Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Periodontology and Implantology

Journal homepage: https://www.ijpi.in/

Review Article

Role of biologic modifiers in periodontal regeneration- A review

Hari Priya N[1], Mohan Kumar P[1,*], V Keerthi[1], Gautami S Penmetsa[1], NVS Sruthima G[1], KSV Ramesh[1]

[1] *Dept. of Periodontics, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 24-05-2022
Accepted 17-06-2022
Available online 26-11-2022

Keywords:
Growth factors
Periodontal
Regeneration
Soft tissue grafting

ABSTRACT

Regenerative techniques, which aim to replace damaged periodontal ligament, bone, cementum, and connective tissue, are newer approaches to periodontal care. In periodontology and oral implantology, the development of molecular mediators has accelerated substantially over the last decade. At various cellular levels, different growth agents cause distinct reactions in periodontal tissues. The potency of biologics in regenerating the periodontal tissues is the call attention in this review paper, in which it discusses the structure, mechanism of action, indication and FDA (Food and Drug Administration) approval to use in regenerating periodontal tissues. The working activity of biologic agents together with reasons for utilizing them in regenerating tissues of periodontium lost due to disease are discussed, as well as the expected benefits as compared to traditional approaches.

1. Introduction

Biological substances like PDGF- platelet-derived growth factor, BMP- bone morphogenic proteins, FGF- fibroblast growth factor, TGF-β- Transforming growth factor-beta and EMD- enamel matrix derivatives seemed to recommend to improve clinical outcomes in regenerating the tissues of periodontium when lost due to the disease process.[1,2]Table 1 Cellular activities of epithelium, connective tissue, bone, and regulating immunity and its function are in control of growth factors.[3,4]

Over the last two decades, many of the biological mediators have been developed, including rh-PDGF, rh-BMP FGF-enhanced substitute, and EMDs.[5–8]

1.1. Platelet-rich fibrin versus platelet-poor plasma

Marx along with colleagues suggested using individuals own platelet concentrates to alter bone healing. Blood platelet concentrates made by centrifuging and activating platelets from venous autologous blood to provide a concentrated growth factor preparation.[9–11] Platelets are enucleated protoplasmic pieces derived from megacaryocytes with various granules enriched with growth factors such as PDGF- AA, BB, and AB, two types of TGF like beta1 and beta2, VEGF, bFGF-2, along with EGF). Additionally it carries fibrin, fibronectin, and vitronectin, which impact key biotic schemes for recovering tissues during healing.[12–14]

2. Platelet-Rich Fibrin

PRFG is created from un-coagulated blood centrifuged with commercially available equipment to create a layer with increased platelet and leukocyte concentrations inside a fibrin scaffold.[15,16] Increased chemotaxis, proliferation, differentiation, and angiogenesis are the mechanisms through which PRF enhances wound healing.

* *Corresponding author*.
E-mail address: mosups@gmail.com (Mohan Kumar P).

https://doi.org/10.18231/j.ijpi.2022.032

Thrombocytes are indeed a spontaneous supply of growth factors that play a pivotal part in tissue repair, therefore they're important for periodontal wound healing. PRP, Pure-PRP, Leukocyte-PRP, PRF, and Leukocyte-PRF), and TPRF are the many varieties formed based on centrifugation measures and technique.[17,18]

Platelet alpha granules contain growth factors such as PDGF, vascular endothelial growth factor-VEGF, insulin-like growth factor- IGF, platelet-derived angiogenic factor- PDAF, and transforming growth factor-beta- TGF-β, making it a potent biologic agent for periodontal regeneration.[19–21]

3. Indications

PRP, PRFG, as well as L-PRF were all investigated as soft tissue substitutes, sinus augmentation grafting materials, and a periodontal regeneration barrier membrane. Nonetheless, because of the wide diversity of research methodologies, material regimens (graft, barrier, or combination), surgical techniques, and some other factors, determining the efficiency of various concentrates is difficult. It is, nonetheless, beneficial in a wide range of therapeutic circumstances. However, the outcomes might not even be better to classic GTR for periodontal regeneration or regular CTG for recession treatment. In contrast, platelet concentrates have yet to be used in implant or major bone grafting therapies. Tissue repair has been shown to benefit from platelet-derived concentrates, which indirectly aids bone production.[22–24]

3.1. Structure and methods of action of the growth factor

Growth factors comprise small molecules that bind to cell receptors and cause a biological reaction. With almost 800 members, G protein-coupled receptors were the most numerous receptor family. Growth factors bind to the G protein-coupled receptor and change the phosphorylated state of tyrosine, serine, and threonine to activate intercellular signalling.[25,26]

4. Platelet-Derived Growth Factor (PDGF)

The multifaceted peptide PDGF (platelet-derived growth factor) comes in five isoforms: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. These interact to tyrosine kinase receptors on cellular membrane and then perform basic tasks. With increasing overall number of stem cells, platelet-derived growth factor enhances wound repair and bone regeneration, capillary ingrowth by enhancing endothelial cell proliferation, and connective tissue regeneration and collagen synthesis by replicating and activating fibroblasts.[27,28]

Platelet-derived growth factor induces cellular proliferation at healthy doses of 0.1 to 1 g/ml, which is increased by interaction with v3 integrin. It activates Rac, which improves cell chemotaxis in monocytes, gingival fibroblasts, especially periodontal ligament cells. Rac is a GTPase that plays a role in actin reorganization including lamellipodia production. Platelet-derived growth factor alters the actin cytoskeletons of periodontal cells by activating focal adhesion kinase, protein kinase B, commonly referred to Akt, and serine/threonine protein kinase.[29,30]

The platelet-derived growth factor's therapeutic potential was already explored both in-vitro and in-vivo by delivering it to locally injured tissues. Recombinant platelet-derived growth factor was approved by the US Food and Drug Administration (FDA), and Linche and colleagues examined it in an animal model, with the results indicating that platelet-derived growth factor promotes healing process in periodontitis.[1,2,6]

4.1. Indications and surgical intervention

To speed up osseous repair as well as angiogenesis in large lesions, Schwartz and colleagues employed recombinant platelet-derived growth factor–BB in conjunction to biphasic calcium phosphate. Clinical experiments using recombinant platelet-derived growth factor –BB as well as insulin growth factor indicated better osteo fill 9 months following surgery. Recombinant platelet-derived growth factor-BB improves periodontal healing of Class II furcation deficiencies when combined with allogeneic bone as a carrier.[1,3]

5. Transforming Growth Factor-Beta

TGF beta proteins are extracellular signalling peptides that attach to heteromeric complex type 1 and type 2 II receptors. Throughout periodontal healing process, both receptors have been increased, and the type I receptor controls the receptor complex's signalling specificity. When TGF-BETA binds with the type II receptor, it activates the type I receptor by serine phosphorylating Smad proteins. By chemically reacting with a shared partner, activated Smads drive transcriptional modifications in the target gene (Smad4 in mammals). Human DNA encodes seven type I receptors (activin-like kinases 1–7), five type II receptors, and two auxillary receptors, Endoglin and Betaglycan. Type II receptor kinase 5 complex activates Smad2 and Smad3, while type II receptor–activin-like kinase 1 complex activates Smad1, Smad5, and Smad8 representing an alternative signaling route.[2,4] Beta glycan binds to type II receptors and then delivers the ligand to them. Endoglin binds to transforming growth factor beta1 as well as beta3, which are mainly produced in endothelial cells, providing a link between tumour angiogenesis and inflammation. In endothelial cells, it also suppresses transforming growth factor beta/activin-like kinase 5/Smad3 cellular responses

Table 1: Describes the summary of mechanism of action, indications, and FDA approval status of common biologic agents used in periodontal regeneration.

Agent	Indications	Functions	FDA approval
EMD	Treating intra-bony defects In aesthetic zones, EMD is also utilised to optimise tissue height.	Promotes periodontal wound healing Promotes soft and hard tissue regeneration.	The therapy of intra-bony defects has been approved by the FDA by using EMD
PDGF-BB	Used in the socket augmentation Used in Guided bone regeneration.	Enhances wound healing soft and hard tissue regeneration promoted	Intra-bony defects, furcations, and gingival recession treatments by using PDGF-BB have been authorized by the FDA.
BMP-2	Used in the sinus augmentation Alveolar ridge augmentation is enhanced	Enhances mature bone formation Bone regeneration for implant related therapy is promoted	The FDA has approved use of BMP-2 in sinus augmentation and alveolar ridge augmentation procedures.
PRF	Used in sinus augmentation as graft material	Bone healing is enhanced Used in soft and hard tissue regeneration	Not regulated by the FDA
FGF-2	FGF-2 significantly improves defect fill	Promotes hard tissue regeneration	Currently seeking FDA approval

while enhancing activin-like kinase 1/Smad1 signalling, allowing it to exert control over the pathway.[5,6]

TGF-beta1 also generates a range of responses in various cellular subtypes by activating the prototypic signalling pathway, which includes mitogen-activated protein kinase activation, extrinsic signal-regulated kinase, p38, and c-Jun N-terminal kinase. Because transforming growth factor-beta is produced as a latent precursor complex and remains connected to the extracellular matrix in an inactive state, the most critical degree of control is exerted post-transcriptionally.[8,10]

During periodontal wound healing, gingival epithelial cells and macrophages release TGF-beta1, which aids in myofibroblastic differentiation as well as the formation of extracellular matrix components like type I collagen and fibronectin.[30]

6. Bone Morphogenic Proteins (BMP)

The transforming growth factor superfamily includes BMPs, which seem to be multifunctional polypeptides. BMPs aid in bone and cartilage production throughout the embryonic period, and also aid in regeneration after birth. Based on sequence similarity and function, BMPs are classified into four subgroups: BMP 2,4,5,6,7; BMP 8a,8b; BMP 9,10,12,13,14; and growth differentiation factor-5. BMPs are 400–500 amino acid polypeptides that are thought to be powerful osteoinductive mediators. Hence Periodontal healing and remodeling are aided by bone morphogenic proteins. In an in-vitro investigation, Hakki and colleagues discovered that bmp7 affects the expression of mineralized tissue-related genes in cementoblasts. Various growth factor reactions to tissue formation were discovered in baboon furcation defects: osteogenic protein-1 had a more selective impact on cementogenesis, whereas bone morphogenic protein-2 promoted osteogenesis. When recombinant human bone morphogenic protein-2 was employed, Miyaji and his colleagues noticed cementum-like tissue development in exposed roots in Beagle dogs.[11,31] Based on their concentration gradient and chemotactic capabilities, BMPs can operate as mitogenic agents or stimulate the development of chondroblasts or osteoblasts. Clinical research conducted by Fiorellini et al indicated considerable bone growth in a human buccal wall defect model when rhBMP-2 was combined with collagen sponge vs. collagen sponge alone.[30,31]

7. Enamel Matrix Derivative (EMD)

Among the most commonly used biologics within periodontology is enamel matrix derivative (EMD). EMD is hypothesised to improve periodontal regeneration by replicating basic processes that take place throughout periodontium regeneration. EMD, such as the cell from Hertwig's epithelial root sheath, works as a cementogenesis initiator.[31,32]

When tissue formation cells are exposed to EMD, the phenotype of the cells changes, resulting in an increase in the expression of growth and differentiation factor-related genes, including transforming growth factor beta.[32]

8. Fibroblast Growth Factor-2 (FGF-2)

Acidic FGF (aFGF, FGF-1) and basic FGF (bFGF, FGF-2) are two forms of fibroblast growth factor-2 (FGF-2) that communicate via receptor-type tyrosine kinase12. Whenever Fibroblast Growth Factor interacts with a receptor as just a consequence of receptor dimerization with autophosphorylation, tyrosine kinase is activated. Fibroblast Proliferation Factor encourages fibroblast and osteoblast growth, as well as angiogenesis, which aids tissue repair and regeneration. FGF-2 induces periodontal ligament cells to produce osteopontin, heparin sulphate, and hyaluronan, resulting in a favourable local environment during tissue engineering.[32]

9. Conclusion

This review's specific goal is to update the function of numerous biologic modifiers that are employed as a treatment option for periodontal regeneration. According to the findings of the aforementioned investigations, these biological modifiers have significant effects on cell activity, making them beneficial in periodontal regeneration treatment. Even though biologics have proven to be advantageous for better clinical results, the function of good patient and case selection, type of bone augmentation, and basic surgical principles remain critical elements that influence success.

Active research into the biology of the healing site, including the identification of relevant cells to target, along with administration systems to control agent delivery just at specified location, should be able to create the suitable framework for periodontium tissue repair.

10. Source of Funding

None.

11. Conflict of Interest

None.

References

1. Shin SY, Rios HF, Giannobile WV, Oh TJ. Periodontal regeneration: Current therapies. *InStem Cell Biol Tissue Eng Dent Sci*. 2015;11:459–69.
2. Amo FSLD, Monje A, Padial-Molina M, Tang Z, Wang HL. Biologic agents for periodontal regeneration and implant site development. *BioMed Res Int*. 2015;p. 957518. doi:10.1155/2015/957518.
3. Smith PC, Martínez C, Cáceres M, Martínez J. Research on growth factors in periodontology. *Periodontology*. 2000;67(1):234–50.
4. Bashutski JD, Wang HL. Biologic agents to promote periodontal regeneration and bone augmentation. *Clin Adv Periodontics*. 2011;1(2):80–7.
5. Bieler G, Hasmim M, Monnier Y, Imaizumi N, Ameyar M, Bamat J, et al. Distinctive role of integrin-mediated adhesion in TNF-induced PKB/Akt and NF-κB activation and endothelial cell survival. *Oncogene*. 2007;26(39):5722–54.
6. Hughes FJ, Turner W, Belibasakis G, Martuscelli G. Effects of growth factors and cytokines on osteoblast differentiation. *Periodontology*. 2000;41(1):48–72.
7. Hosseinpour S, Walsh LJ, Moharamzadeh K. Regenerative Approaches in Dentistry: An Evidence-Based Perspective. Springer Nature; 2021. p. 320.
8. Mccauley LK, Somerman MJ. Biologic modifiers in periodontal regeneration. *Dent Clin North Am*. 1998;42(2):361–87.
9. Karateew E. Implant Aesthetics: Keys to Diagnosis and Treatment. Springer; 2017. p. 361–87.
10. Kao RT. The use of biologic mediators and tissue engineering in dentistry. *Periodontol*. 2000;50:127–53.
11. Miron RJ, Choukroun J. Platelet rich fibrin in regenerative dentistry: biological background and clinical indications. John Wiley & Sons; 2017. p. 288. Available from: https://www.amazon.com/Platelet-Rich-Fibrin-Regenerative-Dentistry/dp/1119406811.
12. Juengel JL, Mcnatty KP. The role of proteins of the transforming growth factor-beta superfamily in the intraovarian regulation of follicular development. *Hum Reprod Update*. 2005;11(2):144–61.
13. Larjava H, Yang Y, Putnins E, Heino J, Häkkinen L. Biological agents and cell therapies in periodontal regeneration. *Endod Top*. 2012;26(1):18–40.
14. Zocchi ML, Vindigni V, Pagani A, Pirro O, Conti G, Sbarbati A. Regulatory, ethical, and technical considerations on regenerative technologies and adipose-derived mesenchymal stem cells. *Eur J Plastic Surg*. 2019;42(6):531–79.
15. Van Den Bergh JP, Bruggenkate CT, Groeneveld HH, Burger EH, Tuinzing DB. Recombinant human bone morphogenic protein-7 in maxillary sinus floor elevation surgery in 3 patients compared to autogenous bone grafts. A clinical pilot study. *J Clin Periodontol*. 2000;27(9):627–63.
16. Nevins M, Giannobile WV, Mcguire MK, Kao RT, Mellonig JT, Hinrichs JE. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. *J Periodontol*. 2005;76(12):2205–15.
17. Corso D, Vervelle M, Simonpieri A, Jimbo A, Inchingolo R, Sammartino F, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 1: Periodontal and dentoalveolar surgery. *Curr Pharmaceut Biotech*. 2012;13(7):1207–37.
18. Andrés R, Sheridan PJ, Kupp LI. PhD Is Platelet-rich Plasma the Perfect Enhancement Factor? A Current Review Int. *J Oral Maxillofac Implants*. 2003;18(1):93–103.
19. Sykaras N, Opperman LA. Bone morphogenic proteins (BMPs): how do they function and what can they offer the clinician? *J Oral Sci*. 2003;45(2):57–73.
20. Fiorellini JP, Howell TH, Cochran D, Malmquist J, Lilly LC, Spagnoli D. Randomized study evaluating recombinant human bone morphogenic protein-2 for extraction socket augmentation. *J Periodontol*. 2005;76(4):605–18.
21. Lyngstadaas SP, Lundberg E, Ekdahl H, Andersson C, Gestrelius S. Autocrine growth factors in human periodontal ligament cells cultured on enamel matrix derivative. *J Clin Periodontol*. 2001;28(2):181–9.
22. Thomas KA, Candelore MR, Fitzpatrick S. Purification and characterization of acidic fibroblast growth factor from bovine brain. *Proc Natl Acad Sci U S A*. 1984;81(2):357–61.
23. Nyman S, Lindhe J, Rosling B. Periodontal surgery in plaque infected dentitions. *J Clin Periodontol*. 1977;4(4):240–9.
24. Rosling B, Nyman S, Lindhe J. The effect of systematic plaque control on bone regeneration in infrabony pockets. *J Clin Periodontol*. 1976;3(1):38–53.
25. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;101(3):51–5.
26. Boyapati L, Wang HL. The role of platelet-rich plasma in sinus augmentation: a critical review. *Implant Dent*. 2006;15(2):160–70.
27. Shepherd N, Greenwell H, Hill M, Vidal R, Scheetz JP. Root coverage using acellular dermal matrix and comparing a coronally positioned tunnel with and without platelet-rich plasma: a pilot study in humans. *J Periodontol*. 2009;80(3):397–404.
28. Khairy NM, Shendy EE, Askar NA, El-Rouby DH. Effect of platelet rich plasma on bone regeneration in maxillary sinus augmentation. *Int J Oral and Maxillofac Surg*. 2013;42(2):249–55.
29. Kawase T, Kamiya M, Kobayashi M. The heatcompression technique for the conversion of platelet-rich fibrin preparation to a barrier membrane with a reduced rate of biodegradation. *J Biomed Materials Res B Appl Biomate*. 2015;103(4):825–31.
30. Barbero JEF, Moreno PG, Ortiz GA, Caba O, Fern ES, ´. Flow cytomet- ´ric and morphological characterization of platelet-rich plasma gel. *Clin Oral Imp Res*. 2006;17(6):687–93.
31. Cochran DL, Wozney JM. Biological mediators for periodontal regeneration. *Periodontol*. 1999;19(1):40–5.
32. Gestrelius S, Lyngstadaas SP, Hammarstrom L. Emdogain-periodontal regeneration based on biomimicry. *Clin Oral Investig*. 2000;4(2):120–5.

Author biography

Hari Priya N, PG Student

Mohan Kumar P, Reader https://orcid.org/0000-0001-7797-1890

V Keerthi, Senior Lecturer

Gautami S Penmetsa, Professor and Head

NVS Sruthima G, Professsor

KSV Ramesh, Associate Professor

Cite this article: Hari Priya N, Mohan Kumar P, Keerthi V, Penmetsa GS, NVS Sruthima G, Ramesh KSV. Role of biologic modifiers in periodontal regeneration- A review. *IP Int J Periodontol Implantol* 2022;7(4):145-149.