# The Role of Stem Cells in Regenerative Dentistry

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**Abstract**
Regenerative medicine is the branch of medicine that aims to repair and regenerate damaged tissues and presents promising avenues for addressing a wide range of currently incurable diseases. Regenerative medicine is based on the use of cell therapy with stem cells that can differentiate into differentiated cells of specific tissues. There are various types of stem cells, which are different in potential and derivation.
The donor cells and immune cells play a prominent role in determining the clinical success of MSCs therapy. In line with the promising future that stem cell therapy has shown for tissue engineering applications, dental stem cells have also attracted the attention of the relevant researchers in recent years. The current literature review aims to survey the variety and extension of SC-application in tissue-regenerative dentistry.

## 1. Introduction

Regenerative strategies in dentistry are revolutionizing traditional dental care by focusing on repairing, restoring, and regenerating damaged or lost dental tissues, including enamel, dentin, pulp, and periodontal structures [1]. Traditionally, dentistry has been concerned with filling procedures, crowning and bridgework, and root canal treatment. As in the case of lambs, these methods of re-establishing function failed to restore tissues at the same level at which they replaced structures. For example, the very common dental filling material that can treat a cavity, which is either an amalgam or a composite resin, or even gold, cannot rebuild the missing tooth structure and can pose problems, such as wear, crack or recurrent decay [**2**].Likewise, crowns and bridges restore areas of the mouth that are missing or have injured teeth; however, these restorations demand extensive removal of healthy tooth tissue and have limited resistance to damage. Despite the usefulness of endodontic therapy in managing a diseased tooth and retaining it within a dental arch, this makes the tooth non-vital and brittle, due to extraction or degeneration of the pulp tissue that brings nutrients and sensitivity [**3**]. Furthermore, some of these treatments may comprise biological incompatibility, which may cause side effects such as allergic reactions, hence the need for more biologically compliant solutions.
Due to the globally ageing population and dental diseases including caries and periodontal diseases, the need for an efficient and more environmentally friendly approach is increasing [**4**]. Thus, the attractive concept of regenerative dentistry is being developed as an answer to these challenges, mainly based on biologically created tissue repair mechanisms. Stem cell therapy, tissue engineering and bioactive materials are used in an attempt to recreate the normal mechanical and structural properties of the dental hard tissues, thereby accounting for the shortcomings of conventional restorative procedures [**5**].
For instance, stem cell applications have indicated the capability of reconstructing dental pulp, whereas bioactive materials have been identified as having re-healing properties in reconstructing both tooth dentin and enamel [6]. Techniques of periodontal regeneration are also constantly improving, which provides treatment solutions for regeneration of the supporting tissues of the teeth, i.e., gums and alveolar bone, which are usually affected by periodontal diseases.The transition to regenerative dentistry is, therefore, not only a reaction to the ineffectiveness of conventional practices but, rather, a chance to disrupt the dental field [**7**]. These strategies directly address biologically incorporated forms of treatment that can minimize the invasiveness of processes, the results of which are long-lasting, and elevate the overall level of patient care. Obviously, they can also contribute to reducing the harm that dental materials cause to the environment and reducing the frequency of procedures for patients' safety and environmental conservation [8].

### 2. Stem Cells in Dental Tissue Regeneration

Stem cells are undifferentiated cells having the ability to differentiate into many cell types within a particular cell lineage. Among all cells, stem cells are the most promising in the context of regenerative dentistry because these cells can engage both in self-renewal and differentiation to produce cells required for the effective repair of tissues [9]. Moreover, these cells have the capability of regenerating dental structures, like pulp, dentin, periodontal tissues, and alveolar bones. Sources of stem cells employed in dental regeneration can be classified into dentogenesis-derived stem cells and non dentogenesis-derived stem cells, which makes them quite diverse and suitable for use in a distinct manner to repair afflicted oral tissues [10].These stem cells are sourced from human dental pulp stem cells (DPSCs), which can help in formation of dentin and pulp tissue whereas stem cells from apical papilla (SCAPs) help in the formation of roots and repair of pulp [11]. Several types of stem cells have been found; periodontal ligament stem cells (PDLSCs) which self-renew and differentiate into periodontal ligament, and alveolar bone and dental follicle progenitor cells (DFPCs), which facilitate periodontal and bone formation.

### 2.1. Types of Stem Cells Utilized in Dental Tissue Regeneration

#### 2.1.1. Dental-Derived Stem Cells

Dental derived stem cells are sourced directly from dental tissues and are known for their tremendous capability in tissue engineering [**12**]. Dental pulp stem cells (DPSCs) derived from the dental pulp of permanent teeth are considered suitable for pulp and dentin regeneration due to their high proliferative potential and ability to differentiate into odontoblast-like cells.

SHED cells have been derived from harvested baby teeth and have proved to be very functional in tissue regeneration, and specifically in the formation of dentin and connective tissues [**13**]. PDLSCs are more involved in the repair process or formation of new periodontal tissue, such as ligament, cementum, and alveolar bone, which makes these cells therapeutic for periodontal diseases [**14**].Likewise, the apical papilla stem cells (SCAPs) present in the root tip of the teeth of the developing stage immature teeth are involved in root development and cell differentiation, evidencing future potential in pulp and dentin regeneration [**15**]. It has been revealed that dental follicle progenitor cells (DFPCs) derived from the dental follicle of developing teeth are capable of differentiating into osteoblasts and fibroblasts involved in periodontal and bone formation [**16**].

#### 2.1.2. Non-Dental Mesenchymal Stem Cells (MSCs)

Other mature human somatic stem cells are sourced from different regions within the body and provide a balance to the dental-derived stem cells when used in tissue engineering. MSCs obtained from bone marrow are noted for their ability to differentiate into osteogenic cells and are thus useful in augmenting alveolar bone repair [17]

#### 2.1.3. iPSCs (Induced Pluripotent Stem Cells)

This is a process in which human adult differentiated cells are forced to revert back to stem cells with the ability to differentiate into any desired cell type, including odontogenic cells.

### 2.2. Mechanisms Underlying Stem Cell-Mediated Tissue Repair and Regeneration

Stem cell characteristics for tissue repair and regeneration strongly depend on their quality to proliferative, differentiate and dynamically communicate with their surrounding environment Activated by injury or damage, stem cells increase their numbers and move towards the injured area with a direct supply of a constant stream of cellular components that are necessary for tissue regeneration [**18**]. These cells turn into dental-specific cell lineages, like odontoblasts, which contributes to the formation of dentin, cementoblasts, which contribute to cementum, fibroblasts, which form connective tissue, and osteoblasts, which form alveolar bones [**19**].

## 3.Originated Stem Cells in Dental Regenerative Treatments

### 3.1.Stem cells from apical papilla

The stem cells from the apical papilla (SCAPs) belong to a unique SC line locating at the apical tissues of the growing tooth roots when at least two-thirds of the root have formed[20],While SCAP derives from the dental papilla, they express a mesenchymal surface marker (STRO-1) and contribute to the epithelial-mesenchymal interactive process of tooth development [21]. The apical papilla is separated from the epithelial diaphragm with a cell-rich zone and has access to a collateral circulation that enables the apical papilla to survive a necrotic pulp in just adjacent tissues [20].Compared to DPSCs and PDLSCs, SCAP seems to be a better source to be used in cell-based tooth regeneration because of its higher proliferative and mineralization properties. Primary odontoblasts are mainly differentiated from SCAP during root dentin formation, while replacement odontoblasts are likely derived from DPSCs leading to reparative dentin formation [22].

### 3.2. Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) were first obtained from the bone marrow of the iliac crest [23]. MSCs have a specifically better coating on surface-treated plastic with plasma gas (so-called tissue-culture-treated plates), which makes them distinguishable among all SC types [24].

### 3.3. Postnatal Human Dental Pulp Stem Cells

Similar to muscles' and nerves' tissues, the dental pulp is a specialized tissue during postnatal life that also contains SCs conferring it the tissue regeneration ability in response to injury [25]. Dental pulp stem cells (DPSCs) are a subpopulation of mesenchymal cells residing within the pulp tissue that differentiate into odontoblasts during tooth formation under the influence of epithelial and dental papilla cells' interactions [26]. Generally, the origin and nature of postnatal cells as the precursor of various specialized tooth-associated cell types are little known [27].

### 3.4. Dental Follicle Stem Cells

The dental follicle stem cells (DFSCs) are located within the dental follicle or bilayered Hertwig's epithelial root sheath (HERS); they originate from the ectomesenchymal progenitor cell population and differentiate into cementoblasts or osteoblasts (cementogenesis) during tooth root formation [26].

## 4.Biomaterials in Dental Regeneration

Biomaterials are fundamental for dental regeneration because they offer the proper structural framework needed to support cellular mechanisms involved in tissue repair [28]. When used in conjunction with stem cells and growth factors, these materials also provide the necessary scaffolding for the growth of new dental tissues, like dentin, pulp, periodontal ligament, and alveolar bone.

### 4.1. Types of Biomaterials Used in Dental Regeneration

Stem cell therapies and tissue repair in dental restoration require biomaterials that aid in regeneration. Hydrogels are water-swollen, three-dimensional cross-linked hydrophilic polymer networks that mimic the ECM, and their applications are in the regeneration or repair of soft tissues, like dental pulp and periodontal ligament [29]. They can easily support cell adhesion, proliferation and differentiation and can be mixed with stem cells or growth factors to aid in regeneration. Chemotactic factors, based on the soluble proteins that influence cell functions, including migration and differentiation, are the dominant component in growth. In dentistry, BMPs, PDGF, VEGF and TGF-β are some of the growth factors used in dental applications to regenerate bones, periodontium and dental pulp [**30**]. Scaffold materials that are artificial or synthetic can be designed or fabricated to suit the required dental application.

### 4.2. Advances in Biomaterial Design for Enhanced Dental Tissue Repair

New developments in biomaterial design for dental tissue repair have greatly improved regenerative medicine. Other advanced biomaterials include thermo-sensitive hydrogels, which can load the bioactive molecules and release them in response to a stimulus and thereby enhance dental pulp regeneration [31]. Nanomaterials, such as nanohydroxyapatite and nano-silver, show improved mechanical properties and antimicrobial properties, which promote bone formation and prevent infection.

## 5. Techniques in Regenerative Dentistry

### 5.1. Protocols for Incorporating Stem Cells and Biomaterials in Dental Repair

The conceptual frameworks and significance of stem cells and biomaterials are noteworthy and provide guidelines for dental tissue regeneration. Dental stem cells can be harvested from tissues, such as the pulp or periodontal ligament, then extracted and classified based on differentiation potential [**32**].

### 5.2. Application of Platelet-Rich Plasma (PRP) and Platelet-Derived Growth Factors

PRP stands for platelet rich plasma, a concentrated autologous plasma with platelet counts 1.5–2 times higher than baseline platelet concentration, containing growth factors, such as PDGF, TGF-β and VEGF, responsible for stimulating cell proliferation, migration and differentiation. PRP is prepared from the patient's blood and then can act directly on the sites of lesions or in combination with bioactive materials to stimulate tissue repair [33]. It enhances angiogenesis and supports cell differentiation and chemo-taxis, helps in regeneration of the periodontal ligament and bone, and is of great importance in osseo-integration of dental implants.

### 5.3. Tissue Engineering and Biomolecules in Dentistry

Tissue engineering in dentistry is fundamentally built upon the triad of scaffolds, cells, and signalling molecules, which collectively drive effective tissue repair and regeneration. stem cells and biomaterials, bioactive molecules and growth factors play a pivotal role in directing cellular behaviour, differentiation, and extracellular matrix deposition. Key bioactive molecules involved in this tissue engineering include BMPs, TGF-β, FGF, VEGF, PDGF [**34**]

## 6. Clinical Applications and Success in Regenerative Dentistry

The concept of regenerative dentistry is dynamic and holds much potential for the reconstruction of dental and periodontal tissues using technology that incorporates stem cells, biomaterials, and growth factors. Clinically, there are several potential uses of these regenerative manners with reference to tooth regeneration, periodontal regeneration, bone repair, and dental implant integration [35].

### 6.1. Clinical Studies and Success Rates in Tissue Repair

Several clinical trials have been published regarding the application of regenerative medicine in dentistry and the topic mainly deals with tissue recovering and regeneration. Clinical investigation of periodontal tissue regeneration has suggested favourable results when stem cells, growth factors including PDGF and BMPs, and scaffold matrices are employed. For instance, the properties of woody dental pulp stem cells (DPSCs) incorporated with a collagen scaffold and PDGF have been demonstrated to achieve the formation of periodontal ligament, alveolar bone, as well as cementum [36]. It is difficult to definitively report success rates for periodontal regeneration, though they are commonly reported to be between 60% and 80% for patients based on the severity of periodontal disease, age, and the quality of the material used for regeneration [37].

### 6.2. Case Reports Demonstrating Regeneration of Dental and Periodontal Tissues

Over the years, regenerative procedures have been applied in the treatment of root canal therapy in a bid to improve the status of the damaged per apical tissues among patients. Stem cells combined with scaffold material show some degree of success in regenerating the root canal space with the help of platelet-rich plasma (PRP) or growth factors. The clinical findings reveal an enhanced rate of recovery and prevention of reinfections in patients [38].

### 6.3. Novel Approaches in Regenerative Dentistry

The goal of regenerative dentistry involves dental tissue restoration through the use of stem cells together with scaffolds and bioactive materials. Through stem cell technology based tissue engineering, scientists have discovered the possibility of replacing dental implants by developing root replacements. Development of optimal regenerative dentistry depends upon continued research for selecting the best stem cells and scaffold materials and cell-scaffold recombination methods.

## 7. Conclusions

Stem cell and biomaterial for regeneration dentistry is one of the most promising dental technologies because of its ambitious ability to bring new and revolutionary solutions for patients. In the future, this technique will transform treatment with the aim of masking the teeth and surrounding soft tissues to a condition which aims at rejuvenating the teeth and other tissues in their functional and anatomic form; regenerative dentistry focuses on recovering damaged tissues instead of removing them, which can create lasting improvements in patient care and minimize invasiveness. Despite the current barriers in terms of biological and technical optimization techniques, the advancement made so far gives hope for exemplary dental treatments in the future. Further enhancement of these regenerative strategies holds the promise to transform the ways oral tissue repair and regeneration are implemented by dental practitioners, thus setting the stage for regenerative dentistry as a leading concept in contemporary dental practice. This proposes a transfer of the focus on the patient for the management of these cases and subsequent restoration of dental health in a manner that is biologically effective for the patient and propels the dental specialty forward.

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