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REVIEW ARTICLE

EXPLORING THE ROLE OF STEM CELLS IN REGENERATIVE DENTISTRY AND THERAPEUTIC APPLICATIONS: A COMPREHENSIVE REVIEW

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ABSTRACT

Stem cells are components of developing and mature tissues, where they are involved in the self-healing and self-repair of the body. Scientists have directed significant efforts toward investigating their possible applications in treating different diseases in the last few years. Self-replication and differentiation characterizes these cells into a variety of special somatic cells, making them ideal for future clinical therapy, drug discovery, and biomedical research. Currently, five macroscopically distinguishable subgroups of dental pulp have been described: dental pulp stem cells (DPSCs), stem cells extracted from exfoliated deciduous teeth (SHED), stem cells generated from apical papilla (SCAP), periodontal ligament stem cells (PDLSCs), and dental follicle precursor cells (DFPCs). They are easy to obtain, live, and multipotent. Therefore, the isolation and use of these cells in a safe, efficient, and inexpensive manner is an important area of investigation. Interestingly, jaw, facial, and oral cavity tissues are rich sources of stem cells that are more accessible than other sources. Consequently, stem cell-based and tissue engineering applications in dentistry have gained increasing interest and clinical relevance in the recent years. This review is prepared to attract attention to the uniqueness of DSCs and their different functional roles, and to assess their clinical translational potential. The recent discovery of their ability to regenerate has provided great impetus for future investigations of their potential therapeutic use in a variety of conditions.

***Keywords*:** Oral habits, Dentofacial development, Malocclusion, Pediatric dentistry, Cross-sectional study, Maxillofacial growth.

INTRODUCTION

Mesenchymal stromal cells (MSCs) are commonly known as mesenchymal stem cells (MSCs) because of their ability to self-renew and differentiate into various cell types (such as adipocytes, chondrocytes, osteoblasts, and myofibroblasts) in the presence of specific inflammation- or differentiation-inducing signals [1].

Their extensive multipotency and immunomodulatory features, which have been successfully performed in vitro, easy access from different tissues, and substantial expansion potential make them attractive candidates for clinical applications in regenerative medicine, autoimmune diseases, and hyperinflammatory diseases. The relative ease of isolation of these antigens ensures that they are available for investigation and potential therapy [2]. Mesenchymal stem/stromal cells (MSCs) are an extremely heterogeneous population, originating from a range of postnatal tissues of meso- and ectodermal origin [3]. Differences in functional properties condition their translational potential and confer both clinical and therapeutic implications. The remarkable capacity of stem cells to differentiate into functional somatic cells has led to a growing preference for recombinant or precursor cell types in various therapeutic contexts [4].

Oral tissues are an abundant and readily accessible source of stem cells and have garnered significant interest among dental researchers and clinicians. These cells possess distinct regenerative capabilities, which make them highly valuable in the fields of tissue engineering and regenerative medicine. In dentistry, common challenges, such as alveolar bone resorption following tooth extraction, periodontal disease, dental caries, or trauma-induced fractures, pose significant clinical concerns. Tooth loss, particularly in the lower jaw, frequently results in progressive bone atrophy, compromising the feasibility of implant-based rehabilitation. Consequently, stem cell-based tissue engineering approaches aimed at regenerating periodontal structures and alveolar bone to restore lost dentition represent a critical advancement in contemporary dental treatment strategies [5].

Many studies have explored stem cell (SC)-mediated tissue engineering approaches to induce oral and dental tissue regeneration using cellular in vitro systems and animal models to develop clinically applicable therapies [6]. However, further in vivo studies are required to draw more definitive and translatable conclusions. Because of the relative novelty of the use of these cells in dentistry and because basic research has to precede the implementation of clinical protocols, the identification and characterization of the best SC sources in different oral, maxillary, and facial districts is still poorly understood [7]. Dental stem cells (DSCs) that have been isolated, characterized, and identified as candidates for transplantation therapies are promising because of their ready accessibility, high plasticity, isolated niche with some degree of immune-privileged features, and multi-potent differentiation potential [8]. Additionally, combining dental stem cells with personalized biomimetic scaffolds with bioactive molecules such as growth factors and cytokines can notably increase the proliferation, differentiation, migration, and overall regenerative potency of DSCs [9].

2. Diverse Lineage Variants of Stem Cells

The leading global organization in stem cell research, The International Society for Stem Cells Research (ISSCR), provides internationally recognized guidelines on stem cell definitions, uses, and therapeutic applications, and has divided SCs into various groups (Figure 1):

2.1. Embryonic Stem Cells (ESCs)

ESCs are obtained from the inner cell mass of preimplantation embryos. ESCs, which were first isolated from mice, have now been derived from several species, including rats, humans, and nonhuman primates [10]. Human ESCs are pluripotent, and thus capable of differentiating into virtually all body cell types [11]. Based on dental applications, it can be anticipated that differentiation from pluripotent stem cells (PSCs) into diverse oral tissues and structures, that is, periodontal tissues, alveolar bone, oral mucosa, and teeth, can be directed in vitro and in vivo [12]. However, this field faces two significant obstacles in research: ethical and technical concerns. Embryonic stem cells (ESCs), as allogeneic cells, can induce donor-recipient immunological mismatch [13].

2.2. Induced Pluripotent Stem Cells (IPSCs)

Induced Pluripotent Stem Cells (IPSCs) are derived from the conversion of adult somatic cells to a pluripotent state. This reprogramming method was initially described in mice and was subsequently reproduced in human cells [14]. Compared to embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) are clinically more applicable in the dental field, as they are derived from more accessible tissue originating from the oral cavity. This ease of access provides source cells with relatively little invasiveness to dental practitioners who use them. iPSCs are derived from a variety of oral mesenchymal cell populations, such as stem cells from the apical papilla, dental pulp stem cells, stem cells of exfoliated deciduous teeth, progenitor cells from tooth germs, and fibroblasts from the buccal mucosa, gingival tissues, and periodontal ligament [15].

2.3. Adult stem cells

Adult stem cells remain undifferentiated at the periphery of fully developed tissues and organs and possess a remarkable ability to self-renew and differentiate into specialized cell types, tissues, or even entire organs. Their principal function within an organism is to contribute to the maintenance, regeneration, and repair of the native tissues from which they originate [1]

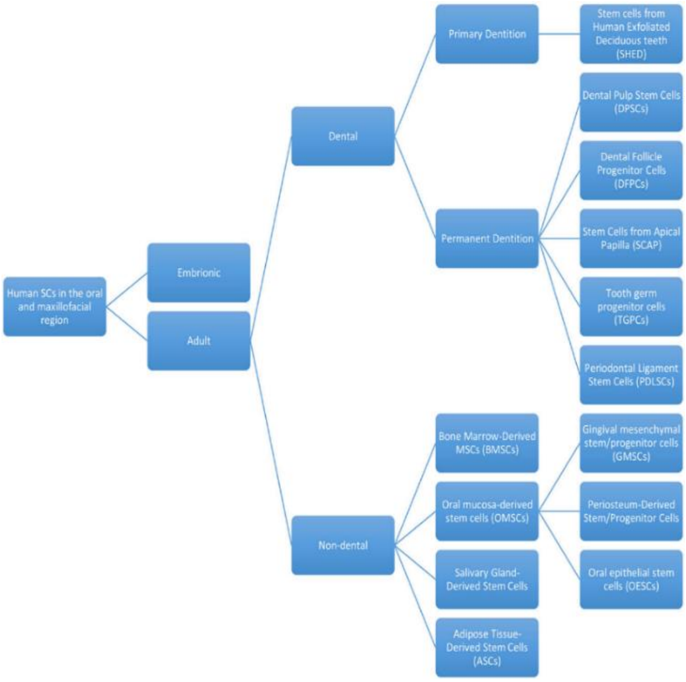

Figure 1. Classification of Human Stem Cells.[16], [Source: 16.Mosaddad, S. A.; Rasoolzade, B.; Namanloo, R. A.; Azarpira, N.; & Dortaj, H. Stem cells and common biomaterials in dentistry: a review study. Journal of Materials Science: Materials in Medicine. 2022, 33, 55.]

2.3.1. Bone marrow-derived MSCs

Bone marrow (BM) is a major source of adult stem cells such as bone marrow-derived mesenchymal stem cells (BMSCs), which have the potential to differentiate into multiple cell types. Because of their regenerative capacity, BMSCs have been proposed as potential candidates for the repair and regeneration of dental and osseous tissues [17]. These cells may be obtained from multiple locations in the body, including the iliac crest and orofacial bone. BMSCs isolated from the iliac crest, considered the most dominant source, are capable of differentiating into myogenic, chondrogenic, osteogenic, adipogenic, and non-mesenchymal neurogenic lineages. However, it is invasive for the donor, as the BMSCs must be isolated from the iliac crest, which is considered a critical bottleneck for clinical applications [18]. Despite this disadvantage, this method has long been utilized in dental and bone prosthetic schemes. Another serious problem is the age-related reduction in regeneration potential of BMSC of the iliac crest. Donor age is an important factor that affects the efficiency of bone tissue engineering methods because cells from older individuals gradually lose their multi-potent differentiation and regenerative abilities [19]. Thus, caution should be exercised when using BMSCs and donor age for clinical applications. Another advantage of oral BMMSCs over iliac crests is that the donor criteria range from young to old. Oral BMSCs can be derived from patients aged 6–60 years, with little effect of age on their gene expression signature. A more remarkable factor is that oral bone marrow stem cells and iliac BMSCs have distinct embryological sources that lead to functional variations [20]. Neural-crest cells give rise to both the maxillary and mandibular bones, while the mesoderm gives rise to the iliac crest. Therefore, oral BMSCs are phenotypically and functionally different from their iliac counterparts. These data suggest that grafted bones from craniofacial (membrane) sources play a significant role in autogenic grafting on the skull and facial bones. Furthermore, these grafts can augment the quantity and regeneration capacity of intramembranous bone from the iliac crest [21].

2.3.2. Dental tissue-derived stem cells

Mature stem cells in tooth tissues are mainly oral epithelial stem cells (OESCs) and mesenchymal stem cells (MSCs). Interestingly, some parts of the tooth (e.g., dental pulp and periodontal tissues) can regenerate and produce reparative dentin under conducive conditions and dental treatments. These tissues represent an attractive and convenient source of MSCs, as well as other stem cell populations for transplantation [22]. Over the years, various sources of dental mesenchymal stem cells have been identified, each with its restorative prospects in regenerative dentistry. Dental Pulp Stem Cells (DPSCs), Dental Follicle Progenitor Cells (DFPCs), Exfoliated Deciduous Stem Cells (ED), Tooth Germ Stem Cells (TGSCs), Periodontal Ligament Stem Cells (PDLSCs), Tooth Germ Progenitor Stem Cells (TGPCs), and Gingival Mesenchymal Stem Cells (GMSCs) [23].

2.3.2.1. Dental pulp stem cells (DPSCs)

Dental pulp stem cells (DPSCs) are a unique type of stem cells located in the soft center of the tooth and can be obtained using a minimally invasive enzymatic approach from third molars (wisdom teeth). These cells are usually fibroblast-like when removed. Owing to their regenerative and reparative potential and favorable characteristics, DPSCs have emerged as an exciting subject of dental and medical research. What certainly distinguishes Dental pulp stem cells (DPSCs) differ in their cellular plasticity, allowing them to differentiate into a wide range of cell types such as osteoblasts, adipocytes, chondrocytes, melanocytes, and endothelial cells [24]. Their capacity to establish clusters analogous to pancreatic islet cells is of particular interest, thereby rendering them potential candidates for future diabetes therapies [25]. Furthermore, DPSCs express proangiogenic factors and anti-apoptotic molecules, thereby increasing their potential for therapeutic use in cardiac tissue regeneration, particularly after myocardial infarction. In preclinical animal models, DPSCs implanted in immunocompromised mice can form highly organized structures of complex tissues, similar to native dental pulp and dentin. Interestingly, these cells exhibit the ability to differentiate towards functional neurons and can therefore be used in neuro-regenerative therapy for diseases of the nervous system [26].

2.3.2.2. Dental follicle progenitor cells (DFPCs)

The tooth follicle is loose mesenchymal tissue around the growing bud of the tooth and is involved in the formation of periodontal progenitor cells. DFPCs isolated from the follicles of human third molars presented fibroblast-like morphology. DFPCs can differentiate into bone cells, adipocytes, chondrocytes, neural cells, periodontal ligaments, fibroblasts, and hepatocyte-like cells (HLCs) [27].

2.3.2.3. Stem cells from Human Exfoliated Deciduous Teeth (SHED)

Stem cells from Human Exfoliated Deciduous Teeth (SHED) are mesenchymal cells found inside the pulp tissue of scaly deciduous teeth. SHEDs are highly proliferative, clonogenic, and generate sphere-like clusters [28]. These cells can differentiate into myocytes, chondrocytes, adipocytes, osteoblasts, odontoblasts, and nerve-like cells and have high plasticity. Morphologically, DPSCs and DFPSCs are similar to the fibroblasts. SHEDs differ from DPSCs in several respects. Their difference lies in their high proliferative capacity, bone formation, odontogenic ability in vivo, and inability to form pulp/dentin complexes [29]. When transplanted into immunocompromised mice, these cells form dentin-like tissues and react with dentin-specific sialophosphoprotein antibodies. Moreover, unlike DPSCs, SHEDs cannot differentiate into osteoblasts or osteocytes; however, they can induce host cells to differentiate into the bone. By absorbing host cells, they induce the formation of a bone-like matrix with a layered structure [30]. The transplantation of SHEDs into the striatum in mice with Parkinson’s disease has been documented to partially improve disease-induced rotational movements, suggesting that SHEDs can be used as a source of postnatal stem cells in the treatment of Parkinson’s disease [31].

2.3.2.4. Tooth germ progenitor cells (TGPCs)

The tooth germ is an accumulation of progenitor cells that form teeth and their tissues. Because the tooth germ of the third molar is formed after the age of 6 years, and the tissues remain undifferentiated from the embryonic period until then. Hence, the proliferative capacity of these cells is extremely high. TGPCs are relatively new SCs isolated from human third molars. These cells can differentiate into chondrocytes, adipose tissue, osteoblasts, odontoblasts, and neurons. In vitro, they show the ability to differentiate into liver cells, providing the basis for curing liver diseases using these cells [32].

2.3.2.5. Periodontal ligament stem cells (PDLSCs)

Periodontal ligament stem cells (PDLSCs) are SCs located around the periodontal arteries surrounding the tooth. They are responsible for regenerating periodontal elements such as the alveolar bone, cementum, and ligament periodontal fibers. PDLSCs are crest-originated neural tissue. These cells connect to bone and cementum. If grafted to an appropriate host, they can also form PDL/cement structures [33]. PDLSCs provide the biological balance of teeth and repair of damaged tissues. These cells are available for the enzymatic digestion of the periodontal ligament area. The cells obtained from this region have characteristics of mesenchymal stem cells [34].

2.3.2.6. Oral mucosa-derived Stem Cells (OMSCs)

The oral mucosa includes stratified squamous epithelium above the connective tissue, termed lamina propria. It is an area with vascularized tissue and the submucosa with adipose tissue, minor salivary glands, lymphatic tissues, and neurovascular bundles, depending on the site. The oral mucosa encompasses various forms of adult human stem cells, including oral epithelial stem cells and progenitor cells, as a subpopulation of small oral keratinocytes. These cells are unipotent stem cells, suggesting that they can only develop into epithelial cells; however, they are clonogenic and can reproduce a well-organized and highly stratified oral mucosal graft ex vivo, indicating their effectiveness for intraoral grafting [35].

2.3.2.7. Gingival mesenchymal stem/progenitor cells (GMSCs)

Gingival mesenchymal stem/progenitor cells (GMSCs) can be easily removed from the gums with minimal pain and discomfort. GMSCs exhibit clonogenicity, self-renewability, multipotent differentiation capacity, and SC-like and immune-regulating features. GMSCs can self-renew, form connective tissue structures in vivo, and differentiate into minerals, fat, and cartilage in vitro. Wang et al. found that GMSCs acquire the ability to differentiate into osteogenic cells in vivo after undergoing the incubation steps in vitro. These findings suggest the clinical use of GMSCs for tissue regeneration and repair [36].

2.4. Salivary gland-derived stem cells

These glands are located intraorally, originate from the endoderm, and consist of acinar and duct epithelial cells with exocrine functions. Salivary glands are classified into two groups: major and minor glands. The major glands included the submandibular, sublingual, and parotid glands. Minor glands are mainly located on the roof of the mouth and lips, and are found in different areas of the throat and larynx. In head and neck cancer, patients undergoing radiation therapy experience irreversible dysfunction of the salivary glands, making the mouth dry and affecting their quality of life. This implies that stem cells in salivary glands can help treat autologous transplantation in tissue engineering and direct cell therapy [37]. To date, in vitro studies have been conducted to isolate SCs from salivary glands, and successful results have been achieved. For example, researchers isolated salivary gland progenitor SCs from the submandibular glands of mice. They observed that these cells expressed acinar, ductal, and myoepithelial cell lineage markers. In another study, a specific population of SCs was isolated from the submandibular glands of mice using the laboratory floating sphere culture method. This study revealed that these cells can differentiate into salivary gland and acinar cells, producing mucin and amylase in vitro. Such findings are also promising regarding the use of salivary gland stem cells to treat cancer patients in the head and neck area undergoing radiotherapy [38].

3. Therapeutic Applications of Dental Stem Cells Across Dental Specialties

3.1. Regenerative Therapies in Endodontics

Progress in pulp regeneration has progressed significantly in research and clinical applications in recent years. Several regenerative endodontic approaches have been suggested that combine different scaffolds, growth factors, and/or stem cells [39]. These techniques also underline key clinical issues such as effective canal disinfection and dentin surface treatment, which are mandatory to succeed in these procedures. A pilot study by Nakashima et al. used mobilized dental pulp stem cells (DPSCs) for complete pulp regeneration in pulpectomized permanent teeth [40]. Although the sample size was small, the findings were promising, indicating safety and biological efficacy, with no signs of toxicity and favorable pulp responses. Leveraging this evidence, a monocentric RCT is now in progress to evaluate the efficacy of SHEDs in rehabilitating immature, necrotic permanent teeth [40].

3.2. Stem Cell-Driven Periodontal Repair

The World Health Organization has specified that advanced periodontitis, marked by deep periodontal pockets, affects approximately 10-15% of the adult population worldwide [41]. Over the years, numerous surgical techniques employing various materials have been rigorously explored, yielding encouraging clinical outcomes in the regeneration of periodontal defects. A New era of periodontal regenerative medicine has started with the discovery of dental stem cells (DSCs), and a new horizon of periodontal therapy has started. As Hynes et al. concluded, these stem cell types have great potential to alter future approaches toward periodontal regeneration [42]. While all five identified types of DSCs have been investigated in animal models for their therapeutic potential in repairing periodontal defects, two, dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs), have demonstrated promising results in early human clinical trials [43].

3.3. Stem Cells-Utilized Regeneration of Oral and Maxillofacial Tissues

The potential use of stem cells in craniomaxillofacial bone regeneration, alveolar cleft repair, and extraction socket preservation has also been well described [44]. The most frequently used stem cells include dental pulp stem cells (DPSCs), dental follicle progenitor cells (DFPCs), and stem cells from human exfoliated deciduous teeth (SHED). These cells, along with biocompatible scaffolds and bioactive growth factors, contribute positively to bone regeneration and structural reconstruction of the oral and maxillofacial segments [45].

3.4. Regenerative Therapeutics in Pediatric Dentistry

The therapeutic potential and future applications of Exfoliated Stem Cells (SHED) have recently emerged in a noticeable manner. These cells are available through natural exfoliation of primary teeth, thereby being a non-invasive and ethical source. Compared to their adult stem cell counterparts, SHEDs have greater proliferative and plasticity capacity and show higher differentiation potential [46]. These cells promote the formation of pulp-like tissue, root continuation, and apical closure, all of which lead to better long-term tooth survival. They also have immunomodulatory properties that would promote healing and reduce inflammation and can be considered prospective cells in cell-based therapy in pediatric dentistry [47].

3.5. Tissue Engineering in Prosthodontics and Implantology

Dental stem cells (DSCs) are promising sources for bone repair and implant therapy [48]. Enhancing osseointegration and reinforcing the biological bonding between the bone and the surface of dental implants, when alveolar bone is insufficient, is one of the most important applications. By introducing DSCs, for example, DPSCs and DFPCs, into TE scaffolds, practitioners can support localized bone regeneration around implants. This technique is of special value in atrophic bones or deficient areas because of trauma, infection, or congenital anomalies, resulting in a lack of space for the insertion of traditional implants [49]. Stem cell-based materials, frequently supplemented with osteoinductive growth factors and biocompatible scaffolding materials, contribute to new peri-implant bone growth and enhance the durability and stability of prosthetic restorations. In addition, they provide a new approach for site-specific bone augmentation without depending on autografts or allografts, causing less damage to the donor site. As knowledge progresses, including DSCs in prosthodontic and implant protocols, the concepts of the standards of care in complex restorative cases will soon change, with protocols whereby the expected results can be better predicted and more biologically reasonable [50].

CONCLUSIONS

Dental stem cell-derived induced pluripotent stem cells (iPSCs): Current and Future Perspectives on Regenerative Dental Medicine contribute to enhancing regenerative outcomes by activating resident progenitor stem cells and modulating the local microenvironment. In addition, the potent immunomodulatory properties of dental stem cells are increasingly being recognized for their therapeutic relevance, as shown in this review. Although further validation is required to confirm the safety and long-term efficacy of DSCs in autologous therapies, particularly in immune-mediated conditions, the initial findings are encouraging. These stem cells may be key to developing novel treatments for autoimmune diseases.

Dental stem cells are gaining substantial attention in dentistry, where they offer significant promise in preserving and regenerating teeth, and across multiple medical disciplines, where their regenerative versatility is being increasingly recognized. Although additional studies are needed to confirm and refine their clinical potential, DSCs stand out as an exceptionally accessible, lifelong source of multipotent cells with the capacity to revolutionize regenerative therapies across a broad spectrum of diseases.

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