A121 DUAL ROLE OF IL-21 IN EXPERIMENTAL ARTHRITIS VIA SOCS REGULATION AND TH17 DIFFERENTIATION

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Objectives Interleukin-21 (IL-21) is a pleiotropic cytokine that is produced mainly by activated CD4+ Th17 cells. The purpose of this study was to investigate the role of IL-21 in joint pathology during chronic experimental arthritis, in particular the effect of IL-21 receptor (IL-21R) deficiency on innate and adaptive immune responses in vivo.

Methods IL-21R–/– mice and their wild-type (WT) controls were used for this study, and two experimental arthritis models were induced: chronic streptococcal cell wall (SCW) induced arthritis and antigen-induced arthritis (AIA).

Results At day 28 of SCW arthritis, histological analysis of the knee joints showed significantly reduced inflammation in IL-21R–/– mice compared to their WT controls. These IL-21R–/– mice also demonstrated suppressed serum levels of IL-6, but interestingly this proinflammatory cytokine tended to be increased in the local patella-washouts. This increased local activation in IL-21R–/– mice was studied in more detail in the early phase of SCW-arthritis. Before onset 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, both crucial for a response to the injected SCW fragments. However, while the WT controls showed a massive upregulation of SOCS1/3 at day 4 of arthritis, IL-21R–/– mice were significantly less capable in upregulating these genes. This failure to upregulate SOCS expression in the joint resulted in increased local expression of inflammation and destruction markers in IL-21R-deficient mice, probably due to disturbed negative regulation of cytokine and TLR signaling pathways.

Interestingly, despite the increased local activation in the IL-21R–/– mice, detailed histological analysis of the joints at day 28 of the chronic SCW-arthritis demonstrated that IL-21R-deficiency protected against cartilage proteoglycan depletion and chondrocyte death. FACS analysis of synovial cells showed a significant reduction of the percentage IL-17+ T cells. These findings were confirmed in a second model of chronic destructive arthritis, the mBSA-induced AIA. Also in this model, IL-21R-deficiency resulted in a significant reduction of joint inflammation and destruction compared to wild-type controls, 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 IL-21 via SOCS regulation, IL-21 has a more dominant prodestructive role driving Th17 cells and cartilage and bone pathology during chronic experimental arthritis. However, this dual role makes IL-21 a complicated target in the treatment of rheumatoid arthritis.