Implication of toll-like receptors (TLRs) on the pathogenesis of rheumatoid arthritis (RA)

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by synovial hyperplasia, neovascularization, and progressive destruction of cartilage and bone. Toll-like receptors (TLRs) are pattern-recognition receptors that connect innate and adaptive immunity. TLRs trigger signals that result in the production of pro-inflammatory cytokines as well as the activation of antigen presenting cells, which regulate adaptive immune system. Considering the TLRs are important bridge between innate and adaptive immunity, continuous activation or dysregulation of TLR might contribute the pathogenesis of autoimmune diseases like RA. Recently, data providing evidence of TLR expression and/or up-regulation in the synovium of patients with RA has been published. More encouraging evidence comes from animal models that demonstrate pathogen initiated models of arthritis, but the exact role and extent to which TLRs influence RA need to be elucidated.

We investigated whether the stimulation of TLR-2 and TLR-4 by their specific ligands up-regulated the production of interleukin (IL)-15, a pleiotropic pro-inflammatory cytokine in fibroblast-like synoviocytes (FLS) of RA patients. IL-15 production increased in RA FLS stimulated with peptidoglycan (PGN), a TLR-2 ligand. Lipopolysaccharide (LPS), a TLR-4 ligand augmented the stimulatory effect of PGN on IL-15 production. Inhibition of nuclear factor (NF)-κB with a specific inhibitor abrogated the stimulatory effect of PGN or PGN plus LPS on IL-15. Levels of vascular endothelial growth factor (VEGF) and IL-8 was up-regulated in culture supernatants of RA-FLS stimulated by TLR-2 ligand, which suggested that TLR-2 activation in RA FLS could be involved in the induction of VEGF and IL-8 and thereby promote inflammation via angiogenesis. IL-16, a chemoattractant for CD4+ cells was also increased by TLR-2 stimulation by its specific ligand, PGN. The expression of TLR2, TLR4 and TLR6 was increased in the synovial tissues obtained from IL-1 receptor antagonist (Ra) deficient mice. Stimulation of TLR-2, TLR-4 and TLR-6 by their specific ligands increased the production of tumor necrosis factor (TNF) -α and IL-1β, dose-dependently and synergistically, which suggest that TLRs contribute to the perpetuation of spontaneous arthritis in IL-1Ra deficient mice.

Overall, TLRs possibly contribute to the perpetuation of inflammation of RA, and TLRs and their signaling pathways may provide an interesting potential therapeutic target for RA. However, much more work needs to be done to determine the exact functional link between TLRs and RA.