Journal of Innovative Optical Health Sciences
Vol. 2, No. 1 (2009) 93–100


World Scientific
www.worldscientific.com



# EXTRAOCULAR CELLULAR PHOTOTRANSDUCTION

LING ZHU[*,†], TIMON CHENG-YI LIU[*,†,‡], MIN WU[*,†],
JIAN-QIN YUAN[*] and TONG-SHENG CHEN[†]

[*]*Laboratory of Laser Sports Medicine*
*South China Normal University*
*Guangzhou, GD 510006, China*

[†]*MOE Key Laboratory of Laser Life Science*
*South China Normal University*
*Guangzhou, GD 510631, China*
[‡]*liutcy@scnu.edu.cn*

Photobiomodulation (PBM) is a modulation of monochromatic light or laser irradiation (LI) on biosystems. It is reviewed from the viewpoint of extraocular phototransduction in this paper. It was found that LI can induce extraocular phototransduction, and there may be an exact correspondence relationship of LI at different wavelengths and in different dose zones, and cellular signal transduction pathways. The signal transduction pathways can be classified into two types so that the Gs protein-mediated pathways belong to pathway 1, and the other pathways such as protein kinase Cs-mediated pathways and mitogen-activated protein kinase-mediated pathways belong to pathway 2. Almost all the present pathways found to mediate PBM belong to pathway 2, but there should be a pathway 1-mediated PBM. The previous studies were rather preliminary, and therefore further work should be done.

*Keywords*: Phototransduction; photobiomodulation; homeostasis.

## 1. Introduction

Phototransduction is the process by which a photon of light captured by a molecule of visual pigment generates an electrical response in a photoreceptor cell.[1] In this pathway, the photoreceptor-specific G protein, transducin, mediates between the membrane visual pigment, rhodopsin, and the effector enzyme, cGMP phosphodiesterase. Extraocular phototransduction was discussed as a mechanism of laser biostimulation in the quasi-hormone model on laser biostimulation (QHML) by Liu *et al.*[2] in 1996. The concept of extraocular circadian phototransduction was put forward by Campbell and Murphy in their 1998 report that 3 hours of bright light exposure to the area behind the knee caused phase shifts of the circadian rhythms of both body temperature and saliva melatonin in humans.[3] However, in 2002, Wright and Czeisler found the absence of circadian phase resetting in response to bright light behind the knees.[4] The first extraocular cellular phototransduction phenomenon was observed in 2001 in low intensity He–Ne laser (LHNL) irradiation-induced respiratory burst of polymorphonuclear neutrophils (PMNs).[5] Since then, many extraocular cellular phototransduction phenomena have been observed.[6–9]

[‡]Corresponding author.

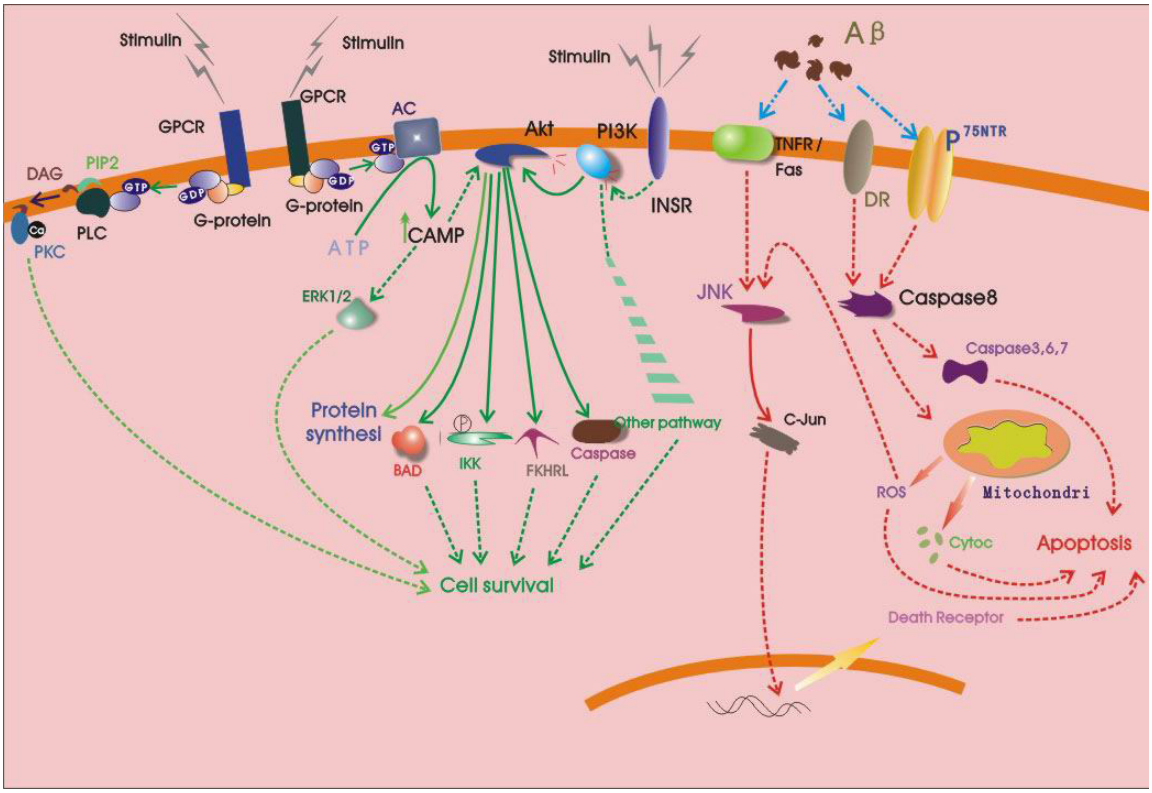


Fig. 1. Signal transduction pathways of amyloid-$\beta$ (A$\beta$)-induced neurons apoptosis and its inhibition.

Extraocular cellular phototransduction has always been found in laser biostimulation[10] or photobiomodulation (PBM).[11] PBM is a modulation of monochromatic light or laser irradiation (LI) on biosystems, which stimulates or inhibits biological functions but does not result in irreducible damage. The LI used in PBM is always low intensity LI (LIL), $\sim$10 mW/cm$^2$. However, moderate intensity LI (MIL), $10^{2\sim3}$ mW/cm$^2$, is of PBM if the radiation time is not so long that it damages organelles or cells. The PBM of LIL and MIL is called LPBM and MPBM, respectively. There are two kinds of pathways mediating cellular PBM: the specific pathway which is mediated by the resonant interaction of LI with endogenous photosensitizers such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidases consisting the membrane-bound cytochrome b558[12] and the non-specific pathway which is mediated by the non-resonant interaction of LI with the proteins in the membrane of cells or organelles.[13,14] The concentration of endogenous photosensitizers is so low that LPBM is mainly mediated by the non-specific pathways, but MPBM is mainly mediated by the specific pathways.[14]

Genetic studies have shown that a dysfunction of amyloid-$\beta(A\beta)$ or tau is sufficient to cause Alzheimer's disease (AD). The signal transduction pathways of A$\beta$-induced cell apoptosis and its inhibition were reviewed and illustrated in Fig. 1. The signal transduction pathways can be generally classified into two types so that the Gs protein-mediated cAMP pathways belong to pathway 1, and the other pathways such as protein kinase Cs (PKCs)-mediated pathways and mitogen-activated protein kinase (MAPK)-mediated pathways belong to pathway 2.[13] Almost all the present pathways found to mediate PBM belong to pathway 2.[5,6,9,15–17] These phototransduction phenomena and their mechanism would be reviewed in this paper.

## 2. Non-Specific Pathway-Mediated Phototransduction

The concentration of endogenous photosensitizers is so low that LPBM is mainly mediated by the non-specific pathways.[14] The non-specific pathways-mediated phototransduction have always been observed in LPBM.

The first extraocular cellular phototransduction phenomenon was observed in our laboratory.[5] We have probed signal transduction pathways of respiratory burst of bovine PMNs which were induced by LHNL at a dose of 300 J/m$^2$ for 100 s by using genistein, a protein tyrosine kinases (PTKs) inhibitor, U-73122, a phospholipase C (PLC) inhibitor, and calphostin C, a PKC inhibitor, and found the inhibitor of PTKs can completely inhibit LHNL-induced PMN respiratory burst, and PLC and PKC inhibitors can obviously reduce it, but not fully inhibit it. These results suggested that PTKs play a key role in LHNL-induced PMN respiratory burst and [PTK–PLC–PKC–NADPH oxidase] signal transduction pathways may be involved in this process.

The second research was done using the cDNA microarray technique.[6] The gene expression profiles revealed that 111 genes of human fibroblasts were regulated by LIL at 628 nm and can be grouped into 10 functional categories. Two types of signaling pathways, the p38 MAPK signaling pathways and the platelet-derived growth factor signaling pathways, were found to be involved in cell growth promoted by the LIL.

The third research was done by using fluorescence resonance energy transfer (FRET) imaging.[9] The human lung adenocarcinoma (ASTC-a-1) cells were irradiated with LHNL at 0.8 J/cm$^2$ in the dark after 24 hours of serum deprivation. Its FRET imaging indicated the PBM was mediated by PKCs. Serum withdrawal to a 1% level was used as a positive apoptosis control for human cells from the anulus *in vitro*.[18] In experiments by Gao *et al.* on effects of LHNL at different doses on serum-starved ASTC-a-1 cells, ASTC-a-1 cells were cultured in DMEM supplemented with 1% serum so that there would be serum-deficiency-induced ASTC-a-1 cell apoptosis. Therefore, the PBM phenomena observed by Gao *et al.* should be PKCs-mediated antiapoptosis.[19]

A$\beta$25-35 induced PC12 cell apoptosis is a cellular model of AD (Fig. 1). In our laboratory, Duan *et al.* has found red light at 640 ± 15 nm from light-emitting diode array (RLED at 640 nm) at 0.09 mW/cm$^2$ for 60 min inhibited A$\beta$25-35-induced PC12 cell apoptosis;[20] Zhu *et al.* further found that A$\beta$25-35 enhanced intracellular cAMP level, and RLED at 640 nm promoted further the enhancement but induced the secretion of the anti-apoptosis factors.[7] Zhang *et al.* found LHNL at 0.52 mW/cm$^2$ for 5–40 min also inhibited A$\beta$25-35-induced PC12 cell apoptosis, and its FRET imaging indicated that the inhibition was mediated by PKC.[8]

## 3. Reactive Oxygen Species-Mediated Signal Transduction

Although excess reactive oxygen species (ROS) are toxic, physiological concentrations of ROS may function as signaling molecules to mediate various responses, including cell migration and growth. An abundance of scientific literature exists demonstrating that oxidative stress influences the MAPK signaling pathways.[21] It has been shown that different ROS levels activate different MAPK pathways, that is, the low-level ROS activates extracellular signal-regulated kinase (ERK)-mediated MAPK — a signal for proliferation, differentiation and survival; the moderate-level ROS activates the stress signals Jun N-terminal kinase (JNK) or p38-mediated MAPK, which leads to cell survival or apoptosis, and the high-level ROS leads to cellular apoptosis or necrosis.[22,23] ROS also increased phosphorylation of Akt kinase in a dose-dependent manner and promoted the rapid activation of phosphatidylinositol 3 kinase (PI3K), and activated nuclear factor-$\kappa$B.[21]

ROS may be produced in response to receptor activation. However, given that ROS are diffusible and short-lived, localizing the ROS signal at the precise sub-cellular compartment is essential for stimulation of specific redox signaling. As a type of localized ROS signal, MIL-induced ROS production has been directly found in PBM. Wu *et al.* have studied the apoptotic effect of moderate intensity He–Ne laser irradiation (MHNL) (200 mW/cm$^2$) on ASTC-a-1 cells, and found immediate generation of mitochondrial ROS following MHNL, reaching a maximum level 60 min after irradiation.[24] Zhang *et al.* use FRET to visualize the dynamic Src activation in HeLa cells immediately after irradiation with MHNL (64.4 mW/cm$^2$), and found that it was ROS that mediated MHNL-induced Src activation.[25]

An Israeli group has studied the effects of MHNL at 177 mW/cm$^2$ on mouse skeletal muscle satellite cells, pmi28 or i28.[15,16,26] The MHNL affected pmi28 proliferation in 5% horse serum (HS) in a bell-shaped manner, with a peak at 3 seconds of irradiation.[26] The 3s-MHNL drives quiescent i28 cells after 36 hours of fetal calf serum (FCS) deprivation into the cell cycle and enhances their proliferation via the PI3K/Akt and Ras/Raf/ERK pathways.[15,16] The ROS-mediated mechanism of

the MHNL effects is supported by the phenomenon the thymidine incorporation of the group irradiated for 10 s in 5% HS was significantly lower than the control, which shows the 10 s-MHNL might induce pmi28 apoptosis.[26]

Schieke *et al.* have found 60 min exposure of cultured human dermal fibroblasts to infrared in the range of 760 nm–1400 nm (infrared-A, IRA) at 333 mW/cm$^2$ (MIL) induced the expression of matrix metalloproteinase 1 at the mRNA and protein level via activation of MAPK/ERK1/2. P38 MAKP was also activated but did not mediate the expression of matrix metalloproteinase 1, which might be due to the long irradiation time so that the ROS activates the stress signals.[27] Miyata *et al.* have studied the effects of a Ga-Al-As semiconductor 810 nm laser 90 s-irradiation at 231 mW/cm$^2$ (MIL) on human dental pulp-derived fibroblast-like cells (dental pulp cells) obtained by the primary culture of human dental pulp tissues extracted from third molar teeth, and found that the MIL activated MAPK/ERK, but did not activate the stress signals p38 MAPK and JNK in human dental pulp cells.[28]

Ultraviolet A (UVA) (320 nm–400 nm) exposure is associated with increased production of ROS and MAPK activation.[29] Low and moderate intensity UVA activated MAPK/ERK and p38/JNK MAPK, respectively.[30–32] The effects of UVA (360 nm–400 nm) at 40–44 mW/cm$^2$ and 12 minutes approximately and singlet oxygen are similar in their activation of MAPKs in human skin fibroblasts. In this study, the UVA induced a rapid transient activation of p38 kinase and JNKs, but had little effect on ERKs. The UVA-induced phosphorylation of p38 kinase was diminished in the presence of $^1O_2$ scavengers, sodium azide, or imidazol, but not in the presence of hydroxyl radical scavengers, mannitol, or dimethylsulfoxide, indicating that $^1O_2$ may be a mediator of UVA-induced effects in these cells.[32] In melanocytes pre-treated with *N*-acetyl-l-cysteine, a thiol-containing compound and a general free radical scavenger, UVA (365 nm, 0.2 mW/cm$^2$, 500 s)-induced activation of ERKs was inhibited. In the pre-treated melanocytes, no DNA damaged products were detected, suggesting that the activation of ERKs occurred due to upstream signals originating from ROS or from activated tyrosine kinase receptors, but not due to signals originating from damaged DNA.[30] In NCTC 2544 keratinocytes, experimental quenching or enhancing of singlet oxygen levels also indicated an involvement of ROS and MAPK/ERK activation in UVA (4 mW/cm$^2$, 25, 50, 75 and 100 min)-induced activation of AP-1.[31]

## 4. Homeostatic Regulation

Homeostasis is a term that refers to constancy in a system. If a biosystem is in homeostasis, it normally functions. There are two kinds of regulation on a biosystem: homeostatic regulation and developmental regulation. For homeostatic regulation, there is no regulation on the biosystem in homeostasis, but there is regulation on the biosystem far from homeostasis. The developmental regulation can disrupt the homeostasis and change the homeostatic processes from one to another. LPBM is a homeostatic regulation so that there is no PBM on a biosystem in homeostasis and there is PBM on a biosystem far from homeostasis.[33] MPBM-induced low-level ROS is a homeostatic regulation, but MPBM-induced high-level ROS is a developmental regulation. For convention, LPBM and the MPBM which induces low-level ROS is called homeostatic PBM (hPBM), and the MPBM which induces high-level ROS is called developmental PBM (dPBM).

MPBM-induced antiapoptosis has been observed for serum-free-induced apoptosis of myofibers and their adjacent cells, as well as cultured myogenic cells with MHNL (177 mW/cm$^2$, 3 s),[34] and nutritional deficiency induced Cho K-1 cell apoptosis with a semiconductor laser irradiation (810 nm, 1990 mW/cm$^2$, 1 s).[35] Both Shefer *et al.* and Carnevalli *et al.* have found MIL-induced proliferation (homeostatic process 1) of the cells in serum-deprivation-induced apoptosis (homeostatic process 2),[34,35] but it was mediated by MIL-induced ROS and its MAPK activation.[34] In these cases, MPBM can change homeostatic processes from one to another so that it is not a homeostatic regulation.

In most cases, MPBM is not a homeostatic regulation. The respiration burst of PMNs from 20 healthy male volunteers is in homeostasis, but can be attenuated by the infrared diode laser (GaAlAs), 830 nm continuous wave at 150 mW/cm$^2$.[36] For NCTC 2544 keratinocytes in 10% FCS, the MAPK/ERK was strongly activated, but can be further activated by UVA (4 mW/cm$^2$, 75 min).[31] Dexamethasone (DEX) might induce G1 cell cycle arrest (homeostatic process 1),[37] but MPBM (GaAlAs diode 780 nm laser, 250 mW/cm$^2$, 12 s) acts as a proliferative stimulus (homeostatic process 2) on osteoblast-like cells, even under the influence of DEX.[38] Agkistrodon contortrix

laticinctus (ACL) myotoxin might induce muscle injury (homeostatic process 1), in which regeneration (homeostatic process 2) cannot be promoted by hPBM (GaAs diode 904 nm laser, 7.5 mW/cm$^2$, 2.2 or 8 min),[39] but can be promoted by non-homeostatic MHNL (371 mW/cm$^2$, 7 s).[40]

Intravascular low energy laser therapy (ILELT) is an intravascular application of MIL. MPBM might promote ROS generation, but the concentration of endogenous photosensitizers is so low and the radiation time is so short that the PBM in ILELT is a homeostatic regulation.[33] Wang *et al.* have studied MHNL of extracorporeally circulatory blood on ATP phosphohydrolase (ATPase) activities of erythrocyte membrane in 13 cases of patients with insulin-dependent diabetes mellitus.[41] The results showed that ATPase were significantly lower in insulin-dependent diabetes mellitus than that in control healthy subjects in FSH ($P < 0.01$); MPBM could markedly activate the $Na^+/K^+$-ATPase, $Ca^{2+}/Mg^{2+}$-ATPase of the patients with insulin-dependent diabetes mellitus ($P < 0.05$ or 0.01), but could not significantly affect the ones of the control ($P > 0.05$).

There is no hPBM on a biosystem in homeostasis. It might be the cause why both studies by Campbell and Murphy[3] and the one by Wright and Czeisler[4] are reasonable. In Campbell and Murphy's experiment,[3] the ambient light less than 20 lux might disturb sleep homeostasis so that there was PBM on the popliteal region and then on circadian rhythms through meridian. However, the participants in Wright and Czeisler's experiment[4] were shielded from ocular light (0 lux) during extraocular light exposure so that they might be in sleep homeostasis and no PBM was found.

## 5. Biological Information Model of Photobiomodulation

As to phototransduction in laser biostimulation, we have put forward QHML.[2] After laser biostimulation was extended to PBM,[11] we modified QHML and put forward the biological information model of photobiomodulation (BIMP).[13,14] According to BIMP, LI is the input, and the LI-induced cellular functions are the observed output. As the LI-induced cellular functions are mediated by pathway 1 or 2, BIMP have found the correspondence relationship of LI and the signal transduction pathways for hPBM on the cells far from homeostasis and dPBM on cells. According to BIMP, the color of LI from UVA to IRA can be classified into two types: cold colors such as green, blue, violet, or UVA; and hot colors such as IRA, red, yellow, or orange. The dose zones are named $1, 2, \ldots$ beginning from the lowest dose. The LI at the same wavelength but at different doses in the same dose zone has PBM similar to one another, but the one in different dose zones has PBM different from the other. The correspondence relationship of LI at different wavelength in the $n$th dose zone and signal transduction pathways was then called BIMP $n$. In the $(2n + 1)$th $(n = 0, 1, 2, \ldots)$ dose zone, the cold LI and hot LI activate pathway 2 and 1, respectively, according to BIMP $(2n+1)$. In the $2n$th $(n = 1, 2, \ldots)$ dose zone, the cold LI and hot LI activate pathway 1 and 2, respectively, according to BIMP $2n$.

For the inhibition of A$\beta$-induced PC12 cell apoptosis (Fig. 1), Zhu *et al.*[7] found the PBM of RLED at 640 nm at 0.09 mW/cm$^2$ for 60 min (dose zone 1) was mediated by cAMP (BIMP 1 holds), but Zhang *et al.*[8] found the PBM of LHNL at 0.52 mW/cm$^2$ for 5–40 min (dose zone 2) was mediated by PKC (BIMP 2 holds). BIMPs 1–3 hold for MAPK–mediated PBM of UVA (cold color) on fibroblasts.[29] BIMP 2 holds for the PBM of LHNL (hot color) on PMNs and ASTC-a-1 cells, and the PBM of 628 nm light (hot color) on fibroblasts.[5,6,9,19] BIMP 4 holds for the PBM of MHNL (hot color) on skeletal muscle satellite cells and skeletal muscle myoblasts, and the PBM of IRA (hot color) on fibroblasts.[15,16,27] Almost all the found pathways of extraocular cellular phototransduction belong to pathway 2.

Although there were a few studies on extraocular cellular phototransduction, there have been much more studies on cellular PBM which support BIMP.[2,13,14] Of course, the previous studies on extraocular cellular phototransduction were rather primary, and therefore further work should be done.

## 6. Discussion

As has been reviewed in this paper, LI can induce extraocular phototransduction. Moreover, BIMP has put forward the exact correspondence relationship of LI at different wavelengths and in different dose zones and signal transduction pathways for hPBM on the cells far from homeostasis and dPBM on cells. This BIMP can be used to predict PBM of LI on a biosystem.

There might be PBM on bacterial virulence factors or exotoxins–induced PMN dysfunction

according to BIMP. Any response to an external stimulus may have profound consequences for the biology and even the viability of a cell. However, in the case of inflammatory responses triggered by bacterial or viral components and inflammatory cytokines such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$) or interleukin-1$\beta$, the consequences of excessive or sustained transcription may be far more important because they may affect the entire tissue or even the entire organism. Inflammation is a chemical storm in which a large number of active mediators are released from cells in the affected area that acts both on the neighboring cells and distant sites (including the vital organs and the brain) after having been transported from the site of production through blood circulation. As a possible mechanism, bacterial virulence factors or exotoxins might inactivate MAPK which plays an important role in PMN anti-microbial functions such as the NADPH oxidase in phagosomes and ROS-induced neutrophil extracellular traps (NETs) by modifying the enzyme MAPK kinase (MAPKK) with acetyl moieties or removing phosphate groups from phosphothreonine but not from the phosphotyrosine residue in the activation loop of MAPKs,[42–44] or induce PMN apoptosis or necrosis, and then lead to persistent infection.[45,46] According to BIMP, PBM might help PMN to seize control. Bacterial virulence factors or exotoxins might inhibit PMN functions by inactivating MAPK, but LIL might recover PMN functions by activating PTK.[5] Treatment of PMNs with either anti-oxidants or synthetic cAMP analogues significantly abrogated pyocyanin-induced PMN apoptosis.[45] PBM might do the same thing according to BIMP. PBM-induced antiapoptosis has been also observed for A$\beta$-induced PC12 cell apoptosis and nutritional deficiency-induced Cho K-1 cell apoptosis.[20,35]

## 7. Conclusion

LI can induce extraocular phototransduction. There may be an exact correspondence relationship of LI at different wavelengths and in different dose zones and signal transduction pathways for hPBM on the cells far from homeostasis and dPBM.

## Acknowledgments

Our study was supported by the National Science Foundation of China (60878061, 60478048, 60178003, and 60278012); National Postdoctoral Foundation of China (20070420143); the Opening Project of MOE Key Laboratory of Laser Life Science, South China Normal University, Guangzhou 510631, China.

## References

1. Arshavsky, V. Y., Lamb, T. D. and Pugh, E. N. Jr., "G proteins and phototransduction," *Annu. Rev. Physiol.* **64**, 153–187 (2002).
2. Liu, T. C. Y., Gao, Y. Q. and Liu, S. H., "Light-cell interaction: Quasi-hormone model and time theory," *Proc. SPIE* **2887**, 140–151 (1996).
3. Campbell, S. S. and Murphy, P. J., "Extraocular circadian phototransduction in humans," *Science* **279**(5349), 396–399 (1998).
4. Wright, K. P. and Czeisler, C. A., "Absence of circadian phase resetting in response to bright light behind the knees," *Science* **297**(5581), 571 (2002).
5. Duan, R., Liu, T. C. Y., Li, Y., Guo, H. and Yao, L. B., "Signal transduction pathway involved in low intensity He–Ne laser-induced respiratory burst in bovine neutrophils: A potential mechanism of low intensity laser biostimulation," *Laser Surg. Med.* **29**(2), 174–178 (2001).
6. Zhang, Y. O., Song, S. P., Fong, C. C., Tsang, C. H., Yang, Z. and Yang, M. S., "CDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light," *J. Invest. Dermato.* **120**(5), 849–857 (2003).
7. Zhu, L., Hu, B. and Liu, T. C. Y., "Mechanism of inhibition of red light on amyloid beta 25–35 peptides induced PC12 cell apoptosis," *Laser Surg. Med.* **40**(S20), 108 (2008).
8. Zhang, L., Xing, D., Zhu, D. and Chen, Q., "Low-power laser irradiation inhibiting Abeta25–35-induced PC12 cell apoptosis via PKC activation," *Cell Physiol. Biochem.* **22**(1–4), 215–222 (2008).
9. Gao, X., Chen, T., Xing, D., Wang, F., Pei, Y. and Wei, X., "Single cell analysis of PKC activation during proliferation and apoptosis induced by laser irradiation," *J. Cell Physiol.* **206**(2), 441–448 (2006).
10. Gamaleia, N. F., Shishko, E. D. and Ianish, I. V., "New data on the photosensitivity of the animal cell and the mechanism of laser biostimulation," *Dokl. Akad. Nauk. SSSR* **273**(1), 224–227 (1983).
11. Friedmann, H. and Lubart, R., "Competition between activating and inhibitory processes in photobiology," *Proc. SPIE* **2630**, 60–64 (1996).
12. Lubart, R., Eichler, M., Lavi, R., Friedman, H. and Shainberg, A., "Low-energy laser irradiation promotes cellular redox activity," *Photomed. Laser Surg.* **23**(1), 3–9 (2005).
13. Liu, T. C. Y., Jiao, J. L., Duan, R., Li, Y., Yeung, Y. Y. and Liu, S. H., "Membrane mechanism of low intensity laser biostimulation on a cell,"

Simunovic, Z. (ed). *Lasers in Medicine, Surgery and Dentistry* (European Medical Laser Association, Croatia, 2003).
14. Liu, T. C. Y., Jiao, J. L., Xu, X. Y., Liu, X. G., Deng, S. X. and Liu, S. H., "Photobiomodulation: Phenomenology and its mechanism," *Progr. Biomed. Opti. Imag.* **5**(33), 185–191 (2005).
15. Shefer, G., Oron, U., Irintchev, A., Wernig, A. and Halevy, O., "Skeletal muscle cell activation by low-energy laser irradiation: A role for the MAPK/ERK pathway," *J. Cell Physiol.* **187**, 73–80 (2001).
16. Shefer, G., Barash, I., Oron, U. and Halevy, O., "Low-energy laser irradiation enhances de novo protein synthesis via its effects on translation-regulatory proteins in skeletal muscle myoblasts," *Biochim. Biophys. Acta* **1593**, 131–139 (2003).
17. Khrenov, M. O., Cherenkov, D. A., Glushkova, O. V., Novoselova, T. V., Lunin, S. M., Parfeniuk, S. B., Lysenko, E. A., Novoselova, E. G. and Fesenko, E. E., "The role of transcription factors in the response of mouse lymphocytes to low-level electromagnetic and laser radiations," *Biofizika* **52**(5), 888–892 (2007).
18. Gruber, H. E., Norton H. J. and Hanley, E. N. Jr., "Anti-apoptotic effects of IGF-1 and PDGF on human intervertebral disc cells *in vitro*," *Spine* **25**(17), 2153–2157 (2000).
19. Wu, M. and Liu, T. C.-Y., "Single-cell analysis of protein kinase C activation during anti-apoptosis and apoptosis induced by laser irradiation," *Photomed. Laser Surg.* **25**(2), 129–130 (2007).
20. Duan, R., Zhu, L., Liu, T. C., Li, Y., Liu, J., Jiao, J., Xu, X., Yao, L. and Liu, S., "Light emitting diode irradiation protect against the amyloid beta 25–35 induced apoptosis of PC12 cell *in vitro*," *Laser Surg. Med.* **33**(3), 199–203 (2003).
21. Dröge, W., "Free radicals in the physiological control of cell function," *Physiol. Rev.* **82**(1), 47–95 (2002).
22. Bladier, C., Wolvetang, E. J., Hutchinson, P., de Haan, J. B. and Kola, I. "Response of a primary human fibroblast cell line to $H_2O_2$: Senescence-like growth arrest or apoptosis?" *Cell Growth Differ.* **8**(5), 589–598 (1997).
23. Owuor, E. D. and Kong, A. N., "Antioxidants and oxidants regulated signal transduction pathways," *Biochem. Pharmacol.* **64**(5–6), 765–770 (2002).
24. Wu, S., Xing, D., Wang, F., Chen, T. and Chen, W. R., "Mechanistic study of apoptosis induced by high-fluence low-power laser irradiation using fluorescence imaging techniques," *J. Biomed. Opt.* **12**(6), 064015 (2007).
25. Zhang, J., Xing, D. and Gao, X., "Low-power laser irradiation activates Src tyrosine kinase through reactive oxygen species-mediated signaling pathway," *J. Cell Physiol.* **217**(2), 518–528 (2008).
26. Ben-Dov, N., Shefer, G., Irintchev, A., Wernig, A., Oron, U., Halevy, O. and Irinitchev, A., "Low-energy laser irradiation affects satellite cell proliferation and differentiation *in vitro*," *Biochim. Biophys. Acta* **1448**(3), 372–380 (1999).
27. Schieke, S., Stege, H., Kurten, V., Grether-Beck, S., Sies, H. and Krutmann, J., "Infrared-A radiation-induced matrix metalloproteinase 1 expression is mediated through extracellular signal-regulated kinase 1/2 activation in human dermal fibroblasts," *J. Invest. Dermatol.* **119**(6), 1323–1329 (2002).
28. Miyata, H., Genma, T., Ohshima, M., Yamaguchi, Y., Hayashi, M., Takeichi, O., Ogiso, B. and Otsuka, K., "Mitogen-activated protein kinase/extracellular signal-regulated protein kinase activation of cultured human dental pulp cells by low-power gallium-aluminium-arsenic laser irradiation," *Int. Endod. J.* **39**(3), 238–244 (2006).
29. Bode, A. M. and Dong, Z., "Mitogen-activated protein kinase activation in UV-induced signal transduction," *Sci. STKE* **RE2**, 167 (2003).
30. Yanase, H., Ando, H., Horikawa, M., Watanabe, M., Mori, T. and Matsuda, N., "Possible involvement of ERK 1/2 in UVA-induced melanogenesis in cultured normal human epidermal melanocytes," *Pigment Cell Res.* **14**(2), 103–109 (2001).
31. Djavaheri-Mergny, M. and Dubertret, L., "UV-A-induced AP-1 activation requires the Raf/ERK pathway in human NCTC 2544 keratinocytes," *Exp. Dermatol.* **10**(3), 204–210 (2001).
32. Klotz, L. O., Pellieux, C., Briviba, K., Pierlot, C., Aubry, J. M. and Sies, H., "Mitogen-activated protein kinase (p38-, JNK-, ERK-) activation pattern induced by extracellular and intracellular singlet oxygen and UVA," *Eur. J. Biochem.* **260**(3), 917–922 (1999).
33. Liu, T. C. Y., Yuan, J. Q., Wang, Y. F., Xu, X. Y. and Liu, S. H., "Cellular rehabilitation of photobiomodulation," *Proc. SPIE*, **6534**, 653403-1∼-6 (2007).
34. Shefer, G., Partridge, T. A., Heslop, L., Gross, J. G., Oron, U. and Halevy, O., "Low-energy laser irradiation promotes the survival and cell cycle entry of skeletal muscle satellite cells," *J. Cell Sci.* **115**(Pt 7), 1461–1469 (2002).
35. Carnevalli, C. M. M., Soares, C. P., Zangaro, R. A., Pinheiro, A. L. B. and Silva, N. S., "Laser light prevents apoptosis in Cho K-1 cell line," *J. Clin. Laser Med. Surg.* **21**(4), 193–196 (2003).
36. Fujimaki, Y., Shimoyama, T., Liu, Q., Umeda, T., Nakaji, S. and Sugawara, K., "Low–level laser irradiation attenuates production of reactive oxygen species by human neutrophils," *J. Clin. Laser Med. Surg.* **21**(3), 165–170 (2003).

37. Funakoshi, Y., Shiono, H., Inoue, M., Kadota, Y., Ohta, M., Matsuda, H., Okumura, M. and Eimoto, T., "Glucocorticoids induce G1 cell cycle arrest in human neoplastic thymic epithelial cells," *J. Cancer Res. Clin. Oncol.* **131**(5), 314–322 (2005).
38. Fujihara, N. A., Hiraki, K. R. and Marques, M. M., "Irradiation at 780 nm increases proliferation rate of osteoblasts independently of dexamethasone presence," *Laser Surg. Med.* **38**(4), 332–336 (2006).
39. Oliveira, N. M., Parizzotto, N. A. and Salvini, T. F., "GaAs (904 nm) laser radiation does not affect muscle regeneration in mouse skeletal muscle," *Laser Surg. Med.* **25**(1), 13–21 (1999).
40. Amaral, A. C., Parizotto, N. A. and Salvini, T. F., "Dose-dependency of low-energy He–Ne laser effect in regeneration of skeletal muscle in mice," *Laser Med. Sci.* **16**(1), 44–51 (2001).
41. Wang, T. D., Dong, W. R., Xiao, Y. Q., Lin, Y. Q. and Xuan, G. H., "Effects of low-energy He–Ne laser irradiation of extracorporeally circulatory blood on ATPase activities of erythrocyte membrane in patients with IDDM," *Chinese Laser J.* **13**(6), 324–326 (1992) (in Chinese).
42. Fuchs, T. A., Abed, U., Goosmann, C., Hurwitz, R., Schulze, I., Wahn, V., Weinrauch, Y., Brinkmann, V. and Zychlinsky, A., "Novel cell death program leads to neutrophil extracellular traps," *J. Cell Biol.* **176**(2), 231–241 (2007).
43. Mukherjee, S., Keitany, G., Li, Y., Wang, Y., Ball, H. L., Goldsmith, E. J. and Orth, K., "Yersinia YopJ acetylates and inhibits kinase activation by blocking phosphorylation," *Science* **312**(5777), 1211–1214 (2006).
44. Li, H., Xu, H., Zhou, Y., Zhang, J., Long, C., Li, S., Chen, S., Zhou, J. M. and Shao, F., "The phosphothreonine lyase activity of a bacterial type III effector family," *Science* **315**(5814), 1000–1003 (2007).
45. Usher, L. R., Lawson, R. A., Geary, I., Taylor, C. J., Bingle, C. D., Taylor, G. W. and Whyte, M. K., "Induction of neutrophil apoptosis by the Pseudomonas aeruginosa exotoxin pyocyanin: A potential mechanism of persistent infection," *J. Immunol.* **168**(4), 1861–1868 (2002).
46. Russo, T. A., Davidson, B. A., Genagon, S. A., Warholic, N. M., Macdonald, U., Pawlicki, P. D., Beanan, J. M., Olson, R., Holm, B. A. and Knight, P. R. III, "*E. coli* virulence factor hemolysin induces neutrophil apoptosis and necrosis/lysis *in vitro* and necrosis/lysis and lung injury in a rat pneumonia model," *Am. J. Physiol. Lung Cell Mol. Physiol.* **289**(2), L207–L216 (2005).