Photobiomodulation Therapy and Dental-derived Mesenchymal Stem Cells: a Review of Literature

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Introduction: The role of PBMT in regulating cellular activity as well as its biostimulation effect on cell proliferation or inhibition has led a group of studies to investigate its effect on stem cells. The aim of this review study was to investigate the effect of photobiomodulation therapy (PBMT) on the function of Dental Derived Mesenchymal Stem Cells (DDMSCs). **Materials and Methods:** The study was done by reviewing laboratory and clinical studies conducted until 2020 according to the following keywords: Photobiomodulation therapy, Low Level Laser Therapy, Regeneration, Dental Derived Mesenchymal Stem Cells using "and" conjunction in Pub med, Medline, Springer, Elsevier, and Science direct databases. **Results:** The findings of 9 related articles indicated the role of PBMT in improving proliferation and viability of DDMSCs. Also, the functional improvement of stem cells in the regeneration of dental pulp can be one of the most crucial effects of PBMT. **Conclusion:** In general, the most important finding of this study was the positive effect of PBMT in proliferation and differentiation of Mesenchymal stem cells (MSCs). However, the insufficient clinical trials remain an obstacle in achieving definitive results in examining the relationship between PBMT and MSCs.

Keywords: Photobiomodulation Therapy; Low Level Laser Therapy; Regeneration; Dental- derived Mesenchymal Stem Cells

Introduction

Photobiomodulation therapy (including low-level light / laser therapy and low-level laser irradiation) can be considered as a kind of Interaction between low energy density light and cells without thermal effects (maximum temperature changes below 98 ° F) caused by photons. In Photobiomodulation (PBM) technique from electromagnetic radiations with wavelengths in the visible range (380–700 nm) or near infrared region (700–1070 nm) and power radiation between 250-500 mW or less than 250 mw is used (1, 2).

PBMT as a noninvasive and painless method, it has known stimulatory effects on tissue growth and regeneration, reducing inflammation and pain, wound healing, fibroblast and chondrocyte proliferation, collagen synthesis and nerve cell regeneration (1, 2).

The Biomodulation effects PBMT can cause photophysical, photochemical and photobiological reactions in the cellular photoreceptors and effects on the respiratory chain (3, 4). Photochemical reactions can be caused by the effect of visible light or Near Infra-Red (NIR) radiation on mitochondrial photoreceptors as well as on the Adenosine triphosphate (ATP) synthesis process. The effects of light irradiation on the Ca ++ channels present in the cell membrane can be the basis of Photophysical reactions (5-9).

Light absorption by the respiratory chain components causes short-term activation of the respiratory chain and oxidation of the Nicotinamide adenine dinucleotide (NAD) pool. This stimulation of oxidative phosphorylation results in a change in mitochondrial redox position as well as in the cell cytoplasm. The electron transport chain is capable of providing increased levels of excitatory forces to the cell through increased ATP storage, as well as an increase in the electrical potential of the

mitochondrial membrane, cytoplasmic alkalization, and activation of nucleic acid synthesis. Therefore, PBMT has the potential to stimulate normal cell functions by affecting the ATP storage as a common form of energy in the cell.

With increased respiratory cell metabolism, PBMT can also affect the cell's electrical-physiological properties (10, 11). Stimulation of cell proliferation and inhibition of cell death as well as the effect on the production of extracellular matrix proteins are the most important effects of PBMT on cellular gene expression (4). The mechanism of the effects of PBM on the process of stem cell proliferation or differentiation is based on the stimulation of cellular photoreceptors. Absorption of visible light and NIR by Mitochondria photoreceptors activates the respiratory chain including NADH dehydrogenase, cytochrome C reductase, and oxidase as well as ATP synthase (12, 13). It is also hypothesized that infrared radiation will transmit biological messages by activating ion channels and affecting cell membrane permeability as well as the concentration of Na + -K + flux and Ca + 2 ions (6).

In general, the biostimulating effect of PBM can be expressed as increased microcirculation, increased synthesis of ATP, RNA, and DNA, improved oxygen delivery, nutrition, and consequently regeneration (14).

This review aims to present the role of PBMT in the function of MSCs in regeneration of Maxillofacial tissues by reviewing laboratory and clinical studies conducted until 2020.

Materials and Methods

Search strategy

A comprehensive search of the studies was conducted until April 2020 in the following databases: Pub med, Medline, Springer, Elsevier, and Science direct. The strategy of search was according to the following keywords: Photobiomodulation therapy, Low Level Laser Therapy, Regeneration, Dental Derived Mesenchymal Stem Cells using "and" conjunction.

Study selection

The Inclusion Criteria in our study was based on the Full-text articles with English language published until 2020. Due to the lack of valuable clinical studies, animal and laboratory studies were also considered. The Exclusion Criteria in our study was based on the non-English language studies or articles that are not available in full text.

Results

The findings of 9 related articles indicated the role of PBMT in improving proliferation and viability of DDMSCs. Another important finding of laboratory studies was an increase survival as well as proliferation of stem cells from apical papilla (SCAP) in chitosan scaffold by PBMT. Also, improving the biological function of stem cells in the regeneration of dental pulp can be one of the most important effects of PBMT. Most studies have evaluated the effect of PBMT on stem cells from exfoliated deciduous teeth (SHED). The fewest findings were related to the relationship between PBMT and Dental follicle progenitor cells (DFPCs).

Discussion

Mesenchymal stem cells (MSCs) are one of the types of adult stem cells that were isolated from bone marrow for the first time. These cells are not hematopoietic and have been found in addition to bone marrow in the liver and skeletal muscles. MSCs are capable of prolonged proliferation without loss of function and they can be differentiated into cartilage, bone, fat. Therefore, MSCs are a more proper and promising source in tissue engineering than other types of adult stem cells for therapeutic application.

Relative ease of cell culture, limited immunogenicity, ability to suppress immune system activity, multilineage ability can be considered as the most crucial characteristics of MSCs (4, 15-17).

The most common source of MSCs is bone marrow, but limitations such as the painful sampling process and the small number of stem cells have led new research to find an alternative source. Identification and isolation of stem cells from dental pulp and follicles were reported in 2000 by Gronthos *et al.,* and in 2005 by Morsczeck *et al.,* (18-20).

Other sources of MSCs include the third molar tooth. In humans, the formation of third molar teeth is unique. Because the process of organogenesis begins after birth at the age of 6 years and until this time the fetal tissues remain undifferentiated in the dental tissues. Since the third molar tooth is routinely extracted for prophylactic or orthodontic reasons and discarded without use, isolation of MSCs from the third molar tooth is an appropriate option (19).

Although wisdom teeth are one of the most common dental sources for isolation of stem cells, the newer source is deciduous teeth, which have their own benefits, including: ease of access, lack of tissue destruction at the donor site, reduction or elimination of patient pain and discomfort, a greater number of cell sources as well as the ability to obtain cells from younger patients (resulting in faster and easier cell proliferation) and a longer period of time for accessing MSCs throughout the Mixed Dentition period. Studies on dental pulp stem cells have demonstrated the ability of differentiation into several types of different cells including: osteogenic, chondrogenic, adipogenic, myogenic, neurogenic, and of course odontogenic (18).

So far, five important types of Dental- derived Mesenchymal Stem Cells (DDMSCs) have been isolated:

1. Dental pulp stem cells (DPSCs)
2. Stem cells from exfoliated deciduous teeth (SHED)
3. Periodontal ligament stem cells (PDLSCs)
4. Stem cells from apical papilla (SCAP)
5. Dental follicle progenitor cells (DFPCs)

Photobiomodulation therapy and MSCs

Some laboratory studies have indicated a positive effect of PBMT on the rate of proliferation and differentiation of MSCs (4, 21, 22). Theocharidou *et al.,* showed that PBMT increased the expression of Runx2 / CBFA-1 transcription factors and subsequently Osterix as key factors in the process of bone marrow MSCs differentiation (4, 21). Also, Manzano-Moreno *et al.,* have suggested that the expression of osteoblast differentiation markers such as ALP, Osterix, and Runx2, as well as BMP-2 is significantly increased by PBM (21). Other effects of PBM include activation and synthesis of growth factors such as FGF, VEGF, TGF-β1, and prevention of cell death. The findings of the studies indicate the improvement of biological function of stem cells in dental pulp regeneration following PBMT (24-26).

Photobiomodulation therapy and DPSCs

Dental pulp is a rich source of MSCs called DPSCs, which have the ability of multilineage differentiation. DPSCs are considered a very good cellular source for tissue regeneration and in the tissue engineering technique, they are transferred to the desired site as cell-scaffold constructs by inserting them into the tissue scaffolding (4, 27). DPSCs are able to regenerate the dentin-pulp complex and can even be used in the reconstruction of a complete tooth (28-30).

The PBM and Vitamin C (ascorbic acid) on DPSCs culture media increases the expression of mesenchymal stem cell markers, such as mitofilin. Therefore, the association of Vitamin C and PBMT can play an important role in the future of regenerative dentistry for the reconstruction of dental tissues such as periodontal ligament and bone (20, 31).

Photobiomodulation therapy and SHED

SHED are another type of stem cells that the effect of PBM therapy has been studied on them. Increased expression and activity of alkaline phosphatase and dentin sialophosphoprotein, as well as increased collagen synthesis, are among the most important effects of PBM therapy on the SHED culture medium, which ultimately led to the differentiation of osteoblasts. Also, other findings of PBM therapy on stem cells from deciduous teeth are increased viability, proliferation and production of mineral tissue (32-34). Study of Diniz et al. It has also been shown that PBM increases SHED survival in cell culture medium (35).

Photobiomodulation therapy and PDLSCs

PDLSCs are a type of MSCs that were isolated from periodontal ligament in 2004 and were able to regenerate tooth specific attachments such as Cementum / PDL-like complex in animal mice. In fact, PDLSCs can differentiate into osteoblasts, fibroblasts, and cementoblasts. Accordingly, animal and human studies have shown an improvement in periodontal reconstruction following transplantation of PDLSCs. However, one of the most important problems with using PDLSCs is the limitation of the number of stem cells (36-39).

Soares *et al.,* In a laboratory study, examined the effect of PBMT (Low-level laser irradiation or LLLI) on PDLSCs proliferation. The results of their study showed a positive effect of infrared radiation with an energy density of 1.0 J / cm^2 on PDLSCs proliferation (39). Findings from Wu *et al.,* study have also been shown that PBM can stimulate proliferation as well as osteogenic differentiation in PDLSCs (40).

Photobiomodulation therapy and SCAP

Sonoyama W *et al.,* were among the first to isolate SCAP from the papilla of the root tip of young people's teeth. SCAP are isolated from the apical papilla tissues of teeth whose root dentin is forming and have the ability to self-renewal, high proliferation, and multilineage differentiation into dentin, osteoblasts, and vascular nerve cells. *In vitro* studies show that

SCAP are more potent for proliferation and differentiation than other odontogenic stem cells (41-46). According to *in vitro* findings, PBM increases survival as well as proliferation of SCAP in chitosan scaffold (20).

Photobiomodulation therapy and DFPCs

DFPCs are another group of MSCs that were isolated from the wisdom teeth follicles by Morsczeck *et al.,* In 2005. DFPCs are able to regenerate all types of periodontal tissues, including cementum, periodontal ligament, and alveolar bone (47). There are few valuable studies related to the effect of PBM on DFPCs, and it is generally stated that PBM has no deleterious effects on effect on their performance. However, it seems that PBMT can improve viability and proliferation of DFPCs (48).

Conclusion

Based on the findings of laboratory and animal studies, biostimulation of PBMT has a positive effect in DDMSCs proliferation and differentiation. Improving biological function and increasing the survival of stem cells in tissue scaffolds are other important effects of PBMT on DDMSCs. However, achieving valid results and evidence-based treatment protocols requires further clinical studies.

Conflict of Interest: 'None declared'.

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