PERIODONTAL BIOENGINEERING

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

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I. 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.

II. 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:

- **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.
- **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.
- **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.
- **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.
- **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.

- **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.

1. **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. Incorporating bioactive compounds into the scaffolds can be done in one of two ways: during manufacturing [1] or after [2]. Directly inserted bioactive compounds in bioresorbable scaffolds often release through a diffusion-controlled manner that is determined by the scaffold's pore diameters. The tortuosity of the scaffold is influenced by the various pore sizes, which in turn regulates the release of proteins [3]. Growth factor release and diffusion through the pores of the scaffold are both influenced by the type and rate of delivery device degradation. Human parathyroid hormone (PTH) was incorporated into biodegradable PLGA microspheres, which showed a regulated release of PTH [4]. Polymer microspheres successfully preserved the bioactivity of PTH, as shown by the activation of cAMP release. 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.

2. **Scaffold and Extracellular Matrix:** The extracellular matrix (ECM), a dynamic tissue made up of a complex mixture of macromolecules, not only supports the structure of an organism but also has a significant impact on its many cellular functions [9]. Cell adhesion, migration, proliferation, and differentiation are some of these processes that are impacted by the nature and structural layout of the ECM around them [10]. Especially in craniofacial morphogenesis and regeneration, where interactions with the ECM are contact-mediated, BMPs (bone morphogenetic proteins) play a crucial role in bone induction [11]. The ECM includes substances such heparan sulfate, heparin, type II procollagen, fibrillins, proteoglycans, noggin, chordin, DAN, and types I and IV collagen. When rhBMPs are administered to wounds, they bind to these substances. For active morphogens, these contacts result in the best conformation possible, facilitating contact-mediated reactions. The rate of material deterioration must be carefully taken into account when designing scaffolds that resemble the ECM since it has a substantial impact on tissue replacement for manufactured structures. The scaffold's growth factor release rate has a significant impact on the outcomes [13].

   Furthermore, the behavior of BMPs in bones, periodontium, and teeth may be different from how they behave when incorporated into biomaterials like collagen and hydroxyapatite [14]. This variation is attributable to BMP retention at the implantation site, which is influenced by the morphogens' isoelectric point and charge properties [15]. For specific applications, improving the efficiency of BMPs in stimulating tissue regeneration and bone formation requires an understanding of these parameters.

3. **Angiogenic Factors for Periodontal Repair:** The periodontium, a highly vascularized tissue that surrounds and supports teeth, receives its essential blood supply from three primary sources: supraperiosteal arterioles running along the surface of the alveolar bone, vessels within the periodontal ligament (PDL) region that connects teeth to the bone, and arterioles stemming from the interdental septum that extend into the gum and sulcus regions [16]. This network of blood vessels is crucial as it provides nourishment to newly formed tissues, maintains local stability, and contributes to the body's defense by transporting immune cells and defensins to the gingival crevice [17]. However, a significant challenge in periodontal regeneration lies in stimulating the growth of new blood vessels in areas of the tooth root that lack them.

Following an injury, capillaries infiltrate a fibrin clot, delivering vital nutrients, oxygen, and inflammatory cells to the wound site, thus facilitating the early formation of granulation tissue [18]. Furthermore, newly developed blood vessels play a pivotal role in fostering processes such as cell migration, proliferation, differentiation, and the production of extracellular matrix—essential elements of the initial stages of periodontal healing [19].

FGF-2, also known as basic fibroblast growth factor (bFGF), was shown to have strong angiogenic properties [20] and the ability to stimulate the development of immature PDL cells [21]. Additionally, it has been discovered that FGF-2 stimulation increases the mRNA expression of laminin, a protein crucial for angiogenesis, in PDL cells [22]. Additionally, recent studies have looked at how enamel matrix derivative (EMD) affects the angiogenesis of periodontal wounds, indicating that it may has the ability to speed up the regeneration of periodontal tissues [23].

However, the rapid initial healing that EMD generated might not have been the only factor in it. Additional mechanisms are most likely to blame for this acceleration. It has been demonstrated that growth factors like as TGF-b1, IL-6, and PDGF-AB that PDL cells exposed to EMD may release expedite periodontal wound repair by promoting PDL cell proliferation in particular [24]. Additionally, studies have shown that EMD has no detrimental effects on the normal flora and can inhibit the bacterial expansion of periodontal pathogens during the healing of periodontal wounds [25].

Vasculature tissue engineering poses a number of technological difficulties [26]. It is essential to choose the right vascular cells and scaffold materials. This frequently entails in vitro growing bone marrow or smooth muscle cells with a collagen-based matrix to create tubular structures, which then permit endothelial cells to adhere to the arterial wall. The mechanical qualities of scaffolds must be similar to those of native arteries in order for them to sustain fluid shear stress, strain, and physiological blood pressures and promote the appropriate development of vascular tissue. Further consideration must be given to potential conflicts between native blood vessels and synthetic manufactured grafts.

Growth factors are essential for facilitating tissue regeneration because they stimulate angiogenesis and give cells oxygen and nutrients. However, because of their variable in vivo stability, drug delivery mechanisms must be used. To encourage the creation of new vessels, it may be necessary to include angiogenic growth factors directly into scaffolds or use gene therapy for targeted delivery [27]. Angiogenesis is enhanced,

blood vessel maturation is induced, and mature vascular networks can be formed quickly using a dual growth factor delivery method using PDGF + VEGF [28].

4. **Gene Therapy for Periodontal Engineering:** Challenges and future directions: Conventional surgical techniques for regenerating periodontal tissues face limitations due to the short lifespan of growth factors in the body, requiring high concentrations of these factors [29]. Gene therapy emerges as a promising solution to this challenge by introducing specific genes into cells, either directly or indirectly through a matrix, to achieve the desired biological effects. This approach can be employed to replace dysfunctional mutant genes with functional ones or enhance the body's response to mutations. Gene therapy leverages vectors or direct delivery methods for targeted gene modification.

   To facilitate the regeneration of alveolar bone, tooth root cementum, and the periodontal ligament (PDL), Jin et al. employed an ex vivo approach to periodontal repair. They transplanted syngeneic dermal fibroblasts into substantial alveolar bone defects, which were previously transduced with Ad-BMP-7 or its antagonist, Ad-noggin. This method effectively restored periodontal defects, demonstrating a rapid progression from chondrogenesis to osteogenesis, cementogenesis, and the anticipated bridging of bone defects. However, the introduction of the noggin gene hindered periodontal bone and cementum recovery in both tissue-engineered cementum and periodontal defects [30]. PDGF, known for its potential to promote gingival, alveolar bone [31], and cementum regeneration in various wound healing models, was utilized. Adenovirus encoding PDGF-B was administered for treating periodontal issues, resulting in significant bone and cementum regeneration compared to control vectors. This approach led to nearly four-fold increases in bridging bone and six-fold increases in tooth-lining cement repair [32]. Moreover, the localized production of the luciferase reporter gene persisted in periodontal lesions for up to 21 days following gene transfer. These findings underscore the potential of gene therapy as an effective and durable method for stimulating the regeneration of periodontal tissues [33].

5. **Challenges and Future Directions:** In periodontal medicine, the currently used therapies, which are based on "damage to heal approaches," have had only patchy effectiveness. Tissue-engineering techniques have paved the way for the successful regeneration of numerous different tissues, offering significant solutions and hope for the treatment of periodontal disease in the face of an aging population. The currently available therapy options for periodontal repair have been greatly enhanced by the discovery of biological transplants for reconstructive therapies. Interest in the potential clinical application of stem cells has been sparked, in part, by the quickening speed of research in the field of stem cells and the growing volume of knowledge [34]. Because of its significant economic and therapeutic potential, both the corporate and public sectors are paying greater attention to this emerging subject. The field is heading toward human therapeutic utility, however there are important measures to take [35]. Particularly, there is a lack of understanding of what happens after cell transplantation, which emphasizes the critical need for reliable preclinical modeling to assess the safety and effectiveness of stem cells. Researchers and clinicians should be aware of the potential side effects of stem-cell therapies even if the clinical use of stem cells for the regeneration of periodontal tissue has already started.

There are two key requirements for effective tissue engineering. First and foremost, it is essential to understand technical principles related to scaffold biomechanics, architectural geometry, and space maintenance. In order to distribute cells and factors, biomaterials that resemble in vivo stem cell habitats are being developed. But it's possible that the intricacy of natural stem cell regulation mechanisms is not adequately captured by existing techniques. Second, effective differentiation and tissue regeneration depend on the biological functions of the engineered construct, including cell recruitment, proliferation, survival, neovascularization, and growth factor supply. Controlling stem cell behavior in a complicated in vivo environment, however, is still a difficult task.

Periodontal therapy is being revolutionized by tissue engineering, and human patient clinical studies using stem cell transplantation have already started or are almost set to get started. A novel therapeutic paradigm for usage in clinical settings is being investigated by researchers who also want to improve and direct the healing of periodontal wounds. Host modulation therapies are essential for managing periodontal disorders and encouraging tissue reengineering, and it is necessary to understand that tissue regeneration alone might not be sufficient for long-term stable therapy.

Investigating engineering techniques in polluted or infectious wound beds brought on by periodontitis is becoming more and more important in the field of periodontal tissue engineering. It is extremely difficult to maximize treatment effectiveness in passive or permissive settings with few biological signals. Critical issues that need to be addressed include selecting the best cell sources, figuring out therapeutically useful cell quantities, discovering efficient delivery techniques, incorporating new cells into preexisting tissue matrices, and achieving functional qualities using a variety of biomaterials.

A major barrier that needs careful study is the clinical implementation of tissue engineering technologies' practical, safety, and regulatory considerations.

REFERENCES

[1] Whang K, Tsai DC, Nam EK, Aitken M, Sprague SM, Patel PK et al. Ectopic bone formation via rhBMP-2 delivery from porous bioabsorbable polymer scaffolds. J Biomed Mater Res 1998;42:491–9.
[2] Fournier N, Doillon CJ. Biological molecule-impregnated polyester: an in vivo angiogenesis study. Biomaterials 1996;17:1659– 65.
[3] Babensee JE, McIntire LV, Mikos AG. Growth factor delivery for tissue engineering. Pharm Res 2000;17:497–504.
[4] Wei G, Pettway GJ, McCauley LK, Ma PX. The release profiles and bioactivity of parathyroid hormone from poly(lactic-co-glycolic acid) microspheres. Biomaterials 2004;25:345–52. 32. Murphy WL, Peters MC, Kohn DH, Mooney DJ. Sustained release of vascular endothelial growth factor from mineralized poly(lactide-co-glycolide) scaffolds for tissue engineering. Biomaterials 2000;21:2521–7.
[5] Peters MC, Polverini PJ, Mooney DJ. Engineering vascular networks in porous polymer matrices. J Biomed Mater Res 2002;60:668–78.
[6] Elisseeff J, McIntosh W, Fu K, Blunk BT, Langer R. Controlledrelease of IGF-I and TGF-beta1 in a photopolymerizing hydrogel for cartilage tissue engineering. J Orthop Res 2001;19:1098–104.
[7] Lutolf MP, Weber FE, Schmoekel HG, Schense JC, Kohler T, Muller R et al. Repair of bone defects using synthetic mimetics of collagenous extracellular matrices. Nat Biotechnol 2003;21:513–8.
[8] Terranova VP, Wikesjo UM. Extracellular matrices and polypeptide growth factors as mediators of functions of cells of the periodontium. A review. J Periodontol 1987;58:371–80.
[9] Kleinman HK, Philp D, Hoffman MP. Role of the extracellular matrix in morphogenesis. Curr Opin Biotechnol 2003;14:526–32.

[10] Reddi AH. Morphogenesis and tissue engineering of bone and cartilage: inductive signals, stem cells, and biomimetic biomaterials. Tissue Eng 2000;6:351–9.
[11] Reddi AH. Interplay between bone morphogenetic proteins and cognate binding proteins in bone and cartilage development: noggin, chordin and DAN. Arthritis Res 2001;3:1–5.
[12] Lu L, Zhu X, Valenzuela RG, Currier BL, Yaszemski MJ. Biodegradable polymer scaffolds for cartilage tissue engineering. Clin Orthop 2001;391(Suppl.):S251.
[13] Brandao AC, Brentegani LG, Novaes AB Jr, Grisi MF, Souza SL, Taba M Jr et al. Histomorphometric analysis of rat alveolar wound healing with hydroxyapatite alone or associated to BMPs. Braz Dent J 2002;13:147
[14] Egelberg J. The topography and permeability of vessels at the dento-gingival junction in dogs. J Periodontal Res Suppl 1967;
[15] McKay MS, Olson E, Hesla MA, Panyutich A, Ganz T, Perkins S et al. Immunomagnetic recovery of human neutrophil defensins from the human gingival crevice. Oral Microbiol Immunol 1999;14:190–3.
[16] Arnold F, West D, Kumar S. Wound healing: the effect of macrophage and tumour derived angiogenesis factors on skin graft vascularization. Br J Exp Pathol 1987;68:569.
[17] Okuda K, Murata M, Sugimoto M, Saito Y, Kabasawa L, Yoshie H et al. TGF-beta1 influences early gingival wound healing in rats: an immunohistochemical evaluation of stromal remodelling by extracellular matrix molecules and PCNA. J Oral Pathol Med 1998;27:463–9.
[18] Folkman J, Klagsbrun M. Angiogenic factors. Science 1987;235:442–7.
[19] Murakami S, Takayama S, Ikezawa K, Shimabukuro Y, Kitamura M, Nozaki T et al. Regeneration of periodontal tissues by basic fibroblast growth factor. J Periodontal Res 1999;34:425– 30.
[20] Yuan K, Chen CL, Lin MT. Enamel matrix derivative exhibits angiogenic effect in vitro and in a murine model. J Clin Periodontol 2003;30:732–8.
[21] Dennison DK, Vallone DR, Pinero GJ, Rittman B, Caffesse RG. Differential effect of TGF-beta 1 and PDGF on proliferation of periodontal ligament cells and gingival fibroblasts. J Periodontol 1994;65:641–8.
[22] Sculean A, Auschill TM, Donos N, Brecx M, Arweiler NB. Effect of an enamel matrix protein derivative (Emdogain) on ex vivo dental plaque vitality. J Clin Periodontol 2001;28:1074–8.
[23] Zisch AH, Lutolf MP, Ehrbar M, Raeber GB, Rizzi SC, Davies N et al. Cell-demanded release of VEGF from synthetic, biointeractive cell ingrowth matrices for vascularized tissue growth. FASEB J 2003;17:2260–2.
[24] Liu PY, Tong W, Liu K, Han SH, Wang XT, Badiavas E et al. Liposome-mediated transfer of vascular endothelial growth factor cDNA augments survival of random-pattern skin flaps in the rat. Wound Repair Regen 2004;12:80–5.
[25] Richardson TP, Peters MC, Ennett AB, Mooney DJ. Polymeric system for dual growth factor delivery. Nat Biotechnol 2001;19:1029
[26] Fang J, Zhu YY, Smiley E, Bonadio J, Rouleau JP, Goldstein SA et al. Stimulation of new bone formation by direct transfer of osteogenic plasmid genes. Proc Natl Acad Sci U S A 1996;93:5753– 8.
[27] Anusaksathien O, Webb SA, Jin QM, Giannobile WV. Plateletderived growth factor gene delivery stimulates ex vivo gingival repair. Tissue Eng 2003;9:745–56.
[28] Jin Q, Anusaksathien O, Webb SA, Printz MA, Giannobile WV. Engineering of tooth-supporting structures by delivery of PDGF gene therapy vectors. Mol Ther 2004;9:519–26.
[29] Anusaksathien O, Jin Q, Zhao M, Somerman MJ, Giannobile WV. Effect of sustained gene delivery of platelet-derived growth factor or its antagonist (PDGF-1308) on tissue-engineered cementum. J Periodontol 2004;75:429–40.
[30] Chen FM, Zhao YM, Jin Y, Shi S. Prospects for translational regenerative medicine. Biotech Adv 2012;30:658
[31] Lu H, Xie C, Zhao YM, Chen FM. Translational research and therapeutic applications of stem cell transplantation in periodontal regenerative medicine. Cell Transplant 2013;22:205.
[32] Chen FM, Sun HH, Lu H, Yu Q. Stem cell-delivery therapeutics for periodontal tissue regeneration. Biomaterials 2012;33:6320.
[33] Bartold PM, Xiao Y, Lyngstaadas SP, Paine ML, Snead ML. Principles and applications of cell delivery systems for periodontal regeneration. Periodontology 2000;2006(41):123
[34] Zhang Y, Wang Y, Shi B, Cheng X. A platelet-derived growth factor releasing chitosan/coral composite scaffold for periodontal tissue engineering. Biomaterials 2007;28:1515.
[35] Rios HF, Lin Z, Oh B, Park CH, Giannobile WV. Cell- and genebased therapeutic strategies for periodontal regenerative medicine. J Periodontol 2011;82:1223.

