RHEUMATOID ARTHRITIS

IFN γ drives synovial tissue remodelling

IFN γ promotes a migratory and invasive phenotype in fibroblast-like synoviocytes (FLSs) through the Janus kinase (JAK) pathway and drives inflammatory tissue remodelling, according to new findings published in *Rheumatology*. “Our data might partially explain how JAK inhibition prevents inflammation-induced structural joint damage in rheumatoid arthritis (RA),” explains corresponding author Thomas Karonitsch.

In RA, FLSs reorganize into a mass of aggressive cells that proliferate extensively and destroy the articular cartilage and bone. The cytokines produced by immune cells that have infiltrated the synovial tissue, such as IFN γ , could potentially drive or influence this process. “In the context of the complex microenvironment of the inflamed joint, it has been difficult

“
IFN γ
stimulation
... increased
the migratory
activity of
[fibroblast-like
synoviocytes]
in vitro”
”

to distill specific contributions from individual inflammatory mediators to the architectural changes in the synovial tissue,” states Karonitsch. To determine the individual effects of IFN γ on mesenchymal tissue remodelling, Karonitsch *et al.* used an *in vitro* 3D model system of the synovial membrane. Using this model, IFN γ stimulation attenuated synovial lining formation and resulted in FLSs with an elongated cellular phenotype and long cellular extensions, compared with the untreated control. By contrast, TNF stimulation resulted in aggregation of FLSs in both the lining and sublining area, suggesting that the two pro-inflammatory cytokines have differing effects on synovial tissue remodelling.

IFN γ stimulation also increased the migratory activity of FLSs *in vitro*. As focal adhesion kinase (FAK) is a known regulator of FLS migration, Karonitsch and colleagues investigated the signalling events controlling FAK phosphorylation. Stimulation of FLSs with IFN α , IFN β or TNF did not increase phosphorylation of FAK, whereas IFN γ increased phosphorylation of

FAK at Y925, a phosphorylation site implicated in FAK-mediated cell migration. Silencing of JAK2, but not JAK1, with small interfering RNA (siRNA) abrogated IFN γ -induced phosphorylation of Y925. Similarly, inhibition of JAK signalling with baricitinib decreased IFN γ -induced phosphorylation of Y925 in a dose-dependent manner. In an *in vitro* invasion assay, IFN γ stimulation increased the invasiveness of FLSs compared with the unstimulated control; this increased invasiveness was inhibited with baricitinib treatment.

“The data reveal that the T cell cytokine IFN γ promotes the invasive potential of FLSs via the JAK signalling circuit,” remarks co-author Hans Kiener. “These results suggest that therapeutic inhibition of JAKs not only targets immune cells but also tissue resident cells (FLSs) in rheumatoid synovitis.”

Jessica McHugh

ORIGINAL ARTICLE Karonitsch, T. *et al.* Targeted inhibition of Janus kinases abates interferon gamma-induced invasive behaviour of fibroblast-like synoviocytes. *Rheumatology (Oxford)* <http://dx.doi.org/10.1093/rheumatology/kex426> (2017)