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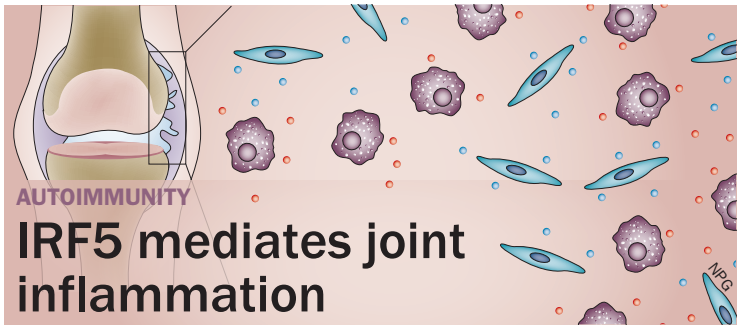

Interferon regulatory factor 5 (IRF5), a transcription factor involved in several immune-mediated mechanisms, was identified as a new link between the pathogenetic activation of RNA-sensing Toll-like receptors (TLRs) and proinflammatory cytokine production in inflamed joints of arthritic mice.

Genetic polymorphisms in *IRF5* (the gene encoding IRF5) were previously associated with increased risk of several autoimmune diseases, including rheumatoid arthritis (RA). These findings led Ian Rifkin and colleagues to investigate the role of IRF5 in arthritic disease; according to Rifkin, "understanding the role of IRF5 in RA might help identify biological pathways of importance in the pathogenesis of this disease."

By using the K/B×N serum transfer mouse model of arthritis, the researchers found that IRF5-knockout ($Irf5^{-/-}$) mice developed milder joint inflammation compared with wild-type controls, as shown by a smaller increase in ankle thickness and lower disease scores derived from histological analysis. Importantly, and in contrast to control mice, no IL-1β was detected in serum samples from arthritic $Irf5^{-/-}$ mice, suggesting an important role for IRF5 in the production of this cytokine. Supporting this hypothesis, analysis of mRNA expression in arthritic joints identified caspase-1 and cathepsin G—both proteases involved in IL-1 processing—among the genes with reduced expression in arthritic $Irf5^{-/-}$ mice compared with controls.

As IRF5 has been implicated in TLR responses, the researchers also tested whether deletion of specific TLRs affected arthritis development. Whereas disease was at least as severe in TLR2–TLR4 double-knockout mice as in controls, mice deficient for TLR3 or for TLR7 had milder disease. "As TLR7 and TLR3 are both RNA-sensing TLRs, this suggests that endogenous RNA ligands are likely to be involved in disease pathogenesis," adds Rifkin. Furthermore, myeloid-cell-specific deletion of IRF5 led to less severe arthritic disease than in $Irf5^{-/-}$ mice, suggesting that IRF5 also acts in nonmyeloid cells such as synovial fibroblasts. Notably, production of growth-regulated α protein (CXCL1) and IL-6 by synovial fibroblasts after TLR7 activation *in vitro* was found to be dependent on IRF5.

This study identified IRF5 as a crucial mediator of joint inflammation, integrating TLR signals and instructing proinflammatory cytokine and chemokine production. Rifkin and colleagues now plan to confirm these findings in humans and "to extend this analysis to look at the *in vivo* role of IRF5 in other immune and nonimmune cells, in particular synovial fibroblasts."

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Original article Duffau, P. *et al.* Interferon regulatory factor 5 promotes inflammatory arthritis. *Arthritis Rheumatol.* doi:10.1002/art.39321