BIOLOGIC MODIFIERS IN PERIODONTAL REGENERATION

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Biologic modifiers-primarily growth factors are basically proteins that may act locally or systemically to affect the growth and function of cells in various ways. They may act in an autocrine fashion, where the cells producing them are also affected by them or more commonly, in paracrine fashion, such that production of a growth factor by one cell type affects the function of a different cell type. (Cochran DL et al 1999)[1]

Periodontal tissues have the capacity for repair and regeneration. This process is regulated by local production of growth factors, which have the capacity to stimulate cellular chemotaxis, proliferation, differentiation and formation of extra cellular matrix components. Regeneration is also affected by the participation of cells other than those that produce the supporting structures of periodontium, such as endothelial cells and inflammatory cells. Both maybe important sources of growth factors.

In periodontal regeneration, several endogenous sources of growth factors may exist which are either produced or activated locally, these sources potentially include: (Graves DT 1994)[2].

a) Inflammatory cells - leucocytes particularly macrophages that have been recruited to sites of injury.
b) Osteoblasts those are capable of producing several growth factors.
c) Endothelial cells
d) Cells in the periodontal ligament
e) Factors stored in bone and released during bone resorption.
f) Factors that have been previously produced and are released from binding proteins or alterations in the pH level.

BIOLOGIC MODIFIERS AND ITS SOURCES AND ACTION[3]

Factor	Source	Actions
PDGF (AA, AB, BB)	Platelets, macrophages	Competence factor, j protein synthesis
IGF-I	Blood, liver, bone	Progression factor, j fibroblast growth j DNA synthesis
IGF-II	Bone	Proliferation, differentiation, j DNA synthesis
TGF-ɲ	Epithelial cells	Stimulates epithelium
TGF-N	Platelets, bone	Effects dependent on cell stage of differentiation, inhibits growth of epithelium stimulates growth of mesenchymal cells, immunosuppressive

Cont. Table....

PGF (acidic)	Brain, pituitary	Competence factor, mitogene for endothelial cells, promotes cartilage repair
PGF (basic)	Brain, pituitary	Same as FGF acidic but more potent
BMP-2	Bone	Stimulates cartilage and bone formation
BMP-3 (osteogenin)	Bone	Initiates endochondral bone growth
BMP-7(OP-I)	Bone, kidney	Stimulates bone formation
Interleukin-1 (ɲ,ɴ)	Macrophages, PMN's	Stimulates bone resorption
Interleukin-6	Osteoblast's hematopoietic cells	Stimulates osteoclasts
G-CSF	Many cell types including fibroblasts and osteoblasts	Support colony forming cells of granulocytes lineage
GM-CSF	Many cell types	Support colony forming cells of the granulocyte-macrophage lineage
Interleukin-3 (multi-CSF)	Activated T-cells	Stimulates wide range of colony-forming cells
PTHrP	Keratinocytes activated lymphocytes, osteoblasts, mammary gland	Stimulates bone resorption and formation
EGF	Submandibular glands	↑ keratinocyte proliferation, inhibits collagen synthesis
Fibronectin	Connective tissue cells	↑ cell attachment
Osteoprotein	Osteoblasts activated T-cells, carcinomas	↑ cell attachment, may regulate mineralization
Bone sialoprotein	Osteoblasts, odontoblasts, cementoblasts	↑ cell attachment, may initiate mineralization

STUDIES ON USE OF GROWTH FACTORS IN PERIODONTAL REGENERATION ANIMAL STUDIES

Authors	Animal model used	Results and conclusion
PLATELET- DERIVED GROWTH FACTOR AND INSULIN LIKE GROWTH FACTOR		
Lynch SE, Williams RL, Reddy MS (1989)[4]	application of PDGF and IGF-I to periodontitis affected teeth in beagle dogs	that in-vivo application of combination of PDGF and IGF-I may enhance the regeneration of periodontal structures.
Matsuda N, Kumar NM, Cho MI (1992)[5]	conducted a study to assess the mitogenic, chemotactic and synthetic responses of rat PDL fibroblastic cells to epidermal growth factor (EOF), transforming growth factor-p (TGF-p) recombinants human platelet derived growth factor (rh PDGF)-AB, rh PDGF-BB PDL cells obtained from the coagulum of healing tooth sockets.	concluded that rhPDGF-BB and IGF-I stimulate proligeration and chemotaxis of PDL and fibroblastic cells and may be useful for clinical application in periodontal regeneration procedures.
PLATELET DERIVED GROWTH FACTOR AND GTR		
Park JB, Masahiro M, Han KY et al (1995)[6]	periodontal regeneration in class III furcation defects of beagle dogs using GTR regenerative therapy with PDGF.	A newly formed bone filled 80% of the lesions at 8 weeks and 87% at 11 weeks with P-GTR therapy, compared to 14% of the lesions at 8 weeks and 60% at 11 weeks with GTR therapy alone. They concluded that P-GTR therapy effectively promoted regeneration.
PLATELET DERIVED GROWTH FACTOR AND BONE MORPHOGENIC PROTIEN		
Mohammed S, Arc P, Kardos TB (1998)[7]	conducted a study to analyse the effect of TGF-p on wound healing in standardized class-11 furcation defect of 48 mandibular second premolar teeth in 24 sheep.	This study demonstrated that TGF- ù, encouraged bone regeneration in class II furcation defects in sheep, an effect enhanced by presence of barrier membrane.
TRANSFORMING GROWTH FACTOR		
Wikesjo U, Guglielmoni P, Promsudhi A et al (1999)[8]	conducted a study to evaluate alveolar bone and cementum regeneration following surgical implantation of recombinant transforming growth factor-P (rh TGF P) in conjunction with GTR in periodontal defects created in beagle dogs.	Cementum regeneration was limited without obvious difference between experimental conditions, within the limitation of study, it may be concluded that rh TGF-p has a restricted potential to enhance alveolar bone regeneration in conjunction with GTR.
BONE MORPHOGENIC PROTIEN		
Sigurdsson TJ, Lee MB, Kubota K et al (1995)[9]	conducted a study to evaluate bone and cementum regeneration following periodontal reconstructive surgery using rh-BMP-2 in six beagle dogs.	. Results suggest that wound conditioning with rh BMP-2 has a significant potential for stimulating periodontal regeneration.

HUMAN STUDIES

Authors	Objective	Results and conclusion
PLATELET- DERIVED GROWTH FACTOR AND INSULIN LIKE GROWTH FACTOR		
Howell TH, Joseph PF, Lynch SE et al (1997)[10]	conducted a study to assess the safety of rh PDGF-BB and IGF-1 when applied to periodontal osseous defects in humans.	The results from this study suggest that the local application of rh PDGF-BB and rh IGF-I to periodontal lesions is safe at the dose-levels studied. LD-PDGF-BB and IGF-1 did not elicit increased defect fill compared to the control. However, HD-PDGF/IGF-1 resulted in a significant promoter in bone regeneration.
Zhur Z, Lee CS, Tejeda KM, Giannobile WV (2001)[11]	conducted a study to test the ability of recombinant adenoviruses (rAds) encoding PDGF-A or PDGF-1308 (a PDGF-A dominant ergative mutant that disrupts endogenous PDGF bioactivity) to affect cells derived from periodontium.	They concluded that Ad2-PDGF could effectively transduce cells derived from periodontium and promote biologic activity equivalent to PDGF-AA. This supports the use of gene therapy for sustained PDGF release in periodontal tissue.
PLATELET DERIEVED GROWTH FACTOR, EPIDERMAL GROWTH FACTOR AND FIBROBLAST GROWTH FACTOR		
Blom S, Holmstrup P, Dabelsteen E (1994)[12]	Investigated the mitogenic and morphogenic effects of recombinant epidermal growth factor (rEGF), natural platelet derived growth factor (rPDGF) and natural fibroblast growth factor (nFGF) on periodontal ligament fibroblast like cells	They concluded that growth factors in high concentrations have no diametric effects on the morphology of PDL fibroblast like cells. However, variation in the mitogenic potency of the growth factors should be considered when these growth factors are used in periodontal treatments in future.
FIBRONECTIN		
Wikesjo UME, Claffey N, Christersson LA et al (1988)[13]	conducted a study to examine the effects of root surface demineralization and topical fibronectin as adjuncts to reconstructive periodontal surgery.	application of fibronectin to root surfaces did not enhance the amount of connective tissue repair and did not alter pattern of root resorption and ankylosis.
FIBROBLAST GROWTH FACTOR		
Terranova VP, Odziemiec C, Tweden KS, et al (1989)[14]	conducted a study to evaluate the effects of bFGF on repopulation of dentine surfaces by periodontal ligament cells and endothelial cells.	They concluded that bFGF could stimulate PDL and human endothelial cell migration and cell proliferation.

DISCUSSION:

Existing evidence supports a role for biologic modifiers 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 biologic modifiers in an attempt to regenerate periodontal tissues is based on knowledge as to the function of these molecules at the cellular and molecular level.

Growth factors and morphogens present in bone include those belonging to the TGF-p superfamily (TGF-p and BMP), IGF-I and IGF-II, PDGF, FGF and EGE. The knowledge that these molecules are present in the local wound-healing environment, coupled with an increased appreciation as to the function of these individual growth factors (as discussed earlier), has resulted in an increase in studies targeted at using these molecules to promote wound healing and regeneration . In addition to growth factors, other proteins such as those that can promote adhesion (e.g., bone sialoprotein) as well as proteins involved in regulation tissue integrity (e.g., proteoglycans and collagens) and proteins influencing angiogenesis (e.g., thrombospondin, FGF) may prove important for promoting periodontal regeneration under specific situations.

SUMMARY AND CONCLUSION

The specific objective of this review was to provide an update on biologic modifiers being used or suggested of use in therapies directed at regenerating periodontal tissues. As indicated from the studies presented here, many of these biologic modifiers have significant influences on cell behavior and with great promise for use in regenerative therapies. As discussed here, however, additional investigations are required both at the molecular level and at the clinical level to improve the predictability of regenerative therapies. With active investigations directed toward understanding the biology of the healing site, including identifying appropriate cells to target, coupled with designing delivery systems that can control release of agents at the local site, establishing the required environment for regeneration of periodontal tissues should be feasible.

REFERENCES:

1. Cochran DL, Wozney JM. Biologic indicators for periodontal regeneration. Periodontology 2000; 1999:40-58.
2. Graves DT. Periodontal regeneration with polypeptide growth factors. Curr Opin Periodontol 1994; 178-186.
3. McCauley LK, Somerman MJ. Biologic modifiers in periodontal regeneration. Dent Clin of North America 1998;42:361-387.
4. Lynch SE, Williams RC, Reddy MS. A combination of platelet derived and insulin like growth factors enhances periodontal regeneration. J Clin Periodontol 1989; 16: 545-548.
5. Matsuda N, Kumar NM, Cho MI. Mitogenic, chemotactic and synthetic responses of rat periodontal ligament fibroblast cells to polypeptide growth factors in vitro. J Periodontol 1992; 63: 515-525.
6. Park JB, Masahiro M, Han KY. Periodontal regeneration in class II furcation defects of beagle dogs using guided tissue regenerative therapy with platelet derived growth factor. J Periodontol 1995; 65: 462-477.
7. Mohammed S, Arch P, Kardos TB. The effect of transforming growth factor β1 on wound healing with or without barrier membranes in class II furcation in sheep. J periodontal Res. 1998; 33: 335-365.
8. Wikesjo U, Guglielmoni P, Promsudhi A et al. Periodontal repair in dogs: effect of Rh BMP-2 concentration on regeneration of alveolar bone and periodontal attachment. J Clin Periodontol 1999; 26:392-400.
9. Sigurdsson TJ, Lee MB, Kubota K et al.

Periodontal repair in dogs: Recombinant human bone morphogenic protein-2 significantly enhances periodontal regeneration. J Periodontol 1995; 66: 131-138.
10. Howell TH, Joseph PF, Lynch SE et al. A phase I/II clinical trial to evaluate a combination of recombinant human platelet derived growth factor-BB and recombinant human insulin like growth factor-1 in patients with periodontal disease. J Periodontol 1997; 68: 1186-1193.
11. Zhur Z, Lee CS, Tejeda KM, Giannobile WV. Gene transfer and expression of platelet-derived growth factors modulate periodontal cellular activity. J Dent Res 2001; 80: 892-897.
12. Blom S, Holmstrup P, Dabelsteen E. A comparison of the effect of epidermal growth factor, platelet derived growth factor and fibroblast growth factor on rat periodontal ligament fibroblast like cells, DNA synthesis and morphology. J Periodontol 1994; 65: 373-378.
13. Wikesjo UME, Claffey N, Christersson LA et al. Repair of periodontal function defects in beagle dogs following reconstructive surgery including root durface demineralization with tetracycline hydrochloride and topical fibronectin application. J Clin Periodontol 1988; 15: 73-80.
14. Terranova VP, Odziemiec C, Tweden KS, et al. Repopulation of dentin surfaces by periodontal ligament cells and endothelial cells: effects of basic fibroblast growth factors. J Periodontol 1989; 60: 293.