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Current concepts in periodontal bioengineering

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Abstract

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Repair of tooth supporting alveolar bone defects caused by
periodontal and peri-implant tissue destruction is a major goal
of reconstructive therapy. Oral and craniofacial tissue
engineering has been achieved with limited success by the
utilization of a variety of approaches such as cell-occlusive
barrier membranes, bone substitutes and autogenous block
grafting techniques. Signaling molecules such as growth
factors have been used to restore lost tooth support because of
damage by periodontal disease or trauma. This paper will
review emerging periodontal therapies in the areas of materials
science, growth factor biology and cell/gene therapy. Several
different polymer delivery systems that aid in the targeting of
proteins, genes and cells to periodontal and peri-implant
defects will be highlighted. Results from preclinical and clinical
trials will be reviewed using the topical application of bone
morphogenetic proteins (BMP-2 and BMP-7) and platelet-
derived growth factor-BB (PDGF) for periodontal and peri-
implant regeneration. The paper concludes with recent
research on the use of *ex vivo* and *in vivo* gene delivery
strategies via gene therapy vectors encoding growth
promoting and inhibiting molecules (PDGF, BMP, noggin and
others) to regenerate periodontal structures including bone,
periodontal ligament and cementum.

Key words: angiogenesis; gene therapy; periodontal disease;
regeneration; scaffolds; tissue engineering

Introduction

Tissue engineering, according to National Institute of
Health definition, is an emerging multidisciplinary field
involving biology, medicine, and engineering that is
likely to revolutionize the way we improve the health
and quality of life for millions of people worldwide by
restoring, maintaining, or enhancing tissue and organ

function (1). For periodontal tissue engineering, this specifically relates to repair of alveolar bone, tooth-associated cementum and periodontal ligament (PDL) (2).

Roughly, 20 000 organ transplants, 500 000 joint replacements, and literally millions of dental–oral–craniofacial procedures, ranging from tooth restorations to major reconstruction of facial hard and soft tissues are performed annually. According to the National Institute of Dental and Craniofacial Research, 86% of adults over 70 years have at least moderate periodontitis and over a quarter have lost their teeth, which has serious repercussions on health and quality of life (3).

To date, artificial replacements possess significant limitations when compared with the natural original tissues in terms of function and esthetics. Bridges and dentures have been used for centuries in dentistry but require periodic maintenance or even replacement after a period of time because of usage or loss of adaptation. The new generation of titanium dental implants emerged as an innovative predictable treatment for edentulism and support for prosthetic restorations (4). Nevertheless, the procedure is technically sensitive, costly and requires considerable recipient bone quality and volume characteristics for acceptable functional and esthetic outcomes.

The field of dental tissue engineering, once viewed only as an experimental area of interest, is now revealing early success for human application (5). In this review article, we will highlight emerging concepts and results of the application of biomaterials, growth factors and cell/gene therapy in periodontology that aid in the targeting of proteins, genes and cells to bioengineer the periodontium.

The foundation of dental bioengineering has ancient roots. Replacing body parts goes back at least 2500 years, when the Etruscans learned to substitute missing teeth with bridges made from artificial teeth carved from the bones of oxen (6). Evidence of crude dental implants dates back to Roman populations of the first or second century AD and to pre-Columbian cultures of Central and South America (7). The first use of dental amalgam to repair decayed teeth was recorded in the Chinese literature in the year 659 (8).

Contemporary discoveries provide historic background for the advances of the bioengineering field discussed in this paper. Urist hypothesized that a bone-inducing substance, which he subsequently termed 'bone morphogenetic protein' (BMP), was responsible for these observations (9). Melcher suggested that cells that repopulate the periodontal wound would determine the type of new attachment onto the root surface. Based on Melcher's theory, physical barriers have been used to retard apical migration of epithelial cells favoring the healing by cells from the PDL region and adjacent alveolar bone (10).

Achieving periodontal regeneration

The regeneration of the periodontal tissues is dependent on four basic components. The appropriate signals, cells, blood supply and scaffold need to target the tissue defect (Fig. 1). Each of these elements plays a fundamental role on the healing process in a simultaneous
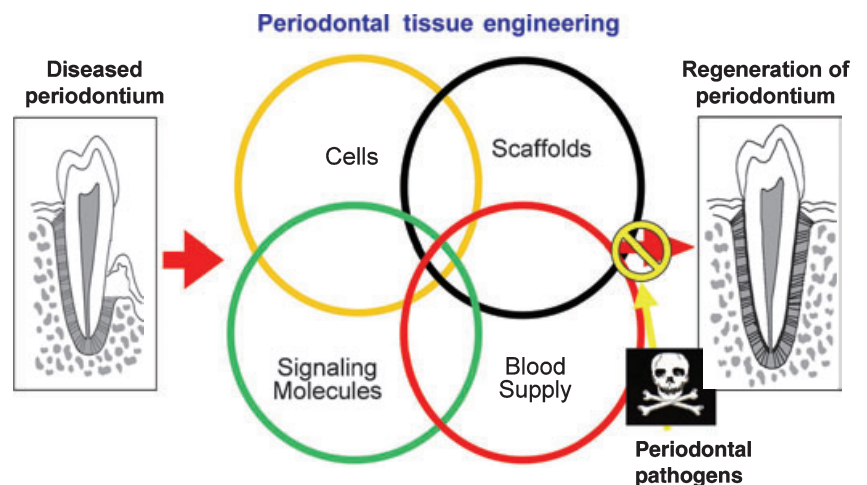

Fig. 1. Schematic representation of critical elements required in periodontal tissue engineering. Reconstruction of lost periodontal tissue requires the combination of cells, scaffolds, signaling molecules, and a blood supply. A limiting factor in the achievement of periodontal regeneration is the presence of microbial pathogens that contaminate periodontal wounds and reside on tooth surfaces as plaque-associated biofilms.

and temporal timeframe and is interconnected into the generation of new tissues. Cells provide the machinery for new tissue growth and differentiation. Growth factors or morphogens modulate the cellular activity and provide stimuli to cells to differentiate and produce matrix toward the developing tissue. New vascular networks promoted by angiogenic signals provide the nutritional base for tissue growth and homeostasis. Finally, scaffolds guide and create a template structure three-dimensionally to facilitate the above processes critical for tissue regeneration. A major complication and limiting factor in the achievement of periodontal regeneration is the presence of microbial pathogens that contaminate periodontal wounds and reside on tooth surfaces as plaque-associated biofilms (11). Appropriate strategies in controlling infection at the reparative wound site are required to optimize periodontal regeneration.

Cells contributing to periodontal repair

Specialized tissues such as the periodontium include epithelial–mesenchymal interactions and junctional complexes (to the tooth and connective tissues). The native periodontium includes alveolar bone, cementum, junctional epithelium and a gingival connective attachment. Based on its embryonic origin, the periodontal tissues form by the interaction of mesenchymal and epithelium cells that respond differently to a variety of stimuli (12). Moreover, the sequence of events necessary for periodontal regeneration relies on the following independent but linked processes: osteogenesis, cementogenesis, and connective tissue formation. Indeed, the harsh environment and the continual presence of pathogens and their by-products (notably endotoxin) contaminate the tooth root surfaces and wounds, which are considered significant limiting factors for achieving predictable periodontal regeneration (5,11).

The cellular constitution of the gingival connective tissue and alveolar bone include: fibroblasts, macrophages, mast cells, osteoblasts and osteoblast precursor cells, cementoblasts and cementoblast precursor cells, osteoclasts and odontoclasts, assorted inflammatory cells, and cells that make up vascular channels and nerves. Inflammatory cells include polymorphonuclear leucocytes, lymphocytes, and plasma cells (13). The connective tissue also contains undifferentiated ectomesenchymal cells that serve as a replacement source for more differentiated cells, primarily fibroblasts. Fibroblasts are irregularly shaped cells responsible for the maintenance and remodeling of the connective tissue, synthesizing and removing connective tissue fibers and the ground substance in which they are embedded (14).

The PDL contains fibroblasts, macrophages, undifferentiated ectomesenchymal cells, cementoblasts and cementoclasts, osteoblasts and osteoclasts, cell rests of Malassez and vascular and neural elements that are capable of generating and maintaining three distinct tissues, PDL, and the mineralized tissues: cementum and alveolar bone (13,15). As specific cell lineages retain the potential of regeneration (12,16), stimulatory (9) and selective (10) approaches have been attempted to re-engineer lost periodontal supporting tissues.

Guided tissue regeneration and cell re-population

The biological principle of using cell-occlusive barriers was described by Melcher on the repair potential of periodontal tissues (10). It was demonstrated that guided tissue regeneration (GTR) could be driven by excluding or restricting the re-population of periodontal defects by epithelial and gingival connective cells. Thus, providing space and favorable niche to maximize PDL cells, cementoblasts, and osteoblasts to migrate selectively, proliferate and differentiate within the periodontal defects help in promoting the reconstruction of the supporting tissue and attachment (17).

Cellulose membranes were the first biomaterial applied as surgical barriers for periodontal GTR, followed by expanded polytetrafluoroethylene (ePTFE) (18) and a variety of absorbable polymers (19). Current used materials include polylactic acid, polyglycolic acid, polyglactin, and both soluble and non-soluble collagen barriers (20). A list of cell-occlusive devices including non-absorbable and absorbable barriers is shown in Table 1. The use of non-absorbable barriers requires a second surgical procedure for barrier removal, usually performed after 4–12 weeks following surgery. Absorbable barriers made from synthetic polymers are biocompatible, and biodegradable through physicochemical hydrolysis. Collagen barriers, made of type I collagen from bovine or porcine tissues,

Table 1. Cell-occlusive barriers used for periodontal regeneration

Cell-occlusive barrier	Trade name
Non-resorbable	
Cellulose, ePTFE	Millipore filter®, Gore-Tex®
Resorbable	
Polylactic acid and poly-glycolic acid, Polyglactin-910, poly(L-lactide)	Resolut®, Atrisorb®, Vicryl-Netz®
Collagen	
Bovine tendon type I, Porcine dermis type I + III	Biomend®, BioGide®, Ossix®
Plaster of Paris	
Calcium sulfate	Cap-Set®, Hap-Set®

Fig. 2. Cell therapy for periodontal tissue engineering: (A) SEM image of poly-lactide-co-glycolide acid (PLGA) scaffold and seeded cells into scaffolds; (B) tissue engineering approach for ectopic mineralization in mice, cells are expanded in culture prior to being seeded into the scaffolds for implantation; (C) periodontal ligament cells (PDL) do not promote mineralization *in vivo*, while cementoblasts show mineralization, 20× magnification.
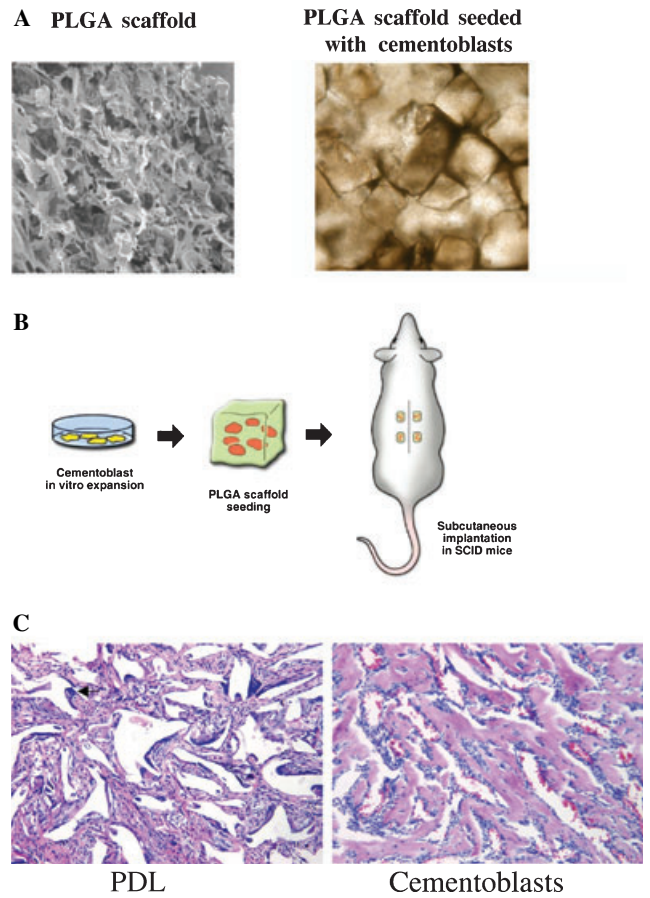
are degraded through enzymatic processes that may take from 6–8 weeks to as long as 4–8 months. In comparison with non-absorbable barriers, the absorbable types exhibit the advantage of easy adaptation to the defect area without need for barrier removal (21).

More recently, Lee et al. have shown that ceramic barriers impregnated with BMP-2 greatly improved craniofacial bone regeneration *in vivo* (22). This new approach of combining (selective and stimulatory) physical barriers with bioactive molecules offers tremendous possibilities for bone tissue engineering (23).

Cell therapy

To date, cell therapy aimed to engineer tissues has just recently been employed to periodontology (Fig. 2). A human oral mucosa equivalent was successfully assembled *ex vivo* by Izumi et al. (24). The engineered mucosa, consisting of epidermal and dermal components, in a defined essential-fatty-acid-deficient serum-free culture medium without a feeder layer, can potentially be used for intra-oral grafting in humans (24). The use of cell expansion in an *ex vivo* environment for subsequent transplantation provides extra material in cases of insufficient donor tissue.

Somerman et al. have also demonstrated the potential use of cell therapy with cloned cementoblasts (25). In a series of reports, the group has cloned and characterized a cementoblast cell line, which possesses many of the phenotypic characteristics of tooth-lining cells *in vivo*. More recently, it has been demonstrated that transplantation of cloned cementoblasts into poly-lactide-co-glycolide acid (PLGA) carriers leads to the repair of large periodontal alveolar bone defects in rodents (26). The achieved regeneration was only limited by the size of the transplanted PLGA carrier. Jin et al. have also shown that skin fibroblasts transduced by the BMP-7 gene promoted the tissue engineering of periodontal bone defects including new bone, functional PDL and tooth root cementum (27). By utilizing strategies to better understand the basic biologic mechanisms involved in cementogenesis, optimal therapies for periodontal wound healing may be developed.

Growth factors for periodontal regeneration

In order to enhance the *in vivo* efficacy, incorporation of bioactive molecules into scaffolding materials may

facilitate sustained factor release for periods of time. There are two basic modes of incorporating bioactive molecules into the scaffolds at the time of fabrication (28) or after the fabrication (29). Bioactive molecules incorporated directly into a bioresorbable scaffold are generally released by a diffusion-controlled mechanism that is regulated by the pore sizes such that different pore sizes affect the tortuosity of the scaffold and thereby control the release of protein (30). The rate of growth factor release depends on the type and rate of degradation of the delivery device, and the rate of growth factor diffusion through pores of the scaffolds. Wei et al. has incorporated human parathyroid hormone (PTH) into biodegradable PLGA microspheres and demonstrated that PTH could be released in a controlled fashion (31). These polymer microspheres were able to preserve the bioactivity of the PTH as evidenced by the stimulated release of cAMP by rat osteosarcoma cells *in vitro* as well as increased serum calcium levels when injected subcutaneously into mice. Murphy et al. have shown the release of vascular endothelial growth factor (VEGF, a potent mitogen specific for endothelial cells) from PLGA scaffolds for up to 15 days (32). Moreover, enhanced vascularization in the scaffold has been observed when the VEGF-incorporated polymers seeded with endothelial cells were implanted *in vivo* (33). In addition, it has been shown that insulin-like growth factor (IGF)-1/transforming growth factor (TGF)-1 incorporated in PLGA microspheres is gradually released over 15 days (34). The *in vitro* culture of IGF-1/TGF-1 containing microspheres photoencapsulated with chondrocytes in a hydrogel system resulted in increased cell numbers and glycosaminoglycan production compared with the control gels either with or without microspheres at 2 weeks (34). Recently, Lutolf et al. showed that hydrogels that contain cell adhesive molecule motif RGD (arginine-glycine-aspartic acid) and substrates for matrix metalloproteinases as linkers to polymer chains work as biomimetic scaffolds (35). This approach works efficiently as cell invasion into the scaffolds regulates the release of BMPs to heal craniofacial defects. Development of suitable controlled-release of the bioactive molecules devices and/or alternative mode of delivery is needed.

Several bioactive molecules have demonstrated strong effects in promoting periodontal wound repair in preclinical and clinical studies. These bioactive molecules include PDGF (36), IGF-I (37), basic fibroblast growth factor (FGF-2) (38), TGF-1 (39), BMP-2 (40), -4 (41), -7 (42) and -12 (43), and enamel matrix derivative (EMD) (44) that have shown positive results in stimulating periodontal regeneration. In addition, PDGF, BMP-2, and BMP-7 have been shown to promote peri-implant bone regeneration (2). Recently, a comparative study in periodontal defects found that rhBMP-2 in association with collagen sponges promoted superior bone regeneration than rhBMP-12. Cementum formation is similar for both BMPs, however, only the rhBMP-12 treatment induces to functionally oriented PDL bridging newly formed bone and new cementum (43).

The details of preclinical and clinical studies have been reviewed in several articles (2,5,12,45–47). In general, the results from the *in vivo* studies have shown that all of the above-mentioned bioactive molecules, with the exception of TGF-1, exhibited an ability to promote periodontal tissue regeneration. BMPs showed the greatest potential in critical-size defects, as they are potent osteoinductive mediators. A phase I/II human trial using a combination of PDGF and IGF-I demonstrated the stimulation of alveolar bone repair in patients with severe periodontal disease (48). Table 2 presents a list of growth factors and their effects on PDL cells, cementoblasts and osteoblasts. Future therapy using various combinations of growth factors promoting optimal periodontal tissue regeneration warrant further investigation.

Scaffold and extracellular matrix

The extracellular matrix is a biologically active tissue composed of a complex mixture of macromolecules, that in addition to serving a structural function, also profoundly affect the cellular physiology of an organism (47). Cell adhesion, migration, proliferation and differentiation are examples of biological processes influenced by the composition and structural organization of surrounding extracellular matrices (49).

Studies have shown the critical role of the extracellular matrix substrata in bone induction by BMPs, particularly in craniofacial morphogenesis and regeneration, which is contact-mediated (50). For example, the rhBMPs delivered on wounds bind to heparan sulfate, heparin, type II procollagen, fibrillins, proteoglycans, noggin, chordin, DAN, and types I and IV

Table 2. Effect of growth factors on periodontal ligament (PDL) cells, cementoblasts (CM) and osteoblasts (OB)

Growth factor effects	Migration			Proliferation			Differentiation			Matrix gene expression		
Cell types	PDL	CM	OB	PDL	CM	OB	PDL	CM	OB	PDL	CM	OB
PDGF	++	?	++	+++	+++	+++	−	−	−	++	+/−	+
IGF-1	++	?	++	+	++	+	−	?	+	+	+/−	++
FGF-2	+++	?	+/−	+++	?	+++	−	?	−	+/−	?	+/−
TGF-β	+	?	++	++	++	++/−	+	−	+/−	++	+/−	++
BMPs	?	?	++	0	−	+	−	+	+++	?	++	++
EMD	++	?	++	++	++	++	+	+/−	+	+	++/−	++/−

(−) Inhibition; (0) no effect; (+) effect; (?) unknown effect; PDGF, platelet-derived growth factor; IGF, insulin-like growth factor; FGF, fibroblast growth factor; TGF, transforming growth factor; BMP, bone morphogenetic protein; EMD, enamel matrix derivative.

collagen of the extracellular matrix. Thus, extracellular matrix components combine active morphogens to confer the optimal conformation, which then can initiate contact-mediated interactions (51).

Considering that scaffolds simulate the extracellular matrix, the rate of material degradation plays a critical role on the initiation of tissue replacement for engineered structures. A list of commercially available biomaterials for tissue repair applications is shown in Table 3. It was demonstrated by Lu et al. that the release rate of growth factor from the scaffold can profoundly affect the results (52). Furthermore, the pharmacokinetics of the BMPs incorporated on biomaterials, such as collagen and hydroxyapatite (53), may be different from the kinetics in the bone, periodontium and teeth because the retention of BMPs at the site of implantation is dependent on the charge characteristics and isoelectric point of the morphogens (54).

Table 3. Scaffold materials for periodontal repair

Biomaterial	Trade name
Allografts	
Calcified freeze-dried bone, decalcified freeze-dried bone	Grafton®, Lifenet®, Musculoskeletal Transplant Foundation®
Xenografts	
Bovine mineral matrix, bovine-derived hydroxyapaptite (HA)	Bio-Oss®, OsteoGraf®, Pep-Gen P-15®
Alloplasts	
Hydroxyapaptite (dense HA, porous HA, resorbable HA)	Osteogen®, Periograf®, ProOsteone®
Tricalcium phosphate, calcium phosphate cement	Synthograft®, α-BSM®
Hard-tissue replacement polymers	Bioplant®
Bioactive glass (SiO_2, CaO, Na_2O, P_2O_5)	PerioGlas®, BioGran®
Coral-derived calcium carbonate	Biocoral®
Polymers and collagens	
Collagen	Helistat®, Collacote®, Colla-Tec®, Gelfoam®
Poly(lactide-co-polyglycolide)	
Methylcellulose	
Hyaluronic acid ester	Hy®
Chitosan	
Enamel matrix derivative	Emdogain®

Angiogenic factors for periodontal repair

The periodontium is a highly vascularized tissue. Three major sources of blood supply comes from 1) supra-periosteal arterioles along the surface of alveolar bone, 2) vessels of the PDL region, and 3) arterioles from the interdental septum extending into the gingival and sulcus area (55). It is not only important to maintain the local homeostasis and adequate host defense by transporting cells and defensins to the gingival crevice (56), the blood supply has a key role on the nutrition of newly engineered tissues. However, a major challenge in periodontal regeneration is the targeting of angiogenesis to an avascular tooth root surface.

Subsequent to an injury, capillaries invading a fibrin clot will deliver nutrients, inflammatory cells, and oxygen to the wound site for early granulation tissue formation (57). Additionally, new blood vessels will contribute to provide an adequate environment for cell migration, proliferation, differentiation and extracellular matrix synthesis; all essential features noted during the initial phases of periodontal healing (58).

Basic fibroblast growth factor (bFGF or FGF-2) has been demonstrated to have potent angiogenic activity (59) and potential to induce the growth of immature PDL cells (38). The mRNA level of laminin in PDL cells, which plays an important role in angiogenesis, is upregulated by FGF-2 stimulation (38). Also, a recent report addressed the effect of the EMD on the stimulation of angiogenesis of the periodontal wounds (60). These factors may in turn accelerate periodontal regeneration.

Although EMD has angiogenic effects both *in vitro* and *in vivo* (60), the more rapid initial healing may not be directly influenced by the angiogenic effect of EMD alone. At least two other mechanisms probably contribute to the acceleration of wound healing. First, PDL cells can secrete growth factors, including TGF-β1, IL-6, and PDGF-AB after exposure to EMD (44,61). TGF-β1 and PDGF-AB have been shown to accelerate the rate of healing in periodontal wounds by specifically stimulating the proliferation of PDL cells (12,37,62,63). Second, it has been demonstrated that EMD can modulate the bacterial growth of putative periodontal pathogens (*Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella intermedia*), but not the normal flora during periodontal wound healing (60,64).

The technical challenges confronting the tissue engineering of vasculature are many (65). First is the selection of appropriate vascular cells and scaffold materials. The majority of studies to date typically involve *in vitro* culturing of bone marrow cells or smooth muscle cells in combination with a collagen-based matrix until a tubular structure is formed, subsequently allowing endothelial cells to attach to the vessel wall (66). Scaffolds need to be designed to support the proper formation of vascular tissue and possess the mechanical properties that can match those of native arteries. The synthetic vessel must withstand the fluid shear stress and strain from blood flow and have an adequate burst strength to withstand physiological blood pressures (65). Finally, incompatibilities between synthetic engineered grafts and native blood vessels must be quantified and evaluated.

Growth factors are often required to promote tissue regeneration, as they can induce angiogenesis, which supplies oxygen and nutrients to cells in order to maintain their biological functions. However, the biological effects of growth factors cannot always be expected because of their poor *in vivo* stability, unless a drug delivery system is contrived. Present and future studies involving the incorporation of angiogenic growth factors (most notably VEGF) directly into scaffolds (67), or using gene therapy to deliver growth factors to these sites may prove to be an important key for stimulating new vessel formation (68). In a dual growth factor delivery model targeting rapid formation of mature vascular networks, it was demonstrated that both PDGF + VEGF, each with distinct kinetics, improve angiogenesis by leading the formation of a significant number of blood vessels and inducing their maturation (69).

Gene therapy for periodontal engineering

As the half-life of growth factors *in vivo* is transient (on the order of minutes to hours), periodontal regeneration is not a common outcome following conventional surgical therapy. Typically, high concentrations of growth factors are required to promote tissue regeneration (70). Therefore, supplemental local growth factor production via gene transfer could be superior to bolus delivery methods.

Simply stated, gene therapy consists of the insertion of genes into an individual's cells either directly or indirectly with a matrix to promote a specific biological effect. Gene therapy typically aims to supplement a defective mutant allele with a functional one in a therapeutic approach but can also be used to induce
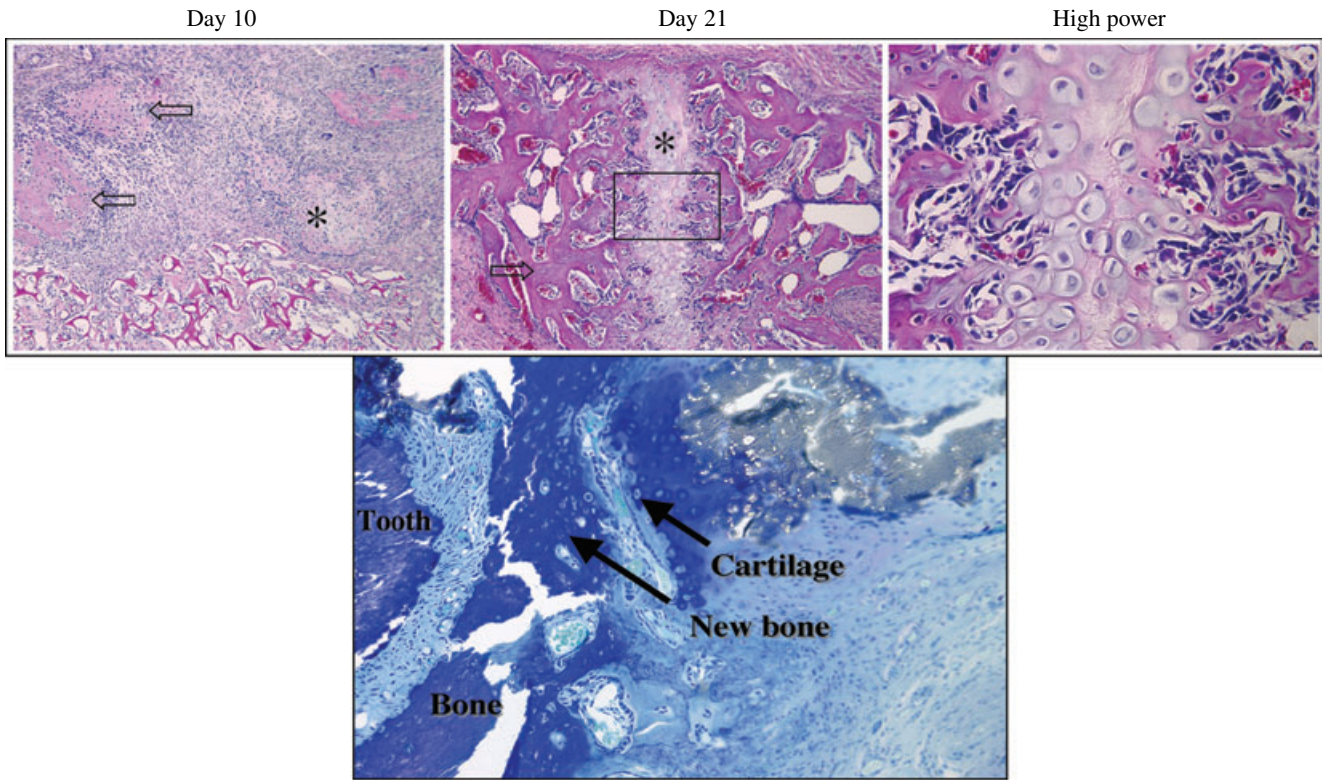

Fig. 3. Bone regeneration via cartilage intermediate: recombinant adenovirus encoding murine BMP-7 (Ad-BMP-7) promoting periodontal bone regeneration via a cartilage intermediate evaluated after 10 and 21 days of *ex vivo* gene transfer to periodontal wounds. After 10 days, specimens demonstrated islands of cartilage and chondroblast-like cells. After 21 days, specimens demonstrated woven bone and mature cartilage intimately associated with newly formed bone. The bottom panel shows an image of chondroblast-like cells and cartilaginous matrix surrounded by new bone adjacent to the tooth surface. H&E and toluidine blue staining at 10× magnification, high power image at 20× magnification. Reprinted in part from Jin et al. (27), with permission.
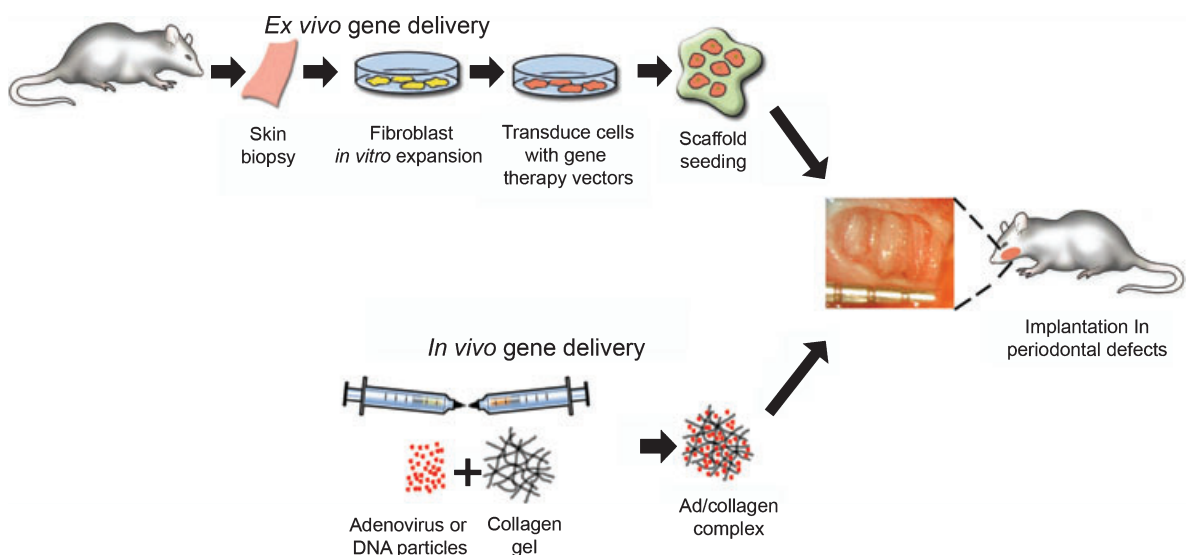

Fig. 4. Gene delivery strategies for tissue engineering: *ex vivo* approach, tissue biopsy from donor site have cells isolated and expanded in cell culture. Vectors (e.g. adenovirus or plasmids) are used to transduce the cells *in vitro*. Cells are then seeded onto biodegradable scaffolds delivered to the wound site. In the *in vivo* approach, genes are directly delivered to the wounds using (in this example) collagen gel as a carrier.

a more favorable host response. Targeting cells for gene therapy requires the use of vectors or direct delivery methods to transfect them.

Using an *ex vivo* approach for periodontal repair, Jin et al. used BMP-7 gene transfer to stimulate new alveolar bone, tooth root cementum, and PDL (27). Ad-BMP-7 or its antagonist, Ad-noggin transduced syngeneic dermal fibroblast that were seeded onto gelatin carriers and transplanted into large alveolar bone defects. The repair of periodontal defects was observed through a rapid chondrogenesis, followed by osteogenesis, cementogenesis and predictable bridging of the bone defect (Fig. 3) (27). Noggin gene transfer on the other hand blocked periodontal bone and cementum repair both in periodontal defects (27) and in tissue-engineered cementum (42).

PDGF has demonstrated strong potential in promoting gingival (71), alveolar bone (72), and cementum (73) regeneration in a variety of wound healing models (Fig. 4) (72). When periodontal defects were treated with adenovirus encoding PDGF-B, strong evidence of bone and cementum regeneration beyond that of control vectors, consisting of nearly fourfold increases in bridging bone and sixfold increases in tooth-lining cemental repair was seen (72). In addition, it was demonstrated that a sustained and localized expression of the luciferase reporter gene was ascertained at the periodontal lesions for up to 21 days after gene transfer (72).

Future perspectives

Many advances have been made over the past decade in the reconstruction of complex periodontal and alveolar bone wounds. Developments in polymeric and ceramic scaffolding systems for cell, protein and gene delivery have undergone significant growth. The targeting of signaling molecules or growth factors (via proteins or genes) to the periodontium has lead to significant new knowledge generation using bioactive molecules that promote cell proliferation, differentiation, matrix biosynthesis, and angiogenesis. A major challenge that has been overlooked has been the modulation of the exuberant host response to microbial contamination that plagues the periodontal wound environment. For improvements in the outcomes in periodontal regenerative medicine, scientists will need

to examine dual delivery of host modifiers or anti-infective agents to optimize the results of therapy. Further advancements in the field will continue to rely heavily on multidisciplinary approaches combining engineering, dentistry, medicine, and infectious disease specialists in repairing the complex periodontal wound environment.

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