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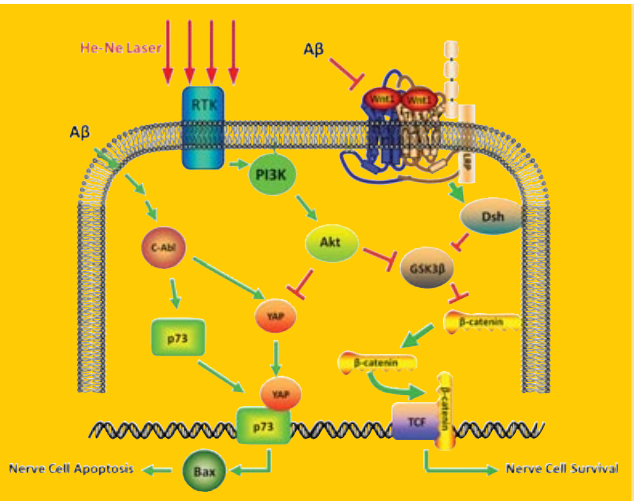
LASER & PHOTONICS REVIEWS

Laser Photonics Rev., 1–16 (2013) / **DOI** 10.1002/lpor.201300015

Abstract Low-level light therapy (LLLT) using red to near-infrared (NIR) (630–1000 nm) light has gained attention in recent years as a therapy in ophthalmology, neurology, dermatology, dentology, and regenerative medicine. Advancement in the basic science fields of photobiology has propelled LLLT into the therapeutic revolution. The potential mechanisms on LLLT-induced biological effects have been investigated by numerous researchers throughout the world. This article reviews the current intracellular signaling cascades in photobiology and photomedicine under the influence of red to NIR light on mammalian cells. Specifically, mitochondrial retrograde signaling initiated by cytochrome *c* oxidase photomodulation is discussed in detail in the treatment of indications using LLLT, such as vitiligo management, retinal protection, and tumor therapy. The pathways through activating receptor tyrosine kinases are also highlighted in LLLT-induced neuroprotection, wound healing, and skeletal muscle regeneration. The understanding of the LLLT-induced biological reactions in cellular and subcellular levels is crucial for the advancement of LLLT in treatment of diseases.



REVIEW ARTICLE

Intracellular signaling cascades following light irradiation

Shengnan Wu and Da Xing*

1. Introduction

Low-level light therapy (LLLT) is a modality using either coherent or noncoherent low-level light in the red to near-infrared (NIR) wavelengths ($\lambda = 630$–1000 nm) to induce nondestructive and nonthermal biological reactions for therapeutic effects. In fact, LLLT achieves its objectives through photobiomodulation [1, 2]. LLLT has gone through several incarnations, such as laser therapy [3], low-level laser irradiation (LLLI) [4], low-energy laser irradiation (LELI) [5], and low-power laser irradiation (LPLI) [6]. In this review we will use LLLT since it has become the most commonly used term in the literature and on the internet. Since 1960, more and more researchers have become involved with LLLT as a modern phototherapy. Health specialists and general practitioners have used LLLT for a variety of indications, such as tissue repair [7], pain attenuation [8], and anti-inflammation [9]. LLLT has shown unique effects in biology and medicine, yet its photobiological mechanism of action at the cellular level is still unclear. The intracellular mechanisms involved in tissue repair, including neuroprotection, vitiligo management, wound healing, bone repair, and skeletal muscle regeneration, are currently reviewed. Also reviewed is the effect of high-intensity light in cancer treatment.

Cell proliferation and differentiation induced by LLLT are important physiological effects in clinical practice. Increased proliferation and differentiation after LLLT have been shown in many cell types in vitro, including fibroblasts from different systems [10, 11], keratinocytes [12], osteoblasts [13], mesenchymal stem cells (MSCs) and cardiac stem cells [14], Schwann cells [15], aortic smooth muscle cells (SMCs) [16], endothelial cells [17, 18], melanocytes [19], and quiescent satellite cells [20]. However, the mechanisms of cell proliferation and differentiation induced by LLLT are poorly understood. Various mechanisms for the mitogenic effects of LLLT have been proposed [21]. Karu, a pioneer in the LLLT field, proposed that red to NIR light could be absorbed by mitochondrial respiratory chain components, resulting in the conversion of luminous energy to metabolic energy with a subsequent modulation of the biological function of cells [22]. This mechanism allows broadening of the understanding of universality phenomenon of LLLT on various kinds of cell proliferation and differentiation, and has been demonstrated in retinal protection, Parkinson's disease (PD) attenuation, and vitiligo management. Another mechanism involved ligand-free dimerization and activation of specific receptor tyrosine kinases (RTKs) that are in the "right energetic state" to accept the laser energy, leading to their autophosphorylation and downstream effects [23]. This mechanism can be used to explain the similarity between LLLT-induced biomodulation effects and that by many kinds of growth factors, as manifested in Alzheimer's

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disease (AD) attenuation, wound healing, bone repair, and skeletal muscle regeneration.

For biomedical applications, it is most important to understand how LLLT works at the cellular and organism levels; hence optimal treatment protocols can be designed for specific indications. The potential mechanisms on LLLT-induced biological effects have been investigated by numerous research teams (see Fig. 4). Karu has dedicated over 30 years to LLLT research, advancing our understanding of cytochrome *c* oxidase (CcO) both as the photoacceptor and signal transducer, and enables us to understand LLLT as a therapeutic outcome of a broadband action spectrum that to potentially treat various ailments [24]. In the study of cellular signaling pathway by LLLT, scientists choose various subfields of investigations. Wong-Riley and coworkers contributed to the study on retinal protection by LLLT [1, 25–27]. Xing et al. [2, 6] and Wong-Riley and coworkers [28, 29] devoted research to the antiapoptotic pathway by LLLT, promoting the application to neuroprotection. Oron and coworkers extended our understanding of the myocardium protection from ischemic injury by LLLT [18, 30–34]. Yu and coworkers pushed knowledge of CcO/mitochondrial membrane potential ($\Delta\Psi$m)/adenosine triphosphate (ATP)/cyclic adenosine monophosphate (cAMP)/c-Jun NH_2-terminal kinase (JNK)/activator protein 1 (AP1) pathway in LLLT-induced melanoma cell proliferation, providing an improvement for vitiligo treatment [19,35–38]. Xing and coworkers [39] and Hsu and coworkers [40] contributed to the study on extracellular regulated protein kinases (ERK)/specificity protein 1 (Sp1)/vascular endothelial growth factor (VEGF) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/endothelial nitric oxide synthase (eNOS)/nitric oxide (NO) pathways on wound healing upon LLLT. Jimi and coworkers focused on the bone morphogenetic protein (BMP)/Smad pathway that is involved in LLLT-induced bone formation [41]. Halevy and coworkers have advanced the understanding of RTKs/ERK/eukaryotic initiation factor 4E (eIF4E)/cyclin D1 and PI3K/Akt/mammalian target of rapamycin (mTOR)/phosphorylated heat- and acid-stable protein regulated by insulin (PHAS-I) pathway in LLLT-induced skeletal muscle regeneration [5, 20, 23, 42]. Xing and coworkers also contributed to the study of high-intensity light-triggered proapoptotic signal cascades, providing a potential phototherapy for cancer [43–49]. This paper reviews the available literature on molecular signaling pathways involved in LLLT stimulation for the enhancement of cell proliferation, differentiation, or apoptosis in various indications.

2. Increased activity of CcO and retinal protection by LLLT

It becomes more evident that visible light in each spectral region can activate different photoacceptors in mammalian cells. Flavins, small and water-soluble photosensitizers active only at wavelengths shorter than 500 nm, have previously been found to be responsible for visible-light induction of free radical reactions in cardiac and sperm cells [50]. A recent study indicates that visible light illumination in the blue region (400–505 nm) increases ROS levels in isolated sperm plasma membranes [51]. A study performed in Chinese hamster ovarian cells and isolated rat heart mitochondria indicates that iron protoporphyrin IX (PpIX), the prosthetic group of heme in cytochromes *b*, *c*1 and *c*, has high absorption of green light [52]. Absorption of the light energy by PpIX causes photobleaching due to its photodynamic action. The pioneer in the field of mechanism study on the interaction between red to NIR light and its endogenous photoacceptor, Karu provided critical reviews to highlight the role of CcO as the photoacceptor and photosignal transducer of the light in the red to NIR region [22]. CcO is the terminal enzyme of the electron-transport chain in eukaryotic cells, also named as complex IV, mediating the transfer of electrons from cytochrome *c* to molecular oxygen. CcO absorption of light can increase the level of $\Delta\Psi$m, ATP, and reactive oxygen species (ROS), leading to increased energy availability and signal transduction [36,53–58]. It can also be induced by light illumination that can alter cellular homeostasis parameters, cell redox state, and expression of redox-sensitive factors (such as NF-κB) [24, 59–62]. These cellular changes lead to macroscopic effects, including increased cell viability, proliferation, and differentiation [55, 63]. The light stimulation of CcO may perform, under certain circumstances, a protective function on cells against the harmful effects of various chemicals.

Mitochondria play a central role in neuronal physiology. The retina contains neurons that require high energy for excitation and they rely mostly on mitochondrial-derived ATP to meet these requirements [64]. Therefore, retinal neurons are highly vulnerable to events that lead to oxidative stress, energy depletion, and dysfunction of the mitochondrial machinery [65, 66]. LLLT has potentially significant applications against retinal damage in situations of injury due to disruption of mitochondrial energy metabolism. The work by Eells et al. showed a therapeutic benefit of 670-nm light-emitting diode (LED) treatment in the survival and functional recovery of the retina and optic nerve in vivo after acute injury by the mitochondrial toxin, formic acid (an inhibitor of CcO) generated in the course of methanol intoxication [1]. The functional recovery by LLLT was revealed by the prevention of the decrease in the retinal sensitivity to light and attenuation of the maximal electroretinogram response amplitude [1]. These functional recoveries are consistent with the maintenance of retinal architecture. Histological study showed that methanol-induced retinal edema and swelling of photoreceptor inner segments totally disappeared after LLLT [1].

Photoneuromodulation of CcO activity is the most important primary mechanism of LLLT on retinal protection. Wong-Riley and coworkers have demonstrated that 670-nm LED photoirradiation completely reverses the reduction of CcO activity in primary rat visual cortex neurons whose voltage-dependent sodium channels are blocked by tetradotoxin that indirectly downregulates the CcO enzyme levels [25]. In addition, an LED of 670 nm partially

restores CcO enzyme activity blocked by potassium cyanide (KCN), a CcO inhibitor, and significantly reduces neuronal cell death [26,27]. LEDs of 670 nm can significantly restore neuronal ATP content at lower concentrations of KCN [26]. Pretreatment by LEDs of 670 nm significantly decreases the KCN-induced expression of caspase-3. It also reverses the increased expression of Bax and decreased expression of Bcl-2 elicited by KCN to control levels [27]. Thus, LLLT affects neuronal metabolism with not only enhancement of CcO activity, but also enhancement of ATP production, neurotransmission, gene expression, and prevention of cell death. CcO is the primary photoacceptor of light in the red to NIR region. It also serves as a key mitochondrial enzyme for nerve cells in the retina and the brain for cellular bioenergetics. This shows the potential of LLLT to treat visual, neurological conditions; it also supports the view that neuronal energy metabolism could constitute a major target for neurotherapeutics of the eye. It opens a way for exploring the use of light therapy to improve retinal function in the case of acute methanol intoxication or to reverse the detrimental effects of impulse blockade in intoxicated neurons. The authors also suggest that LLLT may facilitate recovery from retinal injuries and other ocular diseases due to mitochondrial dysfunction.

3. Protection of myocardium from ischemic injury by LLLT

Tissue injury due to ischemia and reperfusion (I/R) causes morbidity and mortality in a wide range of pathologies, such as myocardial infarction and trauma [67]. Metabolic supply-demand imbalance within the ischemic organ results in profound tissue hypoxia and microvascular dysfunction. Subsequent reperfusion further accelerates the activation of innate and adaptive immune responses and cell death programs [67]. de Lima et al. investigated LLLT modulation of the pro- and anti-inflammatory mediators in acute lung inflammation caused by intestinal I/R in a rat abdominal trauma model [68]. Their results indicate that the 660-nm light attenuates the I/R-induced lung inflammation that increases interleukin 10 (IL-10) production and reduces tumor necrosis factor (TNF) generation [68]. In an experimental model of the infarcted heart in rats and dogs, LLLT has been shown to be beneficial to infarcted myocardium, resulting in a large reduction in infarcted size [30–33]. This was partially due to the significant elevation in the number of undamaged mitochondria and ATP content in the ischemic zone of laser treatment [32]. It was demonstrated that LLLT elevated the inducible 70-kDa heat-shock protein (HSP70i) content in the ischemic myocardium [31]. HSP70i was considered as an important anti-ischemic and antiapoptotic proteins involved in myocardial protection after ischemic injury, because overexpression of the HSP70i increases the resistance of the heart to ischemic injury [69, 70].

Inducible nitric oxide (iNOS) plays an important role in ischemic myocardium in improving recovery of contractile proteins and reducing infarct size postmyocardial infarction [71, 72]. Thus, iNOS is also known as one of the major cardioprotective proteins [73] and has been used as such successfully in gene therapy [74]. VEGF is a key mediator of ischemia-driven angiogenesis. It induces sprouting and capillary growth toward the ischemic tissue and matches the vascular density according to an increase in oxygen consumption [75]. Oron and coworker demonstrated that VEGF and iNOS expression in the infarcted rat heart was markedly upregulated by 804-nm LLLT and was associated with enhanced angiogenesis and cardioprotection [34]. The proliferation of endothelial cells by low level He-Ne laser was reported in their earlier study, which may partially explain the augmentation of angiogenesis in the infarcted heart. These results may have clinical significance by offering therapeutic options to ameliorate angiogenesis in ischemic conditions [18]. Zhang et al. provided evidence for protection against hypoxia and reoxygenation injury in cardiomyocytes by 670-nm LEDs in the manner of depending upon NO derived from NOS and non-NOS sources [76]. The non-NOS source has been suggested as mitochondrial CcO, as is shown by the results using yeast and rat liver mitochondria that mitochondrial CcO produces NO under hypoxic conditions [77, 78]. These findings demonstrated an alternative role for the mitochondrial respiratory chain under hypoxic or anoxic conditions and suggested that mitochondrially produced NO was involved in hypoxic signaling, possibly via a pathway that involves protein tyrosine nitration [78].

4. LLLT delays neurodegenerative diseases

4.1. PD

Mitochondrial aerobic metabolism in neurons is the basis for many cellular functions, such as electrophysiology, neuroplastics, and neuroprotection. It is crucial for repolarization of cell membranes in neurotransmission, synapse formation, and cell survival. Impaired mitochondrial oxidative metabolism is often associated with neuronal dysfunction, neurological impairment, and neurodegeneration. PD is a movement disorder caused by the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to nigrostriatal degeneration [79]. The inhibition of mitochondrial respiratory chain complex I and oxidative stress-induced damage have been considered as the pathogenesis of PD [79]. Therefore, interventions to improve mitochondrial metabolism could potentially benefit the function of brains.

Recent studies suggest a protective role of LLLT in nervous tissue. Such effects were observed when striatal and cortical rat neuronal cultures were exposed to rotenone and 1-methyl-4-phenylpyridinium (MPP^+) toxins that inhibit mitochondrial complex I. For example, LEDs of 670 nm significantly increased cellular ATP content, decreased the number of neurons undergoing cell death, and reduced the expressions of ROS and reactive nitrogen species (RNS) in rotenone- or MPP^+-exposed neurons [28, 29]. LLLT for the treatment of PD has also been

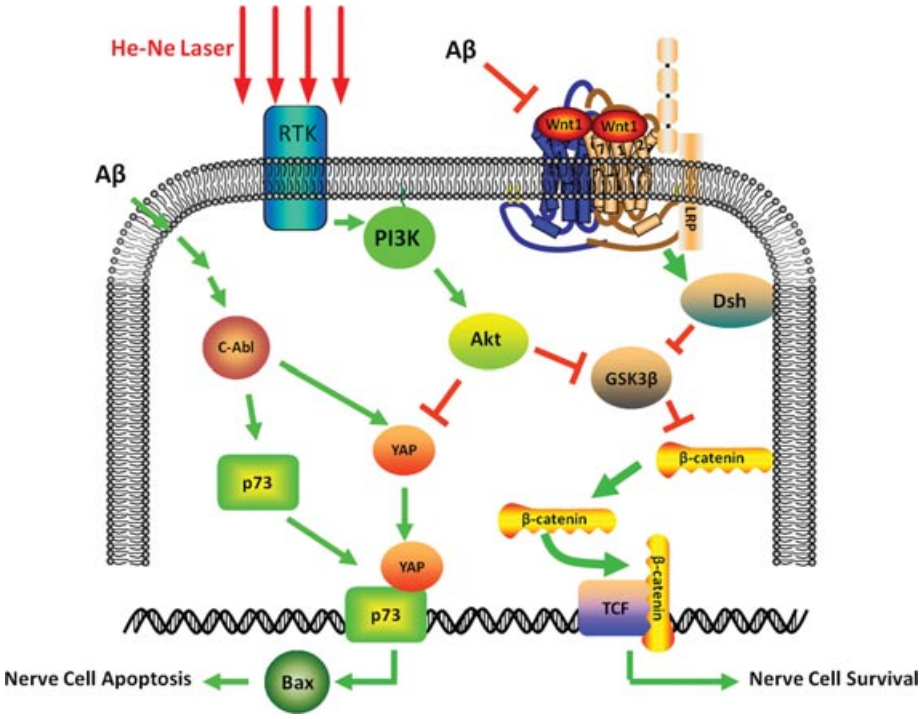

Figure 1 Schematic representation of the signaling pathways for LLLT inhibiting Aβ_{25-35}-induced nerve cell apoptosis.

demonstrated in a mouse model of dopaminergic degeneration induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [80, 81]. These studies show that 670-nm LEDs largely prevented the loss of dopaminergic cells in the substantia nigra [81]. It is also shown that 670-nm LED treatment saves dopaminergic amacrine cells of the retina in an acute and a chronic MPTP mouse model of PD [80].

4.2. AD

Apoptosis caused by deposition and accumulation of amyloid beta (Aβ) has been considered as the pathogenesis of AD [82, 83]. It was first reported in 2003 that LLLT could significantly diminish Aβ-induced apoptosis in PC12 rat pheochromocytoma cells [84]. The inhibition of apoptosis was confirmed by Zhang et al. that LLLT could reverse the increased level of Bax/Bcl-X_L mRNA ratio caused by Aβ treatment [85]. The underlying molecular mechanisms involved in the activation of Akt-mediated pathways by low level He-Ne laser have been explored by Xing and coworkers (see Fig. 1) [2, 6]. Akt mediates distinct biological responses, including promoting proliferation and inhibiting apoptosis [86]. Akt has been considered as a critical mediator of survival signals that protect cells from apoptotic stimuli such as growth factor withdrawal, ultraviolet (UV) irradiation and cell-cycle discordance [87]. Akt phosphorylates and inhibits some proapoptotic protein activities, including that of Yes-associated protein (YAP) and glycogen synthase kinase 3 beta (GSK3β), to promote cell survival [86]. LLLT has been shown to protect against staurosporine-induced apoptosis upstream of Bax translocation via the PI3K/Akt/GSK3β pathway [88]. Recent studies also show that LLLT can inhibit Aβ-induced apoptosis through activating an Akt/YAP/p73 pathway in PC12 cells [6] and Akt/GSK3β/β-catenin pathway in both PC12 cells and SH-SY5Y human neuroblastoma cells [2].

YAP is a transcriptional coactivator that needs to bind its target transcription factors to stimulate gene expression [89]. YAP could positively regulate transcription factor p73 in promoting apoptosis through mediating the expression of cell-death-promoting genes, *bax* or *puma* [89]. Recent studies have demonstrated that YAP accelerates Aβ-induced neural cell apoptosis through binding p73 to stimulate *bax* gene expression and Bax activation [90]. It is reported that Akt can phosphorylate YAP on S127 and promotes cytoplasmic localization of YAP by enhancing its interaction with cytosolic 14-3-3 scaffold proteins [91]. This makes YAP lose its main function as a coactivator in the nucleus. Hence, active Akt impairs YAP from associating with p73, leading to attenuation of p73's transactivation and proapoptotic activity. Zhang et al. reported that LLLT inhibited Aβ-induced YAP nuclear translocation through Akt activation [6]. They also reported that activated Akt by LLLT phosphorylated YAP on S127 and resulted in suppressing the proapoptotic *Bax* gene expression following Aβ treatment [6] . Therefore, LLLT is able to inhibit Aβ-induced apoptosis through activating an Akt/YAP pathway, a potential therapeutic strategy for the treatment of AD.

GSK3β is a serine-threonine kinase involved in different processes such as cellular signaling pathways, metabolic control, embryogenesis, cell death, and oncogenesis [92]. A growing body of evidence shows that GSK3β is implicated in the pathogenesis of AD [93]. GSK3β exerts its function in the neuronal degeneration of AD by phosphorylating

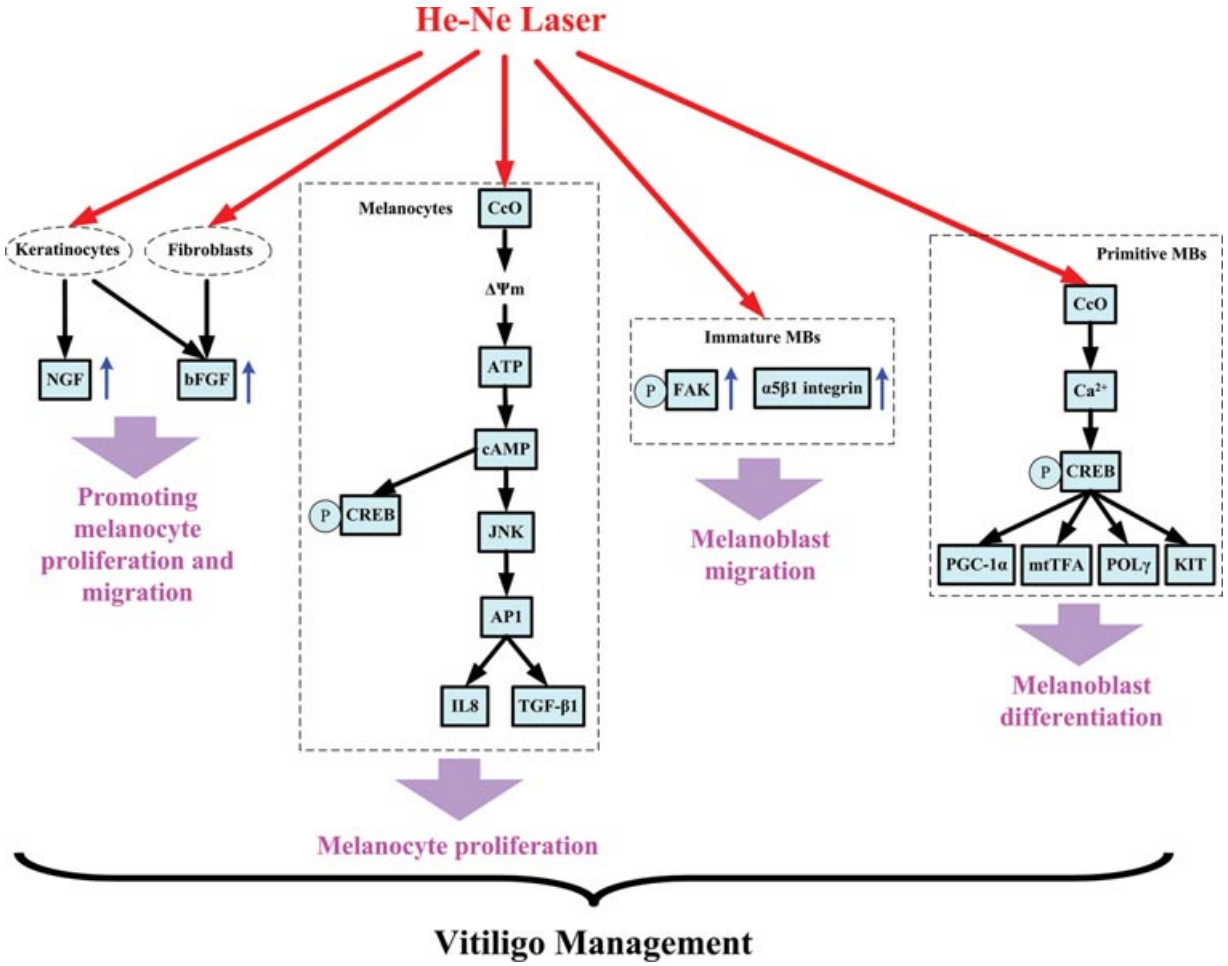

Figure 2 Schematic representation of signaling pathways for vitiligo management by LLLT.

β-catenin [94], which is an integral component in the canonical Wnt signaling pathway [95]. Activation of the Wnt pathway leads to the inhibition of β-catenin phosphorylation by GSK3β. It can stabilize the underphosphorylated form of β-catenin, which cannot be targeted for degradation by the proteasome; it accumulates and travels to the nucleus to form complexes with TCF/LEF and exert its prosurvival function [96]. Reduced Wnt/β-catenin signaling has been implicated in the pathophysiology of neuronal degeneration in AD [97–99]. Liang et al. demonstrated that prosurvival effect of LLLT on Aβ-induced apoptosis was achieved via the Akt/GSK3β/β-catenin pathway [2]. They reported that Akt was activated by LLLT upon Aβ treatment, interacted with GSK3β, and inhibited its activity, leading to the accumulation of β-catenin and subsequent translocation to the nucleus to exert its prosurvival function [2]. Thus, LLLT may be used to treat AD by targeting GSK3β [100].

5. Vitiligo management by LLLT

Low-level He-Ne laser treatment has therapeutic effects in segmental vitiligo. Yu et al. reported that patients with segmental-type vitiligo on the head and/or neck received marked repigmentation after the laser treatment [19]. Vitiligo is a depigmentary disorder characterized by the loss of functional melanocytes. The melanoblasts (MBs) in the outer root sheath of the hair follicles are an important source for repigmentation [101]. The repigmentation of vitiligo skin is initiated by the activation and proliferation of MBs, followed by their upward migration onto the nearby epidermis to form perifollicular pigment islands [101]. At the molecular level, how He-Ne laser induces vitiligo repigmentation has not been fully elucidated. However, several studies have associated the stimulatory events with He-Ne laser treatment for pigment cell migration and proliferation (see Fig. 2) [19, 35–38]. The underlying mechanism of melanocyte disappearance is unclear. However, studies show that MBs, melanocytes, keratinocytes, and fibroblasts may all contribute to the repigmentation process of vitiligo. Therefore, stimulation of these epidermal and dermal cells could be beneficial to patients with vitiligo [101].

MBs are important melanocyte-precursor cells and, upon activation, they migrate upwards to the epidermis and undergo functional development to produce melanin [101]. They may serve as the melanocyte reservoir to repopulate

the depigmented skin. Lan et al. demonstrated that the He-Ne laser induced locomotion of the immature MBs via enhanced phosphorylated focal adhesion kinase (FAK) and $\alpha 5\beta 1$ integrin expression [35]. To induce an advantageous biological effect by laser treatment, the signaling between photoacceptor and its downstream cascade is crucial. Lan et al. also demonstrated that a He-Ne laser irradiation induced differentiation and enhanced mitochondrial biogenesis of the primitive MBs via a Ca^{2+}-dependent mitochondrial retrograde signaling [38]. The differentiation of the primitive MBs by laser treatment was evaluated by the increase in KIT expression [38], a quintessential marker of differentiation for primitive MBs. One of the earliest events in primitive MBs induced by He-Ne laser involves an immediate increase in CcO activity and elevation of intracellular Ca^{2+} level [38]. The high-level Ca^{2+} was known to stimulate mitochondrial gene expression through signaling related to the cAMP response element binding protein (CREB) [102], which binds to cAMP-response element in *Mitf* gene, leading to the upregulations of key regulatory genes required for pigment cell development [103]. For mitochondrial regulation, CREB is known to modulate peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) [104], the master regulator of mitochondrial biogenesis [105]. PGC-1α could induce the expression of mitochondrial transcription factor A (mtTFA), a specific mitochondrial DNA binding protein for mitochondrial transcription and mtDNA replication [106]. Lan et al. reported that the expression of mitochondrial biogenesis-associated genes, such as *PGC-1α*, *mtTFA*, and *mtDNA polymerase γ* (*POLγ*) in primitive MBs, showed a time- and dose-dependent increase upon laser treatment [38]. In addition, the expression of pCREB was also detected [38]. Pretreatment with Ca^{2+} chelating agent could abrogate the enhanced expression of pCREB and the induction of KIT on primitive MBs. Therefore, He-Ne laser irradiation of CcO can increase the intracellular Ca^{2+} level. This event increases the expression of pCREB, which plays an essential role in differentiation and mitochondrial biogenesis of MBs. Taken together, visible light from the sun may provide important environmental cues for the relatively quiescent stem or primitive cells to differentiate.

Melanocytes are important for vitiligo management as restoration of functional melanocytes on vitiliginous skin is the final common pathway that leads to clinical repigmentation. Melanocytes are present in vitiligo lesions even after years of depigmentation [107, 108]. Therefore, stimulation of epidermal melanocytes, either the newly arrived cells or the residual cells, to proliferate would result in recovery from vitiligo. In elucidating the mechanisms involved in He-Ne laser-induced repigmentation, Hu et al. demonstrated that the He-Ne laser stimulated A2058 melanoma cell growth via a mitochondria-related process [36]. They reported that He-Ne irradiation immediately increased the level of $\Delta\Psi$m, ATP and cAMP via enhanced CcO activity and promoted phosphorylation of JNK/AP1 [36]. Induced A2058 cell proliferation was significantly abrogated by the addition of $\Delta\Psi$m and JNK inhibitors [36]. Moreover, He-Ne laser treatment enhanced the release of IL-8 and transforming growth factor-β1 (TGF β1) from A2058 cells [36]. These results indicate that irradiation by He-Ne laser elicits photostimulatory effects in mitochondrial processes, involving JNK/AP-1 activation and enhanced growth factor release, leading to A2058 cell proliferation [36]. For melanocytes to proliferate in vitro, crosstalk between different pathways is needed. Mitogens and UVB radiation could induce melanocyte proliferation but through different pathways [101], which converge on CREB phosphorylation, indicating the importance of this event during melanocyte proliferation [109]. As demonstrated by Lan et al., He-Ne laser irradiation could significantly increase the expression of pCREB. The proliferative effect of the He-Ne laser on melanocytes was abolished and suppression of melanocyte growth was noted by a specific mitochondrial uncoupling agent [37]. Thus, He-Ne laser imparts a growth stimulatory effect on functional melanocytes via mitochondria-related pathways.

It is known that keratinocytes and fibroblasts have intricate relationships with melanocytes, mainly through their growth factors to influence the growth of melanocytes [101]. Therefore, effective stimulation of keratinocytes is likely to induce repigmentation in vitiligo. Fibroblasts have also been shown to influence epidermal pigmentation in vivo and in vitro [101]. Yu et al. showed that the supernatants from He-Ne laser-treated keratinocytes imparted stimulatory effects on melanocyte proliferation [19]. Melanocyte migration was also enhanced either directly by He-Ne laser irradiation or indirectly by the medium derived from He-Ne laser-treated keratinocytes. They observed a significant increase in basic fibroblast growth factor (bFGF) release from both keratinocytes and fibroblasts and a significant increase in nerve growth factor (NGF) release from keratinocytes [19]. It is reported that bFGF is a putative melanocyte growth factor, whereas NGF is a paracrine factor for melanocyte survival in the skin. Both NGF and bFGF stimulate melanocyte migration. It is reasonable to propose that He-Ne laser stimulates melanocyte growth, migration and proliferation through inducing melanocyte-related mitogen release from keratinocytes and fibroblasts for melanocyte. This may also rescue damaged melanocytes, therefore providing a microenvironment for inducing repigmentation in vitiligo.

6. Wound healing by LLLT

Red to NIR light has shown benefits for promoting wound healing in humans and animals, even though its mechanisms are poorly understood. The first application of LLLT in wound healing was reported in 1971 [110]. An excellent review of human experience with NIR therapy for wound healing was published in 2000 [111]. Researchers have investigated LLLT's efficiency on wound healing in a genetically diabetic mouse model of impaired wound healing [112, 113] and excisional wound healing in mouse [114]. Normal wound healing usually involves hemostasis,

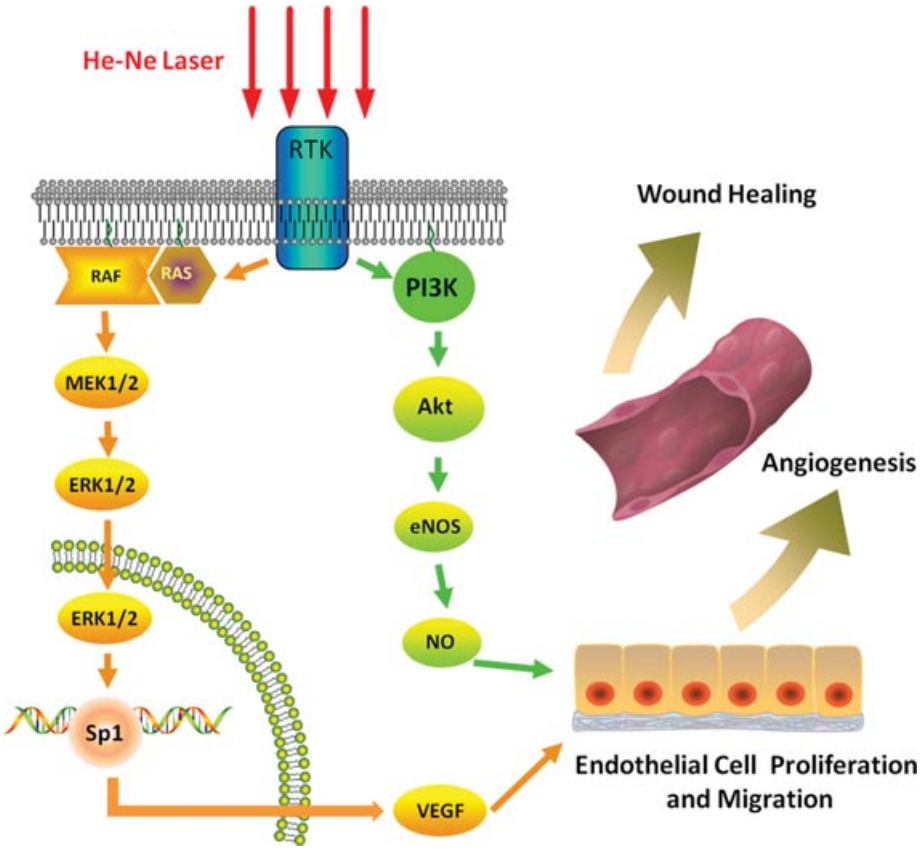

Figure 3 The model of signaling pathways activated by LLLT promoting vascular endothelial cell proliferation and migration.

inflammation, proliferation and remodeling. The current research is showing that laser biostimulation primarily affects cell proliferation phase of the wound-healing process. Human studies with lasers show epithelialization for wound closure and stimulation of skin-graft healing [115, 116]. LLLT also has a positively influence on cellular proliferation for angiogenesis on endothelial cells [17, 39, 40, 117].

Angiogenesis is one of the important biological responses in healing progress [118]. Due to the high metabolic activity at the wound site, there is an increasing demand for oxygen and nutrients. Local factors, such as low pH, reduced oxygen tension and increased lactate, actually initiate the release of many factors needed for new blood supply. Such a process, angiogenesis or neovascularization, is stimulated by VEGF, bFGF and TGFβ [119]. Epidermal cells, fibroblasts, macrophages and endothelial cells produce these factors. The secretion of TGFβ1 by cultured endothelial cells could be enhanced by laser irradiation [120]. VEGF is a potent stimulator of angiogenesis [121]. It causes a massive signaling cascade in endothelial cells. Binding to VEGF receptor starts a tyrosine kinase signaling cascade that stimulates vessel permeability, proliferation/survival, migration and finally differentiation into mature blood vessels. Low-level He-Ne laser irradiation enhances production of VEGF and promotes growth of endothelial cells in vitro [122]. Feng et al. recently reported that He-Ne laser activated ERK/Sp1 pathway to promote VEGF expression and vascular endothelial cell proliferation (see Fig. 3) [39].

The common features of angiogenesis are activation of the proliferation, migration and tube formation programs of endothelial cells for protecting the inner lining of vessels and for delivering oxygen. Many physical and chemical factors exert their effects on angiogenesis through regulation of various endothelial cell activities, including proliferation, survival, migration or tube formation [123–125]. One study reports that Sp1 acts as a G1 phase special transcription factor in epithelial cells [126] and another study shows that the activation of cyclin D1 promoter in endothelial cells largely depends on the Sp1, through the Ras-dependent pathway [127]. It has been identified that proximal GC-rich box of the VEGF promoter bound by Sp1 is the main target for growth-factor stimulation [128]. Sp1-dependent transcription can be regulated through alterating DNA binding activity by post-translational modifications, especially phosphorylation [129, 130] via protein kinases including ERK [131], protein kinase Cζ [132], Akt [133], cyclin-dependent kinase (CDK) [134]. Feng et al. demonstrated that LLLT enhanced DNA-binding activity of Sp1 to VEGF promoter [39]. They also demonstrated that LLLT stimulated ERK-dependent Sp1 activation, and the activation of ERK/Sp1 signaling pathway is crucial for the upregulation of VEGF expression, which promotes cell cycle progression and proliferation [39]. These findings extend the knowledge on the cellular signaling mechanisms mediating LLLT-induced endothelial cell proliferation, providing insight into establishing the therapeutic potential of LLLT for angiogenesis.

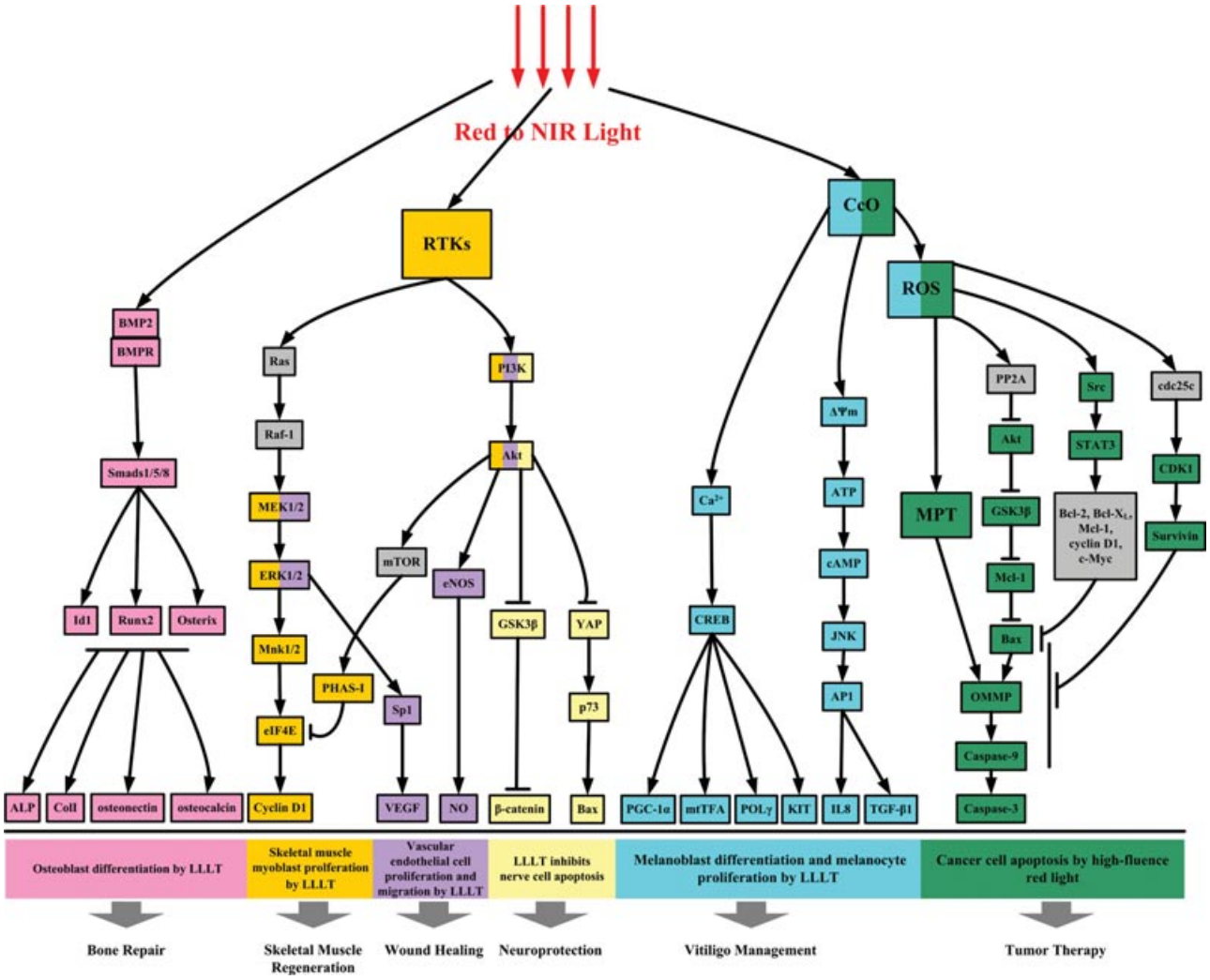

Figure 4 Intracellular signaling cascades by LLLT.

Endothelial cell proliferation, migration and angiogenesis have been reported to be regulated by many growth factors including those via a PI3K/Akt signaling pathway to activate eNOS [135, 136]. The eNOS produces NO constitutively at low levels but can be transiently stimulated to produce high levels of NO by hormones or various environmental stimuli [137]. NO exerts many important functions on the vascular wall, including suppression of the inflammatory response induced by cytokines, inhibition of apoptosis, regulation of cell migration, and angiogenesis in addition to its vasodilatory effect [138]. Thus, a stimulated increase in NO production by endothelial cells could be a potential benefit for wound healing. Chen et al. reported that the increased NO production by LLLT was consistent with the upregulation of eNOS protein expression on human umbilical vein endothelial cells (see Fig. 3) [40]. Moreover, they observed that enhancement in eNOS expression by LLLT was significantly reduced by the addition of PI3K inhibitor [40]. They also found that the migration of cells after laser treatment was greatly enhanced, which was similar to the influence by direct VEGF treatment [40]. These results reveal that the elevated eNOS activation via the PI3K signal pathway after laser irradiation may be associated with the endothelial cell migration event and angiogenesis. These studies provide clues for better understanding of the function of LLLT and help to develop novel therapeutic strategies for regulation of the angiogenic process in wound healing.

NIR light can upregulate the production of matrix metalloproteinase 2 (MMP2) in fibroblasts at both the protein and transcriptional levels [120]. Matrix metalloproteinases matrix metalloproteinase 2 (MMP2) is another major contributor to angiogenesis, since they help degrade the proteins that keep the vessel walls solid. This proteolysis allows the endothelial cells to escape into the interstitial matrix in sprouting angiogenesis. Inhibition of MMPs prevents the formation of new capillaries [139]. These enzymes are highly regulated during the vessel formation process to maintain the integrity of the microvasculature [140]. MMP2 (gelatinase), MMP1 (collagenase)

and MMP3 (stromelysin) are three major MMPs with collagenase activities [141]. These breakdown enzymes are involved in the remodeling phase of wound repair.

7. Bone repair by LLLT

In animal studies, LLLT is widely used to promote bone formation in fracture healing [142] and distraction osteogenesis [143]. LLLT could stimulate osteoblast cells, as shown in numerous studies. In primary osteoblast-like cells from fetal rat calvarias, LLLT could stimulate proliferation and differentiation, inducing expression of alkaline phosphatase (ALP), osteopontin (OP), and bone sialoprotein [144]. Similar results were obtained in cultured SaOS-2 human osteosarcoma cells when irradiated with a 670-nm laser, particularly the early induction of ALP, type I collagen (ColI), and OP [145, 146]. Moreover, LLLT treatment of human osteoblast-like cells induced both proliferation and differentiation depending on the light dose, through increased osteocalcin and TGFβ1 production [147]. Nonconherent red light promoted proliferation but not osteogenic differentiation of MSCs in normal media, while it enhanced osteogenic differentiation and decreased proliferation of MSCs in media with osteogenic supplements [148]. LLLT also promotes bone repair in vivo [149] and stimulates bone formation by increasing osteoblast activity and decreasing osteoclast number [150]. However, its molecular mechanism is not well understood.

Insulin-like growth factor 1 (IGF1) is mainly secreted primarily in the liver after stimulation with growth hormone [151]. It regulates cell growth and development and plays an important role in fracture healing [151]. IGF1 also plays a pivotal role in the anabolic regulation of bone metabolism [152]. It regulates the DNA binding activity of runt-related transcription factor 2 (Runx2) through the PI3K/p21 activated kinase 1 (PAK1) and ERK1/2 signaling cascades [153]. Some studies reported that LLLT stimulated bone-nodule formation, through ALP activity [154] and osteocalcin expression, the process that depended on LLLT-stimulated IGF1 [154, 155]. Kiyosaki et al. investigated the effects of LLLT on signal transduction downstream from IGFI in osteoblasts. They suggest that LLLT stimulates in vitro mineralization through increased IGF1 and BMP production, through Runx2 expression and ERK phosphorylation in osteoblasts [156]. The IGF function is regulated at one level by the presence of insulin growth-factor-binding proteins (IGFBPs), which function as carrier proteins in biological fluids, mediate the transport of IGFs from the vascular area, and increase their half-lives. Saygun et al. reported that that LLLT increased the proliferation of osteoblast cells and stimulated the release of IGF1 and IGFBP3 from these cells [157].

BMP signaling plays important roles in bone formation during mammalian development and exhibits versatile regulatory functions in the body. Hirata et al. reported that low-level 805-nm laser light accelerated the differentiation of BMP-induced osteoblasts by stimulating the BMP/Smad signaling pathway without affecting proliferation [41]. They showed that LLLT enhanced BMP2-induced ALP activity, while laser treatment alone did not affect ALP activity in C2C12 pluripotent mesenchymal precursor cells [41]. Laser irradiation stimulated BMP2-induced phosphorylation of Smad1/5/8 and BMP2 expression, but had no effect on the expression of inhibitory Smads 6 and 7, BMP4, or IGF1. Laser irradiation enhanced Smad-induced Id1 reporter activity as well as expression of BMP2-induced transcription factors such as Id1, Osterix, and Runx2. Laser irradiation could also stimulate BMP2-induced expressions of ColI, osteonectin, and osteocalcin. Therefore, LLLT accelerates the differentiation of BMP-induced osteoblasts by stimulating the BMP/Smad signaling pathway.

8. Skeletal muscle regeneration by LLLT

Skeletal muscle regeneration follows a usual path: necrosis of muscle tissue, local inflammation and proliferation of satellite cells that further fuse to form multinucleated myotubes. He-Ne laser irradiation of the injured site can largely enhance the process of skeletal muscle regeneration in rats [158] and in toads [159], revealed by the appearance of young myotubes in the injured area. This suggests that the satellite cells may be the major candidates responding to laser irradiation in regenerating muscles. Furthermore, markedly skeletal muscle regeneration by laser irradiation was observed in denervated muscle, where satellite cells exist in greater number than in control muscle [160]. LLLT with 830-nm light could also promote recovery from disuse muscle atrophy in association with proliferation of satellite cells [161]. Many studies were performed in satellite cells to investigate the mechanisms involved in skeletal muscle regeneration by LLLT [4, 5, 20, 23, 42].

Ben-Dov et al. showed that He-Ne laser irradiation caused an induction of cell-cycle regulatory proteins, such as cyclin D1, cyclin E, and cyclin A in pmi28 mouse satellite cells, and proliferating cell nuclear antigen (PCNA) in primary rat satellite cells [20]. Myosin heavy chain (MHC) protein levels and fusion percentage were lower in the irradiated cells than in the control cells, whereas the proliferation of the irradiated cells was higher [20]. Zhang et al. also reported similar results that compared with non-irradiated cells, the number of primary rat skeletal muscle myoblasts increased when the cells were exposed to LLLT [4]. The number of cells with PCNA positive expression and the rate of 5-bromo-2′-deoxyuridine incorporation after laser irradiation were also higher than that of the control group, suggesting that LLLT can effectively enhance myoblasts growth [4]. Therefore, laser irradiation can stimulate skeletal muscle regeneration due to the activation of early cell-cycle regulatory genes in satellite cells, leading to increased proliferation and a delay in cell differentiation.

In mammalian cells, at least three distinct mitogen-activated protein kinase (MAPK) cascades can be activated by extracellular stimulation [162]. The ERK pathway plays

an important role in growth-factor-induced proliferation, differentiation and cellular transformation [162]. Epidermal growth factor stimulation can activate Ras, Raf-1, MAPK kinase (MEK1/2) and ERK isoforms (ERK1/2) [162]. Two other MAPK cascades are JNKs and p38 MAPK, which can be activated by stress signals [162]. Shefer et al. reported that LLLT induced ERK phosphorylation with no effect on its expression in serum-starved myoblasts [23]. Moreover, a specific MEK inhibitor inhibited the LLLT-mediated ERK1/2 activation. However, JNKs or p38 MAPK phosphorylation and protein expression were not affected by LLLT [23]. LLLT causes phosphorylation of the hepatocyte growth factor (HGF) receptor, a member of RTKs, previously shown to activate the ERK pathway, but exerts no effect on TNFα receptor that activates the p38 and JNKs pathways [23]. Satellite cells (myoblasts), considered as the precursor cells in the process of muscle regeneration following injury, were normally quiescent, but they can be activated by factors released from the injured muscle fibers. Of all the growth factors, only HGF can activate quiescent satellite cells in primary cultures [163]. HGF was also found to colocalize with its receptor c-Met shortly after injury in normal muscle [164]. Therefore, by specifically activating MAPK/ERK, but not JNKs and p38 MAPK enzymes, probably by specific receptor phosphorylation, LLLT could induce the activation and proliferation of quiescent satellite cells and delay their differentiation.

Shefer et al. studied the signaling pathways involved in the LLLT regulation of protein synthesis in i28 mouse myogenic cells. LLLT can induce different levels of protein synthesis [5]. LLLT elevated the levels of cyclin D1, associated with augmented phosphorylation of the eIF4E and its inhibitory binding protein PHAS-I, indicating the initiation of protein translation [5]. In the presence of the MEK inhibitor, eIF4E phosphorylation was abolished and levels of cyclin D1 were dramatically reduced [5]. Moreover, the LLLT-induced PHAS-I phosphorylation can be inhibited by PI3K inhibitor, wortmannin [5]. LLLT-enhanced Akt phosphorylation can also be attenuated in the presence of wortmannin [5]. These results suggest that LLLT induces protein translation via the PI3K/Akt and Ras/Raf/ERK pathways.

In addition to the studies performed in primary satellite cells as well as in myogenic cell lines, Shefer et al. have extended these studies to isolated myofibers, the minimum viable functional unit of the skeletal muscle, thus providing a close model of in vivo regeneration of muscle tissue [42]. They showed that LLLT stimulated cell-cycle entry and the accumulation of satellite cells around isolated single fibers [42]. Moreover, they showed that LLLT promoted the survival of fibers and their adjacent cells under serum-free conditions that normally led to apoptosis [42]. This survival was manifested by the increased expression of the antiapoptotic protein Bcl-2, and decreased expression of the proapoptotic protein Bax [42]. In irradiated i28 myogenic cells, these changes were accompanied by a reduction in the expression of tumor suppressor p53 and the CDKs inhibitor p21 [42]. These findings emphasize the important functions of these factors against apoptosis when using LLLT, providing a potential method to improve muscle regeneration following injury.

9. Cell apoptosis and tumor therapy by high-intensity light

9.1. Mitochondrial apoptosis pathway

Researchers have demonstrated that the biological effect of LLLT on cells shows obvious parabola features [165–168]. With an increment of laser output energy, its stimulating effect on cells can be increased gradually, but when the dose exceeds a certain threshold, the inhibition action of LLLT emerges [169]. In 2005, Wang et al. first reported that high-intensity He-Ne laser irradiation triggered cell apoptosis in human cancer cells. They observed the activation of caspase-3 in human lung adenocarcinoma cells (ASTC-a-1) after 60 J/cm^2 laser treatment [43]. This study may provide a potential phototherapy using high-intensity red light for human cancers, given that apoptosis is regarded as the major mode of cell death in cancer therapy.

Two distinct but convergent apoptosis pathways exist, namely, the death receptor (DR) pathway and the mitochondrial pathway [170]. The binding of members of the TNF superfamily to their cell surface receptors activates the DR pathway. These changes increase the activity of caspase-8, which is a central mediator of DR pathway. The interplay between proapoptotic and antiapoptotic members of the Bcl-2 family controls the mitochondrial pathway. Caspase-9 regulates the mitochondrial pathway, indicating overwhelming cell damage. The initiators of mitochondrial pathway include increased intracellular ROS, DNA damage, unfolded protein response, and deprivation of growth factors. These initiators ultimately result in increased mitochondrial permeability, thus promoting the release of proapoptotic proteins (e.g., cytochrome *c*) from the intermitochondrial membrane space (IMS) into the cytosol. Activated caspase-8 and caspase-9, in turn, mobilize caspases-3, 6, and 7, which destroy the cell by cleaving numerous proteins and by activating DNases. The mechanisms of apoptosis in ASTC-a-1 cells by 120 J/cm^2 He-Ne laser irradiation were explored. The following temporal sequence of cellular events was observed: (*i*) immediate generation of mitochondrial ROS, (*ii*) mitochondrial depolarization; and (*iii*) activation of caspase-3 after laser irradiation [44]. By monitoring the cellular distribution of Bid, it was revealed that laser treatment did not activate caspase-8, indicating that the induced apoptosis was initiated directly from the generation of mitochondrial ROS, which was independent of the caspase-8 activation [44]. In addition, cytochrome *c* release and caspase-9 activation by laser irradiation were observed in subsequent studies [45,46]. Thus, these studies indicate that high-intensity red light induces cell apoptosis through the mitochondrial pathway.

Under physiological conditions, mitochondria exhibit a high $\Delta\Psi$m, IMS proteins are retained in IMS, proapoptotic members of the Bcl-2 family are in their inactive state, and the mitochondrial permeability transition pore complex

(MPTPC) ensures the exchange of metabolites between the cytosol and the matrix by virtue of its "flickering" activity. One of the mechanisms associated with outer mitochondrial membrane permeabilization (OMMP) may occur through the sustained opening of the MPTPC, which may result in the dissipation of $\Delta\Psi m$, followed by an osmotic imbalance that induces the swelling of the mitochondrial matrix. Swelling may culminate in the physical rupture of the outer mitochondrial membrane (OMM), given that the surface area of the mitochondrial inner membrane largely exceeds that of the OMM [171]. Wu et al. investigated the mechanism involved in mitochondrial apoptotic process by 120 J/cm^2 He-Ne laser treatment in ASTC-a-1 cells. Cytochrome *c* release was ascribed to sustained opening of the MPTPC, because the release was prevented by cyclosporine (CsA), a specific inhibitor of mitochondrial permeability transition (MPT) [45]. Furthermore, mitochondrial permeability for calcein provided further evidence that a laser induced a long-lasting MPT [45]. High-level intracellular ROS generation was observed after irradiation, consistent with their earlier observations [45]. The ROS contributed to the laser treatment-induced onset of MPT, because the ROS scavenger prevented the process [45]. These results show that high-intensity red light induces cell apoptosis via the CsA-sensitive MPT, which is ROS dependent. The observed link between ROS and the activation of MPT could be a fundamental phenomenon in high-intensity red-light-induced cell apoptosis.

Wu et al. reported that CsA failed to prevent high-intensity He-Ne laser-induced cell apoptosis, although MPT was found to be involved in the mitochondrial apoptosis pathway [45]. This finding indicates the existence of other signaling pathways attributed to mitochondrial membrane permeabilization. Another mechanism for OMMP was discussed at length, indicating that activated proapoptotic proteins of the Bcl-2 family (such as Bax) may assemble into large multimers, thus allowing the release of IMS proteins [171]. The activation of GSK3β has been proven to be involved in intrinsic apoptotic pathways under various stimuli [92]. Huang et al. found that GSK3β activation could promote 120 J/cm^2 He-Ne laser-induced apoptosis by promoting Bax activation [49]. They also demonstrated that the activation of GSK3β by laser treatment was due to the inactivation of Akt, an important upstream negative regulator of GSK3β [49]. This finding suggests the existence and the inactivation of Akt/GSK3β signaling pathway. Furthermore, ROS scavenger completely prevented the inactivation of the Akt/GSK3β pathway, indicating that ROS generation is crucial for the pathway [49]. Together, these findings identify a new and important proapoptotic signaling pathway comprising Akt/GSK3β inactivation for high-intensity red light.

9.2. Signaling pathways involved in self-protection by high-intensity light

Survivin is an important member of the inhibitor of apoptosis (IAP) family that can be upregulated by various proapoptotic stimuli, such as UV, photodynamic therapy, and cisplatin [172, 173]. Chu et al. studied the self-protection mechanism in cancer cells in response to high-intensity He-Ne laser and explored whether survivin was involved in the antitumor mechanism. They reported that 120 J/cm^2 laser activated survivin through phosphorylation on Thr34 in ASTC-a-1 cells [46]. One of the critical requirements for survivin stability and function was recently identified in the phosphorylation on Thr34 by CDK1 [174]. This step has been exploited for anticancer therapy, given that inducible expression of dominant negative mutant survivin (T34A-survivin) resulted in caspase-9-dependent apoptosis [175, 176]. The activity of CDK1 is known to be regulated by cdc25c phosphatase. The abrogation of NADPH oxidase 4 (Nox4) generated ROS resulted in the inhibition of cdc25c protein phosphatase activity [177], which leads to the speculation that the level of cdc25c activity is regulated by ROS. Chu et al. demonstrated that the ROS/cdc25c/CDK1 signaling pathway was essential for the upregulation of survivin by laser treatment [46]. Further study revealed that the upregulation of survivin activity reduced apoptosis by laser irradiation, whereas the downregulation of the activity promoted apoptosis [46]. In addition, they found that activated survivin delayed mitochondrial depolarization, cytochrome *c* release, caspase-9 and Bax activation, all of which were typical proapoptotic events by high-intensity He-Ne laser treatment [44–49]. The authors thus conclude that survivin can mediate self-protection during tumor cell apoptosis by high-intensity red light.

Signal transducer and activator of transcription 3 (STAT3) is an important transcription factor in the modulation of cell proliferation and apoptosis [178, 179]. The antiapoptosis function of STAT3 can be manifested by that activated STAT3 molecules can dimerize and accumulate in the nucleus, where they induce the transcription of numerous target genes, such as those encoding Bcl-2, Bcl-X_L, Mcl-1, survivin, which are important antiapoptotic proteins and have been reported to inhibit Bax activation under various apoptotic treatments [46, 180–182]. Therefore, one of the crosslinks between antiapoptotic and proapoptotic pathways by high-intensity red light is believed to be STAT3, which may act via the transcriptional upregulation of the antiapoptotic proteins to attenuate Bax activation. The study by Sun et al. supports this view, given that the inhibition of STAT3 obviously promoted Bax activation [47]. The expression of survivin has also been found to be regulated by constitutively activated STAT3 in cancer cells [183, 184]. However, the protein level of survivin was unchanged in response to laser treatment, although obvious activation was observed [46]. Sun et al. also investigated the changes in the activities of STAT3 in COS-7 cells irradiated by He-Ne laser at 80 and 120 J/cm^2. They found that STAT3 was significantly activated by laser irradiation in a time- and dose-dependent manner [47]. STAT3 activation attenuated laser-induced apoptosis, as shown by the enhancement of cellular apoptosis by both dominant negative STAT3 and STAT3 RNA interference [46]. They also found Src kinase to be the major positive regulator of laser-induced STAT3 activation. The activation of Src kinase by He-Ne laser has

been reported in their earlier study [169]. ROS generation was essential for the activation of Src/STAT3 pathway upon laser treatment, given that scavenging of ROS totally abrogated the activation [47]. These findings show that the ROS/Src/STAT3 pathway mediates a negative feedback inhibition of high-intensity light-induced apoptosis.

10. Conclusion

In this review, we summarized the studies on the molecular mechanisms in LLLT-induced cell proliferation, differentiation, and apoptosis. A large number of clinical trials for tissue repair currently use LLLT, but a relatively small number of research studies on LLLT have been reported. The wavelengths, dosage schedules, and appropriate conditions of laser irradiation remain unclear. Thus, the basic mechanisms of the biological effects of LLLT are examined to enable physicians to match the laser with clinical practice optimally. The close connection between mitochondrial retrograde signaling and cellular molecular events, such as the activation or suppression of kinases in the cytoplasm and subsequent changes of downstream cascades, is evident. The activation of specific receptors to accept the laser energy, leading to their autophosphorylation and downstream effect is also highlighted.

Acknowledgements. We thank the financial support by the National Basic Research Program of China (2011CB910402; 2010CB732602), the Program for Changjiang Scholars and Innovative Research Team in University (IRT0829), and the National Natural Science Foundation of China (81101741), the National Natural Science Foundation of China (81101741), the Research Fund for the Doctoral Program of Higher Education of China (20114407120002), and the Natural Science Foundation of Guangdong Province, China (S2011040003254).

Received: 29 January 2013, **Revised:** 13 March 2013,
Accepted: 3 April 2013

Published online: 29 April 2013

Key words: Low-level light therapy (LLLT), red to near-infrared (NIR) light, signaling pathway, cytochrome *c* oxidase (CcO), receptor tyrosine kinases (RTKs).

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