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Growth Factors in Periodontal Regeneration

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Abstract:- The disintegration of the periodontal ligament, the root cementum and the alveolar bone is the result of periodontal disease, which is caused by bacteria found in dental plaque. The ultimate objective of periodontal therapy is the regeneration of the attachment apparatus. Numerous growth and differentiation variables in periodontal regeneration have been evaluated. The primary regulators of these biological processes are a class of naturally occurring chemicals known as polypeptide growth factors in combination with certain matrix proteins.

Four main growth factors that seem to have a considerable impact on the process of wound healing will be covered in this review article. Bone morphogenetic proteins, fibroblast growth factors, transforming growth factor, and platelet-derived growth factor.

Keywords:- *Platelet-Derived Growth Factor, Transforming Growth Factor, Fibroblast Growth Factors, Bone Morphogenetic Proteins.*

I. INTRODUCTION

Microorganisms in tooth plaque cause periodontal disease, which results in the destruction of the periodontal ligament, cementum and the alveolar bone. The attachment apparatus is impacted by this extremely prevalent illness.[1] Periodontal therapy's ultimate goal is the regeneration of the attachment apparatus. Traditional therapy methods might not be able to regenerate bone, which would be disappointing to both the patient and the physician. Periodontal regeneration methods can be more effective than open flap debridement in repairing angular bone abnormalities, as evidenced by multiple randomised controlled studies and systematic reviews.[2]

Research on periodontal healing reveals that conventional periodontal therapy usually leads to repair rather than regeneration. Periodontal regeneration requires the migration and multiplication of progenitor cells to the denuded root surface. Over the past ten years, a lot of research has been done on the variables influencing cell migration, adhesion and proliferation.[3] Diverse surgical approaches, root conditioning, biomaterials composed of artificial or cadaveric bone and barrier device use are all intended to encourage periodontal regeneration.[4]

In periodontal regeneration, a wide range of growth and differentiation factors have been evaluated. These biological processes are largely regulated by a class of naturally occurring chemicals called polypeptide growth factors in combination with certain matrix proteins. Platelet-derived growth factor, transforming growth factor, fibroblast growth factors and bone morphogenetic proteins are essential for periodontal regeneration.[5]

A. Common Features

Growth factors are produced and secreted by a variety of cell types involved in tissue repair. The producer cells themselves (autocrine stimulation), distant cells (endocrine stimulation), or nearby cells (paracrine stimulation) can all be stimulated by them.

All growth factors work by attaching to and activating particular high affinity receptors on target cells' plasma membranes, including osteoblasts, cement oblasts and fibroblasts of the periodontal ligament. Eventually, when the receptors are activated, many activities, including those involved in wound healing, are stimulated. They might be involved in the tyrosine residue-based phosphorylation of proteins.

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B. Classification

Table 1: Classification of Growth Factors

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

II. MODE OF ACTION

The local modes of action of growth factors (GFs) include juxtacrine, paracrine, intracrine, and autocrine.

A. Autocrine Mode of Action

GFs function in an autocrine manner, meaning that they are made by a single cell, released from it in a soluble state and then bind to its surface receptors to cause a reaction.

➢ *Intracrine Mode of Action*

GFs are synthesised by a single cell and function intracellularly to promote their activities, as opposed to being released, through an intracrine process.

➢ *Paracrine Mode*

GFs produced by one cell interacting with receptors on another cell in the nearby microenvironment are responsible for the paracrine mode of action. In this case, the mediators are released in a soluble form and bind to the receptors on the target cell to exert their intended effect.

➢ *Juxtacrine Mode*

It is similar to paracrine mode. The only difference between it and the paracrine effect is that the factor produced by the source cell is surface bound and requires contact with the target cell to initiate a reaction.

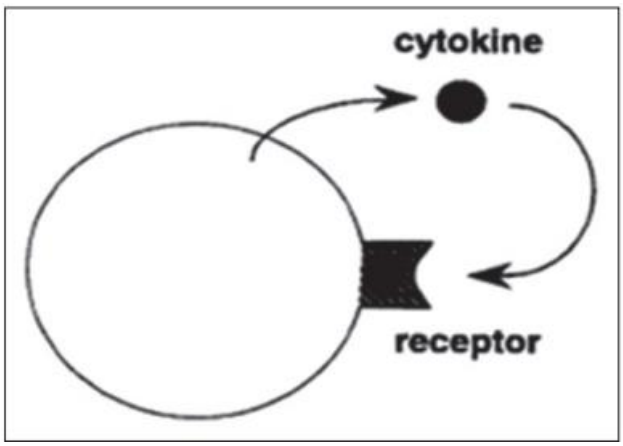

Fig 1: Autocrine Mode

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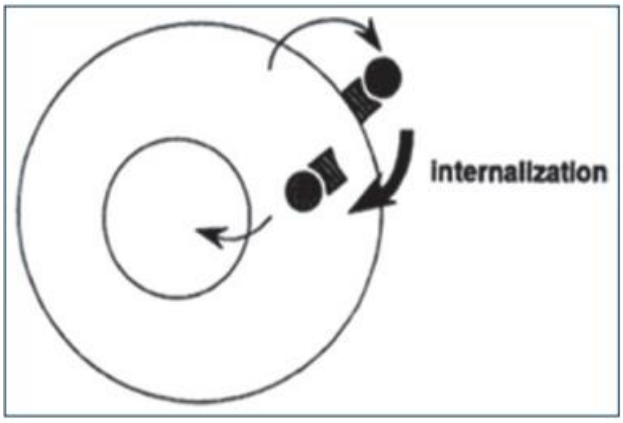

Fig 2: Intracrine Mode

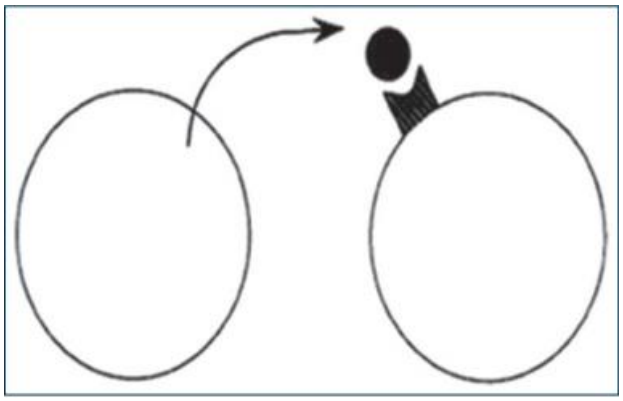
Fig 3 : Paracrine Mode

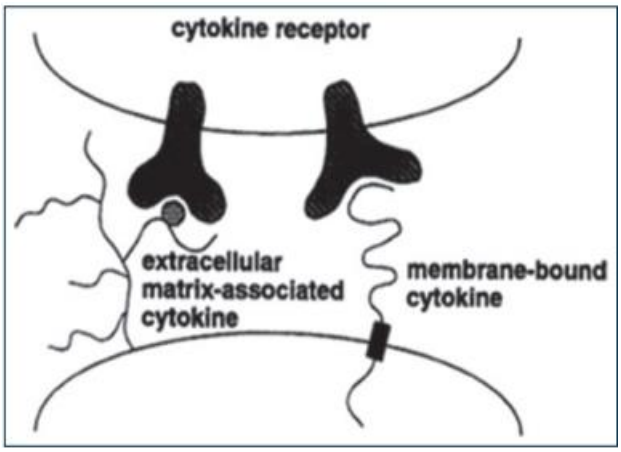

Fig 4: Juxtacrine Mode

B. Polypeptide Growth Factors

A class of naturally occurring biological mediators known as polypeptide growth factors binds to particular cell-surface receptors to regulate important cellular processes in tissue healing, such as cell proliferation, chemotaxis, differentiation and matrix production.[3]

Four main growth factors that seem to have a considerable impact on the process of wound healing will be covered in this review article. Platelet -derived growth factor, transforming growth factor, fibroblast growth factors, bone morphogenetic proteins.

C. Various Growth Factors

➢ *Platelet-Derived Growth Factor*

It is a naturally occurring protein generated by platelets, monocytes, macrophages, fibroblasts and endothelial cells that is found in the bone matrix. It binds to the target cells' α and β receptors on their cell surfaces and activates them. The five PDGF isoforms are PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD. It has been determined whether or not PDGF-A, PDGF-B, and PDGF-AB can encourage periodontal wound healing and regeneration.

➢ *Actions*

Smooth muscle cells, fibroblasts and leukocytes are attracted to it. It enhances extracellular matrix and protein synthesis in combination with IGF-I. It influences the osteogenic cells, promoting their migration and multiplication in the healing region. Moreover, it promotes collagen types I, III and V as well as fibronectin synthesis. Furthermore, plasminogen activator and collagenase are inhibited by PDGF. Hepatocyte growth factor, pro inflammatory cytokine interleukin-6 and vascular endothelial growth factor are all expressed more when periodontal regeneration is indirectly stimulated by PDGF.[1]

III. LITERATURE REVIEW

A. Preclinical Studies Using PDGF for Periodontal Regeneration

PDGF has been used in numerous in vivo preclinical investigations. Lynch and colleagues were the first to document the regeneration capacity of PDGF-BB when applied to treat naturally occurring periodontal abnormalities in dogs. This research showed that PDGF-BB therapy increased cellular activity, hence fostering the regeneration of the periodontal ligament, cementum and bone.

At early time periods in the experiment examining its usage around dental implants, the frequency of peri-implant gaps filled with bone increased two- to three-fold upon direct injection of a rhPDGF/IGF mixture into canine implant sites in dogs.

Five weeks after the injection of human recombinant (rh) PDGF-BB and IGF-I in methyl cellulose gel to thirteen dogs, histological examination showed that the growth factor-treated areas had shown an increase in the formation of new bone and cementum.

B. Clinical Studies Using PDGF for Periodontal Regeneration

In order to evaluate the effect of rhPDGF/ IGF treatment in osseous periodontal defects, Howell and colleagues published a human clinical experiment. These GFs in a methylcellulose matrix were applied immediately to the experimental sites in order to improve retention. Nine months after surgery, there was a statistically significant increase in alveolar bone development at the growth factor-treated sites compared to the untreated control sites.

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An early human experiment conducted by Nevins M and Camelo M examined the effectiveness of rhPDGF-BB therapy for substantial interproximal intrabony defects and Class II furcation lesions associated with advanced periodontitis. To fill the defect at the surgical test sites, demineralized freeze-dried bone allograft (DFDBA) was pre-soaked in a solution containing rhPDGF-BB at three different doses (0.5, 1.0, or 5.0 mg/mL). The results showed that after nine months, all test sites had significantly higher probing depths than baseline levels. The treatment group's BF% was 80.99±14.03, whereas the control group's was 54.16±12.84, according to Thakare. When the studies were combined for meta-analysis, it was discovered that the BF% of patients in the treatment groups—all of whom had received 0.3 mg/ml rhPDGF-BB—was 22.71% higher than that of patients in the control groups.[8]

A study evaluated the application of PDGF in approaches for horizontal ridge augmentation. Bilateral mandibular surgically induced defects were repaired using a split-mouth technique using either β-TCP + CM + rhPDGF-BB or beta-tricalcium phosphate coated in a collagen membrane. The results of the study demonstrated that at three weeks, the group receiving rhPDGF-BB treatment had better results.[8]

IV. TRANSFORMING GROWTH FACTOR

TGF-3 belongs to a broad class of physiologically active protein hormones that share a similar molecular makeup but have quite different functions.[14] The two recognised transforming growth factors are TGF-α and TGF-β.[3]

A. Transforming Growth Factor-α (TGF-α):

It is produced by monocytes, keratinocytes and other tumour cells and is a member of the family of epidermal growth factors. Both TGF-α and EGF are equally effective at binding to the EGF receptor on endothelial cells and promoting endothelial cell proliferation in vitro. It functions in tandem with TGF- $_{\beta}$ to stimulate a mitogenic response and encourage the proliferation of anchorage-independent cells.[1]

B. Transforming Growth Factor-$_{\beta}$ (TGF-$_{\beta}$):

Several multifunctional, structurally related growth and differentiation factors linked to the inflammatory response are members of the TGF-$_{\beta}$ superfamily, which includes TGF-$_{\beta}$. They play a critical role in wound healing, angiogenesis, fibrosis and apoptosis.[1]

C. Cellular Role of TGF-α and TGF-$_{\beta}$ and Role in Wound Healing

In vitro, TGF-α and EGF stimulate the growth of endothelial cells and attach to the cellular EGF receptor. Since it has two functions, it can either promote or prevent cell growth. One important regulator of cell division and replication is TGF.

By altering or promoting the cellular response of other growth factors such as FGF, PDGF and EGF, TGF- $_{\beta}$ has the power to affect how those factors are expressed. It encourages mesenchymal cells while inhibiting the growth of epithelial cells.

TGF- $_{\beta}$ being a fibroblast chemotactic factor, promotes fibrosis and fibroblast accumulation throughout the course of healing. It decreases the effects of enzyme inhibitors and increases collagen synthesis. It affects angiogenesis in a slightly counter intuitive way. In vitro, it inhibits endothelial motility and proliferation, whereas in vivo, it increases angiogenesis.[6]

D. Clinical Studies Using TGF for Periodontal Regeneration

There aren't many studies on periodontal regeneration based on TGF-β. TGF-β and PDGF cooperate to stimulate the growth of pdl cells and gingival fibroblasts alike. According to a study assessing the time sequence response of RNA and protein production by human pdl & gingival fibroblasts in culture, the effects of TGF-β1 on HPDLF & HGF were both time & dosage dependent.

In a study by Teare JA et al, bilateral Class II furcation abnormalities in the maxillary and mandibular molars of four adult baboons were surgically produced. In order to transplant to specific furcation defects, rhTGF-b3 promoted the production of heterotopic ossicles inside the rectus abdominis muscle. Forty days later, rh-TGF-β3 was implanted into the periodontal defects using either rhTGF-β3 plus minced muscle tissue in Matrigel or the harvested rhTGF-β3-induced ossicles as the delivery mechanism. Morphometric analysis showed that experimental abnormalities had more pronounced periodontal regeneration in comparison to controls.

Significant regeneration was observed in defects implanted with fragments of heterotopically generated ossicles or minced muscle tissue + rhTGF-β3. Increased regeneration of periodontal tissue in non-human primates with rhTGF-β3 in Matrigel.[16]

V. FIBROBLAST GROWTH FACTOR

These strong heparin-binding peptides belong to a family that has structural similarities and has been linked to regeneration and healing[1]. Two types of fibroblast growth factors (FGFs) were found in 1984: basic (FGF-2) and acidic (FGF-1).

A. Sources

FGF-2 has also been discovered to be produced in the brain, pituitary gland, kidney, corpus luteum and adrenal gland. FGF-1 and FGF-2 have also been isolated from neural tissue.[11]

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B. Functions:

➢ *Angiogenesis*

Endothelial cell proliferation is stimulated by FGF-1. Due to its binding to heparin, FGF-2 exhibits a wide range of mitogenic and angiogenic properties. FGF-2 has the ability to initiate each step necessary for the growth of new blood vessels both in vivo and in vitro. Type I collagen and laminin synthesis by PDL cells is actively regulated by FGF-2. Laminin is one of the most important biological molecules in the process of angiogenesis.

➢ *Wound Healing*

FGF promotes the migration and/or proliferation of various cell types involved in wound healing, including chondrocytes and myoblasts, as well as fibroblasts, keratinocytes, endothelial cells, and epithelial cells.

Moreover, FGF-2 stimulates the production of proteoglycan, collagen, fibronectin and epithelialization. The quality of the scar and the breaking strength of the wound both improve when FGF-2 is injected during the wound closure process.

➢ *Effect On Bone:*

It has been found to speed up osteoprogenitor cell development, which encourages the growth of new bone. It has also been demonstrated to encourage the migration and proliferation of periodontal ligament cells, making it a viable choice for the regeneration of periodontal soft and hard tissues.[15]

FGF has the potential to be used in the treatment of osteopenia since it systemically encourages the healing of bone fractures, stimulates the synthesis of new bone and improves bone mass. Furthermore, studies on animal models have demonstrated that FGF-2 accelerates healing.

C. Clinical Studies Using FGF for Periodontal Regeneration

In a research by Masahiro Kitamura et al., 3% hydroxypropylcellulose (HPC) and rhFGF-2 were used as a vehicle. Patients were randomly assigned into one of the four groups: first, they received HPC without FGF-2; second, they received HPC with 0.03% FGF-2; third, they received HPC with 0.1% FGF-2; and fourth, they received HPC with 0.3% FGF-2.

As a result, at 36 weeks, Group 1 (23.92%) and Group 4 (58.62%) had significantly different rates of alveolar bone height growth. Alveolar bone height increased linearly in Groups 1 and 4 by 0.95 mm and 1.85 mm, respectively, at 36 weeks. Statistically significant differences were noted for the rate of increase in alveolar bone height between Groups 1 and other groups at 36 weeks, indicating that some efficacy could be expected from FGF-2 in stimulating regeneration of periodontal tissue in patients with periodontitis.[12]

VI. BONE MORPHOGENETIC PROTEIN

BMPs are a class of regulatory glycoproteins that are members of the TGF-β superfamily. Urist came up with the moniker BMP in 1965.[2]

Numerous biological processes including morphogenesis, apoptosis, cell division and the creation of extracellular matrix, are supported by them. Consequently, their main job is to encourage undifferentiated pluripotent cells to differentiate into the cells that make bone and cartilage.[1]

Numerous BMPs have been evaluated for their ability to enhance periodontal wound healing and regeneration. Particular focus has been paid to BMP-2, BMP-3 (also known as osteogenin), BMP-7 (also known as osteogenic protein-1) and GDF-5 (also known as cartilage derived morphogenetic protein).

A. Role of BMPs in Periodontal Regeneration

In order to assess the regeneration capacity of injectable macroporous calcium phosphate cement in conjunction with BMP 2, Oortgiesen DA et al. performed a study in which 30 intrabony periodontal lesions were produced in 15 rats. Following histology and histomorphometry, the animals were euthanized after 12 weeks. The results demonstrated a significant 2–4 fold increase in bone repair when calcium phosphate and BMP 2 were combined.[10]

A Stavropoulos conducted a study evaluating BMP-14 and beta-tricalcium phosphate for periodontal regeneration. Twenty patients with chronic periodontitis were chosen and they were treated with open flap debridement (OFD) alone or in combination with rhGDF-5/b-TCP. In comparison to the control group, which had PD reduction of 3.1 ± 1.8 mm, gingival recession of 1.4 ± 1.0 mm and clinical attachment level gain of 1.7 ± 2.2 mm, the sites receiving rhGDF-5/b-TCP showed numerically greater PD reduction of 3.7 ± 1.2, less gingival recession of 0.5 ± 0.8 and greater clinical attachment level gain of 3.2 ± 1.7 after 6 months. Histologically, compared to OFD alone (0.81 ± 1.02 mm), the rhGDF-5/b-TCP treated sites showed nearly three times higher bone height (2.19 ± 1.59). Sites that had rhGDF-5/b-TCP showed higher levels of PD reduction, CAL gain, and periodontal regeneration than control.[17]

VII. CONCLUSION

To enhance periodontal regeneration, a variety of components associated with growth and differentiation factors have been identified as potential treatment possibilities. Few have undergone a clinical assessment. The aim of growth factors administration in the treatment of periodontitis is to mimic normal development and enhance the normal wound healing response in order to promote complete regeneration of the attachment apparatus. Research, both basic and clinical, is being conducted to evaluate the role of growth factors in the healing process of periodontal regeneration.

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