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REVIEW ARTICLE

Bone Morphogenetic Proteins: Building Blocks for the Periodontium

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ABSTRACT

Bone morphogenetic proteins (BMPs) are a group of regulatory glycoproteins that are members of the transforming growth factor beta superfamily, which play key roles in bone and cartilage formation and various other biological processes, including limb, kidney, skin, hair, and neuronal development, as well as maintaining vascular homeostasis. They primarily stimulate differentiation of mesenchymal stem cells into chondroblasts and osteoblasts. Food and Drug Administration recently approved recombinant human BMPs (rh-BMPs) for accelerating bone repair and fusion and their potential as pharmacological agents for the treatment of slow-healing fractures and tissue fibrosis in patients. This may prove noteful in designing regenerative treatments in periodontics.

Keywords: Glycoproteins, Growth factors, Periodontal regeneration, Periodontitis, Tissue engineering.

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INTRODUCTION

Periodontitis is an inflammatory disease elicited by the bacterial biofilm that forms around teeth, which steadily destroys the periodontal tissue supporting the teeth, including the periodontal ligament, cementum, alveolar bone, and gingival.[1] Conventional nonsurgical and/or surgical treatments can, at the very best, attenuate pocket depth and diminish inflammation in the affected region.[2] It poses a task of enormous importance to establish new treatment modalities that enable the regeneration and rebuilding of the lost periodontal tissue. Utilization of autogenous bone, allografts, xenografts, and various manmade bone substitutes/fillers were hence, developed as an attempt to restore the lost bone.[3] However, limited success was notified by these techniques in periodontal regeneration. Further search led to the development of techniques that exercise use of biological mediators and tissue engineering techniques.[4] Regeneration of periodontal structures embodies a complex multifactor process regulated by interaction between cells, hormones, growth factors, and extracellular matrices.[5] Recent advances in research in molecular biology led to identification of initiators of bone differentiation called bone morphogenetic proteins (BMPs) that regulate cartilage and bone differentiation, which set the base for tissue engineering of bone and related tissues.[6] Bone morphogenetic proteins are glycosylated, secreted extracellular matrix-associated molecules that regulate a wide variety of biological processes, including regulation of bone formation and repair and are also involved in morphogenesis and organogenesis.[5,7] More than 20 BMP-related proteins have been identified, many of which induce bone formation[8] of which BMP-2 (OP-2), BMP-3 (osteogenin), and BMP-7 (OP-1) are of research interest in periodontal regeneration.[9] The aim of this review focuses on various components of BMPs and their potential role in the regeneration of periodontal defects and improvement in periodontal regenerative outcomes.

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STRUCTURE AND CLASSIFICATION

The human genome encodes 20 BMPs. Bone morphogenetic proteins are dimeric molecules critically dependent on the single intermolecular disulfide bond for biological activity. The monomeric subunit has about 120 amino acids, including seven conserved cysteine residues.[10]

The BMP family can be divided into four distinct subfamilies:

- *1st group*: BMP-2 and BMP-4
- *2nd group*: BMP-3, BMP-3B (growth differentiating factor 10 or GDF-10)
- *3rd group*: BMP-5, BMP-6, BMP-7, BMP-8
- *4th group*: GDF-5, GDF-6, GDF-7 (cartilage-derived morphogenetic protein 1, 2, 3).

Here, BMP-1 is not a member of the BMP family, but rather a procollagen C proteinase enzyme involved in the proteolytic processing of soluble procollagen, leading to the self-assembly of insoluble collagen fibers in the extracellular matrix. Members of each subgroup have shown osteoinductivity with an identical mechanism as observed after ectopic implantation of osteoinductive demineralized bone matrix.

Functions of BMP

It regulates various mesenchymal/osteoblastic activities like the following[9]:

- Chemotaxis
- Anchorage-dependent cell attachment (fibronectin)
- Cell replication (mitosis)
- Differentiation of osteoblasts
- Alkaline phosphatase activity
- Osteocalcin synthesis/mineralization.[11]

Moreover, BMPs 2, 4, and 7 are expressed in dental epithelium, and recombinant BMPs 2 and 4 can be used as a substitute for dental epithelium in inducing mesenchyme differentiation. In addition to postfetal osteogenesis, BMP-3 may play a role in embryonic skeletogenesis.[12]

Mechanism of Action

Most of the biological action of BMPs are mediated through the BMP receptors that initiate signaling from the cell surface when bind to two distinct types I and II serine/threonine kinase receptors, required for signal transduction.[13,14] The BMP receptors are composed of three parts: A short extracellular domain, a single membrane-spanning domain, and an intracellular domain with active serine/threonine region.[15] The type II receptor is the primary binding site of the ligand and upon its activation, phosphorylation of type I receptor occurs.[16] Type I receptor (or activin receptor-like kinases) determines the nature of biologic response. Once activated it associates with various specific receptors regulated Smad {human homologous of mothers against decapentaplegic (DPP)} proteins that link the ligand receptors signals to transcription control. Thus, these cytoplasmic Smad proteins associate with specific DNA-binding proteins in the nucleus in order to generate transcriptional complexes.[17]

Recombinant Technologies

Recombinant technologies have been introduced to produce BMP for therapeutic evaluation. Combining the recombinant form of certain BMP molecules, e.g., recombinant human BMP-2 (rhBMP-2), with a carrier, such as demineralized, extracted (to remove endogenous BMP activity) collagenous bone matrix yields bone formation with the same set of processes, i.e., infiltration of implant with mesenchymal cells followed by differentiation of these cells into chondroblasts. These cells hypertrophy and mineralize, and the cartilaginous tissue is removed. Bone formation is observed during the time of cartilage maturation and removal or earlier if higher amounts of rhBMP-2 protein are implanted. Bone can be observed as early as day 5 after administration of high doses of rhBMP-2 and suggests that rhBMP-2 can induce intramembranous ossification, i.e., the direct formation of bone from mesenchyma. The availability of recombinant BMPs has allowed testing of the activities of each individual BMP. Several different BMP molecules, including BMP-2, 4, 5, 6, and 7, are osteoinductive. In 2002, the US Food and Drug Administration approved BMP-2 and BMP-7 for use in bone regeneration.[18]

All in all, BMPs produce multiple effects on bone by:

- Acting as mitogens on undifferentiated mesenchymal cells and osteoblast precursors;
- Inducing the expression of the osteoblast phenotype (e.g., increasing alkaline phosphatase activity in bone cells);
- Acting as chemoattractants for mesenchymal cells and monocytes as well as binding to extracellular matrix type IV collagen;
- Also, BMPs have the potential to obviate the need for autologous bone transplantation and thus eliminate secondary donor-site morbidity.

Chinese hamster ovary cells and *E. coli* transfected to become carriers have been used to produce BMPs in large quantities for preclinical and clinical evaluation.[19,20]

Bone Morphogenetic Protein in Periodontal Regeneration

Bone morphogenetic proteins play a valuable role in bone modeling and remodeling through chemotatic, mitogenic, or differentiating mechanism.[21] In the field of periodontal regeneration two recombinant BMP molecules are currently in clinical testing: BMP-2 and BMP-7 (OP-1). Another study exhibited enhanced new connective tissue attachment, and alveolar bone regeneration with partially purified osteogenin, isolated from human bone matrix, reconstituted with allogenic freeze dried demineralized bone matrix, in a root submerged environment in a series of human biopsies.[22] A study suggested that crude preparations of BMP-2 and BMP-3 applied in surgically induced furcation defects stimulated periodontal regeneration.[6] Recent studies have utilized rh-BMP to determine their potential for correcting intrabony, supraalveolar, furcation, and fenestration defects.[23] Histologic analysis showed periodontal regeneration with areas of ankylosis. Contrary to these findings, a significant increase in periodontal regeneration without any ankylosis was observed with BMP-7 augmentation. Hence, most of the recent research utilizing rh-BMPs has involved in the preparation of implant site for osseointeration.[24]

Bone morphogenetic proteins have also shown enhanced dental implant wound healing. A pilot study in nonhuman primates tested the single application of OP-1 around immediate extraction socket implants and found increased bone growth as measured histologically at 3 weeks.[25] In a recent study, combined adenovirus-mediated human BMP-2 (Adv–hBMP-2)

gene-modified bone marrow stromal cells with allograft enhanced the defect healing and improved the strength of implant fixation with osseointegration in 3-mm bone defect around a titanium alloy implant.[26] A histomorphometric analysis in a dog model showed that bovine BMP (bBMP) increased the rate of osseointegration around cylindrical uncoated endosseous implants as ally 4 weeks after implantation.[27] The tissue reactions to titanium implants coated with bBMP were further assessed by scanning electron microscopy for 12 weeks in the same dog model.[28] The results revealed abundant lamellar bone formation around bBMP-coated implants. This bone was found adjacent to the implant threads and frequently entered the implant holes.

CONCLUSION

Periodontal tissue regeneration requires the induction of periodontal ligament, cementum, and alveolar bone. Bone morphogenetic protein regenerative strategies attempt to simulate normal bone regeneration. Although several studies have depicted significant regeneration of the periodontal tissues with the use of BMP, it is essential to understand the biologic processes of periodontal wound healing and their effects on BMP activity. Further investigations are necessary for the proper isolation and development of improved delivery systems appropriate for controlled release of BMPs and identifying optimal condition for their use in periodontal regeneration.

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