**Migration Letters**

Volume: 19, No: S8 (2022), pp. 1535-1544

ISSN: 1741-8984 (Print) ISSN: 1741-8992 (Online)

www.migrationletters.com

# Exploring New Advancements In Dental Stem Cells And Tissue Regeneration

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**Abstract:**

*Promising paths for tissue regeneration and repair are presented by the use of stem cells in dentistry. Because of their special qualities, which include the capacity for self-renewal and multipotent differentiation, stem cells derived from the dental pulp, periodontal ligament, dental follicle, and root apical papilla are priceless resources in the field of regenerative dentistry. Preclinical and clinical research in this area has mostly concentrated on periodontal tissue engineering and dentin-pulp complex regeneration, with encouraging outcomes. The viability and effectiveness of stem cell-based strategies have increased thanks to cutting-edge methods like cell sheet engineering. Nevertheless, there are still difficulties in converting lab results into clinical settings, including technological barriers, moral dilemmas, and legal constraints. Notwithstanding these difficulties, continued interdisciplinary cooperation and creativity show promise for overcoming barriers and developing stem cell-based treatments in dentistry, which will ultimately enhance patient outcomes and transform dental care.*

***Key words:*** *Stem cells, dental pulp, periodontal ligament, dental follicle, root apical papilla, tissue regeneration, dentin-pulp complex, periodontal tissue engineering, cell sheet engineering.*

## Introduction:

Because stem cells have the ability to self-renew and specialize into several lineages, they can differentiate into various functional cell types or tissues, which is why they are referred to as "universal cells" [1]. Stem cell treatment presents a viable path for tissue and organ regeneration by utilizing these multidirectional differentiation capabilities to address cellular malfunction or restore physiological integrity inside tissues. Novel approaches to tooth and tissue regeneration have been sparked by recent advances in tissue engineering. These approaches make use of a variety of stem cell types and cutting-edge biological techniques, such as the use of bioactive substances [2]. Teeth are complex masticatory structures made up of various components, including enamel, dentin, cementum, pulp, and periodontal tissue. They originate from the tissue of the tooth germ in the jaw. In addition, teeth have complex physiological functions, distinct histological origins, a variety of structural compositions, and complex regulatory processes, all of which present significant challenges for researchers studying tooth regeneration.

One major benefit is that dental stem cells are relatively easily accessible. Dental stem cells are easily obtained from premolar and wisdom teeth, which are frequently taken for orthodontic purposes. This makes them a more desirable source for research on regenerative medicine. In terms of biology, dental tissues that are in good health have large reserves of normative stem cells that are essential for maintaining physiological integrity. In contrast, tissues that are inflamed or wounded have lower populations of stem cells, which makes tissue repair more difficult [3,4]. As a result, ex vivo stem cell multiplication and manipulation becomes a critical tactic to increase host cell populations and promote tissue regeneration [5]. By producing necessary building blocks and secreting trophic factors to control regenerative processes, transplanted cells not only actively support regeneration but also enable it [6]. These developments highlight the expanding field of regenerative medicine research driven by stem cell breakthroughs and provide a solid foundation for translational efforts. This review explores the potential uses in upcoming investigations and clarifies the background, present state, and types of dental stem cells.

**Stem Cells:**

The first population of stem cells to be isolated from adult human dental pulp is known as dental pulp stem cells (DPSCs), which are found inside the pulp tissue [7]. When derived from the third molar, DPSCs have a strong ability to proliferate and have the capacity to self-renew. They can eventually differentiate into lineages that are similar to odontoblasts and osteoblasts, which helps to build dentin and bone [7]. When DPSCs are integrated with hydroxyapatite/tricalcium phosphate (HA/TCP) and transplanted into immunocompromised murine hosts, dentin-like structures containing pulp tissue and an odontoblastic cell lining are produced [7]. Furthermore, stem cells isolated from the pulp of human exfoliated deciduous teeth (SHED) show multipotency and osteo-/odontogenic differentiation, displaying differentiation into different mesenchymal and non-mesenchymal lineages in vitro, such as neural cells and adipocytes [8]. Moreover, it has been demonstrated that SHED and DPSCs can produce bone-like tissues in vivo [9]. Using microarrays, Carinci et al. compared the genetic profiles of DPSCs and normal osteoblasts and found that different functional activities, such as adhesion, cell differentiation, developmental maturation, and cytoskeletal element production, were regulated differently in each group [10]. Interestingly, SHED out proliferate DPSCs more quickly than the latter, although they are less adept at creating whole dentin/pulp-like complexes in vivo.

DPSCs and SHED stand out as viable options for pulp, dentin, and periodontal tissue regeneration because of their unique qualities. When SHED is subcutaneously implanted into the roots of human premolars along with adjuncts like PuramatrixTM or rhCollagen type I, functional dental pulp is produced in immunocompromised murine models [13]. Furthermore, in favorable circumstances, DPSCs and SHED demonstrate the ability to differentiate into brain tissues, indicating their possible therapeutic use in treating neurological impairments [14, 15]. When included into DPSC/collagen sponge biocomposites, DPSCs have already been effectively used in clinical settings, especially in alveolar bone repair, indicating their effectiveness in correcting mandibular bone defects [16]. In summary, pulpal tissue-derived stem cells provide a promising and practical tool for the regeneration of pulp and periodontal tissues, and they may also help advance efforts aimed at tissue and organ repair and regeneration.

The periodontal ligament, which is embedded in fibrous connective tissue and lies between teeth and the inner wall of the alveolar fossa, is home to a wide variety of cells, including stem cells, which are essential for preserving tissue homeostasis and directing the formation of periodontal tissue. Periodontal ligament stem cells (PDLSCs) were first

discovered in 2004 by Professor Songtao Shi using markers linked to mesenchymal stem cells. PDLSCs have the ability to differentiate into mesenchymal lineages and can produce osteoblast-like cells, adipocytes, and collagen-forming cells in vitro [17]. Surprisingly, PDLSCs express more tendon-specific transcription factors, which suggests that they belong to a unique subset of postnatal mesenchymal stem cells [17]. When PDLSCs are transplanted into immunocompromised murine models, cementum/PDL tissue regenerates with thick collagen I-positive structures that mimic Sharpey's fibers' physiological attachment [17]. Notably, after being surgically implanted into the periodontal areas of mandibular molars, human PDLSCs successfully repaired abnormalities and integrated into the PDL compartment, highlighting their potential in periodontal tissue regeneration [18,19]. Strongly differentiating and proliferating PDLSCs live in the alveolar bone surface as well as the root surface, and human deciduous tooth roots are a potential source of these cells that can be purified via magnetic cell sorting [20, 21]. To further enhance periodontal regenerative therapy approaches, different immortalized clonal human PDLSC cell lines have been established [22, 23].

PDLSC-based clinical trials have produced encouraging results in terms of periodontal regeneration, demonstrating the cells' ability to prevent host immune rejection through autologous transplantation, mitigate severe periodontal disease, and promote healthy regeneration of periodontal tissue [24]. Nonetheless, difficulties continue since PDLSCs from individual donors are scarce, which has led to research into the immunomodulatory capabilities of allogeneic PDLSCs to expand therapeutic options [25]. Allogeneic PDLSCs are the treatment of choice for periodontal regeneration in clinical settings because they have demonstrated effectiveness in treating periodontitis in animal models without inducing immunological rejection [18, 26]. PDLSC functioning is significantly influenced by the microenvironment; this is demonstrated by the differentiation of the cells into cementoblastic lineages when the cells are cultivated in conditioned media derived from apical tooth germ cells [28]. This indicates a highly cementogenic milieu. Additionally, through endoplasmic reticulum stress pathways and epigenetic modification, inflammatory microenvironments regulate PDLSC osteogenesis. These findings highlight the critical role that molecular mechanisms play in chronic inflammatory diseases and provide insight into PDLSC-based stem cell therapies for periodontitis [29, 30].

The root apical papilla, which is unique to developing teeth before root maturation, plays a major role in the formation of teeth. It is home to stem cells derived from the apical papilla, or SCAPs, which are isolated from the human immature permanent apical papilla and exhibit characteristics similar to those of mesenchymal stem cells [31]. SCAPs behave similarly to dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED) in that they express STRO-1 and CD146 but do not express CD34 or CD45. However, they are distinct in that they express CD24, which is not present in DPSCs or SHED. Interestingly, during SHED odontogenic development in vitro, CD24 expression decreases. In order to establish clonal cell populations, apical papilla tissue must be digested enzymatically using type I collagenase and neutral protease. This results in a single cell suspension that can be in vitro induced into lineages that resemble odontoblasts, adipocytes, and neurons, with SCAPs exhibiting strong staining even in the absence of neurogenic stimuli. SCAPs show better proliferative capacity and mineralization potential than DPSCs, making them an attractive candidate for cell-based tooth regeneration due to their heightened proliferative potential [32]. Unlike DPSCs, which are involved in the generation of reparative dentin, SCAPs are most likely the principal sources of odontoblasts during the creation of root dentin. Furthermore, after the third passage, SCAPs proliferate more quickly than PDLSCs (periodontic ligament stem cells) [33]. A root/periodontal complex is produced during co-implantation of PDLSCs and SCAPs around the root into minipig alveoli, suggesting the

cooperative potential of these stem cells in regaining root function [31]. Furthermore, new research demonstrates the distinct "embryonic" properties of stem cells produced from growing root apices, demonstrating their capacity to form a conventional cementum/PDL-like complex in vivo [34].

Derived from ecto-mesenchyme, the dental follicle contains progenitor cells that can differentiate into osteoblasts and periodontal ligament cells, as well as the developing tooth germ [35, 36]. Human dental follicle cells (DFCs), which are usually taken out of the third molar sac, are easy to isolate because they stick to plastic surfaces when they are being cultured [37]. DFCs exhibit multipotent properties similar to bone marrow-derived mesenchymal stem cells (BMMSCs) and periodontal ligament stem cells (PDLSCs), expressing potential mesenchymal stem cell markers as Nestin, Notch-1, Stro-1, CD105, and CD90. Because DFCs are heterogeneous, they can differentiate into osteoblasts, cementoblasts, and periodontal ligament (PDL) cells. DFCs differentiate into PDL fibroblasts after being transplanted into naked mice; these cells secrete collagen and aid in the development of cementum/PDL-like tissue [38]. Remarkably, DFCs endure extended passaging without losing their morphological, proliferative, immunological, or mineralization properties, which results in the development of cementum/PDL-like tissue [39]. Moreover, DFCs have the potential to aid in the creation of dental roots because they promote the regeneration of root-like tissue with a pulp-dentin complex and a cementum-like layer when paired with treated dentin matrix (TDM) [39]. Making use of DFCs' heterogeneity and multidirectional differentiation potential could be a tactic for focused root regeneration; this could be impacted by elements like enamel matrix derivatives (EMD) and bone morphogenetic protein (BMP) for the differentiation of cementoblasts and osteoblasts [40, 41]. Recent research suggests that DFC sheets can promote the production of periodontal tissue through interactions between mesenchymal and epithelial cells, as generated by Hertwig's epithelial root sheath cells [42]. Although the exact mechanisms behind DFC differentiation are yet unknown, their adaptability makes them a viable option for dental regeneration projects.

**Dental Stem Cells and Regeneration:**

Despite the significant influence of pulp vitality loss on tooth prognosis, conventional endodontic procedures mostly concentrate on root filling using biocompatible materials, with little attention paid to dentin and pulp tissue regeneration [43]. In endodontic treatments, efforts to regenerate the dentin-pulp complex have increased [44], as advancements in stem cell therapy have created new opportunities for dentin and pulp regeneration. The pulp-dentin complex's functional regeneration may not be sufficiently guided by implantable scaffolds in a harmonic and consistent manner, highlighting the critical role that scaffold-cell interactions play in establishing the right milieu for regeneration. Promising results have been shown when dentin slices seeded with stem cells are prepared in vitro and then subcutaneously implanted into immunocompromised mice [45]. The creation of treated dentin matrix (TDM), which is enhanced with the original extracellular matrix components of dentin, was invented by our research team [46]. The regeneration of whole, prefabricated dentin tissues was aided by the combination of TDM and dental follicle cells (DFCs) [46]. Furthermore, pulp-like tissue was successfully rebuilt within full-length human roots using injectable scaffolds combined with stem cells from human exfoliated deciduous teeth (SHED) [13].

Although scaffold-mediated techniques have demonstrated effectiveness in creating pulp-like tissue following the implantation of dental stem cells, current scaffolds frequently lack the right material composition. Many are unable to replicate essential roles of the extracellular matrix (ECM) in nature. Conversely, scaffold-free techniques that take advantage of monodispersing cells' natural ability to self-assemble into three-dimensional structures have

demonstrated improved intercellular communication and ECM formation [47]. Particularly, the application of pre-vascularized human umbilical vein endothelial cells in scaffold-free microtissue dental pulp stem cell (DPSC) spheroids has shown strong regeneration with established vascularization and pulp-like tissue [47]. Cell aggregates provide advantageous stimuli for organ development and regeneration by imitating cell condensation processes. In order to successfully regenerate pulp-like tissue within tiny pig root canals, autogenous stem cells generated from pig deciduous teeth (SPED) have been used to produce cell aggregates containing both cells and extracellular matrix [48,49]. Notably, cell aggregates avoid important limitations of scaffold-based techniques, such as poor intercellular communication, limited capacity for selective breakdown and remodeling, and inability to accurately replicate the natural extracellular matrix.

The effectiveness of stem cell-based periodontal therapy has gained significant backing in recent times, as demonstrated by multiple animal studies that show improved periodontal regeneration following stem cell implantation into periodontal lesions. Notably, cell sheet engineering has become a viable scaffold-free cell distribution method [50]. This method promotes the growth of extracellular matrix (ECM) and cell-to-cell connections by growing cells in a cell culture plate till confluence. To maintain the sheet structure, the resultant monolayer is then carefully removed without the need for enzymatic intervention. With this approach, we hope to simulate a microenvironment that is favorable to cell motility, metabolism, and communication—all of which are critical for natural tissue regeneration. Cell sheet engineering preserves the integrity of the extracellular matrix (ECM) while avoiding the ECM degradation that is commonly linked to enzymatic cell isolation. This promotes proper cell activity. In conjunction with cell sheet engineering, a variety of scaffold types have been investigated, providing opportunities for functioning cell layers [51, 52]. When combined with carriers such as hydroxyapatite/tricalcium phosphate (HA/TCP), periodontal ligament stem cells (PDLSCs) become an attractive option for periodontal regeneration, especially in the regeneration of typical cementum/periodontal ligament (PDL) architectures. PDLSC cell sheets have been reported to develop well, and when monolayered or layered PDLSCs are grafted in vivo, cementum/PDL complex formation has been seen [53,54]. Pilot studies in a variety of animal models support the regenerative potential of PDLSC sheet transplants by showing periodontal tissue recovery in experimental deficits [16,52,53]. Notably, the creation of cementum-like tissue and new fibrous structures after restoration demonstrate that PDLSC sheet transplanting has positive effects in encouraging periodontal tissue regeneration in rats, dogs, and pigs [55].

Moreover, retrospective pilot investigations have shown the therapeutic efficacy of autologous periodontal ligament progenitor cells (PDLPs) in combination with bone grafting materials [24]. Clinical investigations and the reconstruction of periodontal defects support the safety and effectiveness of autologous PDL cells in the treatment of periodontitis [24]. Autologous PDLSC treatment has been shown to be safe and effective in treating periodontal intrabony abnormalities, according to recent clinical trials [27]. PDLSCs show better potential for periodontal regeneration than other mesenchymal stem cells, making them a prospective resource for periodontal tissue therapy with a minimal risk of immunological rejection.

**Challenges and Future Data:**

Even with major advances in dental stem cell research and clinical applications, the subject is still in its infancy with many unanswered problems. In order to enable effective clinical applications and accomplish true tissue regeneration, many theoretical mechanisms need to be further investigated. Moreover, a number of technical obstacles also need to be overcome. But dental stem cells have unmatched benefits that highlight their enormous promise in dental

tissue engineering. These benefits include their ability to self-renew, their potential for multidirectional differentiation, their global availability, and their minimal risk of autologous transplant rejection. The future seems bright thanks to the scientific and technology fields' quick advances. With increased knowledge, we may be able to genetically alter and stimulate dental stem cells, opening the door to novel strategies for tissue replacement and regeneration. Dental stem cells have the potential to completely transform regenerative medicine and dental care with more study and advancement.

**Conclusion:**

In summary, the study of stem cells in dentistry is a developing topic that has enormous promise to revolutionize regenerative dentistry. Dental pulp, periodontal ligament, dental follicle, and root apical papilla stem cells are among the several dental sources of stem cells that have shown promise for tissue regeneration and repair. These stem cells are priceless resources in regenerative medicine because of their special abilities, which include the capacity for self-renewal, multipotent differentiation, and immunomodulatory qualities. It is clear from the discussion that dental stem cell therapy has potential to overcome the shortcomings of current dental therapies, especially in the areas of endodontics and periodontics. Research has shown that using stem cell-based strategies can effectively promote tissue healing and functional restoration in a variety of applications, including dentin-pulp complex regeneration and periodontal tissue repair. Notably, the viability and efficacy of dental stem cell therapies have been improved by developments in scaffold-free methods such as cell sheet engineering and the creation of innovative biomaterials. Nonetheless, there are still a lot of obstacles to overcome before laboratory results can be used in therapeutic settings. The broad use of stem cell therapies in dentistry is hampered by technical difficulties, moral dilemmas, and legal constraints. Moreover, it is still critical to standardize techniques, conduct long-term safety evaluations, and clarify underlying mechanisms. The future of dental stem cell research is bright, despite these obstacles. Tissue engineering, regenerative medicine, and biotechnology are advancing quickly, and these developments could help dental stem cells reach their full therapeutic potential by overcoming present constraints. Dental stem cell therapies have the potential to completely transform dental care by providing patients with individualized, minimally invasive, and highly effective treatments for a wide range of dental problems. This can be achieved with sustained interdisciplinary collaboration, creative thinking, and rigorous clinical trials. In conclusion, even if there may be challenges in realizing the full potential of dental stem cells, there is no doubt that the future of dental medicine will be bright with opportunities to improve patient outcomes, enhance quality of life, and push the boundaries of dental research.

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