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Low-dose Light Therapy on Host Immune Response: Physiological Effects and Mechanisms of Action*

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Abstract The effect of low-dose light (LDL) therapy, commonly using red and near infrared (NIR) light (600–1 100 nm), has gained attention in recent years as a relatively noninvasive technique in modulating the tissue metabolic system, nervous system, blood circulation system and immune system. The progress in the basic science fields of bioenergetics and photobiology has propelled LDL into the therapeutic revolution. The immune cells including macrophages, mast cells, neutrophils and lymphocytes as responder cells by LDL have been studied in the animals and humans with producing cytokines and protective proteins. The paper will review the mechanisms of immune action of LDL at the molecular, cellular, and tissue levels on mammalian.

Key words Low-dose light, inflammatory reaction, lymphedema, oropharyngeal mucositis, radiation dermatitis, anti-infection and anti-tumor

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Since 1960s, Mester [1] discovered the biological effects of low-dose light (LDL) acting on biological tissue, LDL had gained attention by more and more researchers as a novel scientific approach, which induced nonthermal and nondestructive biological reactions, for therapeutic applications in a variety of experimental conditions. Patients, researchers and clinicians around the world are devoting attention to the potential therapeutic applications of LDL in immunity and other medical fields that have traditionally had a limited therapeutic contribution to patient care.

Recently, the use of LDL has extended beyond the realms of wound healing and pain, and recent research supports its potential applications in neurodegenerative diseases [2–3], type 2 diabetes [4], osteogenic differentiation [5] and thrombocytopenia [6–7]. However, the exact mechanisms of those effects induced by LDL are poorly understood, but the mechanism is probably to be photochemically related. Karu, a pioneer in the LDL field, proposed that cytochrome c oxidase (CcO) was the photoacceptor and signal transducer [8–9], which affected the mitochondrial electron transport system [10] and the biological regulation of reactive oxygen species (ROS) [11–14], adenosine triphosphate (ATP) [15], nitric oxide (NO)[16–17] and intracellular Ca^{2+} [18–19], and further affected the ailment process including inflammation and cytokine and growth factor release (Figure 1). The article summarizes the available literature on molecular mechanisms of the protective or enhancing

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effects of LDL in a number of pathogenic conditions including inflammatory reaction, cancer therapy-induced complications (lymphedema, mucositis and dermatitis), and anti-infection and anti-tumor effects.

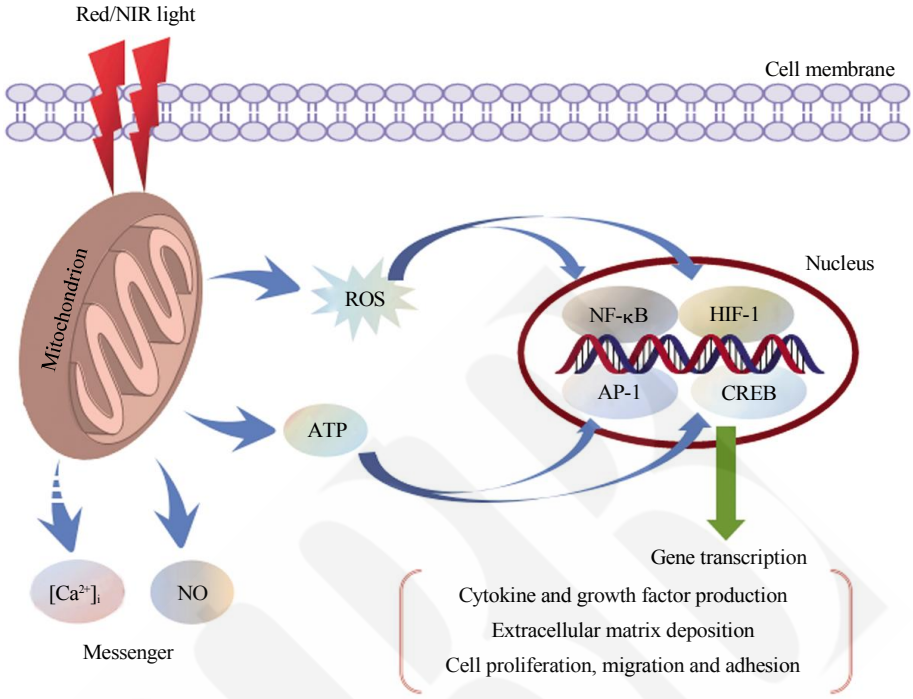

Fig. 1 The mechanism model of LDL

Schematic diagram shows the red or near infrared (NIR) light is absorbed by the photoacceptors (e.g. cytochrome c oxidase) localized in mitochondria. During the process, ROS and ATP production are increased, NO is released, and intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is elevated. These responses may ultimately lead to changes in cell morphology and function *via* activating some transcription factors [e.g., nuclear factor-κB (NF-κB), hypoxia inducible factor-1 (HIF-1), activator protein-1 (AP-1) and cAMP-response element binding protein (CREB)].

1 Reduced inflammatory reaction by LDL

1.1 LDL regulates the secretion of cytokines

Inflammatory reaction is the physiological reaction caused by the stimulation of trauma, bleeding or pathogen infection. It is the innate immune defensive reaction of immune cells and inflammatory factors. Over the years, several studies on humans and animals have shown that LDL has modulatory effects on inflammatory markers of IL-1β, IL-6, IL-8, TNF-α and prostaglandin E2 (PGE2), and relieves the inflammatory process (edema, necrosis, neutrophil cell influx, hemorrhagic formation). According to Chang *et al*.[20], inflammatory symptoms are caused by pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α. Study by de Almeida and colleagues [21] reported LDL significantly decreased the inflammatory mediator levels of IL-1β, IL-6 and TNF-α in acute skeletal muscle injury. Similarly, LDL could reduced those cytokine production in the pathophysiology of osteoarthritis (OA)[22]. 25 J/cm^2 LDL also decreased the level of pro-inflammatory cytokines of TNF-α, IL-1β, and IL-8 in rheumatoid arthritis synoviocytes [23]. Additionally, the trauma-induced pro-inflammatory state assessed by IL-6 and IL-10 was prevented LDL[24]. In parallel, LDL prevented trauma-induced reduction in BDNF and VEGF, vascular remodeling and fiber-proliferating markers. More recently, LDL has been shown very interesting effects on modulation of cyclooxygenase 2 (COX-2). (880 ± 10) nm LDL decreased the inflammatory cell influx and mRNA levels of COX-2 just in initial phase of *Achilles tendinitis* [25]. COX-2 mRNA expressions were also significantly decreased by treatment with 904 nm LDL[26]. Almeida *et al*[27]. also found that 904 nm LDL in 1.0 J group significantly decreases skeletal muscle

damage through less COX-2-derived gene expression. However, the precise mechanism by which light affects the cytokines is not yet known. LDL probably modulated the pro-inflammatory cytokines by reducing the IL-1β and COX-2 mRNA expression and consequently reduced PGE2 levels by reducing cell migration and the quantity of macrophages, neutrophils, and mast cells in the injured tissue [28-29]. Macrophages and mast cells secrete the cytokine of IL-1β, which in turn recruits COX-2, an enzyme which converts arachidonic acid into PGE2 [30-31]. From the above we see that reduced inflammatory reaction by LDL may depend not only on the light irradiation parameters (wave length, radiation dose), but also on pathological condition of the study model.

1.2 LDL increases MMPs and PA activity

Matrix metalloproteinases (MMPs), which are considered to degrade the components of the complex extracellular matrix, and plasminogen activator (PA), which is implicated in the plasminogen-plasmin proteolytic system, play a key role in extracellular matrix degradation, synthesis of kinin and fibrinolysis in the process of inflammation. Both 660 nm and 780 nm verified by Cury and colleagues could decrease MMP2 activity in a model of ischemic skin flap in rats [32]. And MMP9 activity was decreased on induced arthritis in the temporomandibular joint with 830 nm LDL treatment [33]. Additionally, several human and animal studies have shown that LDL with red to infrared wavelengths reduces the release of PA[34-35]. Thus, LDL probably modulates PA activity to degrade cell adhesive molecules and extracellular matrix proteins[36] through activation of MMPs [37]. Furthermore, plasminogen activates the kinin cascade *via* converting prekallikrein into kallikrein[38].

1.3 LDL modulates the immune cell activity

LDL also modulates the activity of mast cells, macrophages, neutrophils and lymphocytes to reduce the inflammatory process. Red LDL has been shown to induce the mast-cell degranulation [39-40], leading to the release of a multiple chemical mediators (VEGF121, VEGF165, VEGF189 and VEGF206) [41], which are related to vasodilation and vascular proliferation, and can optimize the inflammatory process[42]. Song *et al*.[43] reported that in rats LDL altered the macrophage polarization from M1 state to M2 state, which dampens the inflammatory and adaptive Th1 responses[44]. Other studies observed that LDL reduced in the absolute number of macrophages and neutrophils compared with the injury group [22, 45], resulting in decrease of secretion of pro-inflammatory cytokines and enzymes such as IL-6 and TNF-α involved in driving the inflammatory response[46]. For lymphocytes, LDL could activate directly its proliferation *in vivo*[47-49], leading to secrete anti-inflammatory cytokine of IL-10, which inhibited the production of pro-inflammatory cytokines and prevented macrophage and neutrophil infiltration into the injury [50]. Additionally, the presence of hemoglobin amplified the proliferation effect of LDL irradiation on lymphocyte culture [49]. Hemoglobin could catalyze free radical formation in the presence of hydrogen peroxide as in the Fenton reaction[51]. LDL at a given wavelength may promote ROS formation in a hemoglobin rich environment, and then the generation of an oxidative environment has a strong influence on T lymphocytes[52].

2 Reduced cancer therapy-induced complications by LDL

Not only drug resistance caused by chemotherapy and molecular targeted therapy is a major obstacle to the current tumor treatment [53-55], but also cancer therapy-induced complications are a common clinical problem. In human researches, LDL is widely studied to ameliorate cancer therapy-induced complications. Upper limb lymphedema, which is the result of the regional accumulation of amounts of protein-rich interstitial fluid caused by impaired lymph drainage[56], is a common complication of breast cancer surgery. To date, researchers have reported that LDL is benefit for postmastectomy lymphoedema [57-59] through presumably increasing microcirculation[60-61] to reduce the excessive amounts of tissue protein and fluid, and finally improve the limb performance. In particular, a study indicated that LDL was often within hours of irradiation as an efficacy treatment of lymphedema [62]. However, the molecular mechanisms of LDL in lymphoedema tissue remain elusive. At the microcirculatory level, the stimulatory/protective effects of LDL is achieved by modulating the angiogenic factor production by lymphocytes [63] and endothelial cells [64] *in situ*, then to accelerate spontaneous angiogenesis[65].

Oropharyngeal mucositis (OM), known as most painful oral lesions[66], is a major complication of head-and-neck oncologic therapy[67]. LDL was confirmed to be effective in controlling of OM caused by various cancer therapies [68-71]. Studies have unambiguously

demonstrated that the mucositis pathogenesis are complex and associate with pro-inflammatory cytokines[72–73], microvascular injury[74], and extracellular matrix alterations[75–76]. Silva *et al*.[77] showed that LDL increased the levels of IL-10 in blood plasma and MMP-2 in saliva on 7th chemoradiotherapy-induced OM. Study by Oton-Leite[78] demonstrated that LDL significantly reduced salivary concentration of IL-6, EGF and VEGF during radiotherapy session. It seemingly suggested the mechanism of LDL-reduced the severity of OM caused by cancer therapy was linked to the modulation of pro- or anti-inflammatory cytokines, MMPs or growth factors. In an animal model of OM, studies have reported that LDL decreased the expression of COX-2[79], which elicits the synthesis of pro-inflammatory prostaglandins in malignant and inflamed tissues, and reduces the infiltration of neutrophils in inflamed tissues[80], thus further supporting the anti-inflammatory effect.

Radiation dermatitis (RD) occurs in a majority of breast cancer patients who receive radiotherapy and may exhibit symptoms such as redness, itching, dryness, and peeling skin[81]. DeLand *et al*.[82] showed that LDL reduced the incidence of skin reactions in breast cancer patients treated by radiotherapy postlumpectomy. Schindl and co-workers[83–84] demonstrated that LDL healed a long-lasting radiotherapy-induced skin ulcer. Regarding the mechanism of action, LDL have been demonstrated to induce neoangiogenesis *via* the activation of ERK/Sp1 pathway *in vitro*[64] and *in vivo*[83], to accelerate collateral circulation and enhance microcirculation[85], then to possibly improve skin circulation[86], and finally to reduce tissue damage caused by ischemia[87]. An alternative explanation of LDL-induced neoangiogenesis is *via* ROS[88], which lead to increase the level of HIF-1[89], then regulate the transcription of VEGF[90–91]. Additionally, LDL could modulate certain cellular proliferation and migration[92–94], and induce the secretion of fibroblast growth factor family involved in tissue repair[95]. Altogether, these findings suggested a beneficial effect of LDL on cancer therapy-induced complications and patients' quality of life in cancer patients.

3 Enhanced anti-infection and anti-tumor effect by LDL

Recently, the effect of LDL-induced anti-infection was further confirmed by Lu *et al*.[96]. They showed that LDL enhanced anti-infection ability *in vivo* to improve the macrophage phagocytic activity through Rac1-mediated signaling pathway. Simultaneously, Karunarathne *et al*.[97] showed that 488-, 515-, or 595-nm wavelength light could initiate macrophage migration. The production of pro-inflammatory cytokines (TNF-α and IL-1) by murine peritoneal macrophages *in vitro* and *in vivo* was raised by LDL accompanied with increasing the ability of bacterial killing[98]. In neutrophils, LDL also enhanced the ability to kill *Candida albicans via* the generation of ROS[99]. In a wound infection model, it was demonstrated LDL significantly decreased the incidences of microbial flora (*Staphylococcus aureus* and *Bacillus subtilis*) compared with placebo burns[100], and increased the amount of blood vessels, remodeled the collagen matrix, and matured collagen fibers in infected wounds[101].

The obvious parabola features of the biological effect of LDL on cells have been demonstrated by several studies[102–103]. With an increase of light output energy, its moderating action on cells can be increased gradually, but when the light output energy exceeds a certain threshold value, the inhibition effect of LDL emerges[104]. According to Lu and colleagues[105], high fluence, low-dose light (HF-LDL) was reported to kill tumor cell, leading to activate macrophages to create an immune memory response. A few molecular mechanisms revealed that HF-LDL-induced apoptotic tumor cells enhanced the pro-inflammatory cytokines (TNF-α and NO) production in macrophage, through upregulating NF-κB activity[106–107]. Those studies may provide an effective therapeutic approach to induce an antitumor immune response after HF-LDL treatment.

4 Conclusion

In conclusion, LDL has strong evidences for many beneficial effects on inflammatory reaction, cancer therapy-induced complications, and anti-infection and anti-tumor in animal models and human patients. In this review, LDL-induced those effects mainly involve 4 growth factors (FGF, EGF, TGF-β and VEGF), 5 interleukins (IL-1, IL-4, IL-6, IL-8 and IL-10), 5 inflammatory cytokines (PGE2, COX2, TNF-α, MMPs and PA) and 4 immune cells (macrophages, mast cells, neutrophils and lymphocytes). The mediator molecules induced/upregulated by LDL are summarized (Table 1). However, the underlying mechanisms of those effects

caused by LDL are not completely understood. The precise molecular mechanisms are still needed to further experiments for propelling LDL into the therapeutic revolution.

Table 1 Mediator molecules associated with LDL

Mediator classification	Molecules	Actions/effects
Growth factors	NGF, GDNF, BDNF, FGF-1/2, bFGF, IGF-1/2, KGF, PlGF, HGF, PDGF, TGF-α, TGF-β1/2, VEGF	Proliferation/Differentiation/Migration/Chemotaxis/ Angiogenesis/Anti-inflammatory/Extracellular matrix synthesis
Anti-inflammatory cytokines	IL-2, IL-4, IL-8, IL-10	Proliferation/Differentiation/Chemotaxis/Angiogenesis/ Immunological activation
Pro-inflammatory cytokines	IL-1α, IL-1β, IL-6, IFN-γ, TNF-α, PGE2, COX1, COX2	Proliferation/Angiogenesis/Migration/Accelerate inflammation/Immunological activation
Chemokines	MCP-1(CCL2), MIP-1α(CCL3), MIP-1β(CCL4), CCR5	Chemotaxis/Immunological activation
Cell adhesion molecules	ICAM-1, VCAM-1, CD44, PECAM1, CTGF	Proliferation/Differentiation/Angiogenesis/Migration/ Integrin activation
Cell matrix proteins	MMP1, MMP2, MMP3, MMP9, MMP13, Types Ⅰ and Ⅱ collagen	Differentiation/Angiogenesis/Regeneration/ Tissue remodeling
Small molecules	cGMP, cAMP, ATP, GSH, MDA, ROS, Ca^{2+}, NO, H^{+}	Proliferation/Migration/Regulating cell activity/ Vasodilatation/Vasoconstriction
Others	PA, PTH, Leukotriene, iNOS, LP, ET-1	Proliferation/Degradation of fibrin/ Regulating cell activity/ Vasodilatation/ Vasoconstriction

The mediator molecules are involved in different classification as noted. The actions and/or effects of those the mediators were summarized as follows, whereas they are not comprehensive. Rather, it provides insight into those activities associated with LDL. Elements of the table were developed from T. Sonis[108].

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低功率光照疗法对机体免疫应答的影响 *

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摘要 最近几年，采用红至红外波长(600～1 100 nm)的低功率光照(low-dose light，LDL)疗法对组织代谢系统、神经系统、血液循环系统和免疫系统等方面的调节效应已经引起了广泛关注．同时，生物能学和光生物学基础研究的发展推动了低功率光照在疾病治疗领域的革新．有报道指出，巨噬细胞、肥大细胞、中性粒细胞和淋巴细胞等免疫细胞能响应低功率光照，产生细胞因子和保护性的蛋白质分子来缓解一些疾病的进程．因此，本文将从分子、细胞和组织水平对低功率光照改善的一些疾病的免疫学现象及机制进行归纳总结．

关键词 低功率光照，炎症反应，淋巴水肿，口咽黏膜炎，辐射性皮炎，抗肿瘤和抗菌

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