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# An Outline Overview On Growth Factors – A Novel Paradigm In Periodontal Regeneration

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**Abstract**

Periodontal regeneration is aided by growth factors, which are tiny polypeptide molecules. They act as biologic mediators that control cell division, proliferation, and growth, with the cell cycle being their primary focus. They make it easier for stem cells to differentiate into the appropriate cell lines, allowing for proper tissue regeneration. Commercial preparations for clinical usage are available.

***Keywords: growth, differentiation, polypeptides, regeneration, periodontal tissues.***

## I. Introduction

Periodontitis is an inflammatory illness marked by the loss of the periodontal ligament, root cementum, and alveolar bone as a tissue reaction to the deposition of microbial plaque on the tooth root surface.[1] Periodontal structure repair is a complex biological process regulated, among other things, by interactions between hormones and growth factors, which start a series of cellular events that lead to tissue development. The goal of periodontal therapy is to regenerate periodontal tissues, restoring their form, architecture, and function.[2]

Growth factors are biologically active polypeptide hormones that influence immunological function such as epithelial proliferation, chemotaxis, and differentiation, as well as connective tissue and bone. They bind to specific cell-surface tyrosine kinase receptors found on cementoblasts, periodontal ligament, and fibroblasts, among other target cells.[1,2]

## II. Features of growth factors[3]

**Natural Cell Products:** Growth factors are products that are released or activated when they are required. This activity takes place during processes like tissue regeneration and wound healing. **Local action:** Growth factors, with the exception of a few, act locally. **Receptor activity:** As they grow across the cell membrane, they begin by attaching to high-affinity cell membrane receptors. The presence of these factors determines a cell's ability to respond to growth factors. **Regulation:** In a normal situation, the production elements are strictly managed. **Multifunctionality:** Polypeptide growth factors promote a wide range of cellular functions, including growth, migration, differentiation, and production.

## III. Mode of action of Growth Factors (GFs)[1]

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**Local mode of action of growth factors (GFs)** involves paracrine, autocrine, juxtacrine and intracrine modes. **Autocrine mode of action:** Growth factors are produced by one cell, released in a soluble form outside the cell, and then bind to a surface receptor on the same cell to elicit an effect in an autocrine manner. **Intracrine mode of action:** Growth factors are synthesised by a single cell and are not secreted; nonetheless, their intracrine mechanism of action allows them to work intracellularly to facilitate their effects. **Paracrine mode of action:** The paracrine method of action occurs when one cell produces growth factors and their receptors are found on other cells in the nearby microenvironment. The mediators are produced in soluble form in this method, and they bind to receptors on target cells to elicit their impact. **Juxtacrine mode of action:** It works in the same way as a paracrine effect, only the factor produced by the source cell is cell surface bound and requires cell contact by the target cell to elicit a response.

## IV. Various growth factors in periodontal regeneration

### Platelet derived growth factor

PDGF is a growth factor produced by platelets. Human platelets were used to purify PDGF at first. The bioactive mediators generated by platelets are the primary source of mitogenic activity present in serum, and are responsible for the development of many serum-dependent cells in culture, according to Kohler and Lipton (1974) and Ross et al (1974).[4] Other cells, such as monocytes, megakaryocytes, vascular endothelium, smooth muscle cells, and altered cells, have been discovered to generate PDGF.[4]

PDGF is made up of two polypeptide chains that combine to generate three isoforms, either as a homodimer (AA or BB) or a heterodimer (AA or BB) (AB). According to research, both PDGF A and B chains are found in the gingival epithelium, with PDGF-A playing a key role during the early stages of wound healing and PDGF-B appearing afterwards. The physiologic actions of PDGF are primarily mediated by two tyrosine kinase receptors known as alpha and beta PDGF receptors, which are expressed differently in normal and regenerating periodontal cells, showing that PDGF is engaged in a complicated network of healing activities.[5]

Elastase, an essential component for host defence and capable of degrading extracellular matrix proteins, can damage PDGF receptors via direct proteolysis on cell surface, which is not helpful for periodontal regeneration.

### Actions of PDGF

Fibroblasts, leukocytes, and smooth muscle cells all respond to PDGF as a chemoattractant. It works in tandem with IGF-I to promote protein synthesis and ECM formation. It promotes the proliferation and migration of osteogenic cells in the healing area by having mitogenic actions on them. It also encourages the production of fibronectin as well as collagen types I, III, and V. Collagenase and plasminogen activator are both inhibited by it. PDGF increases the expression of angiogenic molecules including VEGF and hepatocyte growth factor, as

well as the proinflammatory cytokine interleukin-6, supporting periodontal regeneration in an indirect manner.[5,6]

The FDA has approved the use of recombinant human PDGF-BB (GEM2 IS). The vehicle for GEM 21 S is tricalcium phosphate, which provides a sufficient localised concentration of PDGF at the wound site for a long length of time, allowing it to have its desired effects during healing.[6]

**Transforming Growth Factor (TGF)**

**Transforming growth factor-α (TGF-α):** It is a member of the EGF (epidermal growth factor) or cytokine family. Monocytes, keratinocytes, and different tumour cells express this mitogenic polypeptide and secreted protein. EGF and TGF-alpha are equally effective at inducing endothelial cell proliferation in vitro and bind to the EGF receptor in endothelial cells. It works in tandem with TGF-beta to promote anchorage-independent cell proliferation and elicit a mitogenic response.[7]

**Transforming growth factor-β (TGF-β):** TGF- β is a member of the TGF- β superfamily, which includes a number of multifunctional, structurally related growth and differentiation factors that are linked to the inflammatory response. Apoptosis, angiogenesis, wound healing, and fibrosis are all affected by these variables. TGF- β is a dimeric polypeptide with a molecular weight of 2500 Da that is made up of two amino acid chains joined together by disulphide linkages. [7] The largest quantities are found in bone and platelets. TGF-1, TGF-2, and TGF-3 are the three genes that code for TGF- β. TGF-1 has 390 amino acids, while TGF-2 and TGF-3 have 412 amino acids each. TGF- β promotes the synthesis of collagen type I, fibronectin, other proteins, bone matrix deposition and chemotaxis of osteoblast.

**Actions of TGF-β**

It acts as an important factor for fibroblast migration and proliferation. It has pleiotropic effects on cell proliferation, which can either stimulate or inhibit proliferation in different cell types and within the same cell type. It increases collagenous matrix formation and modulates extracellular matrix. [7,8]

**Bone Morphogenetic Proteins (BMPs)**

The transforming growth factor (TGF) superfamily, which includes a set of similar peptide growth factors, includes BMPs. They aid in development, morphogenesis, cell proliferation, apoptosis, and ECM production, among other biological processes. BMPs work by committing undifferentiated pluripotent cells to develop into cartilage and bone-forming cells.[9]

**Properties of BMPs**

BMPs, unlike other growth factors like TGF-1 and PDGF, act as mitogens on undifferentiated mesenchymal cells and osteoblast precursors, causing bone production. BMPs stimulate osteoblastic development in human periodontal ligament (PDL) cells, which

has an anabolic effect on periodontal tissue. De novo endochondral bone formation is initiated by BMP 2-12 alone. They cause the osteoblast phenotype to be expressed (i.e. increase in alkaline phosphatase activity in bone cells). Act as chemo-attractants for mesenchymal cells and monocytes, as well as binding to collagen type IV in the extracellular matrix. [9]

**Structure of BMPs**

BMPs are glycosylated homodimers with a molecular weight of 30 to 38 kDa. Cells generate individual BMP proteins, which then dimerize and become glycosylated. Based on amino acid sequence homology, the BMPs were divided into subgroups.

**Role of BMPs in periodontal regeneration**

BMPs have a structure/activity profile, with BMP-2 having mostly osteogenic capabilities and BMP-7 having primarily cementogenic qualities. Periodontal regeneration has been studied using recombinant human morphogenic protein-2 (rhBMP-2). Sigurdsson et al. (1995) and Kinoshita et al. (1997) used rhBMP-2 and a systemic carrier to successfully regenerate periodontal tissue in dogs. Clinical trials of rhBMP-2 in an absorbable collagen sponge carrier have shown promising results, with the protein and carrier being well tolerated both locally and systemically.[8,11]

**Delivery system for BMPs**

There have been three techniques to delivering BMPs. For BMP delivery, there are gene-based, cell-based, and protein-based approaches. The gene-based and cell-based BMP delivery systems are still in the early stages of development. Currently, BMP is delivered through a protein-based method. For the distribution of bioactive chemicals, a delivery system should have some basic features.[8-10]

**Fibroblast Growth Factors (FGF)**

These are a group of structurally related peptides that bind to heparin and have been linked to healing and regeneration. There have been 23 different FGFs found so far.[11]

**Fibroblast growth factor-1 (FGF-1)/acidic FGF (a FGF):**

FGF-1 has a molecular weight of about 15,000 Da and an isoelectric range of 5.6-6.0. It has 155 amino acids. This protein acts as an angiogenic factor and a modulator of endothelial cell migration and proliferation.[12] It is a mitogen for a wide range of cells. FGF-1 is thought to play a role in embryonic development, morphogenesis, angiogenesis, and wound healing, among other physiological and pathological processes.

**Fibroblast growth factor-2 (FGF-2)/ basic FGF (b FGF):**

FGF-2 has a molecular weight of 16,000-18,000 Da and has an isoelectric point of around 9.6. There are isoforms of low molecular weight (LMW) and high molecular weight (HMW). HMW FGF-2 is nuclear and works in an intracrine manner, whereas LMW FGF-2 is predominantly cytoplasmic and functions in an autocrine manner. [13]

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**Action of FGF at cellular level**

FGFs are considered to be competence growth factors. Competence growth factors are referred to as FGFs. A competence growth factor is one that encourages resting cells in the G0 phase to enter the G1 phase of the cell cycle. They're linked to a higher rate of cell mitosis. It is located in basement membranes in conjunction with the ECM and is coupled to heparan sulphate, which protects it from degradation and allows it to retain its biological potential. They serve a crucial function in the healing of wounds. The key FGFs involved in wound healing are FGF-1, FGF-2, and keratinocyte growth factor (KGF). They promote the growth of most major wound-healing cell types, including vascular endothelial cells and fibroblasts.[14-16]

**Insulin-like growth factors (IGFs)**

Salmon and Daughaday were the first to describe IGFs in 1957.[17] They are a group of mitogenic proteins found in a variety of tissues that regulate growth, differentiation, and the maintenance of differentiated function. Three ligands (insulin, IGF-I, and IGF-II), their cell surface receptors (IR, IGF-IR, and IGF-IIR), and at least six IGF-binding proteins make up the IGF family (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 a molecular weight of 7649 Da and an isoelectric point of 8.4. It works in three ways: endocrine, paracrine, and autocrine. IGF-I is primarily produced by the liver, however it can be secreted by practically any tissue for autocrine/paracrine reasons.

**Actions of IGF-I**

It has an essential function in foetal growth and differentiation, as well as in the development of the central nervous system, where it acts as a neuroprotector. It plays a crucial role in the cardiovascular system. IGH-I and its receptors have been found in myocardial, as well as aortic smooth muscles and endothelial cells. IGF-I is critical for the growth and function of T-lymphocytes. It enhances T-cell survival, proliferation, chemotaxis, and maturation by increasing the number of CD4+ CD8+ immature T-cells. It is a potent fibroblast chemoattractant that promotes periodontal regeneration by encouraging the production of mesenchymal tissues including collagen, bone and cementum. It promotes mitogenesis, phenotypic gene expression, and mineralization in cementoblasts. IGF-I has been shown to enhance the number of bone cell mitoses and matrix deposition. IGF-I is an important factor in wound healing because it is a robust chemotactic agent for vascular endothelial cells and a mitogenic factor for keratinocytes.

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

IGF-II is a 67-amino-acid neutral peptide with a molecular weight of 7471 Da, commonly known as multiplication stimulating activity (MSA). IGF-II binds to IGF-II receptor (IGF-IIR), IGF-IR, and insulin receptor quite weakly. It does not have the same

potency as IGF-I. In terms of periodontal regeneration, there is less research data on IGF-II. The impact of IGF-II on gingival fibroblast metabolism is still unknown.[17]

**Epidermal growth factor (EGF)**

The EGF is a multifunctional cytokine that plays a role in epithelial development and differentiation, as well as wound healing. Stanley Cohen was awarded the Noble Prize in 1986 for his work explaining the role of EGF in cell growth and development regulation. The EGF is a 53-amino-acid protein with a modest size. Epithelial cells, fibroblasts, and a variety of other cell types make it. It comes in two forms: membrane-associated and soluble. EGF is active in both soluble and membrane bound forms. [18]

Its effects 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. [19,20]

**V. Conclusion**

According to a review of several studies, growth factors have a considerable impact on cell behaviour and offer tremendous promise for application in regenerative therapies. However, the regeneration techniques currently in use are extremely technique-dependent, only relevant to a small number of cases that are treatable, and are said to have a low predictability. Significant progress has been achieved in promoting the targeted transport of cells, genes, and proteins to chronic periodontal lesions to overcome these restrictions.

Active research is being conducted to better understand the biology of the healing site, including identifying appropriate cells to target, as well as designing delivery systems that can control the release of agents at the local site, using a variety of multidisciplinary approaches that combine engineering, dentistry, and medicine to create the necessary environment for periodontal regeneration.

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