37 1,25(OH)2D3 MODULATES GENE EXPRESSION INVOLVED IN CYTOKINE PRODUCTION, PROLIFERATION, SURVIVAL AND MIGRATION OF TH17 CELLS FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2011-201230.37

Background Vitamin D has suppressive effects on autoimmune diseases, such as rheumatoid arthritis (RA). Within these diseases, T-helper-17 (Th17) cells have been implicated to play a crucial role in the development and progression of chronic inflammation. Recently, the authors have found that the active vitamin D compound, $1,25(OH)_2D_3$, has direct suppressive effects on both human and mouse Th17 cytokine expression and activity. Using gene-expression profiling, the authors aim to identify molecular targets of $1,25(OH)_2D_3$ signaling underlying this suppressive action of $1,25(OH)_2D_3$ in Th17 cells.

Materials and methods Primary Th17 cells were sorted from peripheral blood of treatment naïve patients with early RA and cultured with or without $1,25(OH)_2D_3$. From these cultures gene-expression profiles were generated. Expression of genes of interest was confirmed by Q-PCR and/or specific ELISA.

Results In the presence of $1,25(OH)_2D_3$, protein expression of Th17 associated cytokines IL-17A and IL-22 was inhibited, while in contrast the anti-inflammatory cytokine IL-10 was induced. These findings were supported by the gene-expression profiles from these cultures. Furthermore, $1,25(OH)_2D_3$ inhibited transcription of the cytokine receptors IL-23R and IL-7R, which are involved in Th17 survival and proliferation. Chemokines CCL20 and CXCL10 were down-regulated and chemokine receptors CCR2, CXCR6, CXCR3 and CCR10 were up-regulated. Importantly, Rorγt, which is critically involved in Th17 differentiation and function and the cell-size regulator and oncogene, c-Myc were down-regulated by $1,25(OH)_2D_3$.

Conclusions From these findings, the authors concluded that $1,25(OH)_2D_3$ modulates the expression of genes involved in cytokine production, proliferation, survival and migration of Th17 cells. These data indicate that $1,25(OH)_2D_3$ not only suppresses Th17 cell activity but also regulates migration of these cells to sites of tissue inflammation in RA.