Bone Morphogenetic Proteins: An Overview

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ABSTRACT

For over years research has been carried out for finding the treatment procedures for the regeneration of a lost or injured part so that form and function of lost structures can be restored. This regenerative field holds the promise of engineering damaged tissues with the help of various growth factors including Bone Morphogenetic Proteins (BMPs), by stimulating the body’s own repair mechanisms. BMPs constitute the largest subgroup of transforming growth factor beta superfamily. Till date over 30 members of this family has been identified. They are dimeric molecules and exhibit their effects using specific cell surface receptors. With the development of the techniques required for the isolation and cloning of these molecules, we are now able to understand their properties. They are powerful inductors of the osteogenic activity and have proliferative effects on various cellular types. This made us to use them in various therapeutic procedures including oral maxillofacial reconstruction, periodontal regeneration, enhancing osseointegration around dental implants and in various endodontic procedures. However, their effect is dosage and carrier dependent. Thus, the aim of this review is to help in understanding the structure, classification, signaling and role of BMPs in regeneration of bone and tissues.

Keywords: Bone Morphogenetic Proteins, Regeneration, Growth Factors

Introduction

The advancement in tissue engineering techniques has made it possible to develop various procedures utilizing the biological mediators like bone morphogenetic proteins (BMPs) for the regeneration of bone and tissues lost due to diseases.1,2 BMPs comprises of a group of potent, multi-functional growth factors, belonging to transforming growth factor beta (TGF-β) superfamily, which were discovered by Urist and coworkers3 in 1965.

They have been shown to play an important role in regulating the growth, differentiation and apoptosis of various cell types, including osteoblasts, chondroblasts, neural cells, and epithelial cells, depending on the cellular microenvironment and the interaction with other regulatory factors.4,5 Also when implanted into the bone matrix this protein component resulted in series of cellular events leading to mesenchymal cell infiltration, cartilage formation, vascularization, bone formation, and remodeling of the new bone along with proliferation of hematopoietic bone marrow elements.6

Hence, this review is an attempt to summarise the characteristics and various applications of Bone Morphogenetic Proteins.

Classification of BMPs

Till date only 20 different human BMPs have been discovered and classified into subfamilies, but including activin, inhibin, growth differentiating factors (GDFs) there are nearly 30 members in BMP family.7 BMPs are classified on the basis of their sequence similarities and functions into four subfamilies:-

a. 1st group- BMP2 and BMP4 – (80% homology) - highly related molecules, differs mainly in amino terminal region, where BMP2 contains a heparin-binding domain.

b. 2nd group- BMP3, BMP3B (GDF10) – also called as Osteogenin.

c. 3rd group- BMP5, BMP6, BMP7, BMP8a, BMP8b – (78% homology)

d. 4th group- GDF5, GDF6, GDF7-(cartilage-derived morphogenetic protein 1,2,3)

However, BMP1 is not considered as a member of TGF-β superfamily, as it lacks the structure conserved in the TGF-β superfamily. In some studies, it has been reported as a procollagen C- proteinase, processing procollagen to collagen.8,9

Structure And Signaling Of BMPs

BMPs are synthesized as precursor proteins having polypeptide chains ranging in size from 369-513 amino acids which are cleaved by pro-protein convertases and serine endoproteases to generate mature and active homodimers and heterodimers.3,10,11

These dimeric molecules, constitutes about 120 amino acids. It comprises of seven conserved cysteine residues.
Out of these six forms a cysteine knot motif, linked with three intra-molecular disulfide bonds forming a critical core of the BMP monomer.10,12,13

BMP molecules exhibit their activity by binding to two types of specific cell surface receptors: Bone morphogenetic protein receptor, type 1 (BMPR 1) and Bone morphogenetic protein receptor, type 2 (BMPR 2). The BMP signaling cascade is initiated by binding to these cell surface receptors through-3

- Canonical pathways
- Non-Canonical pathways.

**Dosage And Carriers of BMP-**

The estimated amount of BMP per kilogram pulverized bone is 0.002mg.14 The amount of BMP required to induce bone bridging in osseous defects depends upon- the state of organism in the evolutionary scale, anatomic location of the site of application and the type of defect.15,16

BMP is water soluble, and diffuses very easily in body fluids. For the effectiveness BMPs require a competent carrier in order to be contained.18,19

These carriers can be broadly classified into – naturally occurring polymeric substances, inorganic salts, synthetic polymers and composites of synthetic and naturally occurring polymers and titanium. About 15-55% of increased retention was seen when BMPs were combined with gelatin foam or collagen.17

**Regenerative Potential of BMPs-**

Bowers et al,19 described the first successful use of BMP for periodontal regeneration. BMPs, demonstrates pleotropic effects on the stimulation of several key events required for tissue regeneration including DNA synthesis, chemotaxis, differentiation, and matrix synthesis.19,20

Several tests have been conducted, demonstrating the increased regeneration of alveolar bone, periodontal ligament(PDL) and cementum in bone defects, bone healing, acceleration osteointegration, oral and maxillofacial reconstruction, bone pathology sequel repair, distraction osteogenesis as well as, in endodontic procedures.22,23,24,25 Treatment of endosseous implants with bovine BMP and rhBMP-2 caused the stimulation of a greater amount of bone deposition and bone-to-implant contact, which was more significant after 4 and 12 weeks of healing.26,27,28

The anabolic effect of BMPs on periodontal tissues is through stimulation of osteoblastic differentiation in human PDL cells and by stimulation of alkaline phosphatase activity in periosteal cells thus, enhancing the regeneration of new connective tissue attachment and bone in both root submerged and non-submerged environment.19,23

Thus, concluding that BMPs offer promise as an attractive candidate for treating severe periodontal lesions with significant potential for stimulating periodontal regeneration.23

**Conclusion**

Several studies have highlighted that BMPs provide a framework for the regeneration of the various tissue components of the periodontium and, in addition, may play important physiological roles in repair, regeneration and remodeling. However, despite a great deal of research effort, the ideal treatment modality using BMPs has yet to be established and further basic research is required to elucidate the detailed mechanism of BMP receptor activation and signal transduction to the cell nucleus and the their clinical applications.

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