Position Paper

The Potential Role of Growth and Differentation Factors in Periodontal Regeneration*

POLYPEPTIDE GROWTH AND DIFFERENTIATION factors (GDFs) are a class of biological mediators which have been shown to play a critical role in the stimulation and regulation of the wound healing process, Growth factors involved in repair and regeneration regulate several key cellular processes such as mitogenesis, chemotaxis, differentiation, and metabolism. The sequence of events necessary for periodontal regeneration relies on the above processes for osteogenesis, cementogenesis, and connective tissue formation. Numerous preclinical in vitro and in vivo studies have demonstrated that certain growth factors modulate putative components of periodontal wound healing resulting in substantial regeneration of the periodontium in animals. However, these therapies are currently considered to be in the experimental stage of development and no growth factor therapy to treat periodontitis in humans has received approval by the Food and Drug Administration (FDA). This informational paper reviews the various aspects of GDFs on cells and tissues involved in periodontal wound healing. This paper was prepared by the Committee on Research, Science and Therapy of The American Academy of Periodontology and is intended for members of the dental profession. *J Periodontol 1996;67:545-553.*

INTRODUCTION

Since the initial hypothesis on the potential of periodontal regeneration was proposed by Melcher,[1] research to identify treatment modalities to promote regeneration of lost periodontal tissues has grown rapidly. Examples of current periodontal regenerative therapies include guided tis-sue regeneration (GTR) using bioabsorbable or nonre-sorbable membranes; bone autographs and allografts; and root conditioning agents such as citric acid or tetracycline. (For information on periodontal regeneration, please refer to the Academy's position paper on Periodontal Regen-eration).[2] In the past decade there has been a concerted effort in the field of cell and molecular biology to attempt to better understand the mechanisms of polypeptide growth and differentiation factors (GDFs) on the repair and regeneration of tissues. These natural molecules have been shown to have pleiotrophic effects on wound repair in nearly all tissues, including the periodontium.[3-6]

This informational paper describes GDF effects on periodontal soft tissue components (periodontal ligament [PDL] and gingival connective tissue) and hard tissue structures (alveolar bone and cementum) in vitro and in vivo. It will conclude with remarks regarding future directions as GDFs enter into human clinical trial testing.

Polypeptide growth factors are a class of natural biological mediators which regulate key cellular events in tissue repair; i.e., cell proliferation, chemotaxis (directed migration), differentiation, and matrix synthesis via binding to specific cell-surface receptors. Examples of GDFs found in bone, cementum, and healing wound tissues include platelet-derived growth factor (PDGF), vascular en-dothelial growth factor (VEGF), transforming growth fac-tors (TGF-α and -β), acidic and basic fibroblast growth factors, (a- and bFGF), epidermal growth factor (EGF), insulin-like growth factors (IGF-I and -II), cementum-derived growth factor (CGF), parathyroid hormone-related protein (PTHrP), and bone morphogenetic proteins (BMPs 1-12).

Healing following injury involves a series of well orchestrated cell-cell and cell-macromolecular interactions. In the normal wound healing process, multiple growth-factors act in concert to form an intricate molecular arrangement regulating the activity of cells within and ad-

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jacent to a wound.[5] Following acute tissue injury involving subepithelial tissues, disruption of the wound vasculature leads to fibrin formation and platelet aggregation forming a cellular plug.[7] Activated platelets at the wound margins release several growth factors such as PDGF, TGF-β1, an epidermal growth factor (EGF)-like protein, and platelet-derived endothelial cell growth factor (PDECGF).[8] In addition, the plasma exudate provides an important source of insulin-like growth factors.[9] Cells adjacent to the injured site also are induced to release growth factors such as IGF-I, PDGF, TGF-α, and TGF-β1 within a few hours after injury.[10-14]

Following tissue injury, neutrophils accumulate with subsequent migration of macrophages into the area several days later. Macrophages exert multiple effects on the wound healing microenvironment including debridement of damaged tissue and serving as another source of growth factors such as PDGF, TGF-α, and TGF-β1.[15] In addition, bone and cementum contain large concentrations of growth factors such as IGF-I, -II, TGF-β1, and PDGF which may be released following injury.[16-17] Differentiation (e.g., osteoinductive) factors such as BMPs appear to be expressed in mature bone as well as during fracture repair[18] and embryological development.[19-21] Messenger RNA transcripts of various BMPs have been found in multiple growing tissues such as in developing craniofacial structures, tooth buds, odontoblastic layers, and palatal shelves.[19-21]

The expression of various GDFs following bone and soft tissue injury (possibly during periodontal disease) may regulate the repair and/or regenerative process. Thus, the objective for GDF administration in the treatment of chronic adult-onset periodontitis is to enhance the normal wound healing response which may be of insufficient magnitude to promote complete regeneration of all attachment structures. Basic and clinical research is currently in progress to evaluate the role of GDFs in periodontal wound healing. The following sections specifically discuss the effects of exogenous GDFs on cells and tissues involved in periodontal regeneration.

EFFECTS OF GROWTH AND DIFFERENTIATION FACTORS ON CELLS IN PERIODONTAL SOFT TISSUE WOUND HEALING

As presented above, the wound healing process involves numerous growth factors which act in concert to promote tissue repair. Studies of acute skin injury have shown how several different growth factors promote wound repair and affect parameters such as re-epithelialization, angiogenesis, and synthesis of extracellular matrix.[22-27] Extensive wound healing studies in animals have demonstrated that EGF, TGF-α, PDGF, TGF-βl, and bFGF can enhance soft tissue wound repair.[22-27] When combinations or "cocktails" of different factors are used, greater repair is achieved than when individual factors are applied.[28-31] In the context of periodontal wound healing, gingival epithelial cells, gingival fibroblasts, and PDL fibroblasts are the major cells involved in the soft tissue repair processes for new attachment. Specific studies on the role of GDFs on gingival fibroblasts and gingival epithelium are not as numerous as those involving cultured PDL fibroblasts.

In the periodontium, the PDL represents a soft tissue structure possessing a neurovascular supply, extracellular matrix composed mainly of type I collagen and noncollagenous protein, as well as multiple cell types (e.g., fibroblasts, macrophages, polymorpholeukocytes, etc.). For periodontal regeneration, the coronal re-establishment of the PDL is required together with corresponding cementum and supporting alveolar bone. Thus agents which promote PDL fibroblast (PLF) proliferation and migration as well as collagen biosynthesis would appear to be critical mediators for enhancing new periodontal ligament formation. Currently, the most well-studied growth factors on PLF activity include PDGF-BB, TGF-β1, bFGF, EGF, IGF-I, CGF, and BMP-7 (osteogenic protein-l).

Platelet-Derived Growth Factor (PDGF-AA, -AB, -BB)

PDGF has been the most thoroughly described growth factor on the periodontium in vitro and in vivo. Several investigators have demonstrated the potent effects that all isoforms of PDGF have on PLF proliferative activity in vitro.[32-35] The ability of PLFs to respond to each isoform has been shown by immunoprecipitation of both the (α and β PDGF receptors expressed on rat PLFs harvested from extraction sockets.[36] PDGF is also chemotactic for PLFs and promotes collagen and total protein synthesis.[32] PDGF stimulates gingival fibroblast hyaluronate synthesis, a prerequisite for the formation of large aggregates of proteoglycans that provide the lattice for the extracellular matrix.[37] Furthermore, PDGF can reduced the inhibitory effects of lipopolysaccharide (LPS) on gingival fibroblast proliferation.[38] Recently, PDGF has been shown to promote fibroblast proliferation under expanded polytetrafluoroethylene membranes (ePTFE) in protected fenestration defects in dogs. This study utilized autoradiography to show an increased [^{3}H]thymidine uptake in the defects at 1 and 7 days post-PDGF application to the root surfaces.[39] When IGF-I or dexamethasone is combined with PDGF and applied to PLFs, synergistic effects on mitogenesis are observed as assessed by increased [^{3}H]thymidine uptake.[32,40,41] Thus, PDGF appears to possess a multitude of effects that may promote periodontal soft tissue wound healing.

Transforming Growth Factor-β (TGF-β1)

TGF-β1 has been shown to be a strong promoter of extracellular matrix production in many cell types including PLFs.[32,42-44] While TGF-β1 does not appear to promote

PLF migration, it has modest effects on PLF mitogenesis.[32-34] When TGF-β1 is assessed alone or when combined with PDGF-BB, it selectively stimulates PLF proliferative activity at significantly higher levels than with gingival fibroblasts.[34] TGF-β1 increases the expression of PDGF-β receptors, while reducing the number of PDGF-α subunits.[45] In addition, TGF-β1 inhibits epithelial cell proliferation.[29,46] Taken together, these results suggest that TGF-β1 may have potential use in periodontal wound healing.

Basic Fibroblast Growth Factor (bFGF)

Studies assessing the role of bFGF on PLF activity or cementogenesis are limited. However, early investigations have shown that bFGF is both a potent chemotactic and mitogenic factor for PLFs.[47] Basic FGF-coated dentin blocks also promote human endothelial cell migration and proliferation.[47] This study further demonstrated that bFGF binding is increased by exposing type I collagen on dentinal surfaces.

Epidermal Growth Factor (EGF)

EGF appears to have little effect on promoting PLF mitogenesis, chemotaxis, or matrix synthesis in PLFs.[32] However, EGF and EGF receptor (EGF-R) have been shown to be localized on rat PLFs during differentiation.[48] It has been suggested that EGF-R may act as a PLF phenotype stabilizer, and reports from in vitro studies have concluded that the up-regulation of EGF-R and PLFs is associated with maintaining the cells in an undifferentiated state (with decreased alkaline phosphatase activity); while down-regulation of EGF-R is related to the differentiation of cells into osteoblasts or cementoblasts.[49] Effects of EGF remain to be tested in vivo on periodontal wound healing.

Insulin-Like Growth Factors (IGF-I and -II)

IGF-I has been shown to be chemotactic for cells derived from the PDL.[32] IGF-I also has strong effects on PLF mitogenesis and protein synthesis in vitro.[32] IGF-I receptors have also been localized on the surface of PLFs.[50] The role of IGF-II on parameters of PLF and gingival fibroblast metabolism have not been reported to date.

Cementum-Derived Growth Factor (CGF)

CGF, a newly characterized growth factor, appears to be found exclusively in cementum.[51] This growth factor has been shown to be mitogenic for both PLFs and gingival fibroblasts. It has been suggested that CGF may promote the migration and growth of progenitor cells present in adjacent structures to the dentin matrix and participates in their differentiation into cementoblasts.[52] The specific effects of CGF on collagen synthesis in PLFs have not been documented. However it has been demonstrated that CGF promotes greater collagen synthesis than PDGF-AB or -BB in human lung fibroblasts.[53] Molecular cloning and expression of CGF is needed to provide larger quantities of CGF for in vivo experimentation.

Bone Morphogenetic Proteins (BMPs)

The role of selective BMPs on PLF metabolism has not been evaluated extensively. However, it has been demonstrated that BMP-7 (osteogenic protein-1 or OP-1) at concentrations up to 200 ng/mL is not mitogenic for PLFs.[41] Interestingly, OP-1 stimulates alkaline phosphatase activity in a dose- and time-dependent manner, thus altering the PLF phenotype. Recent studies suggest BMP-2 and BMP-12 also fail to elicit a mitogenic response on cultured PDL fibroblasts.[54] Future studies assessing the effects of other BMPs on PLF activity appear to be warranted.

EFFECTS OF GROWTH AND DIFFERENTIATION FACTORS ON BONE AND CEMENTUM REGENERATION

Growth factors are present in bone matrix and appear to account for coupling bone formation to resorption.[55] The effects of polypeptide growth factors on bone formation have been evaluated in numerous in vitro and in vivo model systems.[56-58] Unfortunately, limited data exist comparing growth factors on alveolar bone metabolism specifically. Thus the information presented here represents growth factor effects on various orthotopic sites other than alveolar bone. Although several growth factors have been found to be sequestered in cementum matrix, their specific effects on cementogenesis are also not well understood.[17]

Platelet-Derived Growth Factor (PDGF)

In bone organ culture, PDGF stimulates DNA synthesis and chemotaxis, as well as collagen and non-collagen protein synthesis.[59-61] In cultures of osteoblast-like cells, alkaline phosphatase activity and osteocalcin are down-regulated by PDGF.[62] In vivo, PDGF enhanced demineralized bone matrix-induced cartilage and bone formation.[63] A recent report found that PDGF-BB in a collagen vehicle promoted bone repair when applied to surgically created tibial osteotomy defects.[64]

Transforming Growth Factor-B (TGF-B1)

The effects of TGF-β1 appear to be highly dependent upon bone cell source, dose applied, and local environment as shown in studies that demonstrate either stimulation or inhibition of osteoblast proliferation.[42,65] TGF-β1 stimulates type I collagen, fibronectin, and osteonectin biosynthesis as well as bone matrix deposition and chemotaxis.[43,55,66,67] In addition, TGF-,βI decreases synthesis of metalloproteinases and plasminogen activator, which increases synthesis of tissue inhibitor of metalloproteinase (TIMP) and plasminogen activator inhibitor (PAI), thus

resulting in a decrease in connective tissue matrix destruc–tion.[44,68,69] TGF-β1 also appears to inhibit formation of osteoclast-like cells but may promote bone resorption via a prostaglandin-mediated mechanism.[70-71] The net result of repeated injections of TGF-β1 in long bones is formation of cartilage which eventually ossifies to bone via endochondral bone formation.[72,73] In addition, TGF-β1 genes are expressed during normal human fracture healing.[74] Therefore, due to its pleiotrophic effects on bone matrix formation and resorption and its relative abundance in bone, TGF-β1 may act as a bone coupling factor linking bone resorption to bone formation.[55]

Fibroblast Growth Factors (a- and b-FGF)

Acidic and basic FGF are found in bone matrix[75,76] and in vitro both forms stimulate DNA synthesis and cell replication.[77] However, the FGFs have no direct stimulatory effect on mature osteoblasts and they decrease alkaline phosphatase activity.[77] In an immortal cell line, bFGF reduces mRNA levels for type I collagen and osteocalcin.[78] Of significance, the FGFs potently stimulate angiogenesis which is critical for the vascular invasion of bone.[79]

Insulin-Like Growth Factors (IGF-I and IGF-II)

Both IGF-I and IGF-II are found in large amounts in bone, with IGF-II being the most abundant growth factor in bone matrix.[57] IGF-I is produced by osteoblasts and stimulates bone formation by inducing cellular proliferation, differentiation, and type I collagen biosynthesis.[80-83] In bone, it has been reported that high levels of IGF-I are synthesized and secreted by osteoblasts and that IGF-I may therefore regulate bone formation in an autocrine manner.[84] IGF-I also increases the number of osteoclastic multinucleated cells.[85] IGF-I application to rat tooth root surfaces promotes cementogenesis within 8 days after reimplantation in IGF-I treated molars.[48] However, when IGF-I was applied to natural periodontal lesions in dogs, only slight increases in new cementum and bone formation were found.[86]

IGF-II has similar effects to IGF-I when tested in vitro, and at high levels binds to the IGF-I receptor.[87] However, most studies suggest IGF-II is not as potent as IGF-I in promoting parameters of bone formation.[88] IGF-II is equivalent to IGF-I in promoting osteoblast chemotaxis in vitro.[89] Combinations of other growth factors with IGFs have also been assessed in vitro and in vivo. In calvarial organ culture the combination of IGF-I plus TGF-β1 or IGF-I plus PDGF increased bone matrix apposition more than TGF-β1, PDGF, or IGF-I individually.[66] IGF-I has been shown to synergistically increase osteoblast mitogenesis in cultured bone cells when combined with other growth factors such as bFGF, PDGF, or TGF-β1.[62] Maximal proliferation of cultured adult human osteoblasts was seen with a cocktail of IGF-I, PDGF, TGF-β1, and EGF.[90] In a tibial osteotomy defect model system, IGF-II combined with TGF-β1 synergistically increased the proportional area of new callus above the additive effects of the individual factors.[91] Thus, several studies suggest that IGF-I or IGF-II combined with other growth factors may augment the osseous wound healing process.

Parathyroid Hormone-Related Protein (PTHrP)

PTHrP is a polypeptide growth factor produced by numerous cell types including keratinocytes, activated lymphocytes, and osteoblasts.[92] Similar to parathyroid hormone, PTHrP stimulates bone resorption and is also a potent anabolic agent in bone.[93] Receptors for PTHrP have been reported on PDL cells, and PTHrP expression has been described on cells which resemble cementoblasts in the developing tooth.[94,95]

Bone Morphogenetic Proteins (BMPs)

BMPs are structurally related members of the TGF-β1 superfamily and BMPs 2-12 singly initiate *de novo* endochondral bone formation.[96-99] The BMPs "induce" new bone formation, whereas other growth factors such as TGF-β1 or PDGF do not. In general, BMPs stimulate proliferation and migration of undifferentiated bone cell precursors with little to no effects on mature osteoprogenitor cells.[100] Thus, the main action of BMPs is to commit undifferentiated pluripotential cells to differentiate into cartilage and bone-forming cells.[6,101,102] BMPs are abundant in bone. They are produced by several cell types including osteoblasts.[103,104] Bone allograft materials used for dental procedures have been found to contain varying levels of BMP, such as BMP-2, -4, and -7.[105] Thus, commercially prepared, allograft-retained proteins have the capacity to influence cell behavior in vivo. BMP-like molecules are also found in dentin and promote reparative dentin formation in vivo.[106-107] A deficiency of BMP-like proteins retards bone cell differentiation and may account for a failure of fractures to heal.[108] Recombinant BMPs (rhBMPs) have been shown to promote osseous union of segmental long bone osteotomies[109] as well as in calvarial defects.[110]

In summary, BMPs produce multiple effects on bone by: 1) acting as mitogens on undifferentiated mesenchymal cells and osteoblast precursors; 2) inducing the expression of the osteoblast phenotype (e.g., increasing alkaline phosphatase activity in bone cells); and 3) acting as chemoattractants for mesenchymal cells and monocytes as well as binding to extracellular matrix type IV collagen.[111]

PRECLINICAL AND CLINICAL STUDIES ON PERIODONTAL REGENERATION

Growth Factors

To date, several preclinical animal studies examining the effects of certain growth factors in periodontal wound

healing have been conducted, while other growth factors remain virtually untested. Some of the earliest in vivo studies assessing the role of growth factors on periodontal regeneration focused on a combination of PDGF and IGF- I. These studies in natural disease lesions in dogs and ligature-induced lesions in non-human primates found that this growth factor combination promoted new bone, cementum, and periodontal ligament in vivo.[112-116] PDGF/ IGF-I has also been shown to promote bone formation around press-fit and immediate extraction socket dental implants.[117,118]

PDGF combined with dexamethasone (Dex) was evaluated for its periodontal regeneration in non-human primates with experimental periodontitis.[119] This growth factor combination also demonstrated significant increases in new bone and attachment measured 4 weeks after PDGF/Dex administration. Most recently, encouraging results have also been reported in the dog model using platelet-derived growth factor-modulated GTR therapy. These studies revealed significant elevations in new bone and attachment structures as measured at 5, 8, and 11 weeks after PDGF/GTR application in Class III furcation defects.[120,121]

The first human clinical trial testing the safety and efficacy of PDGF/IGF-I was recently reported.[122] This study examined 38 patients possessing moderate-severe periodontal disease treated either with 150 μg/mL each of PDGF-BB and IGF-I in a methylcellulose vehicle, vehicle alone, or surgery alone. The results found that patients treated with PDGF/IGF-I responded with 43.2% osseous defect fill while the control group consisting of pooled vehicle and surgery alone treated patients demonstrated 18.5% osseous defect fill. These differences were found to be statistically significant. Future studies are needed to further test higher doses of PDGF/IGF-I and better assess its role on other parameters of periodontal regeneration.

While most studies have examined the effects of PDGF alone or in combination with other factors on periodontal regeneration, few studies have tested the role of other factors on promoting periodontal repair. TGF-β1, bFGF, and IGF-II were tested on osseous regeneration in surgi- cally created fenestration defects in dogs.[123] The results of this study found no enhancement in bone formation at 4 weeks. The authors cited the use of nanogram quantities of growth factors and thus it could be suggested that other growth factor levels may be needed to further test the effects of IGF-II, TGF-βI, and bFGF on periodontal regeneration. Other growth factors and growth factor combinations with varying concentrations remain to be tested in periodontal defects.

Bone Morphogenetic Proteins (BMPs)

The first human study using a BMP to promote periodontal regeneration utilized a single application of BMP-3 (osteogenin) combined with demineralized bone allograft in a submerged tooth model.[124] The investigators found increased new bone and cementum deposition around periodontally involved submerged teeth in the BMP-3 plus bone graft group; while the BMP-3 plus collagen vehicle demonstrated no increases in bone or cementum as compared to control. However, the BMP-3 plus bone graft group was not significantly better than bone grafts alone. Furthermore, pinpoint ankylosis was observed in submerged teeth grafted with BMP-3 plus bone grafts. A recent dog study examining the effects of rhBMP-2 on periodontal regeneration found that BMP-2 applied in synthetic bioabsorbable particles promoted highly significant increases in new bone and cementum formation.[125] These results were achieved 8 weeks following BMP-2 application. Nearly 95% of the bone in surgically created Class III furcation lesions was regenerated. However, a nearly 4-fold increase in ankylosis was found in BMP-2 treated sites as compared to vehicle. The authors state that the proximity of the bone to the cemento-enamel junction may have been a factor responsible for the ankylosis in the submerged defect model. It appears that BMP also needs to be evaluated in non-submerged periodontal models.

BMPs also show much promise in promoting dental implant wound healing. A pilot study in non-human primates tested the single application of OP-1 around immediate extraction socket implants and found increased bone growth as measured histologically at 3 weeks.[126] Bovine BMP (bBMP) tested in a dog model was shown to increase the rate of osseointegration around cylindrical uncoated endosseous implants as evidenced histomorphometrically 4 weeks after implantation.[127] The tissue reactions to titanium implants coated with bBMP were further assessed by SEM for 12 weeks in the same dog model.[128] The results revealed abundant lamellar bone for- mation around bBMP-coated implants by 8 weeks. This bone was found adjacent to the implant threads and frequently entered the implant holes.

FUTURE PERSPECTIVES

Preclinical studies to date have demonstrated varying degrees of success in the promotion of periodontal and peri-implant wound healing by GDF application. These investigations set the stage to further address the biologic mechanisms which may account for the stimulation of tissue regeneration by GDFs. Temporal changes in gene expression by cells within and adjacent to the wound site may be responsible for the prolonged enhancement of new bone and attachment apparatus several weeks to months following GDF application. Additional studies are needed to address this area. Future investigations will also seek to utilize improved delivery systems, since most current vehicles allow only transient (few hours) exposure of periodontal tissues to the selected GDFs. Ongoing human clinical trials assessing the potential therapeutic use of

GDFs for periodontal regeneration seek to provide the conclusive evidence for the addition of this therapy to the reconstructive periodontal treatment armamentarium.

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