Bone morphogenetic proteins: Role in periodontal regeneration

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ABSTRACT

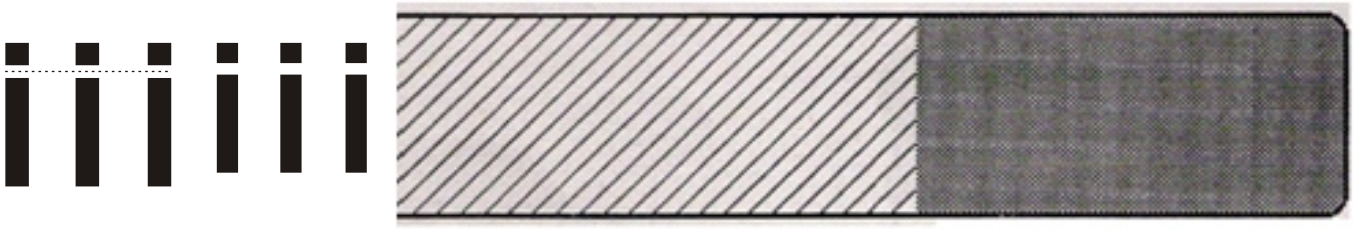
Bone is unique of all the tissues in the vertebrate organism. When injured, it heals by formation of new bone. Bone morphogenetic proteins (BMPs) are powerful inductors of the osteogenic activity during the embryologic bone formation phase and in cases of bone healing. They have proliferative effects on different cellular types, showing chemotactic properties and are able to induce mesenchymal cells differentiation into osteoblastic and chondroblastic line cells Both primary cells and cell lines have been shown to respond to BMPs. Further the ability of embryonic cells to respond to BMPs by differentiating into cartilage and bone cells suggests that they are involved in the development of embryonic skeletal system. Thus, understanding the role of BMPs and their potential advances are necessary to facilitate the process of regeneration in periodontics.

Introduction

Bone Morphogenetic Proteins (BMPs) are a group of growth factors and cytokines which were originally discovered by their ability to induce formation of bone and cartilage, but are now considered to constitute a group of pivotal morphogenetic signals, orchestrating tissue architecture throughout the body. When BMPs bind to their cell surface receptors on mesenchymal cell, a BMP signalling cascade is activated. Signals are sent via specific proteins to the cell nucleus. This results in the expression of genes that lead to the synthesis of macromolecules involved in cartilage and bone formation, and the mesenchymal cell becomes a chondrocyte or an osteoblast. Endochondral bone induction is the result of the combinatorial action of BMPs and the complementary substratum that delivers the osteogenic activity of the soluble molecular signal.[1] In addition to differentiation of cells into the chondrocyte lineage BMPs have been shown to directly differentiate into cells of the osteoblast phenotype.

II. Chemical Structure of BMPs

Bone morphogenetic proteins are members of TGF- (Transforming growth factor-) super family, a large family of growth factors. The TGF- was so named because of its ability to transform cultured fibroblasts.[2] Structural studies indicate that the molecules are synthesized as precursor molecules containing an amino-terminal signal sequence and a pro-domain of variable size (Figure1). Dimerization assembly can result in homodimers and heterodimers and along with glycosylation ability, also influence activities and effects of BMPs.[3]



LEADER
(Amino acid terminal-
HYDROPHOBIC)

PROPEPTIDE
(Folding, Dimerization,
Regulation)

MATURE REGION
(Carboxy terminal)

Mature domain cleaved → monomeric units dimerized, glycosated → Activated dimer expression

Figure 1. Chemical Structure of BMPS

III. Classification of BMPs

The human genome encodes 20 BMPs.[4]

The BMP protein can be broadly classified into three subfamilies as shown in Table 1. [5] :

Table - 1 : Subfamilies of BMPs

BMP-2 and BMP-4 -80% homology	BMP-5, BMP-6, BMP-7 -78% homology	BMP-3 -significantly different from the other members of the BMP family

The classfication of BMPs is shown in Table 2.

Table -2 : Classfication of BMPs

BMP-1	Not part of TGF- family
BMP-2	Osteoinductive, osteoblast differentiation, apoptosis
BMP-3 (osteogenin)	Most abundant BMP in bone, inhibits osteogenesis
BMP-4	Osteoinductive, lung & eye development
BMP-5	Chondrogenesis
BMP-6	Osteoblast differentiation, chondrogenesis
BMP-7 (Osteogenic Protein-1)	Osteoinductive, development of kidney & eye
BMP-8 (Osteogenic Protein-1)	Osteoinductive
BMP-9	Nervous system, hepatic reticuloendothelial system
BMP-10	Cardiac development
BMP-11 (Growth/differentiation factor-8)	Neuronal tissues
BMP-12 (Growth/differentiation factor-7)	Tendon-iliac tissue formation
BMP-13 (Growth/differentiation factor-6)	Tendon & ligament-like tissue formation
BMP-14 (Growth/differentiation factor-5)	Enhances tendon healing & bone formation
BMP-15	Follicle-stimulating hormone activity

IV. Signaling Mechanism of Bone Morphogenetic Proteins

The BMP receptors are made up of Type I and Type II serine / threonine kinase proteins.[2]

Ligand binding → Heterotetramer Complex → Signaling Cascade (fig.2).

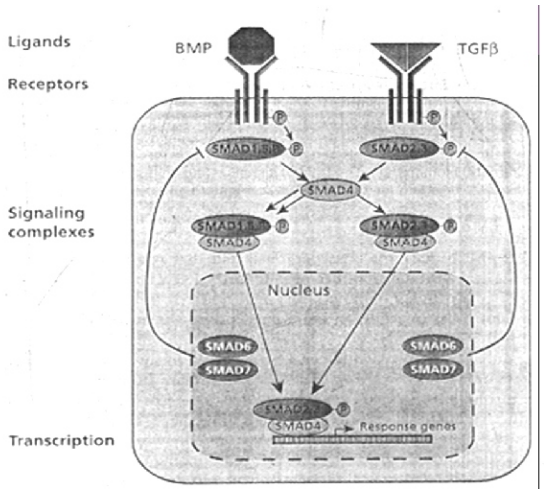


Figure 2. Signaling Mechanism of BMPS

V. BMP in Wound Healing

BMPs directly affect wound healing process.[6] BMPs directly affect the healing in the following sequential phases (Fig 3):-

INJURY → inflammatory response → complement ensues → Extravasation and cell signaling

PROLIFERATION → granulation tissue → binding of growth factors to collagens

REMODELLING → activation-resorption formation → Osteoclasts resorptive pits

VI. Factors Affecting BMPActivity

There are various local & systemic factors that affects the activity of BMPs as shown in Table 3.

Table 3 : Factors affecting BMP activity

	SYNERGISTIC EFFECT	ANTAGONISTIC EFFECT
LOCAL FACTORS	Basic fibroblast growth factor (low dose)	Basic fibroblast growth factor (high dose)[7]
	Transforming growth factor[7]	
	Prostaglandins (PG E1)[8]	
SYSTEMIC FACTORS	Glucocorticoids[9]	
	Vitamin D[10]	
	Beta-estradiol[11]	

Conclusion

Presence of the structural activity of bone morphogenetic proteins amongst soluble osteogenic molecular signals indicates a therapeutic significance in clinical contexts. The challenge lies in applying these drugs with consistent success in various applications. Further, studies are needed for development of carrier materials that have mechanical properties and surgical practicality appropriate for controlled release of bone morphogenetic proteins.

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