Dean&Francis

ISSN 2959-409X

Application and Prospect of Stem Cells and Biomaterials in Oral and Maxillofacial Tissue Regeneration

Yiyang Zhao

Hayuan College of Kunming Medical University, Kunming, Yunnan, China, 650000
Eian.ZHAO@outlook.com

Abstract:

Oral and maxillofacial soft tissue defects are common clinical problems that seriously affect patients' oral function and mental health. Traditional restorative methods have limitations, while regenerative dentistry utilizes oral-derived Mesenchymal Stem Cells (MSCs), such as Dental Pulp Stem Cells (DPSCs), Periodontal Ligament Stem Cells (PDLSCs), and Stem Cells from Human Exfoliated Deciduous Teeth (SHED), combined with biomaterials such as hydrogels, scaffolds, and growth factors, to provide a new strategy for tissue regeneration. This type of stem cell exhibits multidirectional differentiation capacity and can promote the functional repair of dentin, periodontal, and bone tissues. In recent years, cell-free strategies based on the MSCs secretum (such as exosomes and conditioned medium) have also shown regenerative potential. Although challenges remain in MSC sources, vascularization, and material integration, with the advancement of tissue engineering technology and personalized treatment, regenerative dentistry holds broad prospects for the repair of oral and maxillofacial defects..

Keywords: Oral Regenerative Medicine, Mesenchymal Stem Cells, MSCs, Dental Pulp Stem Cells, DPSCs, Oral and Maxillofacial Tissue Regeneration

1. Introduction

Teeth are key organs of the human body. They not only perform core physiological functions such as chewing and assisting speech, but their complete shape is also an important foundation for supporting facial soft tissues and maintaining facial appearance and contours. They are of great significance to ensuring the quality of life and overall health of the human body. However, the self-repair capacity of teeth is significantly limited. When teeth suffer trauma, inflammation, or are lost due to disease or aging, they often fail to self-regenerate.. Currently, the clinical treatment methods for tooth loss mainly focus on restorative methods such as dental implants,

ISSN 2959-409X

dentures, and dental bridges. Although these methods can compensate for functional defects to a certain extent, they cannot accurately replicate the biomechanical properties and sensory functions of natural teeth. In addition, they are accompanied by the risk of failure and complications in clinical applications, making it difficult to meet patients' needs for natural and long-term restorations[1]. At the same time, common oral diseases such as caries and periodontitis often require tooth extraction to alleviate symptoms. Congenital tooth agenesis leaves patients with both functional and aesthetic deficits from birth. Accompanying problems such as alveolar bone resorption, even relying on autologous bone tissue or inorganic material transplantation for auxiliary treatment, cannot fundamentally solve the core problem of tooth and supporting tissue regeneration. In this context, complete tooth regeneration, as an ideal solution that can naturally and completely solve the loss of teeth and supporting tissues, has become a common goal pursued by medical staff and patients in the dental field. As an emerging medical field, regenerative medicine focuses on cell technology and is dedicated to regenerating or replacing damaged and dysfunctional tissues and organs, which is clearly distinguished from autologous transplantation therapies that rely on surgical techniques. In recent years, with the breakthroughs in technologies such as Embryonic Stem Cells (ESCs) and induced Pluripotent Stem Cells (iPSCs), the research and application of regenerative medicine in the field of dentistry have advanced rapidly. Stem Cells (SCs) have become a core direction of tooth regeneration research due to their ability to repair damaged tissues and restore partial organ functions. Among them, Mesenchymal Stem Cells (MSCs) derived from dental tissues, such as stem cells extracted from dental pulp, dental papilla, periodontal ligament, and dental follicle, as well as induced pluripotent stem cells prepared from human somatic cells, provide an ideal cellular basis for tooth regeneration due to their advantages such as pluripotency, high proliferation rate, and easy accessibility. Currently, tooth regeneration research has formed a variety of strategies, including direct induction, multicellular recombination, and tissue engineering. The former uses signal molecules to induce stem cells to differentiate into specific tooth cells. The multicellular recombination strategy uses stem cells and signal molecules to simulate the natural development process of teeth. The tissue engineering strategy integrates stem cells, biomaterials and cytokines to construct a three-dimensional scaffold to help comprehensively repair hard and soft tissues. In-depth exploration of the basic theories of tooth development, clarification of the current status of clinical research, and prospection of future development directions are of great significance for advancing tooth regeneration technology from basic research to clinical translation and providing innovative solutions for the treatment of oral diseases..

2. Cells used for repair

2.1 Mesenchymal Stromal Cells (MSCs)

Mesenchymal Stromal Cells (MSCs) are present in almost all vertebrate organs. Because these cells have the ability to self-renew and are progenitor cells that can generate adipocytes, chondrocytes, osteoblasts, and myofibroblasts in response to differentiation or inflammatory signals, they are often referred to as Mesenchymal Stem Cells (also abbreviated as MSCs). Owing to their multipotential differentiation capacity, immunomodulatory properties, ease of tissue sourcing, and excellent in vitro proliferation capacity, MSCs are considered an ideal therapeutic resource for tissue regeneration, autoimmune, and hyperinflammatory diseases[2]. MSCs have multidirectional differentiation potential and self-renewal ability. Due to the potent immunomodulatory functions of MSCs, MSC-based therapies have been widely used to treat a variety of inflammatory diseases. Accumulating evidence indicates that the therapeutic effects of MSCs are mainly exerted through their paracrine effects. Growth factors, cytokines, chemokines, extracellular matrix components, and metabolites have been found to be functional molecules of MSCs in various therapeutic modalities. These secreted factors contribute to immune regulation, tissue remodeling, and cellular homeostasis during regeneration[3].

2.1.1 Acquisition of MSCs

The most commonly used methods for obtaining MSCs are tissue explant culture and enzymatic digestion. In the first method, the harvested tissue is ground into 1 mm pieces and then placed on a culture dish containing the ideal culture matrix supplemented with fetal bovine serum and antibiotics for the growth of these cells. The cells are then incubated at 37 ℃ and 5% CO2. Additionally, in some procedures, a coverslip may be placed over the tissue block to prevent movement of the tissue during culture. On the other hand, enzymatic digestion is performed by incubating the ground tissue in collagenase I and dispase II. Incubation times can vary from 30 minutes to 2 hours at 37 °C. After digestion, cells are seeded on culture dishes with the same culture conditions as above.. Once the cells have adhered, the culture medium and excess tissue are removed and fresh culture medium is added to continue cell expansion. MSCs are then assessed for their colony-forming capacity, morphology, immunophenotype, and differentiation potential [4-8].

2.2 Dental Pulp Stem Cells (DPSCs)

DPSCs are easier to obtain than bone marrow-derived mesenchymal stem cells. Dental pulp stem cells (DPSCs) are obtained from the pulp tissue of permanent and deciduous teeth. As early as 2000, the Gronthos team first identified that dental pulp tissue exhibits differentiation capacity.. Since then, relevant research on this property has been widely carried out in academia[9]. DPSCs also have the unique ability to form functional dentin-pulp complexes, making them a promising source for complex tissue regeneration. The extraction material of Dental Pulp Stem Cells (DPSCs) comes from teeth that were originally discarded after being extracted during clinical diagnosis and treatment. In actual separation operations, the tissue block method or enzyme digestion method can achieve efficient separation of these cells. After DPSCs are isolated from dental pulp tissue, they can be screened based on high proliferation potential, surface markers, and nuclear staining using high-throughput fluorescent screening technology.. In current practice, cryopreservation is a common method for storing DPSCs. However, this method has an obvious disadvantage, which is that it is time-consuming [10].

3. Materials for tissue regeneration and repair

3.1 Hydrogels

Hydrogels are considered to be highly promising biomaterials. The reasons for this are, on the one hand, that they can well simulate the biochemical properties of the extracellular matrix (ECM), providing a natural-like microenvironment for processes such as cell growth; on the other hand, their unique structure and properties make them useful for drug delivery and cell transport, showing practical value in biomedical applications[11]. Hydrogels serve as effective drug release carriers, facilitating the delivery of various antimicrobial substances to achieve their desired effects. In oral treatment, the application of hydrogels has been extensively studied. Given that most oral conditions currently involve dental pulp, periodontal tissues, and jaw defects, hydrogels offer significant advantages in this field.

3.1.1 Hydrogels are classified into two categories.

The first category is Natural Hydrogels, which mainly include (1) Collagen-Based Hydrogels (2) Hyaluronic Acid (HA) Hydrogels (3) Gelatin Hydrogels (4) Alginate Hydrogels (5) Chitosan (CS) Hydrogels. The second category is Synthetic Hydrogels, which mainly include (1) Polylactic Acid (PLA) (2) Polyethylene Glycol (PEG) (3) Gelatin Methacryloyl (GelMA)[12].

In the field of dental pulp regeneration, biomaterial scaffolds play an indispensable role.They can provide a stable three-dimensional support structure for the adhesion, migration, proliferation, differentiation and functional performance of stem cells. In addition to providing a physical carrier for stem cell growth, this type of scaffold can also actively regulate the various biological behaviors of stem cells, while regulating intercellular signal transmission and signal interaction between cells and

ISSN 2959-409X

extracellular matrix, thereby optimizing the regenerative microenvironment and creating favorable conditions for the regeneration of the dental pulp-dentin complex. In recent years, hydrogel-based scaffolds have become the focus of research in tissue-engineered dental pulp regeneration. This type of hydrogel scaffold exhibits excellent biocompatibility and biodegradability, as well as favorable flexibility, elasticity, and mechanical properties matching the physiological requirements of the human body.. These outstanding advantages make it an ideal delivery system for cells or bioactive ingredients, providing strong support for promoting the efficient regeneration of the pulp-dentin complex. In addition to its application in the field of dental pulp regeneration, hydrogels have also shown wide applicability in oral-related regenerative treatments. They are also used in periodontal tissue regeneration and mandibular regeneration, and play an active role in the soft tissue healing process, providing support for the repair and reconstruction of various oral tissues[11].

3.2 Calcium Compounds

In the field of synthetic bone substitute materials, Calcium Compounds are recognized as one of the categories with the most application prospects, among which Calcium Phosphate (CP) Cement and Calcium Sulfate (CS) Cement occupy an important position. Specifically, CP cement plays a key role in cell adhesion and tissue formation. Its core mechanism is to regulate the adsorption behavior of extracellular matrix proteins on its own surface, providing basic conditions for cell growth and tissue formation. From the perspective of ions, the role of calcium ions is particularly prominent. On the one hand, it can directly promote the formation and maturation of bone tissue through mineralization; on the other hand, it can indirectly affect the bone regeneration process with the help of cell signaling pathways. It can not only activate mature bone cells by generating nitric oxide, but also induce the activation of precursor cells required for bone tissue regeneration. In addition, calcium ions can enhance the bone-forming function of osteoblasts, extend the lifespan of osteoblasts, and regulate the formation of osteoclasts and their bone-resorbing function. Phosphate also plays an important role in bone regeneration. It not only regulates the differentiation and growth of osteoblasts, but also guides the development of the osteoblast lineage. More importantly, phosphate can effectively inhibit the differentiation of osteoclasts by regulating the ratio of nuclear factor κB receptor activating ligand to osteoprotegerin (RANK-ligand: OPG), thereby reducing bone resorption and creating a favorable environment for the stable regeneration of bone tissue [13].

4. Conclusion

Current traditional oral restoration methods have many limitations, making it difficult to achieve physiological reconstruction and functional restoration of oral and maxillofacial tissues. Oral regenerative medicine has opened up a new direction to solve this dilemma with the help of stem cells, biomaterials and tissue engineering technology. From the perspective of stem cells, the discovery and application of various oral and maxillofacial mesenchymal stem cells, such as Dental Pulp Stem Cells (DPSCs) and Periodontal Ligament Stem Cells (PDLSCs), provide a key cell source for tissue regeneration. These stem cells have the ability of self-renewal and multidirectional differentiation. Under appropriate conditions, they can differentiate into odontoblasts, osteoblasts, etc., thereby promoting the regeneration of the dentin-pulp complex, periodontal tissues, and jawbone. In terms of biomaterials, hydrogels can simulate the extracellular matrix, achieve drug and cell delivery, and create a suitable microenvironment for cell adhesion, migration and differentiation; calcium compounds, such as calcium phosphate and calcium sulfate cement, can regulate bone cell function through ion release and promote bone formation. However, the field of oral regenerative medicine still faces multiple challenges. The efficiency of directed differentiation of stem cells is unstable, and the molecular mechanisms regulating their differentiation are not yet fully understood, making it difficult to accurately achieve the regeneration of specific tissues. The performance of biomaterials also requires improvement: Hydrogels generally suffer from insufficient mechanical strength and are prone to deformation under excessive external force, which impairs tissue repair efficacy; the degradation rate of calcium compounds is difficult to match the rate of tissue regeneration in the body. If they degrade too quickly, they may not be able to provide continuous support and nutrition. If they degrade too slowly, they will persist in the body for an extended period, causing potential adverse reactions. In addition, the long-term safety and functional integration of tissues constructed in vitro in the complex oral microenvironment lack sufficient verification, and personalized treatment plans for different patients are scarce, making it difficult to meet diverse clinical needs. Looking into the future, research in these areas still has broad prospects. On the one hand, with the in-depth development of molecular biology technology, it is expected to further reveal the key signaling pathways and regulatory mechanisms of stem cell differentiation, thereby improving the efficiency of directed differentiation and achieving more accurate oral tissue regeneration. For example, we can conduct in-depth research on the regulatory effects of certain key genes on the differentiation of stem cells into odontoblasts, and improve the differentiation efficiency and quality of odontoblasts by gene editing or regulating related signal pathways. On the other hand, in the research of biomaterials, composite modification and other means can be used, such as combining multiple biomaterials to complement each other's strengths and weaknesses, enhance the mechanical strength of hydrogels, and optimize the degradation kinetics of calcium compounds to make them better adapt to the needs of oral tissue regeneration. At the same time, we should strengthen the research on oral microenvironment and develop material systems that can function stably in the complex oral environment. Furthermore, developing personalized treatment plans based on Induced Pluripotent Stem Cell (iPSC) technology and customizing exclusive oral regenerative treatment strategies according to individual patient differences will become an important development trend. By combining advanced manufacturing technologies such as 3D printing, personalized customization of restorative materials and implants can be achieved to precisely match the patient's oral anatomy and physiological needs. In summary, through multidisciplinary integration and continuous resolution of existing challenges, oral regenerative medicine is expected to provide better and more effective treatment options for patients with oral diseases and significantly improve their quality of life.

References

[1] Sui Y, Zhou Z, Zhang S, Cai Z. The comprehensive progress of tooth regeneration from the tooth development to tissue engineering and clinical application. Cell Regen. 2025; 14(1): 33.

[2] Li P, Ou Q, Shi S, Shao C. Immunomodulatory properties of mesenchymal stem cells/dental stem cells and their therapeutic applications. Cell Mol Immunol. 2023; 20(6): 558-69.

[3] Han Y, Yang J, Fang J, Zhou Y, Candi E, Wang J, et al. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Signal Transduct Target Ther. 2022;7(1):92.

[4] Banavar SR, Rawal SY, Paterson IC, Singh G, Davamani F, Khoo SP, et al. Establishing a technique for isolation and characterization of human periodontal ligament derived mesenchymal stem cells. Saudi Dent J. 2021; 33(7): 693-701.

[5] Poblano-Perez LI, Castro-Manrreza ME, Gonzalez-Alva P, Fajardo-Orduna GR, Montesinos JJ. Mesenchymal Stromal Cells Derived from Dental Tissues: Immunomodulatory Properties and Clinical Potential. Int J Mol Sci. 2024; 25(4).

[6] Naz S, Khan FR, Zohra RR, Lakhundi SS, Khan MS, Mohammed N, et al. Isolation and culture of dental pulp stem cells from permanent and deciduous teeth. Pak J Med Sci. 2019;35(4):997-1002.

[7] Poblano-Pérez, L. I., Castro-Manrreza, M. E., González-Alva, P., Fajardo-Orduña, G. R., & Montesinos, J. J. (2024). Mesenchymal Stromal Cells Derived from Dental Tissues: Immunomodulatory Properties and Clinical Potential. International Journal of Molecular Sciences, 25(4), 1986.

[8] Remy M, Ferraro F, Le Salver P, Rey S, Genot E, Djavaheri-Mergny M, et al. Isolation and Culture of Human Stem Cells from Apical Papilla under Low Oxygen Concentration Highlight Original Properties. Cells. 2019; 8(12).

[9] Wang, W., Yan, M., Aarabi, G., Peters, U., Freytag, M., Gosau, M., Smeets, R., & Beikler, T. (2022). Cultivation

ISSN 2959-409X

of Cryopreserved Human Dental Pulp Stem Cells—A New Approach to Maintaining Dental Pulp Tissue. International Journal of Molecular Sciences, 23(19), 11485..

[10] Wang W, Yan M, Aarabi G, Peters U, Freytag M, Gosau M, et al. Cultivation of Cryopreserved Human Dental Pulp Stem Cells-A New Approach to Maintaining Dental Pulp Tissue. Int J Mol Sci. 2022;23(19).

[11] Chen A, Deng S, Lai J, Li J, Chen W, Varma SN, et al. Hydrogels for Oral Tissue Engineering: Challenges and Opportunities. Molecules. 2023;28(9).

[12] J. M. Dodda, K. Deshmukh, D. Bezuidenhout, and Y. Yeh, in Multicomponent HydrogelsSmart Materials for Biomedical Applications, ed. J. M. Dodda, K. Deshmukh, and D. Bezuidenhout, The Royal Society of Chemistry, 2023, ch. 1, pp. 1-25.

[13] Cheah CW, Al-Namnam NM, Lau MN, Lim GS, Raman R, Fairbairn P, et al. Synthetic Material for Bone, Periodontal, and Dental Tissue Regeneration: Where Are We Now, and Where Are We Heading Next? Materials (Basel). 2021;14(20).