Optimizing BMP-2-induced bone repair with FGF-2

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Bone morphogenetic proteins (BMPs) are used clinically in patients to enhance bone regeneration and fracture healing.[1,2] During normal healing, BMP-2 produced by cells is considered necessary for the initiation of fracture healing.[3] Thousands of patients have benefited from BMP-2 applied at the time of surgery to augment fracture healing, but some issues have arisen. Large and multiple doses of BMP-2 can produce uncontrolled ectopic calcification and cause pain, swelling, and neurologic impairment.[4-6] As a possible solution, we discuss the combined use of low-dose fibroblast growth factor-2 (FGF-2) with low-dose BMP-2 to augment bone repair for future clinical orthopaedic applications. In addition, we will review FGF-2 signaling crosstalk with Wnt and BMP-2 signaling as one possible mechanism responsible for the enhanced bone regeneration.

FGF-2 and BMP-2 in Bone Healing

To mitigate some issues with clinical usage of BMP-2, the combined application of low doses of BMP-2 with FGF-2 is being investigated and may be beneficial. There are 22 members of the FGF family; however, FGF-2 has been the most studied growth factor in bone, which is synthesized by osteoblasts/stromal cells and stored in the extracellular matrix.[7] FGF-2 is a potent stimulator of proliferation and has a role in maintaining bone mass,[8] especially with aging.[9] Although no clinical trial of FGF-2 efficacy in fracture repair has been initiated in the United States, a recent clinical trial in Japan found that local administration of FGF-2 accelerated healing in tibial shaft fractures in humans.[10] Several studies have investigated the combined actions of FGF-2 and BMP-2 delivered from biomaterials in animals and have demonstrated synergistic bone-enhancing effects with these two factors.[11-15] In young mice, the concurrent delivery of a few nanograms of FGF-2 with 5 μg of BMP-2 from a collagen sponge caused a modest, but significant, increase in bone, compared with treatment with either growth factor individually.[11] In our laboratories, a low dose of BMP-2 (500 ng/scaffold) delivered on HEALOS scaffolds (70% type 1 collagen and 30% hydroxyapatite; DePuy) in calvarial defects caused complete healing of the defect in FGF-2–overexpressing mice not seen in the BMP-2 only group.[13] However, in vivo administration of larger microgram doses of FGF-2 and BMP-2 consistently inhibited BMP-2–induced bone formation.[14] Pretreatment of mesenchymal stem cells with FGF-2 and BMP-2 before implantation in animals was shown to form bone more rapidly, particularly when cells were cultured with FGF-2 first, followed by BMP-2.[15-17]

Delivery Systems

For clinical use, BMP-2 has been supplied with a bovine collagen carrier/delivery system for products such as InductOsR (Wyeth; not approved by the FDA) and InFUSE (Medtronic). A delivery system is required to modulate BMP dose and to increase the duration of BMP delivery, which are adversely affected by BMP antagonists and the short half-lives of BMPs, respectively.[18,19]

Topics from the frontiers of basic research presented by the Orthopaedic Research Society.

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Several in vitro osteogenesis studies have shown the benefit of administering FGF-2 first to stimulate proliferation, followed by administering BMP-2 to stimulate differentiation in cells from young animals,[20,21] yet co-delivery appears to be beneficial for cells from elderly animals.[21]

Synergistic Mechanisms for FGF-2–enhanced BMP-2 Bone Regeneration

The mechanism of action of FGF-2 is complex and goes beyond increasing proliferation. FGF/FGF receptor signaling has been shown to be a positive upstream regulator of BMP-2 gene expression in chick calvarial cells[19] and human bone marrow stromal cells.[22] In mice, endogenous FGF-2 was shown to be important for maximal response to BMP-2 in bone and appeared to be dependent on the p42/44 mitogen-activated protein kinase signaling pathway.[23] Other studies using FGF-2 and BMP-2 on primary human bone cells showed little effect on BMP receptors BMPR-IA and -II transcript expression but significantly upregulated BMPR-IB mRNA specifically.[24] This led to augmented BMP-2–induced Smad1/5/8 phosphorylation, Dlx5 expression, and alkaline phosphatase activity, compared with that of cells treated with BMP-2 alone, and resulted in enhanced osteogenesis.[24] Low concentrations of BMP-2 have been shown to enhance calvarial defect healing in mice overexpressing FGF-2 in osteoblast progenitors via increased Wnt receptor Lrp5 and Wnt ligand and β-catenin,[13] suggesting that FGF2 can augment BMP-2–induced bone repair via modulation of the Wnt pathway.

Summary

The combined action of low-dose FGF-2 and BMP-2 increases the speed and extent of bone healing and may be a solution to the current problems with high-dose BMP-2. However, development of improved age-specific multigrowth factor delivery systems and further in vivo studies that elucidate the mechanism or mechanisms of the enhanced healing response of the combined factors are still needed.

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