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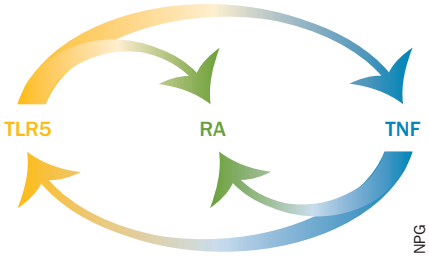
INFLAMMATION

A TLR5–TNF positive feedback loop in rheumatoid arthritis

Researchers have reduced the severity of collagen-induced arthritis in mice by blocking Toll-like receptor 5 (TLR5) with a monoclonal antibody. Published in the *Journal of Immunology*, the study also shows that the bacterial TLR5 agonist flagellin can convert osteoclast precursor cells into fully mature osteoclasts and stimulate chemotaxis of monocytes from patients with rheumatoid arthritis (RA).

Osteoclast differentiation in patients with RA is thought to involve TLR-activated proinflammatory cytokines such as TNF. Endogenous ligands for TLR2 and TLR4 are part of the inflammatory cascade in RA synovia and TLR4 is involved in the pathogenesis of experimental arthritis in mice. Furthermore, Shiva Shahrara, corresponding author of the study, says "TLR5 is highly elevated in RA compared to normal synovial tissue myeloid and endothelial cells." However, until now, a role for TLR5 in the pathogenesis of RA was unclear.



The researchers isolated peripheral blood mononuclear cells from patients with RA treated with DMARDs or with TNF inhibitors plus or minus DMARDs. Flagellin treatment of monocytes *in vitro* had an NF-κB-dependent, dose-dependent, positive effect on chemotaxis, and anti-TLR5 antibody treatment inhibited chemotaxis of these cells.

Monocytes from patients treated with TNF inhibitors had lower TLR5 expression than monocytes from patients who were treated with DMARDs without TNF inhibitors, suggesting that TNF and TLR5 pathways synergize to effect RA pathogenesis. Indeed, Shahrara and colleagues showed that blocking either TNF or TLR5 signalling in mice can prevent flagellin-induced osteoclastogenesis.

Timothy Radstake, an independent expert from the University Medical Center Utrecht, Netherlands, warns "As there is no endogenous ligand for TLR5 known so far, the true value for arthritis has to be investigated further," but he says "this new study ignites the search."

Shahrara responds "We believe TLR5 is the bridge that interconnects formation of new blood vessels with maturation of joint osteoclasts, thereby accelerating the bone destruction process in RA."

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Original article Kim, S.-J. Ligation of TLR5 promotes myeloid cell infiltration and differentiation into mature osteoclasts in rheumatoid arthritis and experimental arthritis. *J. Immunol.* doi:10.4049/jimmunol.1302998