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## RESEARCH ARTICLE

# GROWTH FACTORS IN PERIODONTAL REGENERATION: A REVIEW

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**ABSTRACT**

Periodontitis is a bacterial infection that results in destruction of attachment fibers and supporting bone. The ultimate goal of periodontal treatment is the regeneration of periodontal structures lost during periodontal disease. Periodontal regeneration result in functionally aligned periodontal ligament fibers between newly formed bone and root surface. The regeneration of periodontal tissue requires an appropriate biological environment which induces the differentiation of undifferentiated cells to make required structures. Various molecules such as growth factors and cytokine plays a vital role in regeneration. Growth factors (GFs) are natural biological mediators that regulate key cellular events that are part of tissue repair and regeneration. Growth factors perform their action by binding to specific cell-surface receptors present on various target cells including osteoblasts, cement oblasts and periodontal ligament fibroblasts. Growth factors participate in cell function led to exogenous application during periodontal tissue repair aiming to their use as an alternative therapeutic approach to periodontal therapy. The aim of this article is to review the literature with respect to biological actions of PDGF, TGF, BMP, FGF, IGF and EGF on periodontal cells and tissues, which are involved in periodontal regeneration.



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## INTRODUCTION

Periodontitis is an inflammatory disease characterized by destruction of periodontal ligament, root cementum and alveolar bone as a tissue response to microbial plaque accumulation on tooth root surface. The repair of periodontal structures constitutes a complex biological process regulated among other by interactions between hormones and growth factors triggering a series of cellular events leading to tissue formation. Periodontal therapyaims at regeneration of the periodontal tissues, i.e. the restoration of their form, architecture and function. Different cell types, cellular activity, microbial and cytokine environment as well as host response play an important role. Therefore wide range of treatment modalities are developed to attain primary goal. Different periodontal treatment includes conventional methods such as scaling and root planning, periodontal surgery with or without osseous surgery and new approaches such as root conditioning agents, guided tissue regeneration, the use of different grafting materials. Growth factors are biologically active polypeptide hormones, which affect the immune function as well as proliferation, chemotaxis and differentiation of cells from the epithelium, connective tissue and bone (Bartold *et al.,* 2000).

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They bind to specific cell-surface tyrosine kinases receptors (Terranova and Wikesjo 1987, Posenkarz ana Kazlaukas 1999), which are present on varioustarget cells including cememntoblasts, periodontal ligament, osteoblasts and fibroblasts (Howell *et al.,* 1996). The effect of different growth factors depend on the quantity used and type of carrier that the growth factors is combined with, affecting also their release time.

### Feautures of growth factors

1. Natural cell products: Growth factors are natural cell products that are release or activated when cell division is necessary. This action occurs during the events such as tissue regeneration or wound healing.
2. Local action: Except few, growth factors act locally.
3. Receptor activity: Growth factors can't diffuse across the cell membrane, they exert their activity by first binding to high-affinity cell membrane receptors. The capacity of cell to respond to growth factors depend on presence of these factors.
4. Regulation: The production of polypeptide growth factors is tightly regulated in normal cells.
5. Multifunctional activity: Polypeptide growth factors stimulate wide variety of cellular activities, which include growth, migration, differentiation and production of extracellular matrix proteins.

**Classification of growth factors**

| GROWTH FACTOR FAMILY | MEMBERS |
|---|---|
| Platelet derived growth factor family | PDGF-AA<br>PDGF-BB<br>PDGF-AB<br>PDGF-CC<br>PGGF-DD |
| Vascular endothelial growth factor family | Vascular endothelial growth factor family A (VEGF-A)<br>Vascular endothelial growth factor family B (VEGF-B)<br>Vascular endothelial growth factor family C (VEGF-C)<br>Vascular endothelial growth factor family D (VEGF-D)<br>Vascular endothelial growth factor family E (VEGF-E)<br>Vascular endothelial growth factor family F (VEGF-F)<br>Placenta derived growth factor (PIGF) |
| Transforming growth factor beta superfamily | TGF-$_{\beta}$<br>Inhibins<br>Activin<br>Anti-mullerian hormone<br>Bone morphogenetic protein<br>Decapentaplegic<br>Vg-1 |
| Epidermal growth factor family | Epidermal growth factor<br>TGF-α<br>Schwannoma- derived growth factor<br>Heparin –binding EGF (HB-EGF)<br>Betacellulin<br>Epiregulin<br>Neuregulin (NRG) family |
| Fibroblast growth factor family | Acidic FGF (a FGF, FGF-1)<br>Basic FGF (b FGF, FGF-2)<br>Int-2 (FGF-3)<br>Hst/KS3 (FGF-4)<br>FGF-5<br>FGF-6<br>Kerationcyte growth factor (FGF-7)<br>FGFs 11-14<br>FGF-15<br>FGFs 16-19<br>FGF-20 (XFGF-20)<br>FGFs 21-23 |
| The insulin family | Insulin like growth factors-I (IGF-I)<br>Insulin like growth factor-II (IGF-II) |
| Hepatocyte growth factor family | Hepatocyte growth factor (HGF)<br>Macrophage-stimulating protein (MSP) |
| Colony-stimulating factors (CSF) | IL-3<br>Macrophage- CSF (M-CSF)<br>Granulocyte-CSF (G-CSF)<br>Erythropoietin |
| Neurotrophin family | Neurotrophic factor<br>Brain- derived neurotrophic factor (BDNF)<br>Neurotrophin-3 (NT-3)<br>NT-4<br>NT-5<br>NT-6 |

**Mode of action of Growth Factors (GFs)**

Local mode of action of growth factors (GFs) involve paracrine, autocrine, juxtacrine and intracrine modes.

**Autocrine mode of action:** Growth factors are synthesized by one cell, secreted in a soluble form outside the cell and then it binds to surface receptor on the same cell to evoke effect in autocrine mode of action.

**Intracrine mode of action:** Growth factors are produced by one cell and not secreted, but acts intra-cellularly to facilitate its effects is intra-crinemode of action.

**Paracrine mode of action:** Growth factors are produced by one cell, with receptors present on other cell in local micro environmentis paracrine mode of action. In this mode the mediators are secreted in soluble form and binds to its receptors on target cell to evoke its effect.

**Juxtacrine mode of action:** Its mode of action is similar to paracrine effect except that the factor produced by the cell of origin is a cell surface bound and require cell contact by the target cell to evoke a response.

**Platelet-Derived Growth Factor (PDGF)**

PDGF was originally purified from human platelets. Kohler and Lipton (1974) and Ross *et al.,* (1974) discovered that the bioactive mediators released from the platelets are principal source of mitogenic activity present in serum, and responsible for growth of many cells in culture that are serum dependent. PDGF has been found to be produced by various other cells, monocytes, megakaryocytes, vascular endothelium, smooth muscles cells, and transformed cells (Ross *et al.,* 1986; Raines *et al.,* 1990). PDGF contain two polypeptide chains forming three isoforms either as a homodimer (AA or BB) or as a heterodimer (AB). Research data indicated that PDGF A and B chains are present in gingival epithelium with PDGF-A playing

an important role during early stages of wound healing while PDGF-B appears later (Green *et al.,* 1997). The biologic effects of PDGF are mainly initiated via two tyrosine kinase receptors termed alpha and beta PDGF receptors (Rosenkranz and kazlauskas 1999) which are differentially expressed by normal and regenerating periodontal cells indicating that PDGF is involved in complex pattern in healing events (Parker *et al.,* 2001). PDGF receptors can be degraded via direct proteolysis on cell surface by elastase, which is an essential factor for host defense and has the ability to degrade extracellular matrix proteins and this fact would not be advantageous for periodontal regeneration (Nemoto *et al.,* 2005).

**Actions of PDGF**

PDGF is a chemoattractant forfibroblasts, leukocytes and smooth muscle cells. It acts synergistically with IGF-I, promoting protein synthesis and production of ECM. It has mitrogenic effects on osteogenic cells, promoting their proliferation and migration in the healing area. It also promotes synthesis of fibronectin and collagen type I, III and V. It inhibits collagenase and plasminogen activator. PDGF up-regulates the expression of angiogenic molecule like vascular endothelial growth factor (VEGF) and hepatocyte growth factor, and also the proinflammatory cytokine interleukin-6, thereby indirectly promoting periodontal regeneration. The recombinant human PDGF-BB (GEM2 IS) has received FDA clearance for use. The vehicle used for GEM2 IS is tricalcium phosphate which provide appropriate localized concentration of PDGF at the wound site for sufficient period of time, facilitating its desired effects during healing.

**Transforming Growth Factor (TGF)**

**Transforming growth factor-α (TGF-α):** It belongs to epidermal growth factor family(EGF) or cytokines. It is mitogenic polypeptide and secreted protein which is expressed by monocytes, keratinocytes and various tumor cells. EGF and TGF-α are equipotent at inducing in vitro endothelialcell proliferation and bind equally to endothelial cell EGF receptor. It acts synergistically with TGF-β to stimulate anchorage-independent cell proliferation and produce a mitogenic response.

**Transforming growth factor-β (TGF-β):** TGF-β belongs to TGF-β superfamily, which has many multifunctional structurally related growth and differentiation factors associated to the inflammatory response. These factors play an important role in apoptosis, angiogenesis, wound healing and fibrosis. TGF-β is a highly conserved dimeric polypeptide with a molecular weight of 2500 Da and consists of two amino acids chains linked together to disulphide bonds. It is found in highest concentrations in bone and platelets. TGF-β is encoded by three different genes TGF-β1, TGF-β2 and TGF-β3. TGF-β1 contains 390 amino acids and TGF-β2 and TGF-β3 each contains 412 amino acids. TGF-β increases the biosynthesis of collagen type I, fibronectin and osteocalcin, as well as bone matrix deposition and chemotaxis of osteoblast. TGF-β can also modulate other growth factors such as PDGF, TGF-α, EGF and FGF by altering their cellular response or by inducing their expression. It also has marked effect on ECM homeostasis, being an important mediator fibroblast proliferation and ECM synthesis. It also stimulate mesenchymal cells and inhibits epithelial cell proliferation. During healing process, it promotes collagen fiber deposition and causes fibrosis which is related to gingival enlargement during inflammation.

**Actions of TGF-β**

- It acts as an important factor for fibroblast migration and proliferation.
- It has pleiotropic affects on cell proliferation, which can either stimulate or inhibit proliferation in different cell types and within same cell type.
- It promotes synthesis of collagenous matrix and regulates extracellular matrix.
- A weak mitogen for osteoblast cells.
- It may play an important role in immune regulation.

**Bone Morphogenetic Proteins (BMPs)**

BMPs belong to the transforming growth factor-β (TGF-β) superfamily, which consists of group of related peptide growth factors. They help in numerous cellular functions including development, morphogenesis, cell proliferation, apoptosis and ECM synthesis. Thus, the main action of BMPs is to commit undifferentiated pluripotent cells to differentiate into cartilage and bone forming cells (Ripamonti and Reddi, 1994; Wozney,1992).

**Properties of BMPs**

- They act as mitogens on undifferented mesenchymal cells and osteoblast precursor.
- BMPs induce bone formation, whereas other growth factors such as TGF-β 1 and PDGF do not.
- BMPs have an anabolic effect on periodontal tissue through the stimulation of osteoblastic differentiation in human periodontal ligament (PDL) cells (Eickholz *et al.,* 2007).
- BMP 2-12 singly initate de novo endochondral bone formation (Celeste *et al.,* 1990; Urist, 1965).
- They induce the expression of osteoblast phenotype (i.e. increase in alkaline phosphatase activity in bone cells).
- Act as chemoattractants for mesenchymal cells and monocytes as well as bind to extracellular matrix collagen type-IV (Paralkar *et al.,* 1990).

**Structure of BMPs**

The BMPs are 30 to 38-KDa homodimers, glycosylated proteins. The individual BMP proteins are synthesized by cell which then dimerize and become glycosylated. The BMPs have been grouped into subsets based on amino acids sequence homology. The grouping are as follows:

1. BMP-2 and BMP-4
2. BMP-3 and BMP-3b
3. BMP-5, BMP-6, BMP-7 and BMP-8
4. BMP-9 and BMP-10
5. BMP-12, BMP-13 and BMP-14 and
6. BMP-11 and growth/differentiation factor 8 (GDF-8).

**Role of BMPs in periodontal regeneration**

BMPs possess a structure/activity profile with BMP-2 exhibiting mainly osteogenic properties while BMP-7 was mainly cementogenic in its activities. Recombinant human morphogenic protein-2 (rhBMP-2) has been used to investigate

periodontal regeneration. Sigurdsson *et al.,* (1995) and Kinoshita *et al.,* (1997) successfully achieved periodontal regeneration in dogs using rhBMP-2 and a systemic carrier. Clinical trials using rhBMP-2 in an absorbable collagen sponge carrier (Howell *et al.,* 1997; Cochran *et al.,* 2000) have yielded encouraging results with the protein and the carrier well tolerated, locally and systemically.

**Delivery system for BMPs**

Three approaches which have been used for BMP delivery. These include gene-based, cell-based, and protein-based approach for BMP delivery. The gene-based and cell-based BMP delivery system are still being researched and are in their infancy stage. Presently, the protein-based approach has been used for BMP delivery. A delivery system should have some basic properties for delivery of bioactive molecules. These include,

- It should be biocompatible
- It should be biodegradable
- It should have structural integrity
- It should be free of immunogenicity
- It should release the bioactive molecule at an appropriate rate
- It should be cost effective and easy to handle.

**Fibroblast Growth Factors (FGF)**

These are family of structurally related strongly heparin binding peptides that have been implicated in healing and regeneration. Till date 23 distinct FGFs have been discovered.

**Fibroblast growth factor-1 (FGF-1)/acidic FGF (a FGF):** FGF-1 has an isoelectric range of 5.6-6.0 and a molecular weight of approximately 15,000 Da. It is a 155 amino acid protein. This protein functions as a modifier of endothelial cell migration and proliferation, as well as angiogenic factor. It acts as a mitogen for variety of cells. FGF-1 is considered to function in several important physiological and pathological processes, such as embryonic development, morphogenesis, angiogenesis and wound healing.

**Fibroblast growth factor-2 (FGF-2)/ basic FGF (b FGF):** FGF-2 has an isoelectric point of approximately 9.6 and has a molecular weight in the range of 16,000-18,000 Da. It has low molecular weight (LMW) and high molecular weight (HMW) isoforms. LMW FGF-2 is primarily cytoplasmic and functions in an autocrine manner, whereas HMW FGF-2 is nuclear and exert activities through intracrine mechanism (Arese *et al.,* 1999).

**Action of FGF**

**At cellular level**

- FGFs are considered to be competence growth factors. A competence growth factor is the one which stimulate resting cells in G0 phase to enter the cell cycle in G1 phase.
- They are associated with increased mitogensis of cells.
- It is found in association with the ECM in the basement membranes and is attached to hepran sulphate, which provide protection from degradation and allows it to maintain it biological potential.

**During wound healing**

- They play important role during wound healing. The FGF-1, FGF-2 and keratronocyte growth factor (KGF) are primary FGFs involved in wound healing.
- They stimulate proliferation of most of the major cell type involved in wound healing including vascular endothelial cells, fibroblasts, keratinocyte and chondrocytes.
- FGF-2 also stimulates epithelisation, fibronectin, proteoglycans and collagen synthesis.
- FGF-2 stimulates periosteum derived cells in early stages of bone healing.

**Angiogenesis**

- FGF-2 has ability to induce all steps necessary for new blood vessel formation both in vivo and in vitro. It regulates the production of collagen type-I and laminin by PDL cells.
- FGF-1 stimulates endothelial cell proliferation which enhances new blood vessel proliferation in healing area.

**Effect on PDL cells**

- They have chemotactic and mitogenic effects on PDL cells.
- Due to overall effects, they play vital role in periodontal regeneration.

**Insulin-like growth factors (IGFs):** IGFs are first described in 1957 by Salmon and Daughaday (Salmon *et al.,* 1957). They are family of mitogenic proteins that control growth, differentiation and maintenance of differentiated function, in numerous tissues. The IGF family include three ligands (insulin, IGF-I and IGF-II), their corresponding cell surface receptors (IR, IGF-IR, and IGF-IIR), and atleast six IGF-binding proteins (IGFBPs).

**Insulin-like growth factor-I (IGF-I):** IGF-I is a 70-amino acid protein with a molecular weight of 7649 Da and an isoelectric point of 8.4. It has endocrine, paracrine and autocrine effect. It is mainly produced by liver but virtually every tissue is able to secrete IGF-I for autocrine/paracrine purposes.

**Actions of IGF-I**

**Growth and development**

- Play important role in fetal growth and differentiation.
- It has important role during central nervous system development, where it act as a neuroprotector.
- It has important roleIn cardiovascular system. It has been shown that IGH-I and its receptors are expressed in myocardium and both aortic smooth muscles and endothelial cells (Delafontaine *et al.,* 1991).
- IGF-I plays important role in T-lymphocytes development and function. It can increases the number of CD4+ CD8+ immature T-cells, promotes T-cells

survival proliferation, chemotaxis and maturation (Tu *et al.,* 2000).

**Effect at cellular level**

- It is powerful chemoattractant of fibroblasts and it lead to periodontal regeneration by stimulating the formation of mesenchymal tissues including collagen, bone and cementum (Skottner *et al.,* 1989).
- It upregulates cementoblast mitogenesis, phenotypic gene expression, and mineralization (Saygin *et al.,* 2007).
- IGF-I has demonstrated a capacity to increase bone cell mitoses and increase the deposition of matrix.

**Role in wound healing:**

- IGF-I is an important factor involved during wound healing because it is mitogenic for keratinocytes and is a potent chemotactic agent for vascular endothelial cells. Its levels are increased at healing sites suggesting that its presence is requires for adequate wound healing (Werner and Grose, 2003).

**Effect on periodontal ligament cells**

- In general, IGF increases fibroblast proliferation. One study demonstrated the mitogenic effects of IGF-I on PDL fibroblastic cells and concluded that a synergistic effect result from using a combination of PDGF-AB and IGF-I.

**Insulin-like growth factor-II (IGF-II)**

IGF-II[also known as multiplication stimulating activity (MSA)] is a 67- amino acid neutral peptide with a molecular weight of 7471 Da. IGF-II binds to IGF-II receptor (IGF-IIR), to IGF-IR and weakly to insulin receptor. It is not as potent as IGF-I. Less research data is available for IGF-II in relation to periodontal regeneration. The effect of IGF-II on metabolism of gingival fibroblasts is still uncertain.

**Epidermal growth factor (EGF)**

The EGF is a multifunctional cytokine involved in a variety of functions, including epithelial growth and differentiation and wound healing. In 1986, Stanley Cohen received noble prize for his work elucidating the role of ECF in regulation of cell growth and development (Cohen, 1986). The EGF is a small protein comprising of 53 amino acids. It is produced by epithelial cells, fibroblasts and many other cell types. It is found in membrane associated and soluble form. Both soluble and membrane associated forms of EGF are active. Its actions are activated with its attachment to epidermal growth factor receptor (EGF-R). The EGF-R has 3 major regions:

1. Extracellular domain which contains growth factor.
2. Hydrophobic transmembrane domain.
3. Cytoplasmic domain which contains tyrosine specific protein kinase.

EGF appeared to enhance slightly chemotaxis and to suppress matrix synthesis in rat PDL cells (Matsuda *et al.,* 1992). However, EGF restricted cell differentiation and up-regulated EFG-R expression, which is down regulated in the process of differentiation (Matsuda *et al.,* 1993). EGF receptors decreases when cells differentiate into cell types capable of forming mineralized tissues suggesting that EGF receptors may participate in phenotype stabilization of PDL cells. The interaction between mechanical stress and the EGF/EGF-receptor system might participate in osteoblastic differentiation of human PDL cells and regulate PDL as a source of cementoblasts and osteoblasts. EGF-R appeared to be present in very low amounts in the gingival connective tissue andthe epithelium of normal gingiva, while increased levels of EGF-R were observed in cells from regenerated tissues (Parkar *et al.,* 2001). Although, a lot of research work is going on EGF, but the effect of EGF on periodontal wound healing in vivo remains to be investigated.

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