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Review Article

Pulp Regeneration-Novel Approaches

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Abstract

Introduction: Dental pulp stem cells (DPSCs) possess pluripotent differentiation characteristics. Angiogenesis and neurogenesis play a vital role in the pulp-dentin complex regeneration, and appropriate growth factors play a significant role in promoting the process of angiogenesis and neurogenesis.

Numerous growth factors, specific chemical formulations, and other newly introduced approaches contribute to pulp regeneration. The objective of this review was to discuss the novel approaches in pulp regeneration.

Overview: Insulin-like growth factor-binding protein 5 (IGFBP5) and PTH enhanced osteo/odontogenic differentiation of dental stem cells. Fibroblast growth factors (FGFs) primarily contribute to tooth development, repair, and regeneration.

N3 was the most effective formulation in promoting a neurogenic shift in gene and protein expression. A novel approach entitled "berberine" might promote hDPSCs osteogenic differentiation through activating EGFR-MAPK-Runx2 signaling pathways. Leptin showed the ability to induce angiogenesis, odontogenic differentiation and mineralization.

Conclusion: Several studies provided a potential approach to combine imaging and treatment for promoting effective dental pulp regeneration. Further prospective researches are required to improve the quality of evidence.

Keywords: *Pulp Regeneration; Pulp Vitality; Pulp Stem Cells; Angiogenesis; Neurogenesis*

Introduction

Dental stem cells that induce dental pulp regenerative mechanisms have become a promising strategy for treating pulp conditions such as pulpitis. Angiogenesis and neurogenesis are the two essential mechanisms that play a vital role in the pulp-dentin complex regeneration [1].

Regenerative endodontics aims to replace damaged endodontic structures: pulp connective tissue.

With its vascularization, innervation, and peripheral dentin [2]. There are several different pulp regeneration strategies have been proposed inspired by the advances in regenerative medicine [2].

The endodontic regeneration is solely modulated by challenging clinical conditions that require five categories of tissue pre-requisites including pulp connective-tissue formation, dentin formation, revascularization, re-innervation and radicular formation. Polymer scaffolds contribute as the cornerstone of the different endodontic regenerative strategies [2]. Scaffolds, however, are critical for carrying active molecules and competent cells that ultimately optimize the regenerative process [2].

Hydrogels are known to be beneficial for controlling the viscosity and porosity of endodontic scaffolds. The nanofibrous and microporous scaffolds imitating extracellular matrix is of great importance, as it helps in initiating dentin-pulp formation [2].

Collagen and fibrin are the two major types of polymer scaffolds. Collagen scaffolds mimic native pulp tissue, and thus adequately initiates and promotes pulp tissue regeneration while fibrin scaffolds contribute to promoting stem cell differentiation and revascularization [2].

Pulpitis is a common infection-related clinical condition. A pulpectomy often relieves the clinical signs and symptoms of pulpitis at the expense of sacrificing dental pulp functions [1].

Therefore, teeth that have lost the ability to form reparative dentin against the external stimuli are relatively more prone to vertical root fractures and thus consequently it leads to a higher incidence of extracting the tooth structure [1].

Numerous growth factors, specific chemical formulations, and other newly introduced approaches contribute to pulp regeneration. The objective of this review was to discuss the novel approaches in pulp regeneration.

Overview

Several strategies for pulp regeneration have been proposed widely in the literature. A study was conducted to compare the three different xeno-free protocols for neural differentiation of human dental pulp stem cells (DPSC) [3]. DPSC were treated with three different media to induce neural differentiation including N1 (DMEM for 5 days), N2 (PSC neural induction media for 7 days) and N3 (neural media with B27 supplement, 40 ng/ml bFGF and 20 ng/ml EGF for 21 days) [3].

Cell proliferation (MTS assay), morphology, gene and protein expression of neurogenic markers were assessed at different time points and compared to untreated cells.[4] The authors concluded that N3 was the most effective formulation in promoting a neurogenic shift in gene and protein expression [3]. Cells provided with the N3 formulation exhibited neuron-like morphology, elaborating axonal-like projections concomitant with cell cycle withdrawal and reduced expression of stem genes indicating a greater commitment to a neurogenic lineage [3].

A study by Li., *et al*. supported the use of Insulin-like Growth factor Binding Protein 5. IGFBP5 promoted the angiogenic and neurogenic differentiation potential of DPSCs *in vitro* and provided the possible potential target for enhancing directed differentiation of dental stem cells and dental pulp-dentin functional regeneration [1].

Parathyroid hormone (PTH) is considered a main systemic mediator of calcium and phosphate metabolism in the bone. PTH might influence the proliferative ability and cause osteoporosis/odontogenic differentiation of DPSCs [4]. Purified DPSCs were obtained as a result of enzymatic digestion, which often presented a typical fibroblast-like morphology [4]. Results revealed that 10-9 mol/L PTH was used as the optimal concentration for DPSCs induction [4]. 10-9 mol/L PTH treatment did not change the proliferative rate of DPSCs ($p > .05$) [4]. Particularly, their mRNA/protein levels at Day 7 were markedly higher relative to those on Day 3 ($p < .05$ or $p < .01$) [4]. However, mineralized nodules were formed after PTH induction, and calcium content increased by cetylpyridinium chloride quantitative analysis [4]. Therefore, PTH enhances the osteo/odontogenic differentiation capacity of DPSCs via ERK and P38 signaling pathways [4].

Leptin is secreted as a peptide hormone from adipose tissues. Leptin has the potential ability to induce angiogenesis, odontogenic differentiation, and mineralization in exposed rat pulps [5]. Leptin was also known to exhibit favorable inflammatory responses in the pulp tissue [5]. Osteodentin but also tubular dentin and new vessels were thus observed in the pulp cavity [5].

Besides, Fibroblast growth factors (FGFs) are growth factors that play an important role in tooth development, repair, and regeneration. Of the FGF families, basic fibroblast growth factor (bFGF) has been the most frequently investigated in dentistry. Numerous studies have reported advantages of bFGF, while others did not find any additional benefit [6].

Berberine (BBR), was recently found to induce bone formation by promoting osteogenic differentiation from pluripotent stem cells [7]. However, whether BBR also functions in DPSCs osteogenic differentiation has not yet been reported [7]. An experiment was performed where primary DPSCs were isolated from dental pulp tissues extracted from human-impacted mandibular third molars and identified by flow cytometry for cell surface antigen molecules [7]. A dexamethasone osteogenic medium was used to induce DPSCs osteogenic differentiation [7].

BBR (1 μM and 5 μM) was pre-added into medium, and then cell proliferation, spheroid formation and osteogenic differentiation capacities of DPSCs were analyzed, as well as the underlying molecules modulation mechanism [7]. BBR enhanced the cell proliferation of hDPSCs in a dose-dependent pattern and promoted dexamethasone-induced osteogenic differentiation via enhancing Runx2 transcription factor activity followed by upregulating osteogenesis markers expression, whereas the adipogenic differentiation of hDPSCs was suppressed dramatically by BBR [7]. The EGFR and MAPK pathways were activated by BBR, and inhibitors for these pathways significantly suppressed the osteogenic differentiation promotion of BBR [7]. These results have revealed a novel mechanism that berberine might promote hDPSCs osteogenic differentiation through activating EGFR-MAPK-Runx2 signaling pathways [7].

Essential features of the regenerated pulp tissues

Therefore, the regenerated tissues produce new dentin with a controlled rate similar to the normal pulp, exhibit similar cell density and architecture to the natural pulp, are vascularized, and are innervated [8].

3D analysis strategies for pulp regeneration

The use of 3D analysis strategies to understand the cellular behavior and its contribution to the regeneration process would be of great value for the advancement of the regenerative protocols already used [9]. 3D analysis of the new tissue constructs could be achieved using two different approaches: the reconstruction of images of sequential histological sections or analyzing full-volume images [9]. The first consists of obtaining serial slices of the sample and then aligning the images of these slices into a set of data in 3D [9]. However, it is a very challenging and demanding technique, mainly due to the delicate slicing process [9]. This step of the process, if not prepared carefully, can result in sample distortions that will be reflected in the final image [9].

Conclusion

Several studies provided a potential approach to combine imaging and treatment for promoting effective dental pulp regeneration. Further prospective researches are required to improve the quality of evidence.

Conflict of Interest

The author declares no conflict of interest to the products mentioned in the manuscript.

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