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BIOLOGICALLY ACTIVE FACTORS IN TREATMENT OF PERIODONTAL DISEASE

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ABSTRACT

Regeneration of periodontal structures lost during periodontal diseases constitutes a complex biological process regulated among others by interactions between cells and growth factors. Growth factors are biologically active polypeptides affecting the proliferation, chemotaxis and differentiation of cells from epithelium, bone and connective tissue. They express their action by binding to specific cell-surface receptors present on various target cells including osteoblasts, cementoblasts and periodontal ligament fibroblasts. The observation that growth factors participate in all cell functions led to exogenous application during periodontal tissue repair aiming to their use as an alternative therapeutic approach to periodontal therapy.Cell types and cultures conditions, dose, carrier materials, application requirements are of critical importance in the outcome of periodontal repair. The purpose of this article is to review the literature with respect to the biological actions of PDGF, TGF, FGF, IGF and EGF on periodontal cells and tissues, which are involved in periodontal regeneration.

INTRODUCTION

Periodontitis is an inflammatory disease characterized by destruction of periodontal ligament, root cementum 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 w proliferation, chemotaxis and differentiation epithelium, connective tissue and bone (Bartold *et al.*, 2000).

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, fibroblasts (Howell *et al.*, 1996). factors depend on the quantity used and type of carrier that the growth factors is combined with, affecting also their release time.

Feautures of Biological Active factors

1. Natural cell products: Growth factors are products that are release or activated when 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 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 factors is tightly regulated in normal

5. Multifunctional activity: Polypeptide growth factors stimulate wide variety of cellular activities, which include growth, migration, differentiation and production of extracellular matrix proteins.

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 upregulates 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-$_\beta$ to stimulate anchorageindependent cell proliferation and produce a mitogenic response.

Transforming growth factor-$_\beta$ (TGF-$_\beta$): TGF-$_\beta$ belongs to TGF-$_\beta$ 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-$_\beta$ 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-$_\beta$ is encoded by three different genes TGF-$_\beta$1, TGF-$_\beta$2 and TGF-$_\beta$3. TGF-$_\beta$1 contains 390 amino acids and TGF-$_\beta$2 and TGF-$_\beta$3 each contains 412 amino acids. TGF-$_\beta$ increases the biosynthesis of collagen type I, fibronectin and osteocalcin, as well as bone matrix deposition and chemotaxis of osteoblast. TGF-$_\beta$ 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-$_\beta$
- 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,

1. It should be biocompatible
2. It should be biodegradable
3. It should have structural integrity
4. It should be free of immunogenicity
5. It should release the bioactive molecule at an appropriate rate
6. 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.

Action of FGF

At cellular level

1. 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.
2. They are associated with increased mitogensis of cells.
3. 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

1. They play important role during wound healing. The FGF-1, FGF-2 and keratronocyte growth factor (KGF) are primary FGFs involved in wound healing.
2. They stimulate proliferation of most of the major cell type involved in wound healing including vascular endothelial cells, fibroblasts, keratinocyte and chondrocytes.
3. FGF-2 also stimulates epithelisation, fibronectin, proteoglycans and collagen synthesis.
4. 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.

CONCLUSION

A review of literature on the use of growth regulatory molecules along with gene therapy permits a model to consider approaches to oral tissue engineering. Devel-opments in polymeric and ceramic scaffolding systems for cell, protein and gene delivery have undergone sig-nificant growth. The tar-geting of signaling molecules or growth factors (via proteins or genes) to the perio-dontium has lead to significant new knowledge regarding use of bioactive molecules to promote cell proliferation, differentiation, matrix biosynthesis, and angiogen esis. For improvements in the outcomes in perio-dontal regenerative medicine, scientists will need to examine dual delivery of host modifiers or anti-infective agents to optimize the results of therapy. For future growth and development in the field of oral tissue engineering, combination of several multi disciplinary approaches including engineering, dentistry and medicine will be needed.

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