Bone morphogenetic proteins: Signaling periodontal bone regeneration and repair

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ABSTRACT

Bone morphogenetic proteins (BMPs) are a group of growth factors also known as cytokines and as metabologens. Originally discovered by their ability to induce the formation of bone and cartilage, BMPs are now considered to constitute a group of pivotal morphogenetic signals, orchestrating tissue architecture throughout the body. The important functioning of BMP signals in physiology is emphasized by the multitude of roles for dysregulated BMP signaling in pathological processes. Wherein it was found that protein extracts from bone implanted into the animals at nonbone sites induced the formation of new cartilage and bone tissue. This protein extract contained multiple factors that stimulated bone formation and was termed as “BMP.” There are at least 15 different BMPs identified to date and are a part of the transforming growth factor-β super family. The most widely studied BMPs are BMP-2, BMP-3 (osteogenin), BMP-4, and BMP-7 (osteogenin protein-1). Now, any recombination type of morphogenic proteins have been synthesized, for example - recombinant human BMPs.

KEY WORDS: Bone morphogenetic proteins, cytokines, growth factor, periodontal regeneration

Periodontal disease activity results in the destruction of periodontal tissues namely, periodontal ligament, alveolar bone and cementum, eventually leading to tooth loss if left untreated. Periodontal therapy can be undertaken by nonsurgical and by surgical methods. Periodontal therapeutic procedures are directed to arrest disease progression and achieve regeneration of lost tissues.

Periodontal surgical procedures are carried out as a treatment modality to arrest the disease progression. The tissue levels are not changed to the predisease condition. The periodontal ligament being a very complicated one involves various components for regression. All the components must be restored to their original position, for that the cells have to repopulate the wound created after surgery and create an appropriate matrix and later differentiate to form the respective tissues.

At many occasions, procedures such as bone grafting, use of membrane are undertaken to achieve regeneration. The latest among the regenerative procedures is the use of growth factors. Growth factors include a group of polypeptides and are involved in a variety of cell-to-cell and cell-matrix interactions both during the development of a particular organ, during normal health state, and also most important, i.e., during wound healing.

These growth factors mediate cellular processes such as – DNA synthesis, mitosis, chemosis, and also conversion of cells in the resting phase of the cell cycle into replicating cells. Various growth factors have been isolated and studied, namely, platelet-derived growth factor, fibroblast growth factors, insulin-like growth factor, transforming growth factors, bone morphogenetic proteins (BMPs) with cementum derived growth proteins: Signaling periodontal bone regeneration and repair. J Pharm Bioall Sci 2016;8:S39-41.
factors and periodontal ligament derived growth factors. For a growth factor to affect periodontal regeneration, it must be able to stimulate the formation of both mineralized and nonmineralized tissues. The studies have shown that there has been periodontal regeneration with the use of growth factors alone or in combination. The effects of platelet-derived, insulin-like transforming and fibroblast growth factors, and BMPs in periodontal regeneration have been studied. The studies have promised a bright future for the use of these in the field of periodontal regeneration. The goal of periodontal therapy is to provide a dentition that functions in health and comfort for the life of the patient.

**Discovery of Growth Factors**

Growth factors were first described in the 1960’s when substances such as blood fluids (e.g., fetal calf serum) and tissue extracts were added to cells in tissue culture.\[^{1,3,4}\] They usually involve in cell stimulation and proliferation, differentiation or migration, for example, nerve growth factor, which caused growth of neurons in chick embryos. The study of growth factors is still largely a tissue culture-based (in vitro) science. Since the growth factors occur in such small amounts, it was difficult to isolate and identify them, until sophisticated biochemical methods were developed. Subsequently, these substances were identified and purified as peptides.\[^{5}\] Growth factors are such as hormones regulate cell activity. There are currently about 130 established and characterized growth factors. Some of these factors are associated with the immune system.\[^{5}\]

**Bone Morphogenetic Proteins**

A study done, wherein it was found that protein extracts from bone implanted into the animals at nonbone sites induced the formation of new cartilage and bone tissue.\[^{7-12}\] This protein extract contained multiple factors that stimulated bone formation and was termed as “BMP”. There are at least 15 different BMPs identified to date and are a part of the transforming growth factor-β superfamily. The most widely studied BMPs are BMP-2, BMP-3 (osteogenin), BMP-4, and BMP-7 (osteogenic protein-1). Now, any recombination type of morphogenic proteins has been synthesized, for example - recombinant human BMPs (rh-BMP). The BMPs show sequence homologies with transforming growth factor-β. It is found that BMPs are related to regulatory genes.\[^{11-20}\] The other factors that have homologies with BMPs are activins, inhibins, and nullerian inhibiting substances involved in follicle stimulating hormone release and ductal development. Originally, seven such proteins were discovered. Of these, six (BMP2 through BMP7) belong to the transforming growth factor beta superfamily of proteins. BMP1 is a metalloprotease. Since then, thirteen more BMPs have been discovered, bringing the total to twenty.

**Effects**

- Stimulate bone and cartilage formation (BMP-2)
- Initiate endochondral bone formation (BMP-3, BMP-7)
- The high level of BMPs probably indicates an endocrine-like action
- Role in development of the central nervous system (BMP-3)
- BMP-2 and BMP-4 in RNA transcripts are found to have a role in developing tooth buds, odontoblast layer, and other craniofacial structures
- BMPs are found to help growth of hematopoietic cells and epithelial differentiation
- It is involved in extracellular matrix during repair and regeneration
- It is also found to stimulate angiogenesis by extracellular matrix interactions
- Binds to type IV collagen.

**Conclusion**

BMP represents a set of unique factor that induces new bone formation at the site of implantation instead of changing the growth rate of preexisting bone.\[^{21}\] rh-BMP-2, for example, has shown to induce ectopic bone formation in an in vivo setting. Cell culture studies indicate that rh-BMP-2 can cause mesenchymal precursor cells to differentiate into cartilage and bone forming cells. Additional animal studies have shown that rh-BMP-2 is capable of replacing large defects about 2.5 mm deep in canine mandibles healing a variety of long bone defects in orthopedic models and concluded that these BMPs can be used for a variety of periodontal conditions.\[^{11,22-26}\]

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. McCauly L, Somerman M. Biologic modifiers in periodontal regeneration. Dent Clin North Am 1998;42(2):361-87.
2. Sporn MB, Todaro GJ. Autocrine secretion and malignant transformation of cells. N Engl J Med 1980;303:878-80.
3. McGeachie J, Tennant M. Growth factors and their implications for clinicians: A brief review. Aust Dent J 1997;42:375-80.
4. McKay I, Leigh I. Growth Factors: A Practical Approach. Oxford: Oxford University Press; 1993.
5. Stack JM, Darlington BG, Heath JK, Godslove SF. Mesoderm induction in early Xenopus embryos by heparin-binding growth factors. Nature 1987;326:197-200.
6. Smith JC, Price BM, Van Nijmmen K, Huylenbroeck D. Identification of a potent Xenopus mesoderm-inducing factor as a homologue of activin A. Nature 1990;345:729-31.
7. Khan SN, Bostrom MP, Lane JM. Bone growth factors. Orthop Clin North Am 2000;31:375-88.
8. Hollinger J, Chaudhari A. Bone regenerative materials for the mandibular and craniofacial complex. Cells Mater 1992;2:143-51.
9. Lee MB. Bone morphogenetic proteins: Background and implications for oral reconstruction. A review. J Clin Periodontol 1997;24:355-65.
10. Ripamonti UJ, Reddi AH. Periodontal regeneration: Potential role of bone morphogenetic proteins. J Periodontal Res 1994;29:225-35.
11. Sykara S, Opperman LA. Bone morphogenetic proteins: How do they function and what can they offer the clinician? J Periodontol
12. Wozney JM. The bone morphogenetic protein family and osteogenesis. Mol Reprod Dev 1992;32:160-7.
13. Aspenberg P, Wang E, Thorngren KG. Bone morphogenetic protein induces bone in the squirrel monkey, but bone matrix does not. Acta Orthop Scand 1992;63:619-22.
14. Sampath TK, Reddi AH. Dissociative extraction and reconstitution of extracellular matrix components involved in local bone differentiation. Proc Natl Acad Sci U S A 1981;78:7599-603.
15. Sampath TK, Reddi AH. Homology of bone-inductive proteins from human, monkey, bovine, and rat extracellular matrix. Proc Natl Acad Sci U S A 1983;80:6591-5.
16. Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, et al. Histologic evaluation of new attachment apparatus formation in humans. Part I. J Periodontol 1989;60:675-82.
17. Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, et al. Histologic evaluation of new attachment apparatus formation in humans. Part II. J Periodontol 1989;60:683-93.
18. Arceo N, Sauk JJ, Moeihing J, Foster RA, Somerman MJ. Human periodontal cells initiate mineral-like nodules in vitro. J Periodontol 1991;62:499-503.
19. Thies RS, Bauduy M, Ashton BA, Kurtzberg L, Wozney JM, Rosen V. Recombinant human bone morphogenetic protein-2 induces osteoblastic differentiation in W-20-17 stromal cells. Endocrinology 1992;130:1318-24.
20. Vukicevic S, Lutyen FR, Reddi AH. Osteogenin inhibits proliferation and stimulates differentiation in mouse osteoblast like cells (MC3T3-E1). Biochem Biophys Res Commun 1991;174:96-101.
21. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.
22. Schwartz Z, Mellonig JT, Carnes DL Jr., de la Fontaine J, Cochran DL, Dean DD, et al. Ability of commercial demineralized freeze-dried bone allograft to induce new bone formation. J Periodontol 1996;67:918-26.
23. Schwartz Z, Somers A, Mellonig JT, Carnes DL Jr., Dean DD, Cochran DL, et al. Ability of commercial demineralized freeze-dried bone allograft to induce new bone formation is dependent on donor age but not gender. J Periodontol 1998;69:470-5.
24. Boyns PJ, Marx RE, Nevins M, Triplett G, Lazaro E, Lilly LC, et al. A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation. Int J Periodontics Restorative Dent 1997;17:11-25.
25. Boyns PJ, Lilly LC, Marx RE, Moy PK, Nevins M, Spagnoli DB, et al. De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. J Oral Maxillofac Surg 2005;63:1693-707.
26. Fiorellini JP, Howell TH, Cochran D, Malmquist J, Lilly LC, Spagnoli D, et al. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. J Periodontol 2005;76:605-13.
27. Howell TH, Fiorellini J, Jones A, Alder M, Nummikoski P, Lazaro M, et al. A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. Int J Periodontics Restorative Dent 1997;17:124-39.
28. Triplet RG, Nevins M, Marx RE, Spagnoli DB, Oates TW, Moy PK, et al. Pivotal, randomized, parallel evaluation of recombinant human bone morphogenetic protein-2/absorbable collagen sponge and autogenous bone graft for maxillary sinus floor augmentation. J Oral Maxillofac Surg 2009;67:1947-60.