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A64 FUNCTIONAL INTERACTIONS BETWEEN PI3-KINASE AND NF-κB SIGNALING PATHWAYS PROMOTE JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS

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10.1136/ard.2010.149104.8

Background and objectives Rheumatoid arthritis (RA) synovium is characterised by hyperplasia of fibroblast-like synoviocytes (FLS), which display properties of transformed cells. Regulation of proto-oncogenic phosphatidylinositol 3-kinase (PI3-K) signaling by components of the NF-κB signal transduction pathway has emerged as a candidate molecular mechanism linking inflammation to cancer. Conversely, activation of PI3-K pathways in genetically engineered mice, via reducing expression of PTEN or FoxO transcription factors or transgenically expressing constitutively active PKB, can drive NF-κB-mediated autoimmunity. Here we examined potential functional relationships between PI3-K and NF-κB signaling in RA FLS and synovial tissue.

Materials and methods Expression and/or phosphorylation of IKKβ, $I_{\kappa}B\alpha$, PTEN, a negative regulator of PI3-kinase, PKB and FoxO1, downstream targets of PI3-kinase, was detected by immunohistochemistry combined with digital image analysis in synovial tissue from 15 disease-modifying anti-rheumatic drug (DMARD)-naïve RA patients. Biopsies were obtained at baseline, and x-rays made of hands and feet at baseline and at 2 years follow-up. At 2 years, patients were classified as having non-erosive or erosive disease (Sharp van der Heijde score > 2). Effects of the pan-PI3-K inhibitor LY294002 and inhibitors specific for α/β, γ and δ isoforms of PI3-K on RA FLS IL-1β-induced $I_{\kappa}B\alpha$ phosphorylation and NF-κB p65 activation were assessed by immunoblotting and ELISA, respectively.

Results In vivo we observed a strong correlation between expression of IKKβ and phosphorylation of IκBα (r = 0.83, p

< 0.005) in RA synovial tissue, but IKKβ did not downregulate PTEN or FoxO protein expression, as predicted by tumour models. Instead, we observed a strong positive correlation between PKB activation, phosphorylation of FoxO1 ($r = 0.90$, $p < 0.0001$) and activation of NF-κB signalling ($r = 0.56$, $p < 0.05$), and NF-κB signaling was elevated in patients with accelerated progressive disease ($p < 0.05$). In vitro, sustained phosphorylation of $I_{\kappa}B\alpha$ and activation of NF-κB in RA FLS by IL-1β stimulation required PI3-K activity.

Conclusions Our studies provide evidence that PI3-K signaling pathways may contribute to joint destruction in RA through enhancement of NF-κB-dependent gene transcription and that PI3-kinase inhibitors may be effective in preventing disease progression.

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