

Transforming growth factor beta superfamily members: role in cartilage modeling.

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Normal and abnormal extracellular matrix turnover is thought to result, in part, from the balance in the expression of metalloproteinases and tissue inhibitors of metalloproteinases (TIMPs). The clinical manifestations of an imbalance in these relationships are evident in a variety of pathologic states, including osteoarthritis, deficient long-bone growth, rheumatoid arthritis, tumor invasion, and inadequate cartilage repair. Articular cartilage defects commonly heal as fibrocartilage, which is structurally inferior to the normal hyaline architecture of articular cartilage. Transforming growth factor-beta 1 (TGF-beta1), a cytokine central to growth, repair, and inflammation, has been shown to upregulate TIMP-1 expression in human and bovine articular cartilage. Additionally, members of the TGF-beta superfamily are thought to play key roles in chondrocyte growth and differentiation. Bone morphogenetic protein-2 (BMP-2), a member of this superfamily, has been shown to regulate chondrocyte differentiation states and extracellular matrix composition. It was proposed that, by optimizing extracellular matrix composition, BMP-2 would enhance articular cartilage healing. After determining the release kinetics of BMP-2 from a collagen type I implant (Long-Evans male rats; two implants/rat, n = 14), it was found that, in a tissue engineering application, BMP-2 induced a hyaline-like repair of New Zealand White rabbit knee articular cartilage defects (3-mm full-thickness defects in the femoral trochlea; 2 defects/rabbit, n = 36). The quality of cartilage repair with BMP-2 (with or without chondrocytes) was significantly better than defects treated with BMP-2, as assessed by a quantitative scoring scale. Immunohistochemical staining revealed TIMP-1 production in the cartilage defects treated with BMP-2. When studied in vitro, it was found that BMP-2 markedly increased TIMP-1 mRNA by both bovine articular and human rib chondrocytes. Additionally, increased TIMP-1 mRNA was translated into increased TIMP-1 protein production by bovine chondrocytes. Taken together, these data suggest that BMP-2 may be a useful cytokine to improve healing of cartilaginous defects. Furthermore, these data suggest that the beneficial effects of BMP-2 may be, in part, related to alterations in extracellular matrix turnover.

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