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BONE MORPHOGENETIC PROTEINS: A NEW VISTA IN BONE REGENERATION

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ABSTRACT: Treatment of delayed union, malunion, and nonunion is a challenge to the orthopedic surgeons. Apart from restoration of alignment and stable fixation, in many cases adjunctive measures such as bone-grafting or use of bone-graft substitutes are of paramount importance. Autologous bone remains the "gold standard" for stimulating bone repair and regeneration, but its availability may be limited and the procedure to harvest the material is associated with complications. Bone-graft substitutes can either substitute autologous bone graft or expand an existing amount of autologous bone graft. This review focuses on the role of bone morphogenetic proteins in bone regeneration.

KEYWORDS: Bone regeneration, bone morphogenetic proteins.

INTRODUCTION: Advent in scientific research has improved the various treatment modalities available for the operating surgeons and has paved way for better treatment outcomes and thereby patient satisfaction. Orthopedic surgeons have a close encounter with large bone replacement areas either due to trauma or infections or many other causes and not always autografts are the choice.

Bone is unique of all the tissues in the vertebrate organism. When injured, it heals by formation of new bone. In contrast, most other tissues such as the heart muscle, voluntary muscles, liver, and the brain heal by replacement of connective tissue rather than the original tissue. Another interesting attribute of the bone is that the molecular and cellular processes that lead to the development of the skeletal structures within the embryo are very similar to the cascades that occur in the healing process in an injured bone.¹

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 body². 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.³ This unique activity was observed and researched extensively by an orthopedic 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.^{4,5} He thus named this activity "bone morphogenetic protein."

Since this discovery, a wide range of allogeneic bone grafts has become available as a substitute or extender to autograft, yet with limited success. The goal of these allogeneic bone grafts was to offer the greatest amount of BMP available within the tissue, but these bone graft products are constrained by the small amount of BMPs found within the actual collagen matrix.

The advent of bone growth factors has been widely anticipated since their successful production using recombinant DNA technology. Bone morphogenetic proteins (BMPs) are an important class of bone growth factors. It appears that we are on the brink of tremendous advances

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in the use of bone growth factors as therapeutics, which will revolutionize how clinicians treat such problems. Bone contains a cocktail of growth factors including transforming growth factor beta (TGF- β), platelet derived growth factor (PDGF), bone morphogenetic proteins (BMPs), insulin-like growth factors I and II (IGF-I and IGF-II) and fibroblast growth factors (FGFs). BMPs differ from other growth factors in that they are Osteoinductive.

STRUCTURE AND SYNTHESIS: BMPs consist of dimers that are interconnected by seven disulphide bonds,⁷ this dimerization is a prerequisite for bone induction.⁸ BMPs are active both as homodimer molecules that consist of two identical chains, and as a heterodimers consisting of two different chains. Fifteen BMPs have currently been identified.^{9,7,11}

BMP's, are further divided into subfamilies according to their amino acid sequence similarities. BMPs-2 and -4 form one subgroup, BMPs- 5–8 form a second subgroup, and a third subgroup contains BMP-3 and GDF-10,¹² a related growth factor. Members of each subgroup have shown osteoinductivity BMP-1 is not related to the BMP family.

It does not show osteoinductivity,¹³ and has recently been identified as procollagen-C-proteinase.¹⁴ BMPs are synthesized by osteoblasts as 400–500 amino acid peptides, each consisting of a leader sequence, a propeptide, and a mature osteoinductive domain at the carboxy-terminal. The mature domain of each BMP contains a region of seven conserved cysteine amino acids, six of which are involved in forming a characteristic structural motif: a cysteine-knot with two finger-like double-stranded sheets¹⁵

Dosage of BMP: It has been estimated that normal bone contains approximately 0.002 mg of BMP per kilogram of pulverized bone. At a fracture site, presumably the BMP is released at a higher concentration because of the secretion by the transformed inflammatory cells into osteoprogenitor cells and upregulation of BMP from the released cytokines at the fracture site.

The exact concentration of the BMP at the fracture site as opposed to physiological concentration in the normal bone is unknown. The concentration required for ideal induced bone bridging in osseous defects depends on several factors. First is the state of the organism in the evolutionary scale. Additionally, the type of defect should be considered.

Apparently, the enhanced BMP released locally at the site of fracture is sufficient to induce bridging of the broken fragments if they are in apposition. Therefore, the use of BMP is seldom considered when treating straightforward long bone fractures. On the other hand, fractures in which there are critical segmental defects in the long bones do not heal spontaneously. They require adjuvant autograft or BMP for adequate healing.¹

RECOMBINANT HUMAN BMP-2 IN ORTHOPAEDIC APPLICATIONS: Endogenous BMPs are typically found in the body at a concentration of less than 2 mg/kg in cortical bone.¹⁶ and are difficult to extract in sufficient quantities for clinical use. Recombinant human BMP-2 is highly osteoinductive.¹⁷ In vitro studies show that mesenchymal stem cells incubated with rhBMP-2 have increased alkaline phosphatase activity and undergo matrix mineralisation.^{18,19} When implanted In vivo, rhBMP-2 induces osteoinduction by recruiting mesenchymal stem cells, then inducing the proliferation and differentiation of these cells into an osteoprogenitor lineage. The bone formed has exactly the same composition as bone elsewhere in the body.²⁰

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Early pre-clinical studies of postero lateral fusion showed that while rhBMP-2 plus ACS achieved fusion rates of 100% in lower animal models (rabbit and dog),^{21,22} in higher animal models the ACS appeared to be compressed by muscle fibres, hampering bone formation.²³

In particular, recombinant human bone morphogenetic proteins (rhBMPs) are being used with increasing frequency for spinal fusions because of their potent osteoinductive activities, which have been documented in multiple preclinical and clinical studies.¹⁰⁻¹⁷ With regard to spinal applications, Aryan and colleagues¹⁵ described a series of 15 patients who received rhBMP-2 as part of their treatment regimen for vertebral osteomyelitis and achieved solid fusions by 5 years with no evidence of recurrent infection.

As the biological pathways affected by BMPs continue to be elucidated, it is possible that indications for using rhBMP-2 may expand to include clinical situations such as fusion in the setting of active local surgical site infections. Bone morphogenetic proteins (BMPs) may have an important role in bone and cartilage formation, fracture healing and repair of other musculoskeletal tissues.

There are two BMPs clinically available: BMP-7 (also known as osteogenic protein-1 or OP-1) supplied by Stryker UK, which uses a bovine collagen carrier in granular form (OP-1 Putty in the US and Osigraft ® in the UK), and rhBMP-2 supplied by Wyeth Research Ltd, which uses a collagen sponge carrier (InFUSE in the US and InductOs in the UK).

CONCLUSION: The capability of BMP to regenerate bone has been conclusively proven in a number of animal studies and off late human trials have also shown favorable outcomes with a few limitations. However, in the near future a larger number of clinical trials are to be undertaken to make this material a readily available regenerative material.

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