INCREASED TH17 CELL FREQUENCY AND POOR CLINICAL OUTCOME IN RHEUMATOID ARTHRITIS ARE ASSOCIATED WITH A GENETIC VARIANT IN THE IL-4R GENE, RS1805010

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Background: The minor allele of the interleukin-4 receptor (IL4R) gene single nucleotide polymorphism (SNP), I50V (rs1805010), confers impaired IL-4 signaling and has been associated with an aggressive destructive course of rheumatoid arthritis (RA). IL-4 inhibits the development of Th17 cells, a cell population recently identified to be prominent in RA patients and to associate with cartilage and bone destruction.

Objectives: Here, we investigated whether the I50V IL4R SNP modulates Th17 cell development and, hence, subsequent clinical outcome in RA.

Methods: Patients with early, active RA (n=90; DAS28 4.6±1.1) and controls (healthy subjects, n=24), osteoarthritis patients (OA, n=15) were genotyped. To assess the inhibitory effect of IL-4 on Th17 cell development, we primed CD4 T cells from all patient and control genotype groups for 72 h in the presence or absence of IL-4 and determined Th17 cell frequencies. Further, in all groups, IL-17, IL-22 serum levels were assessed by ELISA, and Th17 cell frequencies were
analyzed *ex vivo* and after activation by flow cytometry. Clinical and radiographic data were collected and evaluated at baseline and one year after disease onset.

**Results:** Gentotyping revealed that 26% of the patients were homozygous for the major allele of I50V *IL4R* SNP (I50/I50), 60% were heterozygous (I50/V50), and 14% were homozygous for the minor allele (V50/V50). RA patients homozygous for the minor allele (V50/V50) demonstrated significantly higher clinical activity associated with the presence of erosions after one year of follow-up as compared to the other patients. The inhibitory effect of IL-4 on Th17 development in those V50/V50 patients with the impaired IL-4R signaling was significantly less prominent or even absent. Accordingly, frequencies of Th17 cells were significantly increased in the V50/V50 group of RA patients correlating with high disease activity. Those patients demonstrated consistently higher IL-17 and IL-22 serum levels as compared to I50/I50 or I50/V50 RA patients, and controls.

**Conclusions:** The data indicate that the minor allele of I50V *IL4R* SNP (V50/V50) contributes to increased Th17 cell frequency, enhanced clinical activity and accelerated radiographic progression in RA by rendering CD4 T cells from RA patients insensitive to the attenuating effect of IL-4 on Th17 cell development. Here, we provide a potential genetic basis for the Th17 cell-driven inflammatory process underlying early RA.

**Disclosure of Interest:** None declared

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