Review Article

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Bone Morphogenetic Protein: An Overview

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ABSTRACT

Background: Bone Morphogenetic Proteins are multifunctional cytokines which are members of the TGF-β superfamily; a large family of growth factors. This review is aimed at describing the history, family, structure, functions and applications of bone morphogenetic proteins.

Materials and Methods: The application and importance of bone morphogenetic protein in humans were discussed through the literature survey.

Results: Bone morphogenetic protein is a water-soluble relatively low–molecular weight protein that diffuses very easily in the body fluids. They constitute a large multigene family whose members are related to each other by relative degrees of sequence similarity, but that possess a wide ranging number of biological functions. They have been observed in nearly all developing visceral and somatic organs, i.e. brain and sympathetic neurons, heart, liver, lung, skin, hair follicles, craniofacial structures, branchial arches, placenta, and skeletal elements.

Conclusion: Discovered a long time ago, BMPs are currently produced through genetic engineering, allowing for studies on their role in development and cell metabolism, particularly through transgenic cells and animals. The BMP guides modulation and differentiation of mesenchymal cells of muscle into bone & bone marrow cells. Although the existing systematic review and meta-analysis support some therapeutic applications, adverse effects of their clinical use have been reported, and several important questions remain to be addressed.

Keywords: Bone Morphogenetic Protein, Transforming Growth Factor, Growth Differentiation Factor, Cytokines, Mesenchymal, Osteogenesis.

INTRODUCTION

Bone tissue engineering is an emerging biomedical form to create a local environment which enables cells to promote the proliferation and differentiation for bone regeneration inductions. There are many approaches to bone tissue engineering, but all involve one or more of the following key ingredients: harvested cells, recombinant signalling molecules, and three-dimensional (3D) matrices. An essential contribution to bone formation and regeneration is given by growth factors such as bone morphogenetic proteins (BMP), platelet derived growth factor (PDGF), insulin-like growth factor (IGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF).[1] The osteogenetic chemical components of the matrix bone, dentin & other hard tissues that are de-insulated by demineralization and associated

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intimately with collagen fibrils are termed as Bone morphogenetic proteins (BMPs).[2] They 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.[3] They have been the most widely investigated proteins for bone regeneration, as they are currently the most potent and only factors able to induce ectopic bone formation.[1]

BMPs are multifunctional cytokines which are members of the TGF-β superfamily; a large family of growth factors. They regulate growth, differentiation, chemotaxis and apoptosis of cells and can singly induce ex novo bone formation both in vitro and, at heterotopic sites, in vivo.[1]

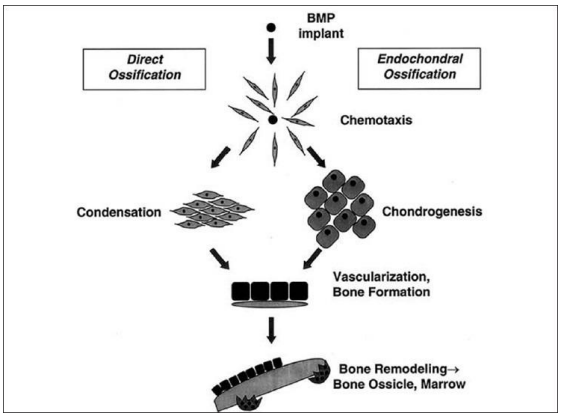

Fig 1: Cellular events after implantation of bone morphogenetic protein (BMP). These proteins induce both endochondral (through a cartilage intermediate) and direct (intramembranous) bone formation. The end result in each case is woven bone that then remodels and becomes populated with hematopoietic bone marrow.[4]

Table 1: History of evolution of Bone morphogenetic protein.[5]

1965	Marshall Urist discovery that demineralised bone matrix (DBM) can induce bone formation.
1971	Urist develops concept of Bone Morphogenetic Proteins (BMPs)
1972	Hari Reddi, Huggins find bone induction is a sequential cascade with multiple steps.
1981	Reddi and Kuber Sampath do associated extraction and reconstitution of BMP activity for bioassay.
1991	Orthopaedic surgeons use BMP,s for the first time as Demineralised Bone matrix (DBM) is available for commercial use.
October 2001	FDA grants humanitarian device exemption (HDE) approval for Osteogenic protein 1 (OP-1; rh BMP 7)
November 2002	FDA approves rh BMP 2 (INFUSE) for a single level spine fusion.
April 2004	FDA grants HDE approval for OP-1 putty for revision spinal fusion.
May 2004	FDA approves rh BMP-2 (INFUSE) for treating acute open tibial shaft fractures.

DISCOVERY OF BMP

The ability of devitalized bone, when implanted in an animal, to induce a cellular response resulting in new bone tissue formation has been known for decades. This unique activity was observed and researched extensively by an orthopaedic surgeon, *Dr. Marshall Urist*. He subsequently demonstrated that this activity could be extracted from the organic component of bone using chaotropic agents, and that a protein or proteins were responsible for this activity. He thus named this activity "bone morphogenetic protein."[4]

Table 2: Milestones in the discovery and use of BMPs[6]

Authors/Company & Year	**Observation/Discovery**
Senn, 1889	Decalcified ox bone promotes healing of osteomyelitic defects
Levander, 1934 & 1938	Crude alcohol extracts of bone induce bone formation
Sharrard & Collins, 1961	EDTA-decalcified allograft induced spinal fusion in children
Urist, 1965	Acid-decalcified bone induced ectopic bone in rat model
Sampath & Reddi, 1981	Crude but reproducible quantitative bioassay for BMP; bone matrix when dissociated from BMP ineffective in bone induction; reconstituted matrix effective

Johnson, et al., 1992	Purified human BMP successful clinically
Creative BioMolecules & Genetic Institute, 1990s	Virtually simultaneous gene sequencing for various BMPs and related patent dispute
Stryker Corp & Medtronic Sofamor Danek, 2002	FDA approval of OP-1 (BMP-7) for long bone defects (Stryker) & BMP-2 in a collagen carrier within a cage for ALIF (Medtronic Sofamor Danek)

BMP FAMILY

The human genome encodes 20 BMPs. Comparisons among the derived amino acid sequences of the BMPs found in osteoinductive extracts of bone indicate that they fall into three subclasses[3]

Table 3: Sub-classes of BMPs[3]

Subclass A	Subclass B	Subclass C
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

Comprising an ever-growing number of identified homologues, the BMPs represents almost one third of TGF-β superfamily, with more than 30 members already described (Figure-4). Individually, the members of this subfamily of secreted molecules are termed either BMPs, osteogenic protein (OPs), cartilage derived morphogenetic proteins (CDMPs), or growth and differentiation factors (GDFs). They have been classified into several sub-groups according to their structural similarities (Figure-4).[6]

Amino acid sequence identities were calculated based on the ligand-binding domain sequence, which is located downstream of the first conserved cysteine residue. The length of the horizontal line connecting one sequence to another is proportional to the estimated genetic distance between the sequences. No asterisk, human/mouse protein; *Drosophilaprotein; **Xenopus protein; ***Sea urchin protein.[6]

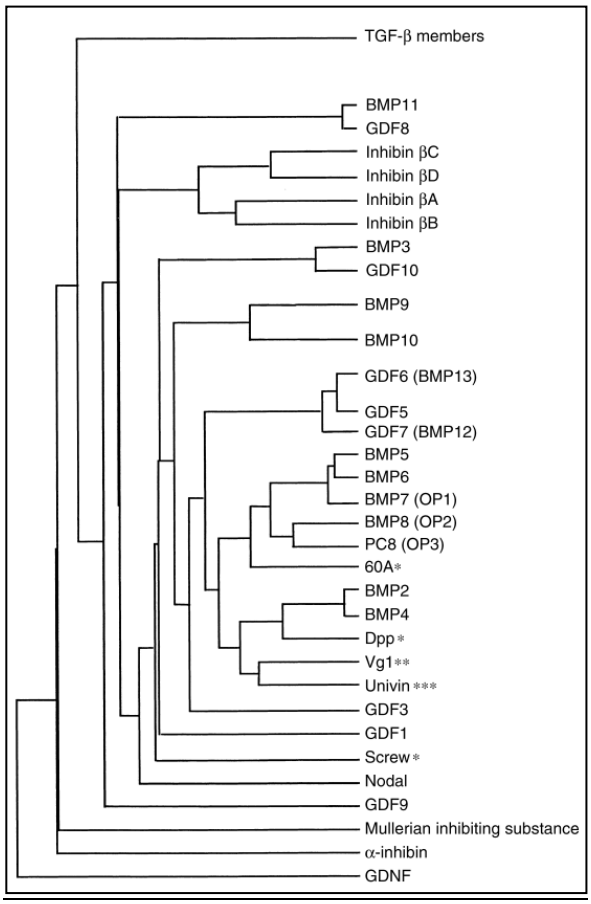

Fig 4: Phylogenetic relationships between bone morphogenetic protein (BMP) family members.

Table 4: Characteristics of various BMPs[7]

Name/type of BMP	**Characterstics of BMP**
BMP-1	Not part of TGF-β family
BMP-2	Osteoinductive, osteoblast differentiation, Apoptosis
BMP-3 (osteogenin)	Most abundant BMP in bone, inhibits Osteogenesis
BMP-4	Osteoinductive, lung and eye development
BMP-5	Chondrogenesis
BMP-6	Osteoblast differentiation, chondrogenesis
BMP-7 (osteogenic Protein-1)	Osteoinductive, development of kidney and eye
BMP-8 (osteogenic Protein-2)	Osteoinductive
BMP-9	Nervous system, hepatic reticuloendothelial system, hepatogenesis
BMP-10	Cardiac development
BMP-11 (GDF-8, myostatin)	Patterning mesodermal & Neuronal tissues
BMP-12 (GDF-7)	Induces tendon-iliac tissue

	formation
BMP-13 (GDF-6)	Induces tendon and ligament-like tissue formation
BMP-14 (GDF-5)	Chondrogenesis enhances tendon healing and bone formation
BMP-15	Modifies follicle-stimulating hormone activity

Basic structure of BMP (Figure 6): It comprises of three proteins they are[8]

1. Signal peptide

2. Propeptide

3. Mature

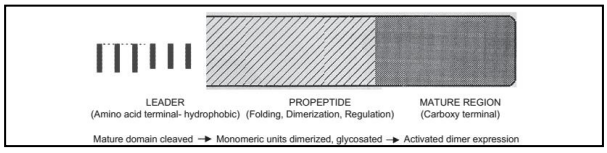

Fig 6: Chemical structure of BMPs[3]

BMPs are dimeric molecules, constituted by about 120 amino acids, including seven conserved cysteine residues, from which six are highly conserved, comprising a cysteine knot motif linked by three intra-molecular di-sulfide bonds. Another cysteine is involved in stabilization of the dimer through an intermolecular cysteine bridge. Some members of the BMP family, namely, GDF3, GDF9 and GDF9B, may form non-covalent dimers due to the lack of this cysteine. BMPs are synthesized inside the cell as large and inactive precursors, carrying an N-terminal hydrophobic signal peptide (s50–100 amino acids), which directs the protein to the secretory pathway, a pro-domain that mediates proper folding and a C-terminal mature peptide(Figure 6). These proteins also display sites for N- and O-glycosylation, which increase their stability and half-life in the body and determine the specificity of receptor coupling. After dimerization, a prerequisite for bone induction, the pro-domain is proteolytically cleaved at a consensus Arg-X-X-Arg region to generate mature and active homo-dimers or hetero-dimers (Figure 7).[9]

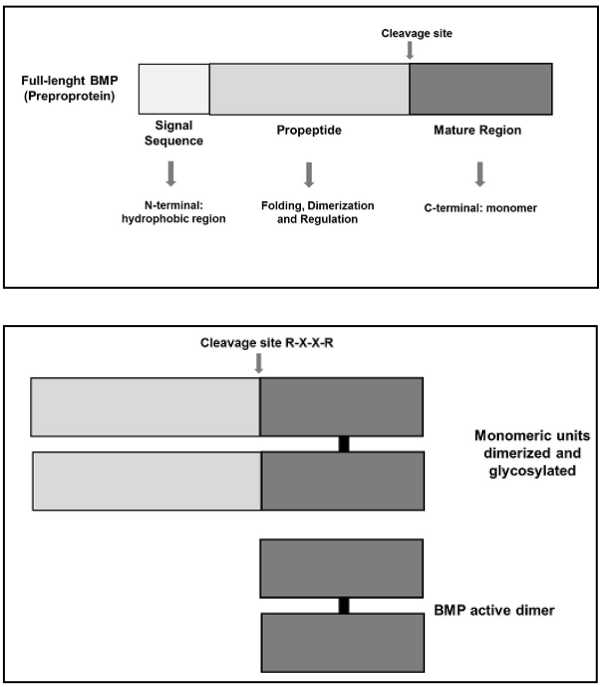

Fig 7**:** Structural organization of BMPs. Full-length BMP consists of a signal sequence, a pro-peptide, and the mature region. The mature protein is secreted as a homo-dimer linked by disulfide bonds. The C-terminal mature protein is proteolytically cleaved from the pro-domain at an R-X-X-R sequence by proteases before dimerization.[9]

BMP- DELIVERY SYSTEMS

The need for a carrier has been recognized since BMP was initially identified. Various carriers have been investigated experimentally and clinically. The BMP carriers can be broadly classified into inorganic salts, naturally occurring polymeric substances, synthetic polymers, and composites of synthetic and naturally occurring polymers.[7]

Carrier for BMP needs to perform a three-fold function:[10]

a. Maintaining a critical threshold concentration of BMP at implantation site for the required period (*Temporal Distribution*)

b. Act as scaffold over which bone growth can occur.

c. Contain the BMP at the localized site and prevent extraneous bone formation. (*Spatial containment*)

An ideal carrier should neither induce an inflammatory response nor immune reaction. Degradation of the carrier should not result in toxic residues. Ideally the carrier should be absorbed concurrent with bone healing, leaving no residue. It should be porous, the porosity being equivalent to cancellous bone. The porosity permits trapping of inflammatory cells and bone growth factors.[7]

APPLICATIONS OF BMP

1. BMPs During Embryogenesis:

The secreted signalling molecules of the transforming growth factor-beta (TGF-β) superfamily play critical roles in the specification and patterning of cells during embryogenesis. BMP family members have been implicated in the development of almost all vertebrate organs and tissues, as well as in early embryonic axis determination (Hogan, 1996).[11]

2. BMPs and Organogenesis:

There is now considerable evidence that BMPs are required for the development of many organs, including the kidney, lung, heart, teeth, gut, and skin. In particular, BMPs may help mediate the inductive interactions between mesenchymal and epithelial cells in these tissues, as well as controlling cell proliferation and apoptosis. Furthermore, in some organs that undergo branching or complex morphogenesis, BMPs are expressed by relatively small groups of cells that may behave as organizing centres.[12]

a) Tooth Development-

Gene expression patterns (Vainio et al.1993; Bitgood and McMahon 1995; Vaahtokari et al.1996a) and the effect of purified protein in vitro (Vainio et al.1993) have implicated BMPs at several different stages in tooth development, in cell proliferation, apoptosis, epithelial-mesenchymal interactions, and differentiation. At the bud and cap stages, cells which express Shh, Bmp2, Bmp4, Bmp1, and FGF4 are tightly localized in nested domains in a central region of the ectodermal epithelium known as the enamel knot (Vaahtokari et al.1996a).[12]

b) Kidney development-

Many BMPs are expressed in the embryonic kidney and urinary system (Bmp3, Bmp4, Bmp5, Bmp6, and Bmp1) (King et al.1994; Bitgood and McMahon 1995; Dudley et al.1995; Luo et al.1995).Genetic evidence demonstrates a role for Bmp5 in ureter development (King et al.1994) and Bmp1 in nephrogenesis (Dudley et al.1995; Luo et al.1995).[12]

c) Lung development

The lung develops from a bud of foregut endoderm surrounded by splanchnic mesoderm, and tissue reconstitution experiments have demonstrated critical interactions between these two cell layers for normal branching morphogenesis. Transcripts for Bmp4, Bmp5, and Bmp1 have been detected in specific patterns in the embryonic lung (King et al.1994; Bitgood and McMahon1995; Bellusci et al.1996). Interestingly, Bmp4 RNA is restricted to the tips of the distal buds and the adjacent mesenchyme.[12]

d) *Gut development*

The gut develops ventrally from an endodermal tube surrounded by splanchnic mesoderm, and tissue reconstitution experiments have provided extensive evidence for reciprocal inductive interactions between these two layers. In both early chick and mouse embryos Shh is expressed at high levels in the endoderm of the fore and hind gut and Bmp4 is expressed at high levels in the surrounding mesoderm (Jones et al.1991; Echelard et al.1993; Roberts et al.1995; Winnier et al.1995). Later in development, localized expression of Shh and Ihh and Bmp4 (Bitgood and McMahon1995) is seen in regions of the gut such as the stomach. [12]

e) Other organs and tissues

BMPs are expressed in many organs and tissues besides those discussed above, including skin and hair, and the germ cells of the ovary and testis. Over expression of Bmp4 in the outer root sheath of the hair in transgenic mice results in inhibition of proliferation in the hair sheath and hair loss (Blessing et al.1993) and a block in papilloma formation in response to chemical carcinogen treatment and promotion (Blessing et al.1995). The relationship between BMP and Shh expression in the hair is not yet clear (Bitgood and

McMahon1995). Growth and Differentiation Factor 9 [GDF9] is expressed specifically in oocytes in the ovary (McGrath et al.1995), and Bmp8a and Bmp8b are expressed in the germ cells of the testis (Zhao and Hogan1996). Inactivation of the Bmp8b gene leads to defects in spermatogenesis and to male infertility (Zhao et al).[12]

3. BMP-2 Is required for Odontoblast Differentiation:

The Bmp2 gene is expressed in post-natal odontoblasts and ameloblasts during tooth cytodifferentiation from birth to approximately 20 days after birth (Aberg et al., 1997). Previous studies have determined key roles for Bmp2 and Bmp4 during embryonic tooth development, but little is known about the specific role of Bmp2 during post-natal tooth cytodifferentiation (Maas and Bei, 1997). Several genes have been linked to dentinogenesis imperfecta (DGI) in humans and several mouse models

(Sreenath et al, 2003). One of the most highly expressed odontoblast-specific terminal differentiation genes is dentin sialophosphoprotein (Dspp). Mutations in this gene have been linked to DGI type III. Studies have shown that Dspp in odontoblasts is regulated by Bmp signalling in vitro and in vivo (Chen et al., 2008, 2009; Cho et al., 2010). Defects in odontogenic collagen type-Ia (Col1a1) production are also linked to dentin defects of various degrees in both humans and mice (Hart and Hart, 2007). It is known that dentin-derived Bmp2 drives dental stem cells from exfoliated deciduous teeth (SHED) into mature dentin-producing odontoblasts (Huang et al., 2009; Casagrande et al., 2010). Deletion of the Bmp2 gene in early odontoblasts results in a permanent tooth phenotype in both the molars and incisors, with a decrease of dentin in the crown, and shows a more pronounced effect on root dentin. The quality of dentin is altered, with patchy unmineralized areas and dysmorphic dentinal tubules. There is a delay in amelogenesis in the absence of odontoblast Bmp2, but no overt change in the quantity of enamel.[13]

4. Application in the Process of Repairing the Dentin Pulp Complex:

Dentin and pulp tissue formation has been made both “in vitro” and “in vivo” using strategies applied in tissue engineering. The great potential in applying this technique is treating teeth with pulpal injury. Grafting enamel matrix derivate has also been evaluated for direct pulp capping suggesting that its use increases the formation of reparatory dentin and effectively producing the dentin bridge (Igarashi et al., 2003; Matsumoto & Lyngstadaas, 2002). This technique was evaluated by Ishizaki et al. 2003 where, after 4 and 8 weeks observation, through microscopic exam, an increase in tertiary dentin was found, suggesting that the material used influenced odontoblasts and endothelial capillary cells to perform the role of neo-formed calcification tissue.[14]

5. BMP in Periodontal Regeneration:

In the field of periodontal regeneration, much of the research interest has focused on BMP-2 (OP-2), BMP-3 (osteogenin), and BMP-7 (OP-1). 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.[15]

Experiments utilizing crude and recombinant BMPs’ combination with other growth factors have provided insight as to their potential use. Crude preparations of BMP-2 and BMP-3 applied in surgically induced furcation defects appeared to stimulate periodontal regeneration.[15]

Recent studies have utilized recombinant human BMP to determine their potential for correcting intrabony, supra-alveolar, furcation, and fenestration defects.[15]

Histologic analysis revealed periodontal regeneration with areas of ankylosis. Contrary to these findings, BMP-7 augmentation resulted in a significant increase in periodontal regeneration without any ankylosis. Healing through ankylosis has been a concern, so most of the recent research utilizing recombinant human BMPs has involved in the preparation of implant site for osseointegration. BMPs also show much promise in promoting dental implant wound healing. A pilot study in non-human primates tested the single application of OP-1 around immediate extraction socket implants and found increased bone growth as measured histologically at 3 weeks.[15]

In a recent study, combined adenovirus mediated human BMP-2 (Adv–hBMP-2) gene modified bone marrow stromal cells (BMSCs) 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.[15]

Bovine BMP (bBMP) tested in a dog model has shown to increase the rate of osseointegration around cylindrical uncoated endosseous implants as evidenced histomorphometrically 4 weeks after implantation. The tissue reactions to titanium implants coated with bBMP were further assessed by scanning electron microscopy (SEM) for 12 weeks in the same dog model. 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.[15]

6. **BMPs in Bone Healing:**

PGE1 has a strong and dose-dependent promotive effect on the osteogenic activity of rhBMP, and glucocorticoids exert similar effects whereas binding of BMP to free heparin at the fracture site could help to localize the growth factor by restricting its diffusion. Another component of the inflammatory process is the acidic conditions that develop and, together with the proteolytic fragments of the plasminogen system, help activate latent forms of growth factors such as TGF-β1 and regulate a positive feed-back system that amplifies activation of TGF-β1 from platelets, thus stimulating cartilage and bone formation. BMPs can also induce chemotaxis of monocytes and stimulate their expression of TGF-β1 mRNA. [16]

TGF-β1 is an important and multifunctional autocrine regulator of bone formation. It has been demonstrated that TGF-β1 down regulates alkaline phosphatase, osteocalcin, osteopontin, collagen I and BMP-2 mRNA expression. This provides evidence that TGF-β1 acts as a powerful bone growth stimulant at the level of pre-osteoblasts, which is needed for the coordinated progression of cell types along their differentiation pathways. TGF-β1 stimulates DNA synthesis and replication of osteoprogenitor cells and is chemotactic for mesenchymal cells and osteoblast-like cells for recruitment of osteogenic cells to sites of bone formation and remodelling. EGF and FGFs are other molecules with demonstrated involvement in the complex molecular cascades involved in cellular change. Implantation of rhBMP-2 resulted in early cartilage formation that was later replaced by bone tissue with bone marrow elements. Invasion of blood vessels into the cartilaginous anlagen lead to bone formation and bone marrow development. When larger doses of rhBMP-2 were used, bone formation was observed concurrently with cartilage formation, suggesting bone induction through both endochondral and intramembranous pathways. BMPs are believed to act through chemotactic, mitogenic or differentiating mechanisms. It is important to understand that BMPs are not the only determinants of cell fates along the above-mentioned lineages. Specific nutrients, growth factors and cytokines at specific concentrations and in a specific sequence of exposures are fundamental for the bone formation process.[16]

During fracture healing, BMP-2/4 affects precursor cells to become chondroblasts and express proteins needed for production of woven bone. When lamellar bone replaces woven bone, BMP expression is significantly reduced. RhBMP-2 can induce bony trabeculae and bone marrow with concomitant shortening of the time required for osteogenesis and increased amount of bone formation. BMP-4 is also expressed in less differentiated cells at fracture healing during distraction

osteogenesis. RhBMP-2 does not increase the mitotic activity of osteoblasts and does not affect DNA synthesis, but rather initiates sequences of gene expression in these cells. RhBMP-2 up-regulates the expression of BMP3/4 mRNA with a mechanism that probably augments the transcriptional rate of the gene rather than stabilizing the mRNA. Evidence of BMP-4 activating the transcriptional factors Msx-1/2 and Egr-1 in epithelial-mesenchymal interactions during tooth development make this mechanism a valid working hypothesis. BMPs 1/2/4/6 are expressed by osteoblasts before they form mineralized bone nodules and during expression of ALP, OC, OP, thereby becoming guiding factors in

osteoprogenitor cells. Unlike the BMPs, the TGFβs do not induce ectopic bone formation and inhibit chondrogenesis but promote bone healing and

fracture repair. However, acting at the level of cell adhesion molecules, they may stimulate mesenchymal cell attraction and proliferation. Being part of a BMP-TGF-β heterodimer can amplify the BMP effect especially at the early stages of the bone repair process. BMP-2 up-regulates the phenotypic expression of osteoblasts and may indeed antagonize the repressing action of TGF-β by cross-reacting with TGF-β receptors. Additional studies have demonstrated a promotive effect of rhFGF or prostaglandin E1 (PGE1) on the action of BMPs, reducing the amount of growth factor needed to elicit a specific biologic response.[16]

7. Bone Morphogenetic Protein in Sinus Augmentation & Extraction socket preservation:

In the oral and maxillofacial region, rhBMP-2 was approved by the FDA in 2007 for use in sinus floor augmentation and extraction socket preservation. There are limited studies involving maxillary sinus augmentation using BMP. Boyne and colleagues were one of the first groups to augment the maxillary sinus with rhBMP-2/ ACS in humans.[17] Triplett et al reported the results of multicenter randomized clinical trials of the rhBMP-2/ACS (absorbable collagen sponge) application for sinus floor elevation and showed that the efficacy and safety of rhBMP-2/ACS was comparable to that of an autogenous bone graft. Herford and Boyne reported that mandibular continuity has been successfully restored by implanting rhBMP-2/ACS in 14 cases. On the other hand, Carter et al reported the reconstruction of segmental bone defects of the mandible using rhBMP-2 and the results were not consistent: rhBMP-2 failed restore bone defects in 2 of 5 patients with continuity defects. It is convincing that BMPs regenerate bone in small bony defects such as extraction sockets or the sinus floor in humans, but it is not conclusive that BMPs restore large bony defects such as segmental bone defects of the mandible, because the responding cells are diminished in higher species and with aging as previously mentioned. Recently, a Finnish group reported successful jawbone regeneration by the implantation of adipose derived stem cells with rhBMP-2. A combination graft of BMP and BMP-responding cells with a carrier may be a reliable method for regenerating large bony defects. Further studies including the development of a suitable carrier for BMP are required to generate efficient and safe approaches for bone regeneration using BMPs.[18]

8. Medical uses:

a. Spinal Fusion-

Spinal fusion applications are an important part of currently ongoing clinical trials (Carlisle and Fischgrund, 2005). Spinal fusions consist of nearly half of all grafting surgery. Furthermore, failure rates of up to 35% have been reported. The interest is in the use of rhBMPs to accelerate healing in patients with disk degenerative disease, removing the need for autograft harvesting and reducing morbidity.[19] The common approach is to use a collagen or other carriers soaked with rhBMP and place these within titanium spacers called cages which are implanted into the spine.[19]

b. Long bone fractures-

In most cases where rhBMPs are applied to fractures, these consist in non-unions of long bones. It is estimated as an example that in the UK, 42% of these fractures are of tibias, 20% are femurs and the rest are of other bones (Giannoudis and Tzioupis, 2005).[19]

RhBMP-2 has received FDA approval for use in treating open tibial fractures. There are numerous studies in the literature suggesting that rhBMP-7/OP-1 is also a safe and effective alternative for the treatment of diverse long-bone fractures and non unions.[19]

c. Bone morphogenetic protein-2 in scleral remodelling-

Scleral fibroblasts are involved in scleral remodelling, which occurs during axial elongation in myopia. Many aspects of scleral extracellular matrix remodelling and fibroblast proliferation are regulated by specific growth factors including transforming growth factor-β (TGF-β), insulin-like growth factors I and II (IGF-I and IGF-II), and basic fibroblast growth factor (bFGF). The matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-2 (TIMP-2) proteoglycans are involved in scleral extracellular matrix remodelling events associated with eye growth under both normal and myopic conditions. Recent research suggests that BMPs have multiple body functions

and are frequently designated "body morphogenetic proteins". BMP-2 is a bone morphogenetic protein and is also a potent osteoinductive cytokine. It induces bone and cartilage formation, controls fibroblast apoptosis, and regulates extracellular matrix synthesis in many tissues. Additionally, BMP-2 expression has been detected in both adult and embryonic tissues of the cornea, the trabecular meshwork, the optic nerve head, the retina, and the conjunctiva. Recent studies have suggested that BMP-2 is possibly involved in the pathophysiology of several ocular diseases.[20]

d. BMPs and angiogenesis-

Angiogenesis is an important event during the development and progression of both primary and secondary tumours. It has been demonstrated that BMPs, including BMP-2, 4, 6, 7 and GDF5, are capable of inducing angiogenesis. This may be one of the ways in which they contribute to the process of bone formation (Yamashita et al., 1997; Mori et al., 1998; Yeh and Lee, 1999; Glienke et al., 2000). The experimental evidence suggests that BMPs promote angiogenesis indirectly through up-regulation of the expression of VEGF in both cancer cells and osteoblasts: since Noggin, the BMP antagonist, produces the same effect as anti-VEGF antibody: it diminishes the pro-osteoblastic activity of osteoblast cells which is induced by conditioned medium from C4-2B cells (Yeh and Lee, 1999; Deckers et al.2002; Dai et al., 2004).[23] Also, the early stage of bone angiogenic agent (TNP-470) (Mori et al., 1998). This evidence indicates that the control of angiogenesis is, to some extent, integrated with the influence which BMPs have over osteoblastic activity. Dai et al. have demonstrated that it is possible for BMP-7 to promote osteosclerosis through VEGF in the skeletal metastases from prostate cancer (Dai et al., 2004). This angiogenesis induced by BMPs can also be synergized by basic fibroblast growth factor (bFGF) and TGF-ß1 (Ramoshebi and Ripamonti, 2000), which suggests that the angiogenesis induced by BMPs is a vital event during the initial stage of bone metastasis development.[21]

e. Other Uses-

Bone morphogenetic protein affects organ systems other than bone. It is believed to be a brain protective agent. In fact, in an ischemic rat model, BMP has been shown to offer protection by reducing the size of the infarct. It is an intriguing possibility that in the future BMP may be useful as a protective agent in severe head trauma and stroke. In patients with chronic renal disease levels of BMP are lower because kidneys are their primary source in the human adult. It is possible that systemic administration of BMP may restore some of the renal functions in patients with chronic renal failure. Additionally, spine surgeons are all too familiar with the renal osteodystrophy syndrome that occurs in patients undergoing long-term dialysis in cases of end stage kidney disease. Fusion rates in these individuals are dismal. Application of BMP locally may be beneficial.[7]

CONCLUSION

Several bone pathologies require combined strategies to regenerate bone morphology and function. BMPs are potent growth factors for bone repair, with FDA approval in orthopaedics having been granted for some of them. Discovered a long time ago, BMPs are currently produced through genetic engineering, allowing for studies on their role in development and cell metabolism, particularly through transgenic cells and animals.[22] The BMP guides modulation and differentiation of mesenchymal cells of muscle into bone & bone marrow cells.[23]

Many questions on the actions and interactions of BMPs and their effects on cells whether mitogenic, chemotactic, or differentiating, in ectopic bone formation, in normal bone development and maintenance, & in non-skeletal systems- remain to be answered.[24]

BMPs were originally discovered in bone tissue, and currently their clinical use lies in promoting bone healing, however, they are expressed in a wide range of non-skeletal tissues during mammalian development, including germ layers, whiskers, hair, teeth, urogenital system, gut, heart and brain.[25]

The safety considerations have to be determined before considering any new technology. Proper isolation and delivery of BMP are needed to give significant results. Hence, future investigations may be necessary to develop improved delivery of BMP. Ongoing human clinical trials assessing the

potential therapeutic use of BMPs will definitely provide conclusive evidence.[15]

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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