Periodontal Bioengineering

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ABSTRACT

Periodontal diseases, such as periodontitis and gingivitis, are prevalent oral health conditions affecting a significant portion of the global population. Traditional treatment approaches for periodontal diseases, such as scaling and root planning, have limitations in achieving complete regeneration of periodontal tissues. In recent years, bioengineering approaches have emerged as promising strategies to regenerate and restore periodontal tissues. This chapter provides an overview of the current state of periodontal bioengineering, focusing on tissue engineering, regenerative therapies, and the use of biomaterials. Furthermore, it discusses key advancements and potential future directions in this rapidly evolving field.

Keywords— Periodontits, Bioengineering, Regenerative therapies, Biomaterials

# INTRODUCTION

 Periodontal disease, is a chronic inflammatory condition that affects the tissues surrounding and supporting the teeth. It is one of the most prevalent oral health issues worldwide and is a leading cause of tooth loss in adults. Periodontal disease is influenced by various risk factors, including: Poor oral hygiene, Smoking and tobacco use, Genetics, Diabetes, Immune system disorders, Hormonal changes, Medications.

 Prevention and management of periodontal disease involve a combination of professional dental care and good oral hygiene practices at home. Regular dental check-ups and professional cleanings are essential to monitor the health of the gums and address any early signs of gum disease. Additionally, maintaining proper oral hygiene through regular brushing, flossing, and using mouthwash can help prevent plaque buildup and reduce the risk of gum disease. In severe cases of periodontitis, treatments may include scaling and root planing (deep cleaning), antibiotic therapy, and, in advanced cases, surgical procedures to repair and regenerate damaged tissues and bones around the teeth.

 Traditional periodontal treatment methods, while effective in many cases, do have some limitations. Some of the key limitations include: Invasiveness, Pain and Discomfort, Limited Tissue Regeneration, Dependency on Patient Compliance, Time-Consuming, Risk of Infection, Potential for Recurrence, Cost.Rationale for periodontal bioengineering.

# PERIODONTAL BIOENGINEERING

 Periodontal bioengineering is an emerging field that aims to apply principles of engineering and regenerative medicine to develop novel treatments for periodontal diseases. The goal is to promote the regeneration of damaged or lost periodontal tissues, including bone, ligaments, and cementum, to restore the health and function of the affected teeth and surrounding structures. This innovative approach holds great promise in overcoming some of the limitations of traditional periodontal treatment methods. Here are some key rationales for periodontal bioengineering:

1. Tissue Regeneration: Periodontal bioengineering focuses on stimulating the body's natural regenerative processes to rebuild damaged or lost periodontal tissues. By using biomaterials, growth factors, and tissue scaffolds, it aims to create an environment conducive to tissue repair and regeneration.

2. Minimally Invasive: Bioengineering techniques often aim to be minimally invasive compared to traditional surgical methods. This can lead to reduced patient discomfort, faster recovery times, and better acceptance by patients who may be anxious about invasive treatments.

3. Personalization: Bioengineering allows for personalized treatment approaches. By tailoring the biomaterials and growth factors to each patient's specific needs, the potential for successful tissue regeneration is increased.

4. Long-Term Results: The goal of periodontal bioengineering is to promote the long-term stability and health of the regenerated tissues. This can lead to more sustainable outcomes and reduce the risk of disease recurrence.

5. Preservation of Tooth Structure: In some cases, traditional periodontal treatments may involve the removal of tooth structure or require the extraction of severely affected teeth. Bioengineering techniques aim to preserve and restore natural teeth whenever possible.

6. Potential for Adjunctive Therapies: Periodontal bioengineering can complement and enhance traditional treatments. For example, bioengineered materials can be used in conjunction with surgical procedures to improve the outcomes of regenerative therapies.

## **Growth factors for Periodontal Regeneration:**

 To facilitate the sustained release of the factors for periods of time, the incorporation of bioactive molecules into scaffolding materials is obligatory. The two basic modes of incorporating bioactive molecules into the scaffolds are at the time of fabrication [1] or after the fabrication [2]. Bioactive molecules incorporated directly into bioresorbable scaffolds are typically released through a diffusion-controlled mechanism, which is governed by the scaffold's pore sizes. The different pore sizes influence the scaffold's tortuosity, thereby controlling the release of proteins [3]. The rate of growth factor release depends on the type and degradation rate of the delivery device, as well as the rate of growth factor diffusion through the scaffold's pores. For instance, Wei et al. conducted a study where they incorporated human parathyroid hormone (PTH) into biodegradable PLGA microspheres and demonstrated a controlled release of PTH [4]. These polymer microspheres effectively preserved the bioactivity of PTH, as evidenced by stimulating cAMP release in rat osteosarcoma cells in vitro and raising serum calcium levels when injected subcutaneously into mice. Murphy et al. also investigated the release of vascular endothelial growth factor (VEGF), a potent mitogen for endothelial cells, from PLGA scaffolds over a 15-day period [5]. The VEGF-incorporated polymers, when seeded with endothelial cells and implanted in vivo, led to enhanced vascularization within the scaffold [6]. Moreover, studies have shown that insulin-like growth factor (IGF)-1 and transforming growth factor (TGF)-1, incorporated into PLGA microspheres, exhibited a gradual release over 15 days [7]. In vitro cultures using IGF-1/TGF-1 containing microspheres photoencapsulated with chondrocytes in a hydrogel system resulted in increased cell numbers and glycosaminoglycan production compared to control gels without microspheres after 2 weeks [7]. Recently, Lutolf et al. presented an approach utilizing hydrogels containing cell adhesive molecule motif RGD (arginine-glycine-aspartic acid) and substrates for matrix metalloproteinases as linkers to polymer chains. These biomimetic scaffolds efficiently regulated the release of BMPs, promoting the healing of craniofacial defects through cell invasion into the scaffolds [8]. However, despite these promising advancements in controlled-release delivery systems, further development is needed to create suitable bioactive molecule devices or alternative delivery methods to optimize therapeutic outcomes in regenerative medicine.

**B. Scaffold and extracellular matrix**

 The extracellular matrix (ECM) is a dynamic tissue containing a complex mixture of macromolecules, which not only provides structural support but also profoundly influences various cellular processes within an organism [9]. These processes include cell adhesion, migration, proliferation, and differentiation, all of which are influenced by the composition and structural organization of the surrounding ECM [10]. Notably, BMPs (bone morphogenetic proteins) play a critical role in bone induction, particularly in craniofacial morphogenesis and regeneration, where interactions with the ECM are contact-mediated [11]. When applied to wounds, rhBMPs bind to specific components of the ECM, such as heparan sulfate, heparin, type II procollagen, fibrillins, proteoglycans, noggin, chordin, DAN, and types I and IV collagen. These interactions create an optimal conformation for active morphogens, enabling contact-mediated responses [12]. Scaffolds, designed to mimic the ECM, must carefully consider the rate of material degradation, as it significantly impacts tissue replacement for engineered structures. Research by Lu et al. demonstrated the profound influence of growth factor release rate from the scaffold on the final outcomes [13].

 Furthermore, the pharmacokinetics of BMPs incorporated into biomaterials like collagen and hydroxyapatite [14] may differ from their behavior in bones, periodontium, and teeth. This difference is attributed to the retention of BMPs at the implantation site, which is affected by the charge characteristics and isoelectric point of the morphogens [15]. Understanding these factors is crucial for optimizing the effectiveness of BMPs in promoting tissue regeneration and bone formation for specific applications.

**C. Angiogenic factors for periodontal repair:**

 The periodontium, a highly vascularized tissue, receives its blood supply from three primary sources: supraperiosteal arterioles along the surface of the alveolar bone, vessels in the periodontal ligament (PDL) region, and arterioles from the interdental septum extending into the gingival and sulcus area [16]. Apart from maintaining local homeostasis and providing adequate host defense through the transport of cells and defensins to the gingival crevice [17], the blood supply plays a crucial role in nourishing newly engineered tissues. However, one of the significant challenges in periodontal regeneration is targeting angiogenesis to an avascular tooth root surface. After an injury, capillaries invading a fibrin clot bring nutrients, inflammatory cells, and oxygen to the wound site, facilitating early granulation tissue formation [18]. Moreover, newly formed blood vessels create a conducive environment for cell migration, proliferation, differentiation, and extracellular matrix synthesis, all essential aspects of early periodontal healing [19].

 Basic fibroblast growth factor (bFGF or FGF-2) has demonstrated potent angiogenic activity [20] and the potential to induce the growth of immature PDL cells [21]. It has also been found that FGF-2 stimulation upregulates the mRNA level of laminin in PDL cells, an essential protein in angiogenesis [22]. Furthermore, recent research has explored the impact of enamel matrix derivative (EMD) in stimulating angiogenesis of periodontal wounds, suggesting its potential to accelerate periodontal regeneration [23].

 However, the accelerated initial healing achieved by EMD may not solely be attributed to its angiogenic effect. Other mechanisms likely contribute to this acceleration. PDL cells exposed to EMD can secrete growth factors, such as TGF-b1, IL-6, and PDGF-AB, which have been known to accelerate the healing rate in periodontal wounds by specifically promoting the proliferation of PDL cells [24]. Additionally, studies have shown that EMD can modulate the bacterial growth of periodontal pathogens without affecting the normal flora during the process of periodontal wound healing [25].

 Tissue engineering of vasculature presents several technical challenges [26]. The selection of appropriate vascular cells and scaffold materials is crucial, often involving in vitro culturing of bone marrow cells or smooth muscle cells with a collagen-based matrix to form tubular structures, which then allow endothelial cells to attach to the vessel wall. Scaffolds must be designed to support proper vascular tissue formation and possess mechanical properties that match those of native arteries, withstanding fluid shear stress, strain, and physiological blood pressures. Additionally, compatibility issues between synthetic engineered grafts and native blood vessels need to be carefully evaluated.

 Growth factors play a critical role in promoting tissue regeneration by inducing angiogenesis and providing oxygen and nutrients to cells. However, their in vivo stability can be a concern, necessitating the use of drug delivery systems. Incorporating angiogenic growth factors directly into scaffolds or employing gene therapy for targeted delivery may be essential for stimulating new vessel formation [27]. A dual growth factor delivery model, utilizing PDGF + VEGF, has shown promise in rapidly forming mature vascular networks, improving angiogenesis, and inducing blood vessel maturation [28].

**D. Gene therapy for periodontal engineering**

 The transient nature of growth factors' half-life in the body limits the effectiveness of traditional surgical approaches for periodontal regeneration, as high concentrations of growth factors are required [29]. To overcome this challenge, gene therapy offers a promising solution by introducing specific genes into cells, either directly or indirectly through a matrix, to achieve the desired biological effect. Gene therapy can be used to supplement defective mutant alleles with functional ones or trigger a more favorable host response. Targeting cells for gene therapy involves using vectors or direct delivery methods for transfection.

 Jin et al. utilized an ex vivo strategy for periodontal repair, employing BMP-7 gene transfer to stimulate the regeneration of alveolar bone, tooth root cementum, and the periodontal ligament (PDL). They transduced syngeneic dermal fibroblasts with Ad-BMP-7 or its antagonist, Ad-noggin, which were then seeded onto gelatin carriers and transplanted into large alveolar bone defects. This approach resulted in successful periodontal defect repair, with rapid chondrogenesis, followed by osteogenesis, cementogenesis, and predictable bridging of the bone defect. However, noggin gene transfer hindered periodontal bone and cementum repair in both periodontal defects and tissue-engineered cementum [30].

 PDGF has shown significant potential in promoting gingival, alveolar bone [31], and cementum regeneration in various wound healing models. When periodontal defects were treated with adenovirus encoding PDGF-B, there was substantial bone and cementum regeneration beyond that observed with control vectors, with nearly fourfold increases in bridging bone and sixfold increases in tooth-lining cemental repair [32]. Moreover, the localized expression of the luciferase reporter gene was sustained at the periodontal lesions for up to 21 days after gene transfer. This underscores the potential of gene therapy as an effective and long-lasting method to promote periodontal tissue regeneration [33].

**E. Challenges and future directions**

The currently available treatments, which are based on the “damage to heal approaches,” have had only limited success in periodontal medicine. With an increasing aging population, tissue-engineering strategies provide important cures and hope for the treatment of periodontal disease, and they have set the stage for successful regeneration of many other tissues. The development of biological transplants for reconstructive therapies has considerably improved the currently available treatment options for periodontal repair. Particularly, the accelerated pace of research in the stem-cell field and the accumulated body of knowledge has spurred interest in the potential clinical use of stem cells [34]. This developing area is attracting increasing attention from both the private and government sectors because of its considerable economic and therapeutic potential. However, there are critical steps in moving the field toward human clinical utility [35]. In particular, the events following cell transplantation are poorly understood, underscoring the considerable need for robust preclinical modeling for the evaluation of the safety and efficacy of stem cells. Although the clinical application of stem cells to the regeneration of periodontal tissue has begun, the risks of stem-cell therapies should not be ignored or underestimated by clinicians and researchers.

 Current treatments for periodontal disease, which rely on "damage to heal" approaches, have shown limited success. However, there is hope for the future with tissue engineering strategies that offer potential cures, particularly with an aging population. The development of biological transplants has significantly improved treatment options for periodontal repair. Stem cell research has also garnered significant interest from both private and government sectors due to its economic and therapeutic potential. Nonetheless, before stem cell therapies can be clinically applied for periodontal regeneration, thorough preclinical modeling is necessary to assess their safety and efficacy.

 Successful tissue engineering is contingent on two main criteria. Firstly, engineering principles concerning scaffold biomechanics, architectural geometry, and space maintenance are crucial. Biomaterials are being designed to mimic in vivo stem cell niches and serve as platforms for cell and factor delivery. However, current methods may not fully capture the complexity of native stem cell regulatory systems. Secondly, the engineered construct's biological functions, including cell recruitment, proliferation, survival, neovascularization, and growth factor delivery, are essential for successful differentiation and tissue regeneration. However, controlling stem cell behavior within a complex in vivo environment remains a challenging task.

 Tissue engineering is revolutionizing periodontal therapy, and clinical trials involving stem cell transplantation in human patients have already commenced or are in preparation. Researchers are also exploring protein- or cell-based therapies to enhance and direct periodontal wound healing, aiming to establish a new therapeutic paradigm for clinical use. Nevertheless, it is crucial to recognize that tissue regeneration alone might not be sufficient for long-term stable treatments, and host modulation therapies play a vital role in controlling periodontal diseases and promoting tissue reengineering.

 In the field of periodontal tissue engineering, there is a growing need to investigate engineering approaches in contaminated or infectious wound beds resulting from periodontitis. Maximizing therapeutic efficacy in passive or permissive environments with limited biological signals is a major challenge. Identifying optimal cell sources, determining clinically relevant cell numbers, finding effective administration methods, integrating new cells into existing tissue matrices, and achieving functional properties using diverse biomaterials are all critical aspects that need to be addressed.

 Furthermore, practical, safety, and regulatory considerations related to the clinical application of tissue engineering technologies are significant barriers that require careful attention.

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