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SOCS genes: Critical regulators of cytokine signaling and immune responses

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Abstract. Immune and inflammatory systems are controlled by multiple cytokines, including interleukins (ILs) and interferons. Many of these cytokines exert their biological functions through *Janus* tyrosine kinases (JAKs) and STAT transcription factors. The CIS (cytokine-inducible SH2 protein) and SOCS (suppressors of cytokine signaling) are a family of intracellular proteins, several of which have emerged as key physiological regulators of cytokine-mediated homeostasis, including innate and adaptive immunity. We investigated the roles of suppressors of cytokine signaling (SOCSs) in regulating dendritic cell (DC) maturation and function. We showed that SOCS1-deficient DCs induced stronger Th1-type responses both in vitro and in vivo. SOCS1-deficient DCs induced higher interferon-γ (IFNγ) production from naive T cells than wild-type DCs in vitro. Lymph node T cells also produced higher amount of IFNγ when SOCS1-deficient bone marrow-derived (BM) DCs were transferred in vivo. Moreover, SOCS1$^{-/-}$ BMDCs raised more effective anti-tumor immunity than wild-type BMDCs. On the other hand, SOCS3-deficeint BMDCs expressed lower levels of MHC, co-stimulators and CD40 in response to LPS. SOCS3-deficient DCs induced lower T cell responses. Thus, SOCS1 and SOCS3 reciprocally regulate DC maturation. © 2005 Published by Elsevier B.V.

Keywords: Cytokine; Tyrosine kinase; STAT; NF-κB; Toll-like receptor (TLR) family

Abbreviations: IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; IBD, inflammatory bowel diseases; RA, rheumatoid antithesis; LPS, lipopolysaccharide; TLR, toll-like receptor; KIR, kinase inhibitory region; STAT, signal transducers and activators of the transcription family of protein; SOCS, suppressors of cytokine signaling; CIS, cytokine-inducible SH2 protein; SH2, src-homology 2.

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1. Introduction

Cytokines regulate many physiological responses and homeostasis, influencing survival, proliferation, differentiation and functional activity of cells of the immune system, as well as those of most other organ systems. Cytokines, including interleukins, interferons and hemopoietins, activate the JAK kinases (JAK1, JAK2, JAK3 and Tyk2) that associate with their cognate receptors. Activated JAKs phosphorylate the receptor cytoplasmic domains that create docking sites for SH2-containing signaling proteins. Among the substrates of tyrosine phosphorylation are members of the signal transducers and activators of transcription family of proteins (STATs) [1]. For example, IFNγ utilizes JAK1 and JAK2 which mainly activate STAT1, whereas IL-6 binding to the IL-6 receptor α chain and gp130 primarily activates JAK1 and STAT3. Interestingly, the anti-inflammatory cytokine IL-10 also activates STAT3.

Suppressors of cytokine signaling (SOCS) and cytokine-inducible SH2 protein (CIS) are a family of intracellular proteins, several of which have been shown to regulate the responses of immune cells to cytokines [2–4]. The discovery of the SOCS proteins appeared to have defined an important mechanism for the negative regulation of the cytokine–JAK–STAT pathway; however, recent studies using gene-disrupted (KO) mice have unexpectedly revealed profound roles of SOCS proteins in many immunological and pathological processes [5].

There are eight CIS/SOCS family proteins; CIS, SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6, and SOCS7; each has a central SH2 domain, an amino-terminal domain of variable length and sequence, and a carboxy-terminal 40-amino-acid module known as the SOCS box. Among them, SOCS1 and SOCS3 have been implicated in immune regulation [5]. Both SOCS1 and SOCS3 can inhibit JAK tyrosine kinase activity since they have the kinase inhibitory region (KIR) in their N-terminal domain, which is proposed to function as a pseudosubstrate [2,5]. While SOCS1 directly binds to the activation loop of JAKs through its SH2 domain, the SOCS3 SH2 domain binds the cytokine receptor (Fig. 3). The SOCS3 SH2 domain has been shown to bind to Y757 of gp130, Y985 of the leptin receptor and Y800 of the IL-12 receptor [5].

Dendritic cells (DCs) are characterized by a high capability for antigen capture and processing, migration to lymphoid organs, and expression of various co-stimulatory molecules for antigen-specific lymphocyte activation. Various DC-derived factors that induce Th-cell-polarization have been identified. Well-documented examples are Th1-cell-polarizing cytokines, such as IL-12, IL-23, IL-27, and type 1 IFNs, as well as Th2-cell-polarizing cytokines such as IL-10 and transforming-growth factor-beta (TGF-β). Among them, IFNγ is an important cytokine that activates macrophage and DC. Recent studies have shown that DCs also produce IFNγ, suggesting the presence of an autocrine-positive feedback pathway for DC activation. It has been proposed that the production of IFNγ by DCs at the time of antigen presentation also causes a strong Th1-cell polarization [6]. In mice, $CD8\alpha^+$ DCs, which produce large amounts of IL-12 and IFNγ, induce Th1 responses, whereas $CD8\alpha^-$ DCs produce lower amounts of IL-12 and preferentially induce Th2 responses [7]. IFNγ secreting Th1-type T cell and cytotoxic T cell (CTL) responses are necessary for effective anti-tumor immunity. Thus, DCs such as $CD8\alpha^+$ DCs are suggested to be suitable for vaccination in cancer immunotherapy [8].