Life Sciences Student Journal

Volume 2023, No1, pp 63-72

DOI:https://doi.org/10.22034/LSSJ.2023.1.58

Low-level laser therapy synergistically improves the effects of natural killer cell-mediated immunotherapy in cancer

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Article Type:
Review Article

Received: 23 May. 2023
Revised: 25 May 2023
Accepted: 6 June 2023
ePublished: 7 June. 2023

Abstract

Introduction: Different kinds of treatments have been developed to fight cancers. The treatments patients receive will depend on the cancer type and its prevalence. Some patients are treated only one way, but most receive combination therapies like surgery, chemotherapy, immunotherapy, and radiation therapy. Low-level laser therapy (LLLT), or photobiomodulation (PBM) therapy, is a low-power monochromatic and coherent light used to heal injuries and combat malignancies.

Results: Immune cell therapy is a promising approach to fight cancers using the cellular immune system. In this regard, natural killer (NK) cells belonging to innate immunity are widely used to kill cancer cells. .

Conclusion: In this article, we hypothesize to explain how PBM therapy can enforce the effect of NK cell-mediated immunotherapy on cancers

Keywords: cancer, immune cell therapy, natural killer cell, low-level laser therapy, photo biomodulation

1. Introduction

1.1. laser therapy

Laser (mild amplification through stimulated emission of radiation) is a tool that generates a quite uniform wavelength, phase, and polarization electromagnetic radiation [1]. Advances in laser sciences have brought laser application to different branches of medicine. For example, low-level laser therapy (LLLT) has been developed for wound healing, tissue regeneration, pain reduction, inflammation, and neurodegenerative illnesses [2]. In addition, the application of laser has been mentioned in the remediation of diverse cancers [3].

1.2 Cellular effects of LLLT

LLLT, called photobiomodulation (PBM) therapy, is a light beam that can impact cellular activities in living systems. Unlike other medical lasers, PBM no longer has ablative or thermal effects on biological systems; instead, the photochemical effects are conducted by light absorption resulting in biochemical changes [4]. One of the cellular targets of PBM located in mitochondria is the cytochrome c oxidase enzyme [5]. This protein contains four redox-active metal centers for the absorbance of laser light.

Under laser light radiation, cytochrome c oxidase mediates the exchange of electrons from cytochrome c to molecular oxygen in the respiratory chain and promotes ATP generation [6]. These changes result the in release of free oxygen radicals (known as ROS) by mitochondria and induce the activation of kinds of transcription factors [7] [8]. PBM diminishes nitric oxide (NO) by mitochondria leading to ATP generation [9]. In addition, modulation of calcium channels after PBM modifies the electrostatic sthe tate of cell membrane and conformation of membrane protein. These events cause changes in cell physiology and communication [10].

Apart from the mitochondrion, PBM promotes angiogenesis in granulosa and HUVEC cells as well as skin flap animal models by upregulation of angiogenesis markers such as VEGF and hypoxia-inducible factor-1α (HIF-1α) and downregulation of matrix metalloproteinase-2 (MMP-2) Promotingn of angiogenesis might be the route by which PBM accelerates wound healing [13].

Previous studies have proved the beneficial effects of PBM on neurodegenerative disorders. For example, in Alzheimer's disease, laser treatment provokes mesenchymal stem cells (MSCs) to phagocytize accumulated amyloid-beta (Aβ) fibrils in the brain. It is supposing that laser activates MSCs and induces their migration from bone marrow into bloodstream. The circulating MSCs then infiltrate into the brain and attack the Aβ particles [14, 15].

Investigating the effects of laser on the cultured tumor cell lines has generated conflicting results and a few of them are consistent with the behavior of tumor cells in vivo [16]. Ottaviani and coworkers showed that laser irradiation inhibits tumor progression, induces tumor angiogenesis and stimulates immune system to produce type I interferons. Their study proved the safety of laser-based therapies in cancers [17]. Another study by Xia et al. revealed that blue laser dose-dependently decreased the cell viability in bladder cancer. Moreover, reduced cell migration and invasion were observed possibly due to suppression of the MAPK/MEK/ERK pathway [18].

1.3 Immune system components

Immune system is a network of biological processes for fighting a wide variety of pathogens and malignant cells. Immune system is divided into innate and adaptive immune responses. Innate immunity supplies a rough recognition and quick first-line of defense. It can react against all pathogens and cancer cells and it is categorized into three defense mechanisms including physical barriers, cellular components, and humoral responses. Contrary to the innate immune response, the adaptive immune system responds very effectively to each specific pathogen. The adaptive immune system consists of humoral and cellular components. B cells are key elements of the humoral adaptive immune response, while T cells are key elements of cellular adaptive immunity.

1.4 The anti-tumoral function of NK cells

NK cells are a part of the innate immune system. In humans, NK cells are usually characterised in flow cytometry by the absence of CD3 and the presence of CD56 on their surface. The natural cytotoxic receptor NKp46 is mostly used to recognise NK cells with the lack of CD3 expression[19]. NK cells come from CD34+ hematopoietic stem cells. Bone marrow is supposed to be the primary site of NK development. However, a recent finding has shown that NK cells can also develop and mature in secondary lymphoid organs, including tonsils, spleen, and lymph nodes [20]. Unlike B cells and T celand T cells, NK cells express stochastic combinations of activating receptors. The net balance of stimulatory versus suppressive signals through these various receptors results in either a response to or tolerance of the target cells [21].

In innate immunity, NK cells are the primary effector cells against tumors. They can detect the absence of "self" MHC class-I molecules on cancer cells, which is known as the "missing self-hypothesis." [22]. Later, this premise was supported following the discovery of inhibitory [23] and activating NK receptors [24]. According to the literature, the most important NK inhibitory receptors are the killer Ig-like receptors (KIRs), which recognize allotypic determinants shared by groups of HLA class-I alleles. [25], and CD94/NKG2A heterodimer [26], which identifies the non-classical HLA-E molecule. Among the activating NK cell receptors, a variety of non-HLA-specific receptors and co-receptors capable of eliciting NK cell stimulation via direct interaction with ligands overexpressed or expressed de novo on malignant cells[27, 28].

In the context of cancer immunotherapy, whether for solid tumors or hematological malignancies, NK cell -based immunotherapy has emerged as a promising and advanced scientific research topic [29].

By releasing cytotoxic granules containing granzymes and perforin, NK cells can cause target cell death. [29]. Furthermore, NK cells engage in antibody-dependent cellular cytotoxicity (ADCC) via the membrane receptor CD16, as well as an apoptotic axis via Fas ligand (FasL) or tumor necrosis factor-alpha (TNF-) -related apoptosis-inducing ligand (TRAIL) [30, 31]. NK cells also play immunomodulatory functions by secreting chemokines and cytokines, such as RANTES and interferon-gamma (IFN-γ) [32, 33]. Even though NK cells can identify and eliminate tumor cells, malignant cells continue to develop mechanisms to avoid detection by NK cells or to limit NK cell activity. Tumor cell immune evasion is thought to primarily depend on the production of immunosuppressive cytokines or chemokines ranging from IL-10 and TGF- to the soluble IL-2 receptor (sCD25), CXCL9, and CXCL10. [34-36]. As well, transformed cells can attenuate the expression of tumor-associated antigens (TAAs) [37] and also raise the expression of MHC class I-related molecules [38] to obstruct NK cell activation.

1.5 Anti-cancer mechanisms of PBM

Low-level lasers with different wavelengths and power affect biological systems differently [39]. Following PBM, photochemical and physical changes occur in the mitochondrial membrane, and cell metabolism switch to oxidative phosphorylation [40, 41]. Cancer cell metabolism alters from oxidative phosphorylation to glycolysis because glycolysis consumes much less oxygen than oxidative phosphorylation. This effect, known as the Warburg effect, leads to resistance of cancer cells to chronic hypoxia caused by the fast growth of tumors. Because of the Warburg effect, the malignant cells might behave differently from the normal cells in response to PBM [42]. In cancer cells with limited ATP supply, the increased amount of ATP by PBM might allow the cancer cells to respond to pro-apoptotic stimuli. However, in healthy cells with an adequate supply of ATP after PBM, the membrane potential is reduced due to oxidative stress. The membrane potential returns to a normal state, and ROS production stops [43-45].

Laser therapy also increases macrophages' phagocytic and antitumor properties by inducing IFN-γ [46]. Moreover, ATP produced after PBM causes activation of protein kinase A and stabilization of arylalkylamine N-acetyltransferase (AANAT) , which is a key enzyme in the biosynthesis of Melatonin from tryptophan [47]. Activation of the nuclear factor kappa B (NF-κβ) has been shown to occur after PBM [48]. The NF-κβ induces expression of the AANAT gene in macrophages, followed by the synthesis of melatonin [49]. Melatonin is a powerful anticancer agent, and its efficiency has been widely documented. Melatonin applies its anticancer abilities by affecting various mechanisms including angiogenesis, apoptosis, autophagy, endoplasmic reticulum stress and oxidative stress. Melatonin also has anti-inflammatory impacts [50]. It can attenuate inflammatory cytokines secreted in the tumor microenvironment that facilitate tumor growing up.

Ottaviani et al. demonstrated that laser treatment not only inhibited tumor growth but also effectively reduced lesion size and altered the tumor microenvironment in melanoma and oral carcinogenesis mouse models. In the cultured cells, however, the laser treatment produced different results. They demonstrated that the effect of laser light on cancer cell growth differed between cultured and transplanted cells. To begin, laser light slows tumor progression while increasing the metabolism of cultured cells. Second, PBM produced a more structured and functional vascular network. Finally, they demonstrated that laser light has a powerful effect on immune modulation and DC activation, which is mediated by type I IFNs. [17].

Type I IFNs, with their anti-proliferative, pro-apoptotic, and anti-angiogenic properties, are critical for cancer immune surveillance and are already being used clinically in a variety of cancer [51] M1-related cytokine and chemokine expression, as well as M1 monocyte polarization Laser light stimulates mitochondrial biogenesis and increases levels of complex I-V transcripts. Polarization of M1 monocytes is associated with histone modification at the promoter region of TNF- and IL-10 genes, which results in gene transcription activation [52].

TNF-α plays critical roles in anti-tumor activity by (1) induction of cellular apoptosis via binding to tumor cell surface receptors; (2) activation of macrophage and NK cells; (3) disruption of neoangiogenesis and inhibition of microvasculature in tumor; (4) alteration of tumor-associated macrophages fates to M1 anti-tumor stage; (5) Increasing the count of neutrophils and monocytes in tumor microenvironment; and finally, (6)) Inhibition of tumor-induced monocyte differentiation - to immunosuppressive phenotypes by decreasing

of IL-13 [53]. IL-10 can exert immunostimulatory effects by activation of NK cells, lymphocytes T and macrophages. In other words, increasing local IL-10 concentrations in the tumor microenvironment causes the increase of CD8+ T cell numbers and secretion of IFN-γ and induces tumor-specific immunity as well [54 -56].

Endogenous chromophores, such as cytochrome c oxidase (CCO), located in the target cell's mitochondrial membrane, absorb laser light. The light energy absorbed stimulates the electron transport chain in the mitochondria, increasing ATP production. Increased ATP levels benefit cellular metabolism and function, including immune system cells. One possibility is that the LLLT increases free nitric oxide (NO) through photolysis of the nitrosyl complex and accelerates programmed cell death via oxidative stress, disrupted energy metabolism, DNA damage, activation of poly (ADP-ribose) polymerase, or dysregulation of cytosolic calcium. Depending on the severity and context of the damage, such disruptions can result in either apoptotic or necrotic cell death. [57-59].

Moreover, PBM activates several transcription factors by stimulating the production of reactive oxygen species (ROS) [60]. ROS is a group of highly reactive molecules that have evolved as regulators of important signaling pathways. The generation of moderate level of ROS by PBM at very low energy densities can initiate redox-signaling and activate redox-sensitive transcription factors such as the Akt/GSK3beta pathway and NF-κβ [48, 61, 62]. These transcription factors stimulate anti-apoptotic and/or cell survival responses. However, PBM at high energy densities that produce a cytotoxic level of ROS can induce pro-apoptotic effects and inhibit proliferation in vitro via inactivation of the Akt/GSK3beta signaling pathway [63-65].

LLLT boosts chemotherapy's anticancer effect. Heymann et al. discovered that LLLT could boost the anticancer effects of cisplatin or zoledronic acid (ZA) in cultured Hela cells. Depending on the tumor microenvironment, tumor cells can switch between glycolysis and mitochondrial metabolism (oxidative phosphorylation). Cisplatin and ZA both have anti-glycolytic activities and the cancer cells fight with such drugs by switching their metabolism from glycolysis to mitochondrial oxidative phosphorylation. Hence, the growth of Hela cells increased when the cells were only exposed to cisplatin or ZA. [66].

1.6 Does laser cause tumor growth and proliferation

Many of the pathways discussed here have been strongly linked to cancer-related behaviors. The PI3-Kinase pathway was first linked to cancer nearly 30 years ago. It is especially relevant to head and neck cancers (HNCs) because it is a component of the PI3K/Akt/mTOR pathway. The PI3K/mTOR pathway has been identified as a potential target for intervention due to its importance in tumor behavior. In colon cancer models, inhibiting the PI3K/mTOR pathway proved effective as a radiosensitizer. Similarly, Leikeret al. used cell culture and animal xenograft models of head and neck SCC (HNSCC). PI3K/mTOR inhibition was found to preferentially radiosensitize human HNSCC cells over normal human fibroblasts. The same PI3K/mTOR inhibitor also inhibited tumor regrowth in a nude mouse xenograft model. Chang also discussed how the PI3K/Akt/mTOR signaling pathway affected radiosensitivity in prostate cancer cell lines. Not only were these cells radioresistant, but they were also linked to more aggressive tumor invasion and stem cell formation EMT and cancer stem cell (CSC) formation were also linked to PI3K/Akt/mTOR signaling inhibition, which improved radiosensitivity and reduced EMT and CSC phenotypes.. PI3K/Akt signaling can also activate downstream pathways and genes, including ERK. Significant for upper aerodigestive tract cancers, ERK/MAPK-activation of EGFR, a component of LLLT activity ,has been identified as potentially important in tumor progression, most likely through the promotion of VEGF and endothelial cell proliferation. Although there is no direct relationship between LLLT and epithelial adhesion molecule (EpCAM), EpCAM's association with the PI3K/Akt/mTOR pathway is well documented. LLLT is responsible for numerous anti-apoptotic activities, which may influence tumor survival and treatment resistance. As previously stated, higher energy LLLT promotes collagen synthesis via the TGF-b/Smad pathway.In oncogenesis, this pathway, which normally inhibits proliferation and induces apoptosis, is frequently inactivated. TGF-tumor b's suppressive roles in early stage tumors change to promote tumor progression in advanced tumors, depending on the tumor stage.[67, 68].

1.7 LLLT can increase the likelihood of metastasis, invasion, and treatment resistance

LLLT stimulates or activates many factors that contribute to tumor migration, invasion, and metastatic potential. Many LLLT-induced cytokines, including VEGF and PDGF, are involved in cell proliferation, tumor angiogenesis, local spread, and metastasis. Laser-induced upregulation of HSP-90 in studies suggests that laser therapy may promote tumor growth while decreasing radiosensitivity. Enhancement of MMP activation by laser may support tumor invasion and/or reduce cancer therapeutic response. Survivin, a protein of the apoptosis inhibitor family, is upregulated by high-power laser irradiation. This molecule promotes cell proliferation, inhibits apoptosis, increases PI3K/Akt and ERK signaling, and decreases PTEN function. Chu et al. Human lung adenocarcinoma cells were studied. showed that LLL radiation induced survivin and affected tumor survival after survivin activation. Also, stimulation of TLR 4 expressed on HNSCC by laser promotes tumor growth and protects tumor immunity[69].

1.8 PBM and NK cells, a synergistic combination

NK cells are generated from hematopoietic stem cells (HSCs) residing in the bone marrow (BM) similar to other blood cells [43, 70]. It seems that PBM could help the process of NK cell generation by increasing the proliferation of HSCs. PBM directs this function by provoking mitochondrial biogenesis resulting in the production of ROS. The balanced levels of ROS are crucial for switching stem cells, including HSCs from dormancy to proliferation state followed by differentiation to the immune cells like NK cells [43, 71-73]. The produced NK cells then target and lyse tumor cells. On the other hand, overstimulation by PBM can cause high levels of ROS which in turn induce permeabilization of the mitochondrial outer membrane and, subsequently, the release of cytochrome c and caspase cascade reaction. These events activate mitochondrial apoptosis pathway, alter cell cycle, inhibit cell proliferation and cause cell death [43]. A recent study has reported that induction of mitochondrial apoptosis pathway is essential for efficient killing of the tumor cells in NK cell immunotherapy (78).

Tumor microenvironment is critical for immune cell activities. Increasing the number of immune cells in the tumor area exclusively is not enough for tumor regression. The tumor environment is hypoxic and NK cell function is inhibited at low oxygen pressure. PBM modulates the intratumoral hypoxic condition by induction of VEGF expression that enhances angiogenesis and improves blood circulation within the tumor. These events allow the activity of tumor-infiltrated NK cells as the result of increasing oxygen pressure and weakening hypoxic conditions within the tumor [74]. Moreover, PBM-induced vessel growth eases the infiltration of immune cells like NK cells into the tumor microenvironment [75, 76]. Secretion of growth-stimulating cytokines into the tumor inflammatory microenvironment can promote tumor progression. For instance, transforming growth factor-β (TGF-β) plays a major role under inflammatory conditions [77] and canencouragee tumorigenesis due to the secretion of growth factors, cytokines, and chemokines [78]. Moreover, TGF-β is one of the most well-known NK inhibitory cytokine that is secreted in the tumor microenvironment [79-82]. However, PBM reduces inflammation reactions around the tumor by increasing the secretion of anti-inflammatory cytokines such as IL-10 [83]. IL-10 increases the expression of activation cytokines and cytotoxicity-related genes within the NK cells, promoting the tumor lysis [84]. Therefore, PBM can suppress tumor-extrinsic inflammation by the secretion of anti-inflammatory cytokines and aid in tumor regression by NK cell activation. PBM increases the production of melatonin. As mentioned above, melatonin has several anti-cancer mechanisms. It stimulates the production of progenitor cells for granulocytes-macrophages. It also promotes NK and helper CD4+ cell production but inhibits cytotoxic CD8+ cells. Melatonin also causes the secretion of various cytokines from NK cells and T-helper lymphocytes that enhance NK cell activity [47, 85]. This showed that the PBM can stimulate the production of NK cells via the path of melatonin.

Altogether, the above descriptions apprehend that applying LLLT could enhance the effectiveness of the tumor's immune cell therapies using NK cells through the balanced levels of ROS, stimulation of NK cell production, and secretion of cytokines.

1.9 Testing Hypothesis

To prove the hypothesis presented in this paper, the effect of laser is tested in the xenotransplanted colorectal cancer mouse models. In the first approach, nude mice will be randomly divided into four experimental groups. The first group will be received serum and albumin as control, and three other groups will be treated

with NK cells, PBM, and combination of PBM and NK cells. The size of tumors will be measured among the four groups to determine the effects of immune cell therapy, laser therapy, and combination therapy on the tumor growth. The mice will be sacrificed at the end of experiments, and the count of NK cells and the cytokine levels will be calculated and compared between the groups.

In the second approach, the mice will be divided into four groups, as mentioned above. However, this time, the proliferation of cultured NK cells will be first stimulated with a laser beam at 600-800 nm. Simultaneously, the transplanted colorectal cancer mouse models will be irradiated with a blue laser 805nm at 5 J/cm2 to induce apoptosis in the tumor cells. The provoked NK cells will be perfused into the grouped mice, and the tumor mass regression, NK cell count, and cytokine levels will be co pared among the groups. Moreover, the results of the two mentioned approaches will be compared to each other for comprehension of the effectiveness of provoked and unprovoked NK cells.

2.conclusion

A cancer treatment approach known as immune cell therapy has become popular in the medical field. In recent years, NK cell-based immunotherapy has emerged as a promising therapeutic approach for solid tumors. Kinds of therapeutic strategies have been proposed to enhance NK cell therapies' influence. Individually, low-level laser therapy and NK cell therapy possess antitumor effects. Based on the literature review, we hypothesized that a compound therapy with PBM (Effective wavelength) and NK cells could synergistically improve anticancer outcomes for them both. In our study, four experimental groups were subjected to cell therapy and laser therapy, respectively, and one group was subjected to a combination of both, and the other group was the control group. In the present study, according to the results of this study, the immunohistochemical test showed the best tumor status in the group that combined both treatments. To improve the effectiveness of treatmentIt, chemotherapy should be performed before cell therapy, and it is suggested that cell therapy should be performed at a more appropriate time so that the solid tumor does not become resistant to treatment. Another suggestion to improve the effectiveness of the treatment is to use CAR NK so that the penetration and impact of the cells in the face of the tumor can be done more effectively.

Acknowledgment

The Authors thank the Middle East Gene Therapy Company for its support.

Conflict of interest statement

The authors state no conflicts of interest regarding this study.

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