

## Bone Morphogenetic Proteins-An Update

C.A. PRAKASH, J.PARTHIBAN, R. BALAKRISHNAN, B. ANANDH and B.LOKESH

Department of Oral and Maxillofacial Surgery, Tagore Dental College and Hospital, Chennai, India.

DOI: <http://dx.doi.org/10.13005/bpj/699>

(Received: August 15, 2015; accepted: September 20, 2015)

### ABSTRACT

Bone Morphogenetic Proteins (BMPs) are a group of growth factors and cytokines known for their ability to induce the formation of bone and cartilage. Originally seven such proteins were discovered. Of these six (BMP2 to BMP7) belong to TGF- $\beta$  superfamily of proteins. BMP1 is a metalloprotease. Since then thirteen more BMPs have been discovered bringing the total to twenty. Marshall Urist proposed the name 'BONEMORPHOGENETIC PROTEIN' in the scientific literature in 'Journal of Dental Research' in 1971. BMPs interact with specific receptors on the cell surface referred to as bone morphogenetic protein receptors (BMPRs). BMPs are now produced using recombinant DNA technology. BMP is the most promising osteoinductive protein for bone induction and regeneration. Recombinant human BMP (rhBMP) stimulates osteoblast differentiation in various cells in vitro and induces ectopic bone formation in vivo. These formulations have found applications in many disciplines of medicine and dentistry. Orthopaedic and Oral surgery have benefitted greatly from commercially available BMP formulations in the last few years.

**Key words:** Bone Morphogenetic Proteins, Growth factors, Osteoinduction, Reconstruction.

### INTRODUCTION

Bone Morphogenetic Proteins (BMPs) are a group of *growth factors* and *cytokines* which induces formation of bone and cartilage. Growth factor is a naturally occurring protein or steroid hormone capable of stimulating cellular growth, cellular differentiation and proliferation. They act as signaling molecules between cells that binds to specific receptors on the target cells. They promote cell differentiation and maturation which varies between growth factors. For example, Bone morphogenetic proteins stimulate bone cell differentiation while fibroblast growth factors and vascular endothelial growth factors stimulate blood vessel differentiation. Recombinant human BMPs (rhBMPs) are widely used in several tissue-engineering products that might serve for the complete regeneration of bone or cartilage.

#### Discovery of BMP

Senn, a surgeon from Chicago, described

the utility of antiseptic decalcified bone implants in the treatment of osteomyelitis and certain bone deformities. Pierre Lacroix proposed, that in bone, osteogenin, that might initiate bone growth. Marshall R. Urist made the key discovery that demineralised, lyophilised segments of bone induced new bone formation. Also proposed the name "Bone Morphogenetic Protein". Bone induction is a multistep cascade. The key steps are chemotaxis, mitosis and differentiation. Hari Reddi indicated morphogens were present in bone matrix, upon which a systematic study was undertaken to isolate and purify putative bone morphogenetic proteins. Reddi laboratory brought out the final purification of bone morphogenetic proteins. John Wozney & colleagues at Genetics Institute enabled the cloning of BMP's. Originally seven such proteins were discovered. BMP1 is a *metalloprotease*. BMP2 to BMP7 belongs to *Transforming growth factor beta superfamily of proteins*. Thirteen more BMP's have also been added to this group.

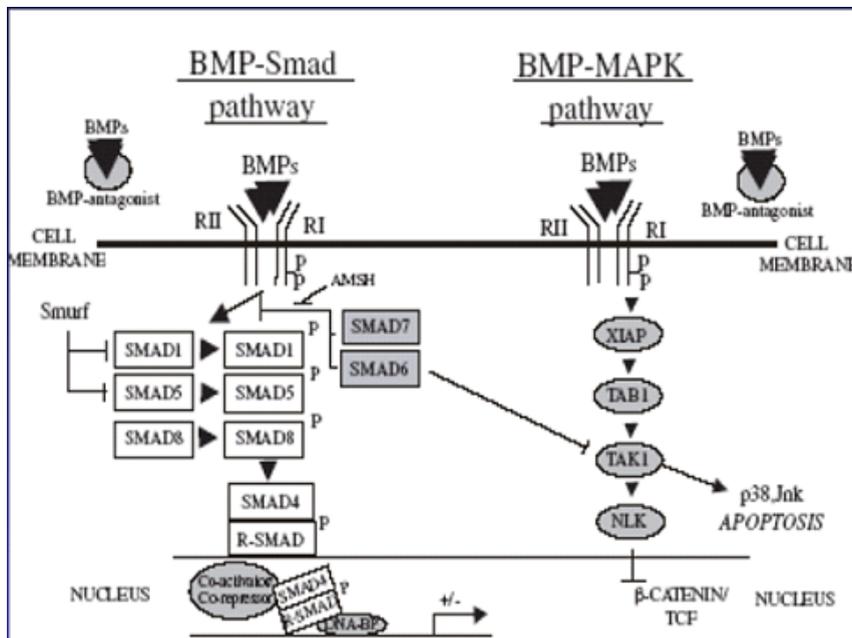
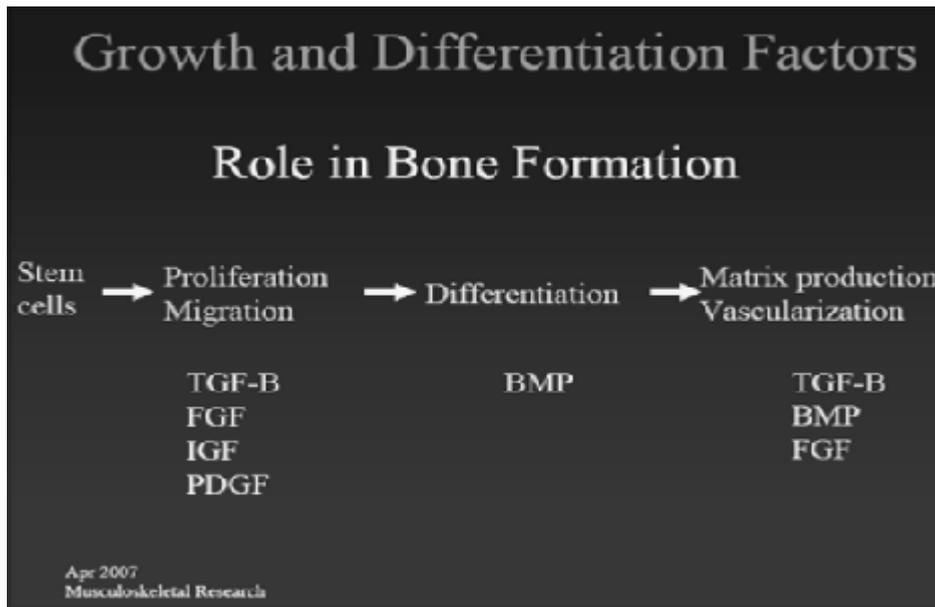
Bone Morphogenetic Proteins help in differentiation of cells and also in matrix production and vascularisation.

BMP receptors.(BMPRs).The signal transduction through BMPRs result in mobilisation of members of SMAD family of Proteins.The signaling pathways involving BMPs,BMPRs and SMADs are important in the development of heart,CNS and cartilage, as well as post-natal bone development.They play an important role during embryonic development on the embryonic patterning and early skeletal formation. BMP4 and its inhibitors noggin and

**DISCUSSION**

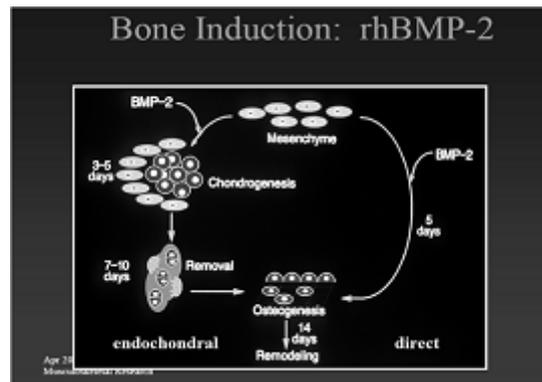
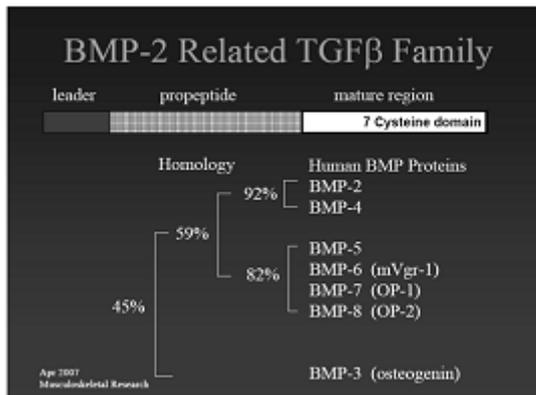
**Functions and applications of BMPs**

Bone Morphogenetic Proteins interact with specific receptors on the cell surfaces known as **The BMP pathways**



**list of bone morphogenetic proteins**

BMP	Known functions	gene locus
BMP1	Acts on procollagen I,II and III. Involved in Cartilage development.	Chromosome : 8 Location :8p21
BMP2	Acts as a disulfide –linked homodimer . Induces bone and cartilage formation.Acts as a retinoid mediator.Key role in osteoblast differentiation.	Chromosome : 20 Location : 20p12
BMP3	Induces bone formation.	Chromosome : 14 Location : 14p22
BMP4	Regulates formation of teeth,limbs and bone from mesoderm. Aids fracture repair.	Chromosome :14 Location : 14q22-q23
BMP5	Acts in cartilage development.	Chromosome : 6 Location : 6p12.1
BMP6	Plays a role in joint integrity in adults.	Chromosome : 6 Location : 6p12.1
BMP7	Key role in osteoblast differentiation. Induces production of SMAD1. Also in renal development and repair.	Chromosome : 20 Location : 20q13
BMP8a	Involved in bone and cartilage development.	Chromosome : 1 Location : 1p35-p32
BMP8b	Expressed in hippocampus.	same as above
BMP10	Trabeculation of embryonic heart.	Chromosome : 2 Location : 2p14
BMP15	Role in oocyte and follicular development.	Chromosome : X Location : Xp11.2



chordin help regulate polarity of the embryo (i.e. back and front patterning). Disruption of BMP signaling can affect body plan of developing embryo. Mutations in BMPs and their inhibitors (such as sclerostin) are associated with a number of human disorders which affect the skeleton.

or partially resected mandible. It is used in facial clefts, cleft palate cases, alveolar ridge augmentation, cartilage repair in TMJ and in oral implants. Bone morphogenetic proteins produce osteo induction which helps in inducing osteoblasts to produce native bone or cartilage.

Bone Morphogenetic proteins have various applications in Oral and Maxillofacial Surgery. It has been used to reconstruct complete

Since the evolution of reconstruction, maxillofacial surgeons could bring back the form and function of the bone resected due to pathologies

associated with it. Various forms of reconstruction has since then been practised. From simple reconstruction plates to non vascularised bone grafts to vascularised free flaps, maxillofacial surgeons had options to choose which depended on their skills and the conditions warranted during those surgeries. Post surgical resection, bone resorption is inevitable which happens with varying degrees except in case of vascularised free flaps. When it comes to free flaps, the technique sensitivity and surgeon's skill play a key role. In such cases, preventing resorption and inducing bone formation was an able substitute to the technique sensitive free flaps. Bone morphogenetic proteins which are a group of growth factors help in osteo induction that is inducing bone producing osteoblasts to deposit bone at the native site. BMPs help in bone induction, differentiation and regeneration which can either form bone or cartilage. BMP2 to BMP7 belongs to *Transforming growth factor beta superfamily of proteins*. Thus BMPs prove to be a boon for reconstruction.

#### Courtesy

Improved Healing and Reduced Morbidity with Bone Morphogenic Protein-2 (BMP-2) In Older Patients with Alveolar Cleft Defects

Brian P. Dickinson, MD, Kristy L. Wasson, BA, Catherine O'Hara, BS, Joubin Gabbay, MD, Justin B. Heller, BS, and James P. Bradley, MD

Serial roentgenograms of long term test animal demonstrating stability of rhBMP2 induced bone. Roentgenograms taken at 3(A) and 30(B) months after reconstruction. The bone remodelling that takes place over the 30 month period is evident.

#### CONCLUSION

Resection of diseased bone and replacement of lost structure to bring back form and function has been practised for many years since the evolution of reconstruction. Formation of new bone and cartilage was not possible with the preliminary form of reconstruction. Non vascularised bone grafts undergo resorption at the recipient site and replacement leading to decreased amount of bone deposition. Vascularised free flaps are technique sensitive and require good surgical acumen which also has its own complications such as flap necrosis. In order to bring back the native bone with the same form and function, osteoinduction, differentiation, maturation and regeneration of the recipient bone by Bone morphogenetic proteins play a vital role in reconstruction and are time tested till date.

#### REFERENCES

1. Abyholm, FE, Bergland, O, Semb, G. Secondary Bone Grafting of Alveolar Clefts. *Scand J Plast Reconstr Surg* **15**: 127 (1981).
2. Alam I, Asahina I, Ohmamiuda K, Enomoto S. Comparative study of biphasic calcium phosphate ceramics impregnated with rhBMP-2 as bone substitutes. *J Biomed Mater Res* **54**:129-38 (2001).
3. Ashinoff RL, Cetrulo CL Jr, Galiano RD, Dobryansky M, Bhatt KA, Ceradini DJ, Michaels J 5th, McCarthy JG, Gurtner GC. Bone morphogenic protein-2 gene therapy for mandibular distraction osteogenesis. *Ann Plast Surg*. **52**(6):585-90; discussion 591 (2004).
4. Boyne, PJ, Sands, NR. Secondary bone grafting of residual alveolar and palatal clefts. *J Oral Surg* **30**: 87 (1972).
5. Boyne, PJ, Sands, NR. Combined orthodontics/ surgical management of residual alveolar cleft defects. *Am J Orthod* **70**: 20 (1976).
6. Jingushi S, Urabe K, Okazaki K, et al. Intramuscular bone induction by human recombinant bone morphogenetic protein-2 with beta-tricalcium phosphate as a carrier: in vivo bone banking for muscle-pedicle autograft. *J Orthop Sci* **7**:490-4 (2002).
7. Kenley RA, Yim K, Abrams J, et al. Biotechnology and bone graft substitutes. *pharm res* **10**: 1393-1401 (1993).
8. Mayer, M, Hollinger, J, Ron, E, et al. Maxillary

- Alveolar Cleft Repair in Dogs Using Recombinant Human Bone Morphogenetic Protein-2 and a Polymer Carrier. *Plast Reconstr Surg* **98**: 247 (1996).
9. Miranda DA, Blumenthal NM, Sorensen RG, Wozney JM, Wikesjo UM. Evaluation of recombinant human bone morphogenetic protein-2 on the repair of alveolar ridge defects in baboons. *J Periodontol.* **76**(2):210-20 (2005).
  10. Rachmiel A, Aizenbud D, Peled M. Enhancement of bone formation by bone morphogenetic protein-2 during alveolar distraction: an experimental study in sheep. *J Periodontol.* **75**(11):1524-31 (2004).
  11. Sakata-Goto T, Takahashi K, Kiso H, Huang B, Tsukamoto H, *et al.* Id2 controls chondrogenesis acting downstream of BMP signaling during maxillary morphogenesis. *Bone* **50**: 69–78 (2012).
  12. Schuckert KH, Jopp S, Teoh SH. Mandibular defect reconstruction using three-dimensional polycaprolactone scaffold in combination with platelet-rich plasma and recombinant human bone morphogenetic protein-2: de novo synthesis of bone in a single case. *Tissue Eng Part A* **15**:493-9 (2009).
  13. Urist MR. Bone: formation by autoinduction. *Science*; **150**: 893-899 (1965).
  14. Valentin-Opran A, Wozney J, Csimma C, Lilly L, Riedel GE. Clinical evaluation of recombinant human bone morphogenetic protein-2. *Clin Orthop Relat Res.* **395**: 110-20. Review (2002).
  15. Yasko AW, Lane JM, Rosen V, *et al.* The healing of segmental bone defects, induced by recombinant human bone morphogenetic protein (rh BMP-2). *J Bone Joint Surg* **74**(5):659-70 (1992).
  16. Zhang H, Sucato DJ, Welch RD. Recombinant human bone morphogenic protein-2-enhanced anterior spine fusion without bone encroachment into the spinal canal: a histomorphometric study in a thoroscopically instrumented porcine model. *Spine.* **30**(5):512-8.