The kinase inhibitory region of SOCS-1 is sufficient to inhibit T-helper 17 and other immune functions in experimental allergic encephalomyelitis.

Abstract:

Suppressors of cytokine signaling (SOCS) negatively regulate the immune response, primarily by interfering with the JAK/STAT pathway. We have developed a small peptide corresponding to the kinase inhibitory region (KIR) sequence of SOCS-1, SOCS1-KIR, which inhibits kinase activity by binding to the activation loop of tyrosine kinases such as JAK2 and TYK2. Treatment of SJL/J mice with SOCS1-KIR beginning 12 days post-immunization with myelin basic protein (MBP) resulted in minimal symptoms of EAE, while most control treated mice developed paraplegia. SOCS1-KIR treatment suppressed interleukin-17A (IL-17A) production by MBP-specific lymphocytes, as well as MBP-induced lymphocyte proliferation. When treated with IL-23, a key cytokine in the terminal differentiation of IL-17-producing cells, MBP-sensitized cells produced IL-17A and IFNγ; SOCS1-KIR was able to inhibit the production of these cytokines. SOCS1-KIR also blocked IL-23 and IL-17A activation of STAT3. There is a deficiency of SOCS-1 and SOCS-3 mRNA expression in CD4(+) T cells that infiltrate the CNS, reflecting a deficiency in regulation. Consistent with therapeutic efficacy, SOCS1-KIR reversed the cellular infiltration of the CNS that is associated with EAE. We have shown here that a SOCS-1 like effect can be obtained with a small functional region of the SOCS-1 protein that is easily produced