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Review Article

The Current Applications and Efficacy of Stem Cells in Dentistry

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Received: August 04, 2023; **Published:** Septemer 22, 2023

Abstract

Regenerative medicine is one of the fastest-growing fields in healthcare, leading to innovation and the development of new treatments for various diseases. In Dentistry, multiple types of stem cells can be used to regenerate different anatomical features and enhance the success of current therapies. This literature review explores the most recent applications of dental pulp stem cells (DPSCs) in Dentistry by reviewing various academic articles on PubMed.

The results reveal that DPSCs have multiple uses, such as regenerating pulpal tissues and applications in treating systemic illnesses. DPSCs can also restore new vascular structures, aiding in angiogenesis and maintaining homeostasis. In endodontics, DPSCs can regenerate pulpal tissues subcutaneously. Moreover, its applications enhanced the regeneration of various tissues, blood vessels, and neurogenesis. Alternatively, in periodontics, DPSCs reduced the inflammatory responses of periodontal tissues. When combined with a Bio-Oss xenograft, DPSCs enhanced the regeneration rate for PDL and cementum. These findings suggest further research to investigate the capacity for DPSCs use in Dentistry.

Keywords: *Regenerative Medicine; Dental Pulp Stem Cells (DPSCs); Dentistry; Bio-Oss Xenograft*

Introduction

Regenerative Medicine/Dentistry is a branch of Medicine/Dentistry that focuses on repairing, replacing, or regenerating injured, diseased, or dysfunctional tissues. It represents a pioneering and interdisciplinary field that combines the wisdom and methods of various biotechnological disciplines (e.g. clinical medicine/dentistry, cell and molecular biology, material science, bioengineering, etc.) [1,2].

There has been outstanding development in tissue engineering in the past twenty (20) years that can be applied to dentistry. Significant changes can be expected in dental treatment due to the recent advances in understanding the cellular and molecular basis controlling the development of regeneration of tooth structures. These procedures could result in continued root development, increased dentinal wall thickness, and induction of apical closure.

Dental stem cells (tooth-derived stem cells) are categorized according to the location from which they are isolated and represent a promising source of cells for regenerative therapy [3,4]. A stem cell is characterized by the ability to renew itself through mitotic cell division and differentiate into a diverse range of specialized cell types. Human stem cells isolated from the dental pulp tissue of extracted teeth have

been named "Dental Pulp Derived Stem Cells (DPSCs)" for their clonogenic properties and ability to differentiate into osteoblast-like cells and form dental pulp-like complexes [5].

Since identifying dental stem cells in the early 2000s, recent advances in cell and molecular-based dentistry have led to promising developments in dental therapies to repair, replace, and regenerate dental tissues. Moreover, new methods have been developed to study human tooth organogenesis [6].

One research scopes of dental regenerative medicine are to optimize tissue engineering techniques with dental mesenchymal stem cells (MSCs) [7]. The abundance, ease of isolation, and homogeneity of dental MSCs represent a promising reservoir for regenerative medicine/dentistry [8].

Two (2) min types of stem cells are being investigated for their potential use in research and medicine/dentistry: embryonic stem cells and adult stem cells. They differ in the degree of differentiation and self-renewal abilities [9].

Clinical dentistry has relied on various dental biomaterials and therapeutic options to prevent and treat dental caries and lost tooth structure. Also, multiple protocols are utilized to avoid and treat periodontal disease. While dental implants may be considered the "Gold Standard" for replacing missing teeth, they do not exhibit many properties of natural teeth. They can be associated with complications leading to their failure. However, developments in tissue engineering and the recognition of the usefulness of stem cells in tissue repair and regeneration have led to an interest in principles and protocols to regenerate the dental complex and/or its associated structures [10,11]. This literature review assesses the applications of stem cells in dentistry.

Tooth development

The process of tooth development follows a series of events throughout odontogenesis. The role of the dental follicle is significant to tooth development (as exhibited in dogs' premolars over four decades prior). If a tooth's crown was removed, but the dental follicle was not impacted, the eruption pathway would continue to prevail without interruptions. Additionally, when no tooth movement is exhibited, the dental follicle will continue to grow adjacent to the gubernacular canal, leading to bone resorption. Furthermore, a rise in mononuclear cells will occur to become osteoclasts. Although the human tooth eruption process differs from mammals, animal studies are beneficial in examining odontogenesis and the development of periodontal tissues. The method of tooth development begins towards the end of the fifth week of growth as the epithelium thickens within the oral cavity.

Additionally, the cap stage involves the emergence of a dental follicle encased by a layer of ectomesenchyme containing the enamel and papilla. Unlike the dental papilla, the fibrillar organization and functions are distinct within its extracellular matrix. Stem cells can be found within the dental follicle and are responsible for developing cementum, periodontal ligament (PDL), and other adjacent tooth structures. The mechanism of the other structure developments is not fully understood. However, the layers are separated based on the structures that it gives rise to. For instance, the ectomesenchymal layer within the dental follicle gives rise to the cementum. As for the alveolar bone and PDL, the perifollicular mesenchyme is responsible for its development. Following the maturation of the alveolar process, tooth germ alignments are determined based on the formation of the bony septa and bridges exhibited at the late bell stage. The tooth movements determine its correct positioning within the occlusal plane as the jaw proceeds with growing. Moreover, there is a linear relationship between the alveolar height and root formation.

The role of the dental follicle in unerupted teeth

Once the tooth completes its anatomical formations, the eruption process occurs in five stages-"pre-eruptive movements, intraosseous stage, mucosal penetration, preocclusal stage, and postocclusal stage" [2]. During the bone remodeling stage, dental follicle cells will differentiate into osteoblasts, signaling osteoclasts to the site in preparation for tooth eruption. The process of tooth eruption involves

a wide range of chemokines, hormones (such as the "parathyroid hormone-related protein (PTHrP), epidermal growth factor (EGF), transforming growth factor-beta 1 (TGF-β1), TGF-α, interleukin (IL)-1α, colony stimulating factor-1 (CSF-1), monocyte chemotactic protein-1 (MCP-1) and their respective receptors, proto-oncogenes, and transcription factors such as c-Fos, nuclear factor-kappaB1 (NFκB1) and NFκB2" [2]. The involved factors vary based on the type of tooth. Additionally, occlusal force, anatomical, social determinants, and developmental factors influence each tooth's eruption pattern. When there are defects in the dental follicle, the results lead to tooth eruption failure.

As the tooth develops during periodontogenesis, dental follicles within the tooth's root differentiate into the cementum, PDL, and adjacent bone structures. The coronal portion continues to lead the eruption process through its attached crown. Once eruption occurs, the perifollicular mesenchyme gives rise to the connective tissues throughout the gingiva. The enamel reduction establishes the junctional epithelium and will experience apoptosis as the tooth erupts. At the end of the apex formation, the perifollicular mesenchyme will hold the tooth in place through its attachment, protecting it from internal insults.

Materials and Methods

A PubMed search was conducted to investigate terms like "dental pulp stem cells," regenerative medicine" (dentistry), "dental pulp stem cells periodontitis," "Dental pulp stem cells endodontics," and "dental stem cells applications." The beginning of the research consisted of forming a background knowledge of dental stem cells and their role in tissue and neurovascular regeneration. The second half of the study explores the clinical studies and current applications of dental pulp stem cells in dentistry. Based on the scope of the search, this review covers a wide range of clinical applications of dental stem cell studies in dental therapies.

Results

Dental pulpal stem cells (DPSCs)

Dental pulp stem cells (DPSCs) were discovered during the early 19th century and possessed homeostatic and tissue regeneration characteristics. The origin of DPSCs was suggested to be related to neural crest and neurovascular bundles based on the markers exhibited on their surfaces. There has been successful isolation of DPSCs from deciduous human teeth, and their high proliferative characteristics confirm their gain function during development stages. Like mesenchymal stem cells, pDPSCs can differentiate into odontoblasts via cellular division. Once implanted, the pDPSCs can generate a complex containing dentin and pulp. Today, DPSCSs have been used for regenerative purposes to create the pulp cavity in teeth. Outside of dentistry, DPSCs can treat systemic illnesses such as lupus erythematosus by inhibiting lymphoid cells (T Helper 17 cells) from enabling their regulatory functions.

Depending on the location of DPSCs (derived from pericytes), they can possess neurovascular regenerative characteristics. Its relationship with neurovascular bundles permits its contribution to angiogenesis. NVB regulates DPSCs via the Sonic hedgehog (Shh) protein, which adds to its homeostatic characteristics and dental tissue regeneration. Some surface markers-such as CD90 and STRO-1, neuro glia two, and Gli1 (signaling molecule)-are found on DPSCs, as seen on MSCs.

Endodontic applications of DPSCs

DPSCs portray a promising result in regenerating dental pulp tissues in preclinical studies. Four techniques are used to characterize DPSCs' regenerative properties and applications: scaffolds, combining scaffolds with cytokines, and DPSC particles.

To begin, scaffolds established an environment supporting stem cell seeding. During its transplantation process, DPSCs were combined with an organic or synthetic material into a tooth treated with partial or complete root canal therapy. The results revealed that DPSCs could

regenerate dental pulp tissues *in situ* subcutaneously. When DPSCs were transplanted using a scaffold combined with the granulocyte-colony stimulating factor (G-CSF), the cytokine's presence enhanced neurogenesis, pulp tissues, and blood vessel regeneration *in situ*. Evidence shows that subcategories of DPSCs (ex: CD31−, CD146−, CD105+ DPSC-SP cells) can regenerate dental pulp tissues. However, when scaffolds are used during the transplant process, DPSCs fail to complete the restoration of the dental pulp chambers because of environmental interruption.

Nakashima., *et al*. (2017) conducted a pilot study to assess the safety and efficacy of transplanting autologous mobilized dental pulp stem cells (MDPSCs) in teeth that were pulpectomized. MDPSCs were isolated from extracted teeth and were expanded following good manufacturing practice (GMP). Karyotype analyses were conducted to ensure the quality of the MDPSCs. Using atelocollagen-containing granulocyte colony-stimulating factor (G-CSF), the MDPSCs were transplanted into five patients experiencing irreversible pulpitis. All the patients were monitored up to 24 weeks post-transplantation [20]. The results reveal a positive electric pulp test at four weeks post-op and no signs of adverse effects. After examining the magnetic resonance imagining intensity, the regenerated tissues found in the experimental group portrayed similar results to an untreated tooth's normal dental pulp. Three of the five patients exhibited functional dentin formation on a cone beam computed tomography. These data conclude that pulpal regeneration is efficacious and safe using human MDPSCs, as observed in the pilot study [20].

Periodontal applications of DPSCs

Periodontal disease is an irreversible chronic condition involving alveolar bone loss, tooth loss, and tissue destruction. Sun., *et al*. (2014) assessed the effects of aggressive periodontitis on DPSCs by isolating the stem cells after selected teeth were extracted. The groups were divided according to the bone resorption (towards the tooth's apex) induced by inflammation before the extractions. The control group consisted of extracted third molars that were non-functional. Each group was evaluated for its mesenchymal-like characteristics (ex: regeneration, proliferation, antigen presentations, differentiation, and cell cycle). The results conclude that DPSCs (presenting STRO-1 and CD146) can be isolated in the presence of aggressive periodontitis [23]. Moreover, the colony-forming ability, tissue regeneration, and division characteristics of the DPSCs were reduced due to periodontal inflammation. Additionally, DPSCs can be found in periodontally compromised teeth, but their regeneration potential for therapy is questionable and requires further investigation.

DPSCs have been used in combination with periodontal stem cells to treat periodontitis in animal studies. The results reveal the importance of various factors (growth and morphological aspects) that would contribute to the tissue engineering process. Amghar-Maach., *et al*. (2019) investigated the regenerative characteristics of DPSCs when treating periodontal defects. After reviewing over 185 studies, the results suggest that PDL regeneration required DSPCs with other ambiguous factors. Several animal studies [17,24] compare the DPSC grafts in miniature pigs with bony defects around the premolar areas of both arches. The DPSCs were either grafted or injected in the presence (or absence) of hepatocyte growth factors. The results reveal a higher rate of new bone development during 12 weeks on the stem cell samples that were grafted as sheets compared to those that were injected.

Alternatively, Khorsand., *et al*. (2013) created a surgical defect consisting of three walls in 20 dogs to compare the efficacy of Bio-Oss xenograft scaffold (with and without DPSCs) use in the premolar area of the maxilla. The results revealed a higher regeneration rate for PDL and cementum when DPSCs were combined with the Bio-Oss xenograft [22].

Piva., *et al*. (2017) further investigated DPSCs' ability to regenerate dentin and pulpal tissues by expanding extracted third molar teeth in fetal bovine serum (DPSCs-FBS) or human serum environments (DPSCs-HS). Once the teeth were characterized and evaluated for the angiogenic features, a scaffold was used to transplant tooth slices with the DPSCs subcutaneously into immunodeficient mice. The teeth slices were considered after 30 days to assess their progress in regenerating dental pulp tissue, dentin, predentin, and angiogenic

properties. The results portray an equal amount of angiogenic growth factors between both groups (DPSCs-FBS and DPSCs-HS). However, DPSCs-HS displayed higher concentrations of angiogenic factors than the DPSCs-FBS. The data elicits the potential for isolating DPSCs and their applications on a clinical scale with further development [21].

Discussion

The results reveal dental pulp stem cells (DPSCs) possessing homeostatic and tissue regeneration characteristics [8,13,14]. Additionally, DPSCs carry neurovascular regenerative characteristics based on their location in dental pulp tissues as it is derived from pericytes [13]. Its relationship with neurovascular bundles permits its contribution to angiogenesis. NVB regulates DPSCs via the Sonic hedgehog (Shh) protein, which adds to its homeostatic characteristics and dental tissue regeneration [13]. Some surface markers-such as CD90 and STRO-1, neuro glia 2, and Gli1 (signaling molecule)-are found on DPSCs, as seen on MSCs [13].

In endodontic preclinical trials, DPSCs can subcutaneously regenerate dental pulp tissues *in situ*. When a scaffold treated with cytokines was used, the neurogenesis, pulp tissues, and blood vessel regeneration processes were enhanced *in situ* [13]. However, when scaffolds are used during the transplant process, DPSCs fail to complete the restoration of the dental pulp chambers because of environmental interruption [13]. Additionally, MDPSCs transplantation has shown safe and efficacious results in regenerating pulpal tissues in pulpectomized teeth [19].

In periodontal applications, the results emphasized the importance of various factors (growth and morphological characteristics) contributing to the tissue engineering process. In general, DPSCs with xenograft transplants exhibit enhanced bone, PDL, and cementum regeneration rates. Moreover, teeth experiencing aggressive periodontitis still exhibit colony-forming ability tissue regeneration and division characteristics at a reduced level. But their regenerative potential remains questionable and requires more insight.

Conclusion

Regenerative medicine has shown promising results for dental treatments. Dental pulp stem cells (DPSCs) have tissue and neurovascular regenerative characteristics that benefit endodontic and periodontal procedures. Although preclinical trials are available to assess, the results call for more investigation to optimize DSPCs integration into dental practices. Additionally, long-term studies are needed to evaluate the tissue and tooth prognosis after DPSCs transplant.

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Volume 22 Issue 10 October 2023

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