Journal of Periodontal Medicine & Clinical Practice

Vol- 1, Issue - 1, Jan - Apr 2014

www.jpmcp.com

Review Article

Biological Role Of Growth Factors In Periodontology: A Review

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Singh B, Garg A, Garg RK. **Biological Role Of Growth Factors In Periodontology: A Review.** J Periodontal Med Clin Pract. 2014;01: 61-70

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ABSTRACT

Periodontal diseases result in destruction of periodontal tissues, including cementum, bone and periodontal ligament, with eventual loss of tooth if left untreated. Various studies and clinical investigations have resulted in improved therapies for the arrest of disease progression and regeneration of periodontal tissues. A key factor for enhancing the predictability of regenerative therapies is an understanding of cellular and molecular events required to regenerate periodontal tissues. It is now recognized that an important link, although not exact, to understanding the requirements for regeneration of tissues is to acquire knowledge as to mechanisms involved in development of tissues. During development, it is now recognized that specific growth factors and morphogens trigger differentiation of epithelial and mesenchymal derived cells during tooth formation. The importance of these growth factors for regeneration of periodontal tissues as well as the function of endogenous factors present at wound sites is currently being examined in *in-vivo* and *in-vitro* modes.

KEYWORDS: growth factors, regeneration, periodontitis, biologic modifiers.

INTRODUCTION

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganism or group of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both."[1] Therapeutic modalities should therefore, aim not only at eliminating the gingival inflammatory process and preventing the progression of periodontal disease, but also at re-establishing and regenerating the periodontal tissues lost due to the disease.[2] However, outcomes of existing regenerative therapies, while having positive results, are often disappointing whenconsidering the extent of regeneration and furthermore, are not predictable. Increased research efforts focused on understanding periodontal disease at the cellular, molecular and clinical level have resulted in improved modalities for arresting disease progression.[3] A critical aspect of periodontal regeneration is the stimulation of a series of events and cascades at some point, which can result in the coordination and completion of integrated tissue formation.[1] Biologic modifiers are materials or proteins and factors that have the potential to alter the host tissue so as to stimulate or

regulate the wound healing process. Classic examples of biologic modifiers are growth factors.[4] Growth factors are natural proteins that regulate the main cellular events involved in tissue regeneration and its application has become an area of increasing interest in periodontal regenerative medicine.[5] These growth factors, primarily secreted by macrophages, endothelial cells, fibroblasts, and platelets, include platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) and transforming growth factor (TGF).[1] These growth factors may have the potential to promote regeneration of periodontal tissues through a variety of cell-tissue interactions.[4]

GROWTH FACTORS IN PERIODONTOLOGY

Growth factors are proteins that may act locally or systemically to affect the growth and function of cells in several ways**.** They may act in an autocrine fashion, where the cells that produce them are also affected by them; or more commonly, in a paracrine fashion, such that the production of a growth factor by one cell type affects the function of a different cell type. These factors may control the growth of cells and hence the number of cells available to produce a tissue. In addition, they may control the metabolism of a particular cell type: for example, the rate of production of an extracellular matrix component such as collagen.[5] Existing evidence supports a role of growth factors for use in clinical treatments targeted at regeneration of oral (periodontal) tissues lost as a consequence of disease. Importantly, the rationale for using most of the growth factors in an attempt to regenerate periodontal tissues is based on knowledge as to the function of these molecules at the cellular and molecular level.[4] Several growth factors, as single agents or in combinations, have been examined for their periodontal regenerative potential in animal models and in the clinic.[6]

PLATELET DERIVED GROWTH FACTOR (PDGF)

Platelet Derived Growth Factor is an ubiquitous mitogen that was originally discovered by Kohler & Lipton and Ross *et al.* in 1974.[7] The original 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.[2,4,8] PDGF is a well characterized regulatory protein with an isoelectric point of 9.8 and a molecular weight of approximately 30,000 Da.[2] It consists of two disulfide-bonded polypeptide chains that are encoded by two different genes, PDGF-A and PDGF-B, located on chromosomes 7 and 22, respectively.[4,9] Consequently, PDGF can exist as a heterodimer (AB) or a homodimer (AA, BB).[4] The mature parts of the A- and B-chains of PDGF are ~100 amino acid residues long and show ~60% amino acid sequence identity.[9] Heldin etal in 2002 have identified two new forms, PDGF-C and PGDF-D.[8] 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.[10] PDGF isoforms exert their effects on target cells by activating two structurally related protein tyrosine kinase receptors, designated as PDGFR α and β, which have different ligand specificities.[8,9] The synthesis of PDGF is often increased in response to external stimuli, such as exposure to low oxygen tension, thrombin, or stimulation with various growth factors and cytokines.[9]

PDGF plays a significant role in wound healing by stimulating connective tissue growth via its mitogenic and chemotactic activities.[4] It stimulates mitogenicity and chemotaxis of fibroblasts and smooth muscle cells and chemotaxis of neutrophils and macrophages. It also stimulates macrophages to produce and secrete other growth factors of importance for various phases in the healing process. Moreover, PDGF stimulates the production and secretion of collagenase by fibroblasts, suggesting a role in the remodeling phase of wound healing. It also has important functions during the embryogenesis, in particular for the development of the kidneys, blood vessels, lungs, and CNS. In these organs, connective tissue-like cell types are dependent on PDGF, including mesangial cells, pericytes, alveolar fibroblasts, and

glial cells. The PDGF receptors are expressed on capillary endothelial cells, and PDGF has been shown to have an angiogenic effect. PDGF has an important role to maintain the interstitial fluid pressure, probably through its ability to stimulate interactions between connective tissue cells and molecules the extracellular matrix.[9]

FIBROBLAST GROWTH FACTOR (FGF)

Fibroblast Growth Factors are polypeptides that are potent mitogens and chemo-attractants for endothelial cells as well as for a variety of mesenchymal cells, including fibroblasts, osteoblasts, chondrocytes, smooth muscle cells,skeletal myoblasts and for cells of neuro-ectodermal origin. FGF have not only growth-promoting effects on most fibroblastic cell types, but it also stimulates angiogenesis, neo-vascularization, wound healing and cell migration.[2,6,11]FGFs are a family of 9 heparin-binding polypeptides, aFGF (FGF-1), bFGF (FGF-2), int-2 (FGF-3), Kaposi sarcoma FGF (K-FGF; also known as the product of hst-1 oncogene: FGF-4), FGF-5, FGF-6, keratinocyte growth factor (KGF: FGF-7), androgen-induced growth factor (FGF-8) and FGF-9.[12] The two most studied members of this family are acid FGF (a-FGF or FGF-1) and basic FGF (b-FGF or FGF-2).[4] FGF-1 has an isoelectric point range of 5.6-6.0 and a molecular weight of approximately 15,000 Da; FGF-2 has an isoelectric point of approximately 9.6 and a molecular weight range of 16,000-18,000Da. FGF-1 and FGF-2 have a similar spectrum of biological activities and exhibit 55% homology in their amino acid sequence. FGF-2 is considered to be more potent than FGF-1 (30-100 fold) *in vitro*.[2]Signal transducing FGF receptors (FGFRs) are encoded by a family of related genes of which 4 members have been encoded so far i.e. FGFR-1(flg), FGFR-2(bek), FGFR-3 AND FGFR-4. There is a high degree of redundancy among FGFRs in terms of their binding to ligands and each bind both FGF-1 and FGF-2 with high affinity.[13]Both FGF-1 and FGF-2 were initially isolated from neural tissue but have been subsequently found in numerous other tissues.[4] FGF-2 has been shown to be produced in the brain, pituitary gland, kidney, corpus luteum, and adrenal gland.[13]

FGFs are multifunctional regulatory peptides with a great impact on studies of tumorigenesis, cardiovascular disease, repair of tissue injury, neurobiology and embryonic development.[12]They are responsible for critical functions in wound healing, tissue repair, angiogenesis, and homeostatic regulation.[10] FGF stimulates the proliferation and/ or migration of most of the major cell types involved in wound healing, including capillary endothelial cells, vascular endothelial cells, fibroblasts, keratinocytes, epithelial cells and specialized cell types such as chondrocytes and myoblasts. The administration of FGF-2 at the time of wound closure not only significantly increases the breaking strength of the wound but also improves the quality of the scar.[8] The FGFs are believed to act as competence growth factors. FGFs initiate a cascade of cellular events but require synergistic action with progression growth factors to maximize DNA synthesis and cell growth.[2] *In vivo* FGF has been shown to increase bone formation, and accelerate the rate of fracture repair.[6] 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 an important role of these proteins in periodontal wound healing and regeneration.[2] Studies on the effects of FGF on individual cell types have shown that it can stimulate endothelial cell and periodontal ligament cell migration and proliferation.[6]

INSULIN LIKE GROWTH FACTOR (IGF)

Insulin like Growth Factors are a family of growth factors, including ligands, receptors and binding proteins that are involved in the regulation of various physiological processes and in pathogenic conditions including the status of oral tissues.[14] They are a family of single-chain serum proteins that share 49% homology in sequence with proinsulin.[2] The IGF family includes three ligands and three cell surface receptors namely; insulin, IGF-1 and IGF-2; Insulin, IGF-

1R and IGF-2R (L-mannose-G-phosphate) receptors respectively. They have atleast six high affinity IGF-binding proteins (IGFBPs-1 to 6), which bind circulating IGFs and modulate their biologic actions.[11,15,16] Two well described members of this group are IGF-1 and IGF-2.[11] IGF-1 is a 70-amino-acid protein with a molecular weight of 7649 Da and an isoelectric point of 8.4. IGF-2 is a 67-amino-acid neutral peptide with a molecular weight of 7471 Da .[2] IGF-1 and IGF-2 have 65% amino acid sequence homology and similar biologic activities; however their synthesis is under different regulating influences.[4] IGF-1 and IGF-2 are anabolic peptides structurally and functionally related to insulin.[17] IGFs bind to specific receptors,[16] i.e. IGF-1R and IGF-2R.[18] The tyrosine kinase receptor IGF-1R mediates most of the actions of IGFs and is expressed nearly ubiquitously.[16] The function of insulin growth factors is regulated at cellular level by the presence of a family of IGFBPs, which may either inhibit the bioactivity of IGFs by preventing receptor interaction or potentiate IGF activities by mechanisms that are not well understood.[6,16] IGFs are produced in largest amounts by the liver. They are also produced by most extra-hepatic organs, like bone, smooth muscle and placenta, and are transported via the plasma. Bone is a storage house for IGFs in their inactive forms.[4,17,19]

IGF is a highly mitogenic and differentiation factor, which exerts endocrine, paracrine and autocrine functions, to control pre- and post-natal growth and development. It is a potent stimulator of cell proliferation and differentiation as well as maintenance of specialized functions in several tissues. IGF-1 is an anabolic peptide that mediates the biological effects of growth hormone.[18] IGF-1 acts as a progression factor in the cell cycle.[2] IGFs have pleotrophic effects on their target cells, including an increase in transport of glucose and amino acids into osteoblasts, an increase in RNA and a decrease in protein breakdown.[4] IGF-1 has the capacity to inhibit apoptotic death. It is a potent chemotactic agent for vascular endothelial cells. It also stimulates mitosis of many cells *in-vitro* such as fibroblasts, osteocytes and chondrocytes.[11]

There are indications that IGFs may play a role in the biology of oral and dental tissues and organs.[16] IGF-1 also participates actively in the cell proliferation and differentiation of developing teeth, being a crucial factor in the mineralizing process during odontogenesis, suggesting potential therapeutic use of IGF-1 in the pulp tissue, both in immature and mature teeth when insulted by external irritants.[18] IGF-1 has a role in pulp healing and reparative dentinogenesis following pulp capping.[11] IGF-1 is a mitogenic protein which is reported to stimulate cell proliferation and chemotactic migration, enhance cellular survival and improve periodontal regeneration.[20] Both gingival and periodontal mesenchymal cells show a dose-dependent migratory response to the presence of IGF-1 and IGF-2. They also increase DNA synthesis and protein production by periodontal ligament cells.[17] IGFs also appear to have a role in bone formation.[2]

TRANSFORMING GROWTH FACTOR (TGF)

Transforming Growth Factors are a family of structurally and functionally different proteins that have been isolated from normal and neoplastic tissues.[17] TGFs were first named for their ability to stimulate anchorage-independent growth of fibroblasts in monolayer.[4] The two best characterized in this category are TGF-α, primarily a growth stimulator, and TGF-β, primarily a growth inhibitor.[17] TGF-α is a 50-aminoacid single-chain protein with a molecular weight of approximately 5600 Da. TGF-α exhibits 42% homology with EGF, competes for the EGF receptor and stimulates epithelial and endothelial cells. TGF-β is a highly conserved dimeric polypeptide with a molecular weight of 25,000 Da and consists of 2 amino acid chains linked together by disulfide bonds.[2] It was originally isolated as a PDGF and later was found in the largest amounts stored in bone in an inactive form.[4] TGF-α is synthesized by epithelial cells. TGF-β is synthesized by multiple tissues like activated macrophages,

endothelial cells, lymphocytes and neutrophils, but bone and platelets are its major sources.[2,8,17]

TGF-α induces epithelial and endothelial cell proliferation.[2] Because of the large diversity of TGF-β effects, it has been said that TGF-β is pleiotropic with a vengeance.[8] It is a multifunctional growth factor structurally related to the bone morphogenetic proteins, but functionally quite different.[6] It is a fundamental regulatory molecule that acts by both autocrine and paracrine mechanisms.[21]The biological effects of TGF-β are highly diverse.[17] It has multiple and often opposing effects depending upon the tissue and the type of injury.[8] TGF-β has proliferative and anti-proliferative, differentiating and antidifferentiating effects depending on the cell type and maturity. It has immunosuppressive characteristics too and has been investigated for its ability to induce cartilage and new bone growth *in-vivo*.[4] TGF-β has bifunctional activity wherein it acts as a multifunctional modulator of cell proliferation.[11] It inhibits epithelial cell proliferation and stimulates mesenchymal cells.[6]It is a potent fibrogenic agent[8] and acts as a progression factor for fibroblasts.[11] It stimulates fibroblast chemotaxis and proliferation, and also induces extracellular matrix production in most culture systems.[2] TGF-β has a strong anti-inflammatory effect.[8] TGF-β has a somewhat paradoxical effect on angiogenesis. *In vivo*, it stimulates angiogenesis, yet *in-vitro* it blocks endothelial proliferation and motility.[11] Several *in vivo* investigations support the role of TGF-β in wound healing. The application of TGF-β increased the formation of granulation tissue. TGF-β has both stimulatory and inhibitory effects on osteoblast proliferation, depending on the *in-vitro* culture conditions.[2] In spite of its effects on augmentation of soft and hard tissue types, no positive data have been reported on *in-vivo* healing in a periodontal setting.[6] TGF-β has been shown to be chemotactic for macrophages and gingival and periodontal ligament mesenchymal cells to stimulate the proliferation of gingival and periodontal ligament mesenchymal cells. TGF-β has also been shown selectively to stimulate the synthesis of extracellular matrix proteins such as collagen, fibronectin, tenascin and proteoglycans by these cells and to inhibit the growth of epithelial, endothelial and certain mesenchymal cells. In addition, TGF-β1 alone or in combination with PDGF increases the proliferation of periodontal ligament mesenchymal cells more than those from gingival tissue.[17]It has been reported that TGF-β1, a multifunctional growth factor highly expressed in gingival tissues subjected to inflammation and wound healing, and is the main mediator responsible for myo-fibroblast differentiation.[22]

EPIDERMAL GROWTH FACTOR (EGF)

Epidermal Growth Factor is a keratinocyte-stimulating growth factor.[4] It is a small polypeptide that stimulates the proliferation of epithelial, endothelial and mesenchymal cells.[17] EGF had been identified as early as 1962, and its receptor was purified and characterized by Stanley Cohen in 1980.[23] EGF was initially discovered in mouse submandibular glands by its ability to cause precocious tooth eruption and eyelid opening in newborn mice.[8,24] It is a single-chain, 53-amino-acid protein with a broad spectrum of activity and with hormone like properties.[2,24] The human-derived form has a molecular weight of approximately 5400 Da.[2] EGF and TGF-α are structurally related, possess similar properties, have the same biological activity and share a common receptor.[2,4,8]The "EGF receptor (EGFR)" is actually a family of membrane tyrosine kinase receptors that respond to EGF, TGF-α, and other ligands of the EGF family.[8] It belongs to a family of related cell surface receptors, including ErbB1 (EGFR), ErbB2/Her-2, ErbB3, and ErbB4.[25] The main EGFR is referred to as EGFRl, or Erb BI.[8] EGFR is highly expressed in many solid tumors including human OSCC and therefore, is a target for cancer therapy and prevention.[26]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 EGF as well. [2,4,8,17,23,24,25,27,28]

EGFR is critical for promoting growth, survival, and differentiation of epithelial cells. It is also critical for wound healing due to its ability to stimulate cell proliferation, cell migration, and angiogenesis.[25] EGFR is a major driving force for cell proliferation in human primary keratinocytes.[29] EGF, *in vivo* promotes angiogenesis. Studies have showed that EGF released following orthodontic force application plays a part in the angiogenic response of the pulp.[27] In healing wounds of the skin, EGF is produced by keratinocytes, macrophages, and other inflammatory cells that migrate into the area.[8] 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.[17] EGF stimulates prostaglandin production and induces bone resorption in cultures of neonatal mouse calvaria.[2]

KERATINOCYTE GROWTH FACTOR (KGF)

Keratinocyte Growth Factor is classified as FGF-7 and belongs to heparin binding FGF family.[30,31] 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.[30] It has specific mitogenic, morphogenic and motogenic effects on epithelial cells.[32] KGF-1 and KGF-2 are two members of the current FGF family and are classically designated as FGF-7 and FGF-10, respectively.[33] They share more than 60% sequence identity with each other.[31] The KGF receptor (KGFR) is a membrane-spanning tyrosine kinase which is alternatively spliced isoform of FGFR-2 and designated as FGFR-2IIIb.[31,34] KGF was initially purified and cloned from a lung fibroblast line as a soluble factor that could stimulate keratinocyte proliferation.[34] Dermal fibroblasts, microvascular endothelial cells, smooth muscle cells and activated ϒδ T cells express KGF-1. In oral tissues, KGF-1 is expressed *in vitro* by fibroblasts isolated from oral buccal mucosa, gingiva, PDL and in the stroma associated with inflammed periapical tissues.[31]

KGF is an androgen-induced stromal growth factor that can stimulate epithelial growth and morphogenesis in the developing prostate and seminal vesicle. KGF has also been shown to be a progestomedin in the endometrium of primates. Its role in the mammary gland, another steroid hormone-dependent tissue, is less well defined.[30] Generally, both KGF family members induce proliferation, migration and matrix metalloproteinase secretion in a variety of epithelial cells.[33] KGF stimulates the re-epithelialization phase of wound healing at periodontal diseased sites.[32] KGF-1 expression in gingival tissues and its up-regulation by pro-inflammatory cytokines and lipopolysaccharide (LPS) support the putative role of KGF-1 in regulating epithelial cell function in periodontal diseases.[31] 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 effective epithelial cell barrier which protects the host from periodontal disease-associated gram-negative pathogens in dental plaque biofilm.[33]

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

Vascular Endothelial Growth Factor is a macromolecule which enhances blood vessel growth and permeability. Thus,

it is also known as vascular permeability factor.[35] VEGF has significant homology to PDGF. VEGF is a heparin-binding homodimeric, disulfide-bound glycoprotein of 45kDa.[36] The VEGF family currently comprises of seven members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, 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/Flk-1), and Flt-4 (VEGFR-3).[37] VEGF also interacts with a family of coreceptors, the neuropilins (NP).[36] 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.[37] Oxygen tension plays a key role in regulating the expression of a variety of genes. Several major growth factors, including EGF, TGF, KGF, IGF-I, FGF, and PDGF, up-regulate VEGF mRNA expression, suggesting that paracrine or autocrine release of such factors cooperates with local hypoxia in regulating VEGF release in the microenvironment. Also, inflammatory cytokines such as IL-1α and IL-6 induce expression of VEGF in several cell types, including synovial fibroblasts, in agreement with the hypothesis that VEGF may be a mediator of angiogenesis/permeability in inflammatory disorders. Hormones are also important regulators of VEGF gene expression.[36]

VEGF is one of the most important proangiogenic factors. VEGF also potentiates microvascular hyperpermeability, which can both precede and accompany angiogenesis.[37] It is also critical for reproductive and bone angiogenesis.[36] VEGF is a highly specific mitogen for endothelial cells.[37] VEGF is likely a factor in the etiology of gingivitis and its progression to periodontitis, possibly by promoting expansion of the vascular network coincident to progression of the inflammation.[35] VEGF has been implicated in having direct chemotactic and mitogenic effects on osteoblasts and osteogenic cells.[38]

CEMENTUM DERIVED GROWTH FACTOR (CDGF)

The mineralized matrix of tooth cementum contains a 14 kDa polypeptide growth factor referred to as cementum-derived growth factor (CDGF). 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 present 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 mitogenic activity, even at suboptimal concentrations, is synergistically potentiated by EGF and serum.[39]

CONCLUSION

Regeneration of the periodontal tissues is a dynamic process involving cell-to-cell and cell–extracellular matrix interactions. Growth factors elegantly co-ordinate these interactions resulting in wound healing and regeneration of tissues. Several growth and differentiation factors have shown potential as therapeutic agents to support periodontal wound healing/regeneration, although optimal dosage, release kinetics, and suitable delivery systems are still unknown. Only a few growth and differentiation factors have reached clinical evaluation. A review of the current existing literature shows that a combination of growth factors in an optimal concentration is best suited for periodontal

regeneration. With the advent of the recombinant technique it is now possible to provide large quantities of purified growth factors for use in *in vivo* studies. Present studies are focusing on the development of a suitable carrier material that has mechanical properties and surgical practicality appropriate for controlled release of growth factors. It appears that well-defined discriminating preclinical models followed by well designed clinical trials are needed to further investigate the true potential of these and other candidate factors.

REFERENCES

1. Newman MG, Takei HH, Klokkevold PR and Carranza FA. Carranza's Clinical Periodontology. St. Louis: Saunders; 2006.
2. Caffesse RG, Quinones CR. Polypeptide growth factors and attachment proteins in periodontal wound healing and regeneration. Periodontal 2000 1993; 1: 69-79.
3. Foster BL, Somerman MJ. Regenerating the periodontium: is there a magic formula. Orthod Craniofacial Res 8, 2005; 285–291.
4. McCauley LK, Somerman MJ. Biologic modifiers in periodontal regeneration. DCNA 1998; 42:361-87.
5. Anitua E, Troya M, Orive G. An Autologous Platelet Rich Plasma Stimulates Periodontal Ligament Regeneration. J Periodontol 2013;84:1556-66.
6. Cochran DL, Wozney JM. Biological mediators for periodontal regeneration. Periodontal 2000 1999; 19: 40-58.
7. Raines EW, Bowen-Pope DF, Ross R. Handbook of Experimental Pharmacology. 1990; 95: 173-262.
8. Kumar V, Abbas AK, Fausto N. Robbins and Cortan Pathologic Basis of Disease. Pennsylvania: 2004 8th ed., pp. 366–372.
9. Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev 1999; 79: 1283-316.
10. Eskan MA, Greenwell H. Theoretical and Clinical Considerations for Autologous Blood Preparations: Platelet-Rich Plasma, Fibrin Sealants, and Plasma-Rich Growth Factors. Clin Adv Periodontics 2011; 1:142-153.
11. Raja S, Byakod G, Pudakalkatti P. Growth factors in periodontal regeneration. Int J Dent Hygiene 2009;7: 82–89.
12. Takayama S, Murakami S, Miki Y, Ikezawa K, Tasaka S, Terashima A, Asano T, Okada H. Effects of basic fibroblast growth factor on human periodontal ligament cells. J Periodont Res 1997; 32: 667-675.
13. Takayama SI, Yoshida J, Hirano H, Okada H, Murakami S. Effects of basic fibroblast growth factor on human gingival epithelial cells. J Periodontol 2002; 73: 1467-1473.
14. Hung PS, Kao SY, Liu CJ, Tu HF, Wu CH, Lin SC. Insulin-like growth factor binding protein-5 enhances the migration and differentiation of gingival epithelial cells. J Periodont Res 2008; 43: 673–680.
15. Takenouchi Y, Ohshima M, Yamaguchi Y, Nishida T, Senda N, Idesawa M, Otsuka K, Ito K. Insulin-like growth factor-binding protein-2 and -3 in gingival crevicular fluid. J Periodont Res 2010; 45: 803–808.
16. Gotz W, Kunert D, Zhang D, Kawarizadeh A, Lossdorfer S, Jager A. Insulin-like growth factor system components in the periodontium during tooth root resorption and early repair processes in the rat. Eur J Oral Sci 2006; 114: 318–327.
17. Manson JD, Eley BM. Outline of Periodontics. Oxford: Wright; 2000.

18. Bucheli JC, Sanchez PC, Sarria NC, Garcia JJ, Vasquez JA, Rivero C, Azuero-Holguin MM, Diaz E, Munoz HR. Expression of insulin-like growth factor-1 and proliferating cell nuclear antigen in human pulp cells of teeth with complete and incomplete root development. International Endodontic Journal 2009; 42: 686-693.

19. Kumamoto H, Ooya K. Immunohistochemical detection of insulin-like growth factors, platelet-derived growth factor, and their receptors in ameloblastic tumors. J Oral Pathol Med 2007; 36: 198–206.

20. Yang L, Zhang Y, Dong R, Peng L, Liu X, Wang Y, Cheng X. Effects of adenoviral-mediated coexpression of bone morphogenetic protein-7 and insulin-like growth factor-1 on human periodontal ligament cells. J Periodont Res 2010; 45: 532–40.

21. Sánchez AR, Sheridan PJ, Kupp LI. Is Platelet-rich Plasma the Perfect Enhancement Factor? A Current Review. Int J Oral Maxillofac Implants 2003;18:93-103.

22. Anitua E, Troya M, Orive G. Plasma Rich in Growth Factors Promote Gingival Tissue Regeneration by Stimulating Fibroblast Proliferation and Migration and by Blocking Transforming Growth Factor-β1-Induced Myodifferentiation. J Periodontol 2012; 83:1028-1037.

23. Mendelsohn J. Targeting the Epidermal growth factor receptor for cancer therapy. Journal of Clinical Oncology 2002; 20: 1s-12s.

24. Oxford GE, Nguyen KHT, Alford CE, Tanaka Y, Beher MGH. Elevated Salivary EGF Levels Stimulated by Periodontal Surgery. J Periodontol 1998; 69: 479-484.

25. Woodworth CD, Michael E, Marker D, Allen S, Smith L, Nees M. Inhibition of the epidermal growth factor receptor increases expression of genes that stimulate inflammation, apoptosis, and cell attachment. Mol Cancer Ther 2005; 4: 650-658.

26. H Ge, H Liu, Z Fu, Z Sun. Therapeutic and preventive effects of an epidermal growth factor receptor inhibitor on oral squamous cell carcinoma. The Journal of International Medical Research 2012; 40: 455-466.

27. Derringer K, Linden R. Epidermal growth factor released in human dental pulp following orthodontic force. European Journal of Orthodontics 2007; 29: 67-71.

28. Demory ML, Boerner JL, Davidson R, Faust W, Miyake T, Lee I, Huttemann M, Douglas R, Haddad G, Parsons SJ. Epidermal Growth Factor Receptor Translocation to the Mitochondria. The Journal of Biological Chemistry 2009; 284: 36592-36604.

29. Xu Y, Baker D, Quan TH, Baldassare JJ, Voorhees JJ, Fisher GJ. Receptor type protein tyrosine phosphatase-Kappa mediates cross-talk between Transforming growth factor-β and Epidermal growth factor receptor signaling pathways in human keratinocytes. Molecular biology of the cell 2010; 21: 29-35.

30. Bansal GS, Cox HC, Marsh S, Gomm JJ, Yiangou C, Luqmani Y, Coombes RC, Johnston CL. Expression of keratinocyte growth factor and its receptor in human breast cancer. British Journal of Cancer 1997; 75: 1567-1574.

31. Li M, Firth JD, Putnins EE. Keratinocyte growth factor-1 expression in healthy and diseased human periodontal tissues. J Periodont Res 2005; 40: 118–128.

32. McKeown STW, Hyland PL, Locke M, Mackenzie IC, Irwin CR. Keratinocyte growth factor and scatter factor expression by regionally defined oral

fibroblasts. Eur J Oral Sci 2003; 111: 42-50.

33. Putnins, EE, Sanaie AR, Qiang Wu, Firth JD. Induction of Keratinocyte Growth Factor 1 Expression by Lipopolysaccharide Is Regulated by CD-14 and Toll-Like Receptors 2 and 4. Infect Immun 2002; 70 (12): 6541–6548.

34. Bellis AD, Crescioli C, Grappone C, Milani S, Ghiandi P, Forti G, Serio M. Expression and Cellular Localization of Keratinocyte Growth Factor and Its Receptor in Human Hyperplastic Prostate Tissue. J Clin Endocrinol Metab 1998; 83: 2186–2191.

35. Johnson RB, Serio FG, Dai X. Vascular endothelial growth factors and progression of periodontal diseases. J Periodontol 1999; 70(8): 848-852.

36. Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocrine Reviews 2004; 25: 581-611.

37. Hoeben A, Landuyt B, Highley MS, Wildiers H, Oosterom ATV, De Bruijn EA. Vascular Endothelial Growth Factor and Angiogenesis. Pharmacol Rev 2004; 56: 549–580.

38. Kaigler D, Silva EA, Mooney DJ. Guided Bone Regeneration (GBR) Utilizing Injectable Vascular Endothelial Growth Factor (VEGF) Delivery Gel. J Periodontol 2013; 84: 230-238.

39. Ikezawa K, Ohtsubo M, Norwood TH, Narayanan AS. Role of cyclin E and cyclin E-dependent kinase in mitogenic stimulation by cementum-derived growth factor in human fibroblasts. FASEB J. 1998; 12: 1233–1239.

Competing interest / Conflict of interest The author(s) have no competing interests for financial support, publication of this research, patents and royalties through this collaborative research. All authors were equally involved in discussed research work. There is no financial conflict with the subject matter discussed in the manuscript.
Source of support: NIL