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REVIEW ARTICLE

ROLE OF BONE MORPHOGENETIC PROTEINS IN PERIODONAL REGENERATION: A REVIEW

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Abstract

Periodontitis is an inflammatory disease characterized by destruction of the alveolar bone, cementum, periodontal ligament, and gingiva as a response to insults elicited by microbial accumulations. The characteristics of periodontal defects may be seen as suprabony, infra bony, or furcation defect or the combination of defects. Recent advances in molecular biology of the bone morphogenetic proteins (BMPs) have set the stage for tissue engineering of bone and related tissues, including the periodontium. Bone-derived BMPs, with a collagenous matrix as carrier, induced cementum and alveolar bone regeneration in surgically created furcation defects in the primate. It is noteworthy that there was morphogenesis of periodontal ligament and a faithful insertion of Sharpey's fibers into cementum.
The observation that BMPs induce cementogenesis and periodontal ligament formation indicates that these proteins may have multiple functions in vivo not limited to cartilage and bone induction. The rapid advances in the molecular biology of BMPs and their receptors bode well for novel strategies to engineer the regeneration of the periodontal tissues.

Introduction

Since antiquity, bone has been known to have a remarkable potential for repair and regeneration (Reddi AH, 2001) .Tissue engineering, defined as the science of fabrication of new tissues for replacement and the regeneration of lost or destroyed tissues, has learned and is still learning, the secrets of its principles from bone repair and regeneration, and it is likely that more secrets still remain to be learned from the principles of bone tissue engineering. (Reddi AH, 2001;Reddi AH,1994)

Recent advances in molecular biology of the bone morphogenetic proteins (BMPs) have set the stage for tissue engineering of bone and related tissues, including the periodontium. Bone-derived BMPs, with a collagenous matrix as carrier, induced cementum and alveolar bone regeneration in surgically created furcation defects in the primate. It is noteworthy that there was morphogenesis of periodontal ligament and a faithful insertion of Sharpey's fibers into cementum.

BMP is the generic name of a family of proteins, identified originally in extracts of demineralized bone that were capable of in ducing bone formation at ectopic sites. BMPs are found in minute amounts in bone material (*approx 1 µg/kg dry wt of bone).*

With exception of BMP-1 members of the family of bone morphogenetic proteins belong to the TGF-β super family of proteins. These factors are able to stimulate the differentiation and proliferation of uncommitted mesenchymal stem cells into chondroprogenitor and osteoprogenitor cells.

Urist in 1960 identified the bone-inducing substance, "***bone morphogenetic protein***" from untreated decalcified bone matrix.

BMP 1 is not a part of TGF-β family. It is a cysteine-rich Zinc peptidase that cleaves several pro-collagens into fragments that form mature collagen fibrils. Members of TGF β superfamily are synthesized as large precursor molecules, and the mature protein is released from a propeptide region by proteolytic cleavage.

BMPs consists of dimers that are interconnected by seven disulphide bonds; this dimerization is a prerequisite for bone induction. BMP's are active both as homodimer molecules that consist of two identical chains, and as a heterodimers consisting of two different chains.

Structure and Classification

The human genome encodes 20 BMPs. BMPs 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.(Ripamonti U,2006)

The BMP family can be divided into four distinct subfamilies:

1 stgroup: BMP-2 and BMP-4

2 ndgroup: BMP-3, BMP-3B (growth differentiating factor 10 or GDF-10)

3 rdgroup: BMP-5, BMP-6, BMP-7, BMP-8

4 thgroup: GDF-5, GDF-6, GDF-7 (cartilage-derived morphogenetic protein 1, 2, 3

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 demineralised bone matrix.

MODE OF ACTION

Histologic characterization has indicated a complex set of cellular events following implantation of bone-derived BMP. Combining the recombinant form of certain BMP molecules, for eg 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. infilteration 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 & suggests that rhBMP-2 can induce intramembranous ossification, that is, the direct formation of bone from mesenchyma.

The availability of recombinant BMP's has allowed testing of the activities of each individual BMP. Several different BMP molecules, including BMP-2, 4, 5, 6 and 7 are osteoinductive.

While BMP's primarily appear to be differentiation factors, additional activities have also been observed. Chemotactic activity on cells of the osteoblastic lineage has been reported, suggesting that BMP's may aid in bringing cells into the area in which the BMP is implanted. Thus, the main action of BMP's is to commit undifferentiated pluripotential cells to differentiate into cartilage and bone forming cells.

In summary, BMP's produce multiple effects on bone by

- Acting as mitogens on undifferentiated mesenchymal cells and osteoblast precursors;
- Inducing the expression of the osteoblast phenotype (eg. 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, BMP's have the potential to obviate the need for autologous bone transplantation and thus eliminate secondary donor site morbidity.

Recombinant human BMP-2 is produced on Chinese hamster ovary (CHO) cells. The delivery system advocated for delivery of rhBMP-2 is in combination with absorbable collagen sponge (ACS).

Histological analysis showed that BMPs, in conjunction with the collagenous matrix, induced cementum, periodontal ligament, and alveolar bone regeneration. Another study reported that partially purified osteogenin, isolated from human bone matrix, when reconstituted with allogenic freeze dried deminerlized bone matrix, enhanced new connective tissue attachment, and alveolar bone regeneration in a root submerged environment in a series of human biopsies.(Ugo Ripamonti,1997; Bowers G etal, 1991)A study where rhBMP-2 was used in a prepared periodontal defect in beagle dogs showed significant regeneration of the periodontal tissues.(Sigurdsson TJ etal ,1996)The effect of rhBMP-2 was evaluated in the surgically created critical size, supra alveolar periodontal defects in mandibular premolar teeth in beagle dogs which were implanted with rhBMP-2/ACS at different concentrations. Extensive alveolar regeneration and limited cementum regeneration were observed. However, ankylosis was observed in all teeth receiving rhBMP-2/ACS without apparent correlation with rhBMP-2 concentration or dose. The ankylotic union was observed in the coronal aspect of supra alveolar defects.(Wikesjo UM ,1999)

Animal studies have shown that application of rhBMP-2 in range of 0.4-0.8 mg/ml appeared to result in superior bone formation.

Clinical studies with human bone derived BMP have proved promising, but have been limited by the lack of availability of material. Two recombinant BMP molecules are currently in clinical testing:

BMP-2 & BMP-7 (OP-1). (The rhBMP-2/ACS was tested to induce bone and augment the maxillary sinus floor).

The first human study using a BMP to promote periodontal regeneration utilized a single application of BMP-3 (osteogenin) combined with demineralized bone allograft in a submerged tooth model. They found increased new bone and cementum deposition around periodontally involved submerged teeth in the BMP-3 plus bone graft group; while the BMP-3 plus collagen vehicle demonstrated no increases in bone or cementum as compared to control. (Nevins M, 2003)

A study on dog examined the effects on rhBMP-2 on periodontal regeneration found that BMP-2 applied in synthetic bioabsorbable particles promoted highly significant increases in new bone and cementum formation. Nearly 95% of the bone in surgically created Class III furcation lesions was regenerated. However, an early 4-fold increase in ankylosis was found in BMP-2 treated site.(Sigurdsson TJ etal,1996)

BMP's also show much promise in promoting dental implant wound healing. A pilot study in non-human primates tested the single application of BMP-7 (OP-1) around immediate extraction socket implants and found increased bone growth as measured histologically at 3 weeks.(Karuppanan P ,2012)

Perspectives in periodontal tissueengineering by BMPs

Periodontal tissue engineering foremost entails the induction of cementogenesis and the genesis ofSharpey'sfibers inserting into newly formed cementum(Several studies have highlightedthat partially purified and purified extracts ofcementum contain a mitogenic growth factor as a
distinct molecular species The presenceofmitogenic growth factors within the cemental
matrix indicates that cementum has the potential toregulate the adjacent periodontal ligament space. The extracellular matrix of the cementum may provide a framework for the regeneration of the varioustissue components of the periodontal ligament and, in addition, may play important physiological roles in sequestration of morphogenetic factors involved in repair, regeneration and remodeling .It will be of importance to bioassay

cemental extracts after 6 M guanidinium or urea dissociativeextraction followed by heparin–Sepharose affinity chromatography. Cemental extracts purified by affinity chromatography may retain osteogenic proteins embedded within the matrix as a memory ofdevelopmental events, as highlighted by demineralised dentine matrix of P. ursinus with osteogenicactivity in the rectus abdominis. If cementum does induce endochondral bone differentiation,it would be tempting to suggest that bone induction modulated by cemental matrices maybe the result of a slow release of embryonic remnants of osteogenic proteins that were required anddeployed during cementogenesis. The capacity of mammalian BMPs/OPs to initiate a programmed
cellular cascade that results in the induction of bone is a functionally conserved process utilized in embry-onic development, recapitulated in postfetalosteogenesis and can be re-exploited for the therapeuticinitiation of periodontal tissue regeneration. There are several challenges that provide opportunitiesto gain mechanistic insights into the regulation ofperiodontal tissue regeneration; a challenge of greatmolecular importance is the biological significance of apparent redundancy. The presence of the structure–activity profile amongst soluble osteogenic molecularsignals indicates a therapeutic significance in clinical
contexts . Significant advances in periodontaltissue regeneration may be expected if ongoing andfuture research is tailored to provide further mechanisticinsights into the relevance of apparentredundancy and the structure–activity profile of there combinant human osteogenic proteins.(UgoRipamonti, 2006)
Nonetheless, at the beginning of the 21st century, asoluble osteogenic and recombinant molecular signal,when combined with an insoluble signal, triggersperiodontal tissue regeneration with the induction ofcementogenesis and insertion of Sharpey's fibers, essential ingredients to engineer periodontal tissue regeneration .

Gene therapy for bone regeneration

Gene therapy is defined as the treatment of disease by transferring genetic materials to induce specific genes that direct an individual's own cells to produce therapeutic agent.(4)In gene therapy, it is critical to establish effective carrier (vectors) systems that facilitate gene transfer to targeted cells. Vectors for gene delivery: (a) Viral vectors such as adenovirus, adeno-associated virus, and retrovirus. (b) Nonviral vectors such as liposomes, polymers, and electroporation and ultrasound. The major advantage of viral vectors is their high transduction efficiency. The main disadvantage of viral vectors is their immunogenic potential.The application of growth factors by gene transfer provides a greater sustainability than that of single protein application. Gene therapy may achieve greater bioavailability of growth factors within periodontal wounds, which may provide greater regenerative potential.

Conclusion

Periodontal tissue regeneration entails the induction of periodontal ligament, cementum, and alveolar bone. Although, several studies have shown significant regeneration of the periodontal tissues with the use of BMP, it is important to understand the biologic processes of periodontal wound healing and the effects of these biologic processes on BMP activity. Further studies are needed for the development of delivery systems that have mechanical and surgical properties appropriate for controlled release of bone morphogenetic proteins and identifying optimal condition for the use of BMPs for periodontal regeneration.

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