25 **IL-17 AND TNFα COMBINATION INDUCES A HIF-1α-DEPENDENT INVASIVE PHENOTYPE IN SYNOVIOCYTES**

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Objectives To examine the effect of IL-17 on rheumatoid arthritis (RA) synoviocyte migration and invasiveness.
Methods IL-17A and tumour necrosis factor α (TNFα) induced mRNA expression in RA synoviocytes was analysed using Affymetrix U133A microarrays. The capacities of IL-17 alone or in combination with TNFα to induce synoviocyte migration and invasion were tested using Boyden and transwell Matrigel invasion chambers. A functional DNA binding assay was used to evaluate the regulation of the key hypoxia related gene HIF-1α expression and activation. The role of metalloproteinase 2 (MMP2) in IL-17 induced invasiveness was assessed using SiRNA. Hypoxia pathway gene expression was measured in blood of RA patients and healthy volunteers (HV) using Affymetrix microarrays.
Results Among the genes induced by IL-17A in RA synoviocytes, a molecular pattern of inflammation-hypoxia-related genes, including CXCR4 and MMP2 was identified. Using immunofluorence microscopy, the expression of CXCR4 on synoviocytes was confirmed. IL-17A and TNFα induced synoviocyte migration and invasion through a CXCR4-dependent mechanism with a synergistic effect. The combination of IL-17A and TNFα activated HIF1-α in synoviocytes through a NFκB pathway. IL-17 enhanced invasion through MMP2 induction as demonstrated using SiRNA.
Finally, hypoxia genes were over expressed in the blood of RA patients.
Conclusion IL-17A, specifically when combined with TNFα may contribute to the progression of RA, notably through their effect on synoviocyte aggressiveness. Part of this effect results from CXCR4/SDF1 and hypoxia mediated pathways.