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Review Article

Dental Stem Cells: Potential Role in Tooth Repair and Regeneration

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ABSTRACT:
Loss of teeth and dental diseases incur a heavy burden on global health. Today's treatment options, which mainly rely on artificial dental materials, do not provide a complete restoration of the natural tooth structure and function. Approaches based on stem cell regeneration seem to be developing as viable alternatives in the field of dental tissue engineering. This review focuses on various categories of dental stem cells, their distinguishing properties, as well as their possible roles in the repair and restoration of teeth. It discusses polymorphic dental stem cells such as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), and stem cells from periodontal Ligament (PDLSC), with special emphasis on dental follicle stem cells (DFPC) and stem cells from the apical region of tooth roots.Considerable attention is paid to the latest advances in the techniques of isolation, the protocols of cell expansion, differentiation, and even the current gaps about the translation of these technologies to clinical practices. This review examines biocompatible scaffolds, growth factors, signaling molecules, and other components relevant to the enhancement of biotherapy at dental stem cell level. Deliberation on the incorporated documents fosters new thinking and focuses on technologies that are considered to shape the future of dental regenerative medicine. Integrating stem cell biology with the practice of clinical dentistry profoundly changes approaches to treating the biological repair and restoration of dental tissues and the improvement of life for the patients.
Keywords: Dental stem cells, Tooth regeneration, Dental pulp stem cells, Tissue engineering, Regenerative dentistry

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INTRODUCTION

Irreversible damage to dental tissues resulting from dental caries, periodontal diseases, and trauma can lead to significant loss of tooth structure with potential for tooth loss [1, 2]. The current treatments available to dentists are based on synthetic materials such as amalgam, composites, ceramics, and metal alloys. Yet, current strategies cannot mimic the biological functions of natural dental tissue [3]. Though these strategies can restore some of the conventional dental functions, there are limitations with such approaches, such as material degradation, secondary caries, or tissue biocompatibility [4]. Tissue engineering and regenerative medicine for the first time can offer us an opportunity for biologically replacing damaged dental tissues [5]. Approaches based on dental stem cells can potentially offer a way towards regenerating functional dental tissues from appropriate cell sources, signalling molecules, and biocompatible scaffolds [6]. The discovery of donor sources and of different populations of dental stem cells has fostered great interest in harnessing their regenerative capabilities for clinical application.

Tooth formation occurs through complex epithelial-mesenchymal interactions and influences via very complex signalling pathways [7]. Our understanding of cellular and molecular processes integral to tooth development has provided guidance in research on tooth regeneration. There have been several stem cell populations identified in the tooth and its supporting structures, each with different properties and regenerative potential [8]. This review will focused on dental stem cells and their potential for tooth repair and regeneration, and will provide a review of dental stem cells, their characterizations, methods of isolation, differentiation potential, and recent developments in regenerative dentistry, as well as challenges and prospects for research in dental stem cells for clinical use.

TYPES AND SOURCES OF DENTAL STEM CELLS

Dental Pulp Stem Cells (DPSCs)

Dental pulp stem cells (DPSCs) were the first dental mesenchymal stem cells which Gronthos and coworkers isolated and identified from human dental pulp in adulthood in 2000. These cells form colonies and proliferate rapidly and these characteristics made DPSCs similar to mesenchymal stem cells from bone marrow (BMMSCs). DPSCs are multipotent meaning they can differentiate into odontoblasts, osteoblasts, adipocytes, chondrocytes, and neuronal cells when exposed to certain signals [9]. The biological purpose of these cells in vivo is to differentiate into odontoblasts in order to produce reparative dentin in response to damage. They express the usual mesenchymal stem cell cell-surface proteins such as CD73, CD90, and CD105, and do not express any hematopoietic markers, e.g. CD45, CD34, and CD14 [10]. DPSCs can easily be procured from with wisdom teeth, premolars excised for orthodontic treatment and teeth extracted due to periodontal pathology and thus can be considered a relatively accessible source for medical use [11].

Stem Cells from Human Exfoliated Deciduous Teeth (SHED)

Dental Follicle Progenitor Cells (DFPCs)

Stem cells from human exfoliated deciduous teeth (SHED), defined as stem cells derived from remaining pulp tissue in naturally shed baby teeth, were first identified by Miura and colleagues in 2003. Compared to dental pulp stem cells (DPSCs), SHED proliferate faster, can undergo more population doublings, and have wider differentiation abilities. Moreover, SHED expresses markers of neural cells and have a higher ability to become neural cells than DPSCs, possibly due to the neural crest origin [12]. SHED are capable of differentiating into odontoblasts, osteoblasts, adipocytes, and neural cells and can stimulate bone formation and formed dentin-pulp-like structures in vivo, respectively. They are a non-invasive source of stem cells due to their naturally exfoliation, providing an attractive source of stem cells for banking and for their future autologous or allogeneic therapeutic offers [13].

Periodontal Ligament Stem Cells (PDLSCs)

Periodontal ligament stem cells (PDLSCs) are derived from the periodontal ligament tissue and were first defined and described by Seo and colleagues in 2004. These cells have markers found in mesenchymal stem cells and have been shown to differentiate into cementoblasts, osteoblasts, adipocytes and collagen-producing cells. PDLSCs have also been transplanted to living organisms and produced cementum and periodontal ligament-like structures, thus demonstrating their potential for periodontal regeneration [14, 15].PDLSCs can be derived from extracted teeth, often third molars, and have shown immunomodulatory behavior that may be useful in inflammatory periodontal conditions. They can form hard and soft periodontal tissues which establish them as essential players in complete periodontal regeneration strategies [16].

Dental follicle progenitor cells (DFPCs), the progenitor source of periodontal tissues, are derived from the dental follicle. The dental follicle is loose connective tissue surrounding the developing tooth bud. DFPCs show typical mesenchymal stem cell properties, including the ability to differentiate into osteoblasts, cementoblasts and periodontal ligament fibroblasts [17]. Furthermore, DFPCs can also express neuron markers and are capable of differentiating into neurons. DFPCs are usually derived from impacted third molars and present future potential as progenitor cells for periodontal tissue engineering [18].

Stem Cells from the Apical Papilla (SCAP)

Stem cells from the apical papilla, known as SCAP, are present in the soft tissue found at the tip of the developing tooth roots. SCAP were first identified and characterized by Sonoyama and colleagues in 2008. SCAP have higher proliferation rates, migration rates, and higher telomerase activity than postnatal dental pulp stem cells. SCAP have markers consistent with mesenchymal stem cells and neurons, such as nestin and STRO-1. SCAP can differentiate into odontoblasts, osteoblasts, adipocytes and neural cells, with the highest potential to differentiate into odontoblasts. SCAP are necessary to root development and continued root development in the presence of pulpal necrosis and periradicular inflammation, which suggests value in potential applications for root regeneration. [19].

Characterization and developmental capabilities of dental stem cells

Molecular Markers and Cellular Properties

Dental stem cells typically express various mesenchymal stem cell surface proteins including CD73, CD90, CD105, CD146, and STRO-1, but not hematopoietic markers like CD14, CD34, and CD45 [10]. Clinical examples of dental stem cells also have unique markers based on their tissue origin and differentiation capabilities. For example, stem cells from shed baby teeth (SHED) and stem cells from the apex of a developing root (SCAP) express greater amounts of CD29 and CD166 markers, as compared to dental pulp stem cells (DPSCs). The difference in cell surface protein expression could explain the rapid proliferation of SHED and SCAP [20]. In addition to specific cell surface markers, pluripotency associated transcription factors such as OCT4, SOX2, and NANOG are variably present in each type of dental stem cell population which are indicative of their primitive characteristics and multipotent potential [21]. Dental stem cells also express neural crest markers notably p75, nestin, and SOX10 reflecting their neural crest origin [22]. Types of dental stem

cells differ in their self-renewal, colony-forming efficacy, and proliferation. Overall, SHED and SCAP generally proliferate and double in number more rapidly than DPSCs and PDL stem cells (PDLSCs) [23]. These differences in proliferation and doubling rate can impact their expansion and therapeutic potential.

Differentiation Pathways and Regulatory Mechanisms

The differentiation of dental stem cells is impacted by intricate signaling networks that involve signaling pathways such as Wnt/β-catenin, BMP, Notch, and FGF. These biological pathways regulate the expression of transcription factors that are associated with specific cell types that regulate their development and the tissues they specialize into [24].The stem cell-derived odontogenic differentiation process begins with early stage markers of DSPP, DMP1, and ALP and progresses to late stage markers of osteocalcin and osteopontin. RUNX2, OSX, and MSX2 together regulate the differentiation pathways in productive odontogenic stem cells by controlling the expression of transcription factors for constitutive and mineralized tissues [25, 26]. Epigenetic adjustments, together with DNA methylation, histone changes, and non-coding RNAs, are essential in figuring out the improvement and specialization of dental stem cells. Specific microRNAs, which include miR-143, miR-a hundred thirty five, and miR-30, were proven to adjust odontogenic differentiation via affecting crucial elements of signaling pathways and transcription elements [27, 28]. The surrounding environment, or niche, which incorporates elements like the extracellular matrix, soluble molecules, and interactions among cells, greatly influences the upkeep and specialization of dental stem cells [29]. A thorough know-how of those manipulate mechanisms is critical for developing techniques to manual the differentiation of dental stem cells for therapeutic purposes.

Dental stem cells in tooth repair and regeneration

Pulp-Dentin Complex Regeneration

Receiving dentin–pulp complicated recuperation is an advanced remedy technique in evaluation to the conventional root canal remedy. The conventional root canal remedy includes accessing the teeth chamber, putting off the diseased pulpal tissue, and then filling the space with an inert material [30].

DPSCs and SHED have verified the ability to regenerate pulp-like tissue with vascularization and innervation whilst transplanted with appropriate scaffolds and growth elements [31]. Several researches have mentioned success pulp regeneration the usage of dental stem cells in animal models. Iohara and co-people confirmed in a 2021 look at that it was possible to gain complete pulp regeneration, along with the formation of blood vessels and nerves, in dogs by using the usage of their very own dental pulp stem cells (DPSCs) together with stromal mobile-derived issue-1 (SDF-1) [32]. The regenerated tissue exhibited comparable cellularity, extracellular matrix composition, and sensory characteristic to native pulp tissue. Clinical trials investigating pulp regeneration have all started to emerge. A sizable have a look at carried out by Nakashima and colleagues in 2017 confirmed success pulp regeneration in people with irreversible pulpitis. This changed into done the usage of their mobilized dental pulp stem cells (MDPSCs). The remedy brought about the regrowth of pulp tissue, and patients confirmed superb responses to electric powered pulp checking out, suggesting a go back of function [33]. Various methods to decorate pulp-dentin regeneration encompass the incorporation of increase factors inclusive of simple fibroblast increase thing (bFGF), transforming increase element-beta (TGF-β), and vascular endothelial increase factor (VEGF) to promote mobile survival, proliferation, and angiogenesis [34]. Additionally, prevascularized mobile-weighted down hydrogels had been developed to triumph over the assignment of oxygen and nutrient diffusion in regenerated pulp tissue [35].

Periodontal Tissue Regeneration

If left untreated, periodontal disease leads to destruction of the tooth-supporting apparatus (the periodontal ligament, cementum, and alveolar bone) and tooth loss [36]. PDLSCs and DFPCs have been found to have a great potential in regenerative therapy in periodontal tissue. When transplanted to periodontal defects, these cells can differentiate into cementoblast-like cells, osteoblasts-like cells, and periodontal ligament-like cells to regenerate new periodontal tissue [37].A study by Seo et al. (2022) found that transplantation of PDLSCs on an biomimetic scaffold achieved successful regeneration of periodontal tissues with good alignment of the periodontal ligament collagen fibers and formation of new cementum and alveolar bone in the miniature pig model [38]. Cell-sheet-based tissue engineering is an attractive approach for regenerating periodontal tissues. It allows the grafting of the cells and their naturally produced ECM [39].PDLSC sheets are superior in regenerative result to cell suspension, probably because the cells and cell-cell contacts and extracellular matrix components were kept [40]. Clinical trials are in progress to test how well dental stem cells can regenerate periodontal tissues. Study by Chen el at. (2023) observed clinical changes along with radiographic bone gain in subjects with periodontal defects treated with autologous PDLSC compared to routine treatments [41].

Whole Tooth Regeneration

The main aim of dental regenerative medicine is to make biological replacements for missing teeth that look and function likes natural ones. There are two main strategies; how to mimic teeth development in

embryos using dental epithelial and mesenchymal stem cells and to createscaffolds (tooth-shaped structures), and implant dental stem cells into them [42]. Animal studies shown the significant advancements in creating tooth-like structures. In 2019, for instance, Ikeda and their team successfully developed bioengineered teeth that worked fully in mice. They achieved this by placing engineered tooth germs into the jawbone of mice. These new teeth developed proper crowns and roots, had good blood flow in the pulp area, and formed the correct periodontal ligament, enabling them to function well for chewing [43]. Despite these progresses, but growing whole new teeth still have challenges. Availability of human dental epithelial stem cells and replication of precise timing and signals required for proper tooth formation are major issues. Furthermore, developing a complete tooth takes a long time. Using induced pluripotent stem cells (iPSCs) can be transformed into dental epithelial and mesenchymal cellsto regenerate full teeth [44].

Biomaterials and Scaffolds for Dental Stem Cell Applications

Natural and Synthetic Biomaterials

Biomaterials in dental stem cell treatmentsplay a key role. They give structure, help cells attach and move, and release growth factors and other active substances [45. Collagen, fibrin, chitosan, alginate, and hyaluronic acid are some natural biomaterials which are very compatible with the body and boost cell activity. However, their quality compositionand mechanical strength affects the purpose [46]. Synthetic biomaterials like polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), and their combition have predictable features. We can adjust them for certain breakdown speeds and strengths [47]. But these materials don't usually act like natural ones biologically. They can result into acidic byproducts, which might harm cell survival and cell development. To get the benefits of both, natural and synthetic materials are comboined to create composite scaffolds. For example, mixing PCL/collagen composite scaffolds has shown improved cell attachment, growth, and development of tooth-related cells in DPSCs compared to using PCL by itself [48].

Advanced Scaffold Technologies

New ways in scaffolds making led to more advanced structures that better replicate the complex arrangement of dental tissues. Building the complex tissue structures with a specific, predetermined design was made with three-dimensional bioprinting which precisely arrange cells, biomaterials and bioactive molecules [49].This technology has been successful to fabricate dental pulp constructs with embedded blood vessel networks, which help solve issues with diffusion [50]. Electrospinning methods are used to produce scaffolds made of very thin nanofibers, resembling the natural extracellular matrix. These scaffolds have surfaces act as guide for cell activity and the development of tissues[51]. Aligned electrospun scaffolds helps to guide the orientation of PDLSCs and promote the formation of aligned collagen fibers that resemble the natural periodontal ligament structure [52]. These intelligent materials can sense changes in their environment, like pH levels, temperature, or enzyme presence which enable them for delivering growth factors and other necessary molecules with controlled approach [53]. This targeted delivery is very controlled, improving the effectiveness of the treatments. Self-assembling peptide hydrogels are another innovative tool for pulp regeneration. Because of minimally invasive injectable approach, these hydrogels can be delivered directly into the root canal area with minimal difficulty and discomfort [54].

Role of Growth Factors and Signaling Molecules in Dental Regeneration

Growth Factors in Dentinogenesis and Pulp Regeneration

The proliferation, migration, and differentiation of dental stem cells during tissue regeneration are regulated by growth factors. Note that the transforming growth factor-beta (TGF-β) family is the one of the contributor in this regard. Bone morphogenetic proteins (BMPs) of mentioned family, regulates odontoblast differentiation and dentinogenesis [54]. Role of various BMPs namely BMP-2, BMP-4, and BMP-7 in promotion of odontogenic differentiation of dental pulp stem cells (DPSCs) and dentinogenesis in vivo is evident [55]. Fibroblast growth factor-2 helps in proliferation of dental stem cells and stimulated angiogenesis then promote pulp tissue regeneration [56].Vascular endothelial growth factor (VEGF) driven formation of blood vessels within pulp tissue ingrowthis critical for providing enough oxygen and nutrients [57]. Dental matrix housed several growth factors including, TGF-β1, BMP-2, insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor (PDGF) released injury for reparative dentin production. The use of these signaling molecules which are endogenous signaling molecules via controlled release of dentin matrix protein may be a valuable strategy to promote pulp-dentin regeneration [58].

Signaling Molecules for Periodontal Regeneration

In periodontal tissue regeneration includes concordance development of cementum, periodontal ligament, and alveolar bone which require specific growth factors and signaling molecules. Periodontal regeneration by stimulating PDLSCs and cementoblast differentiation enhanced by a complex mixture of proteins mainly composed of amelogenins namely enamel matrix derivative (EMD) [59]. Cell proliferation, matrix synthesis, and angiogenesis for periodontal regeneration enhamced by many growth-

promoting factors, such as PDGF, TGF-β, IGF, and VEGF, present in Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). In combination with PDLSCs, these blood concentrates shows clinical promise in periodontal defect cases [60]. Alteration in Wnt signaling by the use of sclerostin antibodies and lithium chloride may provide potential treatments for regenerating periodontal tissue. The reason behind this is their ability to enhance alveolar bone formation and cementum [61]. However, , non-precise control of Wnt signaling activation can lead to abnormal tissue formation.

Delivery Systems for Bioactive Molecules

To ensure the greatest potential for regenerative outcomes a regulated release of growth factors and other signaling molecules is critical. The conventional methods of delivering growth factors through bolus injections or applying them topically result in rapid clearance and degradation, limiting its capabilities. Advanced delivery systems have been engineered to mitigate these problems and offer the sustained release of bioactive molecules. Controlled release of growth factors is possible mechanically, through diffusion, degradation, or responsiveness mechanisms from microparticle (.5 to 1 μm diameter) and nanoparticle (1 nm to 100 μm diameter) systems [62]. Polymer microspheres containing BMP-2 have shown sustained release characteristics and enhanced bone formation in periodontal defects [63]. Gene therapy approaches that utilize viral and non-viral delivery systems have the potential to allow the sustained, localized production of biologically active agents, through genetic modification of either the dental stem cells and/or surrounding tissues ideas [64]. Sequential, layer-by-layer assemblage approaches allow for precise sequential organization of many growth factors and the ability to control the rate at which they were released. This capacity can open up possibilities to manipulate the time-dependent characteristics of the body's innate healing mechanisms [65]. Examples of this are in designing guided tissue regeneration membranes with sequential release of FGF-2 and BMP-2 for periodontal regeneration.

Challenges and Future Directions

Quality assurance and Standards

The clinical translation of dental stem cell-based therapies involves the development of standardized protocols for key steps in the process of cell isolation, expansion (growth), characterization, and storage to promote consistency and reproducibility [66]. At present, a large variation in isolation methods, culture conditions, and characterization criteria exists between research groups making it difficult for direct comparison of results across groups and regulatory approval is unlikely to occur. Developing a standardized method of handling cells that is compliant with good manufacturing practice (GMP)-standards for use in medical treatments is essential. Comprehensive definition of serum-free culture media, automated processing equipment, and validated quality control assessments of cell identity, purity, potency, and safety needs to be achieved [67]. The cryopreservation protocol for stem cells from dental tissue should be made optimal to maintain cell viability, phenotype, and differentiation potential, over long-term storage [68]. Standardized banking protocols that ensures full testing and documentation of the cells will facilitate the storage and use of dental stem cells in either autologous or allogeneic application.

Regulatory and Ethical Considerations

Countries have different regulatory environments surrounding the use of dental stem cells and these are constantly changing as the field progresses [69]. TheFood and Drug Administration (FDA) in the United States, regulates the degree of dental stem cells alterations and intentions as human cells, tissues, and cellular- and tissue-based products [70]. Most of dental stem cell applications are subject to a centralized authorization process as classified in advanced therapy medicinal products (ATMPs) by the European Medicines Agency (EMA) [71]. It would be useful if the regulators and their supporting research communities could standardize rules and guidelines in their various countries to allow researchers worldwide to work together, and potentially facilitate the development of new dental stem cell treatments [72]. Ethical factors with dental stem cell research and clinical applications consist of informed consent for the donation of tissue, such as deciduous teeth from minors, maintaining fair access to dental stem cell-based therapies, and establishing ethical and responsible commercial practices in commercial stem cell banking [73].

Emerging Technologies and Future Directions

With advancements in single-cell RNA sequencing, whole dental stem cell heterogeneity can be characterized, and individuals with greater regeneration ability can be identified [74]. This technology will provide a more accurate cell selective standard, as well as ways of isolating the most relevant cell populations for therapy. CRISPR-Cas9 gene editing provides further opportunity to modify properties of dental stem cells, through efficient and targeted editing of genes necessary for growth, differentiation, immunomodulation and survival [75]. Genetic enhancement strategies may allow for more effective dental stem cell application, but they will require valid and reliable safety and regulatory measures [76].Organ-on-a-chip technologies are emerging tools that allow for the development of miniaturized dental tissues with functional vasculature and innervation and are providing advanced platforms for investigating tooth development, disease, and regeneration [77]. These systems also offer opportunities for drug screening, personalized

medicine strategies, and pre-clinical optimization of regeneration approaches. The emergence of artificial intelligence and machine learning into the study of dental stem cells has begun to provide novel insights into complex biological processes and develop predictive models for the efficacy of treatments. These computational strategies have the potential to accelerate the development of dental regenerative therapies using data-driven optimization of protocols and patient selection criteria [78].

CONCLUSION

Dental stem cells are showing great promise for fixing and re-growing teeth. These cells are easy to obtain, can change into various cell types, and naturally help form parts of teeth. Significant advancements are made in understanding of various dental stem cells and their treatment methodologies. Clinical efficacyin preclinical modelsfrom integration of advanced biomaterials, growth factor delivery systems, and tissue engineering approaches are evident. Yet, several challenges need to be addressed before these therapies can become routine. The key issues like established standard protocols, optimization of scaffold designs, control of cell fate, and regulatory compliance requiring further attention. Additionally, a deeper understanding of the dental tissue formation in terms of governing molecular mechanisms and the integration of regenerated tissues with surrounding structures is needed.Dental stem cell treatments as a practical reality require collaborative efforts among scientists, engineers, dentists, and regulatory experts. Patient-oriented regenerative strategies may be clinically possible, offering solutions for dental tissue restoration than current treatment methods. These changes from conventional tooth repairing to genuine regeneration underscore the bright future of regenerative dentistry. This approach could enhance the treatment outcomes, patient comfort and ultimately better oral well-being.

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