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RHEUMATOID ARTHRITIS

IL-23 assists the transition from autoimmunity to inflammatory disease

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Despite its relatively high prevalence, the mechanisms underlying rheumatoid arthritis (RA) — and other autoimmune diseases — are not completely understood. Apart from autoantibodies and the B cells that produce them, different T cell subsets, in particular type 17 T helper (T_H17) cells, contribute to the pathogenesis of RA. Interestingly, although high levels of T_H17 cells are found in the peripheral blood of patients with RA, T_H17 cells do not predominate within the inflamed joints of these patients, which poses the question of how exactly T_H17 cells contribute to the onset of RA. Now, Krönke and colleagues have shown that the cytokine IL-23 activates T_H17 cells that have accumulated in lymphoid organs, triggering the production of proinflammatory autoantibodies by B cells.

"We dissected the role of IL-23 in different [animal] models of RA in detail and used both classical RA models (such as collagen-induced arthritis (CIA) and the K/B×N model) as well as models in which we transferred autoantibodies to induce arthritis," explains Krönke. These models show an initial break in self-tolerance, followed by the appearance of arthritogenic autoantibodies and the subsequent development of autoantibody-induced joint inflammation, thereby replicating the key immunological and clinical features of RA in humans.

The authors observed that IL-23 was essential for the induction of an arthritogenic autoantibody response during CIA and in K/B×N mice, but did not contribute to the autoantibody-mediated inflammatory effector phase of arthritis. Further experiments showed that IL-23 suppresses the expression of the enzyme β-galactoside α-2,6-sialyltransferase 1 (ST6GalI), causing a decrease in the sialylation of arthritogenic antibodies, which results in a direct increase in its inflammatory activity, and the onset of arthritis.

To explore the mechanisms by which IL-23 controls autoantibody glycosylation, Krönke and colleagues analysed the IL-23-dependent T_H17 cell response to CIA in secondary lymphoid organs and joints, as well as T_H17 cell–derived signals that might regulate ST6GalI expression in plasma cells. They observed that co-culture of B cells with IL-23-stimulated T_H17 cells resulted in significant inhibition of both protein and mRNA expression of ST6GalI in plasma cells, indicating that IL-23 induces a phenotypic switch in T_H17 cells that enables them to suppress ST6GalI in plasma cells.

"The most interesting observation was that IL-23 is not involved in the break of self-tolerance or the production of autoantibodies, but controls (via induction of pathogenic T_H17 cells) the inflammatory activity of autoantibodies. The IL-23-T_H17 axis thus acts as checkpoint during autoimmune arthritis, whereby it promotes the transition from asymptomatic autoimmunity to inflammatory autoimmune disease," summarizes Krönke.

Finally, the authors also analysed the glycosylation patterns of autoantibodies in the serum of asymptomatic anti-citrullinated protein antibody-positive patients who had not yet developed RA, patients with active RA and healthy controls. The analysis showed that patients with active RA had the lowest levels of sialylation and galactosylation. Can inhibition of IL-23 reverse these patterns? "We are planning clinical studies in patients with RA in which we want to test the clinical efficacy of a combined B-cell/T-cell therapy using rituximab and IL-12 and IL-23 blockade in a sequential setting. The aim is to induce remission with rituximab-mediated B-cell therapy and to maintain it by blockade of IL-23 (IL-23 blockade alone is not effective during active RA, but should prevent the emergence of newly arising proinflammatory autoantibodies)," concludes Krönke.

M. Teresa Villanueva

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