14 IL-21 INDUCES SOCS-MEDIATED SUPPRESSION OF TLR TRIGGERING BUT AGGRAVATES TH17-DRIVEN DESTRUCTIVE ARTHRITIS

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10.1136/annrheumdis-2011-201238.14

Background and objective IL-21 is an immune-regulatory cytokine that can have both proinflammatory and immunosuppressive effects. The purpose of this study was to investigate the potential dual role of IL-21 in experimental arthritis.

Material and methods For in vitro studies, freshly isolated C57Bl6 splenocytes were stimulated with TLR2/NOD2-binding ligands in the presence or absence of IL-21. In addition, chronic Streptococcal cell wall (SCW) arthritis and antigen-induced arthritis (AIA) were induced in IL-21-receptor-deficient (IL-21R^{-/-}) mice and wild-type (WT) controls.

Results In vitro stimulation of splenocytes with TLR2/NOD2-binding SCW fragments resulted in enhanced production of IL-6 and CXCL1, but not IL-10. Interestingly, this proinflammatory response was blocked in the presence of IL-21. QPCR analysis demonstrated that IL-21 strongly induced SOCS expression, suggesting a SOCS-dependent immunosuppressive effect of IL-21 on TLR signaling.

In contrast, at first sight our in vivo studies using IL-21R-deficient mice showed a proinflammatory role of IL-21 in experimental arthritis. In both SCW-induced arthritis and AIA, IL-21R-deficiency protected against severe joint inflammation and destruction. This reduced pathology in IL-21R^{-/-} mice was accompanied by suppressed antigen-specific T cell responses, decreased serum IgG1 levels, reduced IL-17 levels in joint lavage, and lower numbers of IL-17⁺ IFN γ ⁺T cells in the joint.

However, during every local (re)challenge of SCW arthritis with TLR ligands, a clearly enhanced joint swelling was found in IL-21R-deficient mice. No differences were found in the expression of TLR2 and NOD2, the most important receptors for SCW. However, while the WT showed a massive upregulation of SOCS1/3 at day 4 of arthritis, IL-21R^{-/-} mice were significantly less capable in upregulating these genes. These data suggest that impaired SOCS regulation in the absence of IL-21 signaling contributes to the increased local activation during SCW arthritis.

Conclusion Despite the proinflammatory role of IL-21 in adaptive immunity, driving IL-17/IFN γ double-positive cells and joint pathology during chronic experimental arthritis, IL-21 also has an important immunosuppressive role in innate immunity by inhibiting TLR signaling via SOCS1/3. This dual role of IL-21 in various immune processes makes IL-21 a difficult therapeutic target in RA.