Effects of Photobiomodulation on Stem Cells Important for Regenerative Medicine

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The use of stem cell therapy to treat various diseases has become a promising approach. The ability of stem cells to self-renew and differentiate can contribute significantly to the success of regenerative medical treatments. In line with these expectations, there is a great need for an efficient research methodology to differentiate stem cells into their specific targets. Photobiomodulation (PBM), formerly known as low-level laser therapy (LLLT), is a relatively non-invasive technique that has a therapeutic effect on damaged tissue or cells. Recent advances in adapting PBM to stem cell therapy showed that stem cells and progenitor cells respond favorably to light. PBM stimulates different types of stem cells to enhance their migration, proliferation, and differentiation *in vitro* and *in vivo*. This review summarizes the effects of PBM on targeted differentiation across multiple stem cell lineages. The analytical expertise gained can help better understand the current state and the latest findings in PBM and stem cell therapy.

Key words

Stem cell differentiation; Photobiomodulation; Low-level laser therapy; Regenerative application; Therapeutic effect

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INTRODUCTION

Stem cells play an important role as the source of tissue-organ maintenance as they pitch in for repair of injured tissues with their self-renewing capacity and ability to differentiate into multiple target phenotypes. Therefore, stem cell therapy may be a promising treatment option for the regenerative medicine field.¹

There are two types of stem cells: embryonic stem cells (ESC) and adult stem cells. However recently, stem cell research has been conducted primarily using adult stem cells. Between 2013 up until writing this review, only one published study used ESC in relation to PBM research,² while all other research papers were using adult stem cells. Adult stem cells exist in various organs of our body and are capable of regenerating when the body is damaged. Mesenchymal stem cells (MSC) can be easily isolated from adipose, bone marrow, umbilical cord, and dental pulp, have been studied extensively in tissue engineering and regenerative medicine of different organs as an alternative to conventional treatment methods.³⁻⁷ Despite the high differentiation potential, the slow proliferation rate of MSCs is an important factor inhibiting its development as an effective treatment. Therefore, establishing a way to

accelerate the MSC's proliferation process is a very important requirement for its success.

Photobiomodulation (PBM) is a non-thermal and non-invasive stimulating process to target using wavelengths from the red to near-infrared light spectrum (600 to 1000 nm). Formerly called as low-level laser (light) therapy (LLLT), it has been reported that both coherent and non-coherent light sources such as light-emitting diodes (LEDs) have the same therapeutic effect. In light of this, the associations have agreed and acknowledged the re-naming of LLLT into PBM.⁸ Its beneficial effects have been shown in many different diseases by modulating cellular functions such as differentiation, proliferation and migration leading to tissue or cell regeneration. In recent years, the potential importance of PBM is emerging as a clinical tool in regenerative medicine.⁹⁻¹¹ PBM has been reported to have positive and promising effects in relation to MSCs proliferation and differentiation.^{6,12-17} However, the bio-stimulation mechanisms of these effects remain partially unclear.

In this review, we summarized the parameters and effects of PBM when applied to various stem cell proliferation and target differentiation in *in vitro* and *in vivo* papers published between 2013-2020 for to understand the cur-

Table 1. Human adipose stem cells related to photobiomodulation (PBM) application

Type of light device	Wavelength (nm)	Energy density (J/cm ²)	Related research fields	Criteria	Ref.
InGaAlP laser	660	20, 70, 180	In vitro	Proliferation at 20 and 70 J/cm ²	5
NIR laser	890	0.2, 6 days per week for 16 days	In vivo, DM wound	Anti-inflammatory, angiogenic differentiation on day 16.	13
Red and NIR diode laser	635 and 809	0.5, 1, and 2	In vitro, osteogenesis	Osteogenic differentiation in the unproliferation state	14
LED, filtered lamp, red diode laser and NIR diode laser	415, 540, 660, and 810	3	In vitro, osteogenesis	Proliferation at 660 and 810 nm	15
Red diode laser	636	5	In vitro, smooth muscle cells	Smooth muscle cells differentiation	18
LED, filtered lamp, red diode laser and NIR diode laser	420, 540, 660, and 810	3, five times	In vitro, osteoblasts	Proliferation and osteogenic differentiation at 420 and 540 nm	19
Red diode laser	660	11-16	In vitro, wound	Proliferation	20
Red diode laser	635 and 655	4	In vitro, wound	Proliferation and migration	21
LED	660	6	In vivo, angiogenesis skin flap ischemia	Functional endothelial differentiation	22
NIR light	810 and 980	0.03, 0.3, 3, and 20	In vitro	Proliferation differentiation in 980 nm	23
He-Ne and diode laser	632.8, 630, and 810	0.6, 1.2, and 2.4	In vitro, wound	Proliferation more effective in hASC	24
Red laser	660	70, three times a week, total 10 times	In vivo, wound	Proliferation increase collagen birefringence	25

InGaAlP, indium-gallium-aluminum phosphide diode laser; NIR, near infrared; DM, diabetes mellitus; LED, light-emitting diode; He-Ne, helium-neon; hASC, human adipose stem cell.

rent state and latest results of PBM in stem cell research.

PBM EFFECT ON MULTIPLE STEM CELLS

Effect of PBM on human adipose derived stem cells (hADSCs)

MSCs are capable of differentiation into multiple lineages such as osteogenic, adipogenic and chondrogenic cell lines. Among the MSCs, ADSCs could be chosen due to their ease of isolation. *In vitro* and *in vivo* studies have shown that PBM can induce ADSC to differentiate into multiple mature cell phenotypes including adipocytes, osteoblasts and chondrocytes. Recently, research has focused to determine whether PBM has the ability of encourage ADSC to differentiate in order to use for regenerative medicine. When analyzing the wavelength of PBM involved in the proliferation and differentiation of ADSC, light source parameters used red light red light from 630 to 660 nm wavelengths as well as near-infrared lights from 809, 810 and 980 nm wavelength bands. Although studies have also been conducted on muscle¹⁸ and bone formation,^{15,19} most of them are experiments aimed at regenerating wound tissues.^{5,13,14,18,20-25} The equipment types, wavelengths and energy densities used in the experiments are summarized in Table 1.

Effect of PBM on human dental pulp stem cells (hDPSCs)

DPSCs are another representative of MSCs, which are easily isolated from the teeth without an invasive treatment. In addition, DPSCs are a promising source of cells

for various regenerative medicine applications especially for dental tissue engineering. DPSCs are derived from the neural cap of the tooth, therefore are distinguished from bone marrow MSCs due to their different developmental origin. These property are being utilized for neurological and odontogenic differentiation. Based on the studies that confirm the effectiveness of PBM on DPSCs, 7 studies used red laser (660 nm),^{7,16,26-30} and the two other articles conducted their studies using near-infrared wavelengths (808 and 810 nm).^{12,31} They confirmed that the application of PBM with the red wavelength is very effective for the proliferation and differentiation of DPSC. The equipment types, wavelengths and energy densities used in the experiment are summarized in Table 2.

Effect of PBM on human bone marrow stem cells (hBMSCs)

MSCs can also be isolated from human bone marrows and utilized for therapeutic purposes. BMSCs are able to support angiogenesis and enhance the formation of new microvessels, secrete nerve growth factors and restore nerve function after ischemic stroke, as well as used to treat non-healing fractures.³² The research results of BMSC and PBM are widely applied to wound healing, fat production and bone formation. Studies were done with the combination of PBM and BMSCs using visible wavelength was also applied.^{17,33} However, more significant results came from the use of wavelengths in the near infrared region (808, 890, 905 and 1064 nm), which showed remarkable results in wound healing and bone formation.^{32,34-38} The equipment types, wavelengths and

Table 2. Human dental pulp stem cells related to PBM application

Type of light device	Wavelength (nm)	Energy density (J/cm ²)	Related research fields	Criteria	Ref.
InGaAlP laser	660	1, 3, 5, 10, 15, or 20	In vitro, osteogenesis	Proliferation in the undifferentiated state	7
CW and PW-LED	810	0.038	In vitro	CW-PBM; proliferation PW-PBM; differentiation	12
GaAlAs diode laser	660	2 and 4, every 3 days for 4 weeks	In vitro, osteogenesis	Odontogenic differentiation with Mg-based scaffolds	16
CW GaAlAs diode laser	660	0.14	In vitro, osteogenesis	Improve osteogenic differentiation	26
InGaAlP laser	660	3 and 5	In vitro, cell sheets	Functional differentiation of cells (collagen and fibronectin)	27
InGaAlP diode laser	660	33.33	In vitro, wound	Proliferation and migration	28
Fiber optic diode laser	660	55.2, 22.1, 1.6, and 0.6	In vitro, neurodegenerative disorder	Dopaminergic neuronal differentiation	29
InGaAlP	660	3 and 5	In vitro/in vivo	Proliferation differentiation	30
GaAlAs laser	808	30 mW	In vitro, neuron	Proliferation neurogenesis differentiation	31

CW, continuous wave; PW, pulse wave.

energy densities used in the experiment are summarized in Table 3.

Effect of PBM on human umbilical cord blood-derived MSCs (hUCMSCs)

In the research of UCMSC and PBM, studies using animal-derived mesenchymal stem cells isolated from human umbilical cord blood have also been reported. UCMSCs also showed the ability of self-renewal and capacity to differentiate into multiple lineages. Compared to the ethical hurdles faced by the use of ESCs, the use of hUCMSCs for scientific studies is regarded as ethically acceptable. However, the combination of UCMSC and PBM with the red wavelength (620, 625, 633, and 635 nm) was effective for the induction of blood vessel and bone formations.^{4,6,39,40} The equipment types, wavelengths and energy densities used in the experiments are summarized in Table 4.

Effect of PBM on animal derived mesenchymal stem cells

Cases of PBM application on animal-derived mesenchymal stem cells have also been reported. The animals

used in the experiments were mouse,⁴¹ rabbit,⁴²⁻⁴⁴ rat⁴⁵⁻⁵³ and equine.⁵⁴ Similar to human-derived MSCs, the wavelengths used for PBM on animal cells were in the visible region of the spectrum (blue, green, and red)^{43,44,46,48-50,52} to near-infrared region (808-1064 nm).^{41,42, 45,47,51,53,54} The effects showed a positive effect on wound healing, bone regeneration, and nerve regeneration. The equipment types, wavelengths and energy densities used in the experiments are summarized in Table 5.

Potential PBM mechanism for stem cell proliferation and differentiation

These reviewed papers suggest several mechanisms in which PBM affects stem cell proliferation and differentiation. What is commonly suggested as a mechanism of PBM is that it causes anti-apoptosis by increasing ATP and reducing oxidative stress.^{30,53} PBM influences ADSCs in wound healing through anti-apoptosis regulation (up-regulated Bcl-2 and downregulated Bax), migration via ERK1/2 and FAK pathway, and inhibited the downregulated TGF- β 1 and Notch-1 expression.²⁰ Another published skin flap ischemia study suggested the possibility of PBM effect was mediated by mitogen-activated protein kinase

Table 3. Human bone marrow stem cells related to PBM application

Type of light device	Wavelength (nm)	Energy density (J/cm ²)	Related research fields	Criteria	Ref.
Red diode laser	630 and 660	1	In vitro, osteogenesis	Osteogenic differentiation	17
NIR laser	808 and 905	0.93-6.27	In vitro, wound	Proliferation	32
LED, diode laser and NIR diode laser	405, 635, and 808	0.4	In vitro, bone	Proliferation, osteogenic differentiation at 635 nm	33
NIR laser	890	0.2	In vivo, DM wound healing	Proliferation shortened the inflammatory phase	34
NIR laser	890	0.2, 6 days a week for 15 days	In vivo, DM wound	Induced anti-inflammatory and angiogenic activities	35
NIR diode laser	808	0.5, 1, 2, 3, and 4	In vitro, in vivo, gingival wound	Gingival migration at 1 J/cm ² in unproliferation	36
Collimated laser to IR light	1064	8.8, 17.6, and 26.4	In vitro, adipocyte	Adipogenic differentiation	37
InGaAlP red laser	660	2.5, 5.0, and 7.5	In vitro, osteogenesis	Osteogenetic proliferation	38

IR, infrared.

Table 4. Human umbilical cord blood-derived mesenchymal stem cells (MSCs) related to PBM application

Type of light device	Wavelength (nm)	Energy density (J/cm ²)	Related research fields	Criteria	Ref.
LED array	633	0.3, 1, 3, and 6	Angiogenesis Radiation-induced enteropathy	Proliferation	4
Red and NIR Laser	635 and 808	0 to 10	In vitro	Neural differentiation 808 more effective	6
LED	620	2	In vitro, osteogenesis	Proliferation and osteogenic differentiation	39
LED	625	1.9	In vitro, gametogenesis	Proliferation and differentiation	40

Table 5. Animal derived MSCs related to PBM application

	Type of light device	Wavelength (nm)	Energy density (J/cm ²)	Related research fields	Criteria	Ref.
Mouse BMSC	Diode laser	808	64, every 24 h for 0, 5, 10, and 15 days	In vitro, osteogenesis	Osteoblast differentiation under down-regulation of the pro-inflammatory cytokines	41
Rabbit BMSCs	GaAlAs laser	810	4, every other day for 3 weeks	In vivo, wound	Promote the healing of osteochondral defects compared with the use of BMSCs alone	42
Rabbit BMSCs	Blue, green, red, and IR laser	470, 532, 660, and 810	4, every other day for 3 weeks	In vitro, osteogenesis	Proliferation and differentiation in red and IR lasers and green	43
Rabbit BMSCs	Laser	485, 532, 660, and 810	4, for 3 weeks	In vitro, chondrogenesis	Osteogenesis (660 and 810) Cartilage differentiation (810 and 810+532)	44
ADSC	NIR laser	890	2.196 and 40.824	In vivo, wound	Proliferation	45
Rat ADSC	GaAlAs laser	660	10, 18, and 27	In vitro	Proliferation inhibited oxidative stress	46
Rat ADSCs	NIR light	808	71.2	In vivo	downregulation of pro-inflammatory cytokines and MPs	47
Rat BMMSC	He-Ne laser	632.8	1.2	In vivo	Proliferation e osteogenic differentiation	48
Rat BMMSCs	He-Ne laser +alendronate	632.8	1.2	In vitro	Proliferation osteogenic differentiation	49
Rat BMMSCs	He-Ne laser	632.8	1.2, three times on other days	In vivo, osteogenesis	Proliferation and differentiation	50
Rat BMMSCs	NIR laser	890	1.5, three times per week for 8 weeks	In vivo, osteoporosis	Proliferation	51
Rat BM-MSCs	He-Ne laser	632.8	0.5, 1, and 2, every other day for three times	In vitro, in vivo, diabetic	Proliferation at 1 J/cm ² under anti-apoptosis	52
Rat BMSCs	PW IR laser	890	1.5, for 3 times a week	In vitro, neuron	Proliferation neural differentiation	53
Equine- MSC	Nd:YAG laser	1064	9.77	In vitro, angiogenesis	No difference in viability but increased of IL-10 and VEGF	54

BMSC, bone marrow mesenchymal stem cells; ADSC, adipose-derived stem cells; Nd:YAG, neodymium-doped yttrium aluminum garnet; VEGF, vascular endothelial growth factor.

Fig. 1. Schematic representation of the application of photobiomodulation (PBM) on stem cell and therapeutic benefits. PBM using wavelengths from the red to near-infrared light spectrum (600 to 1000 nm) induces mesenchymal stem cell proliferation and differentiation for tissue engineering and regenerative medicine. hASC, human adipose stem cell; hUCMSCs, human umbilical cord blood-derived MSCs; hDPSC, human dental pulp stem cell; hBMMSCs, human bone marrow mesenchymal stem cells.

and phosphatidylinositol 3-kinase/Akt signaling pathway.²² Other mechanisms showed a shortened inflammatory stage in diabetic wound model by increasing the gene expression of bFGF, SDF-1 α , and HIF-1 α which results in the wound healing acceleration.³⁴ It has also been reported that PBM enhances MSC migration through the ROS/JNK/NF- κ B/MMP-1 pathway, which increases protein expression of p-JNK, p-IkB, p65 and MMP-1.³⁶

Until now, the parameters of PBM for prevention and treatment of the diseases have not been fully established. The irradiation dosage is one of the important parameters to induce PBM efficiently to stem cells as well as other cell types. PBM is known to have a bipolar effect, as for instance, by stimulating TGF with low-dose or suppressing TGF with a relatively high-dose of LED irradiation for improving skin rejuvenation or treating skin fibrosis.^{55,56} Therefore, it is necessary to accumulate data on dose-dependent effects of PBM. The results of this experiment will help us understand and utilize PBM for stem cell research.

CONCLUSIONS

The application of PBM can be a promising combination to improve mesenchymal stem cell therapy (Fig. 1). Well defined parameters, such as wavelength range, irradiation time, and energy density, can enhance proliferation or differentiation of stem cells.

However, in order to translate into a reliable clinical application, it is necessary to provide a more detailed scientific evidence supporting the clinical use of stem cells by establishing a clear mechanism of how PBM interacts with various stem cells to achieve the intended medical innovations.

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