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The role of TLR4 and neutrophil expression in infection-triggered arthritis
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Background The initial response to Chlamydia-induced arthritis probably involves innate immunity but the nature of this interaction has not been defined. In the present study, we examined the role of neutrophils in experimental arthritis in mice with targeted elimination of the small GTPases Rac1 and Rac2, and the role of toll-like receptors in this model.
Methods Arthritis was induced in either wild-type or Rac-deficient mice by intra-articular inoculation of synoviocyte-packaged Chlamydia trachomatis. The scoring of arthritis was assessed by joint swelling and quantitative histopathological scoring. Immunohistochemistry was used to determine the infiltration of neutrophils into the joint. The persistence of Chlamydia in joints of mice after injection was determined by immunoassay. The expression of TLR2 and TLR4 in neutrophils was detected by semiquantitative PCR. Mice genetically deficient in TLR4 were also assessed.
Results In the acute phase, wild-type mice developed more severe arthritis than Rac-deficient mice. At this stage there was abundant infiltration of neutrophils into the joint. In the chronic phase, the Rac-deficient mice developed more severe arthritis and these mice demonstrated defective clearance of the pathogen from the joint. In vitro stimulation of neutrophils with Chlamydia upregulated expression of TLR4 but not TLR3 in wild-type mice. However, neutrophils from Rac-deficient mice did not show this upregulation of TLR4. Sustained TLR4 expression in neutrophils was found to be dependent on expression of Rac. We examined mice genetically deficient in TLR4 expression and demonstrated that such mice developed more severe arthritis than controls. Thus Rac expression plays a profound role in infection-triggered arthritis and demonstrates a bimodal influence on the disease process, exacerbating acute joint inflammation but controlling chronic arthritis. Rac-deficiency was associated with diminished TLR4 expression, impaired host clearance of the pathogen and more severe chronic arthritis.
Conclusions In infection-triggered arthritis, innate immunity plays a critical role. Effective host clearance of an arthritogenic pathogen depends on intact Rac expression by neutrophils and by appropriation of TLR4 by these cells. A defect in this pathway of host defence profoundly influences the outcome of the infection. This study also highlights the changing microenvironment of the joint over time with implications for therapeutic approaches to arthritis.