Anti-Inflammatory Inhibitors Targeting Jak and Ikk Have An Anabolic Effect on Type II Collagen Turnover ex Vivo - DTU Orbit (12/12/2018)

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Background Rheumatoid arthritis (RA) and a subpopulation of osteoarthritis, inflammatory OA (iOA) are degenerative joint diseases with an inflammatory component. However, the degree of inflammation is much higher in RA than iOA. There are many signaling pathways involved with the inflammation-driven extracellular matrix (ECM) degradation in RA and iOA cartilage that have been suggested as anti-inflammatory targets. However, the results on joint structure in clinical trials have been varying. A better understanding of the intracellular signaling pathways and the downstream effect on ECM turnover could be beneficial for the selection of novel anti-inflammatory treatments for RA and iOA. Objectives The aim of this study was to investigate the direct effect of the anti-inflammatory inhibitors R406 (the active metabolite of Fostamatinib), Tofacitinib, TPCA-1 and SB203580 on the cartilage ECM turnover. Methods Full depth bovine cartilage ex vivo cultures were cultured for 3 weeks with OSM [10 ng/mL] and TNFα [2 ng/mL] (O+T) or together with R406, Tofacitinib or TPCA-1 at 10 μM and a two-fold dilution to 0.16 μM. SB203580 was tested at 3 μM, 1 μM and 0.3 μM. As negative control, untreated explants were included. The ECM turnover of the cartilage was assessed with the biomarkers; C2M, ProC2, AGNx1 and/or ARGS. Additionally, histology of the explants was examined with Safranin O and fast green staining. Results Aggrecanase mediated degradation of aggrecan was assessed with ARGs or AGNx1. The Syk inhibitor R406, the Jak inhibitor Tofacitinib, and the Ikk inhibitor TPCA-1 inhibited the release of ARGs or AGNx1, while the p38 inhibitor, SB203580, had no effect. The turnover of type II collagen was measured by the formation of type II collagen (ProC2) and MMP-mediated degradation of type II collagen (C2M). The ratio between ProC2 and C2M was calculated for week 1–3. Tofacitinib and TPCA-1 increased the area under the curve (AUC) of ProC2/C2M significantly compared to O+T (p<0.001). SB203580 and R406 had no effect at 10 μM, 5 μM, 0.31 μM and 0.16 μM, but tended to increase ProC2/C2M at 2.5–0.625 μM compared to O+T (Figure 1). Safranin O and fast green staining of the explants showed that O+T, SB203580 and 0.16 μM of R406, Tofacitinib, and TPCA-1 lead to loss of proteoglycans from the cartilage explants compared to the untreated explants. R406 at 10 μM retained the proteoglycans in the deep and middle zone of the cartilage, while the proteoglycans of the superficial layer was lost. 10 μM of Tofacitinib and TPCA-1 retained the proteoglycans in all layers of the cartilage explants. Conclusions The four inhibitors tested had a positive effect on the degradation of aggrecan and type II collagen. However, only Tofacitinib and TPCA-1 had an increased anabolic effect on type II collagen turnover. The anabolic effect from Tofacitinib and TPCA-1 on top of the anti-catabolic effect indicates that the chondrocytes can repair the cartilage during treatment opposite to the p38 inhibitor that inhibits the catabolic and the anabolic response.

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