

Growth Factors in Periodontics

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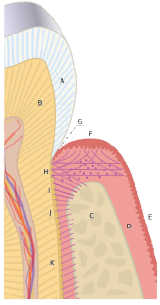
ABSTRACT

Periodontal disease activity results in destruction of periodontal tissues. The principal objective of periodontal therapy is the morphological and functional reconstruction of lost periodontal supporting structure. Over the past few years various new treatment modalities have come up for the treatment of periodontal disease, concept of growth factor is one of them. There are various growth factors present in the system which have their influence on the healing of wound and periodontal structure. This book comprises of all the growth factors which increases likelihood of periodontal regeneration. The content of this article will surely help the research activist at different level of their work.

Keywords: Periodontal disease, Growth factors, periodontal regeneration.

1. INTRODUCTION

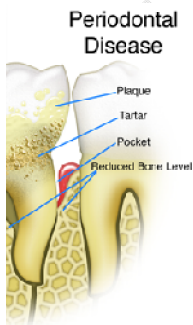
Periodontal disease activity results in destruction of periodontal tissues i.e. periodontal ligament, alveolar bone and cementum, eventually leading to tooth loss if left untreated. The principal objective of periodontal therapy is the morphological and functional reconstruction of lost periodontal supporting structure. In the recent past growth factors has been studied extensively in the regeneration of lost periodontal tissue. Growth factors are signal proteins

Periodontium:

It is the supporting structure of the tooth consisting of gingiva, alveolar bone, cementum, periodontal ligament.

Growth factor:

Growth factors are signal proteins released from local tissue or blood products that activate target cells to replicate or migrate.

Periodontitis:

It is the inflammation of tooth supporting structure, which can lead to loosening of tooth.

released from local tissue or blood products that activate target cells to replicate or migrate. Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Growth factors trigger specific target cells by binding to their high affinity surface membrane receptors.

The growth factors are needed for both development and regeneration, so it can be imagined that these factors that trigger development of periodontium may prove helpful in promoting regeneration of periodontal tissues. There are various growth factors present in the body, which influence periodontal regeneration. They are discussed as below:

Classification of growth factors:**Epithelial proliferation**

- a. Transforming growth factor beta
- b. Epidermal growth factor

Connective tissue formation

- a. Platelet derived growth factor
- b. Insulin like growth factor I
- c. Colony stimulating factor
- d. Basic fibroblast growth factor

Angiogenesis

- a. Vascular endothelial growth factor
- b. Acidic fibroblast growth factor
- c. Platelet derived growth factor

Bone formation

- a. Bone morphogenetic proteins
- b. Insulin like growth factor

Cementum formation

- a. Bone morphogenetic proteins
- b. Platelet derived growth factor

Mode of action:

The mode of action is the way in which the mediator is meant to interact with its target receptor. Hormones traditionally act in an endocrine manner whereby they are secreted by one cell type and travel in the blood stream to a distinct target cell to exert their actions. Local modes of actions are associated with growth factor and involve the following modes:

- a. Paracrine
- b. Autocrine
- c. Juxtacrine
- d. Intracrine

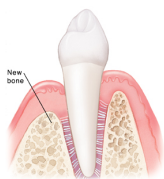
2. PLATELET DERIVED GROWTH FACTOR

Ross et al., (1974) and Kohler & Lipton (1974) provided evidence for a growth factor derived from platelets after it was shown by Balk SD (1971), that whole blood derived serum was more potent than plasma derived serum in promoting growth of chicken fibroblast at low calcium concentration. This growth factor was called as Platelet derived growth factor (PDGF).

PDGF is involved in nearly all wound healing processes by virtue of platelets and plays a dual role as growth factor reservoir and a factor in homeostasis. The presence of potent growth factor in blood clot immediately at the injured site would be expected to promote a faster repair. It is secreted locally during clotting by the blood platelets at the site of soft- or hard-tissue injury that stimulates a cascade of events leading to a wound-healing response. It stimulates the influx of neutrophils to the wound site. It also induces:

1. Mitogenesis: causes increase in the number of healing cells
2. Angiogenesis: generates development of new capillaries
3. Up regulation of other growth factors and cells which results in the promotion of fibroblastic and osteoblastic functions, promotion of cellular differentiation, acceleration of the effects of growth factors on other cells such as macrophages.
4. Chemotaxis
5. Plays an important role in gingival wound healing.

Periodontal regeneration:



It is defined histologically as regeneration of the tooth's supporting tissues, including the alveolar bone, periodontal ligament, and cementum over a diseased root surface.

Piche et al., (1989), isolated cells from the periodontal ligament and demonstrated that PDGF stimulated these cells. Boyan et al., (1994) studied the mitogenic and chemotactic responses of human periodontal ligament cells. They concluded that PDGF is effective in promoting mitogenesis and chemotaxis of periodontal ligament cells.

3. FIBROBLAST GROWTH FACTOR

Fibroblast growth factor (FGF) is a group of polypeptide growth factors which act on the fibroblasts. There are 7 members in the FGF family but of them acidic FGF (aFGF) and basic FGF (bFGF) are the ones that are thoroughly characterized. FGF act as competence factor. It stimulates resting cells in G0 to enter cell cycle in G1 (Raul, 1993). Both aFGF and bFGF are found to stimulate the proliferation of the major cell types involved in wound healing both in vivo and in vitro.

Murakami et al., (1999) examined the role of bFGF in the wound healing and found that bFGF may play important roles in wound healing by promoting angiogenesis and inducing the growth of immature periodontal ligament cells. Sato et al., (2004) examined the effects of bFGF on the regeneration of cementum and periodontal ligament in experimentally induced partial defects in beagle dog model. They concluded that bFGF in a collagen gel is suitable for damaged periodontal ligament and could lead to readily achievable methods of treatment for periodontal disease.

4. TRANSFORMING GROWTH FACTOR

Transforming growth factor (TGF) is one of the several proteins secreted by transformed cells that can stimulate the growth of normal cells. They are polypeptides isolated from normal and neoplastic tissues which are known to cause a change in normal cell growth. Two polypeptides from this group of growth factors are TGF- α and TGF- β . TGF- β is chemotactic for fibroblast and promotes accumulation of fibroblasts and fibrosis in the healing process. It has a potent effect on matrix synthesis, giving rise to increased production of collagen and fibronectin and decreased production of matrix degrading enzymes. TGF- β has a paradoxical effect on angiogenesis. In vivo it is found to stimulate angiogenesis but in vitro it blocks both endothelial proliferation and motility. Mohamed et al., (1998) studied the effect of TGF- β on wound healing in standardized class 2 furcation defects. They thus demonstrated that TGF- β encouraged bone regeneration. Momose et al., (2002) showed that vascular endothelial growth factor and TGF- α were released from human cultured gingival epithelial cells which suggests the potential for promoting wound healing and tissue regeneration after grafting.

5. INSULIN LIKE GROWTH FACTOR

Insulin like growth factors (IGFs) is a family of mitogenic proteins. These proteins control growth, differentiation, and the maintenance of differentiated function in numerous tissues. The 2 different types of IGF are IGF-I and IGF-II. IGF-I and IGF-II are relatively small proteins with molecular masses of 7.7 Kd and 7.5 Kd respectively. IGF is found in platelets. It is released during clotting along with other growth factors present in platelets. IGF is also a potent chemotactic agent for vascular endothelial cells. IGF-1 that is released from platelets or which is produced by fibroblasts may promote migration of vascular endothelial cells into the wound area and thus resulting in increased neovascularization.

Hock et al., (1988) in a study reported that IGF-I stimulates the formation of bone matrix in rat calvarias in organ culture. Blom et al., (1992) examined the binding and activity of IGF-I and human growth hormone on rat periodontal ligament derived cells. This study demonstrated that periodontal ligament cells have specific IGF-I receptors. This has been confirmed by the fact that IGF-I induces DNA synthesis in periodontal ligament cells.

6. EPIDERMAL GROWTH FACTOR

Epidermal growth factor (EGF) is a 53-amino acid polypeptide hormone. The other members of this family are TGF- α , amphiregulin and heparin binding epidermal growth factor. EGF has been shown to elicit a range of biological responses including stimulating cell proliferation, regulating tissue differentiation, modulating tissue repair and promoting angiogenesis. In the periodontal tissues, it has been shown that EGF is involved in control of epithelial growth and differentiation.

Yang et al., (1996) demonstrated the presence and cellular distribution of epidermal growth factor in oral wounds of hamsters by immunohistochemistry technique. EGF was detected within the wound area in inflammatory cells, striated muscle and endothelial cells whereas infiltrating eosinophils contained no detectable epidermal growth factor. The intensity of EGF immunostaining was highest in the keratinocytes, reepithelializing the healing wound. The results suggested that oral mucosal epithelium is a tissue source for EGF and that in addition to salivary EGF, and oral keratinocytes bordering the healing wound may contribute to this cytokine production at the wound site.

7. COLONY STIMULATING FACTOR

The CSFs were named for their ability to induce the development of distinct cell lines. IL-3 is a CSF known as multi-CSF. It stimulates the formation of all nonlymphocyte blood cells. Granulocyte macrophage- CSF (GM-CSF) stimulates cells of the granulocyte and macrophage lineage to differentiate and acts at a later stage than IL-3. Macrophage – CSF (M-CSF) and granulocyte-CSF(G-CSF) more specifically promote the differentiation of macrophages and granulocytes. Erythropoietin was the first CSF commercially available for clinical use.

8. ENAMEL MATRIX PROTEINS

Enamel matrix proteins play an important role in tooth development. The enamel matrix protein harvested from the developing procine teeth is called 'enamel matrix derivative' (EMD). EMD has been successfully employed to restore fully functional periodontal ligament, cementum and alveolar bone in patients with severe attachment loss. When applied to denuded root surfaces, EMD is believed to assemble into a matrix that locally stimulates regenerative responses in the surrounding tissues.

During the formation and development of root and attachment apparatus, the Hertwigs epithelial root sheath (HERS) undergoes apoptosis and because of this there is disintegration of the physical barrier that is present between the mesenchymal cells of dentine and dental follicle. Thomas and Kollar (1988) demonstrated the presence of an obligatory and specific modulating stage in which the HERS cells secretes enamel related matrix proteins.

The ability of enamel matrix proteins to induce cementum formation was first demonstrated by Hammarstrom et al., in 1977. Heijl (1997) applied EMD on a human tooth to investigate its tissue-generating ability histologically. The result showed that, regenerated cementum was found to have covered 73% of the artificial defect, and 65% of the defect was filled with regenerated alveolar bone. The regenerated acellular cementum was firmly attached to the root surface, and the collagen fibers from the cementum were observed extending into the regenerated alveolar bone proper. These results showed that application of EMD may result in true periodontal regeneration.

Sculean et al., (2001) treated intrabony defects with enamel matrix proteins or bio-absorbable membranes and did a 4 year follow up split mouth study. It was concluded from the study that CAL gain obtained following treatment with EMD or GTR can be maintained over a 4 year period.

9. BONE MORPHOGENETIC PROTEIN

Bone Morphogenetic Proteins (BMPs) are a group of growth factors and cytokines known for their ability to induce the formation of bone and cartilage. Originally, seven such proteins were discovered. Of these, six of them (BMP2 through BMP7) belong to the Transforming growth factor beta super family of proteins. Since then, nine more BMPs have been discovered, bringing the total to sixteen.

The maturation of cartilage to bone at ectopic sites occurs by a process which recapitulates the developmental process of primary endochondral ossification. This biological activity is attributable to the endogenous BMP fraction of bone, the bioavailability of which is increased by the process of demineralization. BMP induced bone formation requires an initiating stimulus, a competent cell population and a permissive environment. Following implantation of inductively active demineralized bone matrix/ BMP, 3 phases of osteoinduction are observed.

1. Achemotaxis: Initially brings polymorphonuclear leucocytes into the implanted area, followed by fibroblasts and cell attachment to the matrix.
2. Mitogenesis: Proliferation of mesenchymal cells is seen. Increase in type I collagen mRNA is seen which may be an indicator of increased activity in these cells.
3. Differentiation: Differentiation of mesenchymal cells into chondroblasts takes place by day 5.

Bone morphogenetic protein versus other growth factors

Growth factors	BMPs
<ol style="list-style-type: none">1. Are osteogenic2. Regulate cell proliferation of differentiated tissues.3. Effect limited in large bony defects and not useful in the generation of bone in the absence of osteoprogenitor cells, as growth factors modulate the pre determined osteoprogenitor.	<ol style="list-style-type: none">1. Are osteoinductive2. Contain substances which initiate the development of tissues and organ systems by stimulating undifferentiated cells to convert phenotypically.3. Pre-existence of osteoprogenitor cells in the area is not needed.

10. CONCLUSION

Biological mediators play an important role in wound healing, and the same process has thus been tried to be replicated for achieving periodontal regeneration. They are said to elegantly interact among cells and among cell and extracellular matrix to bring about periodontal regeneration. The concentrations of these molecules vary in different periodontal components. The ability of these molecules to be detected in soft tissue is likely due to their lower concentration. Although substances present in periodontal components can influence other periodontal structures, under healthy conditions these factors are likely to affect mostly the adjacent cells. Under pathologic condition the role of these components is likely to be minor due to the biochemical alteration in the local environment because of the presence of serum and inflammatory cell products in relatively large amounts. As indicated from animal studies, most of the biological mediators have a strong influence on cell behavior and show great promise in regenerative techniques. However owing to inconsistent results in human models, further clinical investigations directed at improving the predictability outcome are needed.

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