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EXPERIMENTAL ARTHRITIS

IL-38 promotes anti-inflammatory effects

A new study shows that IL-38 — a member of the IL-1 cytokine family — reduces inflammation in two experimental models of inflammatory arthritis and promotes an anti-inflammatory effect in macrophages and fibroblasts. "IL-38 seems to be a broad anti-inflammatory cytokine and might not be an antagonist of a specific pathway as previously suggested," says Benoit Le Goff, corresponding author on the paper.

Previous work by this and other groups demonstrated that IL-38 expression is upregulated in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and that polymorphisms in the gene encoding IL-38 are associated with ankylosing spondylitis and RA. Furthermore, studies in mice indicated that IL-38 is a negative regulator of inflammatory arthritis.

To investigate the anti-inflammatory function of IL-38, Le Goff and colleagues injected adeno-associated viruses encoding the immature form of IL-38 into the joints of mice in several models of arthritis, including collagen-induced arthritis (CIA), the K/B×N serum transfer model and antigen-induced arthritis (AIA). "In contrast to other IL-1 family members, the mature form of IL-38 has not been characterized and active recombinant IL-38 is not available," explains Le Goff. Compared with control mice treated with GFP, IL-38 overexpression significantly reduced clinical inflammation in mice with CIA and K/B×N mice during the peak and resolution phases of arthritis, whereas no difference was observed in mice with AIA at any time point. IL-38 overexpression in mice with CIA was associated with a reduced number of macrophages in the inflamed synovial tissue and significantly reduced gene expression level of cytokines such as IL-17, IL-22 and IL-23.

To confirm its role in cytokine production, the investigators overexpressed IL-38 in the THP1 monocytic cell line. Protein levels of IL-6, IL-10, IL-23 and TNF were reduced in lipopolysaccharide (LPS)-stimulated THP1 cells after IL-38 overexpression compared with LPS-stimulated control THP1 cells. Moreover, compared with conditioned media from THP1 control cells, conditioned media from IL-38-overexpressing THP1 cells — which was found to contain IL-38 — reduced the secretion of IL-6 and IL-23 in LPS-stimulated M1 macrophages from healthy donors and reduced the production of IL-6 in IL-1β-stimulated fibroblast-like synoviocytes from patients with RA.

> "IL-38 overexpression significantly reduced clinical inflammation in [mouse models of arthritis]"

These findings indicate that IL-38 attenuates the severity of arthritis by reducing the number of macrophages and the expression of proinflammatory cytokines. "We need now to identify the mature form of IL-38 and the receptor used by this cytokine to dampen inflammation," remarks Frédéric Blanchard, co-corresponding author on the paper. "We also need to better understand the role of IL-38 in cartilage and bone loss because prevention of structural damages represents a major clinical need in inflammatory arthritis," Blanchard concludes.

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