SOCS3 regulates the plasticity of gp130 signaling.

Suppressor of cytokine signaling (SOCS) proteins are feedback inhibitors of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathway. SOCS3 is upregulated by several signals in macrophages and has been implicated as a regulator of various signaling pathways. Here we show that phosphorylation of STAT3 is prolonged in mouse Socs3-deficient macrophages after stimulation with interleukin-6 (IL-6) but not IL-10, indicating that SOCS3 specifically affects signaling mediated by IL-6 and gp130. IL-6 induces a wider transcriptional response in Socs3-deficient macrophages than in wild-type cells; this response is dominated by interferon (IFN)-regulated genes owing to an excess of STAT1 phosphorylation. Thus, SOCS3 functions to control the quality of the response to IL-6 and prevents the activation of an IFN-induced program of gene expression.