Bone Morphogenetic Proteins – Potential Role In Periodontal Regeneration

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Abstract: A significant goal of periodontology in the recent years has been the regeneration of periodontal tissues to their original form, architecture and function after they have been affected by periodontitis. Periodontal regeneration is a complex wound healing process that involves the structural and functional rebuilding of periodontal tissues that have been lost as a consequence of periodontal diseases. Bone morphogenetic proteins (BMPs) are a group of growth factors and cytokines which are known for their ability to induce the formation of bone and cartilage and have now evoked interest among researchers in this field.

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Introduction:A significant goal of periodontology in the recent years has been the regeneration of periodontal tissues to their original form, architecture and function after they have been affected by periodontitis.Periodontal regeneration is a complex wound healing process that involves the structural and functional rebuilding of periodontal tissues that have been lost as a consequence of periodontal diseases.

A variety of molecules participate in the regulation of processes involved in periodontal regeneration. Based on their action they can be growth and inflammatory mediators, adhesion molecules and matrix components. The mediators include cytokines, chemokinesandlymphokines which regulate the migration and proliferation of cells during inflammation and wound repair[1]. The adhesion molecules like fibronectin and laminin localize cells at required sites; and matrix components such as proteoglycans and collagen are necessary for the structural and physiologic integrity of the new tissue[2].

Hallmark of periodontal disease is the destruction of the osseous support of the dentition. This localized bone resorptive process has been the target for therapeutic intervention and preventive strategies. Factors that perturb either bone formation or resorption alter the overall quality of bone. During development it is seen that the bone formation is much greater than bone resorption, with a resultant increase in bone mass and periodontal regeneration attempts to recapitulate this.

Bone morphogenetic proteins (BMPs) are a group of growth factors and cytokines which are known for their ability to induce the formation of bone and cartilage.

The discovery of BMPs: The observation that demineralized bone matrix induces ectopic bone formation in subcutaneous and intramuscular pockets in rodents lead to the beginning of the discovery of certain substances that induce bone formation. Urist and co-workers in the early 1960s discovered that control samples of untreated decalcified bone implanted into muscle pouches of rabbits and rats resulted in new cartilage and bone formation. This led to the hypothesis of bone formation by autoinduction, in which the inductor cell acts upon induced cell causing it to differentiate into either an osteoprogenitor or a chondroprogenitor cell. He referred to this hypothetical bone inducing substance as “Bone Morphogenetic Proteins”

Originally, 7 such proteins were discovered. Of these, 6 f them (BMP 2 through BMP 7) belong to the Transforming growth factor beta super family of proteins. Since then, 9 more BMPs have been discovered, bringing the total to 16. [3]

Actions of BMP’s

1) Cellular role of BMP

- Role of BMP’s during embryonic development has been studied by the impact of gene knockout in ‘transgenic’ animals, either by generating a null allele for theprotein itself or its receptor[4].

- At more advanced stages of development, BMP's appear to play key roles in mediating programmed cell death (aopoptosis)

2) Role in wound healing

- BMPs directly affect the healing in the following sequential phases
- INJURY results in " inflammatory response " and complement activation ensues extravasation and cell signaling
- PROLIFERATION of" granulation tissue " results in binding of growth factors to collagen
- REMODELLING" results in activation-resorption formation leading to osteoclasts resorptive pits. [2]

3) BMP induced osteogenesis

The maturation of cartilage to bone at ectopic sites occurs by a process which recapitulates the developmental process of primary endochondral ossification. This biological activity is attributable to the endogenous BMP fraction of bone, the bioavailability of which is increased by the process of demineralization.

BMP induced bone formation requires

- an initiating stimulus
- a competent cell population
- a permissive environment.

Following implantation of inductively active demineralized bone matrix/ BMP, 3 phases of osteoinduction are observed.

a- chemotaxis : initially brings polymorphonuclear leucocytes into the implanted area, followed by fibroblasts and cell attachment to the matrix.

b- Mitogenesis : proliferation of mesenchymal cells are seen. Increase in type I collagen mRNA is seen which may be an indicator of increased activity in these cells

c- Differentiation :differentiation of mesenchymal cells into chondroblasts takes place by day 5.It occurs through the close matrix cells interaction and results in the synthesis of 'extracellular matrix components typical of cartilage'.

Osteoblasts appear at days 10 through 12 and form new bone matrix while chondrocytes are active in removing the calcified cartilage.

There is a peak in alkaline phosphatase production. From day 12 through, the osteoclasts remodel the newly formed bone and selectively dissolve the implanted matrix, resulting in an ossicle of new bone complete with marrow by day 21.

4) BMP's and periodontal regeneration

The interaction of BMP's with extracellular matrix macromolecules has permitted the formulation of novel conceptual designs of the potential regulatory role of BMPs in osteogenesis.

The restoration of biological activity after dissociative extraction and reconstitution of BMPs with insoluble collagenous matrix indicates that components of the extracellular matrix of bone act as carriers for the functional expression of BMPs.

This has shown that the collagenous bone matrix provides an optimal substratum for the recruitment, anchorage of progenitor cells and subsequent proliferation and differentiation into osteoblasts. [5]

This morphogenetic potential of BMP makes them an ideal candidate for use in periodontal regeneration. Translational studies have been performed to investigate the ability of recombinant human bone morphogenetic protein-2 to stimulate periodontal regeneration.[6,7,8.] These studies indicate that recombinant human bone morphogenetic protein-2 can produce considerable periodontal tissue regeneration if applied with a suitable carrier.[9,10]Several side effects like ankylosis and root resorptionhave been reported with its use.[11]At different concentrations of rhBMP 2 no differences were found in the incidence and extent of root resorption and ankylosis.[12]

Studies indicate that the application of recombinant human bone morphogenetic protein-2 around a periodontal defect induces bone formation but not cementum formation[13,14,15] While recombinant human bone morphogenetic protein-2 enhances the regeneration of alveolar bone that has been reduced as a result of periodontal inflammation, it might not be suitable for regenerating the periodontium between two hard tissues – bone and cementum – because of its

strong osteoconductive property. Recombinant human bone morphogenetic protein-2 has shown favorable results when used during the preparation of implant sites.[14] Recombinant human bone morphogenetic protein-2 within a type I collagen sponge is now commercially available and clinically applicable (Infuse; Medtronic SonfamoreDanek, Memphis, TN, USA).

5) BMPs and implants

The capacity of BMP to induce bone has set the stage for the application in craniofacial surgery for correcting anomalies, to treat large bone defects after excision of neoplasms.

Administration of a single rhBMP, such as BMP2,4 or 7 can initiate the entire cascade of Osteogenesis. BMPs have been used for repair of maxillary sinus.[15]

Implants might benefit from combined use with BMPs, wherein BMPs may be used to stimulate bone growth in and around metallic implants to attain optimal integration.[16]

Conclusion: As indicated from studies, most of the biological mediators have a strong influence on cell behavior and show great promise in regenerative techniques. However owing to inconsistent results in human models, further clinical investigations directed at improving the predictability outcome are needed.

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