

Review Article

Current Understanding of Stem Cells in Oral and Implant Surgery- A Review of the Current Literature

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Abstract

Background: Stem cells have provided promising potential for the field of tissue engineering and regenerative medicine. However, their application in the context of oral surgery and implantology for rehabilitation of bony defects and nerve damage due to iatrogenic injury in the oral cavity remains widely unclear.

Aim: The purpose of this study is to review the current role of stem cells and their clinical implications in osseous defect regeneration and nerve repair.

Methods: Human studies based on systematic reviews in English were used to limit bias. Articles were searched on PubMed with key terms: (stem cells) and (oral surgery) and (regeneration).

Results: Bone marrow-derived mesenchymal stem cells injected into sites of horizontal bone deficiencies due to facial injury resulted in the reproduction of alveolar bone in patients undergoing future implant placement. Immunohistological findings from a human clinical trial showed that Periodontal Ligament-Derived Autologous Stem Cells (PDLSCs) demonstrated optimal regenerative capacity of PDL, alveolar bone, cementum and peripheral nerve, as well as improvement of intrabony defects through increased alveolar bone height and decreased depths of bony defects over time. Introduction of umbilical cord-derived stem cells into the oral cavity resulted in successful bone regeneration and reestablishment of lost tissue at sites of injury or pathology. Sensory testing and histomorphometric evaluation concluded that human PDLSCs injected into damaged mental nerves in rats led to enhanced sensory function, sensory neuronal activity and an increase in mRNA expression at the nerve growth receptor level after mental nerve injury.

Conclusion: The findings implicate stem cell therapy as a promising alternative to autologous bone grafting and a potential avenue for regeneration of iatrogenic nerve damage. Despite the need for more evidence-based support, their multipotent potential remains a hopeful turning point for multiple applications in oral surgery and implantology.

Keywords: Stem Cells; Implants; Oral Surgery; Bone Augmentation; Nerve Regeneration

Introduction

Stem cells exhibit varying levels of differentiation potential and are sourced from different parts of the human body [1]. Embryonic Stem Cells (ESCs) possess totipotency and are capable of forming both embryonic and extra-embryonic structures, while also being able to proliferate indefinitely and differentiate into cell types of the three embryonic germ layers [1]. In contrast, adult stem cells, derived from adult sources, are multipotent and differentiate into cell types specific to their tissue of origin, such as neurons, oligodendrocytes or astrocytes from neuronal tissue [1].

Specifically, stem cells relevant to oral surgery can be obtained from various sources, including dental tissues, bone marrow and adipose tissue [2]. Dental Pulp Stem Cells (DPSCs), derived from the pulp tissue of teeth, offer a readily accessible and ethically

non-controversial source of stem cells [2]. Similarly, Periodontal Ligament Stem Cells (PDLSCs) and Dental Follicle Progenitor Cells (DFPCs) isolated from periodontal tissues exhibit regenerative potential in periodontal tissue repair [2]. Furthermore, Mesenchymal Stem Cells (MSCs) sourced from bone marrow and adipose tissue have shown promising results in promoting bone regeneration and soft tissue repair in oral surgery applications [3].

MSCs, characterized by their plasticity and self-renewal ability, differentiate into various mesenchymal lineages and play crucial roles in tissue regeneration and repair, including bone, cartilage and fat, as well as endothelial cells, muscle cells or neurons under specific conditions [4]. MSCs, present in most human tissues and initially isolated from bone marrow, hold significant therapeutic potential, particularly in treating central nervous system disorders like spinal cord lesions [5]. MSCs can be derived from a number of other different tissue sources. Adult tissue sources include muscle, bone marrow, adipose tissue, blood, as well as the oral cavity, whereas perinatal sources include embryonic or fetal tissue [5]. Their versatility and ethical advantages over ESCs make MSCs a preferred model for regenerative medicine research despite limitations such as teratogenicity associated with induced pluripotent stem cells [5].

As shown in Fig. 1, once isolated from their respective sources, MSCs can undergo one of two defining features of a stem cell: self-renewal or differentiation [6]. The process of self-renewal occurs via symmetric division whereby a parent stem cell gives rise to two identical daughter stem cells [7]. The process of differentiation occurs when a stem cell, given specific environmental cues, becomes a progenitor cell that can give rise to a number of differentiated cell types including: myocytes, osteocytes, adipocytes, chondrocytes and neurons [4,7]. These isolated stem cells can then be purified, sterilized and expanded *in-vitro* to obtain the number of cells necessary for stem cell therapy procedures. Once expanded, these stem cells can then be integrated through various means, often through direct injection into the site of therapy, where their respective differentiation processes can occur as seen in Fig. 2 [6].

Stem cell therapy has garnered significant interest in the field of oral surgery due to its potential to regenerate and repair oral tissues damaged by trauma, disease or congenital defects [7]. Stem cells possess unique properties, including self-renewal and multilineage differentiation capabilities, making them ideal candidates for tissue engineering and regenerative medicine applications [6,7]. Stem cells have provided exciting potential for the field of tissue engineering and regenerative medicine [8]. However, their application in the context of oral surgery and implantology for the rehabilitation of bony defects and nerve damage due to iatrogenic injury in the oral cavity remains widely unclear. Autologous bone grafting still remains the current gold standard for alveolar bone regeneration [9]. Recently, however, stem cell therapy has emerged as an appealing alternative to bone augmentation techniques and tissue rehabilitation [10]. In this review, we aim to elucidate the current understanding of stem cells in oral surgery, highlighting their sources, properties and therapeutic potentials. The purpose of this study is to review the current role of stem cells and their clinical implications in osseous defect regeneration and nerve repair in the oral cavity.

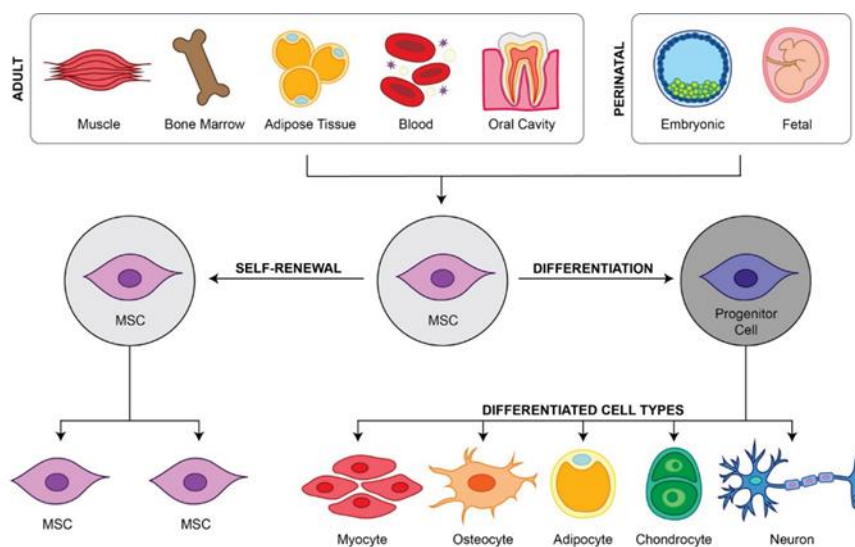


Figure 1: Adult and perinatal mesenchymal stem cell sources, self-renewal and differentiation potential.

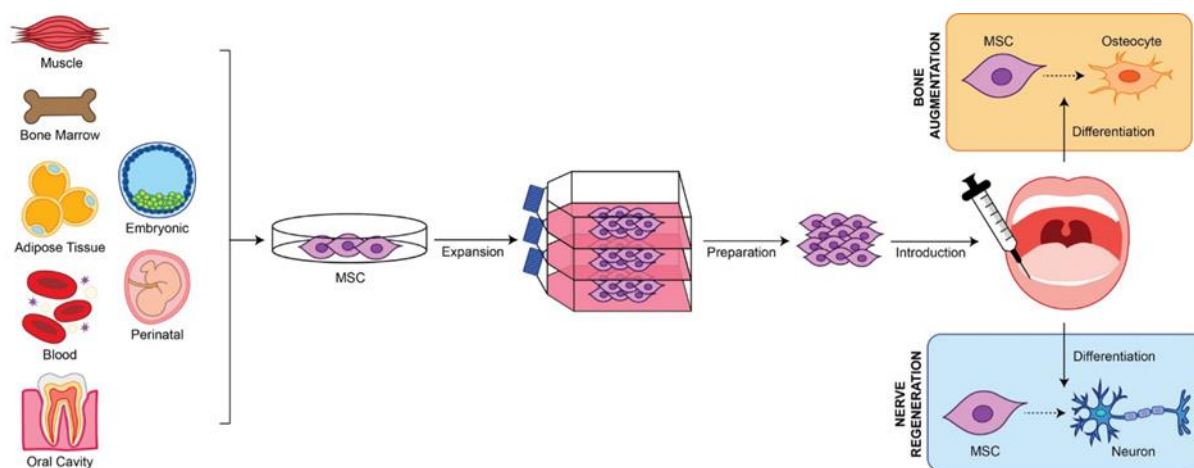


Figure 2: Isolation, expansion and integration of mesenchymal stem cells into sites requiring bone augmentation and nerve repair after injury.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Material and Methods

Methods based on systematic reviews were used to limit bias. Articles were searched on an electronic PubMed with key terms: (stem cells) and (oral surgery) and (regeneration). Inclusion criteria: articles written in English, human studies, clinical trials, systematic reviews and/or meta-analyses. Thirty-three articles have been finally included in this article.

Results

The utilization of stem cells in bone augmentation for oral surgery has demonstrated significant potential in promoting bone regeneration and enhancing treatment outcomes [7]. Studies have shown that MSCs, sourced from bone marrow and adipose tissue, possess the ability to differentiate into osteoblasts and secrete factors conducive to bone formation [7]. In preclinical and clinical studies, MSC-based therapies have been employed either alone or in combination with biomaterial scaffolds to enhance bone healing in alveolar bone defects, maxillofacial fractures and dental implant placement procedures [11]. In a randomized control trial conducted by Bajestan, et al., areas of horizontal alveolar ridge deficiencies in the anterior maxilla were treated either using conventional block graft (control) or a bone marrow stem cell mixture [12]. Alveolar ridge width gain was assessed at 4-month re-entry, demonstrating that both control (3.3 ± 1.4 mm) and stem cell-treated (1.5 ± 1.5 mm) ridges showed significant bone gain after treatment [12]. In another study by Sun, et al., micro-CT of alveolar cleft bone defects of rabbits were filled with either nothing, bone collagen particles only or Human Umbilical Cord-Derived MSCs (HUC-MSCs), 3 and 6 months after surgery, were assessed [10]. Alveolar defects treated with bone collagen particles combined with HUC-MSCs showed a significant increase in percentage bone trabeculae and bone mineral density 6 months after surgery [13].

Additionally, DPSCs have emerged as promising candidates for promoting bone regeneration due to their odontogenic and osteogenic differentiation potential [14]. The integration of stem cell-based approaches with conventional bone grafting techniques has shown promising results in improving bone volume, density and osseointegration, ultimately leading to enhanced functional and aesthetic outcomes in oral surgery patients [14]. A study conducted by Ferrarotti, et al., treated intrabony defects with either collagen sponges supplemented with dental pulp micrografts resulted in significant improvements in residual probing depths (4.9 mm vs. 3.4 mm), gain in clinical attachment loss (4.5 mm vs. 2.9 mm) and bone defect fill (3.9 mm vs. 1.6 mm) of intrabony defects than controls filled with collagen sponges alone 12 months after treatment with dental pulp micrografts [15].

Overall, MSCs have provided a promising alternative to bone augmentation that does not compromise on both bone quality and bone gain. In the realm of oral surgery, stem cells have emerged as promising agents for nerve regeneration, offering novel

strategies to address challenges associated with nerve injury and repair [16]. MSCs exhibit neuroprotective and neurotrophic properties that facilitate nerve regeneration and functional recovery [16]. Preclinical studies have demonstrated that MSCs can differentiate into neuronal-like cells and secrete trophic factors that promote axonal growth, remyelination and synaptic connectivity [17]. Furthermore, DPSCs have garnered attention for their ability to differentiate into neuronal lineage cells and support neurite outgrowth [18]. Incorporating stem cell-based approaches, such as MSC transplantation or DPSC-based scaffolds, has shown promising outcomes in promoting nerve regeneration and functional restoration in animal models of oral nerve injury [19]. Moreover, advancements in tissue engineering techniques, including the development of bioactive scaffolds and growth factor delivery systems, hold potential for enhancing the efficacy of stem cell-based therapies in nerve regeneration [20]. In a study by Sasaki, et al., biodegradable Poly-DL-lactide-Co-glycolide (PLGA) tubes containing either collagen gel alone (control) or embedded with DPSCs were transplanted into a 7 mm gap of a facial nerve in rats. Both treatment groups resulted in facial nerve regeneration both clinically and via immunostaining 9 weeks after implantation with PLGA-tubes supplemented with DPSCs [21].

Discussion

Stem cells utilized in oral surgery possess unique properties that contribute to their therapeutic efficacy [22]. MSCs, for instance, exhibit immunomodulatory effects and secrete various growth factors and cytokines conducive to tissue regeneration [22]. DPSCs, on the other hand, demonstrate high proliferative capacity and multilineage differentiation potential, making them suitable candidates for dental tissue engineering [2]. Additionally, stem cells derived from adipose tissue demonstrate ease of isolation and expansion, along with the ability to differentiate into multiple cell lineages relevant to oral tissue regeneration [23].

Stem cell-based therapies hold immense promise in addressing various oral surgical challenges, including bone augmentation, periodontal regeneration and craniofacial reconstruction [24]. MSCs have been extensively investigated for their ability to enhance bone healing and periodontal tissue regeneration in conditions such as periodontitis and alveolar bone defects [25]. DPSCs, owing to their odontogenic differentiation potential, have been explored for pulp regeneration and dentin-pulp complex engineering [26]. Furthermore, adipose-derived stem cells offer potential applications in soft tissue reconstruction and wound healing in oral surgery procedures [27].

While further research is needed to optimize stem cell delivery methods, assess long-term safety and efficacy and translate these findings into clinical practice, stem cell-based strategies offer a promising avenue for addressing nerve injuries in oral surgery and improving patient outcomes [28].

Recent advancements in stem cell research, including tissue engineering strategies and biomaterial development, have propelled the field of oral surgery towards innovative therapeutic approaches [29]. However, challenges such as optimizing cell delivery methods, ensuring long-term safety and efficacy and regulatory hurdles remain significant barriers to the clinical translation of stem cell-based therapies in oral surgery [30]. Addressing these challenges requires collaborative efforts among researchers, clinicians and regulatory agencies to facilitate the development and implementation of safe and effective stem cell-based treatments [31].

Future directions in stem cell research in oral surgery encompass further elucidation of stem cell behavior and interactions within the oral microenvironment, development of standardized protocols for stem cell isolation, expansion and delivery and clinical trials to evaluate the safety and efficacy of stem cell-based therapies in diverse oral surgical applications [2,8,32]. Additionally, advancements in stem cell-based tissue engineering approaches, including the use of scaffolds, growth factors and gene editing technologies, hold promise for enhancing regenerative outcomes in oral surgery [33].

Conclusion

The findings implicate stem cell therapy as a transformative approach in oral surgery, offering new avenues for bone and tissue regeneration, as well as repair and reconstruction after iatrogenic nerve injury. With continued research and technological advancements, stem cell-based therapies have the potential to revolutionize treatment modalities in oral surgery and implantology, ultimately improving patient outcomes and quality of life.

Conflict of Interests

The authors declare no conflict of interest regarding authorship roles or publication of article.

Acknowledgement

Not applicable

Ethical Statement

Not applicable

Informed Consent Statement

Informed consent was obtained from the subject involved in the study.

Author's Contributions

All the authors have equal contribution and all the authors have read and agreed to the published version of the manuscript.

Financial Disclosure

No funding was not involved in the manuscript writing, editing, approval or decision to publish.

Consent for Publication

Informed consent was obtained from the patient for publication of this case report and is stated in the manuscript.

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