Periodontal Bioengineering

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ABSTRACT

Periodontal diseases, such as periodontitis and gingivitis, are prevalent oral health conditions that impact a substantial portion of the global population, and conventional methods of treatment have been employed to manage these issues, such as scaling and root planning, have limitations in achieving complete regeneration of periodontal tissues. In recent years, bioengineering approaches have arisen as viable strategies with promising potential to regenerate and restore periodontal tissues. Within this chapter, you'll find a summary of the existing situation 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 persistent inflammatory condition that impacts the tissues encompassing and providing support to the teeth. This condition ranks among the most widespread oral health concerns globally and stands as a primary contributor to adult tooth loss.. 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 encompass scaling and root planing, utilization of antibiotic therapy, and, in instances of advanced severity, surgical interventions aimed at restoring and regenerating compromised tissues and bone structures surrounding 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

 The realm of periodontal bioengineering is a burgeoning discipline striving to employ engineering and regenerative medicine concepts in order to create innovative remedies for periodontal diseases. The objective is to facilitate the renewal of impaired or absent periodontal tissues, encompassing bone, ligaments, and cementum, with the intention of reinstating the well-being and operational capacity of the impacted teeth and neighboring 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: Periodontal bioengineering aims to ensure the enduring stability and well-being of the revitalized tissues, aiming for sustained results and mitigated chances of disease relapse.

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:**

 For achieving extended periods of controlled factor release, it is imperative to embed bioactive molecules into scaffolding materials. This can be accomplished either during the fabrication process [1] or post-fabrication [2]. Incorporating bioactive agents directly into bioresorbable scaffolds typically results in diffusion-based release, dictated by the scaffold's pore dimensions. Different pore sizes influence the scaffold's intricacy, thereby regulating protein release dynamics [3]. The pace of growth factor release hinges on the delivery device type, degradation rate, and growth factor diffusion within the scaffold's pores. A case in point is the work of Wei et al., who introduced human parathyroid hormone (PTH) into biodegradable PLGA microspheres, showcasing controlled PTH release [4]. These polymer microspheres effectively maintained PTH's bioactivity, as observed by heightened cAMP release in rat osteosarcoma cells in vitro and elevated serum calcium levels post-subcutaneous injection in mice. Murphy et al. explored vascular endothelial growth factor (VEGF) release from PLGA scaffolds over 15 days [5]. Incorporating VEGF into polymers, seeding them with endothelial cells, and implanting them in vivo fostered scaffold vascularization [6]. Likewise, IGF-1 and TGF-1, within PLGA microspheres, displayed gradual release over 15 days [7]. Cultures using IGF-1/TGF-1-containing microspheres photoencapsulated with chondrocytes in a hydrogel system manifested escalated cell numbers and glycosaminoglycan production compared to control gels without microspheres after 2 weeks [7]. Recently, Lutolf et al. introduced a method employing hydrogels containing cell-adhesive RGD motifs and matrix metalloproteinase substrates as polymer chain linkers. These biomimetic scaffolds aptly regulated BMP release, advancing craniofacial defect healing through scaffold-invading cells [8]. Despite these promising strides in controlled-release delivery systems, refining bioactive molecule devices or alternative delivery approaches is pivotal to optimize regenerative medicine therapeutic outcomes.

B**. Scaffold and extracellular matrix**

The extracellular matrix (ECM) constitutes a dynamic tissue housing a complex assortment of macromolecules, serving not only as a structural scaffold but also profoundly influencing diverse cellular processes within an organism [9]. These encompass cell adhesion, migration, proliferation, and differentiation, all intricately tied to the composition and architectural arrangement of the surrounding ECM [10]. Significantly, in bone induction and craniofacial morphogenesis, BMPs (bone morphogenetic proteins) emerge as pivotal actors, engaging in contact-mediated interactions with the ECM [11]. Upon application to wounds, rhBMPs bind to ECM components like heparan sulfate, heparin, type II procollagen, fibrillins, proteoglycans, noggin, chordin, DAN, and collagen types I and IV. These interactions foster an optimal conformation for active morphogens, thereby enabling contact-based responses [12]. Scaffold designs, mimicking ECM attributes, must meticulously account for material degradation rates, as they significantly affect tissue integration within engineered constructs. Research by Lu et al., [13] underscored the substantial impact of growth factor release velocity from scaffolds on ultimate outcomes.

Furthermore, when BMPs are incorporated into biomaterials like collagen and hydroxyapatite [14], their pharmacokinetics may diverge from behaviors observed in bones, periodontium, and teeth. This disparity arises due to BMP retention at implantation sites, influenced by the charge characteristics and isoelectric point of the morphogens [15]. Comprehending these facets is pivotal for optimizing BMP effectiveness in fostering tissue regeneration and bone formation tailored to specific applications.

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

 The periodontium, a well-vascularized tissue, draws its blood supply from three primary sources: supraperiosteal arterioles along the alveolar bone's surface, vessels in the periodontal ligament (PDL) region, and arterioles from the interdental septum extending into the gingival and sulcus areas [16]. Beyond maintaining local equilibrium and facilitating host defense through cellular transport and defensin conveyance to the gingival crevice [17], the blood supply plays a pivotal role in nourishing newly engineered tissues. Yet, a significant challenge in periodontal regeneration lies in inducing angiogenesis toward an avascular tooth root surface. Post-injury, capillaries infiltrate a fibrin clot, bringing nutrients, inflammatory cells, and oxygen to the wound site, thus fostering early granulation tissue formation [18]. Furthermore, newly formed blood vessels create an environment conducive to cell migration, proliferation, differentiation, and extracellular matrix synthesis – all crucial components of early periodontal healing [19].

Basic fibroblast growth factor (bFGF or FGF-2) has exhibited robust angiogenic activity [20] and the potential to spur immature PDL cell growth [21]. FGF-2 stimulation has also been linked to elevated laminin mRNA levels in PDL cells, a pivotal protein in angiogenesis [22]. Recent investigations have delved into the potential of enamel matrix derivative (EMD) in provoking angiogenesis in periodontal wounds, hinting at its capacity to expedite periodontal regeneration [23].

However, the swift initial healing attributed to EMD might not be exclusively owed to its angiogenic impact. Other mechanisms likely contribute to this acceleration. PDL cells exposed to EMD can secrete growth factors like TGF-b1, IL-6, and PDGF-AB, recognized for accelerating the healing rate in periodontal wounds through specific promotion of PDL cell proliferation [24]. Additionally, studies indicate that EMD can modulate the growth of periodontal pathogens without disturbing the normal flora during the periodontal wound healing process [25].

Vascular tissue engineering is laden with technical complexities [26]. Prudent selection of vascular cells and scaffold materials is critical, often involving in vitro culturing of bone marrow cells or smooth muscle cells within a collagen-based matrix to form tubular structures, facilitating endothelial cell attachment to the vessel wall. Scaffolds must be engineered to foster proper vascular tissue formation and exhibit mechanical properties mirroring those of native arteries, capable of withstanding fluid shear stress, strain, and physiological blood pressures. Furthermore, compatibility issues between synthetic engineered grafts and native blood vessels necessitate careful evaluation.

Growth factors play a pivotal role in spurring tissue regeneration by inciting angiogenesis and facilitating cellular access to oxygen and nutrients. However, their in vivo stability can pose concerns, necessitating employment of drug delivery systems. Direct incorporation of angiogenic growth factors into scaffolds or utilization of gene therapy for targeted delivery may prove vital in stimulating new vessel formation [27]. A dual growth factor delivery approach, combining PDGF + VEGF, has demonstrated promise in rapidly establishing mature vascular networks, enhancing 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 existing treatments in periodontal medicine, following the "damage to heal" paradigm, have exhibited limited success. With an aging population on the rise, tissue-engineering strategies offer promising prospects for addressing periodontal disease, while also setting the groundwork for successful regeneration in various other tissues. The evolution of biological transplants for reconstructive therapies has notably enhanced the available treatment choices for periodontal repair. Notably, the rapid progress in stem-cell research and the accumulation of knowledge have ignited interest in the potential clinical utilization of stem cells [34]. This burgeoning field has garnered growing attention from both private and governmental sectors due to its substantial economic and therapeutic potential. However, pivotal strides are necessary to transition the domain towards human clinical applicability [35]. In particular, the events unfolding after cell transplantation remain insufficiently understood, highlighting the significant demand for robust preclinical models to rigorously assess stem cell safety and efficacy. Despite the initiation of stem cell-based clinical applications for periodontal tissue regeneration, the potential risks associated with stem-cell therapies must not be dismissed or underestimated by clinicians and researchers.

 Current treatments for periodontal disease, which are grounded in the "damage to heal" methodologies, have demonstrated constrained effectiveness. However, there is hope for the future with tissue engineering strategies that offer potential cures, particularly with an aging population The advancement of biological transplants has notably enhanced the array of treatments available for periodontal repair. Additionally, stem cell research has garnered substantial attention from both private and government sectors owing to its promising economic and therapeutic prospects. 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 biological functions of the engineered construct, encompassing cell recruitment, proliferation, survival, neovascularization, and growth factor delivery, are critical for effective differentiation and tissue regeneration. However, exerting control over stem cell behavior within the intricate in vivo environment remains a formidable challenge.

 Tissue engineering is revolutionizing the landscape of periodontal therapy, with clinical trials involving stem cell transplantation in human patients either underway or being prepared. Additionally, researchers are delving into protein- or cell-based therapies to augment and guide periodontal wound healing, aspiring to establish a novel therapeutic paradigm for clinical implementation. Nevertheless, it's imperative to acknowledge that tissue regeneration alone may not suffice for long-term stable treatments, and host modulation therapies hold a pivotal role in managing periodontal diseases and advancing tissue reengineering.

 Within the realm of periodontal tissue engineering, there arises a mounting necessity to explore engineering strategies within contaminated or infected wound beds stemming from periodontitis. Maximizing therapeutic effectiveness in passive or permissive environments characterized by limited biological cues poses a significant challenge. Identifying optimal cell sources, defining clinically relevant cell quantities, devising efficient administration techniques, seamlessly integrating novel cells into existing tissue matrices, and achieving functional attributes through diverse biomaterials all emerge as critical considerations demanding attention.

 Furthermore, practical, safety, and regulatory considerations tied to the clinical application of tissue engineering technologies stand as substantial hurdles that warrant meticulous consideration.

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