BIOLOGICAL REGENERATION OF BONE BY BONE MORPHOGENETIC PROTEINS

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Current procedures in supporting regeneration of bone are dependent on our understanding of the molecular processes responsible for tissue repair. At present, we know how to regenerate bone when physiological mechanisms of fracture repair fail. Since the original description of the potential of demineralised bone matrix to induce bone at an ectopic site, it has taken more than 3 decades to bring bone morphogenetic proteins (BMP) to clinical use. BMPs have a multitude of activities and are considered as general growth factors during embryogenesis and growth of an organism. Clinical trials, although still limited in number, have demonstrated that BMPs are a powerful, safe and feasible regenerative medical approach in conjunction with diverse tissue-engineering products for the enhanced healing of human bone. By proteomic analyses it has been shown that multiple growth factors, like fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), wingless-int (WNT), transforming growth factor beta III (TGFβIII), cartilage acidic protein 1 (CRTAC-1) and BMP are expressed at different stages of bone repair. Bone formation and resorption are coupled processes in which BMP6 has an essential role being released from osteoclasts and recruiting mesenchymal stem cells from the bone marrow to differentiate into osteoblasts. BMP6, unlike BMP2 and BMP7 which are commercially used for bone regeneration, is resistant to noggin, a BMP antagonist, which might be the main reason why small amount of BMP6 *in vivo* can substitute for large amounts of BMP7. This resistance is due to lysine in the position 60 in the amino acid sequence of the finger 2 area of the protein. Mice lacking the BMP6 gene have a decreased bone volume and their long bones heal longer than in their wild type controls. Recently, it has been demonstrated that long bones of mice with a BMP2 limb conditional knock out do not heal at all which might be due to the lack of the cambium layer of the periosteum. During early and late stages of bone repair TGFβIII, CRTAC-1 and BMP6 are released into the plasma of patients with a bone fracture and in a period of 16 weeks serve as potential biomarkers indicating bone healing efficacy. As our understanding of molecular processes of bone repair advances, novel anabolic therapeutical targets for accelerated bone regeneration will rapidly emerge.