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Synovial IL - 21/TNF - producing CD4$^+$ T cells induce joint destruction in rheumatoid arthritis by inducing matrix metalloproteinase production by fibroblast - like synoviocytes

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Abstract

Bone and cartilage destruction is one of the key manifestations of rheumatoid arthritis (RA). Although the role of T helper (Th)17 cells in these processes is clear, the role of IL - 21–producing cells T cells has been neglected. We sought to investigate the role of IL - 21 in RA by focusing on the functional characteristics of the main producers of this cytokine, synovial CD4$^+$IL - 21$^+$ T cells. We show that the frequency of both synovial fluid (SF) CD4$^+$IL - 21$^+$ or CD4$^+$IL - 21$^+$TNF$^+$ T cells in patients with RA was significantly higher compared with patients with psoriatic arthritis (PsA). The frequency of peripheral blood (PB) IL - 21$^+$CD4$^+$ T cells in patients with RA positively correlated with disease activity score 28 (DAS28), serum anticyclic citrullinated peptide (anti - CCP) antibodies and IgM - rheumatoid factor (IgM - RF). IL - 21 levels in RA SF were associated with matrix metalloproteinase (MMP) - 1 and MMP - 3. Related to this, IL - 21 induced significantly the secretion of MMP - 1 and MMP - 3 in RA synovial biopsies. Sorted SF CD4$^+$IL - 21$^+$ T cells significantly induced the release of MMP - 1 and MMP - 3 by fibroblast - like synoviocytes (FLS) compared with medium or CD4$^+$IL - 21$^-$ T cells in a coculture system. Neutralization of both IL - 21 and TNF resulted in significantly less production of MMP by FLS. The results of this study indicate a new role for synovial CD4$^+$IL - 21$^+$TNF$^+$ T cells in promoting synovial inflammation/joint destruction in patients with RA. Importantly, IL - 21 blockade in combination with anti - TNF might be an effective therapy in patients with RA by inhibiting MMP - induced inflammation/joint destruction.

Citing Literature

Supporting Information