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SOCS3

An essential physiological inhibitor of signaling by interleukin-6 and G-CSF family cytokines

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Abbreviations: CIS, cytokine-inducible Src homology 2 protein; CNTF, ciliary neurotrophic factor; EPO, erythropoietin; ERK, extracellular signal-regulated kinase; ESS, extended Src homology 2 subdomain; G-CSF, granulocyte colony stimulating factor; GQM, glycine-glutamine-methionine; IFN, interferon; IL, interleukin; JAK, Janus kinase; JNK, Jun N-terminal kinase; KIR, kinase inhibitory region; LIF, leukemia inhibitory factor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; OSM, oncostatin M; pY, phosphotyrosine; SH2, Src homology 2; SHP-2, Src homology 2-containing phosphatase 2; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2

SOCS3 is an inducible negative feedback inhibitor of cytokine signaling. Conditional deletion of SOCS3 in mice using the Cre-lox system has now been applied to a range of cell types in the steady-state and under inflammatory, pathogenic, or tumorigenic stress, with the resulting phenotypes demonstrating the effects of SOCS3 in physiological and disease contexts. Together with recent structural and biochemical studies on the mechanisms of SOCS3 binding to cytokine receptors and associated kinases, we now have a better understanding of the non-redundant roles of SOCS3 in the inhibition of cytokine signaling via the receptors gp130, G-CSFR, leptinR, and IL-12Rβ. This review discusses the known functional activities of SOCS3 in fertility and development, inflammation, innate and adaptive immunity, and malignancy as determined by genetic studies in mice.

Introduction

Cytokines are essential regulators of diverse biological processes such as embryogenesis, hemopoiesis, and innate and adaptive immunity. Upon binding to their specific receptors on the cell surface, cytokines can induce a range of signaling cascades within the cytoplasm, controlling critical processes such as cell survival, proliferation, differentiation, and functional activation. Many cytokines, including interleukins, interferons, and hemopoietic growth factors, exert their biological effects via the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway.[1] Cytokines binding to specific cell surface receptors leads to the activation of receptor-associated JAK kinases and JAK-mediated phosphorylation of the receptor cytoplasmic domains. Phosphorylated receptors then recruit STAT proteins, which are in turn phosphorylated, translocate to the nucleus and exert transcriptional control via binding to target gene regulatory sequences.[2]

The suppressor of cytokine signaling (SOCS) proteins are key regulators of the JAK-STAT pathway, ensuring that activation of the pathway for essential cellular processes is spatially and temporally controlled to prevent pathology. The SOCS family has eight members—SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6, SOCS7, and CIS (cytokine-inducible SH2 protein). Of these eight proteins only SOCS1 and SOCS3 have thus far been demonstrated to have non-redundant physiological roles in regulating hemopoietic cytokines. Given that overexpression or ectopic expression of SOCS3 may cause inhibition of non-physiological targets, this review will focus on the physiological functions of SOCS3 as demonstrated by gene targeting studies in mice. As the range of cell type-specific *Socs3* deletion models increases, so does our understanding of the multiple biological functions of SOCS3 in health and disease.

The SOCS Family

The founding member of the SOCS family, SOCS1, was discovered in 1997 by three independent groups, as an inhibitor of IL-6 signaling,[3] a JAK-binding protein,[4] and a STAT-induced STAT inhibitor.[5] Sequence analysis revealed that SOCS1 belongs to a family of SH2 domain-containing proteins (SOCS1–7, CIS[6]). Each member of the greater SOCS family of proteins contains a 40-residue motif known as the SOCS box.[7] The family can be further subdivided based on the presence of protein-interaction domains, including SH2 domains (SOCS), SPRY domains (SSBs), ankyrin repeats (ASBs), WD-40 domains (WSBs), and GTPases.[7]

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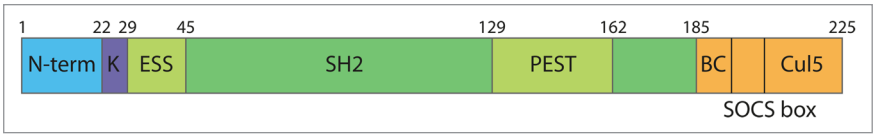

Figure 1. SOCS3 protein domain structure. SOCS3 can be divided into three domains: the N-terminal domain (N-term, residues 1–29), containing the kinase inhibitory region (K, KIR), the Src homology 2 (SH2) domain (residues 30–185, containing an N-terminal extension helix [ESS] and an interpolated PEST sequence), and the SOCS box (residues 186–225, containing a BC box and a Cul5 box).[9,28]

SOCS3 Structure and Biochemistry

The solution structure of SOCS3 was the first of the SOCS protein structures to be solved.[8] SOCS3 can be divided into three domains: the N-terminal domain (residues 1–29), containing the kinase inhibitory region (KIR), the Src homology 2 (SH2) domain (residues 30–185), and the SOCS box (residues 186–225) (reviewed in ref. 9) (**Fig. 1**).

The kinase inhibitory region. The N-terminals of both SOCS3 and SOCS1 contain a 12-residue motif, termed the KIR, that enables these proteins to directly inhibit the activity of JAK1 and JAK2.[10,11] The first eight residues of the SOCS3 KIR are unstructured, and the remaining four residues form the first turn of an α-helix.[8,12] This has led to the reclassification of the KIR as residues 22–29, with residues 30–44 encoding the extended SH2 subdomain (ESS).[9]

The JAKs contain an "activation loop" that must be tyrosine-phosphorylated to reveal the catalytic site and enable kinase activity. When unphosphorylated, the loop blocks ATP and/or substrate binding by acting as a pseudosubstrate. Given the sequence similarity between the KIR and the JAK activation loop, it was suggested that the KIR also acts as a pseudosubstrate for JAK1 and JAK2, thereby inhibiting their activity.[11] This model of SOCS3 inhibition involves binding of the SH2 domain of SOCS3 to the phosphorylated activation loop of JAK, followed by blocking of the active site by the KIR. However, subsequent investigations suggested that SOCS3 does not act as a pseudosubstrate, and instead behaves as a non-competitive inhibitor with respect to both ATP and substrate binding.[13] SOCS3 directly inhibits JAK1, JAK2, and TYK2 by binding to a conserved glycine-glutamine-methionine (GQM) motif in a unique insertion loop in JAKs, and is unable to inhibit JAK3 due to the absence of this motif.[13]

The SH2 domain. SH2 domains are characterized by their ability to interact with phosphotyrosine residues on other proteins. The SOCS3 SH2 domain not only binds to a phosphotyrosine on JAK2 (pY1007),[10] but also to phosphotyrosines on a range of cytokine receptors. In fact, pY757 on the gp130 co-receptor binds the SOCS3 SH2 domain with >1000-fold higher affinity than pY1007 on JAK2.[14,15] The gp130 co-receptor is shared by IL-6, IL-11, LIF, OSM, and CNTF. Other cytokine receptors found to bind with high affinity to the SOCS3 SH2 domain include G-CSFR,[16] leptinR,[17] EPOR,[15,18] IL-12Rβ2,[19] growth hormone receptor,[20] and insulin receptor.[21] The high affinity of the SOCS3 SH2 domain for these particular cytokine receptors (and not for others, such as the IL-10R[22]) is the likely determinant of the specificity of signaling inhibition by SOCS3. As discussed below, genetic deletion of SOCS3 in mice has identified IL-6, IL-11, LIF, CNTF, G-CSF, and leptin as the predominant physiological targets for signaling inhibition by SOCS3. There is evidence that SOCS3 can further influence signal transduction within the cell by competitively blocking recruitment of SHP-2 to Y759 of gp130, thus inhibiting activation of the MAPK-ERK1/2 pathway.[23]

The question of whether SOCS3 first binds the receptor and then JAK, or whether it binds both molecules simultaneously, has recently been answered by solving the crystal structure of a SOCS3/JAK2/gp130 complex.[24] The structure revealed that SOCS3 is bound to both JAK2 and gp130 at the same time, and that SOCS3 in fact targets specific JAK/cytokine receptor pairs. The gp130 phosphopeptide was bound in the canonical phosphotyrosine-binding pocket of the SH2 domain while the reverse face of the SH2 domain along with the ESS helix and the KIR bound in a phospho-independent manner to the JAK2 kinase domain in a region centered around the GQM sequence of the JAK insertion loop. The combined requirement for simultaneous binding to both the receptor and JAK to generate a high avidity complex may explain why SOCS3 can bind JAK1, JAK2, and TYK2, but only inhibit a subset of cytokines known to signal via these JAKs. The usually disordered KIR of SOCS3 folds back into the putative substrate-binding site of JAK2, thus blocking substrate entry and inhibiting JAK activity.

Another feature of the SOCS3 SH2 domain is a 35-residue unstructured loop with sequence similarity to the Pro-Glu-Ser-Thr-rich (PEST) motif.[8,25] The PEST motif is thought to promote proteolytic degradation, usually via the proteasome. Indeed, there is an increase in the half-life of SOCS3 when this region is deleted, indicating that degradation of SOCS3 via the PEST motif may be an important mechanism for limiting cytokine signaling inhibition by SOCS3.

The SOCS box. The C-terminal of SOCS3 contains a 40-residue motif known as the SOCS box—a motif that defines the SOCS family and is now known to be shared by more than 80 human proteins.[26] The SOCS box can be further sub-divided into two interaction sites, the BC-box and the Cul5-box. As their names imply, the BC-box recruits elongins B and C and the Cul5-box binds to the scaffold protein, cullin-5.[27] Together with the Rbx2 RING protein, SOCS3, elonginBC, and cullin-5 form an E3 ubiquitin ligase.[28] This ligase completes the final step in an enzymatic cascade including an E1-activating enzyme and an E2-conjugating enzyme, resulting in the covalent attachment of polyubiquitin to a lysine residue on a target protein. The target protein, bound to the SH2 domain of SOCS3, is thereby ubiquitinated and flagged for proteasomal degradation (**Fig. 2**).

While cullin-5 can bind to all eight of the SOCS proteins (SOCS1–7 and CIS) via the SOCS-box following elonginBC recruitment, SOCS1 and SOCS3 have a significantly lower affinity for cullin-5 than SOCS2, SOCS4, SOCS5, SOCS6, SOCS7,

and CIS.[29] This suggests that the mechanism by which SOCS1 and SOCS3 inhibit the intracellular signaling cascade initiated by cytokine stimulation is primarily via direct inhibition of JAK activity, whereas the primary mechanism of action of the other members of the SOCS family is via ubiquitination of signaling intermediates leading to their proteolysis.

There are a number of reported targets of the SOCS3 E3 ubiquitin ligase—IRS1/2,[30] CD33,[31] Siglec7,[32] indoleamine 2,3-dioxygenase (IDO),[33] FAK1,[34,35] G-CSFR,[36,37] and JAK1[38] (reviewed in ref. 39). In SOCS3-deficient primary mouse embryonic fibroblasts, insulin receptor substrate (IRS)1, and IRS2 do not undergo proteolysis in response to hepatitis C virus core protein, indicating a role for SOCS3 ubiquitin ligase in their degradation.[30] In the case of G-CSFR, SOCS3 binds to pY729 of the receptor via its SH2 domain, directly inhibits receptor-bound JAK via its KIR and also forms an E3 ubiquitin ligase to ubiquitinate lysine 632 of the receptor. This leads to trafficking of the receptor from endosomes to lysosomes and the termination of STAT5 and ERK activation.[36] In primary mouse myeloid progenitor cells, SOCS3 inhibition of G-CSF-induced colony formation is dependent on the SOCS box.[40] Mice with a C-terminal truncated form of the G-CSFR resulting in loss of the SOCS3 recruitment site (Y729) show reduced SOCS3 mRNA and protein expression and an increased STAT5/STAT3 activation ratio in response to G-CSF.[41] SOCS3 has also been shown to bind to phosphorylated JAK1 and promote its proteasomal degradation in a SOCS box-dependent manner.[38]

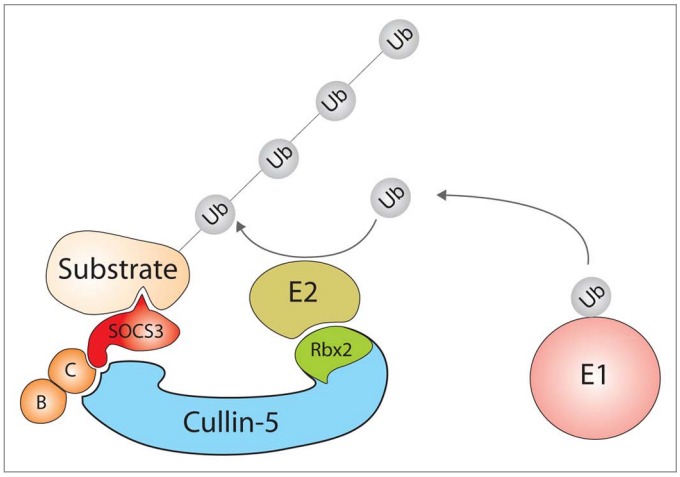

Figure 2. Diagram of the SOCS3 E3 ubiquitin ligase. Scaffold protein cullin-5 binds to Rbx2 and recruits the ubiquitin-conjugating E2 enzyme. By binding to the SOCS3/elonginBC complex, cullin-5 also recruits the SOCS3-associated substrate. The SOCS3 E3 ligase promotes transfer of ubiquitin (Ub) from the E2 subunit to a substrate lysine and subsequent proteasomal degradation of the substrate. Known substrates of the SOCS3 E3 ubiquitin ligase include IRS1/2,[30] CD33,[31] Siglec7,[32] IDO,[33] FAK1,[34,35] G-CSFR,[36,37] and JAK1.[38]

Expression and Regulation of SOCS3 Levels

The expression of SOCS3 is tightly regulated at both the mRNA and protein levels. *Socs3* transcription is rapidly induced by a range of type I and type II cytokines, signaling via STAT1 and/or STAT3.[3] The best characterized of these are members of the gp130 family, including IL-6, IL-11, and LIF.[42] Induction of *Socs3* by IL-6 also requires specificity protein 3 (Sp3),[43] while TNFα induces *Socs3* expression via activation of the MKK6/MAPK cascade,[44,45] and LPS induction of *Socs3* involves the MAPK-ERK1/2 and JNK pathways downstream of Toll-like receptor 4.[46] In addition, growth hormone induces *Socs3* expression via CREB/c-Fos/c-Jun and FOXO3a[47] and cAMP induces *Socs3* expression via Epac-1 (exchange protein directly activated by cAMP 1).[48,49] Other known inducers of *Socs3* transcription include leptin,[50] IFN-λ,[51] IL-1,[52] IL-9,[53] IL-10,[54] and IL-21.[55] Transcription of *Socs3* is repressed by proto-oncoprotein growth factor independence-1B (GFI-1B)[56] and hepatocyte nuclear factor-1β (HNF-1β),[57] and the induction of *Socs3* by IL-6 and IL-21 is inhibited by TGFβ.[58] Posttranscriptionally, *Socs3* mRNA can be stabilized by TNFα via activation of the MKK6/MAPK cascade and MAPK-activated protein kinase 2 (MK2).[44]

SOCS3 protein levels are tightly controlled via proteolysis, using both proteasomal and non-proteasomal pathways. Modification or deletion of the PEST, Lys6, or SOCS box sequences have all been shown to affect SOCS3 protein stability in vitro;[8,59-61] however, the in vivo molecular mechanisms by which SOCS3 protein stability is controlled remain unclear. In vitro data suggests that SOCS2 can induce proteolysis of SOCS3, with accelerated SOCS3 degradation observed in cell lines overexpressing SOCS2.[62,63] The proposed mechanism for this interaction is that SOCS2 binds to both SOCS3 and elonginBC, forming an E3 ubiquitin ligase that mediates the ubiquitination of SOCS3 and its targeting to the proteasome for degradation. However, studies using *Socs2*$^{-/-}$ mice have revealed that SOCS3 protein regulation is independent of SOCS2 in primary cells.[64]

SOCS3 in Fertility and Development

Homozygous null mutation of *Socs3* is lethal between embryonic day 11 (E11) and E13, due to defects in placental development.[65] Compared with controls, the placentae of *Socs3*$^{-/-}$ embryos have a reduced spongiotrophoblast layer, increased giant trophoblast cells, and reduced vascularity of the labyrinthine layer. Contrary to a previous study in which *Socs3*$^{-/-}$ embryos were found to die between E12 and E16 due to excessive EPO-induced erythropoiesis,[66] Roberts and colleagues found no evidence of significantly altered yolk sac or fetal liver hemopoiesis in *Socs3*$^{-/-}$ embryos. Embryonic lethality in *Socs3*$^{-/-}$ mice can be rescued by tetraploid aggregation, in which the embryo is SOCS3-deficient but the extraembryonic cells of the placenta express SOCS3.[67] Rescued *Socs3*$^{-/-}$ embryos survived up to postnatal day 25, after which they succumbed to lethal cardiac hypertrophy. Interestingly, a recent study in which *Socs3* was deleted specifically in cardiomyocytes found that SOCS3 deficiency in the heart leads to death by 33 weeks of age from cardiomyopathy.[68] *Socs3*$^{-/-}$ embryonic lethality can also be rescued by simultaneous deletion of LIF or LIFR or by trophoblast stem cell transplantation, demonstrating that lethality is due to unrestrained LIF signaling in trophoblast cells.[67,69,70]

LIF also has an essential role in the maintenance of pluripotency in embryonic stem (ES) cells. When cultured in LIF, *Socs3*$^{-/-}$ ES cells derived de novo from heterozygous crosses display reduced self-renewal and increased differentiation into primitive endoderm compared with controls.[71] Signaling via both JAK-STAT and MAP kinase pathways was enhanced in these cells, with MAP kinase inhibitors able to partially rescue the SOCS3-deficient phenotype. Interestingly, ES cells in which SOCS3 is moderately overexpressed also undergo spontaneous differentiation in the presence of LIF.[72] SOCS3 is therefore a critical inhibitor of LIF signaling in ES cells, and regulates the balance between JAK-STAT and MAP kinase pathways important for self-renewal and pluripotency.

SOCS3 in Inflammation

Macrophage/neutrophil-specific *Socs3* deletion (*LysM*-Cre). Due to the homozygous embryonic lethality of germline *Socs3* deletion, subsequent investigations into the physiological roles of SOCS3 have been undertaken using the Cre-lox system to specifically delete *Socs3* from discrete cell types. Mice expressing Cre recombinase under the control of the lysozyme M (*LysM*) promoter were crossed with mice in which the entire *Socs3* coding region was flanked by *loxP* sites (*Socs3*$^{fl/fl}$), to produce offspring in which *Socs3* was deleted only in macrophages and neutrophils expressing *LysM*.[22,73] Using this model, SOCS3 was found to have a non-redundant role in the inhibition of gp130-mediated signaling in macrophages, and to specifically inhibit STAT3 activation by IL-6, but not by IL-10.[22,74] In the absence of SOCS3 in macrophages, mice were protected from LPS-induced endotoxemia, and this was likely due to the enhanced anti-inflammatory effects of STAT3 induced by IL-10, IL-6, IL-11, and LIF in these cells.[22] Using two different conditional deletion models—*LysM*-Cre and *Tie2*-Cre—in which *Socs3* was deleted from mature neutrophils and hemopoietic stem cells respectively, SOCS3 was found to inhibit G-CSF signaling in these cells.[75]

In a mouse model of toxoplasmosis, SOCS3 deletion in macrophages and neutrophils sensitized these cells to the anti-inflammatory effects of IL-6, and reduced their production of IL-12.[76] As a consequence, the mice succumbed to toxoplasmosis faster than controls. SOCS3 therefore plays an essential role in directing IL-6 signaling in macrophages and neutrophils in response to *Toxoplasma gondii*, to elicit an effective innate immune response.

The effect of macrophage SOCS3 deficiency on tumorigenesis was examined using a B16 melanoma transplantation model.[77] While subcutaneous tumor size was unaffected, mice with SOCS3-deficient macrophages survived longer than controls, and showed reduced metastases following intravenous melanoma cell injection. In response to tumor lysates in vitro, SOCS3-deficient macrophages displayed prolonged STAT3 phosphorylation, increased CCL8 (MCP-2), and reduced TNF-α and IL-6 production compared with controls. In this context, *Socs3* inhibition had both anti-inflammatory and anti-tumor effects, and may therefore be a potential therapeutic strategy in the prevention of tumor metastasis.

Hepatocyte-specific *Socs3* deletion (*Alb*-Cre). Mice expressing an albumin-Cre (*Alb*-Cre) transgene were crossed with *Socs3*$^{-/fl}$ mice to generate offspring with *Socs3* deleted only in hepatocytes.[73] Following IL-6 injection, STAT1 and STAT3 phosphorylation was prolonged in liver extracts from these mice compared with controls. This effect was specific for IL-6, as *Socs3* deficient livers did not display enhanced STAT1 activation in response to IFN-γ. Using microarray analysis, prolonged IL-6 signaling and STAT3 activation in SOCS3-deficient hepatocytes was found to induce an interferon-regulated pattern of gene expression, possibly due to enhanced STAT1 phosphorylation.[73] These data suggest that in the absence of SOCS3, IL-6 signaling is predominantly immunosuppressive rather than inflammatory. Similarly, *Socs3* deletion in the liver by intravenous injection of adenovirus carrying Cre recombinase resulted in STAT3 hyperactivation and promoted experimentally-induced fibrosis.[78] Expression of TGF-β1 was enhanced by SOCS3 deletion, but suppressed by overexpression of a dominant-negative STAT3 or SOCS3.

Hemopoietic/endothelial cell-specific *Socs3* deletion (*vav*-Cre). Mice with a hemopoietic and endothelial cell-specific deletion of *Socs3* died from chronic inflammatory disease in early adulthood, and this process was exacerbated by administration of G-CSF in vivo.[79] When cultured in G-CSF in vitro, SOCS3-deficient hemopoietic progenitor cells showed increased clonogenicity compared with controls. These data implicate G-CSF as the primary effector in the neutrophilia-induced pathology seen in mice with SOCS3-deficient hemopoiesis, and confirm the findings of another study in which SOCS3 was shown to inhibit G-CSF signaling in neutrophils.[75]

In a mouse model of acute inflammatory arthritis, SOCS3 deficiency in hemopoietic and endothelial cells led to more severe joint inflammation and increased joint and lymphoid tissue neutrophilia.[52] As in previous studies using *vav*-Cre-mediated *Socs3* deletion, this effect was due to enhanced production of and responsiveness to G-CSF and IL-6. The severity of experimentally-induced arthritis was reduced by injection of an adenovirus expressing SOCS3 directly into affected joints, implicating SOCS3 as an important regulator of inflammatory pathology in arthritis.[80]

The precise pro- and anti-inflammatory effects of IL-6 in the absence of SOCS3 were investigated by crossing *Socs3*$^{-/\Delta vav}$ mice onto an IL-6$^{-/-}$ background.[81] In the absence of IL-6, *Socs3*$^{-/\Delta vav}$ mice were protected from the lethal inflammatory disease normally observed in adulthood, indicating an essential pro-inflammatory role for IL-6 in disease progression. Similarly, IL-6 deficiency protected *Socs3*$^{-/\Delta vav}$ mice from lethal inflammation in response to IL-1β administration or LCMV infection, clearly demonstrating deleterious pro-inflammatory activity of IL-6 in these contexts.

SOCS3 SOCS box deletion. Mice expressing a truncated SOCS3 protein lacking the SOCS box (*Socs3*$^{\Delta SB/\Delta SB}$) are also hyper-responsive to G-CSF and develop more severe experimental arthritis compared with controls, but their phenotype is mild compared with the *Socs3*$^{-/\Delta vav}$ model, with no evidence of perturbed steady-state hemopoiesis or spontaneous inflammatory

disease.[82] Unlike *Socs3*$^{-/-}$ mice, *Socs3*$^{\Delta SB/\Delta SB}$ mice are viable and healthy, showing that SOCS3 retains its essential activity in the absence of the SOCS box. As previously discussed, this supports the suggestion that the dominant mechanism of action of SOCS3 is via the KIR and SH2 domains, rather than via the formation of an E3 ubiquitin ligase and subsequent substrate proteolysis.

Lymphoid/keratinocyte-specific *Socs3* deletion (*MMTV*-Cre or *K5*-Cre). Wound healing is controlled by cytokines and chemokines produced by both keratinocytes and resident inflammatory cells, with gp130-mediated STAT3 activation thought to be critical for its normal progression. When *Socs3* was deleted using the mouse mammary tumor virus (*MMTV*)-Cre transgene, expression of phosphorylated STAT3 was increased and wound healing impaired compared with controls.[83] This effect was reversed by simultaneous deletion of *gp130* using *MMTV*-Cre. Wound healing was also impaired in mice with a keratinocyte-specific *Socs3* deletion (*K5*-Cre), but without the neutrophilia seen in the *MMTV*-Cre model. Interestingly, deletion of *Socs3* using *MMTV*-Cre has also revealed a critical role for SOCS3 in inhibiting STAT3 activation and c-myc expression during involution of the mammary gland.[84]

Endothelial cell-specific *Socs3* deletion (*Tie2*-Cre). A role for SOCS3 in inhibiting pathological angiogenesis has recently been demonstrated in mouse models of oxygen-induced retinopathy and tumor growth.[85] Mice with SOCS3-deficient endothelial cells had normal physiological angiogenesis but increased endothelial cell proliferation and vascularization in response to hypoxia, which was associated with enhanced activation of STAT3 and the serine/threonine kinase mTOR. SOCS3-deficient mice also developed larger tumors with greater vessel density than controls following subcutaneous injection of lung cancer or melanoma cell lines.

Mutated SOCS3 binding site of gp130 (*gp130*$^{Y757F/Y757F}$). Mice with a mutation in the SOCS3 binding site of gp130 succumbed to chronic gastric inflammation leading to tumorigenesis.[86] Gastric tumors in these mice were characterized by elevated IL-11 and IL-6 expression and aberrant STAT3 and STAT1 activation, but did not occur in compound mutants lacking IL-11Rα. These data reveal an essential physiological role for SOCS3 binding to gp130 in the inhibition of IL-11 signaling which in the absence of such control leads to inflammation-associated tumorigenesis.

Intestinal epithelial cell-specific *Socs3* deletion (*vilin*-Cre or *T3b*-Cre). Deletion of *Socs3* in the gastrointestinal epithelium using *vilin*-Cre had no effect under steady-state conditions, but led to crypt hyperproliferation and hyperplasia in response to dextran sodium sulfate.[87] These mice were also susceptible to colon tumors with the additional insult of azoxymethane. Similarly, deletion of *Socs3* using *T3b*-Cre also led to gastric tumor development, mediated via enhanced leptin-induced STAT3 activation.[88] These data demonstrate the link between SOCS3 regulation of inflammation and tumor development, and point to the potential use of SOCS3 agonists in cancer treatment.

SOCS3 in Adaptive Immunity

The role of SOCS3 in adaptive immunity is thought to be primarily immunosuppressive, due to its inhibition of cytokine-induced STAT3 and STAT1 activation.

SOCS3 in DCs and NKT cells. Dendritic cells (DCs) form the link between innate and adaptive immunity by activating both antigen-specific effector T cells and T regulatory (Treg) cells. SOCS3 is thought to play a role in determining the nature of the T cell response, as *Socs3*$^{-/-}$ DCs preferentially induce the immunosuppressive *Foxp3*$^{+}$ Treg cells in vivo.[89] Treg cells themselves are naturally deficient in SOCS3, and SOCS3 overexpression in these cells decreases their proliferation and suppressive ability.[90] *Socs3*$^{-/-}$ DCs displayed enhanced STAT3 activation, reduced expression of MHC class II, co-stimulatory molecules and IL-12, and appeared to have a more tolerogenic phenotype than controls. Indeed, adoptive transfer of *Socs3*$^{-/-}$ DCs ameliorated experimental autoimmune encephalomyelitis (EAE)—a mouse model of multiple sclerosis.[89] However, injection of SOCS3-overexpressing DCs has also been reported to suppress EAE.[91]

In transgenic mice in which SOCS3 was overexpressed in NKT cells (*Lck*-SOCS3 Tg), IL-4 and IFN-γ production was reduced, supporting an immunosuppressive role for SOCS3.[92] Conditional deletion of *Socs3* in these cells using *Lck*-Cre had the expected opposite effect, with increased IL-4 and IFN-γ production and hypersensitivity to Concanavalin A-induced hepatitis.[92]

SOCS3 in T helper cell polarization. Following activation, CD4^{+} T cells undergo polarization into phenotypically distinct subtypes of T helper (TH) cells in order to respond appropriately to a variety of immunological challenges. The direction of TH cell polarization is controlled by the cytokine environment at the site of antigen stimulation, and SOCS proteins would therefore be expected to affect the outcome of this process. The TH1 phenotype is driven by IFN-γ and IL-12, signaling via STAT1 and STAT4, and is associated with viral clearance. TH2 differentiation requires IL-4 and STAT6, and is a hallmark of allergic responses and parasitic infections.

SOCS3 is preferentially expressed in TH2 rather than TH1 cells,[93] and its transgenic overexpression in T cells drives TH2 polarization in a mouse model of airway hypersensitivity,[94] as well as reduced production of IL-2 in response to CD28 co-stimulation.[95] Conversely, mice with a dominant-negative mutation in the KIR of SOCS3 or SOCS3 haploinsufficiency showed decreased TH2 polarization. This finding was confirmed in mice with T cell-specific *Socs3* deletion (*Lck*-Cre) that showed reduced ovalbumin-induced airway hyperresponsiveness and increased sensitivity to *Leishmania major* infection compared with controls.[96] This was accompanied by increased TGFβ1 and IL-10 and reduced IL-4 production in T cells compared with controls, which is characteristic of TH3 differentiation.[96]

The ability of SOCS3 to enhance TH2 differentiation may be due to its simultaneous inhibition of the TH1 pathway. SOCS3 can compete with STAT4 for binding to IL-12Rβ, thereby inhibiting IL-12-driven TH1 differentiation.[19] Administration of IL-7

in mice accelerates viral clearance, which is a TH1-mediated effect that requires both induction of IL-6 and suppression of SOCS3.[97] As previously discussed, the interferon-type transcriptional response is dominant over the IL-6-type response in the absence of SOCS3,[73] and this may contribute to increased viral clearance.

A subsequent study using *MMTV*-Cre to delete *Socs3* in T cells showed no effect of SOCS3 on TH1/TH2 polarization.[98] Instead, SOCS3 deletion was found to enhance differentiation into the TH17 phenotype, driven by IL-6, IL-23, and TGF-β and characterized by secretion of IL-17. These contradictory findings may be due to the different expression pattern of *MMTV*-Cre compared with *Lck*-Cre—the former would delete floxed *Socs3* not only in B and T cells, but also in megakaryocytes and erythroid cells and some epithelial and secretory cell types[99] whereas *Lck*-Cre is T cell-specific.[100] A recent study has confirmed the effect of SOCS3 on IL-17 production, with overexpression of SOCS3 in T cells resulting in reduced plasma levels of IL-17 and increased severity of aortic aneurysm.[101]

SOCS3 in B cells. Expression of *Socs3* mRNA is low in B cell progenitors and increases as B cells mature.[35,55] Increased SOCS3 production correlates with egress of mature B cells from the bone marrow into the peripheral circulation, with the mechanism thought to involve SOCS3-mediated proteasomal degradation of FAK leading to reduced adhesion to VCAM-1 within the bone marrow microenvironment.[35] In support of this hypothesis, deletion of *Socs3* using *MMTV*-Cre caused accumulation of immature B cells within the bone marrow. However, this finding was not confirmed when *Socs3* was deleted exclusively in the B cell lineage using *mb1*-Cre, suggesting that SOCS3 produced by other cell types within the bone marrow may regulate B cell migration.[55] Deletion of *Socs3* using *mb1*-Cre was found to prolong IL-6-induced STAT3 activation in plasma cells and alter germinal center function following T cell-dependent immunization.[55]

SOCS3 in Hemopoietic Malignancies

IL-6 signaling has been implicated in the pathogenesis of multiple myeloma,[102] constitutive STAT3 activation is a hallmark of many leukemias (reviewed in ref. 103) and activating mutations and gene fusions involving *JAK2* are associated with myeloproliferative diseases and hemopoietic malignancies (reviewed in ref. 104). As an inhibitor of IL-6, STAT3, and JAK2 signaling, SOCS3 has therefore been implicated as a potential tumor suppressor. In support of this hypothesis, increased expression of SOCS3 mRNA and protein has been demonstrated in murine and human follicular lymphomas.[105] There is also evidence that SOCS3 is pro-apoptotic in a mouse model of multiple myeloma.[106] Numerous studies have investigated *Socs3* methylation in mouse and human hemopoietic malignancies (reviewed in ref. 107); however, no consensus has yet emerged on whether SOCS3 expression is beneficial or detrimental to disease outcome.

SOCS3 in Leptin Resistance and Obesity

Leptin is a cytokine-like hormone of the hypothalamus that signals via the JAK-STAT pathway to suppress food intake and control body weight. Leptin resistance is a common feature of obesity in mice and humans. Transcription of *Socs3*, but not *Cis*, *Socs1*, or *Socs2*, was found to be induced in the hypothalamus following leptin administration, and was increased in mice with leptin-resistant obesity compared with controls.[50] Deletion of *Socs3* in neurons using *nestin*-Cre or *synapsin*-Cre resulted in prolonged STAT3 phosphorylation in the hypothalamus, decreased food intake and increased weight loss following leptin administration.[108] When fed a high-fat diet, SOCS3-deficient mice had lower food intake, gained less weight than controls, and were protected from leptin and insulin resistance. A similar phenotype was observed in mice with *Socs3* haploinsufficiency.[109] Together, these data suggest that SOCS3 contributes to diet-induced leptin and insulin resistance and obesity and could therefore be a therapeutic target for the treatment of these conditions.

Deletion of *Socs3* in specific hypothalamic cell subsets expressing either pro-opiomelanocortin (POMC)[110] or steroidogenic factor-1 (SF-1)[111] has confirmed the role of SOCS3 in suppressing leptin signaling in the brain, but revealed subtle differences in the contributions of these neurons to the regulation of food intake and energy expenditure under high-fat diet conditions. A recent study found that SOCS3 induction in a subset of agouti-related protein (AgRP)-expressing neurons in the hypothalamus was the first step in the development of leptin resistance, and transgenic expression of SOCS3 in these neurons mimicked the metabolic effects of a high-fat diet.[112] On a standard diet, mice with deletion of *Socs3* in the mediobasal hypothalamus had lower food intake, weight gain, and adiposity than controls, suggesting that SOCS3 is also required for normal metabolic homeostasis.[113]

Skeletal muscle is also involved in regulating energy expenditure and insulin sensitivity, and SOCS3 expression is increased in the skeletal muscle of obese compared with non-obese humans.[114] Mice with skeletal muscle-specific *Socs3* deletion showed increased glucose uptake into this tissue due to enhanced phosphorylation of IRS1 and Akt, and were protected against diet-induced hyperinsulinemia and insulin resistance.[115] SOCS3 deletion did not affect normal muscle development, so inhibition of skeletal muscle SOCS3 may be an effective treatment for insulin resistance in obesity.

SOCS3 in Diseases of the Central Nervous System

Mice with neuron-specific *Socs3* deletion (*nestin*-Cre) recovered more quickly from acute spinal cord injury than controls, due to enhanced STAT3 phosphorylation in reactive astrocytes, which limited inflammatory cell-mediated neuron and oligodendrocyte death.[116] Similarly, deletion of *Socs3* in oligodendrocytes led to increased LIF signaling and STAT3 phosphorylation and protected against drug-induced demyelination and apoptosis.[117] Both LIF and CNTF are known oligodendrocyte survival factors,[118] and also targets of SOCS3 suppression, therefore SOCS3 may have a deleterious effect in the context of demyelinating disease. Deletion of *Socs3* in adult retinal ganglion cells promoted optic nerve axon regeneration, and this was enhanced by exogenous CNTF[119] or simultaneous deletion of PTEN.[120]

Concluding Remarks

In the past, overexpression of SOCS proteins in vitro led to the conclusion that all cytokines signaling via the JAK-STAT pathway could be inhibited by a SOCS protein. More recently, the development of new conditional deletion models and biochemical analyses has revealed that SOCS proteins regulate only a limited subset of cytokines in vivo. For SOCS3, those cytokines are LIF, IL-6, IL-11, and CNTF, as well as G-CSF, leptin and IL-12 (**Fig. 3**). It is not yet clear why SOCS3 exhibits such selectivity for these cytokine pathways in vivo, but it is likely to involve its high affinity for the relevant receptors—gp130, G-CSFR, leptinR, and IL-12Rβ. There is as yet no evidence for dysregulated GM-CSF, EPO, or TPO signaling in SOCS3 conditional knockout mice, despite the utilization of the JAK-STAT pathway by these cytokines and their ability to induce expression of SOCS3. This raises the question of redundancy within the SOCS family, which could be addressed using compound conditional deletion models. Novel biological functions of SOCS3 are likely to be revealed by the discovery of additional substrates of the SOCS3 E3 ubiquitin ligase. In addition, the roles of other members of the greater SOCS box family (SSBs, ASBs, WSBs, etc.) in controlling cytokine signaling in the steady-state and under pathological conditions remain to be defined.

The evidence presented here suggests that SOCS3 is broadly anti-inflammatory, immunosuppressive and anti-tumorigenic, but its development as a therapeutic agent in cytokine-driven conditions such as arthritis, viral or bacterial infection, or cancer may be hindered by inconsistent findings in different cellular contexts. For example, *Socs3* deletion in macrophages renders mice resistant to melanoma,[77] but deletion in endothelial cells increases their susceptibility.[85] The anti-inflammatory roles of SOCS3 in arthritis and in the gastrointestinal tract are more well defined, however translation of these findings into the human context for diagnostic and therapeutic purposes will require further analysis of SOCS3 function within the context of the greater SOCS family of proteins.

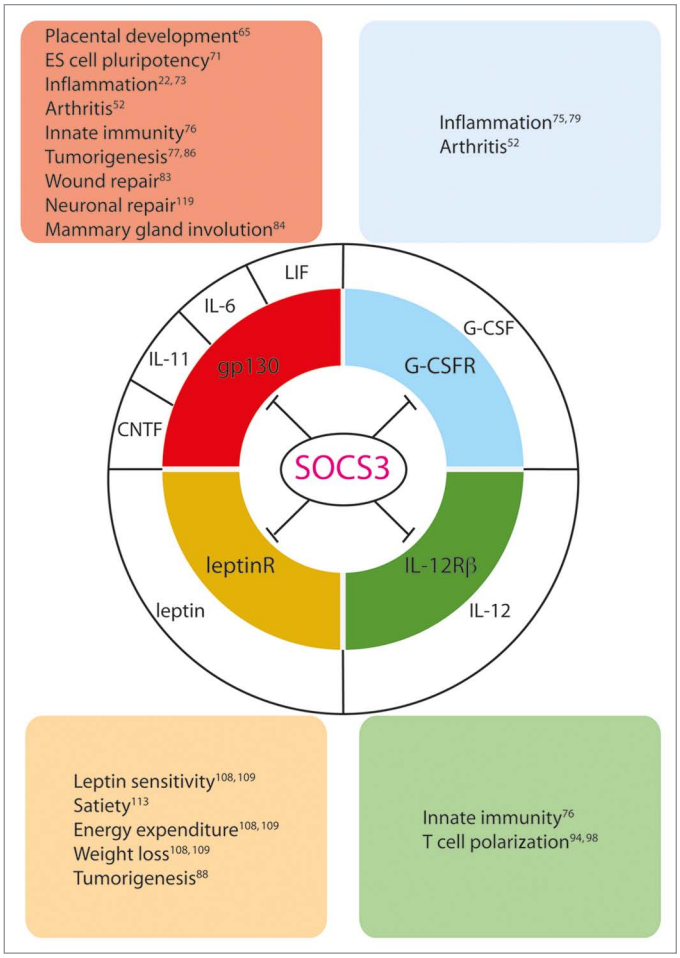

Figure 3. The physiological functions of SOCS3 are mediated via direct binding to gp130, G-CSFR, leptinR, and IL-12Rβ. By binding to these receptors, SOCS3 inhibits signaling by their cytokine ligands, thereby regulating a variety of biological processes.

Disclosure of Potential Conflicts of Interest

NA Nicola is a patent holder on SOCS3 and its activities.

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