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A Concise Review of the Impact of Photobiomodulation (PBM) on Neuronal Differentiation in Adipose-Derived Mesenchymal Stem Cells

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Abstract

Introduction: Photobiomodulation (PBM), utilizing low-level light, has shown significant potential in differentiating adipose-derived mesenchymal stem cells (ADMSCs) into neuronal cells. Critical studies have shown that specific laser parameters, such as wavelength and fluence, significantly impact the trans-differentiation outcomes of immortalized ADMSCs. This review aimed to consider this phenomenon.

Methods: This review was conducted based on several English articles from Google Scholar, Science Direct, and Medline, such as the National Library of Medicine (NLM) and PubMed from 2010 to 2025. The term 'ADMSCs' was searched combined with the following keywords: "Photobiomodulation" OR "low-level laser irradiation" OR "low-power" laser OR "low-intensity laser" OR "Photobiostimulation".

Results: This investigation demonstrated that PBM is a non-invasive, light-based method for facilitating the neuronal differentiation of the ADMSCs. It is effective for increased production of adenosine triphosphate (ATP) and other biomolecules responsible for cell differentiation, proliferation, and migration to induce cell proliferation and cell signaling cascades, favoring neuronal lineage commitment, although results vary across protocols.

Conclusion: This review indicates that PBMT-based regenerative medicine seems promising and applicable for future advances in cell-based regenerative medicine and neurology. However, alongside the potentials, it also underscores challenges of PBM-based neural regeneration, calling for parameter optimization, more in vivo studies, and shifting the focus of future studies to clinical applications.

Keywords: Photobiomodulation therapy, Adipose-derived mesenchymal stem cells, Neurogenesis, Transdifferentiation, Low-level laser therapy

Introduction

Stem Cell Therapy

Stem cell therapy, or regenerative therapy, enhances the healing of impaired or injured tissue by utilizing stem cells or their derivatives. These therapies focus on either substituting damaged cells with new, healthy cells or improving the tissue environment to support regeneration. Stem cell therapy has revolutionized the medical field by providing promising treatments for various conditions such as neurodegenerative diseases[1] Over the past few years, researchers have dedicated significant resources to generating neurons and glial cells from various kinds of stem cells, harnessing other beneficial aspects of stem cells to address neurodegenerative conditions. Various stem cell reservoirs have been explored to identify an efficient approach for utilizing stem cell therapy in treating neurodegenerative conditions.[1-4] The majority of such studies have primarily been carried out in animals during the preclinical stage. These investigations have yielded significant findings, demonstrating the potential of stem cells to influence native cells, facilitate the restoration of nervous tissue, enhance the functionality of cells, transform into neuronal as well as glial cells, and alleviate motor disorders.[5-6] Numerous clinical investigations have explored various facets of stem cell treatments for neurodegenerative conditions.[6-8]

Adipose-Derived Mesenchymal Stem Cells

ADMSCs are becoming increasingly promising compared to other stem cell types due to their widespread presence in the human body and simple extraction process, leading to larger quantities with fewer complications from the donor

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site. Subcutaneous adipose tissue, found in areas like the abdomen, thigh, and arm, is particularly noteworthy as a rich source of ADMSCs.[9] With the abundance of adipose tissue in the body, ADMSCs can be collected in significant numbers, making them easily accessible on a large scale.[10] Their capability to differentiate into multiple cell varieties makes them ideal for applications in cell therapy as well as tissue engineering.[11] ADMSCs are guided in vitro to differentiate using specific culture media containing factors tailored to each cell lineage.[12-13] Notably, ADMSCs have a low risk of disease transmission and tissue rejection.[14] Studies have shown that ADMSCs can differentiate into various cell types in vitro and in vivo, paving the way for a wide range of clinical uses. Despite their mesodermal origins, ADMSCs can differentiate into cells from ectodermal, endodermal, and mesodermal lineages[12,15] When compared to other types of mesenchymal stem cells [MSCs], ADMSCs have been reported to accelerate neural regeneration, and better capacity for neuronal differentiation, and facilitate good proliferation.[16] These unique characteristics, combined with minimal ethical concerns compared to embryonic stem cells (ESCs), make ADMSCs highly suitable for neurodegenerative therapies.[17-19]

Photobiomodulation

Photobiomodulation (PBM), commonly referred to as low-level laser therapy (LLLT), uses laser or light-emitting diodes (LED) devices that emit low-intensity light within the visible to near-infrared (NIR) wavelength ranges to non-invasively stimulate or influence cellular or tissue activity.[20,21] PBM research is actively progressing globally and has exhibited efficacy in clinical practices, such as tissue restoration and pain mitigation, in addition to its application in various medical fields such as sports medicine.[22-28] Extensive research spanning over three decades has been conducted on low-level laser therapy, revealing its diverse range of bioinhibitory and biostimulatory effects.[29] The effects of laser light on cells during PBM can vary depending on various factors such as wavelength, fluence, duration of irradiation exposure, and specific types and physiological characteristics of the cells or tissues involved. These interactions can lead to either inhibitory or stimulatory effects.[30-35]

Although PBM has been widely recognized for promoting tissue repair and regeneration, accumulating evidence suggests that its effects on mesenchymal stem cells (MSCs) are not uniformly beneficial. Under certain conditions, PBM may exert inhibitory or even cytotoxic effects on MSCs, compromising their proliferative and differentiation capacities.[20,36] These drawbacks warrant careful consideration, especially when PBM is used in stem-cell-based regenerative medicine. Some of the drawbacks might be considered as biphasic (hormetic) responses, parameter-dependence, and lack of standardization. Mitochondrial/oxidative stress mechanisms may mediate inhibition, and cellular context and stem cell state dependency.[37-39]

It is crucial to thoroughly evaluate all of these factors, as each one can affect the homeostasis of the cell.[40] PBM activation primarily relies on using red (600 nm–700 nm) and NIR (700 nm–1100 nm) wavelengths, which possess superior tissue penetration capabilities, enhancing their effectiveness in stimulating cellular responses.[41,42] PBM improves cellular metabolism and a range of other functions, resulting in higher rates of cell growth, and specialization due to low-level light irradiation, interaction with Cytochrome C oxidase (CCO), and production of reactive oxygen species (ROS) or ATP which lead cell proliferation or differentiation (Figure 1). In the chromophores' absorption of light energy, CCO, a vital enzyme in respiration of cells, initiates a sequence of biochemical processes and cell signaling pathways crucial for cell differentiation. The activity of CCO

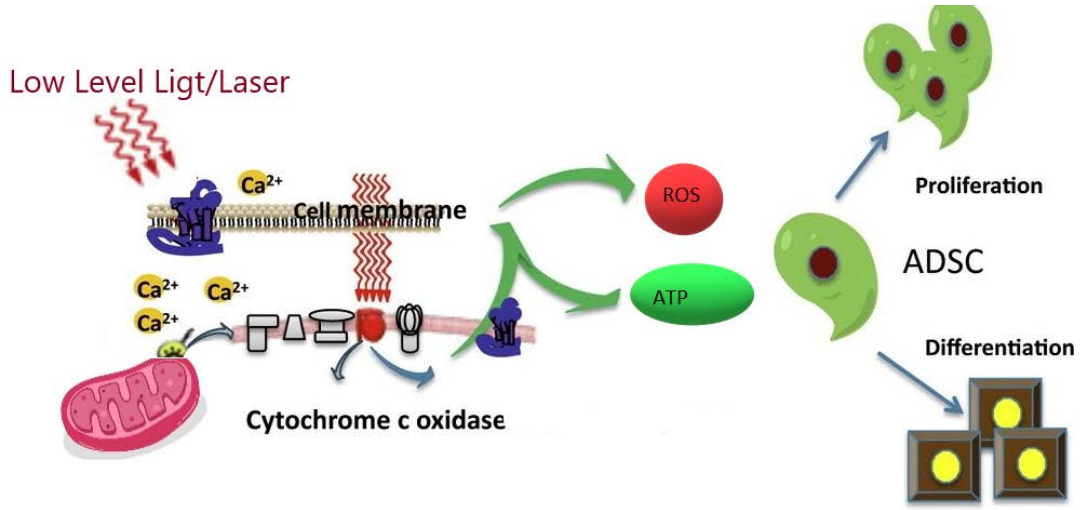

Figure 1. Photobiomodulation effects on adipose-derived mesenchymal stem cells and cellular pathways

directly influences mitochondria.[43-45] Many cell types, including fibroblasts, keratinocytes, human osteoblasts and lymphocytes, have shown increased proliferation after low-level laser irradiation.[46-51]

Data Collection Method

This study was undertaken by an online search in databases, including Google Scholar, Science Direct, Medline (NLM) and PubMed using these keywords: "Photobiomodulation therapy", "Photobiostimulation of adipose stem cells", "Photobiomodulation neural cells", "Photobiomodulation", "low-level laser irradiation", "low-power laser", "low-intensity laser", "Photobiostimulation", "neurogenesis", "low-level laser therapy", and "irradiation on stem cells", from May 2010 until February 2025. More than 120 papers were found in the initial search. Inclusion and exclusion criteria for this review were defined based on the abstracts of the retrieved studies. Studies with no report of outcomes for data extraction were removed. At the first screening, 67 out of all were considered related. Within the context of the impact of PBM on ADMSCs differentiation into neural lineages, nine were included. A database was then planned for summarization, and papers were meticulously reviewed. The experimental dimensions and clinical aspects in the studies were included for this review.

PBM Effect on ADMSCs

Working with ADMSCs has popularly developed since they are simple to extract by means of less invasive strategies, and they are differentiated into different types. Immortalized ADMSCs (iADMSCs) have been considered a reasonable alternative to isolated ADMSCs in various studies.[52,53] ADMSCs differentiation is activated by the induction of biochemical molecules and components alongside PBM. They have great potential for differentiating into a range of cells, such as neuronal, osteogenic, chondrogenic, adipocyte, and myogenic cells.[54-57]

Due to the key role of laser irradiation parameters, like wavelength and energy or power, it is vital to select the optimized parameters for ADMSC differentiation, based on the modeling or empirical experiments of PBM treatments.

Neuronal Differentiation Due to PBM effects on ADMCSs

Regarding the neural differentiation potential, it has been found that adipose derived- mesenchymal stem cells (A-MSCs) present a higher neuronal capacity compared to bone marrow-derived mesenchymal stem cells (BM-MSCs) in vitro and after co-culture with Schwann cells.[58]

Research has explored the influence of brain-derived neurotrophic factor (BDNF) and retinoic acid (RA) on adipose-derived mesenchymal stem cells. Similar observations in bone marrow-derived mesenchymal stem cells (BM-MSCs) have identified sustained structural, surface marker, and electrical activity-related modifications linked to the initial stages of neural development.[8, 59]

After PBM introduction as the inducer for the neuronal differentiation of ADMCSs, there have been some in vitro and in vivo studies. Consequently, PBM may be utilized to repair injured tissues or to mitigate or prevent harm resulting from pathological conditions. Contrary to earlier beliefs, recent research has demonstrated the potential for neuronal regeneration through this approach. Nevertheless, neural cells are widely regarded as possessing a more limited regenerative potential compared to non-neuronal cell types. Subsequently, improving their regenerative capacity improves the therapeutics of neural degeneration. PBM improves neural cell differentiation from stem cells. In this section, we have compiled the impacts of PBM on neural differentiation from potential ADMCSs. We have summarized the results in Table 1.

Other Differentiations of Admcss Following PBM

The special regenerative ability of stem cells presents novel capability for treating more diseases. In stem cell differentiation, unspecialized stem cells transform into specialized cells, following multiple stages and steps.[64] The differentiated stem cells can be stimulated in a more efficient manner to result in more viable, functional cells for better cellular characterization and their applications in regenerative medicine.[65] A multitude of internal stimuli and external ones for cell differentiation include the release of biochemicals and biomaterials in addition to the physical stimuli such as mechanical or electromagnetic stimulants, like the application of low-level laser light or photobiomodulation.[65] Regarding the effects of PBM on ADMCSs differentiation to other cells, there are some previously published in vitro studies.[33,66-69]

Stein et al., in 2005, investigated the impact of low-level laser irradiation on the differentiation of a human osteoblast cell line. They tested osteoblast cells and irradiated them with a He-Ne low-level laser (632 nm; 10 mW power output) after cell culturing. This study concluded that low-level laser light facilitates the proliferation and maturation of human osteoblasts in vitro.[48]

There are also some in vivo studies on the effect of PBM on stem cells in the rat animal model. Liao et al conducted research on rats for the PBM effect using GaAlAs laser irradiation. ADSCs had increased dermal thickness but decreased epidermis thickness in the mice with photoaged skin.[70] In another in vivo study using rats, Wang et al[71] found that ADSC therapy in conjunction with PBM significantly augmented bone regeneration in critical-sized calvarial defects. Strikingly, pre-treating ADSCs with PBM prior to therapeutic application markedly increased their capacity to enhance skeletal repair. One more study by Lucke et al found that PBM was particularly effective in collagen reorganization when added to treat the ASCs.[72]

Table 1. Summary of neuronal differentiation of ADMCSs using PBM

Reference	Study design	Findings
Abrahamse et al, 2024 [52]	Transforming iADMSCs into neural cells was induced, and the supportive impacts of Photobiomodulation at 525 nm and 825 nm were assessed.	Photobiomodulation has no damage to the cell differentiation, while it might enhance the process.
Crous et al, 2022 [53]	ADMSCs immortalized with hTERT ASC52telo were cultured. 825 and 525 nm LLL was applied for PBM.	1. Exposure to near-infrared and green light wavelengths markedly enhanced the growth of adipose-derived mesenchymal stem cells [ADMSCs], elevating both cell density and intracellular ATP production. 2. Near-infrared and green light exposure induced a progressive rise in reactive oxygen species [ROS] generation, correlating with extended treatment duration. 3. NIR-green laser light raised mitochondrial membrane potential [MMP] and facilitated ADMSC migration.
George et al, 2020 [54]	Induced adipose-derived stem cells [ADSCs] were evaluated for their potential to form free-floating neural stem cell clusters [neurospheres] using a multi-stage differentiation protocol. Subsequently, these neurospheres were treated with 825-nm low-level laser irradiation to trigger their transformation into neurons.	1. Exposure to 825 nm LLL irradiation enhanced the differentiation capacity of neurospheres toward neuronal lineages. 2. A dose-dependent elevation in early-stage neuronal biomarkers was observed, with notable increases at 5 J/cm² and more pronounced effects at 15 J/cm², aligning with PBM dose-response dynamics. 3. Comparative analysis of iASCs and primary ASCs highlighted distinct metabolic profiles among primary ASCs, neurospheres, and newly formed neurons during differentiation.
George et al, 2022 [55]	Primary and immortalized adipose-derived stem cells [ASCs] were assessed based on their expression of surface markers CD44, CD90, CD133, and CD166. These cells were subsequently directed to undergo neuronal differentiation via treatment with basic fibroblast growth factor [bFGF] and forskolin, followed by irradiation with 825 nm photobiomodulation [PBM].	PBM, particularly NIR-G, enhanced the transdifferentiation potential of iADSCs when applied in conjunction with the differentiation-inducing culture medium.
Jansen van Rensburg et al, 2022 [56]	Neuronal-like cells were produced by exposing transdifferentiating cells to chemical or biochemical inducers, followed by sequential PBM using 525 nm and 825 nm NIR lasers at a fluence of 10 J/cm². Outcomes were assessed via morphological analysis, viability assays, proliferation measurements, and migration evaluations conducted at 24 hours, 48 hours, and 7 days after treatment.	Near-infrared photobiomodulation increased the expression of neuronal markers significantly.
Da Silva et al, 2025 [57]	The study examined the influence of diverse biochemical and chemical agents on cell transdifferentiation, alongside the effects of PBM delivered via dual-wavelength light [825 nm near-infrared and 525 nm green laser] at a fluence of 5 J/cm².	1. ASCs demonstrate the capacity to undergo transdifferentiation into neuron-like cells when treated with differentiation-inducing agents. Pre-treated cells exhibit elevated proliferation and transdifferentiation rates relative to untreated controls. 2. Green laser irradiation induced structural alterations associated with advanced transdifferentiation, whereas NIR photobiomodulation significantly upregulated neuronal marker expression.
Yang et al, 2018 [60]	In a rat model of ischemic stroke induced by photothrombosis, continuous-wave [CW] 808-nm PBM at an irradiance of 350 mW/cm² was administered to evaluate its impact on behavioral impairments and neuronal regeneration. Post-treatment analysis demonstrated elevated secretion of anti-inflammatory cytokines, enhanced cytochrome c oxidase activity, and increased ATP synthesis in peri-infarct brain regions.	1. PBM demonstrates the ability to shift microglial activity from a pro-inflammatory M1 state to a neuroprotective, anti-inflammatory M2 phenotype. 2. Following ischemic stroke, PBM has been shown to facilitate the regeneration of neuronal tissue, enhancing neurogenesis.
Hong et al, 2022 [61]	1. The study employed male C57BL/6 mice to establish an experimental model of status epilepticus. 2. PBM was administered using an 830-nm diode laser, penetrating both the scalp and cranial bone. 3. Hippocampal cell proliferation and neurogenesis in experimental mice were assessed via IP injection of a cell proliferation marker over three consecutive days prior to inducing status epilepticus with pilocarpine.	1. PBM restored physiological neurogenesis patterns disrupted by status epilepticus. 2. PBM facilitates hippocampal neurogenesis by promoting the migration of developing granular neurons [immature neuronal precursors] into GCL. 3. The PBM-induced normalization of neurogenesis mitigated epileptogenesis-associated neuronal degeneration in the CA1 hippocampal region.
Chen et al, 2019 [62]	1. hUC-MSCs were categorized into four experimental groups: control, inducer-only, laser-only, and laser + inducer combination groups. 2. The study utilized a 635-nm laser and an 808-nm laser, applying energy densities ranging from 0 to 10 J/cm² in the experimental protocols. 3. Neuronal differentiation was stimulated using either normal cerebrospinal fluid [CSF] or injury-modeled cerebrospinal fluid [iCSF] as inductive agents.	Early-phase 808-nm laser irradiation facilitated CSF-mediated neuronal differentiation of hUC-MSCs, promoting a preferential shift toward neuronal lineage commitment over glial cell development.
do Nascimento de Lima et al, 2019 [63]	PBM with a 660-nm wavelength [30 mW power] was applied to rat MSCs prior to treatment with varying doses of doxorubicin [DOX].	LLLI at 0.2 J/cm² attenuated DOX-induced cytotoxicity, reduced apoptosis, and suppressed oxidative stress biomarkers in the MSCs.

Discussion

Low-intensity laser irradiation at 825 nm has been found to be the best wavelength to optimize the differentiation of ADSCs into neuron-like cells, which notably improves the expression of neuronal markers and maintains cell viability. Additionally, using combined wavelengths, such as 825 nm and 525 nm, has further enhanced the differentiation process.

While PBM has shown promise in numerous studies on MSCs, a number of methodological issues hamper the robustness of the evidence and complicate translation to clinical/in vivo settings. One major limitation is the wide heterogeneity of irradiation parameters (wavelengths, irradiance/power density, fluence/energy density, pulse vs continuous wave, exposure time, spot-size, repetition frequency) across in-vitro studies.[73] This parameter heterogeneity leads to parameter-sensitivity bias; results may depend strongly on the specific settings that may cause outcome changes (stimulatory vs inhibitory).[74] While many in vitro studies report positive effects of PBM on MSC proliferation, differentiation, migration, and paracrine factor secretion, in vivo evidence is sparse and less consistent. When in vivo MSC applications are combined with PBM pre-conditioning or concurrent irradiation, variables multiply (host immune response, tissue perfusion, light attenuation by skin/tissue, systemic distribution of MSCs). Contradictions may emerge based on the PBM parameters. In cases, MSC function enhances *in vitro*, while it might have no effect *in vivo* due to excessive ROS, or cytotoxicity.[75]

The electrophysiological alterations in these differentiating ASCs were not investigated by the researchers. Future research should focus on confirming the terminal neuronal differentiation and function through electrophysiology and analysis of sodium ion channel protein expression. Furthermore, developing mature neurons that elicit electrical activity for impulse transmission may require a closer resemblance to in vivo conditions. Since the data obtained from these studies are based on in vitro protocols, it is suggested that future research be focused more on the in vivo potential and clinical application of PBM and ASC therapy for neurological disorders and damage to the nervous system. Future investigations could be optimized by employing varied dose parameters and assessing cellular responses in physiologically representative 3D culture models. The integration of 3D culture systems represents a promising approach to enhance translational relevance by better recapitulating tissue complexity observed *in vivo.* Prospects regarding this novel topic could soon be a promising strategy suitable for treating damage to the nervous system and neurodegenerative disorders.

Conclusion

Photobiomodulation (PBM) has emerged as a promising, non-invasive biophysical stimulus for directing neuronal differentiation in adipose-derived mesenchymal stem cells (ADMSCs). Accumulating evidence indicates that appropriately tuned PBM parameters—particularly wavelength, fluence, and irradiation regimen—can modulate mitochondrial activity, redox signaling pathways that collectively favor neurogenic commitment and maturation. Compared with conventional chemical induction protocols, PBM offers advantages in terms of safety, spatiotemporal control, and the ability to synergize with biochemical cues while minimizing cytotoxicity.

In conclusion, PBM represents a versatile and clinically attractive strategy to enhance neuronal differentiation of ADMSCs, with substantial potential for regenerative neurology and neurorehabilitation. Continued interdisciplinary research combining laser physics, stem cell biology, and neuroscience is essential to fully harness PBM-driven neurogenesis and advance its translation into effective cell-based therapies.

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Competing Interests

The authors declare no competing interests.

Ethical Approval

No ethics for review study.

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