BONE MORPHOGENETIC PROTEIN

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Bone morphogenetic protein (BMP), a low molecular weight hydrophobic glycoprotein, first reported in 1965, that provided substantial morphologic evidence for the theory of induction . In these pioneering investigation, bone formation occurred in extraskeletal implants of decalcified bone matrix and noncollagenous fractions of dentin, bone, and osteosarcoma tissue. The responsible cells at that time were noted to be proliferating pluripotent cells of the host. A major advancement in the isolation of an osteoinductive factor occurred in 1979, when Urist et al extracted what appeared to be a low molecular weight glycoprotein from demineralized rabbit tibia matrix, implanted it ectopically into rats and mice, and observed new bone formation. Since Urist's early work, many researchers have attempted to characterize BMPs.

A substance is termed a BMP if it can induce ectopic bone formation in a standard in vivo rodent assay system. According to the cascade theory, bone development occurs stepwise in embryonic endochondral ossification and postnatal fracture callus formation. The steps observed by Reddi are chemotaxis of progenitor cells, proliferation of mesenchymal cells, differentiation of chondrocytes, calcification of cartilage matrix, angiogenesis and vascular invasion, bone differentiation and mineralization, and bone remodeling and marrow differentiation. Once formed, this bone seems to function as typical endochondral bone, responsive to internal and external stimuli. Nevertheless, the term BMP has been found to be imprecise, because most proteins thus labeled may be found in extraskeletal tissues as well and have functions that regulate the development of other organ systems.

BONE MORPHOGENETIC PROTEIN AND THE TRANSFORMING GROWTH FACTOR-B SUPERFAMILY

Growth factors are polypeptides that bind to specific cell membrane receptors to stimulate or inhibit certain functions within the cell. Transforming growth factor (TGF)-B is named for its ability to transform fibroblastic cells in monolayer culture and to stimulate colony formation. The major role of TGF-B in the musculoskeletal system is to stimulate mesenchymal cells to divide. On

the basis of characteristics that include amino acid similarity, the BMPs are grouped as a family within the TGF-B superfamily. All members of the TGF-B superfamily contain 7 conserved cysteine residues.

The BMPs comprise a growing family of > 12 proteins, 9 of which have been shown individually to induce ectopic bone in an in vivo assay system. They seem to have as their target cell the undifferentiated mesenchymal-type perivascular cell hypothesized by Urist. All but BMP-1 are members of the TGF-B superfamily. Analysis of the primary amino acid sequences of BMP-2 through BMP-7 has allowed researchers to group them into 3 separate sets. Bone morphogenetic protein-3 is the sole member of its subset, sharing 43% to 49% identity with each of the other established subsets. Bone morphogenetic protein-5, BMP-6, and BMP-7 possess an average of 89% amino acid identity and constitute a second BMP subset. Bone morphogenetic protein-2 and BMP-4 are the most closely related of the categorized BMPs, sharing 92% amino acid identity in their carboxy-terminal regions. Like all known TGF-B proteins, BMP-2, BMP-4 and BMP-7 are synthesized with an aminterminal propeptide region that is later cleaved off. Mature BMP, lacking this propeptide regions, is secreted in an active form. Dimerization and molecular maturation seem to occur intracellularly or on secretion. The receptors for BMP-2 and BMP-2 and BMP-4 contain a serine/threonine kinase domain that is related to the kinase fomain in TGF-B receptors.

A large degree of research activity is being directed toward the study and development of osteoinductive bone graft substitutes. BMP clearly potentiates bone healing ; seven individual BMPs have been identified, sequenced, and cloned. Recombinant human BMP-2 (rhBMP-2), when implanted in extraskeletal sites, has been found to induce bone formation through endochondral ossification and, therefore, has undergone the most extensive study. Initial studies have been extremely promising ; in these, rhBMP-2 used in conjunction with a variety of carriers demonstrates healing of bone defects in a high percentage of animals. However, severe practical difficulties with the initial collagen-based carriers (disease transmission, potential rejection, and supply limitations) have resulted in research directed toward the combining of rhBMPs with noncollagenous matrices. Resorbable poly L-lactic acid lattices and hydroxyapatite ceramics hold the most promise. Unfortunately, neither composite is sufficiently strong to serve as a structural graft. The clinical indications for these types of combined osteoinductive proteins and osteoconductive matrices are similar to those for current applications of cancellous bone graft or freeze-dried allograft. Frozen allografts are still considered the most

versatile structural biologic implant available for long-bone reconstruction.