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# BIOMATERIALS FOR PERIODONTAL TISSUE REGENERATION

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**Abstract.** Periodontal diseases are characterized by alveolar bone absorption and destruction of periodontal ligament and cementum and are the main causes of tooth loss in adults. This series of diseases is harmful to both human oral and body health. Although periodontitis is under control because of the implementation of conventional treatment modalities, regenerating damaged periodontal tissues remains a major challenge because of the complex periodontium structure. Scientists in this field have recently focused on biomaterials that promote periodontal tissue reconstruction and regeneration. This review updates the knowledge of biomaterials for periodontal regeneration and their roles in clinical application.

## 1. INTRODUCTION

Biomaterials development for tissue engineering has opened a new research field for functional periodontal tissue regeneration. The high quality of biomaterials can effectively raise regeneration-related stem cells, promote stem cell proliferation and differentiation, and guide new tissue formation [1]. Ideal tissue engineering biomaterials should have the properties of biocompatibility, biodegradability, porous structure, high porosity, surface activity, cellular affinity, bone conductivity and inductivity, good biological and mechanical performance, plasticity, ease of processing, and ease of disinfection and storage [2]. Biomaterial optimization should also have a certain antimicrobial function [3].

## 2. TYPES OF PERIODONTAL BIOMATERIALS

Ceramics and polymers are the commonly used biomaterials for periodontal disease. Ceramic materials include calcium phosphate [4], calcium sulfate [5], and bioactive glass [6]. Polymers can be divided into natural and synthetic. Chitosan (CS; polysaccharides) [7], collagen [8], and gelatin (polypeptides) [9] are natural polymers commonly used for periodontal disease, and poly(glycolic acid) [10], polycaprolactone [11], and poly(l-lactic acid) [12] are synthetic polymers.

### 2.1. Bioceramic materials

Alveolar bone absorption is a main symptom of periodontitis in patients and a common cause of tooth loss. Bone graft materials are commonly used for alveolar bone defect repair. Synthetic bones include hydroxyapatite (HA), calcium phosphate, and biological activity glass. They are mainly obtained from natural resources and possess good biocompatibility and biodegradable properties. Synthetic bones can also prevent the spread of disease and are ideal biomaterials for periodontal regeneration.

Tricalcium phosphate (TCP) is an extensively researched and applied synthetic bone because of its physical and chemical properties similar to bone tissue; it also has good biocompatibility, bone con-

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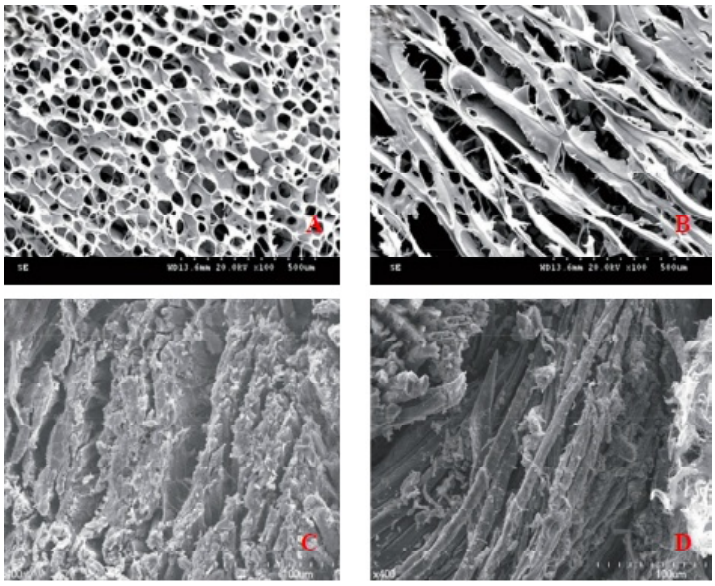


**Fig. 1.** Scanning electron microscopy (SEM) images of nano-hydroxyapatite-coated silk scaffolds before (A and B, ×100) and after (C and D, ×400) cell culture. Cross-sectional views are shown in A and C, and longitudinal views are shown in B and D. Arrows indicate the extracellular matrix. Reprinted with permission from C Yang et al, J. Periodontal Implant Sci vol 43 (2013) p. 315, © 2013 Korean Academy of Periodontology.

duction, and degradation rate [13]. Zhong [14] prepared TCP/CS scaffolds with different ratios through a freeze-drying process. The prepared TCP/CS scaffolds promotes significantly higher cell proliferation of human periodontal ligament (PDL) than pure CS scaffold. Windisch [15] compared the outcomes treated with flap debridement (OFD) alone and OFD combined with rhGDF-5/β-TCP. The treatment with OFD + rhGDF-5/ β-TCP resulted in higher probing depth reduction and clinical attachment level gain than that with OFD alone after 6 months.

HA is the main inorganic mineral composition of animals and human bone; considerable clinical research has shown that HA repairs periodontal bone defect and has a particular clinical effect [16,17]. From the histological perspective, HA only leads mature osteogenesis cell growth, guides cells in lesions on root, forms new bone and osseous adhesion, and causes root surface absorption; however, it does not physically form new teeth attachment, and the long-term outcome is not ideal [18]. Nano-HA offers a new approach for inducing periodontal cell differentiation. When the size of HA at the nanometer level shows a series of unique performance, it possesses the characteristics of nanomaterials; HA has good biocompatibility and wide application prospect in the biomedical field [19]. Many studies have shown that nano-HA increases the protein synthesis of PDL cells (Fig. 1), improves the activity of alkaline phosphatase, induces cell differentiation, effectively promotes periodontal tissue regeneration and formation of new teeth attachments, and affects teeth phenotypic differentiation [20–24].

## 2.2. Natural polymers

Natural polymers include collagen, glycosaminoglycan, and proteoglycan. These derivative materials have biological characteristics, such as weak antigenicity, good tissue tropism, and binding force through different physical and chemical technology processes. The natural size and pore shape of these polymers provide a natural 3D space structure for seed cell adhesion, proliferation, and differentiation.

CS (N-acetylated chitin) is a natural polysaccharide from animals. Its metabolism product is amino polysaccharide, which is a required biological physical material. CS can easily bind negatively charged biomaterials, such as glycoprotein, and form polyelectrolyte complex as well as is suitable for tissue engineering scaffolds. However, CS has low affinity with cells and needs to be modified to other materials using a compound [7]. Xu et al. [7] reported that carboxymethyl CS in local periodontal application demonstrated no potential genetic toxicity. Kashiwazaki [25] studied the mechanical and biological properties of CS-HA nanocomposite materials. These materials do not cause inflammation when implanted into a rat's back, and new blood vessels and cell growth are observed; CS-HA composite has good biocompatibility and biodegradabil-

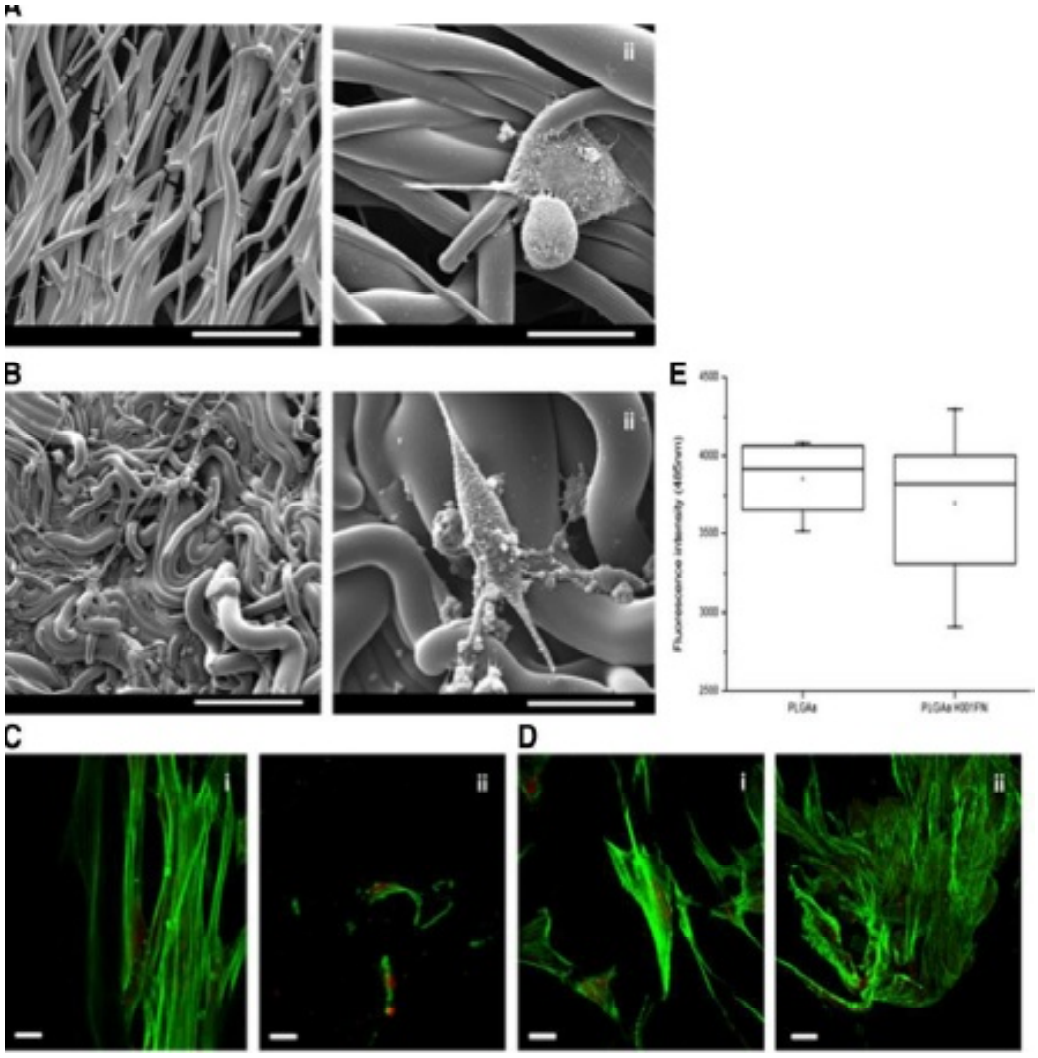


**Fig. 2**. Biocompatibility observations of PDL cells cultured on untreated PLGA and PLGAH001FN samples. (A, B) SEM micrographs of PDL-like fibroblasts cultured on (A) untreated PLGA [scale bar (i) 100 lm and (ii) 30 lm] and (B) PLGAH001FN [scale bar (i) 100 lm and (ii) 30 lm] up to 7 days. (C, D) Confocal images of PDL cells cultured on (C) untreated PLGA surface and (D) PLGAH001FN surfaces up to 24 h; (i) and (ii) correspond to superior and inferior surfaces of samples, respectively. Scale bar (C, D) 100 lm. (E) Quantitative resazurin results of PDL cells cultured on PLGA and PLGAH001FN samples up to 24 h. Data are expressed as mean ± SD (*n* = 3). Reprinted with permission from Doris M et al. BioResearch Open Access. vol 3 (2014), © 2014, Mary Ann Liebert, Inc.

ity. Zhang [26] prepared a homogeneous and transparent CS-HA membrane using a GTR barrier in periodontal therapy and showed that the membrane has good biocompatibility and inductive effect for cell growth.

Collagen is extracted from animal bones through procedures, such as dip boil, and hydrolysis. It has no antigenicity and has good biocompatibility as well as promotes cell proliferation and wound healing. The degradation products of collagen are non-toxic. However, collagen is not widely applied because of its fast degradation rate and poor mechanical strength [27]. Given these limitations, researchers have conducted numerous studies on collagen modification. Studies show that biodegradable, polymer-coated collagen [28] retains its drug release properties and antibacterial effect as well as possesses better mechanical integrity than uncoated collagen sponge. He [29] developed a nano-HA/collagen/poly(L-lactide) scaffold and studied its effect on the attachment, proliferation, and osteogenic capability of dog PDL stem cells in vitro and in vivo. The results showed that the scaffold enhances cell proliferative viability and alveolar bone regeneration.

## 2.3. Synthetic polymers

Synthetic polymer materials have many varieties. These materials have adjustable biological degradation rate and wide selection. The mechanical prop-

erties and processing performance of synthetic polymer materials are better than those of natural materials. Moreover, they are also cost-effective, have good repeatability, suitable for mass production and thus are the most applied materials in the study of tissue engineering biomaterials. Polylactic acid (PLA) [29], polyglycolic acid (PGA) and its copolymers (PLGA), and polycaprolactone are commonly used in periodontal tissue engineering. PLA and PGA are gathered acids. They are synthetic biodegradable materials that have good mechanical strength, elastic modulus, and performance. PLA degrades into lactic acid in vivo, which is a sugar metabolism product [30].

PGA degrades into hydroxy-acetic acid. Polymerization and molding can adjust and control the mechanical properties and degradation rate of PGA by regulating its molecular weight to meet the different clinical requirements. However, the absorption rate and inflammatory reaction of PGA change as the molecular weight is changed. Highly porous PLGA foam provides 3D growth space for tissue engineering (Fig. 2), which is an ideal structure [31].

Poly(e-caprolactone) is a biodegradable and biocompatible polymer applied in periodontal regeneration [32]. This polymer must be modified for clinical applications because of its slow degradation rate and poor water solubility [33].

## 3. ROLE OF PERIODONTAL BIOMATERIALS

The three fabricating modes for tissue engineering are cell-scaffold, cell growth factor-scaffold, and grow factor-scaffold materials. The first two modes are necessary to obtain a sufficient number of seed cells by in vitro cell culture technology. The seed cells are composited with the scaffold materials in vitro and implanted into a defect position. The in vitro reconstruction mode is easy to model and can overcome the difficulty of building in the body. However, in vitro periodontal cell sources and expansion cells are limited for periodontal tissues. Therefore, biomaterials in periodontal tissue engineering are mainly used as the carrier of exogenous growth factor, except for the cell stents outside. They allow a slow release of growth factors to the organization.

Growth factor is a type of biological active factor that exists in the body, which combines with the corresponding receptors on the target cells, as well as regulates cell growth and wound healing, to promote repair and regeneration of organization. Endogenous growth factor is secreted by healthy cells, but sometimes by defective cells because of the decreased number of healthy cells. Endogenous growth factor secretions are inadequate; thus, exogenous growth factors are required at this point. The growth factor is composited to the biological film or scaffold materials along with the degradation materials and then slowly released to the organization. Research has achieved significant results, but the slow-release effect is limited and is still far from the requirement [34,35]. Given the discovery of gels in drug release and their application in the system, the growth factor is wrapped in gel microspheres or micro-capsule. The growth factor is then slowly released along with the degradation of microspheres. This process helps maintain growth factor activity, large drug loading, and high encapsulation efficiency, which are important topics in periodontal tissue engineering. Nakahar [36] prepared basic fibroblast growth factor (BFGF) microspheres with gelatin and combined with spongiform collagen scaffold. The electrostatic attraction between the microspheres is used to delay the BFGF release. The BFGF is slowly released as the microspheres gradually degrade. BFGF can promote angiogenesis, and a rich blood supply improves the periodontal regeneration effect. Chen [37] used a glycidyl-methyl methacrylate-glucan/gelatin gel slow-release system to transport BMP to periodontal defects. Results showed that many periodontal cells land on the stent. Moreover, the BMP is gradually released and stimulates periodontal cells to undergo osteoblast differentiation and promote periodontal tissue regeneration. Researchers continue to study different slow-release system methods of growth factor microsphere [38,39].

## 4. PROSPECT OF PERIODONTAL BIOMATERIALS

### 4.1. Intelligent design

Although the growth factor slow-release system can delay the release of growth factors, many problems remain unsolved because the research is still in its early stages. These problems include the “sudden release effect,” controlled release of growth factors, and coordination release of different factors. The intelligent development of biological materials is expected to solve these problems. Intelligent biological materials can respond to the outside stimulation factors, identify specific cells, and release cells that transmit information. Intelligent biomaterials aim to achieve appropriate timing and quantity as well as continuous administration.

## 4.2. Bionic biological design

Along with the development of learning materials, biological materials are not only limited to performance requirements but also certain technological measures to stimulate tissue growth. These measures include bionic biological design, surface modification material, and other material compounds. Periodontal tissue is a complex organizational structure with two hard organizations (i.e., alveolar bone and tooth bone) and soft tissue (periodontal membrane). Some differences between the three types of organization in periodontal tissue regeneration can possibly be observed in terms of regeneration order and rate. Therefore, a completely regenerated requirement is difficult to reach by separating scaffold materials. Scaffolds used for periodontal tissue regeneration should be inclined to combine two or more biological materials that are complementary, make up for the defect of a single material, and decorate the scaffold material to make it more suitable for organization growth. Cui [40] adopted the bionic method to prepare nano-HA/collagen composite materials and proved the mechanical performance under isotropic conditions. Microhardness can achieve the lower limit of the bone cortex. An implant is placed in the bone marrow cavity for 3 months. It is engulfed by macrophages and extracellularly degradaded as well as deposited with a new bone. Chan [41] manufactured bionic, multidimensional hybrid polymer composite scaffolds using computer design. It has the same structures with the periodontal tissue and vaccination cell transplantation into body. Results showed that the new organization in the structure formation has a normal oblique fiber and level fiber formation that stretch into scaffolds. It eventually contains a tooth bone, PDLs, and an alveolar bone structure. Biomimetic fiber-guiding scaffolds have been manufactured using solid free-form fabrication methods that custom fit complex anatomical defects to guide functionally oriented ligamentous fibers in vivo. Compared with traditional, amorphous, or random-porous polymeric scaffolds, perpendicularly oriented micro-channels provide better guidance for cellular processes that anchor ligaments between two distinct mineralized structures. Therefore, materials of biological molecule bionics can become a modern design idea of hard organization and interface tissue repair materials. They can realize the dominance of a new generation of biological materials.

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