TOLL-LIKE RECEPTOR 7 AND 9 IN THE PATHOGENESIS OF INFLAMMATORY AUTOIMMUNE ARTHRITIS

Anita Fischer, Sonja Herman, Christina Böhm, Victoria Saferding, Eliana Goncalves-Alves, Josef Smolen and Günter Steiner.

Department of Rheumatology, Medical University of Vienna, Vienna, Austria.

Background and Objectives. There is evidence that release and insufficient removal of endogenous nucleic acids is involved in triggering harmful autoimmune reactions important in the initiation of rheumatoid arthritis (RA). Nucleic acid sensing molecules, such as the endosomal Toll-like receptors (TLRs) 7 and 9, have been linked to pathogenic autoimmune processes, particularly systemic lupus erythematosus (SLE), but their role in RA is less clear.
We aimed to study the role of TLR7 and TLR9 in the pathogenesis of inflammatory arthritis by antagonizing them in Pristane-induced arthritis (PIA).
Materials and Methods. Arthritis was induced in rats with the mineral oil pristane. Antagonists or agonists, respectively, for TLR7 and TLR9, a non-inhibitory control sequence or PBS as placebo were applied every other day. Treatment was started before disease-induction. Arthritis was scored using established scoring systems, inflammation and bone erosion were quantified by histological analysis. Serum cytokine levels were measured by ELISA.
Results. While the control sequence showed no effect on arthritis development and severity, the TLR9 antagonist reduced arthritis severity significantly in PIA. A slight aggravation of disease severity was observed in animals treated with the TLR7 antagonist. Inhibition of TLR9 led to strongly reduced bone erosion, whereas it appeared even moderately aggravated in animals treated with the TLR7 inhibitor. IL-6 serum levels were reduced in animals treated with the TLR9 antagonist. Only applying the inhibitor before disease onset led to these effects. When treatment with the antagonists was started at disease-onset, no such effect could be observed. Furthermore, there was no long-term effect of antagonizing TLR7 or TLR9 observable.
Treatment with an agonist for TLR9 or TLR7, respectively, revealed slightly, but not significantly reduced disease severity in animals treated with the TLR9 agonist, but a stronger aggravation of the disease with the TLR7 agonist than it was seen with the TLR7 antagonist.
Conclusions: Inhibition of TLR9 significantly reduced inflammation and bone erosion in PIA. Therefore, these results suggest different roles for TLR7 and TLR9 in the T cell-dependent initiation phase of PIA and thus an important involvement of the DNA (CpG) recognizing TLR9 in the initiation of autoimmune arthritis. Nevertheless, the precise role of TLR9 in the different stages of arthritis needs to be further elucidated.