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Review Article

New Approach in Bioactive Materials for Regeneration Dental Application

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Abstract

Regenerative dentistry is an advancing discipline within the dental profession. Tissue engineering, the cornerstone of regenerative dentistry, primarily emphasizes three essential components: stem cells, bioactive compounds, and scaffolds. Stem cells produced from dental tissue are particularly important owing to their exceptional characteristics. Regenerative treatments have introduced innovative methods to several traditional treatment tactics across dental professions. Bone tissue injuries in oral and dental contexts frequently pose significant challenges, as traditional treatments may fail to restore lost or damaged bone tissue completely. Regenerative endodontic procedures, such as pulp revascularization, offer an alternative to conventional root canal treatment. Furthermore, traditional surgical and nonsurgical periodontal therapies are being supplanted by enhanced methods of directed tissue regeneration facilitated by three-dimensional bioprinting and computer-aided design (CAD), which have transformed oral and maxillofacial tissue engineering.

Keywords: regenerative dentistry, dental stem cells, bioactive materials, tissue engineering, 3D bioprinting

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1. Introduction

Regenerating endodontic approaches mostly involve stem cell transplantation, cell homing, and regenerative endodontic operations (REPs) [1].

REPs, a particular technology widely used in clinical practice for pulp tissue regeneration, is a biologically based approach that incorporates concepts of tissue engineering and repair. As shown in Figure **1**, tissue engineering is conventionally believed to require three important elements: signals for the progenitor/stem cells, morphogenesis, and scaffolds of extracellular matrix components [2, 3].

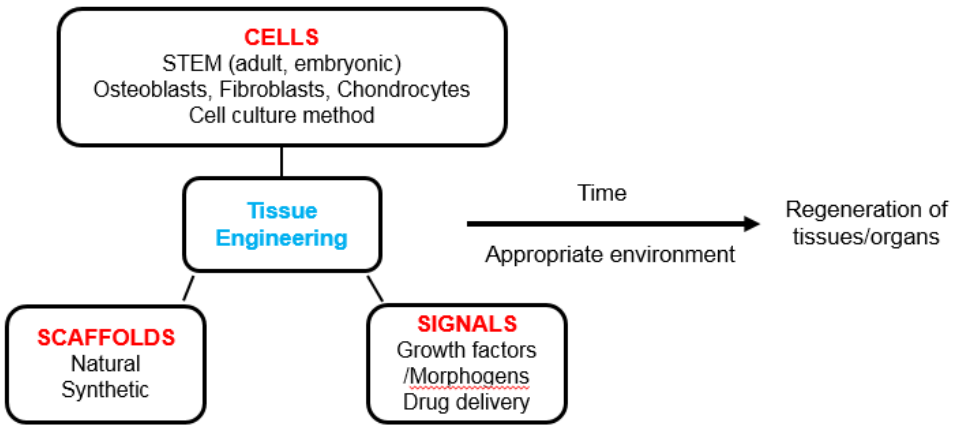

Figure 1: The three key components in dental tissue engineering, involve stem cells, morphogenesis, and a scaffold of extracellular matrix.

It is intended to rehabilitate deficient structures, including dentin and the cells inside the pulp-dentin complex. This method not only repairs apical lesions and mitigates sensations and indicators but also fosters continuous root growth. This holistic method represents a crucial advancement in strengthening dentinal structures to prevent potential root fractures [1, 4-7].

Periodontitis may harm periodontal tissues, such as the periodontal ligament (PDL), cementum, and alveolar bone [8, 9]. Disruption of microbial equilibrium in the oral cavity may increase the risk for various systemic illnesses, such as colitis, myocardial infarction, and Alzheimer's condition [10-12].

Therefore, the effective treatment of periodontitis and periodontal regeneration is crucial for the wellness of humans. Periodontal tissue regeneration includes the repair of the gingiva, alveolar bone, PDL, and cementum [13-15]. The regeneration and natural alignment of the PDL continue to be a significant difficulty in the process of tissue engineering [16, 17].

The temporomandibular joint (TMJ) connects the condyle of the mandible to the glenoid fossa of the temporal bone, featuring a fibrocartilaginous disc that partitions its interior into two compartments [18-20]. This joint is classified as a bilateral diarthrodial joint due to its hinge and sliding movements, as well as its involvement in essential life-support functions such as mastication, deglutition, and phonation [21]. Osteoarthritis (OA) is a degenerative disease that degrades cartilage and adjacent tissues, with TMJ being a significant area of cancer [22-24] n. TMJOA, a subset of TMJ disorders (TMJDs), is

characterized by cartilage degeneration, modified subchondral reconstruction of bones, synovitis, and clinical manifestations include chronic orofacial pain, crepitations, restricted mandibular mobility, and functional impairments [25, 26].

Dynamic bone tissue adjusts to external stimuli. Molecules, both local and systemic, continuously generate and absorb bone tissue, maintaining bone homeostasis. Mechanical forces maintain bone integrity; nonetheless, acute or chronic stress may induce fractures and initiate the bone healing process [27, 28]. The primary inflammatory response, osseous development, and remodeling include several cells and compounds [29-31]. Fractured bones often heal without scar formation; however, certain fragments need surgical intervention. Comprehensive orthopedic and oral/maxillofacial surgeries often result from infections, cancerous tumors, resections, injuries, skeletal deformities, or other conditions like osteoporosis or avascular necrosis, requiring significant bone reconstruction beyond the body's natural regeneration capacity [32, 33].

The advancement of regenerative and tissue engineering depends on three critical elements: stem cells, bioactive compounds, and biomaterials that function as scaffolds and matrices for cellular expansion and maturation. The synergy of these three elements augments tissue healing facilitates stem cell migration to the damage site, and accelerates the total regeneration procedure [34-39]. Multitudes of treatments, mainly cell-free and cell-based, have been devised to enhance the effectiveness and use of these approaches. Cell-free methodologies use bioactive compounds in biomaterials or scaffolds to attract regional cells, including stem cells, therefore enhancing regenerative activities. This phenomenon is referred to as cell homing. Three cell-based therapies use externally sourced cultured stem cells to restore damaged tissue [40-43].

2. Method and Material

2.1. Endodontics

Recurrent endodontics reinstates pulp functionality in teeth exhibiting reversed pulpitis and facilitates the regeneration of the pulp-dentinal complex in necrotic or chronically inflammatory teeth [44, 45]. Pulp revascularization, which facilitates root development in immature permanent teeth with infected necrotic pulp cells and apical periodontitis/abscess, is the only form of regenerating endodontic treatment recognized in the field of dentistry [46, 47].

Stem cells. Numerous adolescent stem cell types may be stimulated to differentiate into odontoblast-like cells, demonstrating their capacity for growth. Potential applications of REP. For instance, dental pulp stem cells, SCAPs, PDLSCs, iPAPCs, and BMSCs [48-51].

Dentin-derived improvement stimulants are essential for the recruitment, proliferation, distinction, and regeneration of progenitor cells [52-54]. TGF-ß1 and FGF2 promote cell migration and proliferation [55, 56]. VEGF governs the expansion of cells and blood vessel formation, while BMP and FGF2 are involved

in signaling for dentin development [56-58]. Non-collagenous protein molecules (NCPs), such as dentin matrix and phosphoprotein, may play a role in odontogenesis [59, 60] Scaffolds. In tissue engineering, scaffolds influence stem cell positioning and regulate cell proliferation, differentiation, and metabolism. It may enhance nutritional uptake and the exchange of gases [61, 62]. Autologous platelet concentrations, including PRP, PRF, and CGF, can be utilized to form a scaffold.

Autologous scaffolds are straightforward to produce and require minimal in vitro modification. Their three-dimensional fibrin matrix and various bioactive compounds may degrade over time. Numerous REPs have demonstrated efficacy with autologous scaffolds [63-65]. Exogenous scaffolds such as collagen type 1, hydrogel, and collagen-hydroxyapatite have been utilized therapeutically in regenerative endodontic procedures. Growth agents are generally incorporated into scaffolds before inserting into immature root canals. Clinical success is indicated by the resolution of symptoms, absence of apical radiographic radiolucency, and ongoing root development.

Research is being conducted on decellularized tooth pulp as a scaffold for pulp regeneration. A study conducted in vivo demonstrated that the implantation of decellularized swine dental pulp into dogs with pulpectomy teeth resulted in the formation of vascularized tissue exhibiting odontoblastic markers [66-68].

2.2. Regeneration of periodontic tissue

Oral microorganism dysbiosis leads to periodontitis through the disruption of the ecologically balanced biofilm. Periodontal tissue homeostasis is compromised, resulting in the degradation of the tooth-attachment devices, including the gingiva, alveolar bone, root cementum, and PDL [69, 70]. The International Association for Cellular Counseling Mesenchymal and Tissue Stem Cell Committee establishes the minimal requirements for the definition of human mesenchymal stem cells (MSCs). MSCs demonstrate plastic adherence in standard culture conditions [71-73]. MSCs exhibit the expression of CD105, CD73, and CD90 while lacking the surface molecules CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR. MSCs demonstrate osteogenic, adipogenic, and chondrogenic plasticity in vitro [71]. Numerous studies indicate that MSCs possess significant potential for the regeneration of bone and dental tissues. Commonly utilized stem cells encompass BMSCs, PSCs, ASCs, and DSCs, which include PDLSCs, DPSCs, GFSCs, DFSCs, and stem cells derived from human exfoliation [74-77]. Tissues obtained throughout the placement of dental implants serve as a notable source of dental stem cells [78, 79]. MSC-CM- based regeneration of periodontal tissue MSC-CM has the potential to facilitate periodontal tissue regeneration. Studies demonstrate that following 4 weeks post-transplantation of MSC-CM, PDL-like constructions were observed between the regenerated cementum and bone [74, 80]. PDLSC-CM comprises growth factors, cytokines, extracellular matrix proteins, and angiogenic factors. Studies demonstrate that PDLSC-CM enhances periodontal regeneration in a concentration-dependent manner [81-83]. Histological images revealed increased bone levels and newly formed periodontal tissues in the PDLSC-moderate and PDLSC-high groups four weeks after CM transplantation, in comparison to

the other groups. All sections demonstrated collagen bundles linking tooth roots and alveolar bone within the periodontal space. The PDL and gingiva serve as significant sources of stem cells.

The PDL exhibits reduced accessibility compared to the gingiva. PDLSC-CM and GMSC-CM significantly influenced periodontal regeneration by decreasing the expression of TNF-α and IL-1β while enhancing the expression of BSP-II and Runx2. The GMSC-CM group exhibited significantly higher IL-10 expression compared to both the PDLSC-CM and control groups [84, 85]. Co-culturing PDLSCs and GMSCs with APTG-CM may facilitate the generation of cementum and PDL-like structures [14, 86]. Research indicates that ASC exosomes may enhance nonsurgical periodontal treatment, with organized PDL tissue observed in the interdental region [87, 88].

2.3. Regeneration of the TMJ

MSCs for TMJOA MSCs are multipotent progenitor cells. Cells possess the capacity for self-renewal and differentiation into many lineages. Owing to the significant variety of MSC populations, the discovery of a unique, definitive phenotypic marker for MSCs remained unachieved; hence, verification depends on a mix of positive and negative markers [89, 90]. The International Society of Cellular Therapy stipulates that MSCs should be defined as plastic-adherent cells that express the markers CD73, CD90, and CD105, while being devoid of hematopoietic markers and HLA class II molecules, and capable of tripotent differentiation into chondrogenic, osteogenic, and adipogenic lineages. In recent years, numerous preclinical and clinical studies have examined the efficacy of MSCs in OA across various joints, including the knee meniscus, demonstrating the therapeutic advantages of MSCs in cartilage regeneration, symptom alleviation, and pain management [91-93]. The therapeutic potential of MSCs and their favorable results have positioned them in the vanguard of TMJOA cellular treatment in recent years [94, 95].

2.4. Regeneration of nerves

Nerve injuries in the orofacial region may result from trauma, neoplasms, or iatrogenic causes. The inferior alveolar nerve, lingual nerve, infraorbital nerve, and facial nerve [96-99]. In modern surgical interventions, autologous nerve grafts and nerve conduits address nerve gaps, accompanied by several advancements and modifications in the latter technique. Nerve conduits were first fabricated from synthesized non-resorbable materials and then advanced to include resorbable substances such as collagen. Nonetheless, owing to the scarcity of cells, their therapeutic outcomes are inferior to those of autologous nerve transplants [99]. Nerve conduits constructed from cell spheroids and 3D printed materials have shown favorable outcomes in animal studies, as they facilitate nerve regeneration by improving cell viability, differentiation, and extracellular matrix (ECM) formation [100].

2.5. Bone regeneration

Bone regeneration is crucial to understanding bone cytoarchitecture and dynamics. The human skeleton relies on bones for movement and organ protection.

Organs facilitate hematopoiesis and maintain mineral and acid-base balance [101-103]. At the microscopic level, bone cells and extracellular matrix components must be distinguished. Osteoblasts are necessary for bone remodeling and osteogenesis. They come from multipotent MSCs, which have been widely studied in regenerative medicine, especially bone repair and regeneration [104-106]. Principles, Technology, and Biomedical Applications of Polymeric Composites Multi-phase polymeric composites have synergistic mechanical properties that no single component can provide. In communication polymers, the matrix phase is ductile and less rigid, whereas the dispersion phase reinforces composites. Polymeric composites are made of two or more distinct and mechanically separable materials, are fabricated to ensure a uniform and controlled distribution of their components, and have enhanced mechanical properties that may differ from their constituents [107]. Mandibular regeneration and polymer composites. The regeneration trio includes (1) 3D printing a biomimetic, bioactive, and osteointegration scaffold for jawbone deficit with growth factor-like BMP-2 and (2) MSCs [108, 109]. Sometimes polymer composites work as scaffolds before dental implants. The 3D-printed PCL structure by Jeong et al. [110] uses osteoconductive ceramics (HA and TCP). These hybrid scaffolds had high porosity and microstructural interconnectivity, outperforming the control group. They concluded that this composite might reduce dental implant surgery costs and time.

Previous study indicates that the rigidity of the combined significantly affects the mobility of the fractured alveolar process, and using a wire of at least 0.9 mm reduces its displacement [111]. So, composition is not the only factor to consider.

2.6. Salivary gland regeneration

Individuals with impaired salivary gland function are now treated symptomatically using artificial saliva and sialagogues [112-114]. Regenerative treatment for salivary glands would be ideal for these patients. The use of DSCs in the regeneration of salivary glands remains undocumented in clinical practice. Studies demonstrate that intravenous infusions of umbilical cord-derived MSCs improve salivary flow rate and alleviate other symptoms of Sjogren syndrome [115, 116].

2.7. Cellular layers

Cell sheets constitute a scaffold-free cellular therapy that produces high-density formations of cells and their extracellular matrix. The extracellular matrix sustains intercellular and cell-matrix integrity.

Forms connections and functions as a scaffold supplying rigidity and stability for cells, as well as a three-dimensional framework for cellular proliferation and transformation [117].

2.8. Spheroids

Spheroids are dense, three-dimensional cellular aggregates featuring a structured network of cells within an extracellular matrix that mimics the microscopic surroundings of natural tissues, capable of producing a potent secretome that promotes angiogenesis, mitigates inflammation, and recruits host cells to enhance repair and regeneration [118, 119].

2.9. Fabrication

The production of organoids is a cell-based regeneration approach that involves the *in vitro* development of three-dimensional tissue constructs that mimic complex microanatomy and functioning. Of the appropriate tissue in vivo using induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), or adult stem cells [120, 121].

Three-dimensional bioprinting. An essential aspect of 3D bioprinting is its ability to regulate the arrangement of cells and materials inside complex, designed tissue-like constructs promoting the maintenance of intercellular growth connections to improve tissue regeneration [122, 123].

2.10. Multilayered scaffolds

Layer scaffolds are very beneficial for periodontal tissue regeneration in dentistry. Employing a layer-by-layer approach, three-dimensional constructions are fabricated from CAD, including stem cells, biomaterials, and growth factors to develop multiphasic scaffolds, with each layer specifically designed to regenerate a unique segment of the periodontium [124].

2.11. Exosome

Exosomes secreted by MSCs are now considered a viable, cell-free therapeutic alternative to cellular treatments [125-127]. The biological functions of exosomes depend on the physiological or pathological state of the cells at the time of release, including immune response regulation, signal transduction, and epigenetic modification [128]. Their advantages over cell therapy include low immunogenicity, significant drug loading capacity, biocompatibility, specificity, stability, and lack of cytotoxicity. Exosomes derived from dental stem cells have considerable potential for the regeneration of dentine-pulp and oral soft tissues in both *in vitro* and *in vivo* environments.

3. Conclusion

Regenerative dentistry is a burgeoning field that has progressed rapidly via the use of MSCs, including dental stem cells, bone marrow-derived MSCs, and adipose-derived MSCs (AMSCs). DSCs have lately

acquired attention due to their superior noninvasive accessibility compared to regularly used BMMSCs. Thus, current research trends highlight the use of DSCsort derivatives as supplements, with other components like biomaterials and bioactive chemicals, to improve cellular function and promote tissue regeneration. Computer-aided design and three-dimensional bioprinting have profoundly altered tissue engineering and regeneration techniques, enabling the creation of patient-specific tailored structures with remarkable accuracy and precision. Recent breakthroughs in regenerative dentistry focus on the repair of absent tissue structures. Nevertheless, considering the advancements in spheroid and organoid generation, significant functional restoration may be achieved in the near future.

Ethical Issue

Authors are aware of and comply with, best practices in publication ethics specifically about authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests, and compliance with policies on research ethics. The authors adhere to publication requirements that the submitted work is original and has not been published elsewhere in any language.

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