Object: IL-1 is thought to be one of the most important cytokines relevant not only to rheumatoid arthritis, but also to osteoarthritis joint disease. IL-1 is thought to reduce the expression of anabolic genes such as aggrecan and collagen type II as well as to up-regulate various catabolic genes such as matrix degrading proteases (MMP-1, MMP-3, MMP-13) and aggrecanase-1 (ADAMTS-4). The aim of this study was to investigate whether there are different effects of low and high concentrations of IL-1ß on the expression level of anabolic and catabolic genes as well as cytokines and whether there is any difference in reactivity of normal and osteoarthritic chondrocytes.

Methods: Gene expression levels (collagen type II, aggrecan, MMP-1, MMP-2, MMP-3, MMP-13, ADAMTS-4, IL-1ß, IL-6, LIF) were detected by real-time PCR in (non-passaged) primary human articular chondrocytes (normal (n=6); osteoarthritic (n=7)) after stimulation with 0.01 ng, 0.1 ng, 1 ng and 10 ng/ml IL-1ß in high-density short-term monolayer cultures.

Results: Primary adult articular chondrocytes showed a moderate expression of collagen type II and aggrecan. They expressed very abundantly MMP-3 and only to a minor extent MMP-1, -2, -13 and hardly any ADAMTS-4. II-1ß, IL-6 and LIF were basically not expressed at all. In normal adult articular chondrocytes the expression of aggrecan and collagen type II genes were both significantly down-regulated by II-1ß. In contrast, matrix degrading proteases - except MMP-2 - as well as the investigated cytokines II-1ß, IL-6, and LIF were induced by IL-1ß dose-dependently. The strongest regulation was found for IL-6 and LIF.

Osteoarthritic chondrocytes, showed strongly increased basal levels of catabolic enzymes and mediators investigated, but appeared to be less responsive to further stimulation with II-1ß.

The responsiveness of chondrocytes to II-1ß was not age-related in our samples for any of the genes tested, neither in normal nor osteoarthritic chondrocytes.

Conclusion: Our study confirms that IL-1ß activity is critically dependent on the applied concentration and the reactivity of the cells stimulated. The responsiveness appears to be significantly reduced in late stage osteoarthritic chondrocytes. However, these cells appear to show high levels of basic stimulation at least as far as catabolic enzymes and mediators are concerned. From our study, it remains open whether this indicates that osteoarthritic chondrocytes are hardly influenced by IL-1 or are already so strongly stimulated during the disease process that they are refractory to further stimulation with IL-1ß.

Acknowledgements: Supported by the Federal Ministry of Education and Research (BMBF) and the Interdisciplinary Center of Clinical Research (IZKF) of the University Hospital of the University of Erlangen-Nürnberg.

References