SOCS1: Regulator of T Cells in Autoimmunity and Cancer

Subburaj Ilangumaran, Diwakar Bobbala and Sheela Ramanathan

Abstract SOCS1 is a negative feedback regulator of cytokine and growth factor receptor signaling, and plays an indispensable role in attenuating interferon gamma signaling. Studies on SOCS1-deficient mice have established a crucial role for SOCS1 in regulating $CD8^+$ T cell homeostasis. In the thymus, SOCS1 prevents thymocytes that had failed positive selection from surviving and expanding, ensures negative selection and prevents inappropriate developmental skewing toward the CD8 lineage. In the periphery, SOCS1 not only controls production of T cell stimulatory cytokines but also attenuates the sensitivity of $CD8^+$ T cells to synergistic cytokine stimulation and antigen non-specific activation. As cytokine stimulation of $CD8^+$ T lymphocytes increases their sensitivity to low affinity TCR ligands, SOCS1 likely contributes to peripheral T cell tolerance by putting brakes on aberrant T cell activation driven by inflammatory cytokines. In addition, SOCS1 is critical to maintain the stability of T regulatory cells and control their plasticity to become pathogenic Th17 and Th1 cells under the harmful influence of inflammatory cytokines. SOCS1 also regulates T cell activation by dendritic cells via modulating their generation, maturation, antigen presentation, costimulatory signaling, and cytokine production. The above control mechanisms of SOCS1 on T cells, T regulatory cells and dendritic cells collectively contribute to immunological tolerance and prevent autoimmune manifestation. On other hand, silencing SOCS1 in dendritic cells or $CD8^+$ T cells stimulates efficient antitumor immunity. Thus, even though SOCS1 is not a cell surface checkpoint inhibitor, its regulatory functions on T cell responses qualify SOCS1as a "non-classical" checkpoint blocker. SOCS1 also functions as a tumor suppressor in cancer cells by regulating oncogenic signal transduction pathways. The loss of SOCS1 expression observed in many tumors may have an impact on classical checkpoint pathways. The potential to exploit SOCS1 to treat inflammatory/autoimmune diseases and elicit antitumor immunity is discussed.

S. Ilangumaran (✉) · D. Bobbala · S. Ramanathan
Immunology Division, Faculty of Medicine and Health Sciences, Department of Pediatrics, Université de Sherbrooke, 3001 North 12th avenue, Sherbrooke, QC J1H 5N4, Canada
e-mail: Subburaj.Ilangumaran@Usherbrooke.ca

Current Topics in Microbiology and Immunology
DOI 10.1007/82_2017_63

Contents

1 Introduction

T lymphocytes play a central role in immune protection against pathogens and provide immune surveillance against neoplastic cells from growing into life-threatening tumors. They also play a key role in the pathogenesis of autoimmune diseases. Physiologic and pathogenic activations of T cells require two essential signals. Signal 1 is delivered via the T cell antigen receptor (TCR) following its engagement by antigenic peptides presented by the MHC:peptide complex. However, concomitant signaling via costimulatory receptors (mainly CD28 and many others such as ICOS, CD27, 4-1BB/CD137, OX40/CD134, etc.) is also required to achieve full activation, elicit cell proliferation, and develop effector functions (Baxter and Hodgkin 2002; Chen and Flies 2013). In the absence of the second signal, TCR-stimulated T cells undergo anergy, which can be prevented by IL-2, an important product of costimulatory signaling (Acuto and Michel 2003; Schwartz 2003; Wells et al. 2001). Besides these two essential signals, activated T cells invariably get additional help from inflammatory cytokines (mainly type-I interferons, IL-12 and IL-27 for CD8 T cells, and IL-1 for CD4 T cells), which provide the third signal to amplify T cell responses (Ben-Sasson et al. 2009; Curtsinger and Mescher 2010; Curtsinger et al. 2005b; Haring et al. 2006; Kolumam et al. 2005). Indeed, loss of the cytokine-mediated signal could lead to impaired effector functions and induction of tolerance (Curtsinger et al. 2003, 2005a; Mescher et al. 2007). Several other cytokines including IL-2, IL-4, IL-6, IL-15, IL-17, and IL-21 also contribute to cell proliferation, differentiation, acquisition of distinct effector functions, prevention of exhaustion and generation of memory cells. Thus, cytokine signals profoundly modulate the quality, type, and magnitude of the T cell response toward pathogen-derived antigens, which also hold good for autoantigens and tumor antigens (Cox et al. 2011).

Regulating the amplitude and duration of the T cell response is essential to minimize potential collateral damage to normal tissues while eliminating harmful pathogens. This balance is achieved through several mechanisms acting at each of the three nodes of the T cell activation cascade namely, the TCR, costimulatory receptors and the cytokine receptors. These regulatory mechanisms may operate

either in a cell-autonomous manner or be modulated following interaction of activated T cells with ligands expressed on other cells. The signal 1 is negatively regulated by downmodulation of the TCRζ chain via CBL-mediated ubiquitination as well as through protein tyrosine phosphatases and many other negative feedback regulators that impact on the various components of the TCR signaling machinery (Acuto et al. 2008; Baniyash 2004; Naramura et al. 2002; Stanford et al. 2012; Wang et al. 2001). Induction of co-inhibitory receptors such as CTLA-4, PD-1, LAG3, TIM3, etc., not only attenuate costimulatory signals by competing for stimulatory ligands (B7-1/CD80, B7-2/CD86) but also inhibit various signaling pathways downstream of TCR by engaging newly induced co-inhibitory ligands such as PD-L1/CD274 that are expressed on antigen presenting cells (APC) and cancer cells (Chen and Flies 2013; Paterson et al. 2009). The third signal provided by cytokines could be regulated by several feedback negative regulatory mechanisms; for example, the one involving suppressor of cytokine signaling (SOCS) family proteins, of which CISH (CIS-1; cytokine-inducible SH2-containing protein 1) has also been recently implicated in modulating TCR signaling (Palmer et al. 2015; Palmer and Restifo 2009; Yasukawa et al. 2000; Yoshimura 2013; Yoshimura et al. 2007).

The checks and balances imposed by the above control mechanisms tightly regulate the temporal sequence, amplitude, and duration of T cell activation thereby modulating the overall T cell response to ultimately benefit the host. Whereas the loss of these control mechanisms invariably leads to autoimmune pathologies, the tumor microenvironment exploits them to dampen antitumor T cell responses. Indeed, the signal 2 of T cell activation influenced by costimulatory and co-inhibitory signaling receptors, particularly CTLA4 and PD-1, is profoundly modulated in autoimmunity and in cancer, earning these molecules the label "checkpoint inhibitors", even though the other regulatory nodes in the T cell activation cascade can also function as important checkpoints to ensure appropriate and adequate T cell response. Many of the "classical" checkpoint inhibitors that impinge on the signal 2 of T cell activation cascade are reviewed elsewhere in this volume. In this review, we will focus on the role of SOCS1 as an important "non-classical" checkpoint regulator of T cell activation at multiple levels and its implications to autoimmunity and cancer.

2 SOCS1-Dependent Regulation of Cytokine Signaling

Three laboratories independently discovered SOCS1 in 1997 as a negative regulator of cytokine receptor signaling that inhibited the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway (Endo et al. 1997; Naka et al. 1997; Starr et al. 1997). SOCS1 shares structural similarity with the previously known CISH and several other newly identified proteins designated SOCS2 to SOCS7, which together constitute the SOCS family proteins (Alexander 2002; Yoshimura et al. 1995). SOCS proteins contain a central SRC homology (SH2)

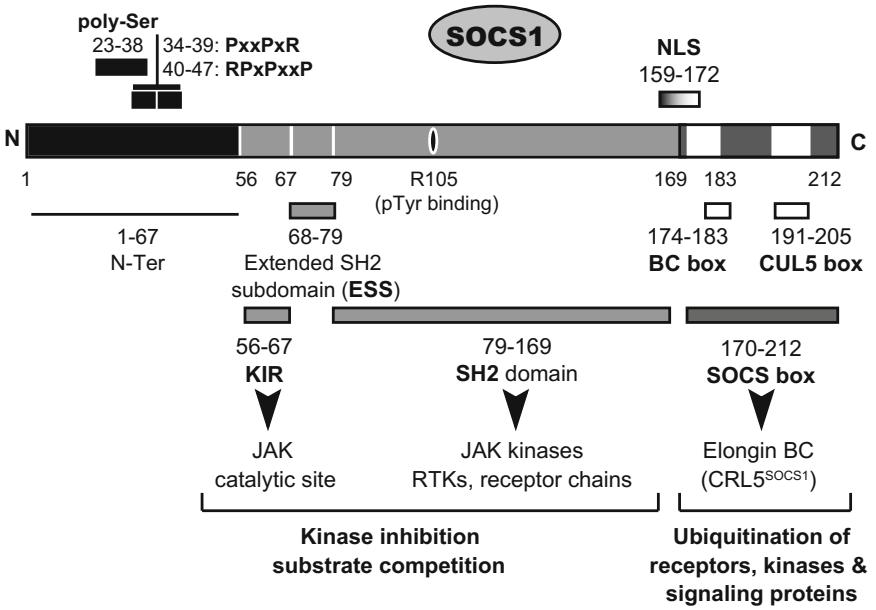

Fig. 1 Structure and functions of SOCS1. SOCS1 contains a central SH2 domain, which mediates interaction with JAK kinases, RTKs and receptor chains. The extended SH2 subdomain (ESS) and the kinase inhibitory region (KIR) are also required to block JAK kinase activity. The N-terminus of SOCS1 contains serine and proline-rich sequences, and the latter may bind SH3 domain-containing proteins. The C-terminal SOCS box includes the BC box and the Cul box, which interact with Elongins B and C, and Cullin 5, respectively. The SOCS box facilitates the assembly of the E3 ubiquitin ligase CRL^{SOCS1}, which promotes ubiquitination of many SOCS1-interacting proteins. SOCS1 harbors a nuclear localization signal (NLS) between the SH2 domain and the SOCS box that is likely involved in its nuclear functions, which are not yet well characterized. The boundaries of the various structural domains and motifs of SOCS1, and their molecular functions are indicated

domain and a conserved structural motif at the C-terminus called the SOCS box (Fig. 1), which is also shared by several proteins outside the SOCS family (Alexander 2002; Kile et al. 2002). The N-terminal region of SOCS proteins is highly variable in length and largely accounts for the difference in their size that range from 198 to 579 amino acids (Fujimoto and Naka 2003). The N-terminal segment may harbor additional structural motifs such as the kinase inhibitory region (KIR) adjacent to the SH2 domain of SOCS1 and SOCS3 (Nicholson et al. 1999; Sasaki et al. 1999; Yasukawa et al. 1999), the N-terminal conserved motif (NTCR) in SOCS4 and SOCS5 (Feng et al. 2012) or a nuclear localization signal (NLS) in SOCS6 and SOCS7 (Hwang et al. 2007; Kremer et al. 2007; Martens et al. 2004). SOCS1 also harbors a functional NLS between the SH2 domain and the SOCS box (Baetz et al. 2008; Strebovsky et al. 2011).

Most SOCS proteins are induced following cytokine stimulation and inhibit further signaling in a negative feedback manner that involves the SH2 domain and

the SOCS box (Alexander 2002; Trengove and Ward 2013). The SH2 domain facilitates binding to phosphorylated tyrosine residues on JAK kinases, receptor chains and signaling proteins. The SOCS box, by virtue of its ability to interact with a Cullin5, Elongin B and C, assembles an E3 ubiquitin ligase that facilitates ubiquitination of the SOCS-interacting proteins and their degradation by proteasomes (Babon et al. 2009; Ilangumaran et al. 2004; Okumura et al. 2012). While most SOCS proteins attenuate cytokine signaling by promoting ubiquitination-dependent turnover of receptor chains, and presumably the associated signaling molecules, SOCS1 and SOCS3 mediate their functions mainly by inhibiting JAK kinase activity (Boyle et al. 2007; Yoshimura and Yasukawa 2012; Zhang et al. 2001). At least a part of this selective mode of action might result from reduced affinity of SOCS1 and SOCS3 toward Cullin5 compared to other SOCS family members (Babon et al. 2009).

Structure–function studies on SOCS1 and SOCS3 have revealed the requirement of the SH2 domain, adjacent N-terminal sequence (called extended SH2 domain or ESS) and the KIR to inhibit JAK activity (Nicholson et al. 1999; Sasaki et al. 1999; Yasukawa et al. 1999). It was initially proposed that while the SH2 domain binds the phospho-Tyr residue within the activation loop of JAKs, the KIR sequence occupies the substrate-binding pocket as a pseudosubstrate, thereby inhibiting enzyme activity (Yasukawa et al. 1999). Structural analysis by nuclear magnetic imaging of the tripartite complex formed by SOCS3, cytoplasmic domains of the IL-6 receptor subunit gp130 and the catalytic JH1 domain of JAK2 indicated that the SH2 domain interacts with gp130 while the KIR domain binds JH1 outside the substrate-binding pocket of JAK1, JAK2 and TYK2 (but not JAK3, which lacks the conserved GQM motif) and inhibit the kinase activity in a non-competitive manner (Babon et al. 2012). However, subsequent studies on the crystal structure of SOCS3-JAK2-gp130 ternary complex ($SOCS3_{22–185}$–$JAK2_{JH1}$–$gp130_{750–764}$) showed that the KIR of SOCS3 occupies the substrate-binding groove of JAK, supporting the original model proposed by Yasukawa and colleagues, without affecting ATP binding to the catalytic site (Babon et al. 2014b; Kershaw et al. 2013; Yasukawa et al. 1999). Like SOCS3, SOCS1 binding to cytokine receptors could subsequently lead to inhibition of the JAKs bound to the receptor chains and signal attenuation. Differences in the amino acid sequence surrounding the phosphor-Tyr-binding groove of the SH2 domain may determine the specificity and potency of SOCS1 and SOCS3 to inhibit different cytokines; for example, IFNγ and IL-2 family cytokines by SOCS1 and IL-6 by SOCS3 (Alexander et al. 1999; Babon et al. 2014a; Croker et al. 2003; Marine et al. 1999; Sporri et al. 2001; Wormald et al. 2006). Similarly, the ability of SOCS3 to inhibit STAT3 activation downstream of IL-6 but not IL-10 receptor, and hence attenuate pro-inflammatory but not anti-inflammatory STAT3 signaling, is determined by the ability of SOCS3 to bind IL-6 receptor but not the IL-10 receptor (Yasukawa et al. 2003). SOCS1 binding via SH2 domain to phosphorylated cytokine receptor chains will also result in competition for other signal transducers such as STAT molecules from being recruited to the receptor and become activated (Trengove and Ward 2013).

Even though SOCS molecules were originally discovered as JAK-binding proteins, SOCS1 was also shown to bind several receptor tyrosine kinases (RTK) including c-KIT, FLT3, CSF-1R, and MET, and modulate downstream signaling (Bourette et al. 2001; De Sepulveda et al. 1999; Gui et al. 2015; Kazi et al. 2014). Indeed, it has now become clear that the SOCS proteins can be grouped by their ability to inhibit predominantly the JAK-STAT pathway (CISH, SOCS2) or RTK signaling (SOCS6, SOCS7), or both (SOCS1, SOCS3, SOCS4, and SOCS5) (Kazi et al. 2014; Trengove and Ward 2013). Non-receptor tyrosine kinases other than the JAK family kinases such as TEC, SYK, and FAK have also been reported to interact with and inhibited by SOCS1 (Liu et al. 2003; Matsuda et al. 2000; Ohya et al. 1997).

While SOCS1-dependent regulation of the JAK-STAT pathway in vivo has been well documented using mice and cells lacking SOCS1 (discussed below), most studies on SOCS1-mediated inhibition of RTKs and NRTKS have been carried out in cell line models. The potential implications of the latter in the immune system also remain to be explored. For instance, HGF-induced MET signaling has been implicated in several immune cell functions including T cell recruitment to the heart during transplant rejection (Ilangumaran et al. 2016; Komarowska et al. 2015). As SOCS1 is an indispensable regulator of MET signaling in hepatocytes and several other RTKs, it will be worthwhile to investigate the role of SOCS1 (and other SOCS proteins) in regulating RTK signaling in T cells and other immune cells.

3 Regulation of T Cell Activation and Homeostasis by SOCS1

Early studies on SOCS1-deficient mice reported neonatal fatality from severe liver damage and systemic inflammation that was accompanied by profound thymic atrophy and marked depletion of T lymphocytes in spleen (Naka et al. 1998; Starr et al. 1998). Subsequent studies that demonstrated SOCS1 as an indispensable regulator of IFNγ signaling also suggested a role for SOCS1 in regulating T cell activation (Alexander et al. 1999; Marine et al. 1999). Perinatal death of *Socs1*-null mice can be reversed not only by simultaneous ablation of the *Ifng* gene or neutralization of IFNγ but also by concomitant RAG deficiency that blocks T cell development and causes peripheral T lymphopenia (Alexander et al. 1999; Marine et al. 1999). Selective loss of TCRαβ$^+$ T cells due to TCRα deficiency also prolonged viability of SOCS1-deficient mice, even though they eventually succumbed to severe colitis (Chinen et al. 2006). Analysis of the T cell compartment in *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice revealed accumulation of CD8$^+$ T cells and reduced CD4/CD8 ratio (Cornish et al. 2003b; Ilangumaran et al. 2003a). SOCS1-deficient CD8$^+$ T cells display a CD44^{hi} CD62L^{lo} CD122^{hi} Ly6c^{hi} phenotype, a characteristic of memory CD8$^+$ T cells and "memory-like" cells that arise from cytokine-driven homeostatic expansion under conditions of T lymphopenia

(Jameson 2002; Murali-Krishna and Ahmed 2000). CD44 is also upregulated following T cell activation; however, SOCS1-deficient $CD8^+$ T cells do not display other activation markers such as CD25 or CD69 (Ilangumaran et al. 2003a). *Socs1*$^{fl/-}$Lck-Cre mice lacking SOCS1 specifically in T cells did not develop lethal inflammatory disease, but displayed all changes in the peripheral T cell compartment caused by global SOCS1 deficiency, including enlarged lymph nodes, increased frequency of $CD8^+$ T cells and altered CD4/CD8 ratio, and elevated CD44 expression on CD8 T cells, indicating that SOCS1 is a cell-intrinsic regulator of $CD8^+$ T cell activation and homeostasis (Chong et al. 2003).

In peripheral T cells, SOCS1 deficiency does not affect TCR-induced calcium flux (Cornish et al. 2003a) or the proximal signaling events (our unpublished data). On the other hand, SOCS1-deficient $CD8^+$ T cells showed increased STAT5 phosphorylation, expression of the anti-apoptotic protein Bcl-xL and cell proliferation in response to IL-15, which promotes homeostatic expansion of memory $CD8^+$ T cells, or the autocrine T cell growth factor IL-2 (Cornish et al. 2003a; Ilangumaran et al. 2003a). IL-7, which is critical for homeostatic expansion of naïve T cells, induced strong STAT5 phosphorylation in SOCS1-deficient T cells but not cell proliferation (Cornish et al. 2003a; Ilangumaran et al. 2003a). Following adoptive transfer to *Rag1*$^{-/-}$ hosts, SOCS1-deficient $CD8^+$ T cells underwent robust homeostatic expansion that was markedly diminished in the absence of IL-7 or IL-15 in the recipient mice (Cornish et al. 2003b; Davey et al. 2005; Ilangumaran et al. 2003a; Ramanathan et al. 2006; Rodriguez et al. 2013). However, only the loss of IL-15 prevented $CD8^+$ T cell accumulation in SOCS1-deficient mice indicating that SOCS1 is an important regulator of IL-15 signaling in these cells (Ramanathan et al. 2006).

IL-15 deficiency in SOCS1-deficient mice also reversed the high CD44 expression on $CD8^+$ T cells without affecting the $CD122^{hi}$ $Ly6C^{hi}$ phenotype, suggesting that SOCS1 controls not only IL-15 but also other factors that contribute to the activation of $CD8^+$ T cells (Ramanathan et al. 2006). The $CD8^+$ T cell compartment in SOCS1-deficient mice still harbors a significant proportion of $CD44^{lo}$ $CD62L^{hi}$ $CD122^{lo}$ $Ly6c^{lo}$ naïve cells (Ilangumaran et al. 2003a), indicating that deregulated IL-15 signaling alone is not sufficient for the accumulation of memory phenotype $CD8^+$ T cells in SOCS1 knockout mice. Analysis of the phenotype of SOCS1-deficient $CD8^+$ T cells expressing the male antigen-specific transgenic TCR H-Y, which is one of the least reactive transgenic TCRs toward environmental antigens, in non-lymphopenic and lymphatic setting shed light on antigen non-specific activation of SOCS1-deficient T cells (Ramanathan et al. 2006). This study revealed that acquisition of the memory phenotype by SOCS1-deficient $CD8^+$ T lymphocytes did not require stimulation by cognate antigen, but required the presence of other activated $CD8^+$ T cells. As $CD8^+$ T cells from *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice that proliferate in response to IL-15 in vitro also produce abundant TNFα, it is possible that the effector molecules of activated SOCS1-deficient $CD8^+$ T cells may contribute, directly and indirectly (through activation of other cell types), to stimulate other naïve $CD8^+$ T cells. In support of this possibility, *Socs1*$^{fl/-}$LysM-Cre mice that seem to lack SOCS1 in myeloid cells

as well as in T cells developed lethal inflammatory disease after four months of age (Chong et al. 2005). $CD8^+$ T cells from *Socs1*$^{fl/-}$LysM-Cre, but not *Socs1*$^{fl/-}$Lck-Cre, mice were also reported to display $CD44^{hi}$ $CD69^{hi}$ $CD25^{hi}$ $CD62L^{lo}$ activated cell phenotype, accompanied by elevated serum levels of IL-12, suggesting that macrophage and dendritic cell-derived IL-12 could contribute to antigen non-specific activation of SOCS1-deficient T cells. However, these findings still do not adequately explain how the initial activation of naïve $CD8^+$ T cells occurs in SOCS1-deficient mice.

Further investigations on SOCS1-deficient $CD8^+$ T cells led to the finding that they can be activated in an antigen non-specific manner by combinations of cytokines, particularly to IL-15 and IL-21, and that the availability of IL-21 markedly diminished the requirement of IL-15 needed for activation (Gagnon et al. 2007). Strikingly, wildtype $CD8^+$ T cells also proliferated in response to synergistic stimulation by IL-15 and IL-21, albeit to a significantly lower extent compared to SOCS1-deficient cells (Gagnon et al. 2007; Zeng et al. 2005). In fact, naïve $CD44^{lo}$ $CD8^+$ T cells expressing polyclonal TCR or transgenic TCR such as H-Y or P14 (specific to the glycoprotein antigen of lymphocytic choriomeningitis virus) showed robust antigen-independent proliferation in the presence of IL-7 and IL-21, and to a lesser extent to IL-15 and IL-21 (Gagnon et al. 2007). SOCS1 deficiency did not augment the naïve $CD8^+$ T cell response to IL-7 and IL-21, but increased responsiveness to the IL-15 and IL-21 combination. Follow-up studies on wild type $CD8^+$ T cells revealed that IL-6, which activates STAT3 similarly to IL-21, could substitute for IL-21 in inducing antigen-independent proliferation of naïve $CD8^+$ T cells (Gagnon et al. 2008). SOCS1 deficiency prolonged the IL-21-induced STAT3 activation in $CD8^+$ T cells. Concomitant stimulation by IL-6 or IL-21 augmented phosphorylation and DNA-binding activity of STAT5 induced by IL-7 or IL-15, although mechanisms underlying this cytokine synergy in activating naïve $CD8^+$ T cells remain to be fully elucidated (Gagnon et al. 2008). These cytokine-stimulated $CD8^+$ T cells show increased TCR responsiveness to limiting concentrations of antigenic peptides and, more importantly, toward altered peptide ligands with low reactivity toward the TCR, in terms of cell proliferation, IFNγ secretion, granzyme B expression, and cytolytic functions (Gagnon et al. 2008; Ramanathan et al. 2011; Rodriguez et al. 2013). Given that IL-6 and IL-15 are expressed by antigen presenting cells and several other cell types following innate immune stimulation, it is likely that SOCS1 may serve to restrain antigen non-specific activation of $CD8^+$ T cells by cytokines and, in that process, also induce their ability to respond to weakly agonistic TCR ligands such as those derived from autoantigens (Fig. 2). In fact, SOCS1-deficient $CD8^+$ T cells fail to undergo homeostatic expansion in TAP1-deficient hosts that express very low levels of MHC-I molecules, indicating that, besides cytokine stimulation, TCR engagement is needed to stimulate SOCS1-deficient $CD8^+$ T cells (Davey et al. 2005).

The checkpoint function of SOCS1 in modulating TCR reactivity (via controlling cytokine responses) may serve two complementary purposes. First, SOCS1 expression may shape the $CD8^+$ T cell response during infections by focusing the response toward dominant antigens through reducing reactivity toward weak

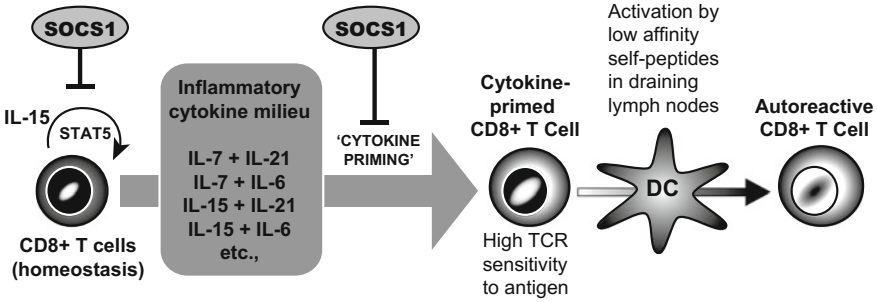

Fig. 2 Possible role of SOCS1 in preventing autoreactive $CD8^+$ T cell activation. SOCS1 regulates homeostasis of $CD8^+$ T cells by regulating STAT5 activation by IL-15. Antigen non-specific activation of naïve $CD8^+$ T cells by inflammatory cytokines leads to increase in antigen sensitivity. By regulating this 'cytokine priming' of $CD8^+$ T lymphocytes, SOCS1 may limit activation of potentially autoreactive cells

antigens. Second, SOCS1 may serve to prevent accidental stimulation of potentially autoreactive cells, whose TCR sensitivity toward autoantigens might lie close to the threshold needed for negative selection in the thymus. While the first possibility has not been yet investigated in detail, there are several indirect and direct evidence that support the second function. Indeed, SOCS1-null mice that express different MHC-I or MHC-II restricted transgenic TCRs survive considerably longer than those bearing a polyclonal TCR: OT-I (specific to ovalbumin, 6 weeks), P14 (4 weeks), Pmel-1 (specific to the melanocyte antigen gp100, 6 weeks) and H-Y (females 8 weeks) and OT-II (5 weeks) (Cornish et al. 2003b; Ramanathan et al. 2006; Rodriguez et al. 2013). OT-I TCR transgenic mice survive a little longer in RAG1 deficient background and die within 10 weeks even under germ-free conditions (Cornish et al. 2003b; Ramanathan et al. 2006; Rodriguez et al. 2013). The in vivo activation of SOCS1-deficient $CD8^+$ T cells was studied following adoptive transfer of SOCS1-deficient TCR transgenic $CD8^+$ T cells into recipients expressing the cognate antigen (Davey et al. 2005; Ramanathan et al. 2010; Rodriguez et al. 2013). This approach was necessary because the transgenic T cells are either deleted by thymic negative selection in mice bearing the cognate antigen (OT-I cells (Davey et al. 2005)), or systemic inflammation caused by SOCS1 deficiency precluded their analysis within the antigen-bearing host (P14 and Pmel-1 cells (Ramanathan et al. 2010; Rodriguez et al. 2013)). These studies showed that SOCS1-deficient TCR transgenic $CD8^+$ T cells displayed potent antigen-specific effector functions, recognized the tissues expressing the cognate antigen more efficiently and caused severe autoimmune manifestation (autoimmune type 1 diabetes by OT-I and P14 cells, and cutaneous inflammation by Pmel-1 cells), indicating that SOCS1 is necessary to control the pathogenicity of potentially autoreactive CD8 T cells (Davey et al. 2005; Ramanathan et al. 2010; Rodriguez et al. 2013).

Intriguingly, SOCS1-deficient $CD8^+$ T cells expressing the transgenic TCR such as P14 and Pmel-1 cells, and $CD8^{lo}$ H-Y transgenic TCR^+ cells (that arise in male H-Y mice in Rag-sufficient background) proliferate poorly to stimulation by cognate antigens compared to SOCS1 sufficient cells but develop potent effector functions (Ramanathan et al. 2006, 2010; Rodriguez et al. 2013). This propensity for effector differentiation of SOCS1-deficient cells is not due to the loss of their proliferation potential per se, as they undergo massive cell division following cytokine stimulation. The molecular mechanisms underlying the decreased antigen-induced proliferation of SOCS1-deficient $CD8^+$ T cells remains to be elucidated.

4 Role of SOCS1 in T Cell Development

The critical role of SOCS1 in regulating the $CD8^+$ T cell compartment already manifests during T cell development and maturation in the thymus, whereas *Socs1*$^{-/-}$ mice show severe thymic atrophy and reduction in thymic cell numbers, these abnormalities are not observed in *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice (Alexander et al. 1999; Naka et al. 1998). As IFNγ is known to cause thymic atrophy, the macroscopic abnormalities observed in SOCS1-deficient thymus are caused mainly by uncontrolled IFNγ signaling (Alexander et al. 1999; Marine et al. 1999). SOCS1 is highly expressed in thymocytes from wild type as well as IL-7R, JAK3, STAT5, or RAG2 deficient mice, indicating that *Socs1* expression occurs early during T cell development, even prior to the expression of rearranged TCRβ chain and independently of the IL-7-mediated signals (Marine et al. 1999). Hence, SOCS1 expression in thymocytes is considered to be constitutive, although stem cell factor (Kit ligand), which is critical for T lymphocyte development and induces the *Socs1* gene in bone marrow-derived mast cells (De Sepulveda et al. 1999; Waskow et al. 2002), could contribute to *Socs1* gene expression in T cell progenitors. Over expression of SOCS1 prevented fetal liver-derived hematopoietic progenitor cells from progressing beyond the stage-I $CD4^-CD8^-$ double negative cells (DN1; $CD44^+$ $CD25^-$) in fetal thymic organ cultures (FTOC) (Trop et al. 2001). As DN1 thymocytes express c-KIT and undergo IL-7-mediated expansion, this developmental arrest could result from inhibition of both Kit and IL-7 receptor signaling by SOCS1 (De Sepulveda et al. 1999; Trop et al. 2001). DN cells rearrange the genes coding for TCRβ, which complexes with pre-TCRα to form the pre-TCR complex that delivers the signal for progression through the DN4 ($CD44^-$ $CD25^-$) stage and gives rise to $CD4^+CD8^+$ double positive (DP) cells. Intriguingly, engagement of the pre-TCR in DN3 ($CD44^-$ $CD25^+$) thymocytes profoundly diminishes *Socs1* gene expression (Trop et al. 2001), although the underlying mechanism remains unknown. Forced expression of SOCS1 in DN3 cells did not affect differentiation toward DP cells but markedly reduced their number in FTOC (Trop et al. 2001). Consistent with the regulatory role for SOCS1 in early T cell development, SOCS1 transgenic mice show a developmental block from DN2 to DN3 stage and a marked reduction in cellularity (Fujimoto et al. 2000).

Hence, it has been proposed that (i) SOCS1 expression in DN cells serves to limit their expansion by IL-7 and Kit ligand and (ii) downmodulation of SOCS1 by pre-TCR signaling would facilitate the selective expansion of DN3 cells that have completed the β selection process.

Analyses of T cell developmental stages in *Socs1*$^{-/-}$ and *Socs1*$^{fl/-}$Lck-Cre mice did not reveal any obvious abnormality within the DN developmental stages (Chong et al. 2003; Ilangumaran et al. 2003a), indicating that either SOCS1 is dispensable for regulating the early DN developmental stages, or that the SOCS1-deficient cells proceed rapidly through these stages in vivo without allowing accumulation of the expanded DN cells. In agreement with the latter possibility, the SOCS1-deficient thymi generate a greater number of $CD8^+CD4^-$ single positive (SP) thymocytes. Intrathymic transfer of SOCS1-deficient DN thymocytes into the thymus of SOCS1 sufficient *Rag1*$^{-/-}$ mice or in FTOC cultures results in an increased generation of $CD8^+$ SP T cells, indicating that SOCS1 exerts a cell-intrinsic regulatory role in developing thymocytes (Cornish et al. 2003b; Ilangumaran et al. 2003b). Several lines of evidence indicate a critical regulatory role for SOCS1 at the DP and $CD8^+$ SP stages. Whereas DN and $CD4^+$ SP cells express the *Socs1* gene only after exposure to γ_c cytokines, DP and $CD8^+$ SP cells show constitutive *Socs1* gene expression (Ilangumaran et al. 2003b). Based on the expression of a Cre-induced human CD4 as a reporter downstream of the *Socs1* promoter, Chong et al. reported high SOCS1 expression in DP cells compared to all other thymocyte subsets (Chong et al. 2003). SOCS1-deficient DP cells displayed high sensitivity to IL-7 in terms of STAT5 phosphorylation, and purified DP cells cultured in the presence of IL-7 gave rise to abundant $CD8^+$ SP cells even in the absence of TCR stimulation, implicating IL-7 in DP to SP differentiation (Chong et al. 2003). Singer and colleagues observed that constitutive SOCS1 expression in pre-selection DP cells (prior to positive selection), which express IL-7Rα, IL-4Rα and γ_c, prevents them from responding to IL-7 or IL-4, thus contributing to the smaller size of DP thymocytes (Yu et al. 2006). This study also showed that TCRαβ signaling, which delivers the positive selection signal, downmodulates *Socs1* expression in DP thymocytes via unknown mechanisms and restores their responsiveness to IL-7 and IL-4, which induce the pro-survival gene *Bcl2*. It has been proposed that SOCS1 may serve to actively suppress cytokine signaling to prevent the rescue of $CD4^+CD8^+$ double positive (DP) thymocytes that are destined to die by neglect through the induction of pro-survival factors by cytokines (Yu et al. 2006). Increased IL-7 signaling in positively selected, SOCS1-downregulated DP cells lead to induction of the transcription factor Runx3, which promotes CD8 lineage specification (Park et al. 2010).

Whereas purified SOCS1-deficient DP cells fail to proliferate in response to IL-7, IL-2 or IL-15 in vitro, $CD8^+$ SP cells undergo robust proliferation following incubation with IL-15 or IL-2 but not IL-7, despite showing prolonged IL-7-induced STAT5 phosphorylation (Ilangumaran et al. 2003b). In agreement with the role of SOCS1 in regulating cytokine-mediated $CD8^+$ SP cell expansion, only the $CD8^+$ SP subset shows increased in vivo proliferation in SOCS1-deficient thymus, which displays an enlarged medulla wherein the SP cells undergo

maturation before emigration to the periphery (Chong et al. 2003; Ilangumaran et al. 2010). Analysis of SOCS1-deficient thymus also lacking IL-7, IL-15 or both implicated these two cytokines in increasing the number of $CD8^+$ SP cells and skewing the CD4:CD8 ratio (Ramanathan et al. 2006). Collectively these studies suggest that SOCS1 regulates cytokine-mediated survival and/or differentiation of the DP cell pool and expansion of $CD8^+$ SP cells (Chong et al. 2003; Ilangumaran et al. 2003b).

Intriguingly, restoration of SOCS1 expression specifically in T cells of mice in which the *Socs1* gene is ablated in all cells ($Socs1^{-/-}$Tg) prevents lethality, but thymocytes from these mice show accelerated maturation of DP toward $CD4^+$ and $CD8^+$ SP cells (Hanada et al. 2003). Peripheral T cells in these mice also display $CD44^{hi}$ activated phenotype. These observations suggest that the T cell developmental abnormalities observed in SOCS1-deficient mice do not arise exclusively from T cell-intrinsic defects. Thymus tissues from these mice contained increased frequency of $CD11c^+CD11b^+$ dendritic cells (DC) that displayed MHC-II. As DCs can produce the T cell stimulatory cytokine IL-15 in response to myriad stimuli (Mattei et al. 2001), it is possible that SOCS1 may regulate T cell development also in a T cell-extrinsic manner by controlling IL-15 availability within the thymic microenvironment. This prediction remains to be tested.

Even though most studies on SOCS1 functions in T cells focused on $CD8^+$ T cells, SOCS1 might also regulate the $CD4^+$ T cell compartment, which is more apparent in the thymus than in the periphery. Thymic cellularity of $Socs1^{-/-}Ifng^{-/-}$ mice is comparable to that of $Ifng^{-/-}$ controls, yet the former harbored nearly twice the number of $CD4^+$ SP cells and six times more $CD8^+$ SP cells (Ramanathan et al. 2006). Analysis of recent thymic emigrants revealed that increased numbers of $CD4^+$ T cells are exported from SOCS1-deficient thymi compared to $CD8^+$ T cells (Ilangumaran et al. 2010). As $CD4^+$ SP cells in SOCS1-deficient thymi do not undergo increased cycling, their increased generation likely results from accelerated maturation from DP cells (Ilangumaran et al. 2010). In fact, IL-21 (another γ_c cytokine) has been shown to expand the DP cell pool undergoing positive selection in an in vitro T cell development model, and increase the number of DP, $CD4^+$ SP, and $CD8^+$ SP cells in vivo following systemic administration (Rafei et al. 2013). IL-21 has also been reported to promote T cell survival (Ostiguy et al. 2007). As SOCS1 attenuates IL-21-induced STAT5 activation in $CD8^+$ T cells (Gagnon et al. 2007), it is not unlikely that SOCS1 may regulate IL-21-mediated DP cell expansion, and hence the loss of SOCS1 would increase $CD4^+$ SP cell generation and export. Notwithstanding the increased generation and export of $CD4^+$ SP cells in SOCS1-deficient mice, pronounced cytokine-driven expansion of $CD8^+$ T cells outnumber $CD4^+$ T cells in the periphery.

Investigations into the role of SOCS1 in thymic selection have reported varying findings. Using the staphylococcal enterotoxin B (SEB) model of negative selection that specifically deletes $TCRV\beta8^+$ thymocytes in FTOC, Chong et al. reported that SOCS1 deficiency did not affect deletion of either $CD4^+$ or $CD8^+$ T cells bearing TCRVβ8 (Chong et al. 2003). Similarly, negative selection of $CD8^+$ SP cells expressing the male antigen-specific H-Y transgenic TCR in male mice was not

affected by SOCS1 deficiency (Ramanathan et al. 2010). On the other hand, SOCS1 was reported to regulate both positive and negative selection of $CD4^+$ T cells expressing the MHC-II -restricted transgenic TCR AND, which is specific to the pigeon cytochrome C (PCC) and the $I\text{-}E^k$ molecule (Catlett and Hedrick 2005). Loss of SOCS1 in *Rag1*$^{-/-}$TcrAND mice resulted in the generation of CD8 SP cells bearing the $V\alpha11^+$ transgenic TCR, accompanied by a reduction in the number of CD4 SP cells. SOCS1 deficiency enabled the generation of these aberrant $CD8^+$ SP cells even in the absence of MHC-I molecules, but not in the absence of the non-selecting $H2^d$, suggesting that these cells were selected by MHC-II but diverted toward the inappropriate lineage in the absence of SOCS1 (Fig. 3). Upon adoptive transfer to mice bearing $H2^{b/s}$, in which TcrAND T cells are positively selected by

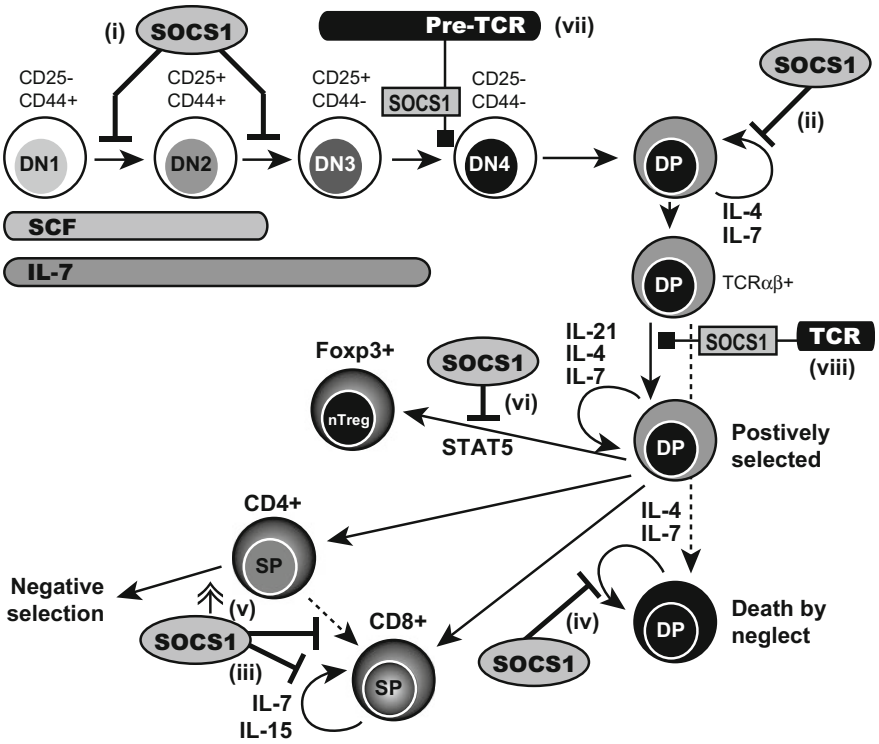

Fig. 3 SOCS1-dependent regulation of thymopoiesis. SOCS1 regulates multiple checkpoints of T cell development. SOCS1 controls cytokine-driven expansion of (i) double negative (DN) cells, (ii) double positive (DP) cells and (iii) $CD8^+$ single positive (SP) cells. SOCS1 is also implicated in preventing the cytokine-mediated rescue of DP cells that had failed positive selection (iv), and in promoting negative selection of $CD4^+$ SP cells by preventing their aberrant skewing toward $CD8^+$ SP cells (v). SOCS1 also controls generation of natural T regulatory cells (vi). Intriguingly, signaling via pre-TCR at the DN3 stage and TCRαβ at the DP stage downmodulate SOCS1 expression (vii, viii), presumably to allow selective expansion of signaled cells at these critical developmental stages

$H2^b$ and then negatively selected by $H\text{-}2^s$, SOCS1-deficient TcrAND $CD4^+$ and $CD8^+$ SP cells failed to undergo negative selection, suggesting that SOCS1 may serve to control generation of potentially autoreactive T cells. The defective positive and negative selection of TcrAND T cells caused by the lack of SOCS1 was reversed by IFNγ deficiency, demonstrating that SOCS1 shields developing thymocytes from the deleterious effects of systemic inflammation (Catlett and Hedrick 2005).

Collectively, SOCS1 impacts on four T cell developmental checkpoints (Fig. 3): (i) at the DN1-DN2 stage, to control signals delivered by SCF and IL-7; (ii) at the DN3 stage, to block the expansion of thymocytes that have not succeeded the β selection process; (iii) in DP thymocytes, to prevent cells that had failed the positive selection from undergoing cytokine-driven survival and expansion; (iv) in post-selection DP thymocytes, to ensure negative selection and prevent inappropriate developmental skewing toward the CD8 SP lineage. Even though SOCS1 deficiency would deregulate all these developmental stages, only the final outcome —accumulation $CD8^+$ SP cells—is discernible in SOCS1-deficient mice, presumably due to dynamic transition of the immature developmental stages.

5 Regulation of Treg Plasticity and Function by SOCS1

Despite thymic negative selection, the mature T cell pool contains potentially autoreactive T cells that can get activated in the periphery and become pathogenic. These cells are regulated by peripheral tolerance mechanisms, in which regulatory T cells (Treg) play a key role. Tregs inhibit activated T cells via direct contact and through secreted cytokines such as TGFβ and IL-10. The development of a multi-organ inflammatory disease in SOCS1-deficient mice, characterized by abundant mononuclear cell infiltration, could result not only from aberrant generation of potentially autoreactive T cells in the thymus and their activation by cytokines in the periphery, but also from the loss of SOCS1-dependent control of Treg stability and functions (Takahashi and Yoshimura 2014) (Fig. 4).

Most Tregs develop in the thymus from $CD4^+$ SP cells that display high avidity TCR interaction with autoantigens, and are called natural or thymus-derived Tregs (nTreg or tTreg) (Hsieh et al. 2012; Ohkura et al. 2013). Under certain conditions, naïve $CD4^+$ T cells in the periphery can also give rise to Tregs, which are designated as induced or peripheral Tregs (iTreg or pTreg) (Schmitt and Williams 2013). Both nTregs and iTregs are required to maintain tolerance and immune homeostasis. The Treg-specific transcription factor Foxp3 is an important regulator of Treg development and functions. However, Foxp3 expression is not static even in terminally differentiated Tregs. Following adoptive transfer to lymphopenic hosts or under inflammatory conditions, Tregs may lose Foxp3 expression and regulatory functions, become the so-called “exFoxp3” cells or “lapsed Tregs”, acquire Th1 or Th17 effector-memory phenotype and exacerbate an inflammatory response (Sakaguchi et al. 2013).

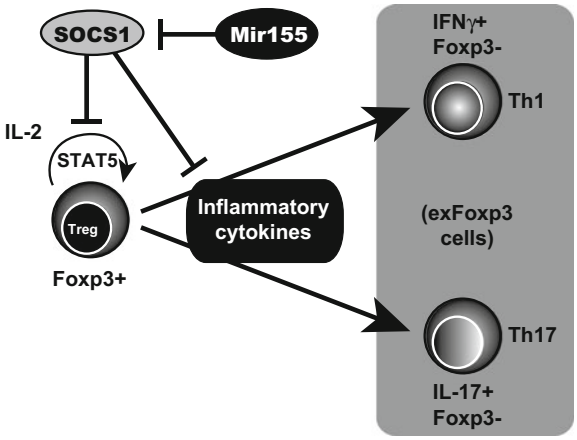

Fig. 4 Regulation of T regulatory cells by SOCS1. SOCS1 controls homeostasis of nTregs by regulating IL-2-mediated STAT5 signaling. SOCS1 also plays a crucial role in regulating Treg plasticity by controlling their responsiveness to inflammatory cytokines that leads to loss of Foxp3 expression (exFoxp3 cells) and differentiation toward Th1 and Th17 cells. SOCS1 also controls the Th1 differentiation pathway by inhibiting IFNγ signaling. By regulating SOCS1 expression, miR-155 exerts control over Treg homeostasis

The phenotypic and functional changes associated with such "Treg plasticity" arise from modulation of the Foxp3 promoter activity in uncommitted Foxp3$^+$ cells, which constitute a small proportion of Foxp3$^+$ cells, and their selective expansion (Hori 2014; Komatsu et al. 2009; Takahashi and Yoshimura 2014). In addition to the TCR signal-responsive Foxp3 promoter, three highly conserved non-coding DNA sequences (CNS 1-3) regulate Foxp3 expression and Treg plasticity. The TGFβ-responsive CNS1 has Smad2/3 binding sites for induced by TGFβ, while CNS2 binds TCR-induced CREB and IL-2-induced STAT5, and CNS3 has binding sites for c-Rel activated by TCR/CD28 co-stimulation. The CNS2 also harbors CpG islands that are hypomethylated in committed Tregs, which is further enhanced by IL-2 signaling (Chen et al. 2011). These Treg-specific demethylated regions (TSDR) become strongly methylated in exFoxp3 cells (reviewed in Takahashi and Yoshimura 2014). The stability of nTreg is regulated by stable expression of Foxp3, and sustained by Smad2/3, STAT5, and NF-κB signaling pathways. Takahashi and colleagues have shown that IFNγ-induced STAT1 can destabilize Foxp3 expression, leading to conversion of nTregs into Th1 cells, and that SOCS1 plays an essential role in preserving Treg functions by regulating the IFNγ signaling pathway (Takahashi et al. 2011).

Investigations into the Foxp3-regulated genes in Tregs led Rudensky and colleagues to identify miR155 and its target SOCS1 as key regulators of Treg homeostasis (Lu et al. 2017a). Loss of miR155 resulted in fewer Treg cells in the thymus and affected their homeostasis in the periphery. Mechanistically, loss of miR155 causes marked increase in SOCS1 expression in Tregs, leading to

decreased sensitivity to their principal growth factor IL-2 and thus reducing their homeostatic fit. In agreement, SOCS1 transgenic mice harbor fewer nTregs in the thymus, whereas T cell-specific SOCS1-deficient (*Socs1*$^{fl/fl}$ Lck-Cre) mice harbor significantly more of these cells in the thymus and spleen, and this increase occurs independently of IFNγ (Lu et al. 2017a; Zhan et al. 2009). Treg-specific SOCS1 knockout (*Socs1*$^{fl/fl}$ Foxp3-Cre) mice also harbors increased numbers of Foxp3$^+$ CD4 T cells in thymus and spleen, indicating that SOCS1 exerts a cell-intrinsic regulation of Treg development (Lu et al. 2010).

Despite increased generation of nTregs, SOCS1-deficient mice develop IFNγ-dependent Th1 type immune pathology (Alexander et al. 1999; Lu et al. 2010; Marine et al. 1999; Takahashi et al. 2011), suggesting defective functioning of SOCS1-deficient Tregs in the periphery. *Socs1*$^{+/-}$ mice also develop severe dextran sulfate sodium (DSS)-induced colitis compared to control mice, with fewer Foxp3$^+$ and more numerous IFNγ$^+$ CD4$^+$ T cells in the intestinal lamina propria (Horino et al. 2008). In addition, SOCS1-deficient CD4$^+$ T cells display higher sensitivity to IFNγ-mediated blockade of Treg differentiation induced by TCR/CD28 stimulation in the presence of TGFβ (Horino et al. 2008). On the other hand, T cell-specific SOCS1 knockout mice showed resistance to experimental autoimmune encephalomyelitis (EAE), a Th17-mediated disease, due to the requirement of SOCS1 to preserve Th17 cell differentiation by preventing Th1 skewing (Tanaka et al. 2008). All these observations suggested a complex regulation of Th cell differentiation and Treg functions by SOCS1 in the periphery. Yoshimura and colleagues elucidated the underlying mechanisms by addressing the role of SOCS1 in regulating nTreg plasticity (Takahashi et al. 2011). In the classical in vivo functional assay, Tregs from *Socs1*$^{fl/fl}$ Lck-Cre mice failed to suppress the induction of colitis by wildtype CD4$^+$ T cells in *Rag1*$^{-/-}$ mice, accompanied by faster loss of Foxp3 and other markers of suppressive activity (CD25 and CTLA4) compared to wildtype Tregs (Takahashi et al. 2011). In this setting, both the Foxp3-maintaining and the Foxp3-losing fractions of SOCS1-deficient Tregs produced higher amounts of IFNγ, despite maintaining IL-10 production. SOCS1-deficient Tregs showed rapid methylation of the CNS2 region of the Foxp3 locus in vivo and in vitro, which was prevented by ablation of the *Ifng* gene, indicating that SOCS1 is essential to thwart conversion of Tregs to IFNγ producing exFoxp3 cells. However, *Socs1*$^{-/-}$*Ifng*$^{-/-}$ Tregs, which did not become exFoxp3 cells in lymphopenic mice, also failed to inhibit colitis induction. The inability of *Socs1*$^{-/-}$*Ifng*$^{-/-}$ Tregs to maintain their regulatory function was explained by their propensity of differentiating toward pathogenic Th17 cells in the absence of IFNγ. In agreement with the role of SOCS1 modulating both Treg and Th17 differentiation, transfection of naïve CD4$^+$ T cells with pre-miR155 promoted, whereas anti-miR155 inhibited, the development of Tregs and Th17 cells under the respective polarizing conditions, accompanied by modulation of SOCS1 and its targets STAT5 and STAT3 (Yao et al. 2012). Increased activation of STAT1 and STAT3 in SOCS1-deficient Tregs, the former by IFNγ and the latter presumably by inflammatory cytokines, is believed to underlie their defective immune regulatory function (Takahashi and Yoshimura 2014). The molecular mechanisms by which

STAT1 and STAT3 destabilize Foxp3 expression and disrupt Treg stability are unclear. Although cytokine-induced STAT molecules are the principal inducers of *Socs1,* they synergize with TCR-stimulated NF-κB to upregulate SOCS1 expression in Tregs, as the deficiency of Ubc13, a ubiquitin conjugating enzyme involved in activating IKK upstream of NF-κB, resulted in a similar loss of Treg function as caused by SOCS1 deficiency (Chang et al. 2012). Hence, SOCS1 plays a crucial role in protecting Tregs from converting to effector T cells under the harmful influence of inflammatory cytokines (Fig. 4). In addition to becoming pathogenic Th1 and Th17 cells themselves under inflammatory conditions, exFoxp3 cells can provide help to activate naïve CD8 T cells (Bailey-Bucktrout et al. 2013; Komatsu et al. 2014; Sharma et al. 2010), raising such a possibility in the activation of potentially autoreactive $CD8^+$ T cells in SOCS1-deficient mice.

6 Influence of SOCS1 on Antigen Presenting Cell Functions

Early investigations into the lethal phenotype of SOCS1-deficient mice revealed that SOCS1 is an important regulator of macrophage activation by innate immune stimuli such as LPS and CpG DNA, and by IFNγ. In response to these stimuli, SOCS1-deficient macrophages produce abundant quantities of inflammatory cytokines such as TNFα and IL-6, as well as IL-12, a key cytokine in promoting the Th1 immune response (Kinjyo et al. 2002; Nakagawa et al. 2002). SOCS1-deficient macrophages show increased ability to control *M. tuberculosis* via increased IFNγ production, which in turn relies on strong MyD88-dependent TLR2 activation and enhanced IL-12 production (Carow et al. 2011). The heightened activation of SOCS1-deficient macrophages by LPS via the toll like receptor 4 (TLR4), results from increased activation of NF-κB and STAT1 (Kinjyo et al. 2002; Nakagawa et al. 2002). SOCS1 blocks LPS-induced macrophage activation by promoting ubiquitination and proteasomal degradation of the key signaling adaptor MAL/TIRAP in the My88-dependent pathway, and possibly by interfering with the key TLR4 signaling adaptor TRAF6 further downstream, thereby blocking NF-κB activation (Kinjyo et al. 2002; Mansell et al. 2006). SOCS1 may also directly inhibit NF-κB signaling by promoting ubiquitination and degradation of the p65RelA component as shown in other cell types (Maine et al. 2007; Ryo et al. 2003). The same mechanisms likely underlie SOCS1-dependent regulation LPS signaling in dendritic cells (DC), which also produce copious amount of IL-12 and IFNγ in the absence of SOCS1 (see below).

SOCS1 exerts control over differentiation of DCs and their functions in stimulating T cell responses. Splenic DCs from SOCS1-deficient mice show an increased frequency of $CD8\alpha^+$ conventional DCs, which are critical for cross-priming $CD8^+$ T cells in vivo (Hanada et al. 2005; Heath and Carbone 2009; Tsukada et al. 2005). This increment could arise from increased generation of these cells due to enhanced

Flt3 and GM-CSF signaling caused by SOCS1 deficiency, as FLT3 is required for the development of CD8α$^+$ DCs and GM-CSF skews DC development away from plasmacytoid DCs (Wu and Liu 2007). SOCS1 inhibits Flt3-induced mitogenic responses and blocks GM-CSF signaling by promoting ubiquitination and proteasomal degradation of the β_c chain of the GM-CSF receptor (Bunda et al. 2013; De Sepulveda et al. 1999). Expression of the *Socs1* gene increases during culture with GM-CSF and IL-4, and is further augmented by LPS (Jackson et al. 2004; Shen et al. 2004). On the other hand, LPS-induced SOCS1 has been shown to block GM-CSF-mediated DC differentiation from human CD14$^+$ monocytes and murine bone marrow precursors (Bartz et al. 2006). In addition to modulating DC generation, SOCS1 may control IL-15-dependent maturation and survival of DCs (Dubois et al. 2005; Hanada et al. 2005). Intriguingly, CD8α$^+$ DCs enriched from spleen show much lower levels of SOCS1 expression than CD4$^+$ or CD4$^-$CD8$^-$ DC subsets, which might underlie the intrinsically stronger ability of CD8α+ DCs to stimulate Th1 responses, and its further augmentation by SOCS1 deficiency (Hanada et al. 2005).

In response to TLR stimulation by LPS or CpG DNA, SOCS1-deficient DCs produce abundant quantities of IL-12 as well as IFNγ, which could contribute to the Th1-type immunopathology observed in SOCS1-deficient mice (Hanada et al. 2005; Tsukada et al. 2005). In addition to the Th1 cytokines, SOCS1-deficient DCs produce abundant quantities of the TNF family growth factors for B cells BAFF/BLyS and APRIL, which likely contribute to the elevated levels of autoantibodies in SOCS1-deficient mice (Hanada et al. 2003). Even though SOCS1-deficient DCs do not efficiently support CD4$^+$ T cell activation in vitro due to increased induction of indoleamine-2,3-dioxygenase (IDO) by autocrine IFNγ, they may efficiently promote T activation in vivo wherein the use of IFNγ by other cells would diminish its availability to T cells (Hanada et al. 2005; Tsukada et al. 2005). This notion is supported by strong proliferation of allogeneic T cells cultured with bone marrow-derived DCs (BMDC) from *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice, and the heightened ability of SOCS1-deficient and *Socs1*-silenced DCs to stimulate IFNγ-producing Th1 cells and CD8$^+$ T cells in vivo (Evel-Kabler et al. 2006; Hanada et al. 2003, 2005; Shen et al. 2004). In mice bearing a polyclonal TCR repertoire, immunization with *Socs1*-silenced or SOCS1-deficient BMDCs that were pulsed with antigenic peptides led to efficient activation antigen-specific CD8$^+$ T cells, which displayed increased proliferation, IFNγ and IL-2 production and effector functions, and caused regression of tumors expressing the cognate antigen (Evel-Kabler et al. 2006; Hanada et al. 2005; Shen et al. 2004). The ability of *Socs1*-silenced DCs to activate antigen-specific CD8$^+$ T cells in vivo was further augmented by innate immune stimuli such as LPS that stimulate DC maturation (Evel-Kabler et al. 2006; Shen et al. 2004).

The ability of SOCS1 to control T cell activation at the level of DCs may operate via limiting and modulating their generation, maturation, antigen presentation, expression of costimulatory signals, and production of cytokines. Of these, increased production of IL-12 and IFNγ by SOCS1-deficient DCs has been well documented. The propensity for SOCS1-deficient DCs to produce copious amounts

of IFNγ is attributed to increased STAT1 signaling and expression of the Eomes transcription factor (Hanada et al. 2005). Using DCs derived from mice lacking the IL-12 subunit p35, or the IL-12Rβ, Chen and colleagues have shown that SOCS1 regulates the quantity and duration of LPS-induced IL-12 production in DCs by controlling autocrine IL-12 signaling (Evel-Kabler et al. 2006). Splenic DCs isolated from SOCS1-deficient mice express elevated levels of costimulatory molecules CD80, CD86 and CD40, and MHC class-II, although their expression levels were not altered in *Socs1*-silenced BMDCs at steady state (Evel-Kabler et al. 2006; Hanada et al. 2003). However, *Socs1*-silenced BMDCs exposed to *Candida albicans* show increased expression of costimulatory molecules and MHC-II (Shi et al. 2015). A recent study has shown that constitutive SOCS1 expression in DCs downmodulates MHC and costimulatory molecules, and that these DCs elicit T cell hyporesponsiveness and facilitate the survival of allogeneic pancreatic islets (Lu et al. 2017b). SOCS1 likely regulates the expression of MHC and costimulatory molecules by regulating both TLR and autocrine IFNγ signaling. Few studies have addressed the influence of SOCS1 on antigen processing and presentation. As SOCS1-deficient BMDCs show increased expression of several IFNγ-responsive genes at the basal level (Hanada et al. 2005), and IFNγ is a key modulator of MHC-I antigen processing pathway, it is quite likely that SOCS1 may regulate antigen processing and presentation functions of DCs.

7 SOCS1 as an Immune Checkpoint Molecule

SOCS1 is critical to control aberrant activation of potentially autoreactive T cells and preserve self-tolerance. This has been clearly demonstrated using SOCS1-deficient mice harboring TCR transgenic $CD8^+$ T cells (Davey et al. 2005; Ramanathan et al. 2010). In mice expressing the cognate transgenic antigen in pancreatic islets, SOCS1-deficient TCR transgenic CD8+ T cells cause autoimmune type-1 diabetes whereas SOCS1-sufficient cells do not. Similarly, SOCS1-deficient mice harboring Pmel-1 TCR transgenic $CD8^+$ T cells develop reactivity toward the endogenous melanocyte antigen gp100 expressed in normal keratinocytes of *Rag1*$^{-/-}$ mice, resulting in widespread cutaneous inflammatory lesions (Rodriguez et al. 2013). Hence, even though the activated phenotype of polyclonal $CD8^+$ T cells in SOCS1-deficient cells might arise from antigen non-specific activation by cytokines (Ilangumaran et al. 2003a; Metcalf et al. 2002; Starr et al. 1998), this activated T cell pool may contain potentially autoreactive T cells. In a mouse model of acute inflammatory arthritis induced by methylated bovine serum albumin (mBSA) BSA, SOCS1-deficient mice develop severe disease accompanied by not only increased myeloid cell infiltration but also an accumulation of activated, mBSA-specific $CD4^+$ T cells in the draining lymph nodes (Egan et al. 2003). The systemic lupus erythematosus (SLE)-like syndrome that develops in SOCS1-deficient mice does not occur in the absence of $CD4^+$ T cells, suggesting that the general inflammatory conditions caused by SOCS1 deficiency stimulate

autoreactive $CD4^+$ T cells that provide help to B lymphocytes (Fujimoto et al. 2004; Hanada et al. 2003). Similarly, decreased activation of Th1 and Th17 cells in mice lacking miR155 (and thus expressing more SOCS1), following immunization with the myelin oligodendrocyte glycoprotein (MOG) peptide MOG_{35-55}, could arise not only from impaired Th cell differentiation, but also from impaired antigen-specific T cell activation (Murugaiyan et al. 2011; O'Connell et al. 2010). Moreover, adoptively transferred wild type $CD4^+$ T cells undergo efficient activation in *Mir155*$^{-/-}$ mice and cause disease, suggesting that the cytokine products of SOCS1-deficient APC are sufficient to activate autoreactive $CD4^+$ T cells (O'Connell et al. 2010). Thus, SOCS1 deficiency either in T cells or loss of SOCS1-dependent control of APCs could promote activation of autoreactive T cells.

As discussed in the previous section, loss of SOCS1 expression in DCs or antitumor T cells would boost antitumor CTL response. However, tumor cells often lose SOCS1 expression and this may dampen antitumor immunity. In fact, SOCS1 has been extensively studied for its role as tumor suppressor in primary human cancers and mouse models. Following the seminal finding that the *SOCS1* gene promoter is repressed by CpG methylation in hepatocellular carcinoma specimens (Yoshikawa et al. 2001), numerous reported have shown similar findings in other cancers including acute and chronic myeloid leukemia, breast cancer, glioblastoma, ovarian cancer, etc., (reviewed in (Inagaki-Ohara et al. 2013; Sasi et al. 2014; Trengove and Ward, 2013)). SOCS1 expression is also downmodulated by microRNAs including miR155, miR19a, and miR30d in breast cancer, multiple myeloma and prostate cancer (Jiang et al. 2010; Kobayashi et al. 2012; Pichiorri et al. 2008). In melanoma and prostate cancer, SOCS1 protein expression correlates with disease severity and metastasis (Chevrier et al. 2017; Huang et al. 2008). Observations in SOCS1-deficient mice also support the tumor suppressor function of SOCS1: *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice that harbor activated T cells are more susceptible to radiation-induced T cell leukemia (Metcalf et al. 2002). On the other hand, mice lacking SOCS1 in all tissues except T cells spontaneously develop colorectal carcinoma, which is dependent on IFNγ signaling in the colonic epithelium (Hanada et al. 2006). Both *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice and hepatocyte-specific SOCS1-deficient mice show high susceptibility to chemically induced hepatocellular carcinoma (Yeganeh et al. 2016; Yoshida et al. 2004). While hematological malignancies are thwarted by SOCS1 mainly by putting brakes on JAK kinases, in epithelial cancers SOCS1 blocks oncogenic receptor tyrosine kinase signaling and diverse signaling molecules that are beyond the scope of this discussion. Clearly, increased tissue inflammation in SOCS1-deficient tissues contributes to neoplastic transformation and cancer growth (Inagaki-Ohara et al. 2013). However, it is possible that SOCS1 deficiency in cancer cells may also indirectly hinder antitumor immune response through "adaptive immune resistance", a process by which cancer cells inhibit tumor antigen-specific T cells by exploiting IFNγ produced by immune cells (Ribas 2015). Hence, even though loss of SOCS1-dependent control of IFNγ signaling would theoretically enhance antigen presentation in cancer cells, their increased IFNγ sensitivity can boost the expression of PD-L1 and IDO to hamper antitumor T

cell response (McGray et al. 2014; Spranger et al. 2013). Thus, loss of SOCS1 in cancer cells might exert an indirect checkpoint blockade on antitumor immunity. It will be worth investigating how SOCS1 deficiency in tumor cells impacts on antitumor immune responses.

8 Targeting SOCS1 in Autoimmunity and Cancer

Relieving the checkpoint functions of SOCS1 to boost antitumor immunity would require its repression in APCs or antitumor T cells, whereas its functional reconstitution in inflammatory cells would be needed to promote its checkpoint functions in case of auto-inflammatory diseases. As an intracellular signal regulator, SOCS1 differs from the cell surface receptor–ligand pairs of classical immune checkpoint regulators (Mahoney et al. 2015). SOCS1 also lacks enzymatic activity, and thus is not an ideal "druggable" target. Hence, approaches other than antibodies or small molecule modulators are needed to modulate SOCS1 expression in target cells.

Johnson and colleagues developed a cell-penetrating derivative of the KIR region of SOCS1 that functions as SOCS1 mimetic in inhibiting cytokine responses (Ahmed et al. 2015). This SOCS1 mimetic has been shown to inhibit EAE by suppressing MOG peptide-specific T cell activation and IL-17A production (Jager et al. 2011). The SOCS1 KIR peptide also partially rescues the functional defects in Ubc13 deficient Tregs, which fail to upregulate SOCS1 due to impaired NF-κB signaling, in vitro and in vivo (Chang et al. 2012). Similar SOCS1 mimetic peptides have been developed with the idea of using them in topical applications, especially for cutaneous inflammatory conditions such as psoriasis (Madonna et al. 2013). A cell-penetrating version of the full-length SOCS1 molecule (CP-SOCS1) has also been reported that inhibits pro-inflammatory cytokine production in cell lines (DiGiandomenico et al. 2009). Delivery through liposomes may be another option, as SOCS1 released from alveolar macrophages has been shown to inhibit IFNγ signaling in airway epithelial cells (Bourdonnay et al. 2015). These SOCS1 delivery approaches may be particularly useful in controlling inflammatory manifestations of unknown etiology and hinder activation of potentially autoreactive cells.

SOCS1 can be exploited to boost antitumor T cell responses at least in two ways (Fig. 5). As documented in animal models, silencing SOCS1 in DCs could be exploited to stimulate antitumor T cell response in the setting of DC-based cancer vaccines to improve their immunogenic potential (Anguille et al. 2014; Evel-Kabler et al. 2006; Palucka and Banchereau 2012; Shen et al. 2004). An alternative approach could use *SOCS1* gene silencing in T cells in the setting of adoptive cell therapy to select for poly-specific antitumor $CD8^+$ T cells from tumor-infiltrating lymphocytes (TIL) (Ji et al. 2015; Palmer and Restifo 2009; Rosenberg and Restifo 2015). As SOCS1-deficient $CD8^+$ T cells show increased cytokine responsiveness and cytokine pre-stimulation increases antigen sensitivity (Ramanathan et al. 2010, 2011), lowering SOCS1 expression in TILs would facilitate the cytokine-mediated expansion of $CD8^+$ T cells and also would allow selection of those bearing low

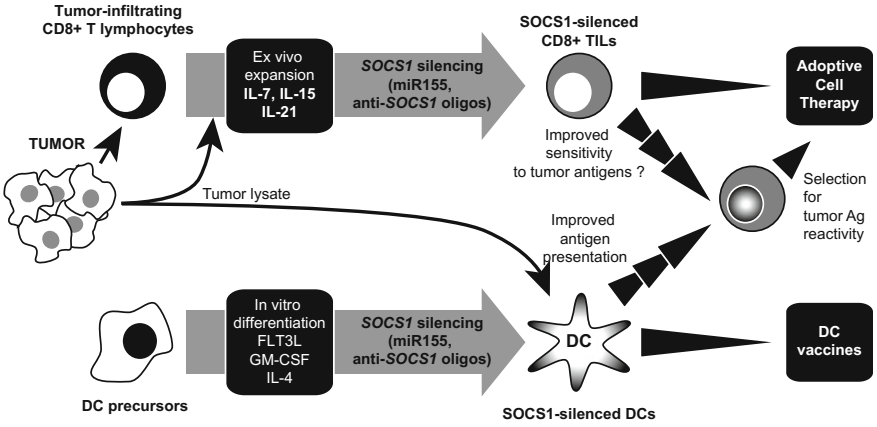

Fig. 5 Targeting SOCS1 for cancer immunotherapy. SOCS1 silencing in $CD8^+$ T cells that are expanded from tumor-infiltrating lymphocytes (TILs) could be useful to generate tumor antigen reactive CTLs for adoptive cell therapy. Alternatively, SOCS1 silencing in dendritic cells (DC) would improve their antigen presenting potential that can be exploited for antitumor DC vaccines or for ex vivo selection and expansion of antitumor CTLS for adoptive cell therapy

avidity TCR toward unknown tumor neoantigens. On the other hand, tackling the possible adaptive immune resistance in SOCS1-deficient tumors would require restoration of SOCS1 function. While the SOCS1 mimetic KIR peptide inhibits cancer cells in vitro, *SOCS1* gene therapy has shown promise in suppressing tumor growth (Flowers et al. 2005; Liu et al. 2013; Natatsuka et al. 2015; Souma et al. 2012). However, as the feasibility of delivering SOCS1 to all cells of primary cancer could be uncertain, combinatorial checkpoint therapy using anti-PD-1 or anti-PDL1 antibody and IDO inhibitors (Mahoney et al. 2015) would be a more practical approach to deal with the adaptive immune resistance in SOCS1-deficient tumors.

Acknowledgments SI and SR acknowledge funding support from Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant.

References

Acuto O, Di Bartolo V, Michel F (2008) Tailoring T-cell receptor signals by proximal negative feedback mechanisms. Nat Rev Immunol 8:699–712

Acuto O, Michel F (2003) CD28-mediated co-stimulation: a quantitative support for TCR signalling. Nat Rev Immunol 3:939–951

Ahmed CM, Larkin J 3rd, Johnson HM (2015) SOCS1 mimetics and antagonists: a complementary approach to positive and negative regulation of immune function. Front Immunol 6:183

Alexander WS (2002) Suppressors of cytokine signalling (SOCS) in the immune system. Nat Rev Immunol 2:1–7

Alexander WS, Starr R, Fenner JE, Scott CL, Handman E, Sprigg NS, Corbin JE, Cornish AL, Darwiche R, Owczarek CM et al (1999) SOCS1 is a critical inhibitor of interferon gamma signaling and prevents the potentially fatal neonatal actions of this cytokine. Cell 98:597–608

Anguille S, Smits EL, Lion E, van Tendeloo VF, Berneman ZN (2014) Clinical use of dendritic cells for cancer therapy. Lancet Oncol 15:e257–e267

Babon JJ, Sabo JK, Zhang JG, Nicola NA, Norton RS (2009) The SOCS box encodes a hierarchy of affinities for Cullin5: implications for ubiquitin ligase formation and cytokine signalling suppression. J Mol Biol 387:162–174

Babon JJ, Kershaw NJ, Murphy JM, Varghese LN, Laktyushin A, Young SN, Lucet IS, Norton RS, Nicola NA (2012) Suppression of cytokine signaling by SOCS3: characterization of the mode of inhibition and the basis of its specificity. Immunity 36:239–250

Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN (2014a) The molecular regulation of Janus kinase (JAK) activation. Biochem J 462:1–13

Babon JJ, Varghese LN, Nicola NA (2014b) Inhibition of IL-6 family cytokines by SOCS3. Semin Immunol 26:13–19

Baetz A, Koelsche C, Strebovsky J, Heeg K, Dalpke AH (2008) Identification of a nuclear localization signal in suppressor of cytokine signaling 1. Faseb J 22:4296–4305

Bailey-Bucktrout SL, Martinez-Llordella M, Zhou X, Anthony B, Rosenthal W, Luche H, Fehling HJ, Bluestone JA (2013) Self-antigen-driven activation induces instability of regulatory T cells during an inflammatory autoimmune response. Immunity 39:949–962

Baniyash M (2004) TCR zeta-chain downregulation: curtailing an excessive inflammatory immune response. Nat Rev Immunol 4:675–687

Bartz H, Avalos NM, Baetz A, Heeg K, Dalpke AH (2006) Involvement of suppressors of cytokine signaling in toll-like receptor-mediated block of dendritic cell differentiation. Blood 108:4102–4108

Baxter AG, Hodgkin PD (2002) Activation rules: the two-signal theories of immune activation. Nat Rev Immunol 2:439–446

Ben-Sasson SZ, Hu-Li J, Quiel J, Cauchetaux S, Ratner M, Shapira I, Dinarello CA, Paul WE (2009) IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. Proc Natl Acad Sci USA 106:7119–7124

Bourdonnay E, Zaslona Z, Penke LR, Speth JM, Schneider DJ, Przybranowski S, Swanson JA, Mancuso P, Freeman CM, Curtis JL, Peters-Golden M (2015) Transcellular delivery of vesicular SOCS proteins from macrophages to epithelial cells blunts inflammatory signaling. J Exp Med 212:729–742

Bourette RP, De Sepulveda P, Arnaud S, Dubreuil P, Rottapel R, Mouchiroud G (2001) Suppressor of cytokine signaling 1 interacts with the macrophage colony-stimulating factor receptor and negatively regulates its proliferation signal. J Biol Chem 276:22133–22139

Boyle K, Egan P, Rakar S, Willson TA, Wicks IP, Metcalf D, Hilton DJ, Nicola NA, Alexander WS, Roberts AW, Robb L (2007) The SOCS box of suppressor of cytokine signaling-3 contributes to the control of G-CSF responsiveness in vivo. Blood 110:1466–1474

Bunda S, Kommaraju K, Heir P, Ohh M (2013) SOCS-1 mediates ubiquitylation and degradation of GM-CSF receptor. PLoS ONE 8:e76370

Carow B, Ye X, Gavier-Widen D, Bhuju S, Oehlmann W, Singh M, Skold M, Ignatowicz L, Yoshimura A, Wigzell H, Rottenberg ME (2011) Silencing suppressor of cytokine signaling-1 (SOCS1) in macrophages improves Mycobacterium tuberculosis control in an interferon-gamma (IFN-gamma)-dependent manner. J Biol Chem 286:26873–26887

Catlett IM, Hedrick SM (2005) Suppressor of cytokine signaling 1 is required for the differentiation of CD4+ T cells. Nat Immunol 6:715–721

Chang JH, Xiao Y, Hu H, Jin J, Yu J, Zhou X, Wu X, Johnson HM, Akira S, Pasparakis M et al (2012) Ubc13 maintains the suppressive function of regulatory T cells and prevents their conversion into effector-like T cells. Nat Immunol 13:481–490

Chen L, Flies DB (2013) Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol 13:227–242

Chen Q, Kim YC, Laurence A, Punkosdy GA, Shevach EM (2011) IL-2 controls the stability of Foxp3 expression in TGF-beta-induced Foxp3+ T cells in vivo. J Immunol 186:6329–6337

Chevrier M, Bobbala D, Villalobos-Hernandez A, Khan MG, Ramanathan S, Saucier C, Ferbeyre G, Geha S, Ilangumaran S (2017) Expression of SOCS1 and the downstream targets of its putative tumor suppressor functions in prostate cancer. BMC Cancer 17:157

Chinen T, Kobayashi T, Ogata H, Takaesu G, Takaki H, Hashimoto M, Yagita H, Nawata H, Yoshimura A (2006) Suppressor of cytokine signaling-1 regulates inflammatory bowel disease in which both IFNgamma and IL-4 are involved. Gastroenterology 130:373–388

Chong MM, Cornish AL, Darwiche R, Stanley EG, Purton JF, Godfrey DI, Hilton DJ, Starr R, Alexander WS, Kay TW (2003) Suppressor of cytokine signaling-1 is a critical regulator of interleukin-7-dependent CD8+ T cell differentiation. Immunity 18:475–487

Chong MM, Metcalf D, Jamieson E, Alexander WS, Kay TW (2005) Suppressor of cytokine signaling-1 in T cells and macrophages is critical for preventing lethal inflammation. Blood 106:1668–1675

Cornish AL, Chong MM, Davey GM, Darwiche R, Nicola NA, Hilton DJ, Kay TW, Starr R, Alexander WS (2003a) Suppressor of cytokine signaling-1 regulates signaling in response to interleukin-2 and other gamma c-dependent cytokines in peripheral T cells. J Biol Chem 278:22755–22761

Cornish AL, Davey GM, Metcalf D, Purton JF, Corbin JE, Greenhalgh CJ, Darwiche R, Wu L, Nicola NA, Godfrey DI et al (2003b) Suppressor of cytokine signaling-1 has IFN-gamma-independent actions in T cell homeostasis. J Immunol 170:878–886

Cox MA, Harrington LE, Zajac AJ (2011) Cytokines and the inception of CD8 T cell responses. Trends Immunol 32:180–186

Croker BA, Krebs DL, Zhang JG, Wormald S, Willson TA, Stanley EG, Robb L, Greenhalgh CJ, Forster I, Clausen BE et al (2003) SOCS3 negatively regulates IL-6 signaling in vivo. Nat Immunol 4:540–545

Curtsinger JM, Lins DC, Mescher MF (2003) Signal 3 determines tolerance versus full activation of naive CD8 T cells: dissociating proliferation and development of effector function. J Exp Med 197:1141–1151

Curtsinger JM, Lins DC, Johnson CM, Mescher MF (2005a) Signal 3 tolerant CD8 T cells degranulate in response to antigen but lack granzyme B to mediate cytolysis. J Immunol 175:4392–4399

Curtsinger JM, Valenzuela JO, Agarwal P, Lins D, Mescher MF (2005b) Type I IFNs provide a third signal to CD8 T cells to stimulate clonal expansion and differentiation. J Immunol 174:4465–4469

Curtsinger JM, Mescher MF (2010) Inflammatory cytokines as a third signal for T cell activation. Curr Opin Immunol 22:333–340

Davey GM, Starr R, Cornish AL, Burghardt JT, Alexander WS, Carbone FR, Surh CD, Heath WR (2005) SOCS-1 regulates IL-15-driven homeostatic proliferation of antigen-naive CD8 T cells, limiting their autoimmune potential. J Exp Med 202:1099–1108

De Sepulveda P, Okkenhaug K, Rose JL, Hawley RG, Dubreuil P, Rottapel R (1999) Socs1 binds to multiple signalling proteins and suppresses steel factor- dependent proliferation. EMBO J 18:904–915

DiGiandomenico A, Wylezinski LS, Hawiger J (2009) Intracellular delivery of a cell-penetrating SOCS1 that targets IFN-gamma signaling. Sci Signal 2:ra37

Dubois SP, Waldmann TA, Muller JR (2005) Survival adjustment of mature dendritic cells by IL-15. Proc Natl Acad Sci USA 102:8662–8667

Egan PJ, Lawlor KE, Alexander WS, Wicks IP (2003) Suppressor of cytokine signaling-1 regulates acute inflammatory arthritis and T cell activation. J Clin Invest 111:915–924

Endo TA, Masuhara M, Yokouchi M, Suzuki R, Sakamoto H, Mitsui K, Matsumoto A, Tanimura S, Ohtsubo M, Misawa H et al (1997) A new protein containing an SH2 domain that inhibits JAK kinases. Nature 387:921–924

Evel-Kabler K, Song XT, Aldrich M, Huang XF, Chen SY (2006) SOCS1 restricts dendritic cells' ability to break self tolerance and induce antitumor immunity by regulating IL-12 production and signaling. J Clin Invest 116:90–100

Feng ZP, Chandrashekaran IR, Low A, Speed TP, Nicholson SE, Norton RS (2012) The N-terminal domains of SOCS proteins: a conserved region in the disordered N-termini of SOCS4 and 5. Proteins 80:946–957

Flowers LO, Subramaniam PS, Johnson HM (2005) A SOCS-1 peptide mimetic inhibits both constitutive and IL-6 induced activation of STAT3 in prostate cancer cells. Oncogene 24:2114–2120

Fujimoto M, Naka T (2003) Regulation of cytokine signaling by SOCS family molecules. Trends Immunol 24:659–666

Fujimoto M, Naka T, Nakagawa R, Kawazoe Y, Morita Y, Tateishi A, Okumura K, Narazaki M, Kishimoto T (2000) Defective thymocyte development and perturbed homeostasis of T cells in STAT-induced STAT inhibitor-1/suppressors of cytokine signaling-1 transgenic mice. J Immunol 165:1799–1806

Fujimoto M, Tsutsui H, Xinshou O, Tokumoto M, Watanabe D, Shima Y, Yoshimoto T, Hirakata H, Kawase I, Nakanishi K et al (2004) Inadequate induction of suppressor of cytokine signaling-1 causes systemic autoimmune diseases. Int Immunol 16:303–314

Gagnon J, Ramanathan S, Leblanc C, Cloutier A, McDonald PP, Ilangumaran S (2008) IL-6, in synergy with IL-7 or IL-15, stimulates TCR-independent proliferation and functional differentiation of CD8+ T lymphocytes. J Immunol 180:7958–7968

Gagnon J, Ramanathan S, Leblanc C, Ilangumaran S (2007) Regulation of IL-21 signaling by suppressor of cytokine signaling-1 (SOCS1) in CD8(+) T lymphocytes. Cell Signal 19:806–816

Gui Y, Yeganeh M, Donates YC, Tobelaim WS, Chababi W, Mayhue M, Yoshimura A, Ramanathan S, Saucier C, Ilangumaran S (2015) Regulation of MET receptor tyrosine kinase signaling by suppressor of cytokine signaling 1 in hepatocellular carcinoma. Oncogene 34:5718–5728

Hanada T, Yoshida H, Kato S, Tanaka K, Masutani K, Tsukada J, Nomura Y, Mimata H, Kubo M, Yoshimura A (2003) Suppressor of cytokine signaling-1 is essential for suppressing dendritic cell activation and systemic autoimmunity. Immunity 19:437–450

Hanada T, Tanaka K, Matsumura Y, Yamauchi M, Nishinakamura H, Aburatani H, Mashima R, Kubo M, Kobayashi T, Yoshimura A (2005) Induction of hyper Th1 cell-type immune responses by dendritic cells lacking the suppressor of cytokine signaling-1 gene. J Immunol 174:4325–4332

Hanada T, Kobayashi T, Chinen T, Saeki K, Takaki H, Koga K, Minoda Y, Sanada T, Yoshioka T, Mimata H et al (2006) IFNgamma-dependent, spontaneous development of colorectal carcinomas in SOCS1-deficient mice. J Exp Med 203:1391–1397

Haring JS, Badovinac VP, Harty JT (2006) Inflaming the CD8+ T cell response. Immunity 25:19–29

Heath WR, Carbone FR (2009) Dendritic cell subsets in primary and secondary T cell responses at body surfaces. Nat Immunol 10:1237–1244

Hori S (2014) Lineage stability and phenotypic plasticity of Foxp3(+) regulatory T cells. Immunol Rev 259:159–172

Horino J, Fujimoto M, Terabe F, Serada S, Takahashi T, Soma Y, Tanaka K, Chinen T, Yoshimura A, Nomura S et al (2008) Suppressor of cytokine signaling-1 ameliorates dextran sulfate sodium-induced colitis in mice. Int Immunol 20:753–762

Hsieh CS, Lee HM, Lio CW (2012) Selection of regulatory T cells in the thymus. Nat Rev Immunol 12:157–167

Huang FJ, Steeg PS, Price JE, Chiu WT, Chou PC, Xie K, Sawaya R, Huang S (2008) Molecular basis for the critical role of suppressor of cytokine signaling-1 in melanoma brain metastasis. Can Res 68:9634–9642

Hwang MN, Min CH, Kim HS, Lee H, Yoon KA, Park SY, Lee ES, Yoon S (2007) The nuclear localization of SOCS6 requires the N-terminal region and negatively regulates Stat3 protein levels. Biochem Biophys Res Commun 360:333–338

Ilangumaran S, Gagnon J, Leblanc C, Poussier P, Ramanathan S (2010) Increased generation of CD8 single positive cells in SOCS1-deficient thymus does not proportionately increase their export. Immunol Lett 132:12–17

Ilangumaran S, Ramanathan S, La Rose J, Poussier P, Rottapel R (2003a) Suppressor of cytokine signaling 1 regulates IL-15 receptor signaling in CD8 + CD44high memory T lymphocytes. J Immunol 171:2435–2445

Ilangumaran S, Ramanathan S, Ning T, La Rose J, Reinhart B, Poussier P, Rottapel R (2003b) Suppressor of cytokine signaling 1 attenuates IL-15 receptor signaling in CD8+ thymocytes. Blood 102:4115–4122

Ilangumaran S, Ramanathan S, Rottapel R (2004) Regulation of the immune system by SOCS family adaptor proteins. Semin Immunol 16:351–365

Ilangumaran S, Villalobos-Hernandez A, Bobbala D, Ramanathan S (2016) The hepatocyte growth factor (HGF)-MET receptor tyrosine kinase signaling pathway: Diverse roles in modulating immune cell functions. Cytokine 82:125–139

Inagaki-Ohara K, Kondo T, Ito M, Yoshimura A (2013) SOCS, inflammation, and cancer. Jak-Stat 2:e24053

Jackson SH, Yu CR, Mahdi RM, Ebong S, Egwuagu CE (2004) Dendritic cell maturation requires STAT1 and is under feedback regulation by suppressors of cytokine signaling. J Immunol 172:2307–2315

Jager LD, Dabelic R, Waiboci LW, Lau K, Haider MS, Ahmed CM, Larkin J 3rd, David S, Johnson HM (2011) The kinase inhibitory region of SOCS-1 is sufficient to inhibit T-helper 17 and other immune functions in experimental allergic encephalomyelitis. J Neuroimmunol 232:108–118

Jameson SC (2002) Maintaining the norm: T-cell homeostasis. Nat Rev Immunol 2:547–556

Ji Y, Wrzesinski C, Yu Z, Hu J, Gautam S, Hawk NV, Telford WG, Palmer DC, Franco Z, Sukumar M et al (2015) miR-155 augments CD8+ T-cell antitumor activity in lymphoreplete hosts by enhancing responsiveness to homeostatic gammac cytokines. Proc Natl Acad Sci USA 112:476–481

Jiang S, Zhang HW, Lu MH, He XH, Li Y, Gu H, Liu MF, Wang ED (2010) MicroRNA-155 functions as an OncomiR in breast cancer by targeting the suppressor of cytokine signaling 1 gene. Can Res 70:3119–3127

Kazi JU, Kabir NN, Flores-Morales A, Ronnstrand L (2014) SOCS proteins in regulation of receptor tyrosine kinase signaling. Cell Mol L Sci: CMLS 71:3297–3310

Kershaw NJ, Murphy JM, Liau NP, Varghese LN, Laktyushin A, Whitlock EL, Lucet IS, Nicola NA, Babon JJ (2013) SOCS3 binds specific receptor-JAK complexes to control cytokine signaling by direct kinase inhibition. Nat Struct Mol Biol 20:469–476

Kile BT, Schulman BA, Alexander WS, Nicola NA, Martin HM, Hilton DJ (2002) The SOCS box: a tale of destruction and degradation. Trends Biochem Sci 27:235–241

Kinjyo I, Hanada T, Inagaki-Ohara K, Mori H, Aki D, Ohishi M, Yoshida H, Kubo M, Yoshimura A (2002) SOCS1/JAB is a negative regulator of LPS-induced macrophage activation. Immunity 17:583–591

Kobayashi N, Uemura H, Nagahama K, Okudela K, Furuya M, Ino Y, Ito Y, Hirano H, Inayama Y, Aoki I et al (2012) Identification of miR-30d as a novel prognostic maker of prostate cancer. Oncotarget 3:1455–1471

Kolumam GA, Thomas S, Thompson LJ, Sprent J, Murali-Krishna K (2005) Type I interferons act directly on CD8 T cells to allow clonal expansion and memory formation in response to viral infection. J Exp Med 202:637–650

Komarowska I, Coe D, Wang G, Haas R, Mauro C, Kishore M, Cooper D, Nadkarni S, Fu H, Steinbruchel DA et al (2015) Hepatocyte growth factor receptor c-Met instructs T Cell cardiotropism and promotes T Cell migration to the heart via autocrine chemokine release. Immunity 42:1087–1099

Komatsu N, Mariotti-Ferrandiz ME, Wang Y, Malissen B, Waldmann H, Hori S (2009) Heterogeneity of natural Foxp3+ T cells: a committed regulatory T-cell lineage and an uncommitted minor population retaining plasticity. Proc Natl Acad Sci USA 106:1903–1908

Komatsu N, Okamoto K, Sawa S, Nakashima T, Oh-hora M, Kodama T, Tanaka S, Bluestone JA, Takayanagi H (2014) Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. Nat Med 20:62–68

Kremer BE, Adang LA, Macara IG (2007) Septins regulate actin organization and cell-cycle arrest through nuclear accumulation of NCK mediated by SOCS7. Cell 130:837–850

Liu E, Cote JF, Vuori K (2003) Negative regulation of FAK signaling by SOCS proteins. EMBO J 22:5036–5046

Liu L, Li W, Wei X, Cui Q, Lou W, Wang G, Hu X, Qian C (2013) Potent antitumor activity of oncolytic adenovirus-mediated SOCS1 for hepatocellular carcinoma. Gene Ther 20:84–92

Lu LF, Boldin MP, Chaudhry A, Lin LL, Taganov KD, Hanada T, Yoshimura A, Baltimore D, Rudensky AY (2010) Function of miR-146a in controlling Treg cell-mediated regulation of Th1 responses. Cell 142:914–929

Lu X, Chen M, Xue Z, Zhang X, Xu J, Wu L, Deng R, Ma Y (2017a) Dendritic cells that highly express SOCS1 induce T-cell hypo-responsiveness and prolong islet allograft survival. Cell Immunol

Lu X, Chen M, Xue Z, Zhang X, Xu J, Wu L, Deng R, Ma Y (2017b) Dendritic cells that highly express SOCS1 induce T-cell hypo-responsiveness and prolong islet allograft survival. Cell Immunol 314:36–41

Madonna S, Scarponi C, Doti N, Carbone T, Cavani A, Scognamiglio PL, Marasco D, Albanesi C (2013) Therapeutical potential of a peptide mimicking the SOCS1 kinase inhibitory region in skin immune responses. Eur J Immunol 43:1883–1895

Mahoney KM, Rennert PD, Freeman GJ (2015) Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov 14:561–584

Maine GN, Mao X, Komarck CM, Burstein E (2007) COMMD1 promotes the ubiquitination of NF-kappaB subunits through a cullin-containing ubiquitin ligase. EMBO J 26:436–447

Mansell A, Smith R, Doyle SL, Gray P, Fenner JE, Crack PJ, Nicholson SE, Hilton DJ, O'Neill LA, Hertzog PJ (2006) Suppressor of cytokine signaling 1 negatively regulates Toll-like receptor signaling by mediating Mal degradation. Nat Immunol 7:148–155

Marine JC, Topham DJ, McKay C, Wang D, Parganas E, Stravopodis D, Yoshimura A, Ihle JN (1999) SOCS1 deficiency causes a lymphocyte-dependent perinatal lethality. Cell 98:609–616

Martens N, Wery M, Wang P, Braet F, Gertler A, Hooghe R, Vandenhaute J, Hooghe-Peters EL (2004) The suppressor of cytokine signaling (SOCS)-7 interacts with the actin cytoskeleton through vinexin. Exp Cell Res 298:239–248

Matsuda T, Yamamoto T, Kishi H, Yoshimura A, Muraguchi A (2000) SOCS-1 can suppress CD3zeta- and Syk-mediated NF-AT activation in a non- lymphoid cell line. FEBS Lett 472:235–240

Mattei F, Schiavoni G, Belardelli F, Tough DF (2001) IL-15 is expressed by dendritic cells in response to type I IFN, double-stranded RNA, or lipopolysaccharide and promotes dendritic cell activation. J Immunol 167:1179–1187

McGray AJ, Hallett R, Bernard D, Swift SL, Zhu Z, Teoderascu F, Vanseggelen H, Hassell JA, Hurwitz AA, Wan Y, Bramson JL (2014) Immunotherapy-induced CD8+ T cells instigate immune suppression in the tumor. Mol Ther: J Am Soc Gene Ther 22:206–218

Mescher MF, Agarwal P, Casey KA, Hammerbeck CD, Xiao Z, Curtsinger JM (2007) Molecular basis for checkpoints in the CD8 T cell response: tolerance versus activation. Semin Immunol 19:153–161

Metcalf D, Mifsud S, Di Rago L, Nicola NA, Hilton DJ, Alexander WS (2002) Polycystic kidneys and chronic inflammatory lesions are the delayed consequences of loss of the suppressor of cytokine signaling-1 (SOCS-1). Proc Natl Acad Sci USA 99:943–948

Murali-Krishna K, Ahmed R (2000) Cutting edge: naive T cells masquerading as memory cells. J Immunol 165:1733–1737

Murugaiyan G, Beynon V, Mittal A, Joller N, Weiner HL (2011) Silencing microRNA-155 ameliorates experimental autoimmune encephalomyelitis. J Immunol 187:2213–2221

Naka T, Matsumoto T, Narazaki M, Fujimoto M, Morita Y, Ohsawa Y, Saito H, Nagasawa T, Uchiyama Y, Kishimoto Ts (1998) Accelerated apoptosis of lymphocytes by augmented induction of Bax in SSI-1 (STAT-induced STAT inhibitor-1) deficient mice. Proc Natl Acad Sci USA 95:15577–15582

Naka T, Narazaki M, Hirata M, Matsumoto T, Minamoto S, Aono A, Nishimoto N, Kajita T, Taga T, Yoshizaki K et al (1997) Structure and function of a new STAT-induced STAT inhibitor. Nature 387:924–929

Nakagawa R, Naka T, Tsutsui H, Fujimoto M, Kimura A, Abe T, Seki E, Sato S, Takeuchi O, Takeda K et al (2002) SOCS-1 participates in negative regulation of LPS responses. Immunity 17:677–687

Naramura M, Jang IK, Kole H, Huang F, Haines D, Gu H (2002) c-Cbl and Cbl-b regulate T cell responsiveness by promoting ligand-induced TCR down-modulation. Nat Immunol 3:1192–1199

Natatsuka R, Takahashi T, Serada S, Fujimoto M, Ookawara T, Nishida T, Hara H, Nishigaki T, Harada E, Murakami T et al (2015) Gene therapy with SOCS1 for gastric cancer induces G2/M arrest and has an antitumour effect on peritoneal carcinomatosis. Br J Cancer 113:433–442

Nicholson SE, Willson TA, Farley A, Starr R, Zhang JG, Baca M, Alexander WS, Metcalf D, Hilton DJ, Nicola NA (1999) Mutational analyses of the SOCS proteins suggest a dual domain requirement but distinct mechanisms for inhibition of LIF and IL-6 signal transduction. EMBO J 18:375–385

O'Connell RM, Kahn D, Gibson WS, Round JL, Scholz RL, Chaudhuri AA, Kahn ME, Rao DS, Baltimore D (2010) MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. Immunity 33:607–619

Ohkura N, Kitagawa Y, Sakaguchi S (2013) Development and maintenance of regulatory T cells. Immunity 38:414–423

Ohya K, Kajigaya S, Yamashita Y, Miyazato A, Hatake K, Miura Y, Ikeda U, Shimada K, Ozawa K, Mano H (1997) SOCS-1/JAB/SSI-1 can bind to and suppress Tec protein-tyrosine kinase. J Biol Chem 272:27178–27182

Okumura F, Matsuzaki M, Nakatsukasa K, Kamura T (2012) The role of elongin BC-containing ubiquitin ligases. Front Oncol 2:10

Ostiguy V, Allard EL, Marquis M, Leignadier J, Labrecque N (2007) IL-21 promotes T lymphocyte survival by activating the phosphatidylinositol-3 kinase signaling cascade. J Leukoc Biol 82:645–656

Palmer DC, Guittard GC, Franco Z, Crompton JG, Eil RL, Patel SJ, Ji Y, Van Panhuys N, Klebanoff CA, Sukumar M et al (2015) Cish actively silences TCR signaling in CD8 + T cells to maintain tumor tolerance. J Exp Med 212:2095–2113

Palmer DC, Restifo NP (2009) Suppressors of cytokine signaling (SOCS) in T cell differentiation, maturation, and function. Trends Immunol 30:592–602

Palucka K, Banchereau J (2012) Cancer immunotherapy via dendritic cells. Nat Rev Cancer 12:265–277

Park JH, Adoro S, Guinter T, Erman B, Alag AS, Catalfamo M, Kimura MY, Cui Y, Lucas PJ, Gress RE et al (2010) Signaling by intrathymic cytokines, not T cell antigen receptors, specifies CD8 lineage choice and promotes the differentiation of cytotoxic-lineage T cells. Nat Immunol 11:257–264

Paterson AM, Vanguri VK, Sharpe AH (2009) SnapShot: B7/CD28 costimulation. Cell 137(974–974):e971

Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, Taccioli C, Zanesi N, Alder H, Hagan JP et al (2008) MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis. Proc Natl Acad Sci USA 105:12885–12890

Rafei M, Rouette A, Brochu S, Vanegas JR, Perreault C (2013) Differential effects of gammac cytokines on postselection differentiation of CD8 thymocytes. Blood 121:107–117

Ramanathan S, Dubois S, Chen XL, Leblanc C, Ohashi PS, Ilangumaran S (2011) Exposure to IL-15 and IL-21 enables autoreactive CD8 T cells to respond to weak antigens and cause disease in a mouse model of autoimmune diabetes. J Immunol 186:5131–5141

Ramanathan S, Dubois S, Gagnon J, Leblanc C, Mariathasan S, Ferbeyre G, Rottapel R, Ohashi PS, Ilangumaran S (2010) Regulation of cytokine-driven functional differentiation of CD8 T cells by suppressor of cytokine signaling 1 controls autoimmunity and preserves their proliferative capacity toward foreign antigens. J Immunol 185:357–366

Ramanathan S, Gagnon J, Leblanc C, Rottapel R, Ilangumaran S (2006) Suppressor of cytokine signaling 1 stringently regulates distinct functions of IL-7 and IL-15 in vivo during T lymphocyte development and homeostasis. J Immunol 176:4029–4041

Ribas A (2015) Adaptive immune resistance: how cancer protects from immune attack. Cancer Discov 5:915–919

Rodriguez GM, D'Urbano D, Bobbala D, Chen XL, Yeganeh M, Ramanathan S, Ilangumaran S (2013) SOCS1 prevents potentially skin-reactive cytotoxic T lymphocytes from gaining the ability to cause inflammatory lesions. J Invest Dermatol 133:2013–2022

Rosenberg SA, Restifo NP (2015) Adoptive cell transfer as personalized immunotherapy for human cancer. Science 348:62–68

Ryo A, Suizu F, Yoshida Y, Perrem K, Liou YC, Wulf G, Rottapel R, Yamaoka S, Lu KP (2003) Regulation of NF-kappaB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA. Mol Cell 12:1413–1426

Sakaguchi S, Vignali DA, Rudensky AY, Niec RE, Waldmann H (2013) The plasticity and stability of regulatory T cells. Nat Rev Immunol 13:461–467

Sasaki A, Yasukawa H, Suzuki A, Kamizono S, Syoda T, Kinjyo I, Sasaki M, Johnston JA, Yoshimura A (1999) Cytokine-inducible SH2 protein-3 (CIS3/SOCS3) inhibits Janus tyrosine kinase by binding through the N-terminal kinase inhibitory region as well as SH2 domain. Genes Cells 4:339–351

Sasi W, Sharma AK, Mokbel K (2014) The role of suppressors of cytokine signalling in human neoplasms. Mol Biol Int 2014:630797

Schmitt EG, Williams CB (2013) Generation and function of induced regulatory T cells. Front Immunol 4:152

Schwartz RH (2003) T cell anergy. Annu Rev Immunol 21:305–334

Sharma MD, Hou DY, Baban B, Koni PA, He Y, Chandler PR, Blazar BR, Mellor AL, Munn DH (2010) Reprogrammed foxp3(+) regulatory T cells provide essential help to support cross-presentation and CD8(+) T cell priming in naive mice. Immunity 33:942–954

Shen L, Evel-Kabler K, Strube R, Chen SY (2004) Silencing of SOCS1 enhances antigen presentation by dendritic cells and antigen-specific anti-tumor immunity. Nat Biotechnol 22:1546–1553

Shi D, Li D, Yin Q, Qiu Y, Yan H, Shen Y, Lu G, Liu W (2015) Silenced suppressor of cytokine signaling 1 (SOCS1) enhances the maturation and antifungal immunity of dendritic cells in response to Candida albicans in vitro. Immunol Res 61:206–218

Souma Y, Nishida T, Serada S, Iwahori K, Takahashi T, Fujimoto M, Ripley B, Nakajima K, Miyazaki Y, Mori M et al (2012) Antiproliferative effect of SOCS-1 through the suppression of STAT3 and p38 MAPK activation in gastric cancer cells. Int J Cancer 131:1287–1296

Sporri B, Kovanen PE, Sasaki A, Yoshimura A, Leonard WJ (2001) JAB/SOCS1/SSI-1 is an interleukin-2-induced inhibitor of IL-2 signaling. Blood 97:221–226

Spranger S, Spaapen RM, Zha Y, Williams J, Meng Y, Ha TT, Gajewski TF (2013) Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. Sci Transl Med 5:200ra116

Stanford SM, Rapini N, Bottini N (2012) Regulation of TCR signalling by tyrosine phosphatases: from immune homeostasis to autoimmunity. Immunology 137:1–19

Starr R, Metcalf D, Elefanty AG, Brysha M, Willson TA, Nicola NA, Hilton DJ, Alexander WS (1998) Liver degeneration and lymphoid deficiencies in mice lacking suppressor of cytokine signaling-1. Proc Natl Acad Sci USA 95:14395–14399

Starr R, Willson TA, Viney EM, Murray LJ, Rayner JR, Jenkins BJ, Gonda TJ, Alexander WS, Metcalf D, Nicola NA, Hilton DJ (1997) A family of cytokine-inducible inhibitors of signalling. Nature 387:917–921

Strebovsky J, Walker P, Lang R, Dalpke AH (2011) Suppressor of cytokine signaling 1 (SOCS1) limits NFkappaB signaling by decreasing p65 stability within the cell nucleus. FASEB J 25:863–874

Takahashi R, Nishimoto S, Muto G, Sekiya T, Tamiya T, Kimura A, Morita R, Asakawa M, Chinen T, Yoshimura A (2011) SOCS1 is essential for regulatory T cell functions by preventing loss of Foxp3 expression as well as IFN-{gamma} and IL-17A production. J Exp Med 208:2055–2067

Takahashi R, Yoshimura A (2014) SOCS1 and regulation of regulatory T cells plasticity. J Immunol Res 2014:943149

Tanaka K, Ichiyama K, Hashimoto M, Yoshida H, Takimoto T, Takaesu G, Torisu T, Hanada T, Yasukawa H, Fukuyama S et al (2008) Loss of suppressor of cytokine signaling 1 in helper T cells leads to defective Th17 differentiation by enhancing antagonistic effects of IFN-gamma on STAT3 and Smads. J Immunol 180:3746–3756

Trengove MC, Ward AC (2013) SOCS proteins in development and disease. Am J Clin Exp Immunol 2:1–29

Trop S, De Sepulveda P, Zuniga-Pflucker JC, Rottapel R (2001) Overexpression of suppressor of cytokine signaling-1 impairs pre-T-cell receptor-induced proliferation but not differentiation of immature thymocytes. Blood 97:2269–2277

Tsukada J, Ozaki A, Hanada T, Chinen T, Abe R, Yoshimura A, Kubo M (2005) The role of suppressor of cytokine signaling 1 as a negative regulator for aberrant expansion of CD8alpha+ dendritic cell subset. Int Immunol 17:1167–1178

Wang HY, Altman Y, Fang D, Elly C, Dai Y, Shao Y, Liu YC (2001) Cbl promotes ubiquitination of the T cell receptor zeta through an adaptor function of Zap-70. J Biol Chem 276:26004–26011

Waskow C, Paul S, Haller C, Gassmann M, Rodewald HR (2002) Viable c-Kit(W/W) mutants reveal pivotal role for c-kit in the maintenance of lymphopoiesis. Immunity 17:277–288

Wells AD, Walsh MC, Bluestone JA, Turka LA (2001) Signaling through CD28 and CTLA-4 controls two distinct forms of T cell anergy. J Clin Invest 108:895–903

Wormald S, Zhang JG, Krebs DL, Mielke LA, Silver J, Alexander WS, Speed TP, Nicola NA, Hilton DJ (2006) The comparative roles of suppressor of cytokine signaling-1 and -3 in the inhibition and desensitization of cytokine signaling. J Biol Chem 281:11135–11143

Wu L, Liu YJ (2007) Development of dendritic-cell lineages. Immunity 26:741–750

Yao R, Ma YL, Liang W, Li HH, Ma ZJ, Yu X, Liao YH (2012) MicroRNA-155 modulates Treg and Th17 cells differentiation and Th17 cell function by targeting SOCS1. PLoS ONE 7: e46082

Yasukawa H, Misawa H, Sakamoto H, Masuhara M, Sasaki A, Wakioka T, Ohtsuka S, Imaizumi T, Matsuda T, Ihle JN, Yoshimura A (1999) The JAK-binding protein JAB inhibits janus tyrosine kinase activity through binding in the activation loop. EMBO J 18:1309–1320

Yasukawa H, Ohishi M, Mori H, Murakami M, Chinen T, Aki D, Hanada T, Takeda K, Akira S, Hoshijima M et al (2003) IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. Nat Immunol 4:551–556

Yasukawa H, Sasaki A, Yoshimura A (2000) Negative regulation of cytokine signaling pathways. Annu Rev Immunol 18:143–164

Yeganeh M, Gui Y, Kandhi R, Bobbala D, Tobelaim WS, Saucier C, Yoshimura A, Ferbeyre G, Ramanathan S, Ilangumaran S (2016) Suppressor of cytokine signaling 1-dependent regulation of the expression and oncogenic functions of p 21 in the liver. Oncog PMID:26725321

Yoshida T, Ogata H, Kamio M, Joo A, Shiraishi H, Tokunaga Y, Sata M, Nagai H, Yoshimura A (2004) SOCS1 is a suppressor of liver fibrosis and hepatitis-induced carcinogenesis. J Exp Med 199:1701–1707

Yoshikawa H, Matsubara K, Qian GS, Jackson P, Groopman JD, Manning JE, Harris CC, Herman JG (2001) SOCS-1, a negative regulator of the JAK/STAT pathway, is silenced by

methylation in human hepatocellular carcinoma and shows growth- suppression activity. Nat Genet 28:29–35

Yoshimura A (2013) CIS: the late-blooming eldest son. Nat Immunol 14:692–694

Yoshimura A, Naka T, Kubo M (2007) SOCS proteins, cytokine signalling and immune regulation. Nat Rev Immunol 7:454–465

Yoshimura A, Ohkubo T, Kiguchi T, Jenkins NA, Gilbert DJ, Copeland NG, Hara T, Miyajima A (1995) A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to tyrosine-phosphorylated interleukin 3 and erythropoietin receptors. EMBO J 14:2816–2826

Yoshimura A, Yasukawa H (2012) JAK's SOCS: a mechanism of inhibition. Immunity 36:157–159

Yu Q, Park JH, Doan LL, Erman B, Feigenbaum L, Singer A (2006) Cytokine signal transduction is suppressed in preselection double-positive thymocytes and restored by positive selection. J Exp Med 203:165–175

Zeng R, Spolski R, Finkelstein SE, Oh S, Kovanen PE, Hinrichs CS, Pise-Masison CA, Radonovich MF, Brady JN, Restifo NP et al (2005) Synergy of IL-21 and IL-15 in regulating CD8 + T cell expansion and function. J Exp Med 201:139–148

Zhan Y, Davey GM, Graham KL, Kiu H, Dudek NL, Kay T, Lew AM (2009) SOCS1 negatively regulates the production of Foxp3 + CD4 + T cells in the thymus. Immunol Cell Biol 87:473–480

Zhang JG, Metcalf D, Rakar S, Asimakis M, Greenhalgh CJ, Willson TA, Starr R, Nicholson SE, Carter W, Alexander WS et al (2001) The SOCS box of suppressor of cytokine signaling-1 is important for inhibition of cytokine action in vivo. Proc Natl Acad Sci USA 98:13261–13265