Growth Factor: The Benevolence to Periodontal Regeneration

Archana Agroya[1], Vishnudas Bhandari[2] , Om H Baghele[3], Gouri M Ugale[4], Shradda Marde[5], Mukesh Aradle[6]

[1] P.G. Student, [2] Professor & HOD, [3] Professor, [4] Reader, [5,6] Lecturer. Dept of Periodontics, MIDSR Dental College, Latur.

Abstract:

Regeneration of tooth-supporting structure destroyed by periodontitis is a leading goal of periodontal therapy. Growth factors are a cluster of naturally occurring proteins showing various potent local properties. These molecules are vital regulators of biological events such as migration, attachment, and proliferation of nearly all cell types. Regeneration of the periodontal tissues is a dynamic course which involves cell to cell and cell extracellular matrix relations. Growth factors classily co-ordinate these interactions resulting in wound healing and regeneration of tissues. This review discusses and educates the knowledge on various growth factors involved in periodontal repair and regeneration.

Keywords: Periodontitis, Growth factor, Regeneration

Corresponding Author: Dr. Archana Agroya, P.G student, Dept of Periodontics, MIDSR Dental College, Latur. Email id.: archana.agroya@gmail.com

INTRODUCTION

Periodontal disease results in the destruction of periodontal tissue, including cementum, bone and periodontal ligament with the eventual loss of tooth if left untreated.Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or group of a specific microorganism, which results in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both.Therapeutic modalities should aim not only at eliminating the gingival inflammatory process and progression of the diseasebut also at re-establishing and regenerating the periodontal tissue loss due to disease.[1]So recent studies and clinical investigations have resulted in improved therapies for the arrest of disease progression and regeneration of periodontal tissue.

A key factor for enhancing the certainty of regenerative therapies is an understanding of cellular and molecular events required to regenerate periodontal tissue.In nature, the proteins responsible for co-ordinating these events are called growth factors. These naturally occurring molecules with certain matrix protein are key regulators of these biological events. They have been shown to have pleiotropiceffects on wound repair, nearly all tissues including the periodontium.[2]Numerous growth factors have been identified and characterized and are, primarily secreted by macrophages, endothelial cells, fibroblast, and platelet, include platelet-derived growthfactor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) and transforming growth factor (TGF). Through this manuscript, we are reviewing the courage to discover how to use them to accelerate and direct the

healing event into one that will produce periodontal regeneration.

Functions of growth factors[3]

- Promote mitogenesis (proliferation) and direct migration of cells
- Metabolism activity of cells
- Potential to accelerate the healing process
- Enhance tissue regeneration

Platelet-derived growth factors (pdgf)

Platelet-derived growth factor stands as a ubiquitous mitogen which was originally discovered by Kohler & Lipton and Ross et al. in 1974.[4]The source of PDGF was from the alpha granules of platelets but it has also been isolated from a variety of other cells and tissues, which include degranulating platelets, smooth muscles, fibroblasts, endothelial cells, macrophages, keratinocytes and many tumor cells.It consists of two disulfide-bonded polypeptides chains encoded by two different genes, PDGF-A AND PDGF-B which are located on chromosomes 7 and 22, respectively. Consequently, PDGF can exist as a heterodimer (AB) or a homodimer (AA, BB). PDGF is the natural wound healing "hormone" which is naturally produced by the body at sites of soft tissue and bone injury.[5]Heldin et al. in 2002 hasidentified two new forms, PDGF-C and PDGF-D. A and B can form homodimers or heterodimers, such as AA, BB, or AB, whereas C and D can only form the homodimers CC or DD.[6]Also, platelet-derived growth factor has been identified as a naturally occurring protein in the bone matrix. PDGF stimulates cell proliferation at physiological concentrations ranging between 0.1 and 1ng/ ml, and this response can be enhanced through crosstalk with v3 integrin.[7]

ROLE OF PDGF

Platelet-derived growth factor stimulates cell chemotaxis in different cell types, including monocytes, gingival fibroblasts, and periodontal ligament cells.PDGF induced chemoattraction and can be described through the activation of Rac, a GTPase involved in actin remodeling and lamellipodia formation. Excision of the Rac1 gene from epidermal cells has been related with delayed closure of cutaneous wounds, and adenoviral gene transfer of PDGF into gingival fibroblasts induces a sustained cellsignaling response responsible for activating focal adhesion kinase, Akt, and Pak, among others.Therefore, the actin cytoskeleton is effectively modified by the action of PDGF in periodontal cells.[8]Both preclinical and clinical assays have estimated the therapeutic potential of PDGF applied locally into damaged tissues. Thereby, recombinant human PDGF has been sanctioned by the US Food and Drug Administration for the treatment of chronic foot ulcers in diabetic individuals and has been tested, either alone or in combination with other growth factors, for tissue regeneration.[9,10]

FIBROBLAST GROWTH FACTOR (FGF)

FGF was learned in 1974 as a protein in cow pituitary glands that powerfully induced proliferation of fibroblasts.[11]In 1984, two proteins with different basic and acidic isoelectric points were identified as acidic FGF (aFGF, FGF1) and basic FGF (bFGF, FGF2).[12,13]The FGFs belongs to a family of polypeptides that are great in mutagens and chemoattractantsfor endothelial cells and for a variety of mesenchymal cells, including fibroblasts, osteoblasts, chondrocytes, smooth muscle cells and skeletal myoblasts.[14]

ROLE OF FGF

These factors have been shown to stimulate the formation of new blood vessels (i.e., angiogenesis and neovascularization). The stimulatory effects of FGFs on neovascularization, in addition to the chemotactic and mitogenic effects on mesodermal cells, in particular to fibroblasts and osteoblasts, suggest a significant role of these proteins in periodontal wound healing and regeneration.They stimulate proliferation and attachment of endothelial cells and PDL cells in wound healing process. FGF-2 is known to attract epithelial cells more meritoriously than FGF-1.[1]

INSULIN-LIKE GROWTH FACTORS (IGF)

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 7.5KDa respectively.The IGF family includes three ligands and three cell surface receptors namely; insulin, IGF-I and IGFII and Insulin, IGF-1 and IGF–l-mannose G-phosphate receptors having at least six high-affinities. IGF binding proteins bind to circulating IGFs and modulate their biologic actions. Both IGF-I and IGF-II are synthesized as large precursor molecules (195 and 156 amino acids) which are proteolytically cleaved to release the biologically active monomeric proteins (70 and 67 amino acids).[15]

IGFs are produced in largest amounts by the liver. They are also produced by most extrahepatic organs, like bone, smooth muscle, and placenta which are transported via the plasma. In their inactive form IGF are stored in bone.

ROLE OF IGF

It is a potent chemotactic agent for vascular endothelial cells. It also stimulates mitosis of various cells in vitro such as fibroblasts, osteocytes and chondrocytes. IGF-1 play a role in the biology of oral and dental tissues and organs.IGF-1 also participates actively in the cell proliferation and differentiation of developing teeth, being a crucial factor in the mineralizing process during odontogenesis, suggestingpotential therapeutic use of IGF-1 in the pulp tissue, both in immature and mature teeth when insulted by external irritants. IGF-1 has a role in pulp healing and reparative dentinogenesis following pulp capping. IGF-1 is a mitogenic protein which is stated to stimulate cell proliferation and chemotactic migration, enhance cellular survival and improve periodontal regeneration. Both gingival and periodontal mesenchymal cells display a dose-dependent migratory response to the presence of IGF-1 and IGF-2.They also proliferates DNA synthesis and protein production by periodontal ligament cells. IGFs appear to have a part in bone formation. IGF-1 increased DNA synthesis in osteoblasts and stimulated the formation of bone matrix in organ culture.[16]

TRANSFORMING GROWTH FACTOR(TGF)

The transforming growth factor are a family of structurally and functionally unrelated proteins that have been secluded from normal and neoplastic tissues. The two greatest characterized polypeptides from this group of growth factors are TGF-a and TGF-b. TGF-a 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-b is aexceedingly 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-b have been recognized namely TGF-b1, TGF-b2 and TGF-b3. TGF b has bifunctional activity in which it acts as a multifunctional modulator of cell proliferation.[2]

ROLE OF TGF

TGF- appears to be a most important regulator of cell replication and differentiation. TGF can modulate other growth factors, such as PDGF, TGF-, EGF and FGF, possibly by varying their cellular response or by inducing their expression. Several in vivo investigations support the role of TGF- in wound healing. The application of TGFincreased the formation of granulation tissue. The topical application of TGF- to epidermal wounds in pigs inhibited re-epithelialization and increased connective tissue volume, collagen synthesis and angiogenesis. Other reports usingimplanted chambers or tubes filled with TGF- alone and in combination with other factors have found significant increase in protein and collagen synthesis, in addition to an enhanced ingrowth of fibroblasts and capillaries.[17]

BONE MORPHOGENETIC PROTEIN (BMP)

Bone morphogenetic proteins comprise an extensive group of conserved growth factors, of which over 30 members have been identified to date and constitute the largest subgroup of the transforming growth factor-betasuperfamily.Bone morphogenetic proteins have been involved in the formation of both cartilage and bone during embryonic development and regeneration in postnatal life and in many other developmental processes. Based on their sequence similarity and known functions, bone morphogenetic

proteins are typically divided into at least four subgroups: bone morphogenetic protein-2/bone morphogenetic protein-4; bone morphogenetic proteins 5 (also known as osteogenic protein-1), 6, 7, 8a and 8b; bone morphogenetic proteins 9 and 10; and bone morphogenetic proteins 12, 13 and 14 and growth differentiation factor-5 (also known as cartilage-derived bone morphogenetic protein-1).. Bone morphogenetic proteins are synthesized as large precursors of about 400–500 amino acids, consisting of an N-terminal signal peptide directing secretion, a prodomain for proper folding and a C-terminal mature peptide. After maturation, bone morphogenetic proteins are secreted as 50- to 100-amino-acid-long polypeptides.[8]

ROLE OF BMP

They are a group of associated proteins that are known to possess the exclusive ability to induce cartilage and bone formation. They trigger cellular effects by way of heterotetrameric serine/ threonine kinase receptors and intracellular signaling proteins known as small "mothers against" decapentaplegic (Smads) BMPs, like PDGF, play a role in the blood vessel formation. They play an important part in the angiogenetic activity by up-regulating the angiogenetic peptides like VEGF, may bind to endothelial cells and stimulate the migration and promote blood vessel formation. The hallmark property of BMP is the differentiation factor. BMP will differentiate an undifferentiated mesenchymal cell into an osteoblast.[18]

EPIDERMAL GROWTH FACTOR (EGF)

Epidermal growth factor is a multifunctional cytokine which is involved in variety of functions including epithelial growth and differentiation, and wound healing.EGF had been identified in 1962, and its receptor was purified and characterized by Stanley Cohen in 1980. EGF was initially discovered in mouse submandibular glands by its ability to cause precocious tooth eruption and eyelid opening in newborn mice. It is a single chain, 53-amino-acid protein with a broad spectrum of activity and with hormone-like properties.The human-derived form has a molecular weight of approximately 5400Da. EGF and TGF- are structurally related, possess similar properties, have the same biological activity and share a common receptor.

The "EGF receptor (EGFR)" is actually a family of membrane tyrosine kinase receptors that respond to EGF, TGF-, and other ligands of the EGF family. It belongs to a family of related cell surface receptors, including ErbB1 (EGFR), ErbB2/Her-2, ErbB3, and ErbB4.The main EGFR is referred to as EGFRl, or Erb BI. EGFR is highly expressed in many solid tumors including human OSCC and therefore, is a target for cancer therapy and prevention. Salivary glands are the primary source of EGF in humans with parotid gland being the major source. In human tissues, EGF has also been isolated from kidneys, thyroid glands, Brunner's gland, pituitary and brain. EGF is present in most human extracellular fluids, including plasma, urine, saliva, milk, sweat, semen, amniotic fluid, cerebrospinal fluid and intestinal contents, though the major sources of EGF are urine and saliva. The serum level of EGF is about 1 to 2ng/ml. EGF is normally expressed by most epithelial cells, although keratinocytes, activated macrophages, platelets and various embryonic cells express EGFas well.[1]

ROLE OF EGF

EGF is mitogenic for periodontal ligament cells, and was also found to stimulate the growth of gingival cells, in vitro. In addition, it showed a slight chemotactic effect on periodontal ligament cells, but suppressed their collagen synthesis. EGF stimulates prostaglandin production and induces bone resorption in cultures of neonatal mousecalvaria.[19] The topical application of EGF to abraded corneas partial-thickness wounds fullthickness wounds and superficial burns significantly enhances re-epithelialization and wound healing. Slow release of EGF from sponges implanted subcutaneously stimulated fibroblast proliferation and angiogenesis as well as granulation tissue formation.

Vascular endothelial growth factors (vegf)[1]

Vascular Endothelial Growth Factor is a macromolecule which enriches blood vessel growth and permeability.Thus, it is also known as vascular permeability factor.VEGF has significant homology to PDGF. VEGF is a heparin-binding homodimeric, disulfide-bound glycoprotein of 45kDa. The VEGF family currently comprises of seven members: VEGF-

A, VEGF-B, VEGFC, VEGF-D, VEGF-E, VEGF , and PIGF. All members have a common VEGF homology domain. Three VEGF tyrosine kinase receptors have been identified : The fms -like tyrosine kinase Flt-1 (VEGFR- 1/Flt- 1), the kinase domain region, also referred to as fetal liver kinase (VEGFR-2/KDR/Flok -1), and Flt-4 (VEGFR-3). VEGF also interacts with a family of coreceptors, the neuropilins (NP). In normal tissues, the highest levels of VEGF-A mRNA are found in adult lung, kidney, heart, and adrenal gland. VEGF-B is abundantly expressed in the adult myocardium, skeletal muscle, and pancreas. VEGF-C is expressed most prominently in heart , placenta, ovary, small intestine, and the thyroid gland, whereas, VEGF-D is found particularly in lung, heart , skeletal muscle, colon, and small intestine. In embryonal tissues, it is abundant in the developing lung.

ROLE OF VEGF

VEGF potentiates microvascular hyper permeability,which can both precede and accompany angiogenesis. It is also critical for reproductive and bone angiogenesis. VEGF is a highly specific mitogen for endothelial cells. VEGF is likely a factor in the etiology of gingivitis and its progression to periodontitis, possibly by promoting the expansion of the vascular network coincident toa progression of the inflammation. VEGF has been implicated in having direct chemotactic and mitogenic effects on osteoblasts and osteogenic cells.[1]

HEPATOCYTE GROWTH FACTOR (HGF)

Hepatocyte growth factor (HGF) is a secreted, heparin sulfate glycosaminoglycan-binding protein. HGF has been shown to have mitogenic effects on osteoblasts; thus, participating in the bone remodeling process.

Yamada et al. cultured fibroblasts in a culture medium containing HGF and concluded that they produced good cell proliferation and vascular endothelial growth factor (VEGF) release. The results suggest that it may provide a new tool for the treatment of gingival recession.[20]

KERATINOCYTE GROWTH FACTOR (KGF)[1]

Keratinocyte Growth Factor is classified as FGF-7 and belongs to heparin binding FGF family. KGF differs from the other members of FGFs by its high specificity for activating epithelial cells.It is expressed in cells of mesenchymal origin such as fibroblasts and endothelial cells but not in epithelial cells. It, therefore seems likely that KGF stimulates epithelial cells in a paracrine manner. It has specific mitogenic, morphogenic and motogenic effects on epithelial cells. KGF-1 and KGF-2 are two members of the current FGF family and are classically designated as FGF-7 and FGF-10, respectively. The KGF receptor (KGFR) is a membranespanning tyrosine kinase which is alternatively spliced isoform of FGFR-2 and designated as FGFR-2IIIb. FGFR2IIIb. KGF was initially purified and cloned from a lung fibroblast line as a soluble factor that could stimulate keratinocyte proliferation.

ROLE OF KGF

Both KGF family members induce proliferation, migration and matrix metalloproteinase secretion in a variety of epithelial cells. KGF stimulates the re-epithelialization phase of wound healing at periodontally diseased sites.[21]KGF-1 expression in gingival tissues and its upregulation by pro-inflammatory cytokines and lipopolysaccharide (LPS) support the putative role of KGF1 in regulating epithelial cell function in periodontal diseases. During the progression of periodontal disease, the epithelial cell barrier gets disrupted, allowing lipopolysaccharide to directly stimulate gingival fibroblasts to express KGF-1. Expression of KGF-1 and subsequent specific stimulation of epithelial cell proliferation, ultimately serve to reestablish and maintain an active epithelial cell barrier which protects the host from periodontal disease associated gram-negative pathogens in dental plaque biofilm.[22]

CEMENTUM DERIVED GROWTH FACTOR (CDGF)

Cementum-derived growth factor (CGF) is an M,23,000 protein, which is sequestered in the mineralized matrix of tooth cementum.[23]This molecule is similar to IGF-1, a growth factor that promotes the proliferation as well as differentiation of many cell types. The CDGF is mitogenic to fibroblasts and osteoblastic cells which are existing in the connective tissues adjacent to the cementum. In the cementum matrix, the CDGF is sequestered along

with other growth factors such as FBFs 1 and 2 and EGF, and adhesion molecules such as collagens , bone sialoprotein, and osteopontin. These molecules are likely to influence the outcome of CDGF action because regulation of cellular activities often involves the combined action of more than one growth factor. The CDGF is a poor mitogen for fibroblasts; however, its mitogenicactivity , even at suboptimal concentrations, is synergistically potentiated by EGF and serum.[24]

CONCLUSION:

Periodontal tissuesare regenerated through a dynamic process involving cell-to-cell and cell–extracellular matrix interactions.Thisco-ordinationand interaction of growth factors results in wound healing and regeneration of tissues.A review of the present existing literature indicates that a combination of growth factors in an ideal concentration is best suited for periodontal regeneration. Nowadays many studies are concentrating on the advancement of a suitable carrier material having both mechanical properties and surgical practicality which are appropriate for controlled release of growth factors. Current human clinical trials evaluating the potential therapeutic use of growth and differentiation factors for periodontal regeneration pursue to provide the definite evidence for the addition of this therapy to the reconstructive periodontal treatment. Also it appears that welldefined selective preclinical models surveyed by well designed clinical trials are desired to further investigate the exactprospective of these factors.

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GROWTH FACTORS IN PERIODONTAL REGENERATION

Growth Factor	Human/Animal studies	Defect Morphology	Periodontal regeneration	Author
PDGF-BB	Animal study on dogs	Lateral ridge defect	Stimulated bone regeneration and revascularization	Schwartz et al[25]
PDGF-BB	Animal study on beagle dog	Class III furcation defects	Effectively promoted periodontal regeneration without significant ankylosis or root resorption	Moon et al[26]
rhPDGF	Human study	Intra bony defect /molar class II furcation defect	Regeneration of a complete periodontal attachment apparatus including new cementum, PDL, and bone	Nevins et al[27]
rhPDGF-BB	Human study	Intra bony defect	Greater clinical attachment level gain and a greater amount of bone fill.	Ivan B. Darby et al[28]
PDGF-BB	Human Study	Localized severe periodontal osseous defects	Promotes long-term stable clinical and radiographic improvements with a gain in CAL and LBG for patients possessing localized periodontal defects.	Nevins M et al[29]

Growth Factor	Human/Animal studies	Defect Morphology	Periodontal regeneration	Author
FGF-2	Human Study	2- or 3-walled vertical bone defect	Significant increase in the alveolar bone height of0.3% FGF-2	Kitamura et al[30]
FGF-2	Non-human primates	Furcation class II bone defects	Topical application of FGF-2 can enhance considerable periodontal regeneration.	Takayama et al[31]
IGF-I	Animal study	Culture study	IGF-I has a potential to enhance the DNA synthesis of PDL fibroblasts without inducing changes in the morphology and growth pattern;	Blom et al[2]
TGF-β	Human study	Culture study	TGF-β may indirectly stimulate DNA synthesis.	Oates et al[32]
rhBMP	Animal Study	-	Positive effect on periodontal ligament regeneration	Miyaji and coworkers[33]
BMP-2	Animal Study	Periodontal defects created over the premolar areas	New cementum formation in bone morphogenetic protein-treated defects.	Chung and coworker[34]