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# The role of Bone Morphogenetic Protein-2 in craniofacial osteogenesis: A literature review



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## ABSTRACT

Bone Morphogenetic Protein (BMP) is a type of growth factor that belongs to the Transforming Growth Factor Beta (TGF- $\beta$ ) group. Bone Morphogenetic Protein-2 (BMP-2) is recognized as one of the first commercially available osteoblast inducers. When new bone is needed, mesenchymal stem cells can develop into osteoblasts, which then implant as osteocytes in the bone, providing additional structure and support. The principal agent that differentiates stem cells into osteoblasts is BMP-2. BMP-2 will be released into the bone matrix or serum in performing their job. BMP-2 activates the SMAD1/5/8 signal via mediating

the physiological action of type I and II serine/threonine kinase receptors. The active SMAD protein will form a complex with the SMAD4 protein, translocate DNA to the nucleus, and bind to particular genes like *Dlx-2/5*, *Osx*, and transcription. According to a recent study, BMP-2 boosts osteogenic growth. BMPs are effective in the treatment of craniofacial defects in current research. The subjects of this paper are the molecular mechanism of BMPs and their involvement in the clinical application of craniofacial deformity patients.

**Keywords:** bone morphogenetic protein-2, BMP-2, osteogenesis.

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## INTRODUCTION

Defects in craniofacial bone are still an issue if they are not addressed properly, and patients' appearance performance suffers as a result. Infectious infections, congenital defects, cancer, and trauma can cause this disability. Extensive flaws make ossification impractical and are frequently seen during the therapy process. Many cases of craniofacial bone injury necessitate reconstruction, and the scarcity of existing options has prompted the creation of new ones, particularly tissue engineering and biomaterials.

Bone Morphogenetic Protein-2 (BMP-2) is the earliest osteoblast inducer commercially marketed and exhibits osteogenic properties.<sup>1</sup> BMP-2 is a versatile cytokine that influences cell differentiation, and its graft replacement has been demonstrated to be beneficial in studies. BMP-2 mechanism of action is activating serine/threonine kinase type I and II receptors, therefore starting SMAD1/5/8 signal. The active SMAD protein forms a complex with SMAD4 protein, translocates DNA to the nucleus,

and binds to particular genes like *Dlx-2/5*, *Osx*, and transcription. Based on a study by Vanhatupa *et al.*, BMP-2 promotes osteogenic proliferation and differentiation in human bone marrow stem cells (hBMSCs). The subjects of this paper are the molecular mechanism of BMPs and their involvement in the clinical application of craniofacial deformity patients.<sup>1</sup>

## STRUCTURE AND EXPRESSION OF BMP-2

BMP is a type of growth factor that belongs to the Transforming Growth Factor Beta (TGF- $\beta$ ) group. It was discovered first in 1988. Since then, more than 20 kinds of BMP have been identified in humans. Each BMP functions in embryogenesis, skeletal formation, hematopoiesis, and neurogenesis. Not all of them are osteogenic.<sup>2</sup> Bone Morphogenetic Protein binds to cell receptors on the surface of mesenchymal cells and then delivers signals to particular proteins, causing mesenchymal cells to develop into osteoblasts or chondrocytes. BMP

is a TGF-like protein that uses signal-like transduction via the transmembrane receptor serine-threonine kinase and the protein SMAD. They are involved in regulating physiological angiogenesis and bone formation during embryonic development. BMPs are produced by endothelial cells and vascular smooth muscle cells. BMP is needed for bone production and regeneration. According to research, BMP 2 acts best in the first 24 hours of healing. BMP-2 is the most powerful osteogenic peptide and was the first commercially marketed osteoblast inducer.<sup>1</sup>

Human BMP-2 has a gravity of 32 kDa and consists of 114 amino acids. This molecule is hydrophobic, which means it won't dissolve at physiological pH. This gene was found abundantly in fat, colon, and 21 other tissues. BMP produces several ligands in the TGF- $\beta$  protein family. The SMAD transcription factors family could be induced when these ligands bind to their receptors. Proteolytic processing of the encoded protein produces each monomer of the disulfide-linked homodimer, important in bone

and cartilage development.<sup>3</sup> Duplication in the downstream region of this gene will cause brachydactyly. Recombinant human rhBMP-2 products at a 1.5 mg/ml concentration are currently available under INFUSE in America and InductOS in Europe and are packed with a collagen sponge as a carrier protein.<sup>2</sup>

## BMP-2 INVOLVEMENT IN OSTEOGENESIS

Molecular signaling pathways in bone regeneration have previously focused on substances that directly control bone formation or increase the number of progenitor cells that generate bone. A system including growth factors and cytokines regulates the process of bone resorption and creation. PDGF, a powerful mitogen of mesenchymal cells, is one of the key biological components involved. When PDGF is phosphorylated by their receptor (PDGFR), the adaptor protein Grt2 and the nucleotide exchange factor Son of Sevenless (SOS) are recruited, activating downstream pathways such as the mitogen-activated protein kinase Erk. The phosphorylated Erk enters the nucleus and activates the c-Myc transcription factor for cell growth. The BMP (Bone Morphogenetic Protein) signaling pathway is the most researched. BMP is most well-known for inducing osteoblasts and chondrocytes, which speeds up intramembranous and endochondral ossification.<sup>1</sup>

Bone Morphogenetic Protein-2 activates the SMAD1/5/8 signal via mediating the physiological action of serine/threonine kinase receptors type I and II. The active SMAD protein will form a complex with the SMAD4 protein, translocate DNA to the nucleus, and bind to particular genes like *Dlx-2/5*, *Osx*, and transcription. Based on a study by Vanhatupa et al a BMP-2 promotes osteogenic proliferation and differentiation in hBMSCs.<sup>1</sup> On the other hand, Mineralization activity remained unaffected, as seen by the non-increasing *Dlx 5* and *Osx* markers.<sup>1</sup> Through specific type I and type II receptors, BMP-2 may promote cartilage and bone production in vivo and in vitro. BMP-2 is important for bone cell proliferation, apoptosis, and differentiation.<sup>4</sup>

Bone Morphogenetic Protein-2 is a part of the TGF group. BMP has a function in tissue formation and regeneration. It is being investigated more and more as the increasing need for modality or substance for bone repair grows. This is especially true in the orthopedic area, where there were a lot of fracture cases and critical-size bone defects.<sup>5</sup> When new bone is needed, mesenchymal stem cells can develop into osteoblasts, which then implant as osteocytes in the bone, providing additional structure and support. The principal agent that differentiates stem cells into osteoblasts is BMP-2. BMP-2 will be released into the bone matrix or serum in performing their job. BMP-2 mechanism of action is by binding into serine/threonine type I and type II receptor kinases, prompting Smad and non-Smad pathways, and therefore produce osteogenic genes such as *RUNX2* and *Osterix (Osx)*.<sup>6</sup> Furthermore, BMP-2 is vital in increasing osteoclastogenesis by converting precursor cells into osteoclasts. Food and Drug Administration (FDA) has approved the human recombinant for BMP-2, which is called rhBMP-2, for use in therapy following lumbar spine fusion because its role is required for bone marrow stem cell development, formation of new bone (osteogenesis), and osteoclastogenesis.<sup>6,7</sup>

Members of Wnt/-catenin such as *Wnt10b*, *BMP2*, and *BMP4* signaling pathways promote mesenchymal stem cell development in bone regeneration, particularly in terms of osteoblast production. The osteogenic transcription factors *Runx2* and *Osterix* are induced by inhibiting the adipogenic transcription factors *C/EBP* and *PPAR* and stimulating the osteogenic transcription factors *C/EBP* and *PPAR*. Immature osteoblasts can still cleave and express low amounts of alkaline phosphatase activity and synthesis type I collagen, accounting for up to 90% of bone's organic components. The transcription factor *Osterix* is required to form mature osteoblasts that actively mineralize the bone matrix.

However, the newly deposited matrix must first mature before it can mineralize. The elevated expression of alkaline phosphatase and non-collagenous proteins such as osteopontin, osteocalcin,

and bone sialoprotein, is linked to matrix maturation. The addition of hydroxyapatite to the freshly formed osteoid completes the mineralization process by collecting calcium and phosphate ions, membrane-bound extracellular entities produced by osteoblasts aid early mineral deposition. This collection of ions comes together to form the first stable crystal. Following bone development, osteoblasts can differentiate further and become osteocytes after being processed in the bone matrix. The remaining osteoblasts are considered to die or become dormant bone lining cells due to apoptosis.

## miRNA REGULATION OF BMP-2

miRNA expression is renowned for regulating several human signaling pathways, including TGF/BMP and Wnt/-catenin transcription factors. Several regulators, including miRNA, also have been discovered to be involved in osteoblast differentiation, and miRNA can influence gene expression during MSC differentiation into osteoblastic cells, culminating in bone production. However, there are many kinds of miRNA, and not all miRNA have roles in osteogenesis or BMP regulation. Approximately there are about 2300 miRNA with different functions regulating many systems in the body.<sup>8-10</sup>

miRNA-133 and 135 are decreased when there is osteoblast development which BMP-2 induced. On the other hand, when there are too much miR-133 and miR-135 being produced and circulated in the body, it could inhibit the expression of the osteogenesis gene since miR-133 targets *RUNX2* and miRNA-135 targets *Smad5*.<sup>11</sup>

## BMP-2'S ROLE IN CRANIOFACIAL DEFECTS: A NEW PERSPECTIVE

Whether in vitro or in vivo, several studies have revealed that BMP-2 promotes MSCs to differentiate into osteogenic cells and has efficacy in spinal fusion surgery and tibial fracture healing cases. Protein administration through a collagen sponge showed that BMP-2 had an 8-day local effect, with a half-life of only 7–16 minutes due to proteinase breakdown. BMP-2 has been used in several different techniques,

including oral maxillofacial procedures and spinal fusion, according to many reports.<sup>12</sup> Treatment with BMP-2 may be more effective at promoting healing. The BMP-2 signaling cascade has been shown in many animal models to start early in the early phase of bone healing, generating an inflammatory response and periosteal activation.<sup>13,14</sup> BMP-2, on the other hand, is critical during the stages of chondrogenesis and osteogenesis.<sup>15</sup> Research to determine a safe dose of BMP-2 is still ongoing. Bone Morphogenetic Protein-2 activates SMAD signaling in vitro and animal cells dose-dependent.<sup>4,16</sup> Until date, there hasn't been a precise dose regimen for BMP-2. In dog experiments, Choi *et al.* found that 50 g/ml was the optimal dose for a 2 cm cranial bone deficit, without complications such as hyper or hypoosteogenesis.<sup>4,16</sup> In the first published study, a dosage of 150-200 g dramatically accelerated bone growth in 5-mm femoral bone defects.<sup>17</sup>

Clinical use of BMPs in craniofacial defect cases has been described in a recent study. Chenard *et al.* described the use of BMP-2 to restore various craniofacial abnormalities such as Apert and Crouzon syndrome.<sup>18</sup> In rare cases, rhBMP-2 and rhBMP-7 have been applied to reconstruct the craniomaxillofacial skeleton, resulting in success. In a retrospective cohort study with rhBMP-2, Fallucco and Carstens *et al.* showed that there was new bone in maxillary clefts after BMP-2 at six months in 94% of 17 patients who undergo cleft repairs. Only one patient didn't detect new bone in this study.<sup>19</sup> Clokie and Sandor also reported that all ten patients had good mandibular alignment and function after applying rhBMP-7. There was still more study ongoing about the clinical use of BMP in craniofacial defects.<sup>20</sup>

## CONCLUSION

Bone Morphogenetic Protein-2 (BMP-2) is an osteoblast inductor that functions in osteogenesis. BMP-2 potential modalities are emerging as an option for difficult craniofacial deformity situations due to their profile, accessibility, and low risk of complications.

## CONFLICT OF INTEREST

We declare that there were no conflicts of interest in this study.

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## AUTHOR CONTRIBUTION

All of authors are equally contributed to the study.

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