Published in final edited form as:

Trends Immunol. 2009 December ; 30(12): 592–602. doi:10.1016/j.it.2009.09.009.

Suppressors of Cytokine Signaling (SOCS) in T cell differentiation, maturation, and function

Douglas C. Palmer¹ and Nicholas P. Restifo¹

¹National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, USA.

Abstract

Cytokines are key modulators of T cell biology but their influence can be attenuated by suppressors of cytokine signaling (SOCS), a family of proteins comprised of eight members, SOCS1-7 and CIS. SOCS proteins regulate cytokine signals that control the polarization of CD4⁺ T cells into Th1, Th2, Th17, and T regulatory cell lineages, the maturation of CD8⁺ T cells from naïve to “stem-cell memory” (Tscm), central memory (Tcm), and effector memory (Tem) states, and the activation of these lymphocytes. Understanding how SOCS family members regulate T cell maturation, differentiation and function might prove critical in improving adoptive immunotherapy for cancer and therapies aimed at treating autoimmune and infectious diseases.

Introduction

Cytokines are key modulators of T cell maturation, proliferation and activation. Recent advances in our understanding of cytokine biology have revealed a non-redundant class of suppressors of cytokine signaling (SOCS). Emerging evidence indicates that SOCS family members can play critical roles in both innate and adaptive immune responses by mediating negative-feedback inhibition of cytokine signaling in complex ways. In this review, we focus on how SOCS proteins affect T lymphocyte differentiation, maturation, and function.

Cytokines in T cell development

Our understanding of how cytokines affect T cell differentiation, maturation, and function has grown considerably in the past several years. Cytokines can direct CD4⁺ T cells into Th1, Th2, Th17, or T regulatory (Treg) cell lineages [1,2]. This lineage differentiation is critical in both activating and inhibiting immune responses in autoimmunity, infection and cancer [3,4]. In addition to lineage selection, cytokines play a critical role in the maturation, homeostasis and function of T cells [5,6] [7]. For example, the common gamma chain (γ c) cytokine IL-7 is involved in the maintenance of naïve T cells [8], while IL-15 is implicated in the generation of central memory (Tcm) and IL-2 in effector memory (Tem) T cells [9]. In contrast to IL-15 and IL-2, IL-21 appears to arrest the differentiation of naïve CD8⁺ T cells at the memory stem cell (Tscm) stage [10,11]. Other cytokines such as interferons (IFN), transforming growth factor- β (TGF- β) family members, and factors such as Toll-like receptor (TLR) agonists also appear to play a critical role at various levels of T cell biology [12-14]. Understanding the

Corresponding author: Douglas C. Palmer (palmerd@mail.nih.gov) and Nicholas P. Restifo (restifon@mail.nih.gov).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

intracellular mechanisms involved in cytokine signaling will be critical to modulating T cell immunity.

Cytokines signal by approximating cognate receptors and associated Janus kinases (JAKs). The JAKs phosphorylate each other, which initiates a series of events that includes phosphorylation of the cytokine receptor, docking of signal transducers and activators of transcription (STATs) to the activated receptor, and STAT phosphorylation by activated JAKs. These activated STATs dimerize and translocate to the nucleus where they activate target gene transcription (Figure 1). While activated STATs drive transcription of many genes related to cell proliferation, function, and survival, they also induce the transcription of *SOCS* genes. Our understanding of how SOCS family members regulate signaling pathways has grown considerably since their discovery nearly a decade and a half ago.

The mechanisms of SOCS-mediated regulation

SOCS members are thought to act as classic negative feedback inhibitors, being induced by cytokines, and subsequently inhibiting their function. There are four major ways that SOCS proteins inhibit cytokine signaling: (1) blocking STAT recruitment to the cytokine receptor; (2) targeting the receptor for degradation by the proteasome; (3) binding to JAKs and directly inhibiting their kinase activity; (4) targeting JAKs for degradation by the proteasome (Figure 1). The SOCS family consists of eight members (SOCS1-7 and CIS) that contain a conserved SOCS box, a central SH2 domain, and an N-terminus of variable length and organization [15,16] (Figure 2A). While SOCS family members share homology in amino acid sequence in the SH2 and SOCS domains, they remain evolutionarily distinct (Figure 2B). The SOCS box is approximately 40 amino acids long and interacts with several ubiquitinating machinery enzymes (Elongin B, Elongin C, Cullin-5 [Cul5], and Ring-box 2 [Rbx2]) and an E2 ubiquitin transferase [17] (Figure 2C-D). This complex forms into an E3 ubiquitin ligase which tags target proteins such as JAKs and cytokine receptors with ubiquitin, marking them for degradation *via* the proteasome [18-20]. While SOCS-mediated ubiquitination has unequivocally been demonstrated in model systems, it is not clear if this has been observed in T cells. The N-terminus and central SH2 domain appear critical in binding target molecules [21], enabling the E2-E3 complex to ubiquitinate them. With respect to CIS, the SOCS box appears to play a significant role in determining substrate binding [22]. Two of the family members, SOCS1 and SOCS3, contain a kinase inhibitory region (KIR) that serves as a pseudo-substrate for JAKs, blocking JAK kinase ability even in the absence of the SOCS box [23, 24]. Interestingly, knocking out the only KIR-containing SOCS members, SOCS1 or SOCS3, results in a fatal phenotype, which has not been observed with any other SOCS member. These findings might highlight the biological importance of the KIR domain.

The regulation of SOCS family members

While SOCS members were initially thought to act as classic negative feedback inhibitors, their induction and regulation appears to be far more complex. SOCS protein regulation can occur at the transcriptional, translational, and post-translational levels. Recently, it has come to light that the transcription of SOCS family member genes can be initiated not only by many cytokines, including those of the γ_C [25], common gp130, and IFN families [26], but also by many factors of non-lymphocyte origin [27] (Table 1). In addition, SOCS protein expression is regulated by alternate splicing and mRNA stability. SOCS1 has two start codons, one of which results in premature termination [28]. Under stress, SOCS3 can undergo alternative mRNA initiation, resulting in the exclusion of an exon encoding an ubiquitination site that enhances SOCS3 degradation [29]. SOCS1 mRNA stability can also be regulated by the addition of cap proteins [28], though this mechanism of regulation remains less defined.

Post-translational regulation of SOCS members is extensive and can involve positive and negative regulators of protein stability. For example, a PEST motif (Pro, Glu, Asp, Ser and Thr) in the SH2 domain of SOCS3 can enhance its degradation [30]. As mentioned above, an internal ubiquitination site in SOCS3 can also enhance its degradation [29]. It has been shown that the interaction of SOCS3 with Elongin B and C can limit its turnover [31]. Phosphorylation by proviral integration site for Moloney murine leukemia virus (PIM) kinases can block SOCS protein turnover, resulting in greater stability and inhibitory function of SOCS1 and SOCS3 [32-34]. In contrast to PIM phosphorylation, phosphorylation in the SOCS box can block the interaction between SOCS family members and Elongin, thus promoting SOCS degradation [23,31,35]. While less studied, it appears that protein-binding partners such as TRIM8 can enhance the stability and function of SOCS1 [36], perhaps indicating a far more complex regulation of SOCS family members. An additional mechanism of post-translation regulation of SOCS members includes changes in sub-cellular localization. CIS, SOCS1, SOCS2, SOCS3, SOCS6 and SOCS7 proteins can be transported to the nucleus [37-39] which might potentiate their inhibition of cytokine signaling [38,40]. In addition to nuclear translocation, SOCS1 can associate with microtubule adaptor protein MAP1S [41], and the microtubule organizing complex [42] which again might be relevant to regulating SOCS1 function.

Some emerging evidence suggests that SOCS molecules might also be degraded by other SOCS family members. SOCS2 appears to enhance the degradation of SOCS1, SOCS3, and possibly CIS [43]. SOCS6 and SOCS7 might also play a role in cross-modulation of other SOCS proteins as well, though this has not been studied in detail [43]. The SOCS box of SOCS2 appears to facilitate the targeting of other SOCS molecules for proteasomal degradation. The ectopic expression of SOCS2 appears to not only degrade SOCS3, but also enhance IL-2, IL-3, and growth hormone (GH) signaling [44,45]. However, the physiological role of SOCS2 remains unclear as both its deletion and overexpression appear to enhance GH signaling, resulting in gigantism [46-48] and furthermore the absence of SOCS2 does not appear to impact SOCS3 levels in hematopoietic cells [49]. These findings indicate that SOCS2, SOCS6 and SOCS7 might counter-regulate other SOCS family members, although the role of this counter-regulation has not been fully elucidated.

SOCS members in T cell biology

As the knowledge of how SOCS family members regulate cytokine signaling has grown in recent years, it has become clear that they play a critical role regulating T cell differentiation, maturation and function by controlling a diverse series of signaling events [50-53] although the role of SOCS in NKT and $\gamma\delta$ T cells remains to be investigated. SOCS1 is highly expressed in the thymus and its overexpression results in reduced numbers of thymocytes at the triple negative stage (DNIII) and skewed development towards CD4⁺ T cells [54]. Conversely, CD8⁺ T cells selectively accumulate in SOCS1 knockout mice [55,56], and suppression of SOCS1 during the DNIII to DP stage appears to be important in thymopoiesis [57]. Interestingly the ectopic expression of SOCS3 in bone marrow appears to promote the generation of CD8⁺ T cells in part by the upregulation of Notch1 on T cells [58]. These data indicate that SOCS1 and perhaps SOCS3 play a critical role in T cell development [59], while the roles of other SOCS family members in thymic development is less clear.

After thymic emigration, naïve T cells require IL-7 for their maintenance and survival [60]. SOCS1 appears to negatively regulate IL-7 signaling, and knockout of SOCS1 results in a hyper-responsiveness to IL-7 [56]. Overexpression of SOCS1 results in reduced survival of naïve CD4⁺ T cells in the periphery [61]. While naïve T cells appear to express SOCS2 and SOCS3, the role of these and other SOCS members in early T cell development is not well defined [44,62]. SOCS regulation of antigen presenting cell's (APC) function can also play a critical role in T cell development and biology, a topic that has been reviewed elsewhere (see

[63]). More recently, it has become clear that SOCS members contribute not only to early T cell development, but also T differentiation, maturation, and function.

SOCS members and T cell differentiation

Various polarizing conditions can direct CD4⁺ T cells to differentiate into Th1, Th2, Th17, and Treg cell lineages. These lineages can be broadly divided into the absence (resulting in Th1 and Th2 cells) or presence (resulting in Th17 and Treg cells) of TGF- β signaling. SOCS1, SOCS3, and SOCS5 appear to play a significant role in Th1 and Th2 cell differentiation (Figure 3). Th1 cells have been shown to be driven by extrinsic factors like IL-12 and IFN- γ signaling through STAT4 and STAT1 respectively [64]. These molecules work in concert where IL-12 induces STAT4, STAT4 induces IFN- γ , and IFN- γ through STAT1 up-regulates T-bet, a critical Th1 cell transcription factor. SOCS1 has been shown to be a critical negative regulator of the IFN- γ and STAT1 signaling pathway [65,66], in part by serving as a pseudo-substrate for JAK2 [67]. SOCS1 also appears critical in IL-12 signaling, as evidenced by rescuing the deleterious SOCS1 phenotype by breeding them on to a STAT4 deficient background [68]. Not surprisingly, the removal of SOCS1 in CD4⁺ T cells augments the generation of Th1 cells [68], while overexpression inhibits it [69]. Interestingly, SOCS1 deletion in T cells resulted in the production of both IFN- γ and IL-4, perhaps indicating the enhanced function of Th2 populations in addition to Th1 cells [70,71].

SOCS3 has also been shown to play a significant role in the differentiation of Th1 and Th2 cells. SOCS3 inhibits STAT4 signaling by binding to Tyr-800 on the IL-12 receptor 2 chain, thus blocking STAT4 docking [72] [73]. SOCS3 is preferentially expressed in Th2 cells [74], and the ectopic expression of SOCS3 in T cells blocks STAT4 signaling and skews them towards a Th2 cell phenotype [75]. Blocking SOCS3 signaling either by a dominant-negative mutant or a heterozygous knockout, diminished the differentiation of Th2 cells [53,76], resulting in skewing of T cells towards the Th1 cell phenotype and reduced allergic responses [75]. Further evidence for SOCS3 in supporting Th2 differentiation comes from its overexpression in T cells which exacerbates Th2 cell mediated eye-allergy, while the inhibition of SOCS3 ameliorates the severity of disease [77]. While the conditional removal of SOCS3 in T cells appears to suppress both Th1 and Th2 cell responses, this inhibition might be due to increased levels of the immunosuppressive cytokines TGF- β and IL-10 [78], and not directly on the differentiation Th1 and Th2 cells [79]. These data indicate a more complex role for SOCS3 in Th1 and Th2 cell differentiation.

It has been observed that SOCS5 plays a role in Th1 and Th2 cell differentiation [80]. IL-4 signaling *via* STAT6 induces the expression of GATA3, a critical regulator of Th2 cell generation. SOCS5 interacts with the cytoplasmic region of the IL-4 receptor α chain, blocking STAT6 recruitment and subsequent induction of GATA3 [80]. Although, SOCS5 is preferentially expressed in Th1 cells, the absence of SOCS5 in CD4⁺ T cells does not appear to alter normal Th1 and Th2 cell differentiation [81]. Interestingly, the overexpression of SOCS5 in CD4⁺ T cells results in increased lymphocyte infiltration in the gut and high levels of the Th1 cell cytokines IL-12, IFN- γ , and TNF- α [82]. The overexpression of SOCS5 also augmented eosinophilic airway inflammation [83] and septic peritonitis [82] in mice. This disparity in knockout models might be due the redundant role of SOCS5, which shares a high degree of homology with SOCS4, or the non-physiological levels of SOCS5 utilized in overexpression studies.

The role of SOCS family members in Th17 and Treg cell differentiation is beginning to surface. Th17 and Treg cell lineages differ from Th1 and Th2 cell lineages in that they receive TGF- β -SMAD signaling in addition to JAK-STAT signaling. It has been demonstrated that IL-6, IL-21, and IL-23 signal through STAT3, which induces ROR γ t, a critical regulator of Th17 cell differentiation. SOCS3 has been shown to block STAT3 signaling and its deletion results

in enhanced generation of Th17 cells [79,84]. Abrogation of SOCS3 binding to the IL-6 receptor using a mouse with a knock-in for mutated gp130 results in Th17-like arthritis [85]. Recent evidence suggests that IL-6 and IL-21 induced expression of SOCS3 can be inhibited by TGF- β , enhancing the generation of Th17 cells [86]. In contrast to SOCS3, the removal of SOCS1 resulted in reduced Th17 cell generation, and reduction of Th17-mediated disease [87].

While the role of SOCS members in Treg cell development is not well established, the indirect generation of Treg cells, through the impaired expression of SOCS3 in antigen presenting cells (APCs), has been shown to promote a Treg cell phenotype [88]. There is limited evidence that suggests that the partial removal of SOCS1 could result in a higher ratio of CD4⁺ IFN- γ ⁺ T cells and a lower frequency of Treg cells in the colon after experimental induction of colitis with dioctyl sodium sulfosuccinate (DSS) treatment [89]. Recent data has brought to light a possible role of a microRNA, Mir-155, in controlling SOCS1 and the generation of Treg cells [90]. FoxP3 expression induces Mir-155, which has been shown to knock down SOCS1 expression, enhancing IL-2-STAT5 signaling and increasing the number of FoxP3⁺ Treg cells. SOCS3 is constitutively expressed at very low levels in Treg cells, and SOCS3 overexpression can inhibit the proliferation and suppressive function of Treg cells [91]. In addition, SOCS3 removal enhanced CD4⁺ T cell activation and production of IL-10 and TGF- β [78]. In conclusion, SOCS1 and SOCS3 might inhibit the differentiation of Treg cells, though more investigation is necessary.

It is now clear that SOCS1, SOCS3, and SOCS5 can modulate CD4⁺ T cell differentiation, but the roles of other SOCS family members are less defined. CIS might be involved in the inhibition of Th2 or Treg cell differentiation because it disrupts STAT5 signaling [92]. Expression analysis has indicated the upregulation of SOCS2 in Treg cells which might positively regulate IL-2 signaling and Treg cell development [93]. Some evidence suggests that SOCS7 might inhibit STAT3 and STAT5 signaling, and thus might be involved in Th2, Th17, and/or Treg cell development, although this remains speculative [94]. The role of SOCS proteins in the differentiation of the various T helper populations is summarized in Figure 3.

SOCS members in T cell maturation

SOCS members play a non-redundant role in CD8⁺ T cell maturation. CD8⁺ T cells mature from the naïve state through development into T memory stem cells (Tscm), through central memory (Tcm) and effector memory (Tem) prior to their senescence and death by apoptosis (Figure 4). CD8⁺ T cells have increased production of IFN- γ and granzymes that enable them to become cytotoxic while simultaneously losing their ability to home to lymph nodes and make endogenous IL-2. Cytokines in the c family, such as IL-2, IL-7, IL-15, and IL-21, have been shown to play a role in the maturation and function of T cells (Figure 4). These cytokine signals are substantially transmitted by STAT molecules [95-97], which are regulated directly and indirectly through the activity of SOCS family members. SOCS1 blocks IL-7 signaling in naïve CD8⁺ T cells, and SOCS1 depletion results in a skewing towards the CD8⁺ T cell lineage [71,98,99]. Naïve cells fail to proliferate in response to IL-7 or IL-15 [100], but do when combined with IL-21 [11,101], perhaps indicating a role for IL-21 in early memory generation. Indeed we have observed that the priming of naïve T cells by IL-21 can arrest differentiation [11], resulting in the generation of a new T cell subset which have been tentatively designated “T memory stem cell” cells (Tscm) [10]. These Tscm cells are capable of differentiating into multiple subsets and appear to maintain the ability to self-renew and combat chronic infection. IL-21 induces SOCS1 expression in CD8⁺ T cells [102] and in the absence of SOCS1, IL-21 dramatically potentiates IL-7 and IL-15 induced proliferation in CD8⁺ T cells [102]. After stimulation of the T cell receptor, it has been well established that IL-15 plays a role in the generation of Tcm [9], whereas IL-2 results in the generation of Tem [103]. SOCS1 knockout

mice have increased numbers of T cells with central memory cell (T_{cm}) characteristics (CD44^{high}, CD62L^{high}) [56,104,105] and the generation of these T_{cm}-like CD8⁺ T cells might be due to unobstructed IL-15 signaling [106]. In summary, SOCS1 appears to play a non-redundant role at all stages of CD8⁺ T cell maturation.

Other SOCS family members could be involved in the generation of effector memory T cells and the blocking of IL-2 signaling. Two SOCS members that might be involved in the generation of T_{em} include SOCS3 and CIS, which have both been implicated in blocking IL-2 signaling [62,107]. It is interesting to note that overexpression of SOCS2, which might be involved in the degradation of SOCS3 and CIS, appears to enhance IL-2 signaling and thus, potentially, the generation of T_{em} cells [44] (Figure 4). While less examined, the counter-regulation of inhibitory SOCS molecules might play a critical role in accelerating the acquisition of T cell memory.

SOCS members in T cell function

The function of T cells can be dramatically altered by SOCS members, in particular SOCS1. SOCS1 is upregulated in T_{em} cells and its removal results in enhanced T_{em} cell proliferation [105] and in the spontaneous release of IFN- γ , resulting in liver toxicity and neonatal death [66] attributed largely to T cell activation [108]. The removal of SOCS1 in ovalbumin (ova) specific TCR transgenic CD8⁺ OT-1 T cells enhances the incidence and severity of diabetes when ovalbumin was expressed in a pancreatic β -cell model [108]. Conversely, forced expression of SOCS1 in CD8⁺ T cells has been shown to prevent autoimmunity in a model of pancreatitis [109]. The conditional deletion of SOCS3, which regulates signaling by IL-2, IL-6, and IL-27 [32,63,110-113], can enhance CD8⁺ T cell proliferation [114]. Although CD8⁺ T cell function was not explicitly addressed in these SOCS3 knockout studies, the overexpression of SOCS3 does not impair CD8⁺ T cell function [58]. Finally, the potential roles of SOCS1 and SOCS3 in CD8⁺ T cell adoptive tumor immunotherapy remain unclear.

The future

Over a decade ago when SOCS family members were first implicated as classic negative feedback inhibitors of cytokine signaling, it appeared that their story would be a straightforward one. However, as our knowledge has grown it has become apparent that the SOCS family is far more complex in both functionality and regulation. Many of these recent findings provoke some critical questions, namely: (1) What are the roles of the less well described SOCS family members in T cell biology?; (2) Do SOCS members inhibit non-cytokine pathways vital to T cell function e.g. TLR signaling?; and (3) What is the therapeutic relevance of modulating these factors? Better understanding of these questions might reveal the significance of SOCS family members in autoimmunity, infection and tumor immunology.

The 'other' SOCS members and T cell biology

SOCS1, SOCS3, and SOCS5 contribute to the differentiation, maturation and function of T cells. How the less defined SOCS family members such as CIS, SOCS2, SOCS4, SOCS6, and SOCS7 contribute to T cell biology is of great interest. CIS is induced early after antigenic or cytokine stimulation [92,115] (Table 1). It is thought to negatively regulate STAT5 signaling, highlighted by CIS transgenic mice, which have a phenotype similar to that of STAT5 deficient mice. CIS has been shown to interact with the IL-2 β -chain receptor and GH receptor, competing for some of the available STAT5 binding sites [116]. This inhibition, however, is not complete as some workers have observed only minimal detriment in STAT5 phosphorylation in the presence of CIS [32,92,117,118]. Curiously, CIS overexpression has been shown to enhance the proliferation of a bulk CD4⁺ T cell population [118], while CIS knockout mice have had no obvious phenotype reported. While still speculative, it is possible

that the overexpression of CIS, and the resultant decreased IL-2 signaling, could inhibit the function of Treg cells. Indeed, this phenomenon is reminiscent IL-2 deficient animals, which develop a profound lymphocytosis, splenomegaly and wasting disease now attributed to impaired Treg cell function [119]. Overexpression of CIS might result in decreased Treg cell function, thus promoting the function of other T cell subsets. However, this does not explain the puzzling absence of a phenotype reported in CIS knockout mice. Despite being the first SOCS family member described, the mechanism of how CIS blocks STAT5 signaling and its role in T cell biology remains elusive [20].

SOCS2 is expressed after activation in CD4⁺ T cells [113], and as mentioned previously, has been shown to enhance IL-2 and IL-3 signaling [44]. Interestingly, SOCS2 expression in lymphocytes appears much later than some other SOCS family members [44], perhaps indicating a delayed counter-regulatory role for SOCS2 [18,43]. However the absence of SOCS2 in primary hematopoietic cells did not appear to affect the levels of SOCS3 [49], indicating that the role of SOCS2 in T cell biology, if any, is unclear.

There is very little known about the physiological role of SOCS4, SOCS6, and SOCS7 in somatic tissue, and even less is known about their impact in immunobiology. SOCS4 shares significant homology with SOCS5, and has been reported as a negative regulator of epidermal growth factor [120]. SOCS6 binds cKIT (CD117) and inhibits p38 and ERK MAPK signaling [121]. In cells of nonlymphocyte origin, SOCS7 has been described to inhibit mast cell degranulation presumably through the negative modulation of thymic stromal lymphopoietin (TSLP) [122]. TSLP increases CD8⁺ T cell survival in the absence of IL-7 [123]. SOCS7 has also been shown to inhibit cell cycle progression through sequestering non-catalytic region of tyrosine kinase (NCK) in the nucleus [39]. NCK has been described to be involved in early TCR stimulation. Both SOCS6 and SOCS7 have been implicated in the cross-regulation of other SOCS members [43], and studies modulating their expression may shed light on the function of these SOCS members in T cell biology.

SOCS in the regulation of non-cytokine pathways

SOCS members have been implicated in the negative regulation of many non-cytokine pathways. SOCS1, SOCS3, and SOCS6 have been shown to inhibit IRS1 and IRS2, and block insulin signaling [27,124]. SOCS1 degrades ASK1 (Apoptosis signal-regulating kinase 1), inhibiting TNF signaling [125]. SOCS1 has been shown to interact with Syk and CD3 ζ , subsequently blocking TCR signaling [126]. SOCS3 has been suggested to play a role in the negative regulation of the transcription factor NFAT, primarily by blocking the catalytic subunit of calcineurin and suppressing subsequent NFAT activation [112]. Furthermore, SOCS3 blocks the interaction of the transcription factors E2F and DP-1, thus inhibiting cell cycle progression [127]. Finally, SOCS3 has been shown to negatively regulate sialic acid binding Ig-like lectin 7 (Siglec 7), an attenuator of TCR signaling [128,129].

Of the many non-cytokine pathways inhibited by SOCS members, regulation of TLR signaling is of particular interest. SOCS members can inhibit TLR signaling through inhibition of MyD88 adapter-like (MAL) [130], TNF receptor-associated factor (TRAF) 2 and 6 [131,132] and its downstream target, NF κ B [133]. SOCS proteins, in particular SOCS1 and SOCS3 can dramatically inhibit APC function by both directly [130] and indirectly (*via* IFN- β signaling) attenuating TLR signaling [63,134]. More recently, a direct role of TLR signaling in T cell activation and memory formation has been uncovered [135-137], but specific roles for SOCS family members in this process remain largely unexplored. SOCS proteins can therefore regulate not only cytokine signaling but also a wide range of other T-cell signaling pathways of potential importance in T cell biology.

SOCS members and translational medicine

Modulating SOCS family members is appealing because targeting the downstream signaling molecules may circumvent intrinsic negative regulation. It has been observed that the knockdown of SOCS1 in APCs can enhance tumor therapy [138,139] and limit HIV infectivity [140]. Conversely, the overexpression of SOCS3 using adenoviruses can limit inflammatory arthritis [141], and SOCS3 delivery using a recombinant cell penetrating moiety can limit septic shock [142]. Recent advances in retroviral engineering have enabled us to stably express either genes of interest or short hairpin encoding RNA in T cells [143]. Knocking down SOCS using short hairpin microRNAs (shMIR) as indicated in Figure 5 might facilitate alterations in T cell differentiation, maturation or function. For example, we found that polarizing tumor-specific CD4⁺ T cells into the Th17 cell lineage could enhance tumor destruction [3]. Expression of short hairpins targeting SOCS3 in these CD4⁺ T cell might therefore be used in the generation and maintenance of Th17 cells [144]. Expression of short hairpins targeting SOCS1 or SOCS3 could also be used to enhance to acquisition of highly-reactive Tcm-like CD8⁺ T cells. Perhaps the removal of CIS might enhance the STAT5 signaling, thus improving the function of CD8⁺ T cells. Conversely, SOCS family members could be overexpressed in order to achieve a desired phenotype. The ectopic expression of SOCS5 has been shown to limit allergic conjunctivitis, thus inhibiting Th2-like immunity [77]. Conversely, ectopic expression of SOCS5 could be used to generate Th1 cells and might prove beneficial in eliciting T cell responses against viruses and tumors. While still largely untested, the translational potential of modulating SOCS family member expression in T cells might prove critical in improving adoptive immunotherapies targeting autoimmunity, infection, and cancer.

Acknowledgments

Research was supported by the intramural program of the National Cancer Institute of the National Institutes of Health. This article was written in partial fulfillment of a PhD degree for the George Washington University, Washington, DC. The authors would like to thank Megan Bachinski, Lindsay Garvin, Robert Reger and Dorina Frasheri for help with this manuscript.

Abbreviations

AKT-1, v-akt murine thymoma viral oncogene homolog 1
 APC, antigen presenting cells
 ASK1, Apoptosis signal-regulating kinase 1
 CIS, cytokine-induced SH-2 protein
 DP-1, transcription factor DP-1
 DSS, dioctyl sodium sulfosuccinate
 E2F, transcription factor E2F
 GH, growth hormone
 IFN- γ , interferon- γ
 KIR, kinase inhibitory region
 JAK, janus kinase
 MAL, MyD88 adapter-like
 NCK, non-catalytic region of tyrosine kinase
 NFAT, nuclear factor of activated T cells
 NF κ B, nuclear factor κ B
 PIM, proviral integration site for Moloney murine leukemia virus kinases
 Rbx2, Ring-box 2
 Siglec, sialic acid binding Ig-like lectin 7
 SMAD, mothers against decapentaplegic Drosophila – homolog
 SOCS, suppressors of cytokine signaling
 STAT, signal transducers and activators of transcription

Tcm, T central memory
 Tem, T effector memory
 Tscm, T memory stem cell
 TGF- β , transforming growth factor- β
 TLR, Toll-like receptor
 TNF- α , tumor necrosis factor α
 TRAF, TNF receptor-associated factor
 Treg, T regulatory cell
 TRIM8, tripartate motif-containing 8
 TSLP, thymic stromal lymphopoietin
 ZAP70, zeta-chain (TCR) associated protein kinase

References

- Harrington LE, et al. Expanding the effector CD4 T-cell repertoire: the Th17 lineage. *Current Opinion in Immunology* 2006;3:349–356. [PubMed: 16616472]
- Rochman Y, et al. New insights into the regulation of T cells by gamma(c) family cytokines. *Nat Rev Immunol* 2009;7:480–490. [PubMed: 19543225]
- Muranski P, et al. Tumor-specific Th17-polarized cells eradicate large established melanoma. *Blood* 2008;2:362–373. [PubMed: 18354038]
- Antony PA, et al. CD8+ T Cell Immunity Against a Tumor/Self-Antigen Is Augmented by CD4+ T Helper Cells and Hindered by Naturally Occurring T Regulatory Cells. *J Immunol* 2005;5:2591–2601. [PubMed: 15728465]
- Surh CD, Sprent J. Regulation of mature T cell homeostasis. *Semin Immunol* 2005;3:183–191. [PubMed: 15826823]
- Gattinoni L, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. *J Exp Med* 2005;7:907–912. [PubMed: 16203864]
- Wrzesinski C, et al. Hematopoietic stem cells promote the expansion and function of adoptively transferred antitumor CD8 T cells. *J Clin Invest* 2007;2:492–501. [PubMed: 17273561]
- Tan JT, et al. IL-7 is critical for homeostatic proliferation and survival of naive T cells. *Proc Natl Acad Sci U S A* 2001;15:8732–8737. [PubMed: 11447288]
- Klebanoff CA, et al. Central memory self/tumor-reactive CD8+ T cells confer superior antitumor immunity compared with effector memory T cells. *Proc Natl Acad Sci U S A* 2005;27:9571–9576. [PubMed: 15980149]
- Gattinoni L, et al. Wnt signaling arrests effector T cell differentiation and generates CD8+ memory stem cells. *Nat Med* 2009;7:808–813. [PubMed: 19525962]
- Hinrichs CS, et al. IL-2 and IL-21 confer opposing differentiation programs to CD8+ T cells for adoptive immunotherapy. *Blood* 2008;11:5326–5333. [PubMed: 18276844]
- Paulos CM, et al. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling. *J Clin Invest* 2007;8:2197–2204. [PubMed: 17657310]
- Lu YC, et al. Differential role for c-Rel and C/EBPbeta/delta in TLR-mediated induction of proinflammatory cytokines. *J Immunol* 2009;11:7212–7221. [PubMed: 19454718]
- Das L, Levine AD. TGF-beta inhibits IL-2 production and promotes cell cycle arrest in TCR-activated effector/memory T cells in the presence of sustained TCR signal transduction. *J Immunol* 2008;3:1490–1498. [PubMed: 18209044]
- Zhang JG, et al. The conserved SOCS box motif in suppressors of cytokine signaling binds to elongins B and C and may couple bound proteins to proteasomal degradation. *Proc Natl Acad Sci U S A* 1999;5:2071–2076. [PubMed: 10051596]
- Hilton DJ, et al. Twenty proteins containing a C-terminal SOCS box form five structural classes. *Proc Natl Acad Sci U S A* 1998;1:114–119. [PubMed: 9419338]
- Bullock AN, et al. Crystal structure of the SOCS2-elongin B complex defines a prototypical SOCS box ubiquitin ligase. *Proc Natl Acad Sci U S A* 2006;20:7637–7642. [PubMed: 16675548]

18. Piessevaux J, et al. The many faces of the SOCS box. *Cytokine Growth Factor Rev* 2008;5-6:371–381. [PubMed: 18948053]
19. Verdier F, et al. Proteasomes regulate erythropoietin receptor and signal transducer and activator of transcription 5 (STAT5) activation. Possible involvement of the ubiquitinated Cis protein. *J Biol Chem* 1998;43:28185–28190. [PubMed: 9774439]
20. Alexander WS, Hilton DJ. The role of Suppressors of Cytokine Signaling (SOCS) proteins in regulation of the immune response. *Annual Review of Immunology* 2004:503–529.
21. Landsman T, Waxman DJ. Role of the Cytokine-induced SH2 Domain-containing Protein CIS in Growth Hormone Receptor Internalization. *Journal of Biological Chemistry* 2005;45:37471–37480. [PubMed: 16154995]
22. Piessevaux J, et al. Elongin B/C recruitment regulates substrate binding by CIS. *J Biol Chem* 2008;31:21334–21346. [PubMed: 18508766]
23. Kamura T, et al. The Elongin BC complex interacts with the conserved SOCS-box motif present in members of the SOCS, ras, WD-40 repeat, and ankyrin repeat families. *Genes Dev* 1998;24:3872–3881. [PubMed: 9869640]
24. Zhang JG, et al. The SOCS box of suppressor of cytokine signaling-1 is important for inhibition of cytokine action in vivo. *Proc Natl Acad Sci U S A* 2001;23:13261–13265. [PubMed: 11606785]
25. Alexander WS. Suppressors of cytokine signalling (SOCS) in the immune system. *Nat Rev Immunol* 2002;6:410–416. [PubMed: 12093007]
26. Kubo M, et al. Suppressors of cytokine signaling and immunity. *Nat Immunol* 2003;12:1169–1176. [PubMed: 14639467]
27. Mooney RA, et al. Suppressors of cytokine signaling-1 and -6 associate with and inhibit the insulin receptor. A potential mechanism for cytokine-mediated insulin resistance. *J Biol Chem* 2001;28:25889–25893. [PubMed: 11342531]
28. Gregorieff A, et al. Regulation of SOCS-1 expression by translational repression. *J Biol Chem* 2000;28:21596–21604. [PubMed: 10764816]
29. Sasaki A, et al. The N-terminal truncated isoform of SOCS3 translated from an alternative initiation AUG codon under stress conditions is stable due to the lack of a major ubiquitination site, Lys-6. *J Biol Chem* 2003;4:2432–2436. [PubMed: 12459551]
30. Babon JJ, et al. The structure of SOCS3 reveals the basis of the extended SH2 domain function and identifies an unstructured insertion that regulates stability. *Mol Cell* 2006;2:205–216. [PubMed: 16630890]
31. Haan S, et al. Tyrosine Phosphorylation Disrupts Elongin Interaction and Accelerates SOCS3 Degradation. *Journal of Biological Chemistry* 2003;34:31972–31979. [PubMed: 12783885]
32. Cohnen SJ, et al. SOCS-3 is tyrosine phosphorylated in response to interleukin-2 and suppresses STAT5 phosphorylation and lymphocyte proliferation. *Mol Cell Biol* 1999;7:4980–4988. [PubMed: 10373548]
33. Peltola KJ, et al. Pim-1 kinase inhibits STAT5-dependent transcription via its interactions with SOCS1 and SOCS3. *Blood* 2004;10:3744–3750. [PubMed: 14764533]
34. Chen XP, et al. Pim serine/threonine kinases regulate the stability of Socs-1 protein. *Proc Natl Acad Sci U S A* 2002;4:2175–2180. [PubMed: 11854514]
35. Hanada T, et al. A Mutant Form of JAB/SOCS1 Augments the Cytokine-induced JAK/STAT Pathway by Accelerating Degradation of Wild-type JAB/CIS Family Proteins through the SOCS-box. *Journal of Biological Chemistry* 2001;44:40746–40754. [PubMed: 11522790]
36. Toniato E, et al. TRIM8/GERP RING finger protein interacts with SOCS-1. *J Biol Chem* 2002;40:37315–37322. [PubMed: 12163497]
37. Lee KH, et al. Increased cytoplasmic levels of CIS, SOCS1, SOCS2, or SOCS3 are required for nuclear translocation. *FEBS Lett* 2008;15:2319–2324. [PubMed: 18538139]
38. Hwang MN, et al. The nuclear localization of SOCS6 requires the N-terminal region and negatively regulates Stat3 protein levels. *Biochem Biophys Res Commun* 2007;2:333–338. [PubMed: 17603019]
39. Kremer BE, et al. Septins regulate actin organization and cell-cycle arrest through nuclear accumulation of NCK mediated by SOCS7. *Cell* 2007;5:837–850. [PubMed: 17803907]

40. Baetz A, et al. Identification of a nuclear localization signal in suppressor of cytokine signaling 1. *Faseb J* 2008;12:4296–4305. [PubMed: 18725457]
41. Zou T, et al. The role of microtubule-associated protein 1S in SOCS3 regulation of IL-6 signaling. *FEBS Lett* 2008;29:4015–4022. [PubMed: 19027008]
42. Vuong BQ, et al. SOCS-1 localizes to the microtubule organizing complex-associated 20S proteasome. *Mol Cell Biol* 2004;20:9092–9101. [PubMed: 15456882]
43. Piessevaux J, et al. Functional cross-modulation between SOCS proteins can stimulate cytokine signaling. *Journal of Biological Chemistry* 2006;44:32953–32966. [PubMed: 16956890]
44. Tannahill GM, et al. SOCS2 can enhance interleukin-2 (IL-2) and IL-3 signaling by accelerating SOCS3 degradation. *Mol Cell Biol* 2005;20:9115–9126. [PubMed: 16199887]
45. Favre H, et al. Dual effects of suppressor of cytokine signaling (SOCS-2) on growth hormone signal transduction. *FEBS Lett* 1999;1-2:63–66. [PubMed: 10403376]
46. Metcalf D, et al. Gigantism in mice lacking suppressor of cytokine signalling-2. *Nature* 2000;6790:1069–1073. [PubMed: 10890450]
47. Greenhalgh CJ, et al. Biological evidence that SOCS-2 can act either as an enhancer or suppressor of growth hormone signaling. *J Biol Chem* 2002;43:40181–40184. [PubMed: 12208853]
48. Greenhalgh CJ, et al. SOCS2 negatively regulates growth hormone action in vitro and in vivo. *J Clin Invest* 2005;2:397–406. [PubMed: 15690087]
49. Kiu H, et al. Regulation of multiple cytokine signalling pathways by SOCS3 is independent of SOCS2. *Growth Factors* 1. 2009
50. Elliott J, Johnston JA. SOCS: role in inflammation, allergy and homeostasis. *Trends in Immunology* 2004;8:434–440. [PubMed: 15275643]
51. Fujimoto M, Naka T. Regulation of cytokine signaling by SOCS family molecules. *Trends Immunol* 2003;12:659–666. [PubMed: 14644140]
52. Dimitriou ID, et al. Putting out the fire: coordinated suppression of the innate and adaptive immune systems by SOCS1 and SOCS3 proteins. *Immunol Rev* 2008;265–283. [PubMed: 18759933]
53. Kubo M, Inoue H. Suppressor of cytokine signaling 3 (SOCS3) in Th2 cells evokes Th2 cytokines, IgE, and eosinophilia. *Curr Allergy Asthma Rep* 2006;1:32–39. [PubMed: 16476192]
54. Fujimoto M, et al. Defective thymocyte development and perturbed homeostasis of T cells in STAT-induced STAT inhibitor-1/suppressors of cytokine signaling-1 transgenic mice. *J Immunol* 2000;4:1799–1806. [PubMed: 10925257]
55. Fletcher J, Starr R. The role of suppressors of cytokine signalling in thymopoiesis and T cell activation. *International Journal of Biochemistry and Cell Biology* 2005;9:1774–1786. [PubMed: 15905116]
56. Chong MM, et al. Suppressor of cytokine signaling-1 is a critical regulator of interleukin-7-dependent CD8+ T cell differentiation. *Immunity* 2003;4:475–487. [PubMed: 12705851]
57. Trop S, et al. Overexpression of suppressor of cytokine signaling-1 impairs pre-T-cell receptor-induced proliferation but not differentiation of immature thymocytes. *Blood* 2001;8:2269–2277. [PubMed: 11290587]
58. Zhang Z, et al. Suppressor of Cytokine Signaling 3 Promotes Bone Marrow Cells to Differentiate into CD8+ T Lymphocytes in Lung Tissue via Up-Regulating Notch1 Expression 2009:1578–1586.
59. Catlett IM, Hedrick SM. Suppressor of cytokine signaling 1 is required for the differentiation of CD4+ T cells. *Nat Immunol* 2005;7:715–721. [PubMed: 15924143]
60. Calzascia T, et al. CD4 T cells, lymphopenia, and IL-7 in a multistep pathway to autoimmunity. *Proc Natl Acad Sci U S A* 2008;8:2999–3004. [PubMed: 18287017]
61. Seki Y, et al. IL-7/STAT5 cytokine signaling pathway is essential but insufficient for maintenance of naive CD4 T cell survival in peripheral lymphoid organs. *J Immunol* 2007;1:262–270. [PubMed: 17182563]
62. Matsumoto A, et al. A role of suppressor of cytokine signaling 3 (SOCS3/CIS3/SSI3) in CD28-mediated interleukin 2 production. *J Exp Med* 2003;4:425–436. [PubMed: 12591901]
63. Yoshimura A, et al. SOCS proteins, cytokine signalling and immune regulation. *Nat Rev Immunol* 2007;6:454–465. [PubMed: 17525754]
64. Murphy KM, Reiner SL. The lineage decisions of helper T cells. *Nat Rev Immunol* 2002;12:933–944. [PubMed: 12461566]

65. Sakamoto H, et al. A Janus kinase inhibitor, JAB, is an interferon-gamma-inducible gene and confers resistance to interferons. *Blood* 1998;5:1668–1676. [PubMed: 9716595]
66. Alexander WS, et al. SOCS1 is a critical inhibitor of interferon gamma signaling and prevents the potentially fatal neonatal actions of this cytokine. *Cell* 1999;5:597–608. [PubMed: 10490099]
67. Waiboci LW, et al. Both the suppressor of cytokine signaling 1 (SOCS-1) kinase inhibitory region and SOCS-1 mimetic bind to JAK2 autophosphorylation site: implications for the development of a SOCS-1 antagonist. *J Immunol* 2007;8:5058–5068. [PubMed: 17404288]
68. Eyles JL, et al. Negative regulation of interleukin-12 signaling by suppressor of cytokine signaling-1. *J Biol Chem* 2002;46:43735–43740. [PubMed: 12221108]
69. Diehl S, et al. Inhibition of Th1 differentiation by IL-6 is mediated by SOCS1. *Immunity* 2000;6:805–815. [PubMed: 11163196]
70. Fujimoto M, et al. A regulatory role for suppressor of cytokine signaling-1 in Th polarization in vivo. *Int. Immunol* 2002;11:1343–1350. [PubMed: 12407025]
71. Cornish AL, et al. 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* 2003;25:22755–22761. [PubMed: 12665516]
72. Yamamoto K, et al. SOCS-3 inhibits IL-12-induced STAT4 activation by binding through its SH2 domain to the STAT4 docking site in the IL-12 receptor beta2 subunit. *Biochem Biophys Res Commun* 2003;4:1188–1193. [PubMed: 14559241]
73. Takatori H, et al. Stat5a inhibits IL-12-induced Th1 cell differentiation through the induction of suppressor of cytokine signaling expression. *Journal of Immunology* 2005;7:4105–4112.
74. Egwuagu CE, et al. Suppressors of cytokine signaling proteins are differentially expressed in Th1 and Th2 cells: implications for Th cell lineage commitment and maintenance. *J Immunol* 2002;7:3181–3187. [PubMed: 11907070]
75. Seki Y, et al. SOCS-3 regulates onset and maintenance of T(H)2-mediated allergic responses. *Nat Med* 2003;8:1047–1054. [PubMed: 12847520]
76. Kubo M, et al. Role of suppressor of cytokine signaling in ocular allergy. *Curr Opin Allergy Clin Immunol* 2006;5:361–366. [PubMed: 16954790]
77. Ozaki A, et al. The control of allergic conjunctivitis by suppressor of cytokine signaling (SOCS)3 and SOCS5 in a murine model. *J Immunol* 2005;8:5489–5497. [PubMed: 16210657]
78. Kinjyo I, et al. Loss of SOCS3 in T helper cells resulted in reduced immune responses and hyperproduction of interleukin 10 and transforming growth factor- β 1. *J. Exp. Med* 2006;4:1021–1031. [PubMed: 16606674]
79. Chen Z, et al. Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. *Proc Natl Acad Sci U S A* 2006;21:8137–8142. [PubMed: 16698929]
80. Seki YI, et al. Expression of the suppressor of cytokine signaling-5 (SOCS5) negatively regulates IL-4-dependent STAT6 activation and Th2 differentiation. *Proc Natl Acad Sci U S A* 2002;20:13003–13008. [PubMed: 12242343]
81. Brender C, et al. SOCS5 is expressed in primary B and T lymphoid cells but is dispensable for lymphocyte production and function. *Mol Cell Biol* 2004;13:6094–6103. [PubMed: 15199163]
82. Watanabe H, et al. Overexpression of suppressor of cytokine signaling-5 in T cells augments innate immunity during septic peritonitis. *J Immunol* 2006;12:8650–8657. [PubMed: 17142765]
83. Ohshima M, et al. Overexpression of suppressor of cytokine signalling-5 augments eosinophilic airway inflammation in mice. *Clinical and Experimental Allergy* 2007;5:735–742. [PubMed: 17456221]
84. Taleb S, et al. Loss of SOCS3 expression in T cells reveals a regulatory role for interleukin-17 in atherosclerosis. *J Exp Med*. 2009
85. Ogura H, et al. Interleukin-17 Promotes Autoimmunity by Triggering a Positive-Feedback Loop via Interleukin-6 Induction. *Immunity* 2008;4:628–636. [PubMed: 18848474]
86. Qin H, et al. TGF- β Promotes Th17 Cell Development through Inhibition of SOCS3. *J Immunol* 2009;1:97–105. [PubMed: 19535626]

87. Tanaka K, et al. 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* 2008;6:3746–3756. [PubMed: 18322180]
88. Matsumura Y, et al. Selective expansion of foxp3-positive regulatory T cells and immunosuppression by suppressors of cytokine signaling 3-deficient dendritic cells. *J Immunol* 2007;4:2170–2179. [PubMed: 17675476]
89. Horino J, et al. Suppressor of cytokine signaling-1 ameliorates dextran sulfate sodium-induced colitis in mice. *Int Immunol* 2008;6:753–762. [PubMed: 18381351]
90. Lu LF, et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. *Immunity* 2009;1:80–91. [PubMed: 19144316]
91. Pillemer BB, et al. Deficient SOCS3 expression in CD4+CD25+FoxP3+ regulatory T cells and SOCS3-mediated suppression of Treg function. *Eur J Immunol* 2007;8:2082–2089. [PubMed: 17621372]
92. Matsumoto A, et al. CIS, a cytokine inducible SH2 protein, is a target of the JAK-STAT5 pathway and modulates STAT5 activation. *Blood* 1997;9:3148–3154. [PubMed: 9129017]
93. Sugimoto N, et al. Foxp3-dependent and -independent molecules specific for CD25+CD4+ natural regulatory T cells revealed by DNA microarray analysis. *Int Immunol* 2006;8:1197–1209. [PubMed: 16772372]
94. Martens N, et al. Suppressor of cytokine signaling 7 inhibits prolactin, growth hormone, and leptin signaling by interacting with STAT5 or STAT3 and attenuating their nuclear translocation. *J Biol Chem* 2005;14:13817–13823. [PubMed: 15677474]
95. Nosaka T, et al. STAT5 as a molecular regulator of proliferation, differentiation and apoptosis in hematopoietic cells. *EMBO Journal* 1999;17:4754–4765. [PubMed: 10469654]
96. Verdeil G, et al. STAT5-Mediated Signals Sustain a TCR-Initiated Gene Expression Program toward Differentiation of CD8 T Cell Effectors. *J Immunol* 2006;8:4834–4842. [PubMed: 16585578]
97. Moriggl R, et al. Stat5 is required for IL-2-induced cell cycle progression of peripheral T cells. *Immunity* 1999;2:249–259. [PubMed: 10072077]
98. Cornish AL, et al. Suppressor of cytokine signaling-1 has IFN-gamma-independent actions in T cell homeostasis. *J Immunol* 2003;2:878–886. [PubMed: 12517953]
99. Ramanathan S, et al. 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* 2006;7:4029–4041. [PubMed: 16547238]
100. Geginat J, et al. Cytokine-driven proliferation and differentiation of human naive, central memory, and effector memory CD4(+) T cells. *J Exp Med* 2001;12:1711–1719. [PubMed: 11748273]
101. Zeng R, et al. Synergy of IL-21 and IL-15 in regulating CD8+ T cell expansion and function. *J Exp Med* 2005;1:139–148. [PubMed: 15630141]
102. Gagnon J, et al. Regulation of IL-21 signaling by suppressor of cytokine signaling-1 (SOCS1) in CD8(+) T lymphocytes. *Cell Signal* 2007;4:806–816. [PubMed: 17126530]
103. Gattinoni L, et al. Acquisition of full effector function in vitro paradoxically impairs the in vivo antitumor efficacy of adoptively transferred CD8(+) T cells. *J Clin Invest* 2005;6:1616–1626. [PubMed: 15931392]
104. Marine JC, et al. SOCS1 deficiency causes a lymphocyte-dependent perinatal lethality. *Cell* 1999;5:609–616. [PubMed: 10490100]
105. Ilangumaran S, Rottapel R. Regulation of cytokine receptor signaling by SOCS1. *Immunol Rev* 2003:196–211. [PubMed: 12670405]
106. Davey GM, et al. SOCS-1 regulates IL-15-driven homeostatic proliferation of antigen-naïve CD8 T cells, limiting their autoimmune potential. *Journal of Experimental Medicine* 2005;8:1099–1108. [PubMed: 16216888]
107. Matsumoto A, et al. Suppression of STAT5 Functions in Liver, Mammary Glands, and T Cells in Cytokine-Inducible SH2-Containing Protein 1 Transgenic Mice. *Mol. Cell. Biol* 1999;9:6396–6407. [PubMed: 10454585]
108. Chong MM, et al. Suppressor of cytokine signaling-1 in T cells and macrophages is critical for preventing lethal inflammation. *Blood* 2005;5:1668–1675. [PubMed: 15899915]

109. Chong MM, et al. Suppressor of cytokine signaling-1 overexpression protects pancreatic beta cells from CD8+ T cell-mediated autoimmune destruction. *J Immunol* 2004;9:5714–5721. [PubMed: 15100317]
110. Croker BA, et al. SOCS3 negatively regulates IL-6 signaling in vivo. *Nat Immunol* 2003;6:540–545. [PubMed: 12754505]
111. Owaki T, et al. IL-27 suppresses CD28-mediated [correction of mediated] IL-2 production through suppressor of cytokine signaling 3. *J Immunol* 2006;5:2773–2780. [PubMed: 16493033]
112. Banerjee A, et al. Cutting edge: Suppressor of cytokine signaling 3 inhibits activation of NFATp. *J Immunol* 2002;9:4277–4281. [PubMed: 11970967]
113. Yu C-R, et al. Suppressor of Cytokine Signaling 3 Regulates Proliferation and Activation of T-helper Cells. *Journal of Biological Chemistry* 2003;32:29752–29759. [PubMed: 12783879]
114. Brender C, et al. Suppressor of cytokine signaling 3 regulates CD8 T-cell proliferation by inhibition of interleukins 6 and 27. *Blood* 2007;7:2528–2536. [PubMed: 17609432]
115. Yoshimura A, et al. A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to tyrosine-phosphorylated interleukin 3 and erythropoietin receptors. *Embo J* 1995;12:2816–2826. [PubMed: 7796808]
116. Aman MJ, et al. CIS Associates with the Interleukin-2 Receptor beta Chain and Inhibits Interleukin-2-dependent Signaling. *Journal of Biological Chemistry* 1999;42:30266–30272. [PubMed: 10514520]
117. Ram PA, Waxman DJ. Role of the Cytokine-inducible SH2 Protein CIS in Desensitization of STAT5b Signaling by Continuous Growth Hormone. *Journal of Biological Chemistry* 2000;50:39487–39496. [PubMed: 10991939]
118. Li S, et al. Cytokine-induced Src Homology 2 Protein (CIS) Promotes T Cell Receptor-mediated Proliferation and Prolongs Survival of Activated T Cells. *J. Exp. Med* 2000;6:985–994. [PubMed: 10727460]
119. Fehérvari Z, et al. The dichotomous role of IL-2: tolerance versus immunity. *Trends in Immunology* 2006;3:109–111.
120. Kario E, et al. Suppressors of cytokine signaling 4 and 5 regulate epidermal growth factor receptor signaling. *Journal of Biological Chemistry* 2005;8:7038–7048. [PubMed: 15590694]
121. Bayle J, et al. Suppressor of cytokine signaling 6 associates with KIT and regulates KIT receptor signaling. *J Biol Chem* 2004;13:12249–12259. [PubMed: 14707129]
122. Knisz J, et al. Loss of SOCS7 in mice results in severe cutaneous disease and increased mast cell activation. *Clin Immunol*. 2009
123. Rochman Y, Leonard WJ. The role of thymic stromal lymphopoietin in CD8+ T cell homeostasis. *J Immunol* 2008;11:7699–7705. [PubMed: 19017958]
124. Rui L, et al. SOCS-1 and SOCS-3 block insulin signaling by ubiquitin-mediated degradation of IRS1 and IRS2. *J Biol Chem* 2002;44:42394–42398. [PubMed: 12228220]
125. He Y, et al. SOCS1 inhibits tumor necrosis factor-induced activation of ASK1-JNK inflammatory signaling by mediating ASK1 degradation. *J Biol Chem* 2006;9:5559–5566. [PubMed: 16407264]
126. Matsuda T, et al. SOCS-1 can suppress CD3zeta- and Syk-mediated NF-AT activation in a non-lymphoid cell line. *FEBS Lett* 2000;2-3:235–240. [PubMed: 10788618]
127. Masuhiro Y, et al. SOCS-3 inhibits E2F/DP-1 transcriptional activity and cell cycle progression via interaction with DP-1. *J Biol Chem* 2008;46:31575–31583. [PubMed: 18687693]
128. Ikehara Y, et al. Negative regulation of T cell receptor signaling by Siglec-7 (p70/AIRM) and Siglec-9. *J Biol Chem* 2004;41:43117–43125. [PubMed: 15292262]
129. Orr SJ, et al. SOCS3 Targets Siglec 7 for Proteasomal Degradation and Blocks Siglec 7-mediated Responses. *Journal of Biological Chemistry* 2007;6:3418–3422. [PubMed: 17138568]
130. Mansell A, et al. Suppressor of cytokine signaling 1 negatively regulates Toll-like receptor signaling by mediating Mal degradation. *Nat Immunol* 2006;2:148–155. [PubMed: 16415872]
131. Machado FS, et al. Native and aspirin-triggered lipoxins control innate immunity by inducing proteasomal degradation of TRAF6. *J Exp Med* 2008;5:1077–1086. [PubMed: 18411340]
132. Frobose H, et al. Suppressor of cytokine Signaling-3 inhibits interleukin-1 signaling by targeting the TRAF-6/TAK1 complex. *Mol Endocrinol* 2006;7:1587–1596. [PubMed: 16543409]

133. Ryo A, et al. Regulation of NF-kappaB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA. *Mol Cell* 2003;6:1413–1426. [PubMed: 14690596]
134. Prele CM, et al. SOCS1 regulates the IFN but not NFkappaB pathway in TLR-stimulated human monocytes and macrophages. *J Immunol* 2008;11:8018–8026. [PubMed: 19017994]
135. Tabiasco J, et al. Human effector CD8+ T lymphocytes express TLR3 as a functional coreceptor. *J Immunol* 2006;12:8708–8713. [PubMed: 17142772]
136. Lye E, et al. IRAK-4 kinase activity is required for IRAK-4-dependent innate and adaptive immune responses. *Eur J Immunol* 2008;3:870–876. [PubMed: 18286567]
137. Quigley M, et al. A critical role for direct TLR2-MyD88 signaling in CD8 T-cell clonal expansion and memory formation following vaccinia viral infection. *Blood* 2009;10:2256–2264. [PubMed: 18948575]
138. Shen L, et al. Silencing of SOCS1 enhances antigen presentation by dendritic cells and antigen-specific anti-tumor immunity. *Nat Biotechnol* 2004;12:1546–1553. [PubMed: 15558048]
139. Evel-Kabler K, et al. SOCS1 restricts dendritic cells' ability to break self tolerance and induce antitumor immunity by regulating IL-12 production and signaling. *J Clin Invest* 2006;1:90–100. [PubMed: 16357940]
140. Song XT, et al. An alternative and effective HIV vaccination approach based on inhibition of antigen presentation attenuators in dendritic cells. *PLoS Med* 2006;1:e11. [PubMed: 16381597]
141. Shouda T, et al. Induction of the cytokine signal regulator SOCS3/CIS3 as a therapeutic strategy for treating inflammatory arthritis. *J Clin Invest* 2001;12:1781–1788. [PubMed: 11748261]
142. Jo D, et al. Intracellular protein therapy with SOCS3 inhibits inflammation and apoptosis. *Nat Med* 2005;8:892–898. [PubMed: 16007096]
143. Abad JD, et al. T-cell receptor gene therapy of established tumors in a murine melanoma model. *J Immunother* 2008;1:1–6. [PubMed: 18157006]
144. Varela-Rohena A, et al. Genetic engineering of T cells for adoptive immunotherapy. *Immunol Res* 2008;1-3:166–181. [PubMed: 18841331]
145. Bayle J, et al. The E3 ubiquitin ligase HOIL-1 induces the polyubiquitination and degradation of SOCS6 associated proteins. *FEBS Lett* 2006;11:2609–2614. [PubMed: 16643902]
146. Li L, et al. Insulin induces SOCS-6 expression and its binding to the p85 monomer of phosphoinositide 3-kinase, resulting in improvement in glucose metabolism. *J Biol Chem* 2004;33:34107–34114. [PubMed: 15123678]
147. Naka T, et al. Negative regulation of cytokine and TLR signalings by SOCS and others. *Adv Immunol* 2005:61–122. [PubMed: 16102572]
148. Davey GM, et al. SOCS1: A potent and multifaceted regulator of cytokines and cell-mediated inflammation. *Tissue Antigens* 2006;1:1–9. [PubMed: 16451196]
149. Ilangumaran S, et al. Regulation of the immune system by SOCS family adaptor proteins. *Semin Immunol* 2004;6:351–365. [PubMed: 15541651]
150. Banks AS, et al. Deletion of SOCS7 leads to enhanced insulin action and enlarged islets of Langerhans. *J Clin Invest* 2005;9:2462–2471. [PubMed: 16127460]
151. Krebs DL, et al. Development of hydrocephalus in mice lacking SOCS7. *Proc Natl Acad Sci U S A* 2004;43:15446–15451. [PubMed: 15494444]
152. Zhang X, et al. Simvastatin inhibits IL-17 secretion by targeting multiple IL-17-regulatory cytokines and by inhibiting the expression of IL-17 transcription factor RORC in CD4+ lymphocytes. *J Immunol* 2008;10:6988–6996. [PubMed: 18453621]

Figure 1.

SOCS can act as classic feedback inhibitors. Cytokines signal by approximating receptors and associated Janus kinases (JAKs), initiating a cascade of phosphorylation (P). This results in the phosphorylation and dimerization of STATs, which translocate to the nucleus initiating gene transcription. In addition to genes involved in survival, proliferation and function, STATs initiate transcription of SOCS. There are four major ways by which SOCS inhibit cytokine signaling; (1) blocking STAT recruitment to the cytokine receptor; (2) targeting the receptor for degradation by the proteasome; (3) binding to JAKs and directly inhibiting their kinase activity; (4) targeting JAKs for degradation by the proteasome.

Figure 2.

The SOCS family of proteins. A) The SOCS family consists of eight family members. All eight members share a central SH2 domain, extended SH2 domain (ESS) and a C-terminal SOCS box. In addition, SOCS1 and SOCS3 possess a kinase inhibitory region (KIR) that serves as a pseudo-substrate for JAKs, blocking JAK function. B) Protein homology indicates that SOCS family members are evolutionarily distinct. C) Crystal structure of SOCS2 reveals the topology of the interaction of the SOCS box with Elongin B and Elongin C, which enables ubiquitination of the target protein bound *via* the SH2 domain. D) A schematic diagram of the extended interactions of SOCS with target proteins. The SOCS box interacts with several ubiquitinating machinery enzymes i.e. Elongin B, Elongin C, Cullin-5 (Cul5), and Ring-box 2 (Rbx2) and an E2 ubiquitin transferase. The central SH2 domain interacts with SOCS target proteins, such as JAKs, bringing them in to close proximity with the ubiquitinating scaffold associated with the SOCS box. Ubiquitination of targets proteins tags them for degradation *via* the proteasome.

Figure 3.

Possible roles for SOCS proteins in T cell differentiation. T cell differentiation from naïve cells into the various functional subtypes (e.g. Th₁, Th₂, Th₁₇, and T regulatory [Treg] cells) primarily depends on the action of cytokines. SOCS regulate the cytokine pathways indicated and thereby dictate CD4⁺ T cell differentiation. Red and green text denote inhibitory and activating signaling respectively.

Figure 4.

SOCS proteins might play critical roles in CD8⁺ T cell maturation. Cytokine signaling drives the maturation of CD8⁺ T cells from naïve to “memory stem cells” (T_{scm}), central memory (T_{cm}), and effector memory (T_{em}) subsets. SOCS family members, in particular SOCS1, counter-regulate these cytokine pathways, dictating the maturation of CD8⁺ T cells. SOCS1 and SOCS3 might in turn be negatively regulated by SOCS2.

Figure 5.

Potential for enhancing T cell function in tumor immunity by knocking down SOCS with short hairpin microRNAs (shMIRs). A) SOCS can inhibit cytokine signaling, thus limiting the effectiveness of adoptively transferred tumor-reactive T cells. B) Transduction of tumor-reactive T cells with SOCS-specific shMIR retroviruses knocks down SOCS expression and may enhance T cell proliferation, effector function, and tumor-killing capability.

Table 1

Columns show factors that induce SOCS family proteins, the phenotypes of mice with knockouts of SOCS genes, and the changes that occur upon forced overexpression of individual SOCS proteins in mice. **CIS**, cytokine-induced SH2 protein; **CNTF**, ciliary neurotrophic factor; **CT1**, cardiotrophin-1; **EGF**, epidermal growth factor; **EPO**, erythropoietin; **G-CSF**, granulocyte-colony stimulating factor; **GH**, growth hormone; **GM-CSF**, granulocyte-macrophage colony stimulating factor; **IFN- α** , interferon alpha/beta; **IFN- γ** , interferon gamma; **LIF**, leukemia inhibitory factor; **OSM**, oncostatin M; **PDGF**, platelet-derived growth factor; **PRL**, prolactin; **SCF**, stem cell factor; **SOCS**, suppressor of cytokine signaling; **TGF- β** , transforming growth factor beta; **TNF- α** , tumor necrosis factor alpha, **TPO**, thrombopoietin; **TSH**, thyrotropin; **TSLP**, thymic stromal lymphopoietin [25,26,51,52,63,105,120,145-152].

SOCS	Inducing factors	Knockout	Transgenic expression
CIS	IL-2, IL-3, IL-6, IL-9, IL-10, CNTF, EGF, EPO, GH, GM-CSF, Leptin, PRL, TPO, TSLP	No reported phenotype	↓ Lactation; ↓NK and ↓ $\gamma\delta$ T cells; ↓ IL-2 signaling, similar to STAT5 KO mice
SOCS1	IL-2, IL-4, IL-6, IL-9, IL-10, IL-21, CNTF, CT1, EPO, G-CSF, GH, IFN- α / β , IFN- γ , Insulin, LIF, PRL, SCF, TNF- α , TSH	Neonatal lethality; ↑IFN γ production and responsiveness; ↑lymphopenia and multiorgan haematopoietic infiltrate	↓CD8 ⁺ /↑CD4 ⁺ development; ↓ $\gamma\delta$ T cells; spontaneous activation and increased apoptosis of peripheral T cells
SOCS2	IL-2, IL-6, CNTF, EPO, GH, Insulin, PRL	Gigantism	Gigantism
SOCS3	IL-1, IL-2, IL-3, IL-4, IL-6, IL-9, IL-10, IL-11, IL-12, IL-22, IL-23, IL-27, CNTF, CT1, EGF, EPO, GH, IFN- α / β , IFN- γ , Insulin, Leptin, LIF, OSM, PDGF, PRL, TGF- β , TNF- α , TPO, TSH	Embryonic lethality due to placental deficiency; ↑ erythrocytosis	Embryonic lethality with ↑ anemia.
SOCS4	EGF	Not reported	Not reported
SOCS5	EGF	No reported phenotype	↑Th1/↓Th2
SOCS6	SCF, Insulin	Slight decrease in growth	Not reported
SOCS7	Simvastatin	↑ Hydrocephalus; Slight decrease in growth; ↑glucose clearance; ↑ hypoglycemia	Not reported