INHIBITION OF INTERLEUKIN-17-INDUCED EFFECTS IN OSTEOARTHRITIS – AN *IN VITRO* STUDY

Purpose

Interleukin-17A (IL-17) is a pro-inflammatory cytokine, which has been reported to be increased in the joint of patients with OA. This study aimed to identify whether IL-17 or its receptors are expressed in the joints of OA patients and establish the effect of IL-17 *in vitro* on primary human chondrocytes and synovial fibroblasts from the joints of OA patients. We further studied whether any anti-inflammatory agents in current clinical use were able to reduce the effects of IL-17. We hypothesize that IL-17 stimulates the production of matrix degrading and inflammatory proteins by acting on IL-17 receptors on chondrocytes and synovial fibroblasts, which can be blocked by clinically used anti-inflammatory therapeutics.

Methods

Formalin-fixed paraffin-embedded synovial tissue from injured and early-stage OA patients was stained for IL-17RA and IL-17RC. Synovial fibroblasts and chondrocytes from end-stage OA patients were cultured to passage 3, treated for 24h with 10 ng/ml rh IL-17, or IL-17 + anti-inflammatory therapeutic, and RNA was harvested for qPCR analysis. Cartilage explants from end-stage OA patients were cultured *ex vivo* for two weeks in the presence of IL-17 and both media and cartilage explants were tested to determine proteoglycan release.

Results

We detected mRNA expression of IL-17 receptors *IL17RA* and *IL17RC* in chondrocytes and synovial fibroblasts, and we showed that IL-17RA and IL-17RC are expressed in synovial tissue derived from patients with osteoarthritis. IL-17RA protein was increased in OA patients with highly inflamed synovium compared to those who had low grade synovitis. IL-17 increased mRNA expression of the cartilage degrading enzymes matrix metalloproteinase 3 (MMP-3) and MMP-13 *in vitro*, and caused a trend toward increasing proteoglycan release from cartilage explants *ex vivo*. In addition, IL-17 increased mRNA expression of the proteins interleukin-6 and TNF alpha induced protein 6, and this expression was significantly reduced

by the anti-IL-17 antibody secukinumab and the corticosteroid dexamethasone, while naproxen, diclofenac, and methotrexate did not show any significant changes.

Conclusions

This study shows that IL-17 is a potential driver of matrix destruction and inflammation in OA. The activity of IL-17 and of therapeutics that target its activity warrant further investigation.