21 **NOVEL REGULATION OF TNF α -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 TNF α -induced-IL-18 bioactivity by blocking the ERK pathway. Here, the authors focused on modulation

of TNF α -induced-IL-18 bioactivity by reduction of caspase-1 expression.

Method Caspase-1 expression in RA synovial fibroblasts treated with TNF α was assessed by qRT-PCR and Western blot. The critical pathways for TNF α -induced caspase-1 expression were determined by using chemical inhibitors: pyrrolidine dithiocarbamate (PDTC; a nuclear factor κ -light-chain-enhancer of activated B cells (NF κ B) inhibitor; 200 μ M), MAPK inhibitors (ERK1/2, PD98059; p38, SB202190; or JNK2, SP600125; 10 μ M), or AG-490 (a Jak2 inhibitor; 10 μ M) followed by TNF α stimulation. Caspase-1 expression was determined by qRT-PCR and Western blot. Immunofluorescence (IF) staining was performed to check IL-18 production induced by TNF α 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 TNF α induced RA synovial fibroblast caspase-1 expression at the mRNA and protein levels in a time-dependant manner ($p < 0.05$; $n \geq 6$ patients). Blocking the Jak2 pathway reduced TNF α -induced-caspase-1 expression at the transcriptional and protein level by approximately 60% and 40%, respectively ($p < 0.05$; $n \geq 4$). Blocking NF κ B, ERK1/2, JNK or p38 pathways had no effect on TNF α -induced-caspase-1 mRNA expression. The authors then confirmed by IF that TNF α -induced IL-18 and investigated roles of ERK1/2 and JAK2 pathways. Blocking the ERK1/2 pathway dramatically decreased IL-18 expression induced by TNF α . However, blocking the JAK2 pathway, TNF α 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 TNF α -induced-IL-18 bioactivity by blocking caspase-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.