

SOCS-1 mimetics protect mice against lethal poxvirus infection: identification of a novel endogenous antiviral system

Abstract:

The suppressor of cytokine signaling 1 (SOCS-1) protein modulates cytokine signaling by binding to and inhibiting the function of Janus kinases (JAKs), ErbB, and other tyrosine kinases. We have developed a small tyrosine kinase inhibitor peptide (Tkip) that binds to the autophosphorylation site of tyrosine kinases and inhibits activation of STAT transcription factors. We have also shown that a peptide corresponding to the kinase-inhibitory region of SOCS-1, SOCS1-KIR, similarly interacts with the activation loop of JAK2 and blocks STAT activation. Poxviruses activate cellular tyrosine kinases, such as ErbB-1 and JAK2, in the infection of cells. We used the pathogenesis of vaccinia virus in C57BL/6 mice to determine the ability of the SOCS-1 mimetics to protect mice against lethal vaccinia virus infection. Injection of mice intraperitoneally with Tkip or SOCS1-KIR containing a palmitate for cell penetration, before and at the time of intranasal challenge with 2×10^6 PFU of vaccinia virus, resulted in complete protection at 100 microg. Initiation of treatment 1 day postinfection resulted in 80% survival. Administration of SOCS-1 mimetics by the oral route also protected mice against lethal effects of the virus. Both SOCS1-KIR and Tkip inhibited vaccinia virus transcription and replication at early and possibly later stages of infection. Vaccinia virus-induced phosphorylation of ErbB-1 and JAK2 was inhibited by the mimetics. Protected mice mounted a strong humoral and cellular response to vaccinia virus. The use of SOCS-1 mimetics in the treatment of poxvirus infections reveals an endogenous regulatory system that previously was not known to have an antiviral function.