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(REVIEW ARTICLE)

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Osteogenic differentiation enhancement of human dental pulp mesenchymal stem cells: A review

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Abstract

Background: The article aims to review osteogenic differentiation enhancement in human Dental Pulp Mesenchymal Stem Cells (hDPMSCs).

Material and Methods: The literature review was carried out in PUBMED with the keywords: human Dental Pulp Mesenchymal Stem Cells (hDPMSCs) and osteogenic differentiation.

Conclusions: Many research investigated the impact of different compounds on the osteogenic differentiation of hDPMSCs and the appliance by which these compounds promote osteogenesis in hDPMSCs which are a potential source for bone regeneration.

Keywords: Differentiation; Dental Pulp; Mesenchymal Stem Cell; Osteogenic

1 Introduction

Stem cells are unspecialized human cells. Stem cells exist in every living organism. Stem cells are able to distinguish between different types of organ cells and develop into specific tissue. Stem cells are also capable of renewing or regenerating themselves (self-regenerate/self-renew). Based on their developmental potential, stem cells are divided into 5 types, namely: Totipotent stem cells, namely stem cells that have the highest differentiation potential. Totipotent stem cells are capable of becoming cells of entire organisms. Example: zygote. Pluripotent stem cells (PSCs) are cells that have pluripotency. Example: Embryonic Stem Cells (ESC), Induced Pluripotent Stem Cells (iPSCs). Multipotent stem cells are stem cells that have a narrower spectrum of differentiation than PSCs. Example: Haematopoietic stem cell (HSC), Mesenchymal stem cell (MSC). Oligopotent stem cells are cells that have the capability to change into multiple cell types. Myeloid stem cell is a sample of an oligopotent stem cell that has the ability to give rise and divide to white blood cells, but it cannot differentiate into red blood cells. Unipotent stem cells are cells that have the narrowest ability to separate, can only become a type of cell, and are capable of undergoing cell division [1]. MSCs are multipotent unspecialized cells that are able to be obtained from numerous tissues in the body such as adipose tissue, bone marrow, cord blood, dermal tissue, and synovial fluid. MSC has shown effectiveness in the treatment of numerous diseases, as a result of its protection and the mechanism of tissue reparative [2].

In the dental pulp of adult human teeth, there is a group of clonogenic cells that exhibit a high performance for proliferation in Dental Pulp Mesenchymal Stem Cells (hDPMSCs). These cells originate from the enzymatic breakdown of human adult dental pulp. hDPMSCs are multipotent cells that can proliferate extensively. They have the ability to

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produce dentin, the hard tissue of teeth, as well as other types of cells such as osteoblasts which form bone. They have high rates of proliferation, clonogenicity, self-renewal, and multilineage differentiation potential. They are considered an encouraging source of cells for regenerative medicine applications, both in dentistry and in other tissues [3][4]. Human Dental Pulp Mesenchymal Stem Cell (hDPMSCs) is capable to distinguish into cells including osteoblasts, odontoblasts, adipose cells, nerve cells, cardiomyocytes, myocytes, and chondrocytes. In addition, hDPMSCs also have the ability to respond to specific environmental signals and can also produce new stem cells for further differentiation [5]. Emerging evidence shows that cell layers taken from DPSCs have better influence in tissue enginering [6]. DPSCs have been used for modeling genetic disorders and for tissue engineering for regenerative medicine [6][7]. DPSCs have a great potential for therapeutic applications in various fields of medicine.

because of their facile surgical reachability, cryogenic preservation capability, higher performance of dentin tissues in comparison to non-dental stem cells, and their anti-inflammatory properties, hDPMSCs are the most valuable dental source for tissue engineering. These cells may be used in maxillofacial and orthopedic repairs, as well as reconstructions outside the oral cavity. All of the evolved tooth's structures can be generated by hDPMSCs [1].

Osteogenic differentiation is the pathway by which MSCs differentiate into osteoblasts, which are cells that form bone tissue. Osteogenesis is initiated by osteoblasts, which are taken from MSCs. hDPMSCs are an attractive source of multipotent mesenchymal stem cells because of their high proliferation rate and potential for multiline differentiation. It has been observed that MSCs can distinguish bone-like cells whenever a suitable environment is provided. As hDPMSCs exhibit MSC-like characteristics, they may be induced to distinguish into osteoblasts, hDPMSCs have high capacity for osteogenic differentiation [8]. Therefore, the aim of this article is to review osteogenic differentiation enhancement in hDPMSCs.

2 Material and methods

2.1 Search strategy

A literature search in English was performed, using the PUBMED database to identify research of osteogenic differentiation in hDPMSCs. Research and literature reviews from 2015 to 2023 were included. The following keywords were searched: osteogenic differentiation, human Dental Pulp Mesenchymal Stem Cells.

3 Results and discussion

3.1 Aspirin Enhance Osteogenic Differentiation of hDPMSCs

Yuan et al. (2018) investigates the impact of aspirin on the osteogenic differentiation of hDPMSCs, a potential source for orofacial bone regeneration. The authors found that aspirin at concentrations up to 100 μg/mL was nontoxic to hDPMSCs and increased their osteogenic potential in vitro and in vivo. Aspirin enhanced the expression of osteogenic markers such as alkaline phosphatase, osteocalcin, runt-related transcription factor 2 and osterix, and mineralization of hDPMSCs. Aspirin also enhanced the osteogenic capacity of hDPMSCs in a rat skull defect model, as demonstrated by radiological and histological analyses. The authors suggested that aspirin might promote osteogenesis in hDPMSCs by inhibiting the production of cyclooxygenases and prostaglandins, which are known to negatively regulate bone metabolism. The paper concludes that aspirin may be an applicable agent to enhance the bone regeneration potential of hDPMSCs [9].

3.2 Berberine Enhance Osteogenic Differentiation of hDPMSCs

Xin et al. (2020) investigates the effects of berberine (BBR), a natural compound with antibacterial properties, on the osteogenic differentiation of hDPMSCs, a potential source of tooth regeneration. The authors found that concentrations of 1 μM and 5 μM BBR stimulated osteogenic differentiation and proliferation differentiation of hDPMSCs in vitro and in vivo. BBR increased osteogenic expression markers including Runx-2, osteocalcin, alkaline phosphatase, and osterix, as well as mineralization in hDPMSCs. BBR also inhibited adipogenic differentiation of hDPMSCs. The authors showed that BBR activates EGFR and MAPK signaling pathways involved in regulating Runx2 activity and osteogenesis. Inhibitors of these signaling pathways attenuated the osteogenic effects of BBR. The article concludes that BBR may be a useful means of enhancing the osteogenic potential of hDPMSCs and promoting tooth regeneration [10].

3.3 Melatonin Enhance Osteogenic Differentiation of hDPMSCSs

Chan et al. (2023) investigates the effects and mechanisms of melatonin, a hormone with multiple biological functions, on the osteogenic differentiation and bone regeneration of hDPMSCs, adult stem cell variety obtained from dental pulp tissue. The authors found that melatonin at concentrations of 1, 10, and 100 μM increased hDPMSCs proliferation, osteogenic marker expression, alkaline phosphatase activity, calcification, and bone-forming gene expression in vitro. Melatonin also activated the osteogenic transcription factor Runx2 and inhibited the inflammatory mediator COX-2/NF-κB. In addition, melatonin stimulated phosphorylation of MAPK p38/ERK signaling pathways involved in regulating osteogenesis. Inhibitors of these signaling pathways attenuated the osteogenic effects of melatonin. The authors demonstrated that by combining hDPMSCs preconditioned with melatonin and MBCP bone graft material, as demonstrated by micro-CT, histological, histomorphometric, and immunohistochemical analyses, in rat skull defects It has also been shown to significantly improve bone regeneration. The article concludes that melatonin promotes differentiation of the osteoblast in hDPMSCs by modulating the COX-2/NF-κB and p38/ERK-MAPK signaling pathways, promoting bone regeneration efficiency in cranial defects [11].

3.4 Sodium Diclofenac Enhance Osteogenic Differentiation of hDPMSCs

Refaat et al. (2021) evaluates the effects of different types and doses of non-steroidal anti-inflammatory drugs (NSAIDs) on viability and osteogenic differentiation of hDPMSCs, a type of adult stem cell with regenerative capacity. The authors used acetylsalicylic acid (ASA), diclofenac sodium, and meloxicam as NSAIDs and tested different concentrations of each drug in hDPMSCs isolated from human dental pulp tissue. The authors assessed hDPMSCs survival, osteogenic marker expression, alkaline phosphatase activity, calcification, and the gene expression of osteogenic in vitro. The authors found that 10 μg/mL ASA, 10-6 M diclofenac sodium, and 0.01 μM meloxicam enhanced hDPMSCs survival and osteogenic differentiation, whereas higher doses of NSAIDs had adverse effects. In this study, diclofenac sodium 10-6 M was used as an effective agent for the first few days after surgery, followed by meloxicam 0.1 μM from day 3 to prevent gastric ulcers, followed by ASA 10 μg/ml. recommended to be treated with Continued from day 5 [12].

3.5 Dexamethasone Enhance Osteogenic Differentiation of hDPMSCs

Moretti et al. (2017) investigated the effect of preoperative dexamethasone (DEX) on the osteoinductive properties of hDPMSCs. The hDPMSCs were splitted into two groups, one group receiving DEX and the other not. The researchers used various methods to assess cell proliferation, viability, and mineralization. Methods used include methylthiazol tetrazolium, trypan blue, and von kossa method. They found that DEX had an osteoinductive effect on hDPMSCs, with cells from patients who received DEX prior to surgery differentiating earlier and producing more mineralized nodules than those who did not receive DEX [13].

3.6 GNP in injectable CPC promote osteogenic differentiation of hDPMSCs

Xia et al. (2018) investigated gold nanoparticles (GNP) incorporation into calcium phosphate cement (CPC) and the enhancement of osteogenesis of hDPMSCs. In this study, two groups were used, the first group was GNP-CPC and the second group without GNP as control. The gene expression of osteogenic markers including ALP, Runx2, OCN, and COLIα in hDPMSCs was tested by qRT-PCR. In addition, mineral synthesis by cells was evaluated by Alizarin Red S (ARS) staining. The results showed that GNP-CPC had higher gene expression of ALP, COLIα, Runx2 and OCN than the control. ARS staining results were three times denser and thicker in media with GNP than control media. These results indicate that GNP can increase bone matrix formation by hDPMSCs. It can be concluded that combining GNP with CPC can increase the osteogenic differentiation of hDPSMCs and also increase the cellular bone matrix mineral synthesis. [14].

3.7 Naringenin Enhance Osteogenic Differentiation of hDPMSCs

Kim et al. (2022), found that naringenin, a compound found in citrus fruits, can help hDPMSCs migrate and differentiate into bone or tooth cells. The researchers used various tests to analyze the cells' differentiation and mineralization, as well as their migration ability. Methods used include scratch wound healing migration assay, transwell chemotactic migration assay, alizarin red S (ARS) staining and alkaline phosphatase (ALP) staining. They also tested the cells' ability to differentiate in a tooth/scaffold model implanted in mice. Naringenin was found to promote differentiation and migration by increasing the expression of certain proteins and signaling pathways [15].

3.8 Co-culture hUCMSCs and hDPMSCs Enhance Osteogenic Differentiation

Huang et al. (2020), compared osteogenic differentiation between monoculture and co-culture of hDPMSCs and hUCMSCs. The researchers found that co-culturing hDPMSCs and human umbilical cord mesenchymal stem cells (hUCMSCs) resulted in stronger osteogenic differentiation and mineralization than culturing the cells separately. The researchers used various tests to analyze the cells' proliferation, differentiation, and mineralization. They found that

the co-culture group had greater proliferation potential, mineralized nodule formation, and alkaline phosphatase activity compared to the monoculture group. The certain genes' expression in relation to osteogenic differentiation was also higher in the co-culture group than in the monoculture group [16].

3.9 hDPMSCs in Alginate-gelatin/Nano-hydroxiappatite Microcapsules Enhance the Osteogenic Differentiation

The study by Alipour et al. (2021) aimed to microencapsulated hDPMSCs in Alg/Gel/nHA microcapsules and assesses the cell proliferation and osteogenic differentiation using Alkaline phosphatase, qRT-PCR, MTT assay, and Alizarin Red S. This study showed that Alg/Gel microencapsulated consisting of nHA exhibited rougher and tighter surface structure compared to Alg/Gel microcapsules. in addition, microencapsulation of hDPMSCs within Alg/Gel/nHA hydrogel demonstrated improved the proliferation of the cell and induced the cell osteogenic differentiation. The addition of nHA to hDPMSCs-laden Alg/Gel microcapsule stimulated RUNX2, osteonectin, and osteocalcin in the interval of 21 and 28 days of the growing period. Furthermore, the deposition of calcium and the activity of ALP in the cells were detected in line with the cell's proliferation results and the analysis of related-genes expression. The research concluded, hDPMSCs that are microencapsulated in Alg/Gel/nHA hydrogel perhaps a promising strategy for future of regenerative dentistry [17].

3.10 hDPMSCs Using Bitter Almond Incorporated nanofibrous scaffold Enhance the Osteogenic Differentiation

Valizadeh et al. (2023) investigated the influence of bitter almond extract loaded on PCL/ Gt nanofibrous scaffolds on the osteoblast differentiation of hDPMSCs. The researchers discovered that the addition of bitter almond extract improved the modulus of elasticity, tensile firmness, and strain at break compared to the neat PCL/Gt nanofibers. Bitter almond extract also increased the expression of osteogenesis genes markers as well as alkaline phosphatase, osteocalcin, runt-related transcription factor 2, osterix, and mineralization of hDPMSCs. The study concluded that bitter almond extract could be an applicable agent to enhance the bone regeneration potential of hDPMSCs [18].

3.11 Chlorogenic Acid Enhance Osteogenic Differentiation of hDPMSCs

Hu et al. (2021) investigated the impact and molecular basis mechanisms of chlorogenic acid (CGA) on the osteogenic differentiation of hDPMSCs. The results demonstrated that CGA treatment promoted the osteogenic differentiation of hDPMSCs, it was observed that CGA promoted the osteogenesis-related genes expression, and while inhibiting the osteoclastogenesis-related genes expression.The analysis of western blot revealed that the treatment with CGA reduced both active and total β-catenin levels, while increasing the levels of total pCamKII, CamKII, and pCREB. The osteogenesis that increased was linked with the canonical Wnt/β-catenin signaling that reduced but the noncanonical Wnt/Ca2+ signaling was increased. These findings suggest that CGA is capable of promoting the cell osteogenic differentiation of hDPMSCs by modulating Wnt signaling. This study provides a foundation for further investigations on repair of defective alveolar bone in patients with periodontal disease (PD) [19].

3.12 Forskolin enhanced Osteogenic Differentiation of hDPMSCs

Jin et al. (2023) examined the impact of forskolin on the osteogenic differentiation of hDPMSCs. This study used hDPMSCs and assessed the cell proliferation and cell osteogenic differentiation using various test including qRT-PCR, Alizarin Red S tests, Alkaline phosphatase, and MTT. qPCR showed Forskolin (5, 10 mM) promoted osteogenic differentiation of hDPMSCs by promoting the bone-related genes. Alizarin red staining and its assesment analysis presented Forskolin in 5 mM and 10 mM also promoted the mineralization deposits of hDPMSCs in vitro [20].

3.13 Oncostatin M Enahnces Osteogenic Differentiation of hDPMSCs

Kim et al. (2020) investigated the impact of oncostatin M (OSM), a cytokine belonging to the IL-6 family, on the osteogenic differentiation of hDPMSCs. OSM has been shown to inhibit adipogenic differentiation and rising osteogenic differentiation of human bone marrow mesenchymal stem cells. The researchers found that OSM stimulation promoted differentiation and remarkably enhanced the genes expression involved in bone regeneration, including BMP6, BMP4, RUNX2, and BMP2. The study concluded that hDPMSCs could be effectively derived from supernumerary teeth and showed characteristics of mesenchymal stem cells in differentiation and maintenance, making them a valuable resource for regenerative therapy [21].

3.14 Concanavalin A Enhances Osteogenic Differentiation of hDPMSCs

Suardita et al. (2020) found that concanavalin A (ConA), a lectin taken from the plant Canavalia ensiformis, promoted the proliferation and osteogenic differentiation of hDPMSCs. ConA is known for its ability to inhibit adipogenic differentiation and stimulate osteogenic differentiation in various animal cells. The researchers isolated hDPMSCs from

third molars and treated them with ConA at concentrations of 5 and 10 μg/mL. They used various tests to analyze the cells' proliferation and differentiation. They found that the addition of ConA remarkably promoted the proliferation and osteogenic differentiation of hDPSMCs [22].

4 Conclusion

This review concluded that many research investigated the influence of different compounds on the osteogenic differentiation of hDPMSCs, which are a potential source for bone regeneration. The compounds studied include aspirin, berberine, melatonin, and sodium diclofenac. The studies found that these compounds, at certain concentrations, were able to increase the osteogenic potential of hDPMSCs in vitro and in vivo by increasing the gene expression of osteogenic markers and mineralization. The studies also investigated the mechanisms by which these compounds promote osteogenesis in hDPMSCs and suggested that they may be useful agents for enhancing bone regeneration potential of hDPMSCs.

Compliance with ethical standards

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Disclosure Conflict of interest statement

We declare that there was no major conflict of this article

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