14 **IFN γ PROMOTES THE INVASIVE BEHAVIOR OF FIBROBLAST-LIKE SYNOVIOCYTES**

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In rheumatoid arthritis (RA), a systemic autoimmune response translates into an inflammatory attack on the synovium that yields the formation of an aggressive cell mass, called pannus, which invades into and destroys the articular cartilage. Cartilage destruction is primarily mediated by fibroblast-like synoviocytes (FLS).

Among the pro-inflammatory mediators produced by infiltrating T cells, interferon γ (IFN γ) may contribute to FLS driven joint destruction. Of note, IFN γ elicits its effects via the JAK1/JAK2-Stat1 signaling pathway.

To establish a role for IFN γ in the invasive potential of FLS, the authors used an in-vitro invasion assay (matrix-associated trans-epithelial resistance invasion-(MATRIN)-assay). Strikingly, FLS that were stimulated with IFN γ demonstrated a markedly increased invasive capacity when compared to unstimulated FLS. Cell invasion involves several steps, including attachment to extracellular matrix (ECM), cell migration, and digestion of the ECM by proteases. As determined by qPCR, however, IFN γ did not up-regulate the expression of metalloproteinases (MMPs) by FLS. Therefore, the authors hypothesised that IFN γ directs FLS motility. Indeed, exposure of FLS to IFN γ resulted in their increased migratory activity as determined in Boyden chamber assays. Since cell motility is partly controlled by focal adhesion kinase (FAK), the authors next analysed whether or not IFN γ modulates FAK activity in FLS. Western blot analysis revealed that activation of the IFN γ -JAK1/2-Stat1 signaling cascade is associated with phosphorylation of FAK. As Stat1 deficient U3A cells similarly responded to IFN γ stimulation, activation of FAK was independent of Stat1. Instead, inhibition of JAK1/2 abrogated IFN γ induced activation of FAK in FLS, indicating that IFN γ regulates FAK activity through JAK1/2, but not Stat1. Importantly, inhibition of JAKs abrogated IFN γ induced invasive activity of FLS. These results confirm that JAK1/2 play a critical role in translating the signal induced by IFN γ to promote invasion in FLS.

These studies suggest a role for IFN γ in the destructive mesenchymal tissue response to inflammation and may provide insight into FLS behavior and function in RA.