Review Article

Growth factors: Role in periodontal regeneration

Suchetha A*, Manjari Lalwani**, Darshan BM***, Sapna N***, Divya Bhat****, Koduru Sravani**

* Professor and Head, ** Post Graduate Student, ***Reader, ****Senior lecturer, Department of Periodontics, DAPM RV Dental College, Bangalore-560078, Karnataka, India.

DOI: 10.5455/jrmds.2015332

ABSTRACT

Periodontitis is caused by bacterial biofilms results in devastation of periodontal tissues, including cementum, bone, and periodontal ligament (PDL), with ultimate tooth loss if left untreated. Studies targeted at understanding the disease at the cellular and molecular level as well as clinical investigations have resulted in improved therapies for arrest of disease progression. Moreover, beyond arrest of disease progression, substantial evidence exists indicating that regeneration of periodontal tissues is a viable treatment for selective situations. There is a need; however, to improve the predictability of regenerative therapies. A variety of regenerative therapies have been introduced, with some success in periodontal tissue regeneration. Growth factors are polypeptide molecules released by cells in the inflamed area that regulate events in wound healing. These are naturally occurring proteins that regulate various aspects of cell growth and development. Researchers are now exploring the potential applications and uses of growth factor in periodontal regeneration.

Keywords: Periodontitis, Regeneration, Growth Factors

INTRODUCTION

Periodontitis, evoked by the bacterial biofilm (dental plaque) that forms around teeth, progressively destroys the periodontal tissues supporting the teeth, including the periodontal ligament, cementum, alveolar bone and gingival [1]. Thus, the rationale of periodontal therapy is to eradicate the inflammation of the periodontal tissues, to seize the destruction of soft tissue and bone caused by periodontal disease, and regenerate the lost tissue, if possible [2]. Periodontal surgical procedures have focused on the removal of hard and soft tissue defects (i.e., probing depths and osseous defects) by regenerating new attachment [3].

Periodontal wound-healing studies, however, indicate that conventional periodontal therapy most commonly results in repair rather than regeneration [4, 5].

In order for periodontal regeneration to occur, progenitor periodontal ligament cells must migrate to the denuded root surface, attach to it, proliferate and mature into an organized and functional fibrous attachment apparatus. Similarly, progenitor bone cells must also migrate, proliferate and mature in conjunction with the regenerating periodontal ligament.

Significant advances have been made during the last decade in understanding the factors controlling the migration, attachment and proliferation of cells.

Polypeptide growth factors are a class of natural biological mediators that control key cellular events in tissue repair, including cell proliferation, chemotaxis, differentiation, and matrix synthesis, by binding to specific cell-surface receptors.

A group of naturally occurring molecules known as polypeptide growth factors in conjunction with certain matrix proteins are key regulators of these biological events. Of these, the fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), insulin - like growth factors (IGFs), transforming growth factors (TGFs), epidermal growth factor (EGF) and certain attachment proteins appear to have an important role in periodontal wound healing.

FIBROBLAST GROWTH FACTOR

FGF was discovered in 1974 as a protein in cow pituitary glands that strongly induced proliferation of fibroblasts [6]. In 1984, two proteins with different basic and acidic isoelectric points were identified as acidic FGF (aFGF, FGF1) and basic FGF (bFGF, FGF2) [7, 8]. The FGFs are a family of polypeptides that are potent mutagens and chemoattractants for endothelial cells as well as for a variety of mesenchymal cells, including fibroblasts, osteoblasts, chondrocytes, smooth muscle cells and skeletal myoblasts [9, 10].

ROLE OF FGF

These factors have also been shown to stimulate the formation of new blood vessels (i.e., angiogenesis and neovascularization) in vivo [11-13]. 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 [14].

FGF stimulates resting cells in G0 to enter the cell cycle in G1.

FGF2 facilitates reactions that are necessary for revascularization, migration, and proliferation of endothelial cells, [15] and regenerates capillary blood vessels *in vivo* [16] in the healing of intractable ulcers. Fibroblasts not only produce collagen, but also develop into myofibroblasts and induce so called wound constriction.

FGF2 promotes the healing of fractures by stimulating both the growth and biochemical functions of mesenchymal stem cells [17].

PLATELET DERIVED GROWTH FACTOR

PDGF is a well characterized regulatory protein with an isoelectric point of 9.8 and a molecular weight of approximately 30,000 Da [18-21]. PDGF is a dimeric molecule and occurs as a combination of two polypeptide subunits, designated as A and B [22]. PDGF acts on the target cells by binding to α and β receptors on their cell surfaces and in turn stimulates them. PDGF has 5 isoforms, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD [23].

The original source of PDGF was from the alpha granules of platelets [24], but it has also been isolated from a variety of cells and tissues including monocytes and macrophages [25], fibroblasts [26], endothelial cells [27] and bone matrix [28].

ROLE OF PDGF

PDGF has been identified as a competence growth factor [29] and acts synergistically with progression growth factors, such as the IGFs [30]. PDGF, however, also acts as a paracrine factor by stimulating certain cells to produce their own progression growth factors [31, 32].

In vivo studies support an important role of PDGF in wound healing. It also promotes synthesis of fibronectin and types I, III and V collagen. It inhibits collagenase and plasminogen activator. PDGF upregulates the expression of angiogenic molecules like vascular endothelial growth factor (VEGF) and hepatocyte growth factor, and also the proinflammatory cytokine interleukin 6; there by indirectly promoting periodontal regeneration.

INSULIN LIKE GROWTH FACTORS

IGFs are a family of single-chain serum proteins that share 49% homology in sequence with proinsulin [33, 34, 35, 36]. IGF-1 and IGF-2 are 2 polypeptides from this group that have been well described.

They are synthesized by multiple tissues, including liver, smooth muscle and placenta [37], and are carried in plasma as complex with a specific binding protein [38, 39].

ROLE OF IGF

IGFs appear to have a role in bone formation. IGF-1 increased DNA synthesis in osteoblasts and stimulated the formation of bone matrix in organ culture [40]. IGFs alone enhanced DNA synthesis and proliferation of chondrocytes [41].

IGF-1 could act synergistically with other growth factors to enhance epidermal and connective tissue wound healing [42]. The combination of IGF-1 and PDGF, as opposed to either factor alone, resulted in a 95% increase in epidermal thickness and a two-fold increase in the width of newly formed connective tissue when applied to skin wounds in pigs. Lynch et al. also suggested that the same combination enhances periodontal regeneration [43] and bone formation around implants [44].

EPIDERMAL GROWTH FACTOR

Epidermal growth factor is a multifunctional cytokine involved in variety of functions including epithelial growth and differentiation, and wound healing. Epidermal growth factor (EGF) is a single-chain protein. The major sources of EGF are urine and salivary glands, although it also has been isolated from Brunner's glands and platelets as well as from cerebrospinal and amniotic fluids. [45] EGF stimulates DNA synthesis and cell growth in a large variety of cells, including those of epithelial, endothelial and mesodermal origin. However, EGF stimulates prostaglandin production and induces bone resorption in cultures of neonatal mouse calvaria [46, 47]. The topical application of EGF to abraded corneas partial-thickness wounds full-thickness 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.

TRANSFORMING GROWTH FACTOR

The TGFs are a family of structurally and functionally unrelated proteins that have been isolated from normal and neoplastic tissues [48]. The two best characterized polypeptides from this group of growth factors are TGF-α and TGF-β. TGF-α is a 50-aminoacid single-chain protein with a molecular weight of approximately 5600 Da [49]. 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 [50].

ROLE OF TGF

TGF-β appears to be a major regulator of cell replication and differentiation. TGF-β can modulate other growth factors, such as PDGF, TGF-α, EGF and FGF, possibly by altering their cellular response [51] or by inducing their expression [52]. Several *in vivo* investigations support the role of TGF-β in wound healing. The application of TGF-β increased the formation of granulation tissue [53].

The topical application of TGF-β to epidermal wounds in pigs inhibited re-epithelialization and increased connective tissue volume, collagen synthesis and angiogenesis. Other reports using implanted chambers or tubes filled with TGF-β 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 [54].

APPROACHES FOR GROWTH FACTOR DELIVERY

Two common types of polymeric materials used in growth factor delivery strategies are natural collagen-derived materials and synthetic polymers of lactic and glycolic acid (i.e.polylactide-co-glycolide) [55].

A variety of new injectable materials such as hydrogels are also being developed for growth factor delivery applications [56]. These injectables are especially attractive because, in clinical application, they can allow for minimally invasive delivery of inductive molecules.

Another area of increasing attention has been the development of shape-memory materials that have one shape at one temperature and another shape at a different temperature. These materials have the ability to memorise a permanent shape that can be substantially different from an initial temporary shape. As an example, a bulky device could potentially be introduced into a surgical site as a temporary shape (such as a string or freely flowing material), penetrate through a small area of the site, and then be expanded in response to different cues into a permanent shape (i.e., a stent or a sheet). The response signals that stimulate the changes in shape in response to environmental cues are incorporated within the material during its fabrication.

These materials have been designated as ‘smart’ materials, having the capability to appropriately change their structural and functional material properties in response to environmental cues [57].

CONCLUSION

The explosion of knowledge and the understanding of the role of growth factors, and their mechanisms of action and molecular signalling pathways, suggest the potential for many novel therapeutic targets, not only for applying growth factors but also for the agents that target specific parts of the intracellular signalling pathways.

In the last, we can say that the most important demanding task is left on us, is to apply some of the knowledge which we have gained from studying the ‘cell- physiology’, into the useful techniques of healing of diseases, in the days to come.

REFERENCES

1. DaroutIS. Oral bacterial interactions in periodontal health and disease. Academic J 2014;6(5):51-7.
2. Reynolds MA, Aichelmann-Reidy ME, Branch Mays GI, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. Ann Periodontol 2003;8:227–65.
3. Froum SJ, Weinberg MA, Tarnow D. Comparison of Bioactive Glass Synthetic Bone Graft Particles and Open Debridement in the Treatment of Human Periodontal Defects. A Clinical Study. J Periodontol 1998;69:698-709.
4. Caton JC, Nyman S, Zander HA. Histometric evaluation of periodontal surgery. Connective tissue attachment levels after four regeneration procedures. J Clin Periodontol 1980;7:224-31.
5. Listgarten MA, Rosenberg MM. Histological study of repair following new attachment procedures in human periodontal lesions. J Periodontol 1979;50:333-44.
6. Gospodarowicz D. Localisation of a fibroblast growth factor and its effect alone and with hydrocortisone on 3T3 cell growth. Nature 1974;249:1237.
7. Bohlen P, Baird A, Esch F, Ling N, Gospodarowicz D. Isolation and partial molecular characterization of pituitary fibroblast growth factor. Proc Natl Acad Sci U S A. 1984;81:5364–8.

8. Thomas KA, RiosCandelore M, Fitzpatrick S. Purification and characterization of acidic fibroblast growth factor from bovine brain. Proc Natl Acad Sci U S A. 1984;81:357–61.
9. Baird A, Walicke PA. Fibroblast growth factors. In: Waterfield MD, ed. Growth factors. Br Med Bull 1989;45:438-52.
10. Centrella M, McCarthy TL, Canalis E. Transforming growth factor beta (TGF-0) is a bifunctional regulator of replication and collagen synthesis in osteoblast-enriched cell cultures from fetal rat bone. J Biol Chem 1987;262:2869-74.
11. Folkman J, Klagsbrun M. Angiogenic factors. Science 1987;235:442-7.
12. Gospodarowicz D, Bialecki H, Thakral TK. The angiogenic activity of the fibroblast and epidermal growth factor. Exp Eye Res 1979;28:501-14.
13. Gospodarowicz D, Neufeld G, Schweigerer L. Fibroblast growth factor: structural and biological properties. J Cell Physiol 1987;5:15-26.
14. Terranova VP, Odziemiec C, Tweden KS, Spadone DP. Repopulation of dentin surfaces by periodontal ligament cells and endothelial cells. Effect of basic fibroblast growth factor. 1 Periodontol 1989;60:293-301.
15. Gospodarowicz D, Ferrara N, Schweigerer L, Neufeld G. Structural characterization and biological functions of fibroblast growth factor. Endocr Rev.1987;8:95–114.
16. Folkman J, Klagsbrun M. Angiogenic factors. Science. 1987;235:442–7
17. Kawaguchi H, Nakamura K, Tabata Y, Ikada Y, Aoyama I, Anzai J et al. Acceleration of fracture healing innonhuman primates by fibroblast growth factor2. J Clin Endocrinol Metab 2001;86:875–80.
18. Antoniades HN. Human platelet-derived growth factor (PDGF). Purification of PDGF-I and PDGF-I1 and separation of their reduced subunits. Proc Natl Acad Sci USA 1981;78:7314-7.
19. Deuel TF, Huang JS, Proffit RT, Baenzinger JU, Chang D, Kennedy BB. Human platelet-derived growth factor: purification and resolution in to two active protein fractions. J Biol Chem 1981;256:8896-9.
20. Heldin CH, Westermark B, Wasterson A. Platelet-derived growth factor: isolation by a large-scale procedure and analysis of subunit composition. Biochem J 1981;193: 907-13.
21. Raines EW, Ross R. Platelet-derived growth factor. I . High yield purification and evidence for multiple forms. J Biol Chem 1982;257:5154-60.
22. Antoniades HN, Hunkapiller MW. Human platelet-derived growth factor (PDGF): amino terminal amino acid sequence. Science 1983;220:963-5.
23. Lynch SE, Williams RC, Polson AM. A combination of platelet derived and insulin like growth factor enhances periodontal regeneration. J Clin Periodontol 1989;16:545-8.
24. Westermark B, Heldin, C-H, Ek B. Biochemistry and biology of platelet-derived growth factor. In: Guroff *G,* ed. Growth and maturation factors, vol. 1. New York Wdey & Sons 1983;73-115.
25. Rappolee DA, Mark D, Banda MJ. Wound macrophages express TGF-alpha and other growth factors in *oiuo:* analysis of mRNA phenotyping. Science 1988;241:708-12.
26. Antoniades HN, Galanopoulos T, Neville-Golden J. Injury induces *in uivo* expression of platelet-derived growth factor (PDGF) and PDGF receptor in RNA's in skin epithelial cells and PDGF mRNA in connective tissue fibroblasts. Proc Natl Acad Sci USA 1991;88:565-9.
27. Sitaras NM, Sariban E, Pantagis P. Human iliac artery endothelial cells express both genes encoding the chains of platelet-derived growth factor (PDGF) and synthesize PDGF-like mitogen. J Cell Physiol 1987;132:376-80.
28. Hauschka PC, Mavrakos AE, Iafrati MD, Doleman SE, Klagsbrun M. Growth factors in bone matrix. J Biol Chem1986;261:12665-74.
29. Pledger Wl, Stiles CD, Antoniades HN, Scher D. Induction of DNA synthesis in BALB/c-3T3 cells by serum components: reevaluation of the commitment process. Proc Natl Acad Sci USA 1977;74:4481-5.
30. Lynch SE, Colvin RB, Antoniades HN. Growth factors in wound healing: single and synergistic effects on partial thickness porcine skin wounds. J Clin Invest 1989;84:640-46.
31. Clemmons DR, Underwood LE, Van Wyk JJ. Hormonal control of immunoreactive somatomedin production by cultured human fibroblasts. J Clin lnvest 1981;67:10-19.
32. Clemmons DR, Van Wyk JJ. Evidence for a functional role of endogenously produced somatomedin-like peptides in the regulation of DNA synthesis in cultured human fibroblasts and porcine smooth muscle cells. J Clin lnvest 1985;75:1914-8.
33. Hollenberg MD. Receptors for insulin and other growth factors: rationale for common and distinct mechanisms of cell action. Clin Invest Med 1987;10:475-9.
34. King GL, Kahn CR. The growth-promoting effects of insulin. In: Guroff G, ed. Growth and maturation factors. New York J. Wiley &. Sons 1984;2:224-65.
35. Rinderknecht E, Humbel RE. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem 1978;253:2769-76.
36. Smith GL. Multiplication-stimulating activity and the role of carrier proteins. In: Guroff G, ed. Growth and maturation factors. New York J. Wiley & Sons 1983;1:293-323.
37. King GL, Kahn CR. The growth-promoting effects of insulin. In: Guroff G, ed. Growth and maturation factors. New York J. Wiley &. Sons 1984;2:224-65.
38. Hintz RL, Liu F. Demonstration of specific plasma protein binding sites for somatomedin. J Clin Endocrinol Metab 1977;45:988-95.

39. Zapf J, Waldvogel M, Froesch ER. Binding of nonsuppressible insulin-like activity to human serum. Arch Biochem Biophys 1975;168:638-45.
40. Canalis E. Effect of insulin-like growth factor I on DNA and protein synthesis in cultured rat calvana. J Clin Invest 1980;66:709-19
41. Hiraki YH, Inoue H, Kato Y, Fukuya M, Suzuki F. Combined effects of somatomedin-like growth factors with fibroblast growth factor or epidermal growth factor in DNA synthesis in rabbit chondrocytes. Mol Cell Biochem 1987;76:185-93.
42. Lynch SE, Nixon JC, Covlin RB, Antoniades HN. Role of platelet-derived growth factor in wound healing: synergistic effects with other growth factors. Proc Natl Acad Sci USA 1987;84:7696-700.
43. Lynch SE, Williams RC, Polson AM. A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. J Clin Periodontol 1989;16:545-8.
44. Lynch SE, Buser D, Hernandez RA. Effects of the platelet-derived growth factor/insulin-like growth factor-I combination on bone regeneration around titanium dental implants. Results of a pilot study in beagle dogs. J Periodontol 1991;62:710-16.
45. Burgess AW. Epidermal growth factor and transforming growth factor-alpha. In: Waterfield MD, ed. Growth factors.Br Med Bull 1981;45(2):401-24.
46. Marti U, Burwen SJ, Jones AL. Biological effects of epidermal growth factor, with emphasis on the gastrointestinal tract and liver: an update. Hepatology 1989;9:126-38.
47. Tashjian AJ Jr, Levine L. Epidermal growth factor stimulates prostaglandin production and bone resorption in cultured mouse calvaria. Biochem Biophys Res Commun 1978;85:966-75.
48. Tashjian A, Voekel EF, Lazzaro M. Alpha and beta human transforming growth factors stimulate prostaglandin production and bone resorption in cultured mouse calvaria. Proc Natl Acad Sci USA 1985;82:4535-8.
49. Keski-Oja J, Leof EB, Lyons RM, Coffey RJ Jr, Moses HL. Transforming growth factors and control of neoplastic cell growth. J Cell Biochem 1987;33:95-107.
50. Derynck R. Transforming growth factor-alpha: structure and biological activities. J Cell Biochem 1986;32:293-304.
51. Assoian RK, Komoriya A, Meyers CA, Miller DM, Sporn MB. Transforming growth factor beta in human platelets.J Biol Chern 1983;258:7155-60.
52. Takehara K, LeRoy EC, Grotendorst GR. TGF-P inhibition of endothelial cell proliferation: alteration of EGF binding and EGF-induced growth-regulatory (competence) gene expression. Cell 1987;49:415-22.
53. Leoff EB, Proper JA, Gousin AS, Shipley GD, Di Corleto AE, Moses HL. Induction of c-sis mRNA and activity similar to platelet-derived growth factor B: a proposed model for indirect mitogenesis involving autocrine activity. Proc Natl Acad Sci USA 1986;83:2453-7.
54. Roberts AB, Sporn MB, Assoian RK. Transforming growth factor type-beta: rapid induction of fibrosis and angiogenesis *in uioo* and stimulation of collagen formation *in oitro.* Proc Natl Acad Sci USA 1986;83:4167-71.
55. Lawrence WT, Norton JA, Sporn MB, Gorschboth C, Grotendorst G-R. The reversal of an Adriamycin-induced healing impairment with chemoattractant and growth factors.Ann Surg 1986;203:142-7.
56. Postlethwaite AE, Seyer JM, Kang AH. Chemotactic attraction of human fibroblasts to type I, II,and III collagens and collagen derived peptides. Proc. Natl. Acad. Sci. USA 1978;75(2):871–5.
57. Halberstadt C, Austin C, Rowley J. A hydrogel material for plastic and reconstructive applications injected into the subcutaneous space of a sheep. Tissue Eng. 2002;8(2):309–19.

Corresponding Author:

Dr. Manjari Lalwani,
Post Graduate Student, Dept. of Periodontics,
DAPM RV Dental College,
Bangalore-560078, Karnataka, India.
Email:manjari.lalwani@gmail.com

Date of Submission: 15/07/2015
Date of Acceptance: 02/08/2015

How to cite this article: Suchetha A, Manjari L, Darshan BM, Sapna N, Divya Bhat, Koduru S. Growth factors: Role in periodontal regeneraion. J Res Med Den Sci. 2015;3(3):166-70.

Source of Support: None
Conflict of Interest: None declared