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INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by neutrophil articular infiltration, joint pain and the progressive destruction of cartilage and bone. IL-22 is a key effector molecule that plays a critical role in autoimmune diseases. However, the function of IL-22 in the pathogenesis of RA remains controversial. In this study, we investigated the role of IL-22 in the early phase of antigen-induced arthritis (AIA) in mice.

METHODS:

AIA was induced in C57BL/6, IL-22(-/-), ASC(-/-) and IL-1R1(-/-) immunized mice challenged intra-articularly with methylated bovine serum albumin (mBSA). Expression of IL-22 in synovial membranes was determined by RT-PCR. Articular hypernociception was evaluated using an electronic von Frey. Neutrophil recruitment and histopathological analyses were assessed in inflamed knee joint. Joint levels of inflammatory mediators and mBSA-specific IgG concentration in the serum were measured by ELISA.

RESULTS:

The IL-22 mRNA expression and protein levels in synovial tissue were increased during the onset of AIA. In addition, pharmacological inhibition (anti-IL-22 antibody) and genetic deficiency (IL-22(-/-) mice) reduced articular pain and neutrophil migration in arthritic mice. Consistent with these findings, recombinant IL-22 joint administration promoted articular inflammation per se in WT mice, restoring joint nociception and neutrophil infiltration in IL-22(-/-) mice. Moreover, IL-22-deficient mice showed reduced synovitis (inflammatory cell influx) and lower joint IL-1β levels, whereas the production of IL-17, MCP-1/CCL2, and KC/CXCL1 and the humoral immune response were similar, compared with WT mice. Corroborating these results, the exogenous administration of IL-22 into the joints induced IL-1β production in WT mice and reestablished IL-1β production in IL-22(-/-) mice challenged with mBSA. Additionally, IL-1R1(-/-) mice showed attenuated inflammatory features induced by mBSA or IL-22 challenge. Articular nociception and neutrophil migration induced by IL-22 were also reduced in ASC(-/-) mice.

CONCLUSIONS:

These results suggest that IL-22 plays a pro-inflammatory/pathogenic role in the onset of AIA through an ASC-dependent stimulation of IL-1β production.