NOVEL REGULATION OF TNFα-INDUCED-IL-18 BIOACTIVITY IN RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS BY REDUCING CASPASE-1 VIA JAK2 INHIBITION

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Background/purpose Rheumatoid arthritis (RA) is the most common inflammatory chronic joint disorder. Interleukin-1 (IL-1) family members play a key part in the pathogenesis of RA. Among the IL-1 cytokine family members, IL-18 is a proinflammatory cytokine, which modulates Th1 development and induces angiogenesis. The authors previously described a regulation of TNFα-induced-IL-18 bioactivity by blocking the ERK pathway. Here, the authors focused on modulation...
of TNFα-induced-IL-18 bioactivity by reduction of caspase-1 expression.

**Method** Caspase-1 expression in RA synovial fibroblasts treated with TNFα was assessed by qRT-PCR and Western blot. The critical pathways for TNFα-induced caspase-1 expression were determined by using chemical inhibitors: pyrrolidine dithiocarbamate (PDTC; a nuclear factor κ-light-chain-enhancer of activated B cells (NFκB) inhibitor; 200 μM), MAPK inhibitors (ERK1/2, PD98059; p38, SB202190; or JNK2, SP600125; 10 μM), or AG-490 (a Jak2 inhibitor; 10 μM) followed by TNFα stimulation. Caspase-1 expression was determined by qRT-PCR and Western blot. Immunofluorescence (IF) staining was performed to check IL-18 production induced by TNFα with or without preinhibition of ERK1/2 or JAK2 by using antibody recognised immature and mature IL-18. IL-18 functional activity was assessed using an IL-18 bioactivity assay using KG-1 cells and culture supernatants.

**Result** TNFα induced RA synovial fibroblast caspase-1 expression at the mRNA and protein levels in a time-dependant manner (p<0.05; n=6 patients). Blocking the Jak2 pathway reduced TNFα-induced-caspase-1 expression at the transcriptional and protein level by approximately 60% and 40%, respectively (p<0.05; n=24). Blocking NFκB, ERK1/2, JNK or p38 pathways had no effect on TNFα-induced-caspase-1 mRNA expression. The authors then confirmed by IF that TNFα-induced IL-18 and investigated roles of ARK1/2 and JAK2 pathways. Blocking the ERK1/2 pathway dramatically decreased IL-18 expression induced by TNFα. However, blocking the JAK2 pathway, TNFα induced intracytoplasmic granularly IL-18 expression suggesting a defect of caspase-1. Finally, blocking the Jak2 pathway, the authors observed a reduction of IL-18 bioactivity by 52% in RA synovial fibroblasts.

**Conclusion** These results show a new way to block TNFα-induced-IL-18 bioactivity by blocking capase-1. These data provide a new role for the Jak2 pathway in RA patients and emphasise the use of Jak inhibitors as a new therapeutic option in the management of RA.