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Growth factors in periodontal regeneration

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Abstract: Inflammatory periodontal disease is an almost ubiquitous disorder in the adult population. Cases or sites with moderate to advanced disease often continue to show signs of inflammation after non-surgical approach. Our current understanding of periodontal healing is based on a hypothesis by Melcher who proposed that the cell type that repopulates the exposed root surface at the periodontal repair site will define the nature of the attachment/repair that take place. If mesenchymal cells from periodontal ligament/perivascular region of the bone proliferate and colonize the root surface, regeneration occurs. Growth factors are natural cell products that are released or activated when cell division is needed. This action typically occurs during such events as wound healing or tissue regeneration. Activated platelets at the wound margins release several growth factors such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-α, epidermal growth factor etc. Cells adjacent to the injured site also are induced to release growth factors such as insulin-like growth factor-I, PDGF, TGF-α and TGF-α within a few hours after injury. In periodontal regeneration, the coronal re-establishment of the periodontal ligament (PDL) is required together with corresponding cementum and supporting alveolar bone. Thus, agents which promote periodontal ligament fibroblast (PLF) proliferation and migration as well as collagen biosynthesis would appear to be mediators for enhancing new PDL formation. When combinations or cocktails of different factors are used, greater repair is achieved than when individual factors are applied.

Key words: growth factors; periodontitis; regeneration

Introduction

Periodontitis is characterized by gingival inflammation and often results in periodontal pocket formation with loss of the supporting alveolar bone and connective tissue around the teeth. Therapeutic modalities aim at eliminating the gingival inflammatory process and preventing the progression of the disease along with re-establishing and regenerating the periodontal tissues previously lost to the disease (1). Complete removal of plaque and calculus from root surfaces especially within deep pockets is unrealistic and rarely attained with scaling and root planing. Cases or sites with moderate to advanced disease often continue to show signs of inflammation after non-surgical approach. Hence gaining surgical access to the various components of the periodontium allows an opportunity for more thorough root debridement and establishment of an oral environment to aid in restoring periodontal health. In addition, surgical treatment provides an opportunity to reconstruct destroyed periodontal tissues and to correct variety of mucogingival and anatomic anomalies that may be present (2). Over these last few years, the emphasis of periodontal surgical procedures has shifted more and more towards regeneration with the idea that this would increase the longevity of the dentition. Regeneration is defined as 'the reproduction or reconstruction of a lost or injured part'. Periodontally this definition implies the formation of new bone, new cementum and a functionally oriented periodontal ligament. This occurs with the formation of new cementum with inserting collagen fibres. Periodontal repair implies healing after periodontal surgery that result in healing without restoration of the attachment apparatus (3).

Recently, investigators have begun to understand the cellular processes necessary for repair or regeneration of the attachment apparatus. The major cellular events in tissue repair are mitogenesis, migration and metabolism. In nature, the proteins responsible for co-ordinating these events are called growth factors. These naturally occurring molecules with certain matrix proteins are key regulators of these biological events. They have been shown to have pleiotrophic effects on wound repair, nearly all tissues including the periodontium (2, 3). Growth factor is a general term used to denote a class of naturally occurring proteins that function in the body to promote the mitogenesis (proliferation) directed migration and metabolic activity of cells (4).

Numerous growth factors have been identified and characterized. Hence, the expression of these various growth and differentiation factors following bone and soft tissue injury may regulate the repair and or regenerative process. The hope is to discover how to use them to accelerate and direct the healing event into one that will produce periodontal regeneration.

Common features of growth factors

1 Natural cell products: Growth factors are natural cell products that are released or activated when cell division is needed. This action typically occurs during such events as wound healing or tissue regeneration (5).

2 Local action: With few exceptions, growth factors are locally acting.

3 Receptor activity: Because growth factors cannot diffuse across the cell membrane, growth factors must exert their activity by first binding to high-affinity cell membrane receptors. The capacity of a cell to respond to a given factor is therefore dependent on the presence of these receptors.

4 Regulation: The production of polypeptide growth factors is tightly regulated in normal cells.

5 Multifunctional activity: Polypeptide growth factors are multifunctional, meaning that they may stimulate a wide variety of cellular activities, which include growth, migration, differentiation and production of extracellular matrix proteins.

6 Mechanism of action: In some cases, growth factors can stimulate the same cell that synthesizes the molecule (autocrine stimulation) or can affect nearby cells (paracrine stimulation).

7 Regeneration: Tissue regeneration *in vivo* probably reflects the combined effect of several different growth factors.

Table 1 summarizes the alternative names and source of various growth factors.

Platelet-derived growth factor

Platelet-derived growth factor (PDGF) is regarded as one of the principal wound healing hormones and its ability to stimulate periodontal regeneration has been studied extensively. The observation of a requirement for serum by cultured fibroblasts led to the discovery that material released from platelets was the principle source of mitogenic activity present in serum and was responsible for the growth in serum and was responsible for the growth of many cells in culture that are serum dependent. This activity was later localized to the alpha granules within platelets and called it PDGF. It was discovered by Lynch and coworkers to promote regeneration of bone, cementum and periodontal ligament in the late 1980s. Serum concentration of PDGF = 15–50 mg ml^{-1}. It is one of the first growth factor to be described. PDGF is composed of two disulfide bounded polypeptide chains that are encoded by two different genes namely PDGF-A and PDGF-B. In nature PDGF can exist as a homodimer – PDGF-AA and PDGF-BB.

Table 1. **Alternative names and source of various growth factors**

Sl. no	Growth factor	Alternative names	Source
1	Platelet-derived growth factor	Fibroblast-derived growth factor Glioma-derived growth factor	Degranulating platelets Endothelial cells Smooth muscles Macrophages Fibroblasts
2	Insulin-like growth factor	Erythropoetic factor Growth-promoting activity for vascular endothelial cells	Macrophages Osteoblasts Plasma stored in bone
3	Transforming growth factor-α	Milk-derived growth factor Transformed cell growth factor	Macrophages Osteoblasts
4	Transforming growth factor-β	Epithelial cell-specific growth inhibitor Tumour-inducing factor-1	Platelet α granules
5	Fibroblast growth factor family aFGF Bfgf	Heparin-binding growth factor-α Adipocyte growth factor Bone-derived growth factor	Macrophage and osteoblasts stored in bone

Role of PDGF in cell division wound healing

At the cellular level, PDGF is an important competence factor for a cell to re-enter the cell cycle from resting G_0 phase and hence initiate cell division (6). It is an important stimulator of cellular chemotaxis, proliferation and matrix synthesis exhibiting anti-apoptosis activity. PDGF is involved in nearly all wound healing by virtue of platelets and dual role as a growth factor reservoir and a factor in haemostasis. The presence of a potent growth factor in blood clot immediately at the injured site (e.g. bone fracture) would be expected to promote a faster repair and thus better survival odds. PDGF stimulates the influx of neutrophils to the wound site.

As such PDGF seems to have numerous positive effects on wound healing including mitogenesis, angiogenesis, up-regulation of other growth factors and cells resulting in promotion of fibroblastic and osteoblatic functions, promotion of cellular differentiation and acceleration of the effects of growth factors on other cells such as macrophages (7).

Role of PDGF in regeneration

Lynch *et al.* (8) treated 13 dogs with human recombinant PDGF-BB and insulin-like growth factor (IGF-I) in methyl cellulose gel. At 5 weeks after surgery, histologic analysis demonstrated a significant increase in new bone and cementum formation in the treated sites over that in control sites. Rutherford *et al.* (9) studied the effect of PDGF and IGF on periodontal regeneration *in vivo* in a non-human primate model and reported that PDGF and IGF stimulated regeneration of periodontal attachment in monkeys. After and weeks, the addition of growth factors stimulated regeneration of 50% of lost attachment while only 14% regeneration occurred in control sites which did not receive PDGF and IGF-I. Cho Moon *et al.* (10) applied PDGF-BB to promote migration and proliferation of periodontal ligament fibroblasts and an expanded polytetra fluoroethylene (e-PTFE) barrier to prevent ankylosis in beagle dogs. It was concluded that PDGF modulated guided tissue regeneration (GTR) therapy successfully promoted full periodontal regeneration more rapidly and efficiently compared to GTR therapy alone.

These studies demonstrated that PDGF has the capacity to stimulate bone formation and periodontal regeneration *in vivo* and indicate that it holds promise as an important adjuvant to periodontal surgery.

Insulin-like growth factor

Insulin-like growth factors constitute a family of single chain proteins that share 49% homology with pro-insulin. Two well-described members of this group are IGF-1 and IGF-2 which are similar in structure and function but independently regulated. IGF-I and II are relatively small proteins with molecular masses of 7.7 and 7.5 KDa respectively. The IGF family includes three ligands and three cell surface receptors namely; insulin, IGF-I and IGF-II and Insulin, IGF-1 and IGF–L-mannose G-phosphate receptors respectively. They have atleast six high affinity IGF binding proteins which bind circulating IGFs and modulate their biologic actions. Both IGF-I and IGF-II are synthesized as large precursor molecules (195 and 156 aa) which are proteolytically cleaved to release the biologically active monomeric proteins (70 and 67 aa) (11).

Cellular role of IGF and role in wound healing

At the cellular level, IGF-I is an important progression factor that is required for the entire cells cycle to be traversed (12). Pituitary derived growth hormone appears to stimulate IGF-I synthesis in many of the tissues particularly the liver. Many of the biologic actions originally attributed to growth hormone are mediated in part by IGF-I. This led to the dual effector theory of GH and IGF-I action i.e. growth hormone initiates cell differentiation and increases the production of IGF-I which then promotes cell division (11).

Insulin-like growth factor-I has the capacity to inhibit apoptotic death. Han and Amar (13) demonstrated that *in vitro* IGF-I substantially enhanced cell survival in periodontal ligament fibroblast compared to gingival fibroblasts by the up-regulation of antiapoptic molecules and down-regulation of proapoptotic molecules. Investigators using mandibular I molars in primary culture demonstrated that IGF-I induced accumulation of several enamel-specific gene products including amelogenin and ameloblastin, suggesting that the IGF system is involved in the induction of enamel biomineralization. IGF-I has a role in pulp healing and reparative dentinogenesis following pulp capping (11).

Insulin-like growth factor-I is found in substantial levels in platelets and is released during clotting along with the other growth factors present in platelets. IGF-I is a potent chemotactic agent for vascular endothelial cells. IGF-I released from platelets or produced by fibroblasts may promote migration of vascular endothelial cells into the wound area resulting in increased neovascularization. Also stimulates mitosis of many cells *in vitro* such as fibroblasts, osteocytes and chondrocytes (11).

Transforming growth factor family

The transforming growth factor (TGFs) are a family of structurally and functionally unrelated proteins that have been isolated from normal and neoplastic tissues. The two best characterized polypeptides from this group of growth factors are TGF-α and TGF-β. TGF-α is a 50-amino acid single-chain protein with a molecular weight of approximately 5600 Da. It exhibits 42% homology with epidermal growth factor (EGF), competes for the EGF receptor and stimulates epithelial and endothelial cells. TGF-β is a highly conserved dimeric polypeptide with a molecular weight of 2500 Da and consists of two amino acid chains linked together by disulfide bonds. Three forms of TGF-β have been identified namely TGF-β_1, TGF-β_2 and TGF-β_3. TGF β has bifunctional activity wherein it acts as a multifunctional modulator of cell proliferation which can either stimulate for inhibit proliferation in different cell types and within the same cell type.

Cellular role of TGF-α and -β and role in wound healing

Transforming growth factor-α is a polypeptide with an 80% homology with EGF and it binds to the cellular EGF receptor. TGF-β acts as a progression factor for fibroblasts. TGF-β appears to be a major regulator of cell replication and differentiation. It is bifunctional or pleiotropic and can therefore stimulate or inhibit cell growth. TGF-β can also modulate other growth factors such as PDGF, TGF-α and EGF) and fibroblast growth factor (FGF) possibly by altering their cellular response or by inducing their expression. It stimulates mesenchymal cells and inhibits epithelial cell proliferation (14). TGF-β is chemotactic for fibroblasts and may be expected to promote fibroblast accumulation and fibrosis in the healing process. It has a potent effect on matrix synthesis, giving rise to increased production of collagen and fibronectin and decreased production of matrix degrading enzymes. Hence for this reason, it is not clear whether administration of exogenous TGF-β to a healing wound results in accelerated normal healing or simply increased fibrosis and scar formation. It is likely that a balance exists between the inhibitory effects of TGF-β and the stimulatory effects of other factors *in vivo*. TGF-β has a somewhat paradoxical effect on angiogenesis. *In vivo*, it stimulates angiogenesis, yet *in vitro* it blocks both endothelial proliferation and motility (6). TGF-β isoforms have multiple regulatory roles in the synthesis, maintenance and turnover of the extracellular matrix. They increase the collagen synthesis, decreases the activity of inhibitors of these enzymes. The net effect is one that favours the collagenous matrix (7).

Role of TGF in immune regulation and regeneration

Studies with transgenic mice in which the TGF-β gene has been 'knocked out' die a few weeks after birth from a massive diffuse inflammatory syndrome, suggesting that TGF-β plays an important role in Immune regulation (15). TGF-β when injected next to periosteal cells enhanced bone formation. Also TGF-β when injected next to periosteum, induced endochondral bone formation, meaning that an intermediate stage of cartilage formation occurs before bone formation.

TGF-β and gingival overgrowth

Cotrim *et al.* (16) studied the effect of cyclosporine on expression and production of TGF-β and matrix metallo protinases

(MMPs) by human gingival fibroblasts. They concluded that TGF-β1 in an autocrine fashion may contribute to a reduction of proteolytic activity of human gingival fibroblast in cyclosporine induced gingival overgrowth which favours the accumulation of extracellular matrix and may underline the clinical changes which present as gingival overgrowth.

Fibroblast growth factor family

Fibroblast growth factor are membranes of the heparin binding growth factor family. There are seven identified members of the FGF family that have similar activities; mitogenicity for cells of mesodermal and neuroectodermal origin and potent angiogenic activity *in vivo*. However, only the two most thoroughly characterized forms are basic FGF (bFGF) and acidic FGF (aFGF). Both aFGF and bFGF are single chain proteins that are proteolytically derived from different precursor molecule to generate biologically active proteins of 15 000 molecular weight. Atleast four FGF receptors have been identified and cloned from human CDNA. They have been named $FGFR_1$, $FGFR_2$, $FGFR_3$ and $FGFR_4$.

Cellular role of FGF and role in wound healing

The FGFS are believed to act as competence growth factors. They have an ability to bind to heparin and heparan sulphate. Immunohistochemical analysis of tissues for bFGF often reveals bFGF in association with the extracellular matrix and in basement membranes attached to heparan sulphate. Three proteins of the FGF family i.e. aFGF, bFGF and keratronocyte growth factor are thought to be important regulators of wound healing. They stimulate proliferation of most of the major cell types involved in wound healing both *in vitro* and *in vivo*, including vascular endothelial cells, fibroblasts, keratinocytes, chondrocytes and myoblasts. In addition, bFGF induces cell migration, neovascularization and formation of granulation tissue in animal models (11).

Role of FGF in periodontal regeneration

Miki *et al.* (17) demonstrated that bFGF enhanced wound healing and regeneration of the periodontal tissues in experimentally prepared three walled bone defects in beagle dogs. Takayama *et al.* (18) surgically created furcation class II bone defects in non-human primates and examined the efficiency of topical application of FGF-2 with periodontal regeneration in the bony defects. They concluded that a topical application of FGF-2 can enhance considerable periodontal regeneration. Sato *et al.* (19) examined the effects of bFGF on the regeneration of cementum and PDL in experimentally induced partial defects in a beagle dog model. Collagen gel was applied to the defects and root surfaces and the teeth were replanted. The results suggested that bFGF in a collagen gel is a suitable therapy for damaged PDL and could lead to readily achievable methods of treatment for periodontal disease.

Effect of various growth factors on osteoblasts and periodontal ligament cells

Platelet-derived growth factor

Unlike most mesenchymal cells *in vitro*, human osteoblasts have a relatively large number of PDGF-α receptors and generally respond well to PDGF-AA and PDGF-BB. Exogeneous PDGF has an initial effect of stimulating bone resorption in organ culture but ultimately stimulates an increase in the formation of new bone (5). It stimulates mitogenic activity and chemotaxis in osteoblasts.

Platelet-derived growth factor is a potent mitogen for PDGF derived cells. Piche *et al.* (20) in isolated cells from the periodontal ligament and demonstrated that PDGF-stimulated their proliferation. Matsuda *et al.* (21) reported that PDGF is highly mitogenic and chemotactic for cells derived from healing socket coagulum which they report as periodontal ligament cells. Nevins *et al.* (22) placed decalcified freeze dried bone allograft saturated with purified recombinant human platelet derived growth factor-BB (PDGF-BB) in intrabony defect/molar class II furcation defect in adult patients with advanced periodontitis. Histologic evaluation revealed regeneration of a complete periodontal attachment apparatus including new cementum, PDL and bone in sites treated with rhPDGF.

Insulin-like growth factor

Insulin-like growth factor-I and IGF-II are usually thought of as growth factors secreted by osteoblasts during bone formation to increase the number of osteoblasts and thereby accelerate bone deposition. IGF are also deposited in bone matrix. When the bone matrix is resorbed, IGFs are released to coupled new bone formation to bone resorption. The presence of IGF in platelets would be expected to act on precursors of osteoblasts. Thus, IGF are mitogenic to osteoblast lineage and are also stimulators of bone formation from existing differentiated osteoblasts (23). Blom *et al.* (24) showed that IGF-I has a potential to enhance the DNA synthesis of PDL fibroblasts likely via binding to

high-affinity cell surface receptors, without inducing changes in the morphology and growth pattern.

Transforming growth factor

Transforming growth factor-β generally acts as a weak mitogen for human osteoblastic cells. While the effects on proliferation are biphasic i.e. stimulating or inhibitory depending on the concentration and cell type, TGF-β generally increases bone matrix formation by cells of the osteoblastic lineage (25). TGF-β may be involved in coupling bone resorption to bone formation. This hypothesis is supported by evidence that relatively large amounts of activated TGF-β are released from resorbing bone after stimulation with calciotrophic hormones. This release is likely to occur as bone matrix is resorbed because it is a large storage site for TGF-β and because acidic environments generated during bone resorption are capable of activating TGF-β. Oates *et al.* (26) compared the mitogenic activity of TGF-β with interleukin-1 and PDGF in fibroblast cells derived from periodontal ligament explants. TGF-β was relatively a weak mitogen for PDL cells compared to PDGF. The response to TGF-β was delayed compared with the response to PDGF, suggesting that TGF-β may indirectly stimulate DNA synthesis.

Fibroblast growth factor

Hauschka *et al.* showed that bFGF and aFGF are stored in bone matrix and may be an important factor in regulating osteoblastic cells (5). Terranova *et al.* demonstrated that PDL cells responded to dentin bound b-FGF as a potent mitogen and chemoattractant (5). Topical application of bFGF may promote periodontal regeneration.

Synergistic effect of growth factors and interaction between growth factors

Lynch *et al.* tested the hypothesis that a combination of PDGF and IGF-I may enhance regeneration of both soft and hard tissue components of the periodontium *in vivo* in 13 beagle dogs. Two quadrants received a combination of recombinant PDGF and IGF-I in a methyl cellulose gel while the contralateral quadrant received gel alone. Combination of growth factors resulted in an increased bone metabolism for 4 weeks after application and increased bone and periodontal regeneration at 4 and 5 weeks after application compared to control sites (8, 9). Giannobile *et al.* (27) compared the effects of a single application of PDGF-BB or IGF-1 individually to or the combination of PDGF-BB and IGF-1 on periodontal regeneration in moderate periodontal defects in cynomologous monkeys. Either a methylcellulose gel or a vehicle containing either PDGF-BB, IGF-1 or both in combination was applied to ligature induced periodontal exposed root surfaces. At both 4 and 12 weeks, control sites revealed minimum osseous defect fill and new attachment. Sites that were treated with combination resulted in significant increase in new attachment and osseous defect fill above control and individual treated sites at both 4 and 12 weeks. IGF-1 and PDGF-BB possess opposing effects on collagen because IGF-1 decreases collagen degradation in foetal rat calvarial cultures, while PDGF-BB does not appear to directly promote collagen synthesis and in fact stimulates MMP type I. Thus when the two factors are combined, PDGF-BB may promote increased cell replication, while IGF-1 may nullify collagen degradation resulting from PDGF giving an increase in collagen content (27). Saygin *et al.* (28) determined the effects of specific growth factors IGF-1, PDGF-BB and TGF-β on cementoblasts *in vitro* and *ex vivo*. Osteocalcin promoter driven transgenic mice were used to obtain immortalized cementoblasts. Growth factor effects on DNA synthesis were assayed by thymidine incorporation. All growth factors stimulated DNA synthesis compared to controls. Results indicated that IGF-1, PDGF-BB and TGF-β influence mitogenesis and biomineralization potential of cementoblasts suggesting that such factors alone or in combination with other agents may provide trigger factors required for regenerating periodontal tissues.

Delivery systems

Although the use of biologic modifiers to treat periodontal diseases has not reached the level of development necessary to ensure predictable results, knowledge of the biology involved surpasses knowledge of how to deliver these agents for optimal results. Studies focused on the biology are important, at the same time, however, studies to determine the mode of administration are critical and are currently under intense investigation.

Ideal characteristics of delivery agents

- Should be biocompatible (23)
- Should be non-toxic
- Easy to handle
- Release kinetics to be considered
- Characteristics of resorbability and retrievability

Agents used for delivery

- Methyl cellulose
- Osseous grafts
- Collagen gels and collagen-based sutures and haemostatic sponges
- Collagen membranes
- Synthetic polymer material

Growth factors were previously applied to wound spaces along with carriers such as methyl cellulose or collagen matrix. Certain disadvantages observed with these materials are that they Affect the half-life of the growth factors in the wounds or wound healing. e.g. PDGF-B applied with methyl cellulose was quickly cleared from the wounds along with the carrier within several days (29). Also Prolonged presence of insoluble collagen in the wound spaces may hinder and delay the formation of new periodontal tissue until it is cleared from the wound space. Osseous grafts have been used for decades to treat periodontal defects and are a valuable source of biologic mediators. Type I collagen gels have been extensively investigated for their space filling properties as well as for their ability to resorb and release putative biologic mediators in wound healing situations. Collagen-based sutures and haemostatic sponges have been used extensively in medicine and dentistry. Resorbable collagen barriers have been used clinically for guided tissue regeneration procedures; however, their combination with biologic modifiers has not been explored.

Discussion

Growth factors are a group of naturally occurring proteins exhibiting varied potent local properties. These molecules are key regulators of such biological events as migration, attachment and proliferation of nearly all cell types. While PDGF and FGF are competence factors, IGF and TGF-β function as progression factors. PDGF and IGF are critically important in the embryologic development of the skeleton. PDGF is an important stimulator of cellular chemotaxis, proliferation and matrix synthesis enhancing influx of fibroblasts into the wound site and increases extracellular matrix production. PDGF being mitogenic and chemotactic for osteoblasts and fibroblasts, functions as an anabolic factor in bone. Both PDGF and IGF exhibit anti apoptotic activity. TGF-β acts as a multifunctional modulator of cell proliferation which can either stimulate or inhibit proliferation in different cell types and within the same cell type. It helps in synthesis of collagenous matrix and regulates extracellular matrix and is a weak mitogen for osteoblastic cells. TGF-β also has an important role in immune regulation. FGF promotes promotion of most of the major cell types including capillary and vascular endothelial cells. bFGF binds to heparin/heparin sulphate which ultimately helps in cell division. Topical application of bFGF may promote periodontal regeneration.

Different growth factors are now on the way to entering clinical practice in dentistry. Hence, it is of utmost importance to assess systematically the effect of the growth factors on the healing of intra-oral bone defects. Current knowledge suggests certain advantages and disadvantages to the use of certain growth factors. Lynch and co workers and many others have suggested that while the effect of IGF-1 alone had only a slight effect on the PDL cells, a combination of PDGF and IGF caused an increased mitogenesis, migration and metabolism of periodontal ligament cells. Hence, it seems more favourable to use a combination of growth factors to predict better regeneration than experimenting with individual growth factors.

There is no definite answer to the question as to which growth factors will promote regeneration of the periodontium. The study of interaction between multiple growth factors on bone metabolism is important because numerous growth factors are sequestered in bone matrix at high concentration and these bone cells release different growth factors. Also during repair, temporal expression of many growth factor genes takes place. Hence potential interaction of various growth factors may exist during development and repair of tissues.

Conclusion

Regeneration of the periodontal tissues is a dynamic process involving cell-to-cell and cell–extracellular matrix interactions. Growth factors elegantly co-ordinate these interactions resulting in wound healing and regeneration of tissues. A review of the current existing literature shows that a combination of growth factors in an optimal concentration is best suited for periodontal regeneration. Combinations of PDGF and IGF have been considered attractive candidates for regenerative therapies. With the advent of the recombinant technique it is now possible to provide large quantities of purified growth factors for use in *in vivo* studies. Present studies are focusing on the development of a suitable carrier material that has mechanical properties and surgical practicality appropriate for controlled release of growth factors. On going human clinical trials assessing the potential therapeutic use of growth and differentiation factors 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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