in tumor cells and makes them more susceptible to subsequent DDR-inducing therapy.

Obviously, there may be an ordinary stress for a normal function/Fmax, and its functional fitness can be upgraded through its successful ordinary stress. The successful ordinary stress might be mediated by redundant genes/pathways. Genetic redundancy means that two or more genes are performing the same function and that inactivation of one of these genes has little or no effect on the biological phenotype [28]. The two or more genes and their corresponding pathways are redundant genes and redundant pathways, respectively. Fibroblast growth factor (FGF) 1 is the prototype of the 22-member FGF family of proteins and has been implicated in a range of physiological processes, including development, wound healing, and cardiovascular changes. Surprisingly, FGF1 knockout mice display no significant phenotype under standard laboratory conditions. Jonker et al. show that FGF1 is highly induced in adipose tissue in response to a high-fat diet and that mice lacking FGF1 develop an aggressive diabetic phenotype coupled to aberrant adipose expansion when challenged with a high-fat diet [29]. Obviously, FGF1 is a redundant pathway which is induced in response to a high-fat diet. Allison et al. have summarized the potential

impacts of a disturbance on microbial composition and/or ecosystem processes [30]. Consider an increasing disturbance applied to an ecosystem and the microbial communities within it. Microbial composition might be resistant to the very-low-level disturbance and might not change. For a low level disturbance, the community is sensitive and does change, it could be resilient and quickly recover to its initial composition through homeostatic mechanism. For a rather-high level disturbance which induces a successful ordinary stress, a community whose composition is sensitive and not resilient might produce process rates similar to the original community through redundant pathways if the members of the community are functionally redundant. For a high level disturbance which induces a successful extraordinary stress, the community performs differently.

4. Photobiomodulation

Modulation can be classified into low level modulation and high level modulation. Low level modulation cannot directly modulate a normal function, but can modulate a chronic stress. High level modulation can modulate a normal function, which might be a successful stress. It has been found [24] that low level modulation cannot promote the functional recovery of self-limiting DOMS, but high level modulation can. From this viewpoint, PBM was discussed in this section.

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 intensity is in the range of 10–1000 mW/cm² [31, 32]. As we have classified [6–8], the LI used in PBM is always low intensity LI (LIL), ~10 mW/cm², which includes the LI used in the so-called ultra-low-level laser therapy [33], but moderate intensity LI (MIL), 0.10–1.0 W/cm², is of PBM if the irradiation time is not so long that it damages organelles or cells. The PBMs of LIL and MIL are denoted as LPBM and MPBM, respectively. The MIL with short irradiation time and LIL are two kinds of low level LI (LLL), and their PBM is a kind of low level modulation and is called low level PBM. The PBM of MIL with long irradiation time is a kind of high level modulation and is called high level PBM.

For a normal function/ F_{max} , there may be a chronic ordinary stress. Low level PBM cannot directly modulate the normal function/ F_{max} , but it can modulate the chronic ordinary stress until it is successful and then upgrade the normal function/ F_{max} . At this point, low level PBM can be divided into two kinds, the direct PBM (dPBM) and indirect PBM (iPBM). Direct PBM cannot directly modulate a normal function, but can modulate a chronic stress. A normal function/ F_{max} cannot be directly modulated by dPBM, but can be upgraded by iPBM if there is at least a chronic ordinary stress. High level PBM, dPBM, and iPBM will then be detailedly discussed.

4.1. Direct Photobiomodulation. There were no dPBM on human osteosarcoma cell line, SAOS-2 [34], HeLa (epithelial adenocarcinoma) and TK6 (lymphoblast) [35], murine fibroblast 3T3 cells, primary human keloid fibroblast cells

[36], and osteogenic cells [37] in 10% FCS. Proliferation in 10% FCS is always normal proliferation so that LLL cannot directly modulate the proliferation. Schwartz-Filho et al. have studied MPBM (685 nm) on osteogenic cells originated from rat calvaria [37]. The cells were irradiated immediately after plating and after each change of culture medium. They found that the MPBM at 3.5 W/cm² cannot modulate their proliferation in 10% FCS at 25, 77, and 130 J/cm², respectively, at days 1, 4, 7, and 11 but promoted mineralized bone-like nodule formation is only at 25 J/cm² at day 14.

Normal erythrocyte deformability is maintained by deformability-specific homeostasis (DeSH). According to Mi et al. [38], the DeSH of pig erythrocytes was maintained in 0 and 0.5 mM CaCl₂ so that the MIL at 532 or 632.8 nm cannot directly modulate the deformability, but it was disrupted in 1.0, 1.5, and 2.0 mM CaCl₂ or 10 μ M A23187 so that the MIL can modulate the deformability.

Many functions of nondiabetic rats may be normal, but the ones of diabetic rats may be dysfunctional. Rabelo et al. have compared diabetic with nondiabetic rats (male Wistar) and found MPBM (632.8 nm) of 15 days has no effects on informatory cells, vessels, and fibroblastic cells of nondiabetic rats but inhibited informatory cells and promoted fibroblastic cells of diabetic rats [39].

Mafra de Lima et al. have found that LIL at 650 nm had no effects on rat lung [40], but attenuated acute lung inflammation induced by aerosol of lipopolysaccharide from *Escherichia coli*. They found the LIL-inhibited pulmonary edema and endothelial cytoskeleton damage, as well as neutrophil influx and activation. Similarly, the LIL reduced the tumor necrosis factor (TNF) α and IL-1 β in lung and bronchoalveolar lavage fluid (BALF). LIL prevented lung intercellular adhesion molecule-1 (ICAM-1) upregulation. The rise of cytokine-induced neutrophil chemoattractant-1 (CINC-1) and macrophage inflammatory protein-2 (MIP-2) protein levels in both lung and BALF, and the lung mRNA expressions for IL-10, were unaffected. Their data suggest that the LIL effect is due to the inhibition of ICAM-1 via the inhibition of TNF- α and IL-1 β . Lima et al. also found that MIL at 660 nm had no effects on rat lung but attenuated intestinal ischemia and reperfusion-induced acute lung inflammation which favor the IL-10 production and reduce TNF generation [41].

Although there is dPBM on sleep that has been discussed from 1998 on, the puzzle remains unsolved. Campbell et al. found 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 participants in ambient illumination <50 lux [42]. However, Wright et al. found the absence of circadian phase resetting in response to the same bright light behind the knees of participants in ambient illumination 0 lux [43]. The environmental light is the key point. Sleep is normal if there is no environmental light, but is dysfunctional if the environmental light is rather intensive.

No dPBM on the functional recovery has been found for self-limited DOMS [44, 45]. However, dPBM can promote the functional recovery of delayed DOMS. Exhaustive downhill running was used to induce muscle injury in

rat gastrocnemius muscle. LIL significantly reduced serum creatine kinase (CK) activity at 48 h after exercise [46]. The load-resistance swimming test forced adult male Wistar rats to swim until exhaustion. 40 s MIL treatment lowered CK activity and muscular apoptosis [47].

LPBM on chronic ordinary stress might be mediated by redundant pathways. In our C2C12 studies [11, 12], normal glucose maintained the PISH in normal glucose (nPISH). We found that low/high glucose disrupted PISH and lowered the proliferation, which was completely recovered by red light from light emitting diode array (RLED) at 640 nm so that PISH in low/high glucose (lPISH/hPISH) was established. We further found that high glucose partially activated insulin-like growth factor (IGF) 1, which was promoted by RLED at 640 nm so that IGF-1 was completely activated [12]. Obviously, IGF-1 is the redundant pathway mediating the successful ordinary stress from nPISH to hPISH.

4.2. High Level Photomodulation. Xu et al. have studied the effects of laser irradiation at 810 nm and doses 1~7 (0.33, 1.338, 2.646, 5.338, 8.220, 11.22, and 14.16 J/cm²) on the reactive oxygen species (ROS) metabolism and mitochondrial function of C2C12 myotubes [48]. They found that the LI at doses 1~5 had no effects on the mitochondrial function, but the one at doses 6&7 induced mitochondrial dysfunction; and the LI at doses 1~3 had no effects on the ROS metabolism, but the one at doses 4~7 increased ROS level. In this case, the mitochondrial function-specific homeostasis (MiSH) holds for the LI at doses 1~5, but breaks up for the LI at doses 6&7; and ROS metabolism-specific homeostasis (RoSH) holds for the LI at doses 1~3, but breaks up for the LI at doses 4~7. They further found that the electrical stimulation at 20 ms, 5 Hz, and 45 V for 75 min broke up MiSH and RoSH, and the LI at dose 1 promoted RoSH establishment and the one at doses 1~5 promoted MiSH establishment.

Ilic et al. have studied the effects of laser irradiation at 808 nm and 7.5, 75, 375, and 750 mW/cm² in either continuous wave (CW) or pulse modes for 2 min on the intact brain of healthy male Sprague-Dawley rats, respectively, and found that the only rats showing an adverse neurological effect were those in the 750 mW/cm², CW mode group, and there was no significant difference between the LI group and the control group for the each other dose [49].

Lacjaková et al. found that LIL at 670 nm improved wound healing in nonsteroid rats, but was not effective after methylprednisolone treatment [50]. However, MIL at 392.9 mW/cm² and 240 s was found to accelerate wound healing of the steroid rats, acting as a biostimulative coadjuvant agent, balancing the undesirable effects of cortisone on the tissue healing process [51].

4.3. Successful Stress. DPBM cannot modulate a successful stress such as self-limited conditions. DPBM can modulate a chronic stress, but dPBM is not sensitive to LI parameters if the successful stress is established because the stress is in its homeostasis.

Iyomasa et al. found no significant differences in the area of newly formed bone between the groups of the MIL

at 780 nm in a single application in contact with the skin surface on the critical bone defect and nonirradiated groups, 14 days after induction of critical bone defect, because the greatest stimulus for bone formation involved application of the recombinant human bone morphogenetic protein 2 (rhBMP-2) [52]. In this case, rhBMP-2 has established a successful stress.

The recovery of cells isolated from animal model is self-limited. Osteoblast-like cells isolated from fetal rat calvariae were irradiated once with an LIL (830 nm) in four different irradiation modes: continuous irradiation (CI) and 1-, 2-, and 8-Hz pulsed irradiation (PI-1, PI-2, and PI-8). Ueda et al. found no significant differences on alkaline phosphatase activity between the control group, CI, PI-1, PI-2, and PI-8 on 18th and 21st day [53]. Bone marrow derived mesenchymal stem cells (BMSCs) were harvested from rat fresh bone marrow and exposed to a 635 nm diode laser (60 mW; 0, 0.5, 1.0, 2.0, or 5.0 J/cm²). 10 days after the isolation, there were no significant proliferation difference between the control and irradiation groups [54].

Inflammation is always self-limited. Gingivitis was induced in ten female dental students by refraining from all oral hygiene measures for 28 days. On days 21 and 24 the marginal gingiva, buccal to one of the lateral mandibular incisors, was exposed to 4 minutes of laser irradiation (total dose = 1 J). Rydén et al. found that the difference between sites at day 28 was not statistically significant. Their results suggest that LLL does not influence the inflammatory reaction of the gingiva [55].

de Souza et al. have studied the effects of daily MIL at 685 nm for 1 (MIL1) and 3 (MIL3) min on amputated worms [56]. They found that MIL1 more strongly promoted stem-cell proliferation than MIL3 on the 4th day, but there were no significant differences between the control, MIL1, and MIL3 on the 7th and 15th day.

Wound healing of healthy animal or human is always self-limited. Patients presenting with a total of 12 wounds after minor surgical procedures (partial/total nail avulsions/electrosurgery) were recruited from the Podiatry Teaching Clinic, Northern Ireland. Wound assessment and recording of pain levels were conducted weekly. Lagan et al. have found no statistically significant differences between weekly MIL (830 nm) and control groups neither for wound closure nor for pain levels reported, and no differences between MPBM of 11 weeks and control groups neither for wound closure nor for pain levels reported [57]. Low level gallium aluminium arsenide (GaAlAs) laser irradiation was administered to full-thickness skin wounds (3 × 3 cm) induced surgically on the dorsal aspect of the metacarpophalangeal joints of 6 crossbred horses in a randomised, blind, and controlled study. There were no wound complications. Petersen et al. have found no significant differences in wound contraction or epithelialization between the laser treated and the control wounds [58]. Pugliese et al. found no dPBM on collagen and elastic fibers of punched healthy rats. Cutaneous wounds were inflicted on the back of healthy Wistar rats [59]. Medrado et al. found no significant differences between the control group, LIL at 4 J/cm², and LIL at 8 J/cm² on the 14th day. Two standardized 1.27 cm² abrasions were

induced on the anterior forearm of healthy youth [60]. Hopkins et al. used a randomized, triple-blind, and placebo-controlled design with 2 within-subjects factors (wound and time) and 1 between-subjects factor (group) and found that the MIL group had smaller wounds than the sham group for both the treated and the untreated wounds on days 6, 8, and 10, but had no significant differences on day 20 [61]. Bayat et al. have found no acceleration of healing of deep second-degree burns in healthy rats after treatment with LIL at energy densities of 1.2 or 2.4 J/cm² although the LIL therapy caused significant decrease in the number of macrophage, depth of new epidermism, and incidence of *S. epidermidis* and *S. aureus* [62]. Prabhu et al. have studied the effects of the LIL at 632.8 nm and human placental extract (HPE) on full-thickness excision wounds on Swiss albino mice of diameter 15 and found the wounds exposed to the LIL at 2 J/cm² immediately after wounding showed considerable contraction on days 5, 9, 12, 14, 16, and 19 of postirradiation compared with the controls and other treatment schedules, but there were no significant differences between LIL, HPE, and the control 30 days after the wound [63]. Medrado et al. found that the MIL group of Wistar rats exhibited significantly more smooth muscle alpha-actin-positive staining cells 7 days after punch biopsy, more desmin-positive staining cells on day 10 around blood vessels, and higher numbers of NG2-positive staining cells, especially on days 3 and 7 post-biopsy, but there were no significant differences between the MIL group and the control group 14 days after punch biopsy [64].

Diabetic wound might be also self-limited. Akyol et al. found that MIL promoted the healing of the wound of streptozotocin- (STZ-) induced diabetes of female Wistar rats on 10th day, but did not on 20th day [65]. Ma et al. found that LIL promoted the healing of the wound of STZ-induced diabetes of male Wistar rats before 9th day, but did not on 14th day. As a fact, even type 2 diabetes might be self-limited [66]. Lim et al. found that normalisation of both beta cell function and hepatic insulin sensitivity in type 2 diabetes was achieved by dietary energy restriction alone [67].

Musculoskeletal conditions like temporomandibular disorders (TMD) are of the self-limiting feature [68, 69]. The factors causing sports injuries can be grouped in 2 separate broad categories: extrinsic and intrinsic factors. However, the great majority of injuries which are sustained are minor and self-limiting, suggesting that children and youth sports are safe [70]. Among them, DOMS is a common but self-limiting condition that usually requires no treatment [71]. Most exercise enthusiasts are familiar with its symptoms. However, where a muscle has been immobilised or debilitated, it is not known how that muscle will respond to exercise, especially eccentric activity [71]. There were no significant differences between the 30 days therapeutic effects of transcutaneous electrical nerve stimulation (TENS) and the ones of laser therapy on TMD [69], and no significant differences between the 30 days therapeutic effects of the microelectronic neurostimulation (MENS) and the ones of laser therapy on TMD [68].

LPBM modulates chronic stress until the successful stress is established. The successful stress is in a kind of homeostasis

so that the LPBM might be dose/intensity-independent if the successful stress is established. Al-Watban et al. have studied the acceleration effects of the LIL at 532, 633, 810, and 980 nm on streptozotocin-induced diabetic rats (male Sprague-Dawley) [72]. Their results suggested that the LPBM of 21 days was dose-independent for each laser irradiation. For the LPBM on round full-thickness skin wounds in non-steroid rats [73], the LPBM of 2 or 6 days was intensity-dependent, but the one of 14 days was intensity-independent. For the LPBM on round full-thickness skin wounds in steroid rats [73], the LPBM of 14 days was still intensity-dependent. After 14 days, the wounds completely recovered in nonsteroid rats so that the successful stress was established, but methylprednisolone inhibited wounds in steroid rats were still far from successful stress. Prabhu et al. have studied the effects of the LIL at 632.8 nm on full-thickness excision wounds on Swiss albino mice of diameter 15 and found that the LPBM of 30 days was dose independent [63]. Morais et al. have studied the anti-inflammatory LPBM on zymosan-induced arthritis and found that there were no significant difference between the effects of the LIL at 685 nm and the ones at 830 nm in increasing vascular permeability and reducing the edema 3 h after zymosan injection and in reducing paw elevation time 4 h after zymosan injection [74].

4.4. Indirect Photobiomodulation. In 10% FCS, the normal proliferation in its PISH is the normal Fmax, but other functions are dysfunctional. LLL cannot directly affect the normal proliferation, but can modulate the other dysfunctional functions whose normalization does not resist normal proliferation. He-Ne irradiation elicits PBM in mitochondria processes, which involve Jun N-terminal kinase/activator protein-1 activation and enhanced the release of growth factors such as IL-8 and transforming growth factor (TGF) beta1, and ultimately lead to enhanced A2058 cell proliferation in 10% FCS [75]. The normal proliferation and normal procollagen of fibroblasts antagonized against each other [76]. Yamamoto et al. found that LIL cannot affect the procollagen synthesis of the fibroblasts in PISH, but promoted the procollagen synthesis of the fibroblasts far from PISH [77]. Coombe et al. have found that a single or daily MIL at 830 nm on SAOS-2 cells in 10% FCS has no effects on the cell viability or proliferation, protein expression, and alkaline phosphatase activity, but it has heat shock response, and increased intracellular calcium [34]. Frigo et al. found the MPBM (660 nm) for 60 s once a day for three days inhibited the death of primary human keloid fibroblast cells in 10% FCS at 630 mW/cm² only at day 2, but cannot modulate the proliferation of murine fibroblast 3T3 cells and primary human keloid fibroblast cells in 10% FCS at 260 mW/cm² at days 1, 2, and 3, and the death of primary human keloid fibroblast cells in 10% FCS at days 1 and 3 and murine fibroblast 3T3 cells in 10% FCS at days 1, 2, and 3 at 630 mW/cm² [78]. In this case, death inhibition maintains proliferation.

For cells in their respective PISH, the functions which promote proliferation may be promoted with LLL. Cultured NIH3T3 fibroblasts from normal mice in 10% FCS were irradiated by RLED at 627 nm and 25 mW/cm² twice, first

at subculture and 24 h later. At day 2, Komine et al. observed the RLED promoted cell growth of NIH3T3 fibroblasts and increased the expression of platelet-derived growth factor (PDGF)-C, but did not affect the expression of PDGF-A, PDGF-B, and TGF-beta [79]. As Komine et al. have pointed out [79], one possible mechanism of fibroblast proliferation induced by RLED involves an increase of PDGF-C expression and activation of the ERK pathway through phosphorylation of the PDGF receptor.

Proliferation of tumor cells in 10% FCS or tumor growth is always normal. Frigo et al. have studied the effects of the MIL at 660 nm and 2.5 W/cm² in vitro for 3 days and in vivo for 10 days [78]. They found that the MIL once a day for three days did not modulate the proliferation of melanoma cells (B16F10) in 10% FCS, but promoted their apoptosis. They have used the in vivo mouse model (male Balb C) of melanoma to analyze the effects of the MIL once a day for ten days on tumor volume and histological characteristics. They found that the outcome measures for the 150 J/cm² dose group were not significantly different from controls, but there were significant increases in tumor volume, blood vessels, and cell abnormalities compared to the other groups for the 1050 J/cm² dose group. The MIL did not modulate a normal function so that it is a LLL and it should not modulate normal growth. The tumor is a complicated system. Its other functions such as telomere function [80] might be dysfunctional so that they may be modulated to promote its growth. Telomerase reactivation following telomere dysfunction yields murine prostate tumors with bone metastases [81]. It needed ten days for the tumor growth to be promoted by the MIL at 1050 J/cm². It suggested that the MIL promotion might be mediated by some protein synthesis. At this point, the tumor itself should not be irradiated with LLL.

A normal Fmax can be enhanced by iPBM if there is at least a chronic ordinary stress. iPBM might be mediated by redundant pathways because successful ordinary stress is mediated by redundant pathways. In our C2C12 studies [13], The Fmax of C2C12 myoblasts in normal glucose is the normal proliferation, and its FmaxSH is nPISH. We found that RLED at 640 nm promoted the normal proliferation of C2C12 myoblasts from 4 days on and IGF-1/FOXO3a (forkhead box O family 3a) was completely activated/inhibited. In other words, the redundant pathways IGF-1 and FOXO3a mediated the iPBM enhancement.

5. Enhanced Recovery

Enhanced recovery after surgery (ERAS) has proven efficacious in improving the quality and efficiency of surgical care [82]. ERAS encompasses a systematic and evidence-based appraisal of all interventions performed in an episode of care. They have been associated with a reduction in duration of hospital stay, readmissions, and reoperations, together with decreased mortality and morbidity, improved pain control, better cost containment, and improved patient satisfaction. Obviously, recovery after surgery is just a stress, and the most rapid recovery is just a successful stress. Therefore, LLL can be used to promote ERAS.

The function recovery of a person suffering from an FSS depends on his/her initial state. The function recovery of the person who initially has a normal related function is more rapid than the one of the person who initially has a dysfunctional related function. Patients with major depressive disorder (MDD) had slower heart rate recovery 1 min after exercise stress than non-MDD patients [83]. MDD is accompanied by a dysregulation in autonomic control of exercise-related cardiovascular recovery, suggesting that depressed individuals have a slow parasympathetic recovery from exercise. Major League Baseball players of body mass index (BMI) 26.2 kg/m² demonstrated a significantly higher return-to-play rate from surgery for lumbar disc herniations than National Football League players of BMI 32.1 kg/m² did [84]. Efendiev et al. found that preliminary influencing upon the site of a future incision with the infrared laser radiation in constant regime within the range of 1 to 150 mW (dosage of radiation per 1 field of 0.06–9.3 J/cm²) facilitated pronounced stimulation of the processes of collagen formation and significant increase in strength of a forming scar [85].

Moreover, the higher the functional fitness of a normal related function before operation, the more rapid his post-operation recovery. The higher the level of heat shock protein (HSP), the higher the functional fitness [4, 86]. Using a pulsed diode laser (1850 nm, 2 ms, 50 Hz, 7.64 mJ/cm²), the skin of transgenic mice that contain an HSP70 promoter-driven luciferase was preconditioned 12 hours before surgical incisions were made. Wilmsink et al. found that an optimized laser protocol increased HSP70 expression by 10-fold, and the laser-preconditioned incisions were two times stronger than control wounds [87].

LLL cannot modulate a successful stress, but can modulate a chronic stress until it is successful. Derkacz et al. have evaluated the influence of low-power 808 nm laser illumination of coronary vessels after percutaneous angioplasty in preventing restenosis with major adverse cardiac events (MACE) rate at the 6- and 12-month follow-up points and found that the LLL did not affect the MACE rate of patients without restenosis, but significantly reduced the MACE rate of patients with restenosis [88].

6. Discussion

MPBM might be mediated by reactive oxygen species, but LPBM might be mediated by membrane proteins [6, 7]. The plasma membrane delimits the cell, and its integrity is essential for cell survival. Lipids and proteins form domains of distinct composition within the plasma membrane. Membrane stress, for example, induced by either inhibition of sphingolipid metabolism or by mechanically stretching the plasma membrane, redistributes Sln proteins between distinct plasma membrane domains [89]. A cellular function is always related to a kind of membrane protein so that the protein is called function-specific protein (FSP). According to our membrane hypothesis [6, 7], the identical FSPs in the membrane may form coherent states if the function is dysfunctional or random states if the function is normal. The nonresonant interaction of FSPs and LI is so weak that its biological response cannot be observed in random states,

but it can be amplified in coherent states so that the PBM is observed. There are interactions between coherent states of one kind of FSPs and random states of another kind of FSPs so that some FSH cannot be established if it can be resisted by the FmaxSH, but a FmaxNSH can be established because its establishment can upgrade the FmaxSH. Each dysfunctional function in a cell has its FSPs in coherent states so that each action spectroscopy of each PBM on each dysfunctional function might be FSP-specific. This was supported by the reference [90]. Karu et al. found that the action spectroscopy of proliferation PBM was different from the one of adhesion PBM [90].

The iPBM might mainly contribute to the low morbidity or mortality of most diseases in the zone of low latitude or in summer. White light may have no effects on cells, but the skin-decayed sunlight is not white light anymore. As the cold light such as green, blue, or violet decays more rapid than the hot light such as red, orange, or yellow does, the skin-decayed sunlight may mainly be hot light, residual hot light (RHL). A normal function can resist internal/external disturbance, but chronic stress is sensitive to it. As a kind of LIL, RHL can modulate a chronic stress until it is successful. Moreover, as a kind of iPBM, RHL may upgrade the functional fitness of a normal function. Therefore, RHL and then sunlight can enhance the resistances to decrease disease morbidity or mortality.

7. Conclusion

DPBM may modulate a chronic stress. When a biosystem in the FmaxSH, dPBM cannot modulate the normal Fmax, but iPBM can modulate a dysfunctional FmaxNS through redundant pathways until it is normal and the normal Fmax is then upgraded. High level PBM can modulate a normal function and may be also a successful stress.

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