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*Review Article*

# SOCS proteins in development and disease

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**Abstract:** Cytokine and growth factor signaling mediates essential roles in the differentiation, proliferation, survival and function of a number of cell lineages. This is achieved via specific receptors located on the surface of target cells, with ligand binding activating key intracellular signal transduction cascades to mediate the requisite cellular outcome. Effective resolution of receptor signaling is also essential, with excessive signaling having the potential for pathological consequences. The Suppressor of cytokine signaling (SOCS) family of proteins represent one important mechanism to extinguish cytokine and growth factor receptor signaling. There are 8 SOCS proteins in mammals; SOCS1-7 and the alternatively named Cytokine-inducible SH2-containing protein (CISH). SOCS1-3 and CISH are predominantly associated with the regulation of cytokine receptor signaling, while SOCS4-7 are more commonly involved in the control of Receptor tyrosine kinase (RTK) signaling. Individual SOCS proteins are typically induced by specific cytokines and growth factors, thereby generating a negative feedback loop. As a consequence of their regulatory properties, SOCS proteins have important functions in development and homeostasis, with increasing recognition of their role in disease, particularly their tumor suppressor and anti-inflammatory functions. This review provides a synthesis of our current understanding of the SOCS family, with an emphasis on their immune and hematopoietic roles.

**Keywords:** SOCS, development, immunity, disease, JAK-STAT, cytokine, growth factor, signalling, receptor tyrosine kinase

## Introduction

### *Overview*

Cytokines and growth factors are important mediators of cell-cell communication. These glycoproteins are secreted by cells in response to normal developmental cues or environmental stimuli to relay information to specific target cells expressing the appropriate receptor on their surface. Receptor binding initiates a range of intracellular signaling cascades that lead to appropriate cellular responses, such as proliferation, differentiation, survival and functional activation [1, 2]. Subsequent dissipation of receptor signaling is essential to ensure the response of the cell does not become pathogenic. The Suppressor of cytokine signaling (SOCS) proteins represent one key mechanism by which this level of control is achieved [3, 4].

### *SOCS structure and function*

There are eight mammalian SOCS family members; SOCS1-7 and the alternatively named Cytokine-inducible SH2-containing protein (CISH) [5] (**Figure 1**). While SOCS proteins are able to regulate signaling downstream of a range of receptors, current evidence indicates that CISH and SOCS1-3 are most often associated with regulation of cytokine receptor signaling through the JAK-STAT pathway, while SOCS4-7 predominantly regulate growth factor receptor signaling [6-8]. This difference reflects their evolutionary history, with the precursors to the SOCS4-7 sub-family existing prior to the emergence of a functional cytokine receptor pathway, while the sub-family comprising of SOCS1-3 and CISH emerged later, co-incident with the cytokine receptor family [9, 10]. Within each sub-family, pairs of SOCS proteins have similar structure and function: CISH/SOCS2, SOCS1/SOCS3, SOCS4/SOCS5 and SOCS6/SOCS7, again reflecting their evolutionary history [9].

Each SOCS protein contains three distinct domains; an N-terminal domain of low conservation, a conserved central Src-homology 2

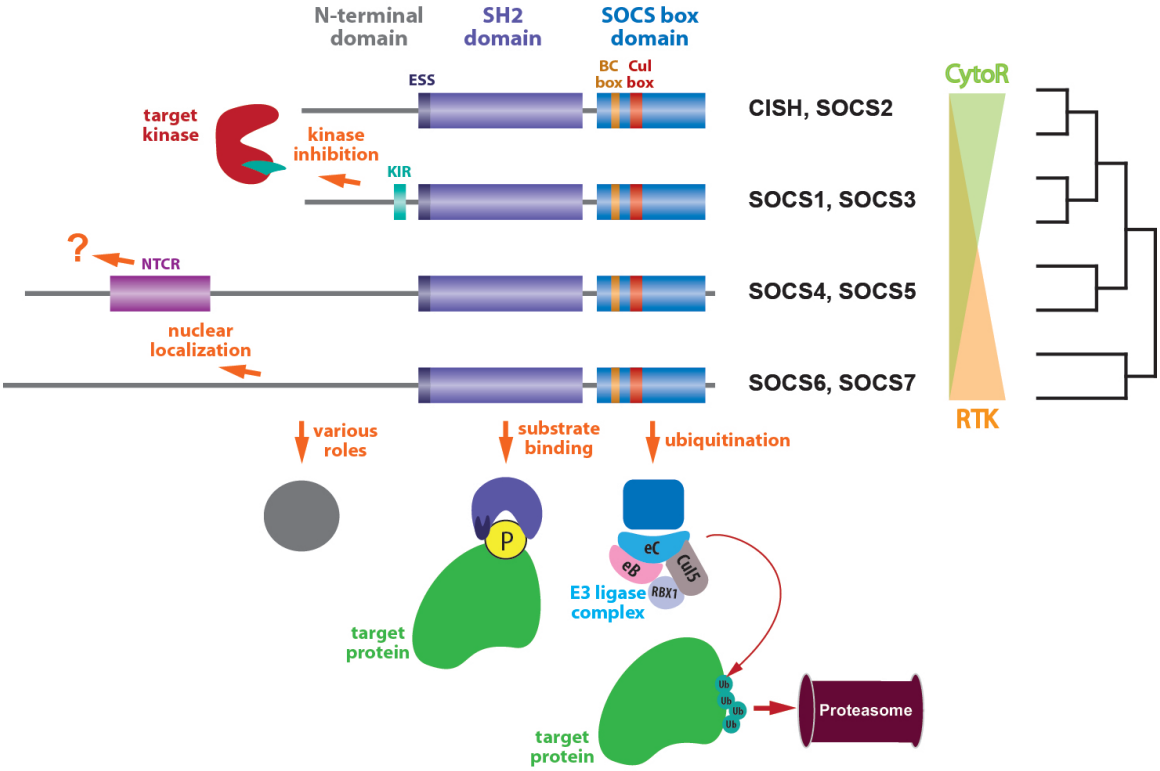


**Figure 1.** Structural and functional relationships amongst SOCS proteins. SOCS proteins can be grouped into pairs with similar structure and function, and these further grouped into those mainly acting on Cytokine receptor (CytoR) signaling and those mainly acting on Receptor tyrosine kinase (RTK) signaling, reflecting evolutionary relationships. All SOCS proteins consist of three conserved domains, the N-terminal, SH2 and SOCS box domains. The N-terminal domain is the least conserved and has a variety of roles, with specific sub-domains identified in certain SOCS pairs, including the kinase inhibitory region (KIR) in SOCS1 and SOCS3 and the N-terminal conserved region (NTCR) in SOCS4 and SOCS5. The SH2 domain is lengthened by the addition of an extended SH2 sequence (ESS) and is involved in substrate binding via interaction with specific phosphotyrosine residues on the target protein. The SOCS box consists of BC box and Cul box sub-domains that recruit Elongin B and C, Cullin5, RBX1 and other E3 ligase components to mediate ubiquitination of target proteins and their subsequent proteasomal degradation.

(SH2) domain, and a more highly conserved C-terminal domain termed the SOCS box. The N-terminal domain is variable in length between members, with SOCS1-3 and CISH having a shorter N-terminal domain in comparison to SOCS4-7 [11]. Within the N-terminal domains of SOCS1 and SOCS3 is a so-called kinase-inhibitory region (KIR), which is responsible for inhibition of cytokine receptor-associated Janus kinases (JAKs) [12]. SOCS4 and SOCS5 also possess a highly conserved region within their N-terminal domain, termed the N-terminal conserved region (NTCR), although the role of this sequence has not been elucidated [13]. In contrast, the N-terminal domains of SOCS6 and SOCS7 have been shown to be required for their respective nuclear translocation and, in the case of SOCS7, appears to be involved in transporting other proteins into the nucleus [14-16]. The SH2 domains of the SOCS proteins interact in a context-specific manner with phosphotyrosine residues present on their target proteins, including cell surface receptors, imparting on SOCS proteins their target specificity [4]. These are longer than typical SH2 domains due to a so-called extended SH2 sequence (ESS) also found in STAT1 and STAT3, which contributes to their function [12]. Finally, the SOCS box is comprised of two functional sub-domains; a BC box that recruits Elongin B and C, and a Cul box that mediates Cullin5 binding. The resulting complex is able to bind RBX2, leading in turn to recruitment of the remaining components of an E3 ubiquitin ligase complex [17, 18].

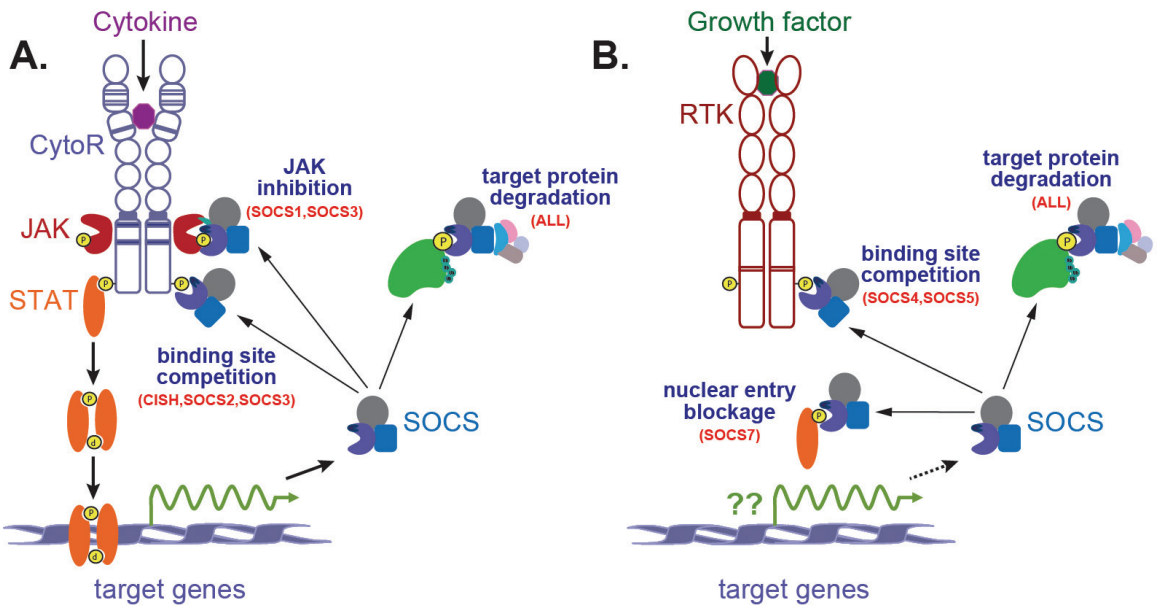


**Figure 2.** Signaling via by cytokines and growth factors and its negative regulation by SOCS proteins. Cytokines (A) or growth factors (B) bind to their respective cell surface receptors, Cytokine receptors (CytoRs) and Receptor tyrosine kinases (RTKs), leading to receptor dimerization. For CytoRs this leads to activation of associated intracellular JAKs, which phosphorylate tyrosine residues on the receptor complex, creating docking site for STATs. These are then phosphorylated, enabling dimerization with other STATs, followed by translocation to the nucleus, where they act as transcription factors to induce expression of target genes that mediate a range of biological processes. These targets include SOCS genes capable of regulating receptor signaling, creating a negative feedback loop. RTKs possess intrinsic tyrosine kinase activity and may by-pass JAK and/or STAT activation. Individual SOCS proteins negatively regulate signaling by several mechanisms: degradation of receptors or associated proteins via the proteasomal pathway; inhibition of JAK tyrosine activity; competition for receptor phosphotyrosine residues thereby blocking other signaling molecules; prevention of nuclear translocation of key signaling molecules.

*Control of signalling by SOCS proteins*

Certain members of the SOCS family, typically SOCS1-3 and CISH, are induced by cytokine receptors and serve to extinguish signaling from the same receptor, providing a classical negative feedback loop [19] (**Figure 2A**). This occurs via activation of receptor-associated Janus kinases (JAKs), which phosphorylate tyrosine residues on the receptor complex to recruit signaling molecules, including Signal Transducer and Activator of Transcription (STAT) proteins. These also become tyrosine phosphorylated, leading to dimerization and nuclear translocation, where they stimulate transcription of target genes. They include *SOCS* genes, the encoded proteins of which are able to inhibit intracellular signaling by a number of different mechanisms that vary between individual family members. All SOCS proteins are able to regulate receptor signaling through the recruitment of proteasomal degradation components to their target proteins, be they specific receptors or associated molecules. This is achieved by binding to these targets through their SH2 domains and recruitment of Elongin B/C heterodimers, Cullin5 and other components of a E3 ubiquitination complex via their SOCS box [18, 20]. SOCS-associated molecules are then readily able to be ubiquitinated, which typically targets these proteins to the proteasome. SOCS members can also regulate signaling via alternate methods. This is particularly true of SOCS1 and SOCS3, which bind Cullin5 at a much lower affinity than other SOCS proteins and remain partially active even in the absence of their SOCS box [20, 21]. As an alternative mechanism, SOCS1 and SOCS3 are able to directly inhibit JAK kinases, binding via their KIR domain to the JAK activation loop to inhibit kinase activity [12, 22-24]. CISH, SOCS2 and SOCS3 can also inhibit signaling via their ability to bind to phosphotyrosine residues typically on receptors, thereby blocking access of other SH2-containing signaling molecules [11, 25-28].

**Table 1.** Function of SOCS proteins revealed by mouse models

| | Knockout | | | | Transgenic | | |
|---|---|---|---|---|---|---|---|
| SOCS protein | Type | Phenotype | Affected pathway | REF | Phenotype | Affected pathway | REF |
| CISH | | *Not yet reported* | | [256] | Growth retardation | GH/STAT5B | [54] |
| | | | | | Lactation failure | PRL/STAT5A | [54] |
| | | | | | Reduced γδ T and NK cells | IL-2/STAT5 | [54] |
| | | | | | Altered T cell response | IL-2/STAT5 | [54] |
| SOCS1 | Complete | Neonatal death | IFNγ | [90, 91] | Spontaneous T cell activation | γc cytokines | [257] |
| | Complete | Lymphopenia | IFNγ | [91] | Defective T cell development | γc cytokines | [257] |
| | Complete | Monocytic organ infiltration | IFNγ | [90] | Fewer γδ T cells | γc cytokines | [257] |
| | Complete | Fatty degeneration /liver necrosis | IFNγ/STAT1 & IL-4/STAT6 | [90] | | | |
| | Complete+IFNγ$^{-/-}$ | Polycystic kidneys | ? | [93] | | | |
| | Complete+IFNγ$^{-/-}$ | Chronic inflammatory lesions | ? | [93] | | | |
| | Complete+IFNγ$^{-/-}$ | Perturbed T cell development | γc cytokines | [94, 95] | | | |
| | Complete+IFNγ$^{-/-}$ | Sensitive to LPS | TLR | [69] | | | |
| | T cell | Increased CD8+ differentiation | γc cytokines | [98] | | | |
| | Complete but T&B cells | Splenomegaly | IL-4/IFNγ | [52] | | | |
| | Complete but T&B cells | Lymphadenopathy | IL-4/IFNγ | [52] | | | |
| | Complete but T&B cells | Spontaneous dermatitis | IL-4/IFNγ | [52] | | | |
| SOCS2 | Complete | Gigantism | GH/STAT5B/IGF-1 | [140] | Gigantism | GH/STAT5B/IGF-1 | [143] |
| SOCS3 | Complete | Embryonic lethal | LIF | [190, 258] | Embryonic lethal/anaemia | EPO/STAT5 | [258] |
| | Complete+LIF$^{+/-}$ | Death by 190 days | ? | [192] | | | |
| | Hematopoietic | Neutrophilia/Inflammatory conditions | G-CSF | [181] | | | |
| | Neuronal | Resistance to diet induced obesity | Leptin | [259] | | | |
| | Complete but T cells | Perturbed CD8+ T cell proliferation | IL-6 & IL-27 | [180] | | | |
| SOCS4 | | *Not yet reported* | | | *Not yet reported* | | |
| SOCS5 | Complete | No reported phenotype | | [233] | Reduced Th2 differentiation | IL-4 | [28] |
| SOCS6 | Complete | Mild growth retardation | IGF-1 | [7] | Increased glucose metabolism | INS/p85 | [241] |
| SOCS7 | Complete (mixed b/g) | Altered glucose homeostasis | INS | [8, 252] | Not yet reported | | |
| | Complete (mixed b/g) | Large pancreatic islets | ?INS | [8] | | | |
| | Complete (C57BL b/g) | Hydrocephalus/growth retardation | ?INS & IGF-1 | [252] | | | |
| | Complete (mixed b/g) | Cutaneous disease | | [254] | | | |

In the case of growth factors, intracellular signalling is mediated by so-called receptor tyrosine kinases (RTKs), with SOCS4-7 more typically involved in their regulation, although the factors regulating their expression are less well characterized (**Figure 2B**). The SOCS proteins regulate RTKs via target protein degradation, and in the case of SOCS4 and SOCS5 also binding site competition, while SOCS7 has been shown to directly bind signaling proteins to prevent their nuclear translocation, thereby inhibiting their ability to signal [29]. However, the division of SOCS proteins between cytokine receptor and RTKs is not strict. Moreover, SOCS proteins can also participate in cross-talk between receptors and also regulate other pathways, such as Toll-like receptors (TLRs).

## Role of SOCS proteins

The function of individual SOCS proteins has been investigated by a range of approaches, with mouse knockout (KO) and transgenic (Tg) models revealing important roles in development (**Table 1**). Moreover, the SOCS proteins are being increasingly implicated in disease (**Table 2**).

### *CISH*

CISH, the founding member of the SOCS family, was identified as an immediate-early gene induced in hematopoietic cells in response to stimulation by a variety of cytokines, including erythropoietin (EPO), interleukin-2 (IL-2), IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which encoded a protein that was able to bind to activated cytokine receptors [30, 31]. Subsequent studies revealed induction by growth hormone (GH), prolactin (PRL) [32-34], IL-9 [35], thrombopoietin (TPO) [36, 37] and granulocyte colony-stimulating factor (G-CSF) [38], each of which also activate STAT5. In mice, strong expression of *Cish* was observed in the kidney, lung and liver [30], with lower expression in heart, stomach, testis, spleen, and thymus [30, 36]. *Stat5a/b* KO mice had no detectable *Cish* expression [39, 40], underpinning the key role of STAT5 in *CISH* gene regulation. Indeed, *CISH* has been shown to be a direct STAT5 target gene, with two sets of conserved tandem STAT5 binding sites present in its promoter [31, 41]. CISH is also induced by IL-6 [36], IL-10 [42], interferon (IFN)α [43], IFNγ [36], tumor necrosis factor (TNF)α [36], thymic stromal lymphopoietin (TSPL) [44], leptin [45], and ciliary neurotropic factor (CNTF) [46]. Finally, CISH has been found to be an early response gene induced by T cell receptor (TCR) stimulation via an alternative pathway not involving STAT5 [47]. Recent studies suggest that *CISH* is regulated post-transcriptionally by microRNAs (miRs), with *miR-98* or *let-7* shown to target the 3' untranslated region (UTR) of the *CISH* mRNA, causing translational repression. Stimulation with bacterial lipopolysaccharide (LPS) or *Cryptosporidium parvum* infection *in vitro* was able to decrease expression of *miR-98* and *let-7*, thereby relieving the miR-mediated translational suppression of *CISH* [48]. The *CISH* 3'UTR also contains ATAA destabilisation motifs, while the CISH protein possesses PEST sequences, which lead to rapid turnover of the mRNA and protein, respectively [30].

CISH is known to negatively regulate signaling induced by EPO [31], GH [26], IL-2 [49], IL-3 [30], and PRL [34, 50]. CISH binds via its SH2 domain to phosphorylated tyrosine residues of activated cytokine receptors, where it suppresses signaling via at least two mechanisms [25, 26]. Firstly, CISH can bind to the same receptor phosphotyrosine sites as STAT5, thereby physically blocking further STAT5 docking, which has been demonstrated for the EPO receptor (EPOR) and growth hormone receptor (GHR) [25, 26, 51]. CISH can also negatively regulate signaling at the receptor level by facilitating proteasomal degradation of activated receptor complexes via interactions between its SOCS box, Elongin B/C and Cullin5 [52, 53]. Interestingly, CISH has been suggested to be a positive regulator of TCR-mediated MAPK activation in T cells, with increased levels of CISH promoting TCR-mediated T cell proliferation and cytokine secretion [47], although the mechanism remains to be elucidated.

Transgenic mice expressing CISH under the control of the β-actin promoter exhibited growth retardation caused by reduced GHR signaling, defective mammary gland development due to disrupted PRL receptor (PRLR) signaling, and altered T and Natural killer (NK) cell responses as a result of blunted IL-2R signaling in T cells [54]. These phenotypes were consistent with those observed in *Stat5a/b*-deficient mice [39, 40], suggesting a specific *in vivo* role in the regulation of STAT5. An alternate transgenic

**Table 2.** Association of SOCS proteins with disease

| SOCS protein | Disease association | Mechanism | Reference |
|---|---|---|---|
| CISH | Infectious disease susceptibility | SNP at position -29 (blunted induction by IL-2) | [56] |
| | Osteoarthritis | Decreased expression | [60] |
| SOCS1 | Acute myeloid leukemia | Hypermethylation | [116, 117] |
| | Glioblastoma multiforme | Hypermethylation | [127] |
| | Barrett's adenocarcinoma | Hypermethylation | [125] |
| | Chronic myeloid leukemia | Hypermethylation | [118] |
| | Breast cancer | Hypermethylation | [128] |
| | Ovarian cancer | Hypermethylation | [128] |
| | Cervical carcinogenesis | Hypermethylation | [123] |
| | Esophageal squamous cell carcinoma | Hypermethylation | [124] |
| | Hepatocellular carcinoma | Hypermethylation & gene loss | [126] |
| | Chronic myeloid leukemia | Constitutive expression | [121] |
| | Hodgkin lymphoma | SOCS1 mutation, enhanced | [113] |
| | Primary mediastinal B-cell lymphoma | Hypermethylation | [115] |
| | Tuberculosis | Increased expression | [134] |
| SOCS2 | Ovarian cancer | Hypermethylation | [128] |
| | Acromegaly associated colonic polyps | Increased expression | [162] |
| | Osteoarthritis | Decreased expression | [60] |
| | Type 2 diabetes | 5' SNP | [61] |
| SOCS3 | Lung cancer | Hypermethylation | [214] |
| | Barrett's adenocarcinoma | Hypermethylation | [125] |
| | Hepatocellular carcinoma | Hypermethylation | [211] |
| | Malignant melanoma | Hypermethylation | [212] |
| | Glioma | Hypermethylation | [219] |
| | Prostate cancer | hypermethylation | [220] |
| | Ulcerative colitis (areas of dysplasia) | Deceased expression | [216] |
| | Breast cancer with lymph node metastasis | Reduced expression | [221] |
| | Atopic asthma/dermatitis (Th2 disease) | Increased SOCS3 expression (peripheral T-cells) | [197] |
| | Breast cancer with lymph node metastasis | Reduced expression | [221] |
| SOCS4 | Gastric cancer | Hypermethylation | [229] |
| SOCS5 | Uveitis | Increased expression | [236] |
| | Thyroid gland cancer | Decreased expression | [239] |
| SOCS6 | Gastric cancer | Hypermethylation & gene loss | [249] |
| | Colorectal cancer | Gene loss | [251] |
| | Primary lung squamous cell carcinoma | Decreased expression | [248] |
| | Liver cancer | Decreased expression | [239] |
| | Thyroid gland cancer | Decreased expression | [239] |
| SOCS7 | Breast cancer | Decreased expression | [228] |
| | Metabolic syndrome | Specific haplotypes | [255] |

mouse expressing CISH in CD4+ T cells showed inhibited TCR signalling, but in a STAT5-independent manner [47].

No *Cish* KO mouse has been described. However, a recent study has indicated a role for CISH during the GM-CSF-mediated *ex vivo* development of mouse bone-marrow-derived dendritic cells (BMDCs). CISH was found to be induced by GM-CSF treatment, and CISH knock-down caused a decline in MHC class I, pro-inflammatory cytokines, and co-stimulatory

molecule expression, concurrent with a substantial increase in the production of BMDCs via increased proliferation and reduced apoptosis. This was associated with enhanced STAT5 activation. Therefore, CISH expression appears to regulate progenitor cell proliferation late in development via feedback inhibition of STAT5 activation to allow differentiation to proceed effectively [55]. Functional analysis of a zebrafish *CISH* homologue, *cish.a*, has revealed it to be a direct downstream target of the JAK2/STAT5 pathway *in vivo*, with specific ablation of *cish.a* leading to a significant enhancement of embryonic erythropoiesis, myelopoiesis and lymphopoiesis, consistent with a role for CISH in the negative regulation of the JAK2/STAT5 pathway *in vivo* (ACW, unpublished).

CISH has also been implicated in disease. An association has been found between *CISH* single nucleotide polymorphisms (SNPs) and susceptibility to infectious diseases, including bacteremia, malaria, and tuberculosis. A SNP at position -292 of the *CISH* promoter was the most highly associated, increasing the overall risk of infectious disease by at least 18% among persons carrying the variant allele. This allele blunted the induction of *CISH* mRNA following IL-2 stimulation, suggesting enhanced IL-2R signaling might be responsible for the increased susceptibility [56]. The -292 SNP was also found to be associated with hepatitis B virus infection in a Vietnamese population [57]. Other studies have suggested that CISH contributes to expansion of regulatory T cells (Tregs) in response to microbial infection [58]. Levels of *CISH* mRNA were also found to be higher in peripheral blood mononuclear cells (PBMCs) from systemic lupus erythematous (SLE) patients in acute phase compared to either normal individuals or patients with inactive phase of disease, suggesting that CISH represents a marker of SLE and may be involved in disease pathogenesis [59]. Alterations in CISH levels have also recently been linked to osteoarthritis, although in this case *CISH* mRNA levels were found to be 10-fold lower in chondrocytes from osteoarthritic patients compared to control samples [60]. This suggests CISH plays a clinically-relevant role that might provide new strategies for controlling infectious agents and inflammatory diseases.

*SOCS1*

SOCS1 was shown to be highly expressed in both mouse and human thymus and spleen [5, 36, 61]. It was also expressed in the lung, testis [36], colon and mesenteric lymph nodes [5]. SOCS1 has been shown to be induced by numerous cytokines *in vitro* and *ex vivo*, including IL-2 [62], IL-4 [22, 63], IL-6 [22], IL-13 [64], IFNα/β [65, 66], IFN-γ [36, 67], EPO [23, 36], G-CSF [22], LIF [22], PRL [34], GH [32], CNTF [46] and TNFα [68]. SOCS1 is also induced by Toll-like receptor (TLR) ligands, such as LPS [69, 70] and CpG DNA [71], as well as INS [72] and thyroid stimulating hormone (TSH) [73]. Bioinformatic analysis has identified the 3'UTR region of SOCS1 as a potential target of *miR-155*. This miR is normally induced by TNF-α through the JNK pathway with knockdown of *miR-155* in mouse osteoblastic cells resulting in increased SOCS1 protein expression following TNFα stimulation. In contrast, transfection with *miR-155* inhibited wild-type SOCS1 [74]. In T cells, FOXP3 negatively regulates *miR-155* thereby contributing to the maintenance of SOCS1 levels in these cells [75].

SOCS1 has also been found to regulate signaling by a raft of receptors *in vitro*, including those for the cytokines IFNα [67], IFNγ [67], EPO [23], PRL [33, 34], GH [32, 51], LIF [22], TNF-α [68], IL-2 [23, 62], IL-3 [23], IL-4 [63], IL-6 [22], IL-7 [76], IL-12 [77], IL-15 [78], EPO [23], TPO [36], TSLP [44], oncostatin M (OSM) [36], and leptin [79], as well as the receptors for INS [80] and IGF-1 [81], and the TLRs [82]. SOCS1 is known to regulate signaling via two mechanisms. Firstly, it can bind directly to cytokine receptor-associated JAK1, JAK2, and TYK2 to inhibit their tyrosine kinase activity via its ESS/KIR domains, and consequently suppress activation of downstream pathways [12, 21-23]. However, like other SOCS family members, SOCS1 can also interact with Elongin B/C and Cullin5 via its SOCS box, facilitating ubiquitination and proteasomal degradation of target substrates [17, 83], including JAK1 [83], JAK2 [84], TEL-JAK2 [85, 86], GEF, VAV [87], insulin receptor substrate (IRS)-1 and IRS-2 [88], as well the TLR2/4 adaptor protein MAL [82]. Interestingly, the SOCS box has also been shown to protect SOCS1 against proteolytic degradation [89].

SOCS1 has been shown to have several essential roles in immunity. *Socs1* KO mice developed a fatal neonatal disease that resulted in death by three weeks of age [90, 91]. These animals exhibited severe lymphopenia and T

cell-mediated autoimmune inflammatory disease, characterized by monocytic infiltration of major organs along with fatty degeneration and necrosis of the liver [90]. These phenotypes were significantly reduced in *Ifnγ/Socs1* double KO mice and in *Socs1* KO mice treated with anti-IFNγ antibodies [92, 93], indicating that hyper-responsiveness to IFNγ was the chief cause and confirming SOCS1 as a potent *in vivo* regulator of IFNγ. However, these *Ifnγ/Socs1* double KO mice developed additional phenotypes, including polycystic kidneys, chronic infections, and inflammatory lesions, which resulted in survival to only 6 months of age [93]. T cell development was also perturbed, including reduced T cells numbers [94], disrupted Th2 responses [95], a reduced CD4/CD8 ratio [94], as well as abnormal development of Th17 cells [96], resulting from hypersensitivity to cytokines acting via the γc receptor: IL-2, IL-4, IL-7, IL-15 [97] and IL-12 [77].

T cell-specific *Socs1* KO mice did not develop the lethal multi-organ inflammation, but rather specific lymphoid deficiencies, including increased differentiation toward CD8(+) T cells and phenotypes correlating with hypersensitivity to γc receptor utilizing cytokines [98]. These mice also showed a 10-fold increase in FOXP3(+) CD4(+) T regulatory (Treg) cells in the thymus, indicating SOCS1 potentially negatively regulates the generation and/or accumulation of these cells [99]. The increase in Treg cells was still apparent when these mice were crossed with those lacking IFNγ or IL-7 indicating other cytokines mediate this effect [99]. Further supporting a Treg role, mice lacking *Socs1* expression in all but their T and B cells developed spontaneous dermatitis, splenomegaly, and lymphadenopathy. They showed an accumulation of DCs in their thymi and spleens, which were hyper-responsive to both IFNγ and IL-4, resulting in increased levels of BAFF/BLyS and APRIL, facilitating the generation of autoantibodies. This resulted in the development of systemic autoimmune-like diseases with hypergammaglobulinemia at an early age [52]. Whilst it has been demonstrated that SOCS1 is important in helper T cell (Th) differentiation, there is conflicting data regarding exactly which cell fate SOCS1 drives differentiation towards. Some studies have suggested that SOCS1 favors Th1 differentiation, while others suggest that IL-6 induced SOCS1 blocks Th1 development via the inhibition of IFNγR, leading to accelerated Th2 differentiation [100]. To add to the complexity, SOCS1 has been shown to be necessary for Th17 differentiation via its suppressive effects on IFNγ [101].

SOCS1 has been demonstrated to have several other *in vivo* regulatory functions. Thus, *Socs1* KO mice also showed impaired osteoblast differentiation [102], as well as enhanced insulin signaling [103]. In addition, cells from SOCS1 transgenic mice were unable to respond to LPS, suggesting that SOCS1 inhibited TLR/NF-κB signaling *in vivo* [69]. *Socs1* deficiency also resulted in excessive macrophage and dendritic cell activation [52, 69], potentially caused by the combined effects of unrestrained signaling via IFNRAR1 [104] and TLRs [82, 105]. Knockdown of zebrafish *socs1* resulted in perturbation of specific myeloid populations during embryogenesis prior to the commencement of lymphopoiesis, along with reduced numbers of T cells. Zebrafish SOCS1 was shown to interact with the zebrafish JAK2/STAT5 pathway both *in vitro* and *in vivo*. This demonstrated SOCS1 has a conserved role in T cell development, but exerts a T cell-independent function in embryonic myelopoiesis likely mediated via regulation of receptors that utilise the JAK2-STAT5 pathway [106].

Defective SOCS1 signaling has been associated with a range of inflammatory disorders. In a murine arthritis model, SOCS1 was expressed in multiple cell types in the arthritic joint, with the extent of joint destruction and synovial inflammation exacerbated in *Socs1* KO mice [107]. *SOCS1* expression has been shown to correlate inversely with the severity of disease in idiopathic pulmonary fibrosis patients, with adenovirally-delivered SOCS1 decreasing fibrosis, inflammation and mortality in a murine model of pulmonary inflammation [108]. However, SOCS1 does not always confer protection against inflammatory/immune diseases. Thus, SOCS1 Tg mice spontaneously develop colitis, with severe intestinal inflammation [109]. Moreover, a SOCS1 promoter SNP that increases SOCS1 expression was associated with adult-onset asthma [110]. SOCS1 was also shown to protect β-cells from cytotoxic T cells in a murine type 1 diabetes model [111]. Further, increased expression of SOCS1 was observed in insulin-resistant mice, with down-modulation

of SOCS1 leading to increased insulin-sensitivity in these mice [112].

SOCS1 has also been suggested to have a tumor suppressor role, particularly in hematological malignancies and proliferative disorders. Thus, the *SOCS1* gene has been found to be frequently mutated in both classical Hodgkin lymphoma [113, 114] and primary mediastinal B-cell lymphoma [115], leading to augmented signaling by STAT5 [113, 115] and STAT6 [114]. The *SOCS1* gene was commonly silenced by hypermethylation (and occasionally mutation) in acute myeloid leukemia [116, 117], with the reintroduction of SOCS1 causing growth suppression in affected cells [117]. Chronic myeloid leukemia patients also demonstrated hypermethylation of *SOCS1* that reverted to an unmethylated state during remission [118]. Some Philadelphia chromosome (Ph)-negative myeloproliferative disorders (MPDs) exhibit SOCS1 hypermethylation, which may complement other mutations, such as the hyperactive JAK2V617F mutation [119]. Others have alternatively found that SOCS1 is overexpressed in Ph-negative MPDs, potentially acting as a compensatory feedback mechanism [120]. Indeed, constitutive expression of SOCS1 has been observed in chronic myeloid leukemia (CML) [121], in line with hypomethylation of this gene [122]. SOCS1 expression in CML also correlated with a poor response to interferon α, treatment, likely due to a direct effect on receptor signaling [121]. Hypermethylation of SOCS1 has been commonly reported in solid tumors, including 61% of cervical cancer samples [123], and 45% of esophageal squamous cell carcinoma samples [124], as well as occasionally in Barrett's adenocarcinoma [125], with combined hypermethylation/gene loss observed in hepatocellular carcinoma [126]. Hypermethylation-mediated silencing has also been seen in glioblastoma multiforme, with concomitant enhancement of radio-resistance, indicative of a pro-apoptotic function [127]. Hypermethy-lation of the SOCS gene has also been observed in breast and ovarian cancer, where SOCS1 reintroduction was again able to suppress cell growth [128]. Spontaneous colorectal cancer was also seen in *Socs1* KO mice in an IFNγ-dependent manner [129]. Finally, SOCS1 has also been shown to suppress oncogenic forms of VAV [87], c-MET [130], ABL and c-KIT [131], as well as TEL-JAK2 and BCR-ABL fusions [131].

SOCS1 also has roles in the response to infectious agents. For example, SOCS1 has been shown to protect against lethal inflammation induced by *Chlamydia pneumoniae*, although it hampered bacterial clearance due to its effects on IFNα/β-induced STAT1 [132]. SOCS1 also inhibited the antiviral response to influenza [133], and increased SOCS1 levels were associated with enhanced disease severity in tuberculosis [134]. In fact, many infectious agents specifically target SOCS1 to augment the infection process. Thus, *Toxoplasma gondii* induces SOCS1 expression leading to inhibition of cytokine signaling and suppression of immune responses [135]. Similarly, *Mycobacterium bovis* increases SOCS1 and SOCS3 to inhibit IFNγ-induced STAT1 [136]. Furthermore, bacterial flagellin was shown to act via TLR5 to induce SOCS1 thereby suppressing TCR-mediated T cell activation [137]. In contrast, hepatitis C core protein down-regulates SOCS1, resulting in enhanced STAT5 signaling in B cells [138].

*SOCS2*

SOCS2 was shown to be highly expressed in the fetal kidney [139], as well as adult kidney, lung, testes, liver [36, 139, 140], pancreatic islets [141], peripheral blood mononuclear leukocytes [142], and to a lesser extent in adult heart, muscle and brain [139, 140]. SOCS2 is most closely related to CISH, and like CISH is induced by cytokines that activate STAT5, including GH [32, 143], EPO [36, 144], PRL [34] IL-2 [145], IL-3, GM-CSF and G-CSF [36]. However, it is also induced by CNTF [46], IFNα [43], IFNγ [36, 142], leukemia inhibitory factor (LIF) [36], IL-1β [142], IL-4 [36], IL-6 [142],IL-15 [146] and insulin (INS) [72].

SOCS2 acts to regulate signaling induced by the cytokines GH [26], PRL [147], LIF [145], IL-2, IL-3 [148] and IL-6 [21], but also by growth factors, such as epidermal growth factor (EGF) [149] and insulin-like growth factor (IGF)-1 [139]. SOCS2 differs from other SOCS family members in two important and interesting ways. Firstly, SOCS2 appears to play a dualistic regulatory role, both inhibiting and potentiating signaling dependent on its concentration and cellular context [21, 34, 150]. *In vitro* studies have demonstrated that low levels of SOCS2 led to a reduction in GH signaling, while higher levels actually increased GH signaling [150]. Secondly, SOCS2 has been shown to possess

the ability to antagonize other SOCS family members [50]. Thus, SOCS1 inhibition of GH signaling was reduced with increasing doses of co-transfected SOCS2 [150], while SOCS2 was shown to exert an antagonistic role in the SOCS1- and SOCS3-mediated negative regulation of IL-2 and IL-3 signaling, respectively [148]. SOCS2 primarily exerts its effects by stimulating ubiquitination of target proteins, including receptors, such as GHR [151], and signaling proteins, such as SOCS3 [148].

*Socs2* knockout mice were indistinguishable from their littermates until 3 weeks of age, at which point they began to demonstrate increased overall growth, being 40% heavier than wild-type (WT) littermates by adulthood [140]. The increase in weight was due to increased bone length and enlargement of internal organs [140]. Constitutive expression of SOCS2 produced a similar phenotype, with SOCS2 transgenic mice being significantly larger than WT animals [152], consistent with the dualistic nature of SOCS2. A naturally-occurring mouse mutant, high growth (*hg*), which exhibited a 30-50% increase in postnatal growth, has been mapped to the *Socs2* region, indicating that *hg* is most likely an allele of *Socs2* – although whether it is hypomorphic or hypermorphic allele remains to be determined [153]. *Socs2* KO mice exhibited prolonged STAT5B activation in response to GH, and crossing with *Stat5b* KO mice partially relieved the growth enhancement [143]. This suggests that SOCS2 regulates the GH/IGF-1 axis through negative regulation of the downstream STAT5B [140, 143]. SOCS2 also has a role in controlling prolactin-induced mammary gland development, which appears to be the result of enhanced STAT5A activation [147]. SOCS2 also exerts a dualistic role in the regulation of EGF signaling, with increased intestinal growth in *Socs2* KO mice due to enhanced responsiveness to EGF [154], and increased neural outgrowth of cortical neurons derived from SOCS2 transgenic mice, apparently also due to enhanced EGF signaling [155]. Transgenic mice overexpressing SOCS2 specifically in pancreatic β-cells using the rat insulin promoter displayed hyperglycemia and glucose intolerance, but did not exhibit overt diabetes [156]. In contrast, the pancreatic β-cells of *Socs2* KO mice showed unaltered insulin and glucose tolerance when compared to WT mice [157].

SOCS2 also functions in immune cells, with roles in both DCs as well as CD4+ T cells. When SOCS2 was silenced in DCs, maturation was disrupted and a reduction in LPS stimulated MAPK activation was observed [158], suggesting a requirement for SOCS2 in TLR-induced DC activation. However, others have argued that SOCS2 is a TLR-responsive gene with its delayed expression providing a mechanism for late-phase counter-regulation to limit inflammation-driving DC activity [159]. SOCS2 silencing in CD4+ T cells resulted in increased preference for helper T cell (Th)2 differentiation, which is consistent with elevated Th2 responses observed in SOCS2 KO mice [160]. In human NK cells, SOCS2 was shown to be induced by IL-15 and targeted PYK2 for degradation, with SOCS2 knockdown resulting in defective NK cell effector functions [146].

Like its close homologue CISH, SOCS2 has been linked to osteoarthritis, with *SOCS2* mRNA levels also found to be 10-fold lower in osteoarthritic samples when compared to control samples, with increased expression seen following cytokine treatment [60]. A SNP in the 5' region of the SOCS2 gene was associated with type 2 diabetes (T2D) in a Japanese population. Adenovirus-mediated expression of the *SOCS2* gene in pancreatic islets significantly suppressed glucose stimulated insulin secretion, suggesting a likely mechanism by which SOCS2 may influence susceptibility to T2D [61]. SOCS2 also appears to be a cellular target of the HIV-1 transactivator protein (Tat) in primary human monocytes, leading to increased SOCS2 levels, which was shown to suppress IFNγ-activated STAT1 phosphorylation, resulting in dysregulated cytokine production and immune evasion [161]. Finally, SOCS2 has been implicated in oncogenesis, where it also shows a dualistic nature. Patients with active acromegaly and colonic polyps showed a significantly increased SOCS2 expression, which mediated a reduction in SOCS1, leading to elevated STAT5B levels, potentially resulting in upregulation of GH-mediated proliferation of colonic epithelial cells [162]. In contrast, *SOCS2* expression was shown to have a favorable prognostic value in breast cancer [163], and hypermethylation of SOCS2 was detected in ovarian but not breast cancer [128].

*SOCS3*

SOCS3 has been shown to be expressed in a wide variety of murine and human tissues. In

mice, SOCS3 was found to be expressed in the spleen, thymus, and lung [36], while in humans, SOCS3 was expressed in the colon, spleen, bladder, peripheral blood leukocytes, trachea and placenta, with very high expression in the lung, adipose tissue, ovary and aorta [61]. SOCS3 has been demonstrated to be induced by the cytokines IL-1β [164], IL-2 [165], IL-3 [166], IL-4 [63], IL-6 [167], IL-9 [35], IL-10 [42], IL-11 [168], IL-13 [36], IL-22 [169], IFN-γ [67], IFNα [67], EPO [170], LIF [32], PRL [34], GH [32], leptin [171], G-CSF [36], GM-CSF [172], CNTF [46], TPO [66], TNFα [173], cardiotrophin (CT)1 [174], OSM [175]. It is also induced by several growth factors, including EGF [176, 177], platelet-derived growth factor (PDGF) [176], thyroid stimulating hormone (TSH) [73], insulin [72], and basic fibroblast growth factor (BFGF) [178].

SOCS3 has been demonstrated to play a regulatory role in signaling downstream of a wide range of cytokine receptors, including those for IL-2 [165], IL-4 [63], IL-6 [21], IL-9 [35], IL-11 [168], IL-23 [179], IL-27 [180], IFNα/β [67], IFNγ [67], G-CSF [181], EPO [170], PRL [33, 34], GH [32, 51], LIF [32], leptin [171], CNTF [46], IL-1β [182], OSM [175] and CT1 [174], as well as IGF-1 [81], INS [183], CD28 [184] and calcineurin [185]. Like its closest homologue, SOCS1, the SOCS3 protein can directly inhibit receptor-bound JAKs, although it achieves this via a high-affinity interaction between its SH2 domain and a phosphotyrosine residue on the receptor (e.g. GP130), rather than the JAK [170], binding simultaneously to both [186]. SOCS3 also regulates signaling via binding site competition. Thus, SOCS3 has been shown to bind to the same site as the SH2-domain hematopoietic phosphatase (SHP)-2 on several receptors [27] and with STAT4 on others [187]. Finally, like other members of the SOCS family, SOCS3 can also regulate signaling by targeting proteins for degradation, however this is not its primary mechanism of action, as it can still regulate signaling without its SOCS box [21]. It has been demonstrated that an IL-6 transcriptional response can be converted to one mimicking that of interferons when SOCS3 is absent [167, 188], while IL-7-induced viral clearance occurred via a mechanism that required both the induction of IL-6 and inhibition of SOCS3 expression [189]. Collectively, this suggests that SOCS3 primarily functions by dampening cytokine-induced STAT3 and STAT1 activation. Induction of SOCS3 is most pronounced by cytokines that strongly activate STAT3, with its regulatory specificity determined by the presence of high-affinity SOCS3-binding sites on target receptors.

*Socs3* mouse KO embryos exhibited fatal placental defects during embryonic development and although anatomically sound, they did not survive past 13 days of gestation. These embryos showed expanded numbers of giant trophoblast cells in the placenta, as well as abnormities in the spongiotrophoblast and labyrinth placental layers [190]. LIFR deficit was able to rescue the *Socs3* KO placental defect and embryonic lethality, establishing SOCS3 as an essential regulator of LIFR signaling during placental formation [191]. However, these double KO mice died by 190 days of age due to neutrophilia accompanied by inflammatory-cell tissue infiltration [192]. Hematopoietic-specific *Socs3* KO mice developed a variety of inflammatory conditions, including a prolonged and enhanced responses to G-CSF that facilitated neutrophilia and enhanced progenitor cell survival, suggesting SOCS3 is an important *in vivo* regulator of G-CSFR signaling [181]. Interestingly, differentiation of SOCS3-deficient progenitors was skewed toward a macrophage state in response to G-CSF and IL-6 stimulation, suggesting that SOCS3 is also important in maintaining the specificity of biological responses mediated by cytokine signaling [193]. SOCS3 was also shown to be a positive regulator of TLR4 responses in macrophages via inhibition of IL-6R-mediated STAT3 activation [194] as well as endogenous TGFβ-mediated/SMAD3 [195]. *Socs3* deficiency in either hepatocytes or macrophages resulted in prolonged IL-6-induced activation of STAT1 and STAT3, but normal IFNγ and IL-10 signaling [167, 188, 194]. These observations strongly suggest that SOCS3 targets GP130 dependent signal transduction pathways *in vivo*.

SOCS3 has been shown to be selectively expressed in Th2 cells [196] and required for Th2 development. Mice heterozygous for *Socs3* or expressing a dominant-negative SOCS3 showed reduced Th2 development, while those expressing a SOCS3 transgene exhibited enhanced Th2 polarity [197]. T cell-specific *Socs3* KO mice showed increased CD8(+) T cell

proliferation via enhanced IL-6 and IL-27 signaling [180]. It has been suggested that the ability of SOCS3 to skew T cell differentiation to the Th2 phenotype may be due to an ability to compete for the STAT4-binding site on the IL-12Rβ2 chain, thus inhibiting IL-12/STAT4-driven polarization to the alternative Th1 phenotype [187], or alternatively via its inhibition of interferon-induced STAT1 activation that is also associated with Th1 polarization [167].

SOCS3 has diverse roles outside of the immune and hematopoietic lineages. Mammary stem/progenitor cell-specific *Socs3* KO mice exhibited impaired lactation resulting from reduced proliferation [198]. Loss of SOCS3 from differentiated luminal cells resulted in accelerated tissue remodeling upon weaning [198]. SOCS3 has also been shown to play a role in fine-tuning photoreceptor cell differentiation [199], while SOCS3 transgenic mice showed reduced pancreatic β-cell mass and proliferation [200]. SOCS3 was also shown to be required for normal wound healing, again via action on GP130 signaling [201]. Finally, elevated levels of SOCS3 in the arcuate nucleus of the hypothalamus have been associated with leptin resistance and obesity in mice [171].

SOCS3 has also been associated with the progression of a number of inflammatory conditions. SOCS3 expression has been reported in synovial tissue from mice during experimental arthritis, and in peripheral blood mononuclear cells in patients with rheumatoid arthritis (RA) [202]. Mice with a GP130 receptor mutation that ablates SOCS3 binding develop a RA-like joint disease [203]. Similarly, hematopoietic and endothelial cell-specific *Socs3* KO mice exhibited severe phenotypes in experimental arthritis models, most likely due to enhanced responsiveness of IL-6, G-CSF and possibly IL-1 [204]. Moreover, adenoviral delivered SOCS3 could eliminate joint inflammation in mice with experimental autoimmune arthritis, mediate via inhibition of IL-6 signaling [205]. SOCS3 was found to be highly expressed in lamina propria and epithelial cells in the colon of mice with inflammatory bowel disease (IBD), as well in human patients with both ulcerative colitis and Crohn's disease (CD), again suggested to be due to enhanced IL-6 signaling (via STAT3) [206]. In contrast, SOCS3 has been found to be upregulated in the peripheral T cells from patients with Th2 type diseases, such as atopic asthma and dermatitis, where its expression has found to correlate tightly with disease severity [197]. Similarly, SOCS3 has been associated with allergic conjunctivitis (AC), with high expression at the site of disease, with reduction of SOCS3 leading to decreased clinical severity [207].

SOCS3 appears to also play a tumor-suppressor/anti-proliferative role. For example, overcoming SOCS3 regulation seems to be a common theme in proliferative syndromes. Thus, the myeloproliferative disease-associated $JAK2^{V617F}$ mutant is no longer able to be negatively-regulated by SOCS3 [208]. Similarly, G-CSFR truncations associated with severe congenital neutropenia leading to acute myeloid leukemia have lost the sequences required for SOCS3-mediated control of STAT5 activation [209]. Once again though, the exact role for SOCS3 is complex. For example, overexpression of SOCS3 associated with decreased survival in a cohort of patients with *de novo* follicular lymphoma [210], while SOCS3 may in fact potentiate the $JAK2^{V617F}$ mutation [208]. However, hypermethylation of SOCS3 occurs frequently in both Barrett's adenocarcinoma [125] and hepatocellular carcinoma [211], in the latter case leading to increased JAK2/STAT3 activation [211]. Hypermethylation mediated reduction in SOCS3 expression has also been observed in malignant human melanoma [212], while constitutive SOCS3 expression was shown to confer a proliferative advantage to a human melanoma cell line [213]. SOCS3 was also found to be frequently silenced by hypermethylation in human lung cancer where it suppressed cell growth [214]. SOCS3 was able to limit inflammation-associated tumorigenesis in the colon, via regulation of STAT3 and NFκB [215], while in ulcerative colitis, loss of SOCS3 expression was observed in the areas of colon dysplasia [216]. SOCS3 was protective against hepatitis-induced hepatocellular carcinoma, with loss of SOCS3 leading to resistance to apoptosis and increased proliferation [217]. Similar epigenetic silencing of SOCS3 has been seen in cholangiocarcinoma cells, resulting in enhanced IL-6/STAT3 signaling and reduced apoptosis [218]. SOCS3 hypermethylation was also seen in glioma [219], and prostate cancer tissues – although not in benign prostate hyperplasia [220]. Finally,

reduced expression of SOCS3 was also specifically observed in breast cancer with lymph node metastasis, suggesting a role in tumor spread [221].

SOCS3 has also been associated with infectious diseases. For example, the severe inflammation mediated by SARS virus infection was found to correlate with lower expression of SOCS3 in infected cells [222]. In contrast, SOCS3 was able to inhibit the antiviral response to influenza [133]. Indeed, pathogenic strains of *Salmonella* sp. could increase SOCS3 expression in macrophages to mediate suppression of immune responses [135]. Similarly, *M. bovis* was able to induce SOCS3 to mediate inhibition of IFNγ-induced STAT1 [136]. Finally, high levels of SOCS3 have been found to be associated with non-responsiveness to combined IFN antiviral therapy [223].

*SOCS4*

SOCS4 remains the least studied member of the SOCS family. It has been shown to be particularly highly expressed in the intestine and thymus of adult pig [224], with the zebrafish *socs4a* homologue expressed in the embryonic nervous system (MCT and ACW, unpublished). Available mouse data suggests it is widely expressed, with higher expression in the olfactory bulb (http://biogps.org/#goto=genereport &id=122809). To date, SOCS4 has been shown to be induced only by EGF, at least *in vitro* [225]. Similar to CISH, *miR-98* and *let-7* are thought to post-transcriptionally regulate SOCS4, facilitating translational repression by targeting its 3'UTR region. Infection of binary epithelial cells with *C. parvum* decreased *miR-98* and *let-7*, leading to increased SOCS4 expression [226].

SOCS4 has been demonstrated to regulate EGFR signaling *in vitro* [6, 225]. This appears to be mediated through docking of SOCS4 to phosphotyrosine residues on the activated EGFR, subsequently targeting the receptor for proteasomal degradation by recruitment of E3 ubiquitin ligase activity [6, 11]. However, SOCS4 binds with high affinity to the same EGFR phosphotyrosine as STAT3 and therefore may also inhibit STAT3 activation directly by blocking its ability to dock to EGFR [11]. SOCS4 also has a low micromolar affinity for JAK2 and c-KIT, the biological consequences of which remain to be determined [11]. A recent report has suggested a role for SOCS4 in the regulation of primordial follicle activation, a process initiated by LIF activation of the JAK1/STAT3 pathway. This occurred concurrently with SOCS4 induction, with SOCS4 shown to interact with several proteins involved in ovarian follicular development [227]. No *Socs4* KO mouse has been reported.

Several studies have suggested a tumor suppressor role for SOCS4. An inverse relationship between *SOCS4* expression levels and tumor node metastasis stage has been reported in human breast cancer [228]. SOCS4 expression was also found to be significantly lower in cancerous tissue compared to non-cancerous tissue in a patient with gastric cancer, mediated by hypermethylation of CpG sites in the promoter region of the *SOCS4* gene leading to *SOCS4* silencing [229]. Mouse studies also suggest a tumor suppressor in epithelial cells via RUNX1-mediated repression of the *SOCS4* promoter, leading to decreased SOCS4 levels and increased STAT3 activity, thereby contributing to tumor development [230].

*SOCS5*

SOCS5 is most closely related to SOCS4, and also has not been fully characterised. SOCS5 has been shown to be expressed in a variety of adult tissues including heart, brain, retina, lung, colon, bladder, testis and skeletal muscle as well as the placenta [5, 225, 231, 232]. Expression was particularly high in lymphoid organs including the spleen, lymph nodes, thymus, and bone marrow, with specific expression in primary B and T cells [233], suggesting possible immune-related functions [231]. Like SOCS4, SOCS5 expression has been shown to be induced by EGF *in vitro* [225].

SOCS5 appears able to regulate both RTK and cytokine receptor signaling. Thus, SOCS5 has been shown to negatively regulate EGFR *in vitro* [6, 225], and more weakly IL-6R, LIFR [21] and IL-4R signaling [28]. This seems to be a conserved function since overexpression of the *Drosophila melanogaster* SOCS5 homologue, SOCS36E, resulted in several phenotypes consistent with reduction in both cytokine receptor and EGFR signaling. SOCS5 is thought to regulate signaling by initiating the proteasomal degradation of its target proteins, as seen in the regulation of EGFR, where both its SH2 domain and SOCS box required for initiation of degrada-

tion [6, 225]. Interestingly, the SOCS5 protein has been found to associate with EGFR independent of ligand stimulation, binding via its N-terminal domain [225].

Consistent with its expression in lymphoid organs and *in vitro* effects on IL-4 signaling, SOCS5 has been implicated in T helper cell differentiation, particularly in the balance between Th1 and Th2 cells, with SOCS5 protein preferentially expressed in Th1 cells. SOCS5 Tg mice showed a significant reduction in Th2 development, thought to be facilitated by the ability of SOCS5 to inhibit IL-4R mediated STAT6 activation that normally stimulates differentiation of naïve T cells toward a Th2 fate [28]. Interestingly, SOCS5 was found to associate with the IL-4R regardless of tyrosine phosphorylation [28, 225]. However, *Socs5* KO mice showed no abnormalities in Th1/Th2 differentiation, indicating possible redundancy in its lymphoid role [233].

SOCS5 has been implicated in a variety of disease states, such as allergic conjunctivitis [207], atopic dermatitis [234], asthma [235] and uveitis [236], although some of these associations have so far only been identified in rodent models. These studies also provide further support for a role for SOCS5 in regulating the balance between Th1 and Th2 cells. For example, SOCS5 expression was decreased in patients with the Th2 dominant disease atopic dermatitis (AD) compared to healthy controls, with patients demonstrating eosinophilia showing even lower levels of SOCS5 [234]. Moreover, constitutive SOCS5 expression has been found to reduce eosinophil infiltration in allergic conjunctivitis [207], further implicating SOCS5 in the balance of Th1/Th2 cells, since eosinophil production is stimulated by Th2 cytokines, including IL-4. This notion was further supported in a murine model for allergic conjunctivitis, an ocular disease that is characterized by IL-4-mediated eosinophil infiltration. In mice constitutively expressing SOCS5 under the control of the *lck* proximal promoter and Eμ enhancer, decreased conjunctival eosinophil infiltration was observed [207]. These mice also showed decreased lethality to septic peritonitis and significantly lower bacterial burden compared to WT controls. This was associated with accumulation of neutrophils and macrophages, with these cells showing increased bactericidal properties and impaired IL-4-induced STAT6 activation [237]. Since STAT6 knockout mice have also been found to be resistant to septic peritonitis [238], this suggests a regulatory role for SOCS5 on the IL-4/STAT6 pathway. SOCS5 transgenic mice also showed increased peritoneal IL-2 and IFN-γ, cytokines involved in the promotion of Th1 differentiation [237]. Finally, a reduction in SOCS5 expression was observed in cancer of the thyroid gland [239], suggesting a possible tumor-suppressor function.

*SOCS6*

SOCS6 has been shown to be ubiquitously expressed during mouse embryonic development, while in the adult mouse expression has been reported in areas of the bone marrow containing monocytes and immature granulocytes [7] and in the retina [232]. SOCS6 was found to be induced by both INS [240, 241] and IGF-2 [242].

SOCS6 has been demonstrated to negatively regulate signaling by IGF-1 [242], INS [240], FLT3 [243], Stem Cell Factor (SCF) [244] and TCR [245]. Like other SOCS proteins, SOCS6 likely exerts its regulatory effects primarily through ubiquitination and degradation of target proteins [7]. However, SOCS6 interacts with an alternate E3 ligase component, heme-oxidized IRP2 ubiquitin ligase-1 (HOIL-1), which induces the poly-ubiquitination and degradation of SOCS6-associated proteins [244]. Like SOCS2, SOCS6 also has the ability to degrade other SOCS proteins, including SOCS7 [246]. The SOCS6 N-terminal domain has been shown to drive localisation to the nucleus, where it appears to negatively regulate STAT3, although the exact mechanism by which SOCS6 regulates STAT3 has not been identified [14].

SOCS6 has been shown to control TCR-mediated T cell activation *in vitro* through negative regulation of p56*lck*. SOCS6 was shown to bind to the kinase domain of active p56*lck*, targeting it for ubiquitination and subsequent degradation, with SOCS6 overexpression resulting in repression of TCR-dependent IL-2 promoter activity [245]. SOCS6 also appears to negatively regulate signaling of several important hematopoietic receptor tyrosine kinases. SOCS6 binds to the juxtamembrane region of c-KIT following stimulation with SCF, thereby regulating activation of members of the MAPK pathway,

such as ERK1/2 and p38 [244]. SOCS6 can also bind to FLT3 and negatively regulate its signaling, reducing downstream ERK1/2 signaling and concomitant cell proliferation [243].

A potential role for SOCS6 in neural stem cell differentiation has also been suggested. Expression of SOCS6 was upregulated during differentiation of these cells. SOCS6 overexpression resulted in enhanced neurite outgrowth cells, while siRNA-mediated knockdown of SOCS6 decreased neurite extension [242]. Neurite outgrowth was also enhanced by IGF-1, which increased SOCS6 levels, but reduced in the presence of a JAK/STAT pathway inhibitor that could not be rescued by IGF-1 treatment [242]. There is also a large body of *in vitro* data supporting a role for SOCS6 in glucose homeostasis. SOCS6 has been shown to inhibit pathways downstream of the INS and IGF-1 receptors [240]. This was facilitated by direct binding of SOCS6 to the IRS-4 adaptor protein following its phosphorylation in response to IGF-1 or insulin and more weakly to IRS-2 in response to IGF-1, allowing it to indirectly associate with the p85 regulatory subunit of PI3K in response to IGF-1 or insulin stimulation [7, 241]. It has been suggested that the mechanism of regulation in this case might be via preventing recruitment of other downstream signaling proteins [7]. SOCS6 has also been found to interact with PIM3, a protein upregulated in β-cells in response to glucose stimulation. *Pim3* KO mice showed greatly reduced levels SOCS6 expression in their pancreatic islets, while overexpression of SOCS6 inhibited glucose-induced ERK1/2 activation, suggesting a role for SOCS6 and PIM3 in the negative regulation of ERK1/2 in response to glucose stimulation [247]. Reduced endogenous SOCS6 in retinal pigment epithelia cells was found to coincide with inhibition of insulin signaling. It has therefore been suggested that SOCS6 expression may serve to maintain high basal insulin/AKT signaling in retina and improve glucose metabolism [232].

*Socs6* KO mice displayed an 8-10% reduction in body weight compared to WT littermates, thought to be due to perturbation of IGF-1R signaling [7]. However, despite the *in vitro* data, *Socs6* knockout mice did not display any alterations in glucose metabolism [7]. It has been suggested that this may be due to compensation by other SOCS family members implicated in the regulation of insulin receptor signaling, such as SOCS7 [7] or SOCS1 [80]. However, SOCS6 Tg mice utilizing the elongation factor I promoter displayed enhanced AKT activation in response to INS and increased glucose metabolism, supporting an *in vivo* role for SOCS6 in the regulation of INS signaling [241]. Finally, despite its expression in the bone marrow, no hematological phenotypes could be identified in *Socs6* KO or SOCS6 Tg mice [7, 241]. Again, redundancy between SOCS family members may play a role in the absence of a phenotype in these mice.

Altered SOCS6 expression has been described in several disease states, including cancer. However, similar to other SOCS proteins, SOCS6 does not appear to function exclusively as a tumor suppressor. Thus, low SOCS6 expression has been associated with recurrent primary lung squamous cell carcinoma [248] and cancers of the liver and thyroid gland [239]. Loss of SOCS6 was also observed in over 50% of patients with gastric or colorectal cancer, with SOCS6 inactivation predominantly caused by allelic loss or promoter hypermethylation [249, 250]. However, in the case of colorectal cancer, this did not correlate with disease-free survival or overall survival [251]. Ectopic SOCS6 expression supressed gastric cancer cell growth and colony formation *in vitro* [249]. However, a recent study found that levels of SOCS6 expression in colon and rectum tissue samples taken from healthy individuals varied widely, and demonstrated that SOCS6 expression was increased in gastric cancer [239].

*SOCS7*

SOCS7 has been shown to be expressed in many murine tissues [7], but the relative levels vary between different mouse strains [8]. In the C57BL strain, *Socs7* expression was highest in isolated pancreatic islets, whole brain, and skeletal muscle, with lower levels detected in the liver, perigonadal fat, skin, whole pancreas, testis and spleen [7, 8]. Expression in the 129S6 strain was similar overall, but with a 5-fold decrease in whole brain expression, a 6-fold increase in spleen expression and a 2,000-fold decrease in expression in isolated pancreatic islets, when compared to the C57BL strain [8]. Other sites of expression in this strain were the testes, kidney and eye [252]. SOCS7 has been shown to be induced by the

cytokines GH and PRL [142], as well as EGF [253], INS and IGF-1 [7].

SOCS7 has been found to regulate signaling by GH, PRL, leptin [29] and INS [8]. SOCS7 appears to control signaling in a number of ways. It was able to inhibit PRL and leptin mediated activation of STAT5 and STAT3, respectively [29], achieved by direct interaction of SOCS7 with phosphorylated STAT3 and STAT5, which in the case of STAT3 prevented its nuclear translocation [29]. SOCS7 can similarly inhibit the nuclear transport of the adaptor protein NCK [16]. SOCS7 was also demonstrated to interact via its SH2 domain to EGFR [253] and INS receptor [8], along with the adaptor proteins IRS-1 [8], IRS-2 [7], IRS-4 [7], the p85 subunit of PI3K [7] and GRB2 [253]. In these instances, SOCS7 likely regulates signaling activity through recruitment of E3 ubiquitin ligase activity and subsequent proteasomal targeting of associated proteins [8].

There have been conflicting reports regarding the *in vivo* function of SOCS7, probably due to differences in the genetic background of the respective mouse knockouts. One *Socs7* KO mouse line exhibited a 7-10% reduction in body size compared to wild type littermates, with no abnormalities in circulating glucose or insulin levels [252]. Approximately 50% of these *Socs7* KO mice died by week 15 due to hydrocephaly [252]. However, the hydrocephaly was not consistent in other mouse strains [8]. When the *Socs7* KO allele was on a mixed genetic background the hydrocephalus was obviated, which revealed increased insulin sensitivity when compared to WT mice [8]. These mice also showed an increase in the number of pancreatic islets and a hyperplasia of islets that was not present at birth but developed with age [8]. These observations suggested an active role of SOCS7 in insulin signaling, consistent with the findings that SOCS7 can interact with the INS receptor and their adaptor proteins [7, 8]. More recently it was demonstrated that approximately 50% of hydrocephaly-resistant *Socs7* KO mice developed a severe cutaneous disease by 16 months of age, with the dermis appearing hyperplastic with an infiltration of leukocytes. The skin of both affected and unaffected Socs7 KO mice possessed significantly increased mast cell numbers compared to controls, which were hyperactive to IgE-mediated stimuli. This resulted in increased production of the pro-inflammatory cytokines IL-13, IL-6 and TNFα, with levels of TSLP and a component of its receptor also upregulated [254].

There has only been very limited examination of the role of SOCS7 in human disease. However, a potential tumor-suppressor role has again been indicated, with one study demonstrating higher SOCS7 expression was significantly associated with earlier stages of cancer and overall survival [228]. A recent study has also found there to be associations between SOCS7 haplotypes and various metabolic traits, including obesity, insulin resistance and lipid metabolism [255].

## Conclusions

Research to date has highlighted a number of important roles for SOCS proteins in both development and disease. Indeed, all have been directly or indirectly implicated in immunity and/or hematopoiesis. Many have been shown to be involved in disease pathogenesis, including inflammatory and other immune disorders, susceptibility to infectious diseases and cancer. This suggests that there is considerable potential for the development of therapeutics based on augmenting (or antagonizing) SOCS function.

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