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Biomaterials for periodontal regeneration
A review of ceramics and polymers

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Abbreviations: GTR, guided tissue regeneration; GBR, guided bone regeneration; RP, root planing; OFD, open flap debridement; PDL, periodontal ligament; CAL, clinical attachment level; GR, gingival recession; ABL, linear alveolar bone level; FFB, fresh frozen bone; FDBA, freeze-dried bone allograft; DFDBA, demineralized freeze-dried bone allograft; HA, hydroxyapatite; CaP, calcium phosphate; PD, probing depth; TCP, tricalcium phosphate; β-TCP, β-tricalcium phosphate; BCP, biphasic calcium phosphate; CS, calcium sulfate; MGCSH, medical grade calcium sulfate hemihydrate; ePTFE, polytetrafluoroethylene; BG, bioactive glass; PLA, polylactic acid; PGLA, poly(lactic-co-glycolicacid)

Periodontal disease is characterized by the destruction of periodontal tissues. Various methods of regenerative periodontal therapy, including the use of barrier membranes, bone replacement grafts, growth factors and the combination of these procedures have been investigated. The development of biomaterials for tissue engineering has considerably improved the available treatment options above. They fall into two broad classes: ceramics and polymers. The available ceramic-based materials include calcium phosphate (e.g., tricalcium phosphate and hydroxyapatite), calcium sulfate and bioactive glass. The bioactive glass bonds to the bone with the formation of a layer of carbonated hydroxyapatite in situ. The natural polymers include modified polysaccharides (e.g., chitosan,) and polypeptides (collagen and gelatin). Synthetic polymers [eg, poly(glycolic acid), poly(L-lactic acid)] provide a platform for exhibiting the biomechanical properties of scaffolds in tissue engineering. The materials usually work as osteogenic, osteoconductive and osteoinductive scaffolds. Polymers are more widely used as a barrier material in guided tissue regeneration (GTR). They are shown to exclude epithelial downgrowth and allow periodontal ligament and alveolar bone cells to repopulate the defect. An attempt to overcome the problems related to a collapse of the barrier membrane in GTR or epithelial downgrowth is the use of a combination of barrier membranes and grafting materials. This article reviews various biomaterials including scaffolds and membranes used for periodontal treatment and their impacts on the experimental or clinical management of periodontal defect.

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Introduction

Periodontitis is a disease that is characterized by the destruction of periodontal tissues: gingiva, alveolar bone, periodontal ligament and cementum. If left untreated, it will lead to tooth loss, phonetic and aesthetic problems. Approximately 48% of US adults have chronic periodontitis, and similar results were reported in other nations.[1]

Phases including scaling and root planing (SRP) or open flap debridement (OFD) are conventional methods used for treatment of periodontitis. But the use of specific biomaterials/biologicals was more effective than OFD in improving attachment levels in periodontal defects.[2-4]

Periodontal regeneration developed in the last few decades and includes soft tissue grafts, bone replacement grafts, root surface biomodifications, guided tissue/bone regeneration (GTR/GBR) and delivery of growth factors or gene therapies.[5] Various types of materials are used in the treatment. An ideal graft material should be biocompatible, safe, non-allergenic, non-toxic and have no risk of disease transmission. They should be strong enough to maintain space and the rate of degradation should be appropriate.[6] Four major graft materials commonly used in clinics are autogenous grafts, allografts, xenografts and synthetic grafts or alloplasts. Autografts are graft materials obtained from the same individual and are thought of as the "gold standard" with the ideal properties of grafts. It is easy to collect the slurry during the periodontal surgery, but the volume of bone may be limited and the resorption may be unpredictable.[7] Also, the autogenous bone collected during the surgery may be contaminated by the microorganisms in the oral cavity.[8] Allografts are graft material derived from a donor of the same species, which may be a fresh frozen bone (FFB), freeze-dried bone allograft (FDBA) or demineralized freeze-dried bone allograft (DFDBA). It can act not only as osteoconductive scaffolds, but also as osteoinductive material, due to the remaining proteins (BMP, etc.).[9] Xenografts

are graft materials derived from another species and are widely used in the clinic.

Besides the bone grafts above, there are alloplastic materials including ceramics and polymers. These biomaterials are either natural, synthetic or biocompatible bone-graft substitutes. They are easy to get and with allografts no need of a donor site as is necessary. They have no risk for disease transmission, which may accompany the use of allografts and xenografts.[10] Much more attention was therefore paid to them. In this review, our focus will be on alloplastic or synthetic biomaterials used in periodontal regeneration, its properties and applications and also the future prospects.

Periodontal Regeneration

Different treatment modalities have been suggested to regenerate the periodontal tissues damaged in cases of both gingival recession and periodontitis. All of these strategies aim to correct defects due to disease, and regenerate new periodontal tissues. Periodontal regeneration is defined as the regeneration of the tooth-supporting tissues including cementum, periodontal ligament (PDL) and alveolar bone.[11] The development of new cementum with PDL fibers connected to alveolar bone is the main goal of periodontal regeneration.[12,13] As in a healthy tooth, the newly formed periodontal fiber should orient perpendicularly to the cementum and alveolar bone. During the healing period of periodontal therapy, epithelial cells, which have the fastest migration rate, form the long junctional epithelium.[14] This type of healing retards other apparatus regeneration. In order to prevent the downgrowth of the epithelium along the tooth-root surface, placement of membrane can be applied or process, which is called guided tissue regeneration (GTR). In recent years, a number of combinations of conventional regenerative techniques have been evaluated: GTR, hard tissue graft and application of tissue growth factors.

Calcium Phosphate (CaP)

Calcium phosphate (CaP) biomaterials have outstanding properties: a similar composition to bone mineral, bioactivity (formation of bone apatite like material or carbonate hydroxyapatite), ability to promote cellular function and expression leading to formation of a uniquely strong bone-CaP biomaterial interface and osteoconductivity. In addition, CaP biomaterials with appropriate three-dimensional geometry are able to bind and concentrate endogenous bone morphogenetic proteins in circulation, may become osteoinductive (capable of osteogenesis), and can be effective carriers of bone cell seeds. Therefore, CaP biomaterials are potentially useful in tissue engineering for regeneration of hard tissues.

Hydroxyapatite (HA). Hydroxyapatite (HA) is one of the most widely used CaP graft biomaterials in both the research and clinical fields. HA has a similar composition and structure to natural bone mineral.[15] It is known to chemically bond directly to bone when implanted.[16] This initial bone matrix on the implant surface was either composted of globular deposits or an organized network of collagen fibers, which may have enhanced bonding of the bone matrix to the hydroxyapatite.[17] De novo bone formation was observed primarily on the HA surface without fibrous tissue interposition after the subcutaneous implantation of marrow stromal stem cells.[18] The osteoblastic cells were found on the HA surface, which initiated partially mineralized osteoid formation. This osteoid matured into fully mineralized bone, resulting in firm bone bonding to the HA surface. With the 6 mo implantation in periodontal defect, small apatite crystals appeared in the center of the aggregates between the relatively large crystals of synthetic hydroxyapatite.[19] They were similar to those found in adjacent alveolar bone and gave similar diffraction patterns. Clinical and radiological parameters such as probing depth (PD), clinical attachment level (CAL), intrabony defect depth and percent of defect fill are usually used to evaluate the periodontal regeneration. A 9-mo investigation showed that the superior regenerative effects observed with HA compared with an OFD group.[20]

Though it's a type of material widely used in clinic, the inconsistent cell reactions depending on the surface properties limit its application in clinic.[21] Some HA with modifications was proved to improve protein adsorption.[22] A customized hydroxyapatite nano-particle was prepared using the sol-gel process. Ca $(NO_3)_2$-$4H_2O$ and $(OC_2H_5)_3P$ were used as precursors of the HA sol. Porous n-HA block scaffolds were prepared using prefabricated n-HA powders and a polymeric sponge. With the application in one-wall intrabony defect, the material was well maintained within the defect site and minimal inflammation was observed in the periodontal defects.[23] New attachment formed between the remaining HA block and the denuded root surface. At the base of the defect, the new attachment included a thick, cellular, mixed-fiber, stratified cementum and many fibers inserting into the newly formed cementum. However, the bone regeneration was limited.

In order to develop HA coating to promote rapid attachment to bone, HA was immobilized on the poly(ethylene-co-vinyl alcohol) (EVA) by alternate soaking method followed by introduction of carboxyl groups through ozone exposure.[24] HA-EVA might stimulate PDL cells to differentiate to osteoblastic cells, which makes it possible to prepare a further highly organized hybrid graft possessing PDL and cementum on the surface of artificial dental implant.

Tricalcium phosphate (TCP). The use of TCP as a bone substitute has been growing in recent years. The α and β phases of TCP have excellent resorbability. Though these two substitutes are chemically identical, they have different behavior in a physiological environment. β-tricalcium phosphate (β-TCP) has been shown to exhibit good biocompatibility and osteoconductivity in both animal and clinical studies.

TCP has been used in human clinical studies to repair marginal and periapical periodontal defects, as well as apexification and miscellaneous alveolar bony defects.[25] In a clinical evaluation 6 mo following therapy, the PD reduction and CAL reduction were observed.[26] Sites treated with OFD + β-TCP showed a significant defect fill compared with those treated with OFD alone.[26] However, the regenerative potential of β-TCP was similar to that of autogenous bone, demineralized freeze-dried bone,

anorganic bovine allograft(DFDBA) and collagen sponge.[27] On the other hand, the periodontal regeneration was clinically and histologically evaluated with the implantation granular β tricalcium phosphate (β-TCP) and OFD. The data indicates that the treatment of intrabony periodontal defects with TCP has substantial clinical improvements to some extent, such as PD reduction and CAL gain, but it does not seem to regenerate cementum, periodontal ligament or bone.[28]

In recent years, highly purified β-TCP has been shown to have osteoconductive activity and biodegradable nature in human bone.[29] Cerasorb® M (Curasan) is a new synthetic pure-phase β-TCP. The special micro-, meso- and macro-porosity of the granules enormously expands the surface area of the material, making it better for wetting by plasma and tissue fluids and the adhesion of special proteins for regeneration. With the application of this material in dogs, early osteogenesis and bone formation were induced.[30]

The resorption of TCP is controversial. Two different modes were hypothesized: a process dependent on interstitial fluids and one based on cellular processes.[31] The first mode of resorption mechanism is dissolution by biological fluids because of the absence of osteoclasts around the materials.[32] Another hypothesis is the cell-mediated bioresorption. Considerable numbers of osteoclast-like giant cells were observed in defect areas in many studies,[33] which suggests the role of cells in material resorption.

Other calcium phosphate materials. Degradation rate is an important factor assessing optimal biomaterials. The biodegradation of calcium phosphate depends on many factors, such as porosity, degree of bony contact, specific surface, type of bone, species of animal, etc.[34]

In order to intensify the biodegradation, biphasic calcium phosphate (BCP) was developed for bone defect. This is a composite of HA and β-TCP, and the ratio of the two materials was changed. The first implantation of BCP was developed in 1986 with the weight ratio of HA/β-TCP 20:80.[35] Alveolar bone dehiscence defects were surgically created bilaterally at the labial aspects of maxillary third incisors in 12 beagle dogs.[36] The defects were either filled with BCP (40 HA/60 β-TCP) or cured with OFD. It was indicated that BCP may enhance periodontal regeneration in acute-type labial dehiscence defects.

Calcium Sulfate (CS)

CS has a compressive strength greater than that of cancellous bone.[37] It can also act as a barrier, which makes it ideal for using as an adjunct with other graft materials. Fortoss® Vital (Biocomposites) is a combination of β-TCP and CS, which does not require a membrane, reduces surgical time, lowers cost and has the potential to treat periodontal intrabony defects spanning more than two teeth.[38] The treatment of periodontal defects with such biomaterials has led to a significant improvement in the clinic.[38,39]

CS is usually applied as a barrier to improve the periodontal regeneration.[40] The use of CS may minimize post-surgical recession compared with the collagen membrane in a 12-mo randomized controlled clinical trial.[41] In a treatment with either medical grade calcium sulfate hemihydrate (MGCSH) or polytetrafluoroethylene (ePTFE), the latter group showed greater horizontal defect fill. However, attachment level gains were achieved with MGCSH 12 mo later.[42] The short-term (90 d) histological results using CS barrier showed incomplete regeneration of bone and connective tissue.[43]

The CS is usually mixed with demineralized bone matrix (DBM) or autogenous bone graft and used without a membrane, since the periodontal regeneration of mixture and bone graft with bioabsorbable membrane showed no difference between each other.[44,45] The clinical results suggest an alternative to membrane position during the operation, especially the non-resorbable membrane (e.g., ePTFE),[46] which may decrease the time of practice. The mixture of demineralized freeze-dried bone allograft (DFDBA) with CS enhanced the clinical outcome more than calcium sulfate alone for the treatment of class II mandibular molar furcation defects.[47]

Bioactive Glass (BG)

Most of the biomaterials are osteoconductive, which are involved with a three-dimensional process. This is proved when porous structures are implanted, osteoprogenitor cells and other tissues migrate into the porous space and form new bone.[48] In contrast, osteoinductive materials alter the bone healing process by affecting the osteoblast gene expression during cell differentiation.[49] Heat treatment of an $MgO\text{-}CaO\text{-}SiO_2\text{-}P_2O_5$ glass gave a glass ceramic containing crystalline apatite $[Ca_{10}(PO_4)_6O,F_2)]$ and β-wollastonite ($CaO{\cdot}SiO_2$) in an $MgO\text{-}CaO\text{-}SiO_2$ glassy matrix, and this CaO, SiO_2-based glass is called bioactive glass (BG).[50] It showed bioactivity and a fairly high mechanical strength which decreased only slowly, even under load-bearing conditions in the body. An in vivo study showed that BG nanoparticles induced cementoblasts to proliferate. The ionic products from BG nanoparticles increased cementoblast viability, mitochondrial activity and induced cell proliferation, indicating that they could be a potential material for use in cement regeneration through tissue engineering.[51]

Ions such as calcium and silicon from BG were indeed concerned with the formation of nodules on the periodontal-ligament cells.[52] Commercial Bioglass™ [45S5 (Mo-Sci)] and experimental bioactive coating glass (6P53-b) were used for the evaluation of periodontal ligament fibroblast osteocalcin expression.[53] After being dissolved in cell culture, a glass conditioned medium was made. The ionic products were Ca^{2+}, PO_4^{3-}, Si^{4+} and Na^+ for 45S5 glass conditioned media (GCM) and Mg^{2+}, K^+, Ca^{2+}, PO_4^{3-}, Si^{4+} and Na^+ for 6P53-b GCM. The enhanced expression of type I collagen, osteocalcin and alkaline phosphatase gene expression and osteocalcin protein expression indicated the osteogenic potential of bioactive coating glass.[53] The studies above suggest that BGs are osteoinductive, which was demonstrated by others.[54]

The property of bone formation in bioactive glass has been called osseostimulation by Schepers and Ducheyne.[55] Using a periodontal defect model in monkeys, the new bone formation on the bioactive glass particles were located distant from the defect

walls.[56] It was thought that there was an active deposit of osteoid matrix directly on the surface of the particles, which is different from osteoindution or osteoconduction and acts as nuclei for subsequent bone repair. Autogenous grafts are osteoinductive and result in the formation of new bone faster than alloplastic materials.[57] BG grafts can be used as a supplement when the mount of the harvested autogenous grafts is not sufficient.[58]

In clinical evaluation, bioactive glass, such as PerioGlas (U.S. Biomaterials Corp.),[59] has the ability of inhibiting the down-migration of epithelium. Mengel et al.[60] evaluated the effect of BG in the treatment of intrabony in the patients with generalized aggressive periodontitis. Highly statistically significant improvements in the parameters PD, CAL and distance from the alveolar crest to the defect base were recorded after 6 and 12 mo. The 5-y results of bioactive glass were still optimal.[61] The systematic review of literature demonstrates the significant improvement in both PD and CAL compared with OFD.[62]

However, Nevins et al.[63] suggested that although the clinical results are encouraging while clinical examination and radiographs revealed improvement, the human histological analysis evidenced limited regenerative outcomes of BG. Poor regeneration was also shown by another re-entry operation.[64]

Chitosan

Chitosan is an important ingredient in medicine and food. It's a polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine and can be derived by partial deacetylation of chitin from crustacean shells.[65] In addition to the properties of good biocompatibility, degradation appears to have no toxicity, an appropriate degradation rate and hemostatic activities. It has bacteriostatic properties, the ability to inhibit growth of gram-negative and gram-positive bacteria, *Actinobacillus actinomycetemcomitans* and *Streptococci mutans*.[66] The application of chitosan gel in patients with chronic periodontitis showed reduction of the gingival inflammation markers, due to the antimicrobial properties.[67]

Chitosan has been reported as an effective delivery system for DNA[68] and growth factors[69,70] in vitro and holds promise for the future. In recent studies, composites of bone paste with HA nanocrystals incorporated with chitosan could be produced using a wet chemical method at low temperature[71] or by using a freeze-drying process.[72] In another study, chitosan/collagen sponge was evaluated for the periodontal regeneration ability.[73] Eight weeks after operation of one wall intrabony defect in dogs, histological examination showed that the material inhibited apical migration of epithelium and increase and formation of new bone and cementum. An especially conspicuous increment of new cementum was observed due to the application of chitosan, which demonstrated that chitosan may induce the differentiation of mesenchymal cells into cementoblasts. Yeo et al. reported that chitosan non-woven membrane effectively contributed to the formation of new bone and cementum in surgically created one-wall intrabony defects in beagle dogs.[74] This biodegradable membrane was easy to manipulate and had a porous structures. These properties make it a promising material in the GTR/GBR.

Polylactic Acid (PLA)

Along with hydrogels, such as chitosan and alginate, a variety of membrane materials have been synthesized for GBR and GTR. The biomaterials used as membrane should meet several prerequisites, such as being biocompatible, non-immunogenic and non-toxic.[66] To avoid surgical re-entry and the removal of the membrane after healing, biodegradable materials would be better. Other factors such as space maintaining, cell occlusivity and tissue integration should be taken into consideration.[75]

In the early stages of GTR, membranes such as expanded polytetrafluoroethylene (ePTFE) and dense-polytetrafluoroethylene, belong to the first generation of GTR membranes, which are characterized by being non-absorbable. And the second regeneration of membrane is absorbable and currently popular for periodontal regeneration since there is minimal membrane exposure and no need of membrane retrieval.[76] But the bioabsorbable membrane may provide a greater bone area than the non-resorbable membrane.[77]

PLA is a bioabsorbale membrane. In a 3-y follow-up study, treatment outcomes of GTR were investigated with a synthetic absorbable PLA membrane [Atrisorb® (Atrisorb, Atrix Laboratories Inc.)] in intrabony defects, and treatment with OFD was the control group. The parameters includes PPD, GR, CAL and ABL. The results showed that the outcome of treatment with membrane may be similar to open flap debridement.[78] A randomized controlled clinical trial showed that there was no regeneration when bioresorbable PLA barrier (Atrisorb®) was used with autogenous bone grafting.[79] Astrisorb is a commercialized PLA biomaterial (DL-lactide polymer, Atrix Laboratories Inc.) was introduced in 1996. It's composed of 37% of a liquid polymer of lactic acid that is dissolved in 63% N-methyl-2-pyrrolidone (NMP). The potential of periodontal regeneration ability was ensured in both animal and human class II furcation defect.[80,81] The evaluation was conducted with parameters such as PD, CAL, GR, PLI and GI. It showed a favorable regeneration. Long-term study and histologic observations of tissue healing are needed to evaluate this kind of material.

Many kinds of membranes combined with other polymers are developed so as to improve the properties and the clinical results are promising. A biodegradable GTR barrier membrane was constructed by a biodegradable PLA/poly (glycolide-co-lactide) copolymer (PLGA) membrane with polyglycolic acid (PGA) mesh.[82] It exhibits suitable permeability of nutrients, ability of retaining space, good biocompatibility and non-cytotoxicity in animal tests.

Poly(lactic-co-glycolicacid) (PGLA)

PLGA is another type of synthetic biomaterial for drug and growth factor delivery and barrier in GTR/GBR. It is a combination of PLA and poly (glycolic acid) (PGA) in various proportions. A three-dimensional PLGA scaffold was developed to evaluate the potential of periodontal regeneration using cloned cementoblasts (OCCMs), periodontal ligament fibroblasts (SV-PDLs), and dental follicle (SV-F).[83] This porous PLGA scaffold was conducive for mineral formation by cementoblasts and has no toxic effect on the other cells.[83]

As the application in dental area for GTR, a novel film made from PLGA was developed with MePEG or diblock copolymer.[84] This film is elastic at room/body temperature which is easy for handling, but it gets swollen and stiffened in water to inhibit epithelium and gingival connective tissue from down migration. Membrane degradation occurs over a 2–6 mo period so that re-entry is not needed. It can be enhanced by casting topographical cues so as to accelerate osteoblast repopulation and differentiation.

Future Perspectives of Biomaterials

Many advances have been made over the past few decades for the regeneration of periodontal apparatus. Grafts have been developed from the application of one type of material to combinations of different biomaterials and finally to a delivery system to biological factors. Developments in scaffolds as cell, protein and gene deliveries have demonstrated to promote periodontal regeneration.[85,86] More research needs to be focused on in vivo systems to improve the outcome of biomaterial-based delivery systems. Further approaches in this field will rely on a combination of therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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