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Essential role of neutrophils in initiation of arthritis

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Steven C Ghivizzani,[Aff1]

Aff1 Harvard Medical School, Boston, MA, USA

Keywords

Animal model, autoantibody, autoimmunity, neutrophil, rheumatoid arthritis

Context

Although elevated numbers of neutrophils are present in the rheumatoid joint, their specific contribution to the onset of arthritis has not been determined. Neutrophils secrete a number of bioactive molecules, including destructive enzymes and proinflammatory cytokines. Also released are oxidative species such as nitric oxide (NO) and hydrogen peroxide that may lead to metalloproteinase activation or cartilage damage. During the acute onset of disease in animal models there is an immediate influx of these cells. As inflammation develops into a chronic condition, however, populations of infiltrating neutrophils are largely replaced by macrophages and lymphocytes. In the K/BxN transgenic mouse model of arthritis, affected mice spontaneously generate autoantibodies to a ubiquitous antigen, glucose-6-phosphate isomerase (GPI). Intraperitoneal transfer of serum or purified immunoglobulin from K/BxN mice will induce joint-specific inflammatory disease in recipient mice similar to that found in rheumatoid arthritis (RA). This K/BxN serum transfer model was used to evaluate the role of neutrophils in the onset of arthritis.

Significant findings

Following intraperitoneal injection of serum from K/BxN mice, B6.AKR mice developed inflamed ankle joints that progressed in severity over several days. Within 48 hours of injection there was joint edema and neutrophilic infiltration. Depletion of neutrophils by repeat administration of a neutrophil-specific antibody, RB6-8C5, before and after delivery of K/BxN serum prevented the onset of arthritis in the B6.AKR mice. Inhibition of disease by RB6-8C5 antibody was observed up to 5 days post-serum transfer. Administration of antibody specific for $CD4^{+}$ T cells had no such effect. Serum transfer to $RAG1^{-/-}$ mice, which lack functional T and B cells, also resulted in arthritis that could be blocked by neutrophil depletion. Knockout mice deficient for NO synthase 2 or $gp91^{phox}$, an enzyme in the

NADPH oxidase pathway, developed arthritis normally following K/BxN serum transfer, indicating that NO and hydrogen peroxide are not specifically required for arthritis induction.

Comments

This paper provides evidence that neutrophils are essential to disease development in the K/BxN serum transfer model of arthritis. The recent demonstration of elevated GPI and anti-GPI autoantibodies specifically in the joints of patients with RA (see Additional information) provides added impact to the relevance of these findings to human disease. Although neutrophils are generally found in RA joints, they are not usually considered to be prime mediators of pathogenesis. Emphasis among researchers is generally placed upon the roles of macrophages, T cells and the ratios between Th1 and Th2 cells. These data, however, suggest a critical role for neutrophils in the development of disease and that factors responsible for neutrophil recruitment could be important targets for therapeutic intervention. This stucy was limited in that it was restricted to the serum transfer model; effects of neutrophil depletion were not evaluated in other murine models of arthritis.

Methods

Serum transfer, antibody depletion *in vivo*, histology, K/BxN mouse model

Additional information

Schaller M, Burton DR, Ditzel HJ. **Autoantibodies to GPI in rheumatoid arthritis: linkage between an animal model and human disease.**

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References

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