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Review Article

The Role of Mesenchymal Stem Cells in Dentistry: A Review

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Abstract

Mesenchymal stem cells (MSCs) have garnered significant attention in regenerative dentistry due to their remarkable ability to differentiate into various cell types and their immunomodulatory properties. This review provides a comprehensive overview of recent advancements in MSC research relevant to dentistry, focusing on their potential applications in periodontal tissue regeneration, dental pulp regeneration, and maxillofacial bone repair. Periodontal diseases, which affect the tissues surrounding and supporting the teeth, are a significant challenge in dentistry. Current treatments often involve surgical intervention and tissue grafting. MSCs have shown promise as a potential alternative for periodontal tissue regeneration, as they can differentiate into periodontal ligament cells, cementoblasts, and osteoblasts. Several preclinical and clinical studies have demonstrated the efficacy of MSC-based therapies in periodontal regeneration. Dental pulp regeneration is another area where MSCs hold promise. Damaged or infected dental pulp can lead to pulpitis or pulp necrosis, necessitating root canal treatment. MSCs have been studied for their ability to regenerate dental pulp tissue and promote pulp healing. They can differentiate into odontoblast-like cells and regenerate dentin-like tissue, making them a potential treatment option for dental pulp regeneration. In maxillofacial bone repair, MSCs have been investigated for their osteogenic differentiation potential and ability to stimulate bone regeneration. Studies have shown promising results, suggesting that MSC-based therapies could be a viable treatment option for maxillofacial bone defects. The mechanisms underlying MSC-based therapies in dentistry are not fully understood but are thought to involve a combination of paracrine effects, immunomodulation, and differentiation into specific cell types. Future research should focus on addressing these challenges and exploring novel approaches for enhancing the regenerative potential of MSCs in dentistry.

Keywords: mesenchymal stem cells, regenerative dentistry, periodontal tissue regeneration, dental pulp regeneration, maxillofacial bone repair, immunomodulation, tissue engineering, stem cell therapy

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1. Introduction

Mesenchymal stem cells (MSCs) are a type of multipotent stromal cells that possess the remarkable ability to differentiate into various cell types, such as osteoblasts, chondrocytes, adipocytes, and myocytes [1]. This unique characteristic, combined with their immunomodulatory properties, has positioned MSCs at the forefront of regenerative dentistry research [2]. In recent years, MSCs have garnered significant attention as potential therapeutic agents for a range of dental applications, owing to their capacity for tissue regeneration and immune response modulation [3].

Dental MSCs, including those from the dental pulp, periodontal ligament, and dental follicle, have gained attention for regenerative medicine [4]. This is attributed to their accessibility and ability to differentiate into neural-like cells, making them promising candidates for treating neurological disorders [5]. The classification and neurogenic induction properties of these cells are often based on the expression of specific markers on their cell surface, such as CD73, CD90, and CD105 [6]. These markers not only characterize the MSCs but also indicate their potential to differentiate into neuronal lineage cells [6]. Understanding the anatomical niches and surface marker expression of dental MSCs is crucial for harnessing their neuroregenerative properties effectively (Figure **1**).

This minireview aims to provide a comprehensive overview of the pivotal role that MSCs play in dentistry. It will delve into their applications in three key areas: periodontal tissue regeneration, dental pulp regeneration, and maxillofacial bone repair. These areas represent critical aspects of dental care where the regenerative potential of MSCs holds great promise for improving treatment outcomes and patient quality of life.

2. Embryonic Origin of Dental Stem Cells

In recent years, there has been a growing interest in understanding the embryonic origin of dental stem cells, as it provides crucial insights into their regenerative potential and therapeutic applications (Figure **2**). One of the fascinating aspects of dental stem cells is their origin from the neural crest during embryonic development [7]. Among these, dental pulp stem cells (DPSCs) have garnered considerable attention due to their multipotent nature and capacity for tissue regeneration [8].

During early embryogenesis, neural crest cells migrate from the neural tube and give rise to a diverse array of cell types, including those contributing to the formation of craniofacial structures and dental tissues [9]. Within the dental pulp, DPSCs are believed to originate from the cranial neural crest, specifically from the dental papilla of developing teeth [10]. This neural crest origin endows DPSCs with unique properties that make them well-suited for therapeutic interventions in dentistry [11].

Understanding the neural crest origin of DPSCs not only sheds light on their developmental biology but also underscores their potential for tissue regeneration. The neural crest-derived nature of DPSCs may explain their ability to differentiate into various cell lineages relevant to dental tissue regeneration, including odontoblasts, adipocytes, and neuronal-like cells [12]. Moreover, this embryonic origin may influence the behavior and function of DPSCs in the context of disease pathology and regenerative medicine strategies [13].

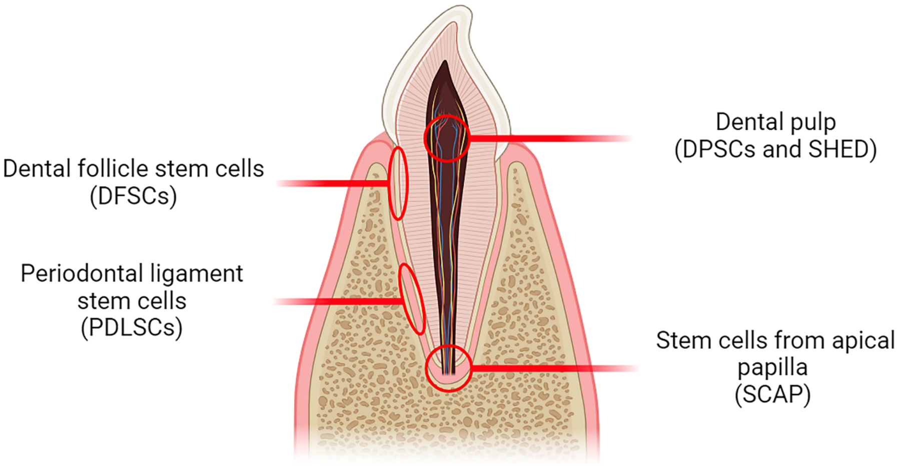

Figure 1: Anatomical niches of dental mesenchymal stem cells relevant to regenerative approaches.

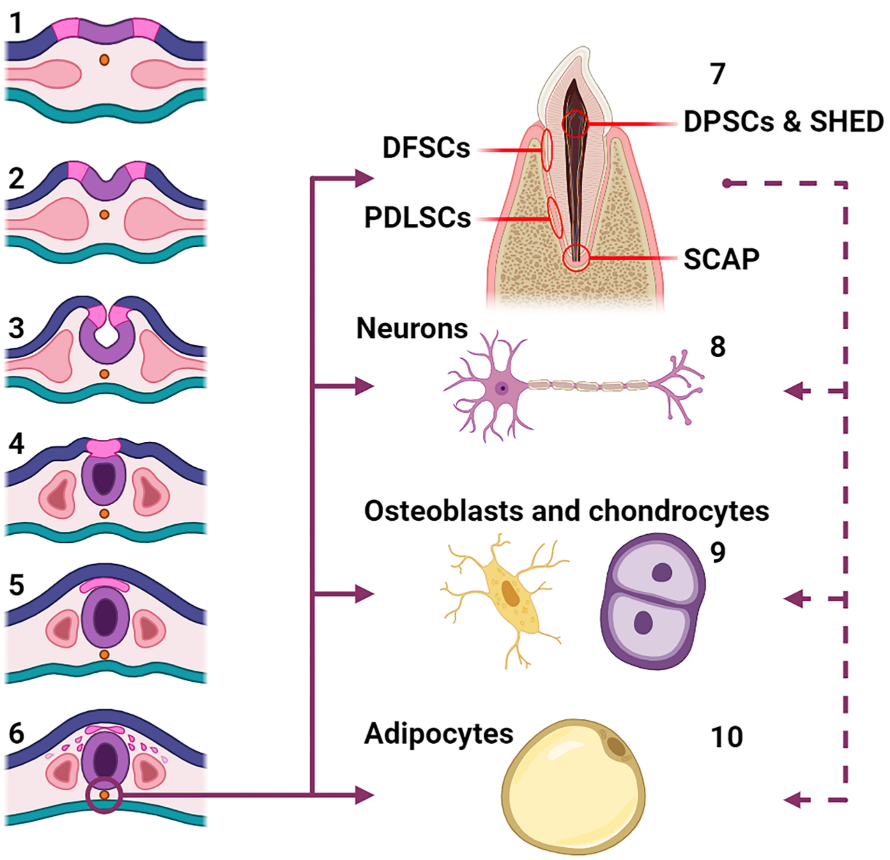

Figure 2: Neural crest cells serve as the progenitors for a diverse range of cell types, highlighting both, origin and the differentiation capabilities of dental stem cells. Cells 1 through 6 depict the genesis of neural crest cells, while cell 7 represents dental stem cells. The dotted arrow signifies the differentiation potential of dental stem cells, with cells 8, 9, and 10 illustrating their capacity to differentiate into adipocytes, osteoblasts, chondrocytes, and neurons, respectively.

MSCs offer promising therapeutic avenues for various dental and maxillofacial disorders [14]. These include periodontal diseases, dental pulp diseases, maxillofacial bone disorders, oral mucosal disorders, and temporomandibular joint disorders [15]. MSC-based therapies have demonstrated potential in promoting tissue regeneration, reducing inflammation, and alleviating symptoms associated with these conditions [16]. Through their ability to differentiate into specialized cell types and modulate the local microenvironment, MSCs hold immense promise for improving oral health outcomes and enhancing the quality of life for patients affected by a wide range of dental and maxillofacial diseases [17].

3. Periodontal Tissue Regeneration

Periodontal diseases are inflammatory conditions that affect the tissues surrounding and supporting the teeth, including the gums, periodontal ligament, and alveolar bone [18]. These diseases are typically caused by bacterial infections, which can lead to gum inflammation, gum recession, tooth loss, and even systemic health issues if left untreated [19].

Current treatments for periodontal diseases often involve scaling and root planing (deep cleaning), antibiotics, and in more severe cases, surgical procedures such as flap surgery and tissue grafting [20]. However, these treatments have limitations, and there is a need for more effective and less invasive therapies.

MSCs have emerged as a potential alternative for periodontal tissue regeneration [3]. MSCs are multipotent stromal cells that can differentiate into various cell types, including periodontal ligament cells, cementoblasts (cells that form the outer layer of tooth roots), and osteoblasts (cells that form new bone) [21]. This differentiation potential makes MSCs attractive for regenerating damaged periodontal tissues.

Both preclinical and clinical studies have shown promising results with MSC-based therapies for periodontal diseases [22]. In preclinical studies, MSCs have been shown to regenerate periodontal tissues and promote tissue healing [3]. In clinical studies, MSC-based therapies have demonstrated improvements in clinical parameters such as pocket depth reduction, clinical attachment gain, and regeneration of periodontal defects [23].

Overall, MSC-based therapies hold great promise as an effective and less invasive treatment option for periodontal diseases [24]. However, further research is needed to optimize treatment protocols, ensure safety and efficacy, and determine the long-term outcomes of MSC-based therapies in periodontal tissue regeneration.

4. Regenerative Endodontics

Dental pulp is a vital soft tissue located in the center of the tooth, containing blood vessels, nerves, and connective tissues [25]. When the dental pulp becomes damaged or infected due to trauma, decay, or other factors, it can lead to inflammation (pulpitis) or tissue death (pulp necrosis) [26]. In immature permanent teeth, pulp necrosis results in the death of the root growth zone, subsequently leading to the cessation of root development. This manifests in root wall thinning, failure of root apex closure, and the absence of apical foramen formation [27].

MSCs have emerged as a promising approach for dental pulp regeneration in immature permanent teeth with necrotic pulps [28, 29]. MSCs can differentiate into odontoblast-like cells, which are responsible for dentin formation, and other cell types found in dental pulp [30]. This differentiation ability makes MSCs well-suited for regenerating damaged dental pulp tissue and promoting pulp healing in immature roots [31].

Several studies have demonstrated the potential of MSCs in dental pulp regeneration [28]. These studies have shown that MSCs can differentiate into odontoblast-like cells and secrete dentin-like tissue, mimicking the natural process of dentin formation [32]. Additionally, MSCs have been found to promote the formation of new blood vessels and the regeneration of nerve fibers, further aiding in pulp healing [33].

MSC-based therapies for dental pulp regeneration offer several advantages over traditional root canal treatment [34]. They have the potential to preserve the vitality of the tooth, maintain its functionality, and reduce the risk of complications associated with root canal treatment, such as fracture or discoloration of the tooth [35].

Overall, MSC-based therapies hold great promise for dental pulp regeneration and have the potential to revolutionize the treatment of pulp-related dental issues. However, further research is needed to optimize the use of MSCs in dental pulp regeneration, ensure their safety and efficacy, and establish standardized protocols for clinical application.

5. Maxillofacial Bone Repair

Maxillofacial bone defects are defects in the bones of the face and jaw that can occur due to a variety of reasons, including trauma, infection, or surgical procedures [36]. These defects can lead to functional impairments and aesthetic concerns, necessitating effective treatment options [37].

Current treatment options for maxillofacial bone defects, include autologous bone grafts (bone taken from the patient's own body), allogeneic bone grafts (bone taken from a donor), and synthetic bone substitutes [38]. While these treatments have been used successfully, they are associated with limitations such as donor site morbidity (pain and complications at the donor site), limited availability of donor bone, and the risk of immune rejection in the case of allogeneic grafts [38].

MSCs have been investigated as a potential alternative for maxillofacial bone repair due to their ability to differentiate into osteoblasts (cells that form bone) and their capacity to stimulate bone regeneration [39]. MSCs can be isolated from various sources, including bone marrow, adipose tissue, and dental pulp, making them readily accessible for therapeutic use [40].

Preclinical studies have shown promising results with MSC-based therapies for maxillofacial bone repair [41]. These studies have demonstrated that MSCs can effectively regenerate bone tissue and enhance bone healing in experimental models of maxillofacial bone defects [42].

Overall, MSC-based therapies offer a promising alternative for maxillofacial bone repair, with the potential to overcome the limitations associated with current treatment options. However, further research is needed to optimize the use of MSCs in maxillofacial bone repair, establish standardized protocols for clinical application, and ensure the safety and efficacy of these therapies in human patients.

6. Mechanisms of MSC-based Therapies

The mechanisms underlying the regenerative properties of MSCs in dentistry are complex and not yet fully elucidated [43]. However, several key mechanisms have been proposed based on current research.

Paracrine effects: MSCs secrete a variety of bioactive molecules, including growth factors (such as vascular endothelial growth factor, transforming growth factor-beta, and fibroblast growth factor), cytokines, and chemokines [44]. These molecules act in a paracrine manner, stimulating nearby cells to proliferate, differentiate, and migrate. This paracrine signaling plays a crucial role in promoting tissue regeneration and repair [45].

Immunomodulation: MSCs possess immunomodulatory properties, which enable them to regulate the immune response [46]. They can suppress the activity of immune cells, such as T cells, B cells, and natural killer cells, and reduce the production of pro-inflammatory cytokines [46]. This immunomodulatory effect is beneficial in reducing inflammation and promoting tissue healing [47].

Differentiation into specific cell types: MSCs can differentiate into various cell types, including osteoblasts (bone-forming cells), chondrocytes (cartilage-forming cells), and adipocytes (fat cells) [1]. In the context of dentistry, MSCs can differentiate into odontoblasts (dentin-forming cells) and periodontal ligament cells, contributing to the regeneration of dental tissues [48].

Extracellular vesicles: MSCs release extracellular vesicles, such as exosomes, which contain bioactive molecules including proteins, lipids, and nucleic acids [49]. These vesicles can transfer functional molecules to target cells, influencing their behavior and function [50]. Exosomes derived from MSCs have been shown to promote tissue regeneration and modulate the immune response [51].

Overall, the regenerative properties of MSCs in dentistry are thought to be mediated by a combination of paracrine effects, immunomodulation, differentiation into specific cell types, and the release of extracellular vesicles [52]. Further research is needed to fully understand these mechanisms and optimize the use of MSC-based therapies in dental regenerative medicine.

The therapeutic effects of MSCs in dental applications are multifaceted and often involve complex mechanisms of action [46]. While our article primarily focuses on summarizing the therapeutic potential of MSCs in dentistry, it is essential to elucidate the underlying mechanisms that contribute to their efficacy [53]. Specifically, MSCs exert their therapeutic effects through various mechanisms, including their regenerative capacity, immunomodulatory properties, and paracrine signaling [46]. The secretion of bioactive factors such as growth factors, cytokines, and extracellular vesicles by MSCs play a crucial role in promoting tissue repair, modulating immune responses, and facilitating microenvironmental remodeling within the oral cavity [44]. Furthermore, MSC-derived extracellular vesicles, which contain a diverse array of bioactive molecules, have emerged as key mediators of intercellular communication and tissue regeneration [54].

7. Routes of Stem Cell Transplantation for Cell Therapy in Dentistry

The success of stem cell-based therapies in dentistry not only depends on the choice of stem cell type but also the route of stem cell administration [55]. Various routes of stem cell transplantation have been explored for delivering therapeutic cells to target sites within the oral cavity [56]. Understanding these routes is crucial for optimizing treatment outcomes and enhancing the efficacy of stem cell-based interventions in dental regenerative medicine.

Local administration: It involves the direct delivery of stem cells to the target tissue site within the oral cavity [57]. This can be achieved through minimally invasive procedures such as intraoral injections or topical application of stem cell-containing scaffolds or hydrogels [58]. Local administration offers the advantage of precise targeting and may be particularly suitable for treating localized dental defects such as periodontal defects or dental pulp injuries.

Systemic administration: This involves the systemic delivery of stem cells via intravenous infusion or other systemic routes [59]. Stem cells administered systemically can be home to injured or inflamed tissues within the oral cavity, exerting therapeutic effects through paracrine signaling, immunomodulation, and tissue regeneration [44]. While systemic administration offers the potential for treating widespread oral conditions or systemic diseases affecting the oral cavity, it may pose challenges related to cell homing efficiency and off-target effects [60].

Surgical implantation: Involves the placement of stem cell-seeded scaffolds or constructs directly into the defect site during surgical procedures such as periodontal surgery or dental implant placement [61]. This approach enables the localized delivery of stem cells and provides a supportive matrix for tissue regeneration [62]. Surgical implantation may enhance the integration of stem cells into the host tissue and promote long-term tissue repair and regeneration.

Combination approaches: In addition to individual routes, combination approaches involving the sequential or simultaneous use of multiple delivery methods have been explored to enhance the therapeutic efficacy of stem cell-based therapies in dentistry [63]. These approaches aim to capitalize on the complementary advantages of different administration routes, thereby maximizing the regenerative potential of stem cells for dental tissue repair and regeneration.

8. Future Perspectives

Despite the promising results of MSC-based therapies in dentistry, several challenges need to be addressed before their widespread clinical application. These include standardization of isolation and culture protocols, safety concerns regarding tumorigenicity and immunogenicity, and regulatory issues. Future research should focus on addressing these challenges and exploring new avenues for enhancing the regenerative potential of MSCs in dentistry.

9. Conclusion

MSCs have emerged as promising candidates in regenerative dentistry, with potential applications in periodontal tissue regeneration, dental pulp regeneration, and maxillofacial bone repair. MSCs hold great promise for improving the outcomes of various dental treatments. However, further research is needed to fully understand the mechanisms underlying MSC-based therapies and address existing challenges.

10. Author Contributions

Conceptualization, M.K.; Data curation, M.K., A.A.; Formal analysis, M.U.; Investigation, M.K.; Methodology, M.K.; Project administration, G.A.; Resources, M.K., M.U., G.A., A.A.; Software, M.K.; Supervision, M.K.; Validation, M.K.; Writing—original draft, M.K.; Writing—review and editing, M.U., G.A., A.K., A.A. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data were available upon request due to ethical restrictions.

Conflicts of Interest

Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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