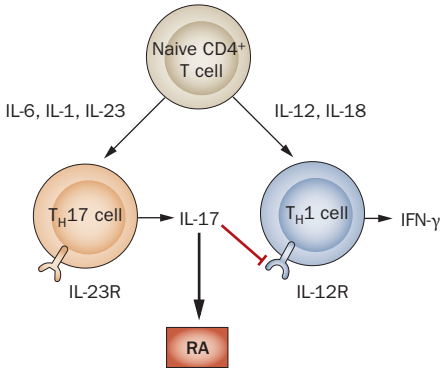
RHEUMATOID ARTHRITIS

IL-17 the multitasker—a dual role in RA pathogenesis

Patients with rheumatoid arthritis (RA) are known to be particularly susceptible to infection owing to systemic defects in type 1 T helper (T_H1) signaling—characterized by decreased interferon (IFN)-γ production and reduced responsiveness to interleukin (IL)-12 and IL-18. New evidence from an *ex vivo* study by Toh *et al.* suggests that IL-17 not only drives a type 17 T_H (T_H17) immune response, but also directly contributes to the T_H1-related defects by selectively inhibiting the β2 subunit of the IL-12 receptor (IL-12Rβ2).

The researchers, from the University of Lyon, France, isolated peripheral blood mononuclear cells (PBMCs) from 16 patients with RA and 10 age-matched healthy controls. Following 24 h stimulation of the PBMCs with IL-12 or IL-17, or both, decreased IL-12-induced IFN-γ mRNA and IL-12Rβ2 mRNA levels were observed in RA PBMCs in comparison with those from healthy individuals. Moreover, the investigators noted that these decreases were augmented in both RA and control



PBMCs in the presence of IL-17 and inhibited by blocking the IL-17 receptor. "IL-17 acts by reducing the expression of IL-12Rβ2," explains Pierre Miossec, lead investigator of the study, who goes on to say that "in turn, cells become insensitive to the effect of IL-12, leading to reduced IFN-γ production." The IL-17-mediated inhibition of IL-12-induced IFN-γ mRNA and IL-12Rβ2 mRNA expression was specific; by contrast, IL-12Rβ1 mRNA and IL-23R mRNA levels increased under the same conditions.

Miossec's team next examined synoviocytes from patients with RA and found increased relative mRNA expression of IL-17 and IL-23R in comparison with IFN-γ and IL-12Rβ2, respectively, indicating a shift to a T_H17 immune response. Furthermore, following *ex vivo* stimulation of RA synoviocytes with IL-17 (but not IFN-γ), the researchers observed decreased IFN-γ mRNA levels, and increased IL-1, IL-6 and matrix metalloproteinase 8 mRNA expression.

Overall, these findings indicate that in the process of promoting T_H17 differentiation, IL-17 contributes to the observed systemic T_H1 defects in patients with RA by inhibiting IL-12 and IFN-γ signaling. Therapeutic IL-17 blockade, therefore, might restore protective IFN-γ expression in individuals with RA.

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Original article Toh, M. L. *et al.* Role of IL-17 in the T_H1 systemic defects in rheumatoid arthritis through selective IL-12Rβ2 inhibition. *Ann. Rheum. Dis.* **69**, 1562–1567 (2010)