

## IL-1 $\beta$ AND BMP-7 – INTERACTIVE PLAYERS OF CARTILAGE MATRIX DEGRADATION AND REGENERATION

Th. Aigner

*Institute of Pathology, University of Leipzig, FRG*

**INTRODUCTION:** Catabolic cytokines and anabolic growth factors are thought to be important for maintaining the tissue homeostasis of articular cartilage in the adult. This relates mainly to their important role in regulating the expression and synthesis of matrix constituents (anabolism) as well as the expression of matrix-degrading proteases (catabolism), namely matrix metalloproteinases (MMPs) and molecules of the ADAMTS-family of proteinases. In this respect, over the last years and decades in particular interleukin 1 and members of the BMP/TGF $\beta$ -superfamily gained a lot of scientific interest<sup>1,2</sup>.

**METHODS:** In vitro experiments were performed using freshly isolated adult human articular chondrocytes from normal knee joints (femoral condyles). (Non-passaged) High-density monolayer cultures were stimulated with and without IL-1 $\beta$  (1 and 10ng/ml) and BMP-7 (50ng/ml; kindly provided by Stryker Biotech). Gene expression levels (collagen type II, aggrecan, MMP-1, MMP-2, MMP-3, MMP-13, ADAMTS-4) were detected by real-time PCR.

**RESULTS:** After OP-1 stimulation, the anabolic genes collagen type II and aggrecan were significantly up-regulated in articular chondrocytes. No significant changes were observed for the matrix degrading enzymes. Interleukin 1 showed a significant down-regulation of aggrecan and collagen type II genes. In contrast, the matrix degrading proteases - except MMP-2 - were induced by IL-1 $\beta$  dose-dependently.

**DISCUSSION & CONCLUSIONS:** Clearly, interleukin 1 and BMP-7 (but according to results by Sandell et al.<sup>3</sup> also e.g. BMP-2) exert opposite effects on anabolic and catabolic expression on the effector level. This interplay appears to play an important role in physiological cartilage tissue homeostasis. Thus, the knockout of BMP stimulation by antisense technology showed a catabolic imbalance in cartilage tissue culture<sup>4</sup>.

Additionally, the balance of anabolic-catabolic stimulation is likely to be very important also in cartilage destruction occurring in rheumatoid arthritis and osteoarthritis.

Of note, work by Sandell and colleagues<sup>3</sup> showed additionally a close influence of interleukin 1 activity also on BMP gene expression itself suggesting that both mediators are directly interwoven also on the gene expression levels.

**REFERENCES:** <sup>1</sup> S.Chubinskaya and K.E.Kuettner (2003) Regulation of osteogenic proteins by chondrocytes, *Int. J Biochem. Cell Biol.* **35**:1323-40. <sup>2</sup> M.B.Goldring (2000) Osteoarthritis and Cartilage: The Role of Cytokines, *Curr. Rheumatol. Rep.* **2**:459-65 <sup>3</sup> Fukui, N.; Zhu, Y.; Maloney, W. J.; Clohisy, J.; Sandell, L. J. (2003) Stimulation of BMP-2 Expression by Pro-Inflammatory Cytokines IL-1 and TNF-Alpha in Normal and Osteoarthritic Chondrocytes. *J Bone Joint Surg. Am* , **85 Suppl 3**, 59-66 <sup>4</sup> S.Soeder, A.Hakimiyan, D.Rueger, K.Kuettner, T.Aigner, and S.Chubinskaya (2005) Antisense inhibition of osteogenic protein-1 disturbs human articular cartilage integrity, *Arthritis Rheumat* **52**:468-78.

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