RHEUMATOID ARTHRITIS

Control of T_H17 cell activity in RA by a combination of vitamin D receptor signaling and TNF-blockade

Regulating T helper type 17 (T_H17) cell-mediated inflammation is a key therapeutic goal in inflammatory autoimmune diseases such as rheumatoid arthritis (RA). According to research from the Netherlands published in *Annals of the Rheumatic Diseases*, treatment with 1,25(OH)₂D₃—an active vitamin D metabolite—plus an anti-TNF agent inhibits T_H17 cell activity and blocks synovial inflammation in RA, whereas this is not achieved by TNF-blockade alone.

Previous work has shown that 1,25(OH)₂D₃ inhibits IL-17A production by T cells. “Based on these findings we hypothesized that vitamin D receptor pathway activation by 1,25(OH)₂D₃ may directly regulate the pathogenic activity of T_H17 cells from patients with RA”, explains Erik Lubberts, the lead researcher on this study.

To test this hypothesis the authors investigated the effects of 1,25(OH)₂D₃ or TNF-blockade, or both, on cytokine

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expression in co-cultures of T_H17 cells and RA synovial fibroblasts from patients with early RA, and in RA synovial biopsy cultures from patients with established disease undergoing knee joint replacement surgery. Levels of the proinflammatory cytokines IL-17A, IL-22, IL-6 and IL-8, and of the matrix metalloproteinases MMP-1 and MMP-3, were reduced in cultures after stimulation with 1,25(OH)₂D₃ in comparison with control cultures or those to which just an anti-TNF agent was added. “We found that 1,25(OH)₂D₃, in contrast to TNF-blockade, directly regulates T_H17 cytokine expression in cultures”, says Lubberts. A combination

of 1,25(OH)₂D₃ and TNF-blockade had additive effects on reducing the levels of these mediators of inflammation and joint destruction in comparison with anti-TNF agents alone. As Lubberts states, “1,25(OH)₂D₃ in combination with TNF-blockade is essential to fully neutralize pathological T_H17 cell activity in RA synovial inflammation”.

“This study shows the therapeutic potential of 1,25(OH)₂D₃ and TNF-blockade combination as a treatment to control synovial inflammation in RA, in particular in the presence of IL-17/T_H17 cell activity,” concludes Lubberts. “Future research will focus on the identification of 1,25(OH)₂D₃ targets in T cells.”

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Original article van Hamburg J. P. *et al.* TNF blockade requires 1,25(OH)₂D₃ to control human T_H17-mediated synovial inflammation. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2011-200424