

Review Article

An Overview of Biomaterials in Periodontology and Implant Dentistry

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Material is a crucial factor for the restoration of the tooth or periodontal structure in dentistry. Various biomaterials have been developed and clinically applied for improved periodontal tissue regeneration and osseointegration, especially in periodontology and dental implantology. Furthermore, the biomimetic approach has been the subject of active research in recent years. In this review, the most widely studied biomaterials (bone graft material, barrier membrane, and growth or differentiation factors) and biomimetic approaches to obtain optimal tissue regeneration by making the environment almost similar to that of the extracellular matrix are discussed and specifically highlighted.

1. Introduction

Periodontitis, a common periodontal disease, is an inflammatory disease that damages soft tissue and induces periodontium destruction [1]. Gingival recession or alveolar bone resorption, which is caused by periodontal disease or trauma, has been a challenge for both dental clinicians and researchers. Over the years, many studies reported the success of periodontal regeneration using various strategies, including root planning, gingival curettage, and open flap debridement procedure [2]. However, these therapeutic approaches without the use of supportive materials present limitations to induce genuine tissue regeneration in the compromised sites. With the progress in the development of biomaterials for tissue engineering, several methods of regenerative periodontal therapy, including the use of bone graft, growth factors, barrier membrane, and combined procedures, have been investigated [3]. Guided tissue regeneration (GTR) [4] or guided bone regeneration (GBR) [5] was introduced to regenerate periodontal tissue in the defect site and has been performed with various biomaterials.

2. Biomaterials in Periodontology

2.1. Tissue Engineering in Periodontology. Tissue engineering is an interdisciplinary field, which advanced from the development of biomaterials to restore or maintain the function of impaired tissue or organ. *Langer* and *Vacanti* proposed tissue engineering as a possible technique for the regeneration of lost tissues [6]. Tissue engineering approaches in periodontology mainly focus on oral soft tissue and alveolar bone regeneration, and they are combined with three key elements to enhance tissue regeneration: progenitor cells, scaffold or supporting matrix, and signaling molecules [7].

2.1.1. Oral Soft Tissue Wound Healing: Repair versus Regeneration. Soft tissue healing around the teeth, dental implant, and edentulous ridge follows a pattern similar to that of skin wound healing, including hemostasis, inflammation, cell proliferation, and maturation/matrix remodeling [8, 9]. The common outcome of wound healing is soft tissue repair by formation of a long junctional epithelium between the root surface and gingival connective tissue [10]. However, wound healing via regeneration is characterized by de novo

TABLE 1: Types of barrier membrane in periodontal regeneration.

Type	Material	Brand
Resorbable	<i>Natural membrane</i>	
	A cellular dermal allograft	Alloderm
	Oxidized cellulose mesh	Surgicel
	Type I collagen membrane	Biogide, Biomend, Ossix plus, Biosorb
	<i>Synthetic membrane</i>	
	Polylactic acid derivatives	Epiguide, Atrisorb, Osmed, Guidor
Nonresorbable	Combination of polylactic and polyglycolic acid derivatives	Ethisorb, Resolute, Vicryl mesh
	Cellulose acetate filter	Millipore paper filter
	Rubber dam	Rubber filter
	Expanded polytetrafluoroethylene (e-PTFE)	Gore Tex
	Dense polytetrafluoroethylene (d-PTFE)	Cytoplast
	Titanium mesh	Cytoflex
	Ethylene cellulose	BenaCel

formation of cementum and periodontal ligament (PDL) with a short epithelial attachment establishing the gingival unit. For tissue regeneration, various technologies using barrier membrane to obtain selective cell colonization, growth factor to alter the microenvironment increasing soft tissue healing, and scaffold to improve the ingrowth of cells and maintain the grafted space have been developed [10].

(1) *Barrier Membranes.* The application of membrane originated from the principle of GTR, which is a technique to place a barrier membrane between the surgical flap and root surface, allowing selective cell recruitment and formation of new cementum, PDL, and bone [11, 12]. The membranes are derived from a natural or synthetic origin and are divided in two types, resorbable versus nonresorbable material (Table 1). The first developed membrane was nonresorbable. However, the additional surgical procedure to remove the membrane led to the development of resorbable membranes. Resorbable membranes are mainly animal derived or synthetic polymers. They are easy to use, without additional surgery, as they are gradually degraded. Compared to nonresorbable membranes, resorbable membranes allow for lesser exposure that reduces the risk to bacterial infection in the grafted site. However, it is difficult to support the grafted materials for a long time. On the other hand, nonresorbable membranes present the advantage of maintaining the space [13–15]. Therefore, an appropriate selection suitable for the tissue defect is required to obtain good clinical outcome.

(2) Growth or Differentiation Factors

- (i) Enamel matrix derivative (EMD, for example, Emdogain®, Straumann, Basel, Switzerland) is an extract of enamel matrix and contains amelogenins, which are used to biomimetically stimulate the soft and hard tissues surrounding the teeth to regenerate following tissue destruction [16, 17].
- (ii) Platelet rich plasma (PRP) is a platelet concentrate, which accelerates soft and hard tissue healing. The main substance is platelet-derived growth factor

TABLE 2: Types of bone graft materials in periodontal regeneration.

Type	Material	
Autograft	<i>Extraoral</i>	
	Iliac Crest, Tibia, Fibula, Ribs	
	<i>Intraoral</i>	
Allograft	Chin, Exostosis, Ramus, Tuberosity	
	Mineralized (FDBA) and demineralized freeze-dried bone allografts (DFDBA)	
Xenograft	Bovine derived, porcine derived, equine derived	
Alloplast	Hydroxyapatite, calcium phosphate, β -TCP, bioactive glass, synthetic glass	

(PDGF), which is involved in wound healing by stimulating angiogenesis, granulation tissue formation, initial epithelial migration, and hemostasis [18]. GEM 21S® (Osteohealth, Shirley, NY, USA) is a product available for clinical use. It consists of a concentrated solution of pure recombinant human PDGF-BB and an osteoconductive beta-tricalcium phosphate (β -TCP) as a scaffold.

- (iii) Bone morphogenetic protein is an important cytokine for the development of bone and cartilage [19]. BMP-2 and BMP-7 are osteoinductive BMPs, which stimulate osteoblast differentiation [20, 21]. Recombinant human BMP-2 (rhBMP-2) is available for orthopedic surgery or periodontal tissue regeneration [22].

(3) *Bone Graft Material.* Bone grafting is a technique for the replacement of missing bone with alternative materials. Bone graft materials are used as scaffold or filler to promote bone formation and wound healing. These materials are broadly divided into autograft, allograft, xenograft, and alloplast (Table 2), which act as a mineral reservoir to assist new bone formation [23, 24].

2.1.2. *Bone Remodeling at a Glance [50].* Bone remodeling is a complex and highly coordinated process in which the old bone is continuously replaced by new tissue [51]. The

remodeling cycle is composed of five consecutive phases: the activation phase, which involves the initiation of the bone remodeling signal; the resorption phase, during which osteoclasts digest the old bone; the reversal phase, which generates an osteogenic environment; the formation phase, a process by which new bone is produced; the termination phase, which informs the remodeling machinery to cease the remodeling cycle [52]. The bone remodeling process requires an intimate interaction between different cell types and is regulated by cellular and molecular mechanisms [53, 54].

2.2. Osseointegration around the Dental Implant. Osseointegration or osteointegration is defined as a direct connection between the living bone and the surface of the dental implant without insertion of nonbone tissue [55]. After the initial observation of osseointegration by Brånemark et al., the concept of osseointegration was defined at various levels, clinically [56], anatomically [57], structurally [58], and histologically [59]. The bone healing procedure around dental implants involves cellular and extracellular biological events, which occur at the bone-to-implant interface until the implant surface is finally covered by new bone formation [60]. This cascade of biological events is similar to those involved in bone healing, activating osteogenic processes regulated by various growth or differentiation factors [61]. Titanium (Ti) is a widely accepted dental implant material because of its biocompatibility and durability [62–64]. As osseointegration is involved in the bone to material interface, the surface characteristic is a major factor to accelerate osseointegration. Therefore, many studies focused on improving Ti surface conditions by incorporation of optimal surface roughness (e.g., machined [65], sandblasted [66], acid etched [67, 68], anodized [69, 70], and laser modifications [71, 72]) and surface coating with osteoconductive compounds (e.g., hydroxyapatite [73] and calcium phosphate [74]) and biomolecules (BMP-2 [75]) to enhance osteointegration [76–80]. Osteoinductive biomolecules could elicit the differentiation of mesenchymal cells to osteoblasts [81]. These methods enable the induction of de novo bone formation, thereby accelerating bone formation. One attractive approach to bestow osteoinductivity is to mimic the native environmental structure of the extracellular matrix (ECM), that is, biomimetics, which garnered considerable interest in the field of dental implantology [82].

2.3. Biomimetics. Biomimetics is defined as the imitation of the models, systems, and elements of nature for the purpose of solving complex human problems [83, 84]. Biomaterials play an important role as scaffolds to maintain the space and synthetic ECM environment for tissue regeneration [85, 86]. The ECM is a 3D microenvironment composed of various proteins, fiber-forming proteins such as collagens, and elastic fiber and non-fiber-forming proteins such as proteoglycan (e.g., glycosaminoglycan), glycoprotein (e.g., fibronectin and integrin), and other soluble factors [87]. Cells residing in the ECM bind to the ECM via cell surface receptors, inducing the activation of cellular responses such as migration, proliferation, and differentiation [88, 89]. Therefore, the components, biomechanics, and structures mimicking the

TABLE 3: ECM components and biomimetic applications.

Components	Publications
Collagen (types I, III)	(1) Yang et al. (2004) [25]
	(2) Sachlos et al. (2006) [26]
	(3) Davidenko et al. (2012) [27]
	(4) Lee et al. (2013) [28]
Proteoglycan (chondroitin sulfate, hyaluronic acid)	(1) Correia et al. (2011) [29]
	(2) Weyers and Linhardt (2013) [30]
	(3) Lian et al. (2013) [31]
	(4) Credi et al. (2014) [32]
Glycoprotein (fibronectin, integrin)	(1) Kim et al. (2011) [33]
	(2) Lee et al. (2014) [34]
	(3) Cho et al. (2016) [35]
	(4) Chang et al. (2016) [36]
Silk fibroin	(1) Park et al. (2006) [37]
	(2) Yeo et al. (2008) [38]
	(3) Kundu et al. (2010) [39]
	(4) Chen et al. (2012) [40]
	(5) Wang et al. (2013) [41]
	(6) Zhang et al. (2015) [42]
Chitosan	(1) Shi et al. (2005) [43]
	(2) Zhao et al. (2012) [44, 45]
	(3) Algul et al. (2015) [46]
	(4) Algul et al. (2016) [47]

ECM are highly important to induce an excellent biological effect of biomaterials.

2.3.1. Current Technologies and Applications with a Biomimetic Approach

(1) ECM Proteins (Table 3)

- (1) Collagen: type I collagen is a structural framework molecule found in connective tissues that plays an important role in de novo bone formation [25].
- (2) Fibronectin (FN): FN is a noncollagenous protein of the ECM that is mainly expressed in the early stage of osteogenesis [90, 91].

(2) *Growth Factors with a Biomimetic Delivery System.* Delivery of growth factors combined with biomimetic scaffolds such as micro- or nanoparticles and controlling their bioavailability are key points for an effective approach toward the improvement of tissue engineering [92]. Many studies highlighted the use of biomimetic materials forming ECM-like structures. The rationale for using biomimetic scaffolds is based on the consideration that the ECM is a natural scaffold, because the ECM provides proper physical, chemical, and biological cues for cellular response [93].

(3) *Surface Modification of Dental Implant.* Surface activation of dental implants with biomolecules has been investigated

TABLE 4: Experimental surface alteration [48].

Experimental surface alteration	Publications
Collagen	(1) Schliephake et al. (2002)
	(2) Rammelt et al. (2004)
	(3) Bernhardt et al. (2005)
	(4) Morra (2006) [49]
	(5) Reyes et al. (2007)
	(6) Stadlinger et al. (2008)
RGD-including sequence	(1) Schliephake et al. (2002)
	(2) Bernhardt et al. (2005)
	(3) Germanier et al. (2006)
	(4) Jung et al. (2007)
	(5) Rammelt et al. (2007)
	(6) Park et al. (2007)
	(7) Petrie et al. (2008)
	(8) Stadlinger et al. (2008)
Growth factors	(1) Franke Stenport et al. (2003)
	(2) Fuerst et al. (2003)
	(3) De Ranieri et al. (2005)
	(4) Anitua (2006)
	(5) Becker et al. (2006)
	(6) Park et al. (2006)
	(7) Liu et al. (2007a, 2007b)
	(8) Stadlinger et al. (2008)
	(9) Wikesjö et al. (2008)
	(10) Freilich et al. (2008)

to accelerate bone healing. Generally, a specific ECM protein is coated onto the dental implant surface, which stimulates cellular proliferation or differentiation [94]. ECM plays key roles in cell attachment, which is mediated by cell adhesion receptors such as integrin. Usually, integrin binds to a specific amino acid motif, “RGD,” which mainly exists in type I collagen, fibronectin, osteopontin, and bone sialoprotein. Besides, ECM regulates cellular migration, proliferation, survival, and morphological change [95]. Type III collagen acts as a scaffold for cell migration, and ECM glycoproteins or proteoglycans bind to cytokines and growth factors [96]. Based on these data, implant surface modification by ECM component might improve the healing potential and function. Although various biomimetic approaches have been introduced (Table 4), they are still experimental. Mechanical or chemical methods (e.g., resorbable blast media, anodizing, and sandblasted large grit acid-etching) are widely used in the dental field due to problems with clinical application of biomimetic approaches such as surface coating efficiency, osteogenic potential in vivo, and inflammatory reaction [48].

2.3.2. Research Trends in Biomimetic Materials

(1) *Three-Dimensional (3D) Bioprinting*. 3D bioprinting is a technology developed to create the native 3D environment of the ECM in a confined space where cellular response is

preserved within a printed structure. This technique would contribute to significant advances in the tissue engineering field. Compared to nonbiological printing, 3D bioprinting requires additional complexities such as biomaterials, type of cells, and growth or differentiation factors [97].

(2) *3D-Printed Bioresorbable Scaffolds for Periodontal Regeneration*. As the reconstruction of complex tissues or organs such as the periodontium requires a well-fitted biomaterial at the defect site, 3D-printed templates with synthetic ECM environment might be promising tools for tissue engineering [98]. The efficacy of 3D-printed biomaterials was recently demonstrated preclinically [99, 100]. However, there are many limitations to overcome for more personalized clinical applications with a proper structure and resorption rate of the materials [101, 102].

3. Conclusions and Perspectives

In this review, we highlighted the use of biomaterials in periodontology and implant dentistry. Although several studies highlighted the success of tissue engineering applications in periodontology and implant dentistry using various types of biomaterials such as bone materials, cell-occlusive barrier membrane, and growth or differentiation factors, it would be more important to understand the biological processes involved in tissue regeneration to mimic them. On that note, the biomimetic approach seems promising and enhances the biomaterial research with previous achievement in the tissue regeneration field. Although some progress has been observed in the reconstruction of periodontal tissue and alveolar bone defects over the past decade, further biomimetic studies are still needed to challenge the current problems for clinical application. The selected biomimetic approach involves the design of a biomaterial to which the host-biological system could respond in a more favorable and effective manner, providing an exciting new era for the research and development of biomaterials.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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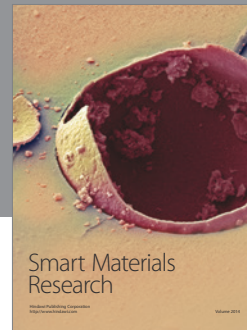
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