A186 IL-21R DEFICIENCY DURING EXPERIMENTAL ARTHRITIS INCREASES LOCAL EXPRESSION OF INFLAMMATORY MEDIATORS BUT PROTECTS AGAINST JOINT PATHOLOGY BY SUPPRESSING TH17 CELLS

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Purpose One of the cytokines that contributes to the formation of Th17 cells is interleukin (IL)21, a pleiotropic cytokine produced by Th17 cells themselves. The purpose of this study was to investigate the effect of IL21R deficiency on joint pathology in relation to Th17 cells during chronic experimental arthritis.

Method In IL21R-/- mice, chronic streptococcal cell wall (SCW) arthritis was induced by intra-articular injections of SCW fragments at days 0, 7, 14 and 21.

Results At day 28, histological analysis showed significantly reduced inflammation in IL21R-/- mice compared with wild-types. Although IL21R-/- mice demonstrated suppressed levels of IL6 in the serum, this proinflammatory cytokine tended to be increased in the local patella washouts. This increased local activation in IL21R-/- mice was studied in more detail in the early phase of SCW arthritis. Before and 4 days after the first

intra-articular injection with SCW fragments, the expression level of various receptors and regulators was determined by QPCR. No differences were found in the expression of TLR2 and NOD2, the most import receptors for SCW. However, while the wild-type mice showed a massive upregulation of SOCS1/3 at day 4 of arthritis, IL21R-/- mice were significantly less capable of upregulating these genes. This failure to upregulate SOCS expression in the joint might contribute to the increased local expression of inflammation and destruction markers in IL21R-deficient mice. Interestingly, despite the increased local activation in the IL21R-/- mice, detailed histological analysis of the joints at day 28 of the chronic SCW arthritis demonstrated the IL21R-deficiency protected against cartilage proteoglycan depletion and chondrocyte death. FACS analysis of synovial cells showed a significant reduction in the percentage IL17 T cells. These findings were confirmed in a second model of chronic destructive arthritis, the mBSA antigen-induced arthritis. Also, in this model, IL21R deficiency resulted in a significant reduction in joint inflammation and destruction, again in striking contrast to the local increase in cytokine expression, but accompanied by suppressed numbers of Th17 cells.

Conclusion Despite the local suppressive role of IL21 via SOCS, IL21 has a more dominant prodestructive role driving Th17 cells and joint pathology during chronic experimental arthritis.