Cell. Mol. Life Sci. (2016) 73:3323–3336
DOI 10.1007/s00018-016-2234-x

Cellular and Molecular Life Sciences

REVIEW

SOCS3 revisited: a broad regulator of disease, now ready for therapeutic use?

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Received: 23 December 2015 / Revised: 24 March 2016 / Accepted: 19 April 2016 / Published online: 2 May 2016

Abstract Since their discovery, SOCS have been characterised as regulatory cornerstones of intracellular signalling. While classically controlling the JAK/STAT pathway, their inhibitory effects are documented across several cascades, underpinning their essential role in homeostatic maintenance and disease. After 20 years of extensive research, SOCS3 has emerged as arguably the most important family member, through its regulation of both cytokine- and pathogen-induced cascades. In fact, low expression of SOCS3 is associated with autoimmunity and oncogenesis, while high expression is linked to diabetes and pathogenic immune evasion. The induction of SOCS3 by both viruses and bacteria and its impact upon inflammatory disorders, underscores this protein's increasing clinical potential. Therefore, with the aim of highlighting SOCS3 as a therapeutic target for future development, this review revisits its multi-faceted immune regulatory functions and summarises its role in a broad ranges of diseases.

Keywords Suppressor of cytokine signalling (SOCS) · Janus kinase/signal transduction and activator of transcription (JAK/STAT) · Rheumatoid arthritis · Cancer · Diabetes · Infection

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Introduction

SOCS regulation of intracellular signalling

Inflammation represents a fundamental response to microbial, chemical and physical injury. Cytokine signalling regulates various pathophysiological processes and the generation of immune responses and inflammation [1]. Cytokines, such as interleukins (IL) and interferons (IFNs), activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [2], a critical intracellular cascade for the transduction of extracellular signals to the nucleus. The association of a ligand with its receptor results in receptor dimerisation, leading to JAK autophosphorylation. Activated JAKs phosphorylate cytoplasmic domains of the receptor, which provide docking sites for STATs. Phosphorylated STATs dissociate from the receptor, dimerise and translocate to the nucleus, where they interact with various regulatory elements that induce target gene expression [3–5]. Although cytokines are required to control infection, their overproduction can lead to local and/or systemic pathology. Several well-characterised mechanisms exist to prevent the overproduction of these mediators and down-regulate their signalling, including the upregulation of suppressor of cytokine signalling (SOCS) proteins [6, 7]. SOCS are intracellular, cytokine-inducible proteins that regulate the JAK/STAT pathway in numerous cell types, including those of the immune system [8, 9]. The SOCS family consists of 8 members, the cytokine-inducible Src homology 2 protein (CIS) and SOCS1-SOCS7 [10–12]. This group of proteins shares structural similarity: a central Src homology (SH)2 domain, a conserved C-terminal SOCS box and an amino-terminal domain of variable length and sequence [13]. SOCS1 and SOCS3 contain an additional kinase inhibitory

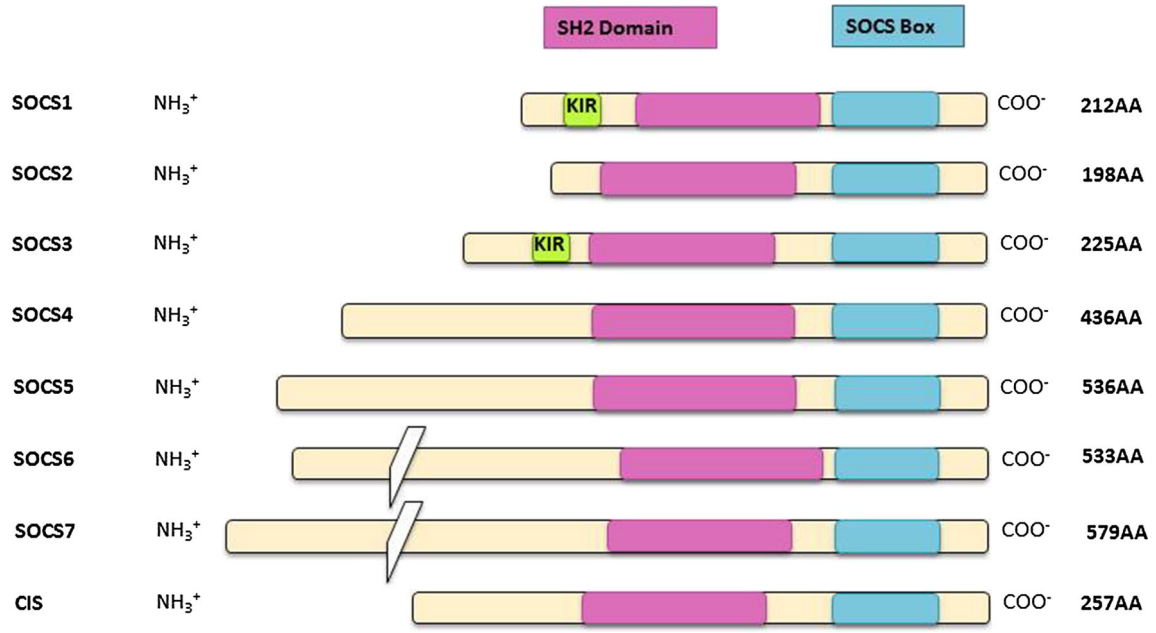

Fig. 1 Suppressor of cytokine signalling (SOCS) protein family members; there are eight members of the SOCS family of proteins, with each member possessing a SOCS box domain (*blue*), an SH2 domain (*pink*) and an amino-terminal region. The highly conserved SOCS box domain, located at the carboxy-terminus, is 40 amino acids in length and is the site of recruitment for the components of the E3 ligase, used for protein degradation. The SH2 domain is centrally located and also exhibits a considerable level of homology between members of the SOCS family. However, the amino-terminal domain is more variable in terms of both length and sequence. In SOCS1 and SOCS3 only, there is a kinase inhibitory region (KIR) just upstream of the SH2 domain, which yields another method of inhibiting the catalytic activity of JAKs, in addition to E3 ligase assembly. The KIR is thought to bind to the activation loop of JAKs with high affinity and thereby act as a pseudo-substrate. The importance of this region to the suppressive activity of SOCS1 and SOCS3 is emphasised by the fact that point mutations in this region completely abrogate their capacity to regulate cytokine signalling

region (KIR) [14] (Fig. 1). SOCS proteins can be induced by numerous cytokines, including IL-6 and TNF-α, growth factors, chemokines and pathogenic components (Fig. 2), including lipopolysaccharide (LPS) [11, 15–18]. Once upregulated, SOCS act via a negative feedback loop to inhibit further signal transduction. SOCS1 and SOCS3 proteins directly bind to JAKs through the SH2 domain and inhibit their activity. Babon et al. identified a new model of SOCS3 signalling inhibition. Once SOCS3 is recruited to receptors via high affinity binding sites, such as gp130, it binds to and inhibits the catalytic activity of JAK1, JAK2 and TYK2 [19]. This process is elegantly reviewed by Babon and Nicola [20]. Both SOCS1 and SOCS3 also compete for the acquisition of phosphorylated cytokine receptor tyrosine residues, thereby blocking STAT binding. SOCS use the ubiquitin proteasome system to degrade JAKs and other signalling molecules, via interaction with their SOCS box [21], which is also important for the stabilisation and/or degradation of SOCS1 and SOCS3 themselves [22] (Fig. 3). Interestingly, SOCS1 and SOCS3 retain some activity even after truncation of the SOCS box, highlighting that the SOCS box is not solely responsible for degradation of SOCS1 and SOCS3 target proteins [23]. Furthermore, compared to the other SOCS family members, the SOCS box of SOCS1 and SOCS3 binds with lower affinity to the E3 ligase protein, Cullin-5, revealing their differential mechanisms of action [24]. Among the SOCS family, SOCS1 and SOCS3 are the best characterised in their inhibition of JAK-STAT signalling. SOCS1 and SOCS3 also inhibit other signalling pathways, such as Ras/Extracellular Signal-Regulated Kinase (Ras/ERK), Phosphatidylinositide 3-kinases (PI3K) and focal adhesion kinase (FAK) signalling and the NF-κB cascades [25–29]. In recent years, increasing evidence detailing SOCS3's broad-acting regulation of many biological processes has implicated it in several immune disorders, diabetes, infectious disease progression and oncogenesis, thus identifying SOCS3 as a key protein at the cross roads of numerous intracellular and pathological events.

SOCS3 signalling regulation

SOCS3 is a well characterised regulator of STAT3 activation in response to several cytokines, including those in the gp130-containing IL-6 receptor family [30–36], but has also been documented to inhibit STAT1 [37], STAT4 [38], STAT5 [39] and STAT6 [40]. Moreover, SOCS3's broad regulation of several immune pathways is clearly

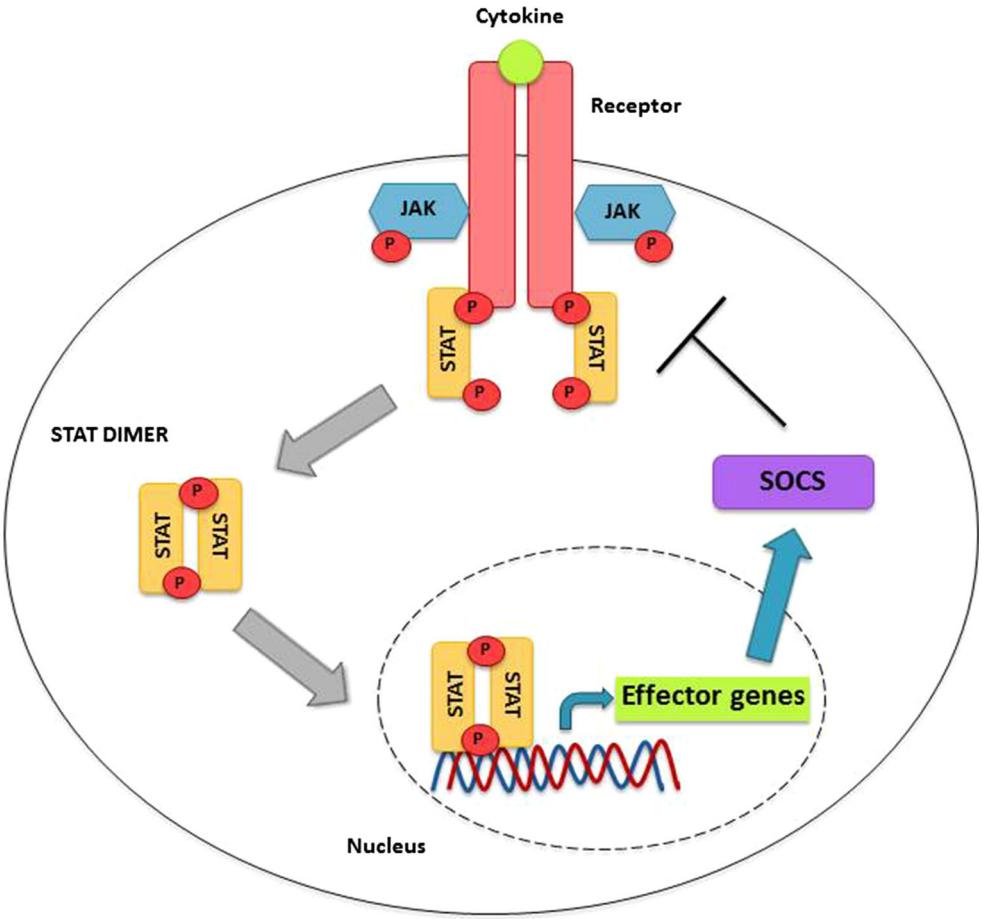

Fig. 2 SOCS protein induction by JAK/STAT signalling; when a cytokine or growth factor binds to its cognate receptor, the two chains of the receptor become more closely associated, which in turn brings the JAKs closer. This allows the JAK proteins to phosphorylate and activate each other and subsequently phosphorylate specific sites on the receptor chains. This leads to STAT recruitment to the phosphorylated sites on the receptor, through specific interactions via their SH2 domains. The STATs themselves are phosphorylated and activated by the JAKs, which enables their dimerisation and translocation to the nucleus, where they induce the transcription of their target genes. These genes include the SOCS family members. In this manner, a negative feedback loop is established, as SOCS proteins will go on to attenuate cytokine signalling by targeting JAKs and STATs, as represented in Fig. 3

demonstrated through its inhibition of IL-1-TRAF6 and TNF-α-TRAF2 signalling [29, 41], and its enhancement of FAK-mediated CCL11 signal transduction [28]. SOCS3's important regulatory role during infection is evidenced by its rapid induction upon detection of TNF-α, IL-6 and several pathogen-associated molecular patterns (PAMPs), such as LPS and CPG-containing DNA [1, 42, 43]. While SOCS3 is mainly characterised for its role in negative feedback inhibition [44–46], silencing of SOCS3 decreases LPS-induced production of TNF-α and IL-6 in macrophages, revealing its "alternative" role in positively regulating TLR4-induced macrophage activation [47]. While these seemingly contradictory roles may be cell-type specific, they highlight the multi-functional and versatile effects of this molecule. Along with innate immune regulation, SOCS3 is an important regulator of adaptive immunity and plays a crucial role in T cell activation and polarisation. Differentiation of naive T-helper (Th) cells into the mature antigen-specific Th2 phenotype is associated with SOCS3 expression [48], with Egwuagu et al., finding 23-fold higher SOCS3 levels in Th2 cells, compared with $CD4^+$ naive T cells [49]. In addition, SOCS3 is important for the onset and maintenance of Th2-mediated allergic immune disease, with SOCS3 transgenic mice displaying amplified Th2 responses and features characteristic of asthma [50]. Furthermore, SOCS3 inhibits Th1 differentiation via regulation of IL-12-induced STAT4 activation [48, 49, 51]. SOCS3 also plays a role in restricting Th17 cell generation, by inhibiting IL-23 signalling [52]. This SOCS3-mediated skewing towards Th2 differentiation has implications for asthma onset and development, with Veenbergen et al. showing that in SOCS3-transduced antigen-presenting cells (APCs), splenic $CD3^+$ T cells had decreased antigen-specific proliferation and a significant reduction in IFN-γ (−43 %), IL-4 (−41 %), and IL-17 (−70 %) production [53]. In order to highlight these broad regulatory functions of SOCS3, Table 1 summarises several of its key roles.

Abnormal levels or dysfunction of SOCS3 have been linked to the onset and/or development of several human diseases, including rheumatoid arthritis (RA), hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV) infection, diabetes and cancer [29, 54–56]. Therefore, this review documents the role of SOCS3 in these disorders, with the aim of encouraging discussion around the therapeutic potential of SOCS3 and development of novel treatments.

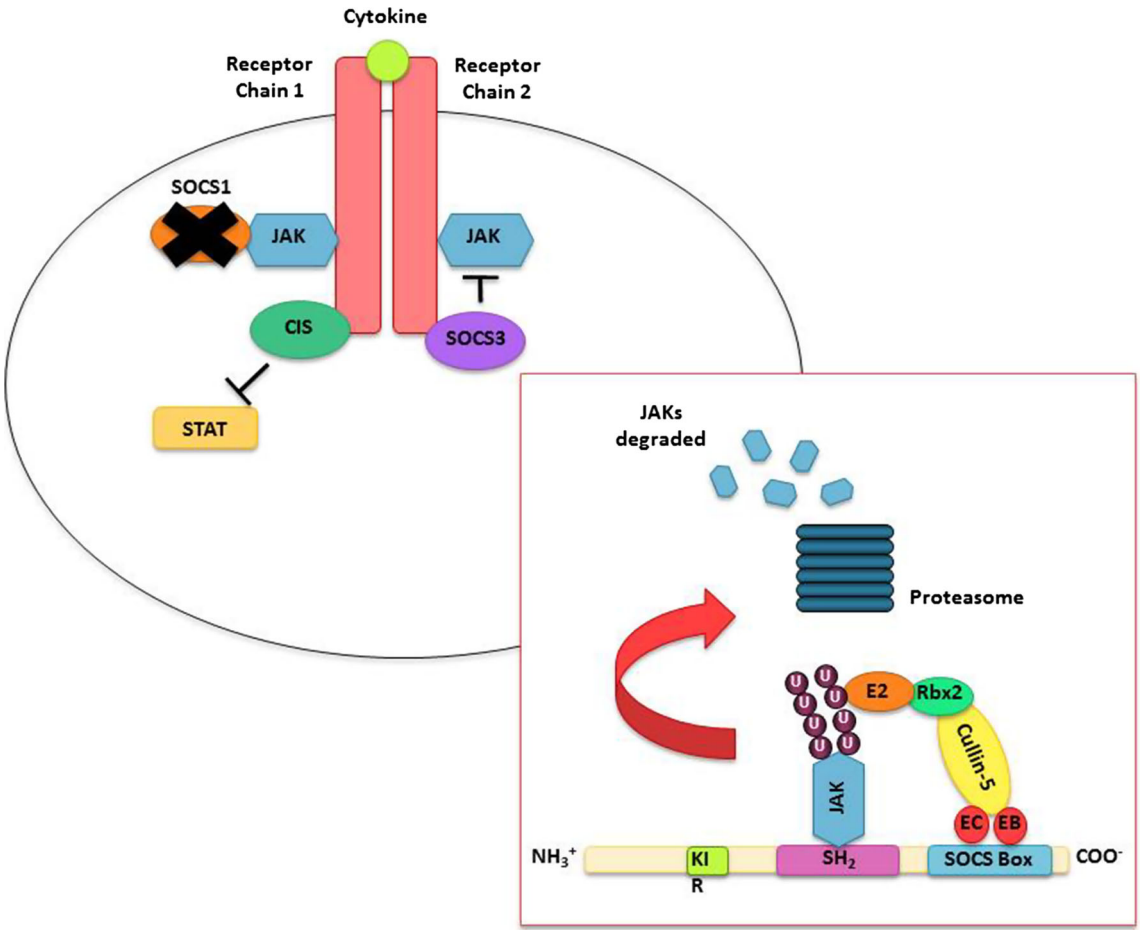

Fig. 3 Mechanisms of SOCS-mediated inhibition of the JAK/STAT pathway; SOCS1 can inhibit the kinase activity of JAKs by directly binding to them, while it is thought that SOCS3 first binds to the receptor to hinder the activity of JAKs. It is believed that CIS also binds to the cytokine receptor chains, but in doing so obstructs the recruitment and therefore activation of the STAT proteins. SOCS proteins can also mediate the degradation of JAKs via the ubiquitin–proteasome system (box overlay). The highly conserved SOCS box domain directly interacts with Elongin B and C, two components of an E3 ligase complex, which then interact with Cullin-5 and RING-box 2 (Rbx2), as well as an E2 ubiquitin conjugating enzyme. The assembly of this complex allows the polyubiquitination of JAK proteins to occur, which labels them for degradation by the proteasome

SOCS3 and rheumatoid arthritis

RA is a common autoimmune disease characterised by chronic inflammation of multiple joints, resulting in mononuclear cell infiltration and progressive cartilage destruction [57–59]. The exact trigger for RA remains unknown, although pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6 and IL-17, have been shown to play an important role in its pathology [60–63]. Deregulation of TNF-α expression in transgenic mice is sufficient to cause chronic inflammatory polyarthritis [64]. Furthermore, blocking TNF-α with a monoclonal antibody or soluble receptor significantly improves the clinical status of patients [65–67]. IL-6 strongly signals via the JAK/STAT pathway and accumulating evidence suggests that STAT and SOCS proteins play important roles in RA pathogenesis [53, 54, 68]. In 1995, Wang et al. reported activated STAT3, but not STAT1, in cells isolated from the synovial fluid (SF) of patients with inflammatory arthritis [69, 70]. Moreover, the SF from RA patients has been shown to induce STAT3 activation in monocytes [71]; while hyper-activation of STAT3, as well as increased SOCS3, was reported in synovial tissue from an arthritis murine model [54, 61]. In 2001, Shouda et al., found that adenoviral delivery of SOCS3 or a dominant negative STAT3 in synovial tissue of mice with antigen-induced arthritis (AIA) and collagen-induced arthritis (CIA) significantly reduced the severity of arthritis and joint swelling, compared to control groups. SOCS3 expression suppressed bone destruction and reduced joint inflammation, which subsequently resulted in decreased IL-6 production. SOCS3 was found to be more effective than the

Table 1 The functions of SOCS3

Role	Mechanism
Inhibits JAK/STAT signalling	Binds to JAKs via SH2 domain and inhibits activity
	Competes for phosphorylation sites on cytokine receptors and inhibits STAT activation
	Ubiquitinates and degrades JAKs via SOCS box
Inhibits Ras/extracellular signal-regulated kinase (Ras/ERK) signalling	Interacts with the Ras inhibitor; p120 RasGAP
	Maintains activation of ERK
	Ensures cell survival and proliferation
Inhibits phosphatidylinositide 3-kinases (PI3K) signalling	Prevents PI3K p85 activation
Inhibits focal adhesion kinase (FAK) signalling	Interacts with FAK (Y397) via SH2 and KIR domains
	Inhibits kinase activity and phosphorylation of FAK
	Ubiquitinates and degrades FAK via SOCS box
	Inhibits cell motility on fibronectin
Inhibits NF-κB pathway	IL-1β-induced NF-κB-dependent pro-apoptotic early response genes are inhibited by SOCS-3, e.g. iNOS, ICAM, complement C3, Mob-1, MIP-1, CX3C, NF-κB-p105, IRF-1 and fibrinogen
T helper (Th) cell polarisation	Highly expressed in Th2 cells
	Prevents differentiation into Th1 cells
	Restricts IL-17 induction

dominant negative STAT3 in the CIA model, suggesting that SOCS3 induction in synovial cells could represent an effective therapeutic strategy for treating RA [61]. Additionally, high expression of SOCS3 in splenic APCs led to decreased production of IL-6 and TNF-α, but high production of the anti-inflammatory cytokine, IL-10. These altered splenic cellular responses were accompanied by a profound protective effect against the development of CIA [53]. Furthermore, deletion of SOCS3 in hematopoietic and endothelial cells was associated with severe IL-1-dependent inflammatory arthritis, characterised by a prominent neutrophil synovial infiltrate and increased bone destruction [58]. This absence of SOCS3 enhanced T lymphocyte and macrophage activation, resulting in upregulation of IL-17 and IL-6, respectively, most likely feeding uncontrolled, detrimental STAT3 signal transduction [58]. A mutation in the gp130 receptor chain (Y757F) of mice blocked SOCS3 binding and thus led to the development of a spontaneous RA-like phenotype associated with autoantibody production and T cell abnormalities with advanced age [72]. In addition, Van de Loo et al., showed that SOCS3 mRNA and protein are increased in human pathological chondrocytes, suggesting that SOCS3 dysregulates normal chondrocyte function, thereby playing a major role in the development of cartilage pathology observed in RA patients [54].

Together these findings reveal the significant role SOCS3 plays in RA progression and emphasise that signal inhibition of STATs, especially STAT3, by SOCS3 could be an effective strategy in the treatment of RA.

SOCS3 and diabetes

Diabetes is a significant metabolic disorder characterised by impaired insulin activity [73]. Pro-inflammatory cytokines, such as IL-6 and TNF-α, have been shown to play a critical role in insulin resistance and are associated with type 2 diabetes [74]. Several studies have shown that SOCS3 participates in the regulation of insulin signalling [75–78]. SOCS3 expression is elevated in the adipose tissue of insulin-resistant obese mice, while SOCS3 is induced transiently by insulin in the liver, muscle and white adipose tissue [75]. Even though insulin sensitivity was enhanced in the liver of hepatocyte-specific SOCS3-deficient mice, they exhibited obesity and systemic insulin resistance with age, suggesting that deletion of the SOCS3 gene in the liver can even modulate insulin sensitivity in other organs [76]. However, a separate study showed that in mice exposed to IL-6, increased hepatic SOCS3 inhibited both insulin receptor auto-phosphorylation and insulin receptor substrate 1 (IRS1) phosphorylation [79]. Furthermore, Jorgensen et al., reported that mice lacking SOCS3 in skeletal muscle were protected against the development of hyper-insulinemia and insulin resistance. This protection was thought to be mediated through increased glucose uptake as a result of enhanced IRS1 and protein kinase B (Akt) phosphorylation in the skeletal muscle [77]. In addition, overexpression of SOCS3 in adipocytes causes local adipocyte insulin resistance in mice. Shi et al., found that overexpression of SOCS3 in adipocytes decreased both total and phosphorylated IRS1 protein levels, limited p85

binding to IRS-1 and attenuated glucose uptake in adipocytes. This impaired insulin signalling in the adipose tissue of transgenic mice overexpressing SOCS3, decreased lipogenesis and blocked insulin's anti-lipolytic activity [81]. SOCS3 was also shown to inhibit insulin action by binding to IRS1 and IRS2 and targeting them for proteasomal degradation [82].

These studies clearly demonstrate a crucial role for SOCS3 in regulating insulin signalling and highlight the significant impact clinical regulation of SOCS3 might have in therapeutically controlling insulin activity in patients with diabetes.

SOCS3 and viral infection

The interferon (IFN) response represents an early host defence mechanism against viral infection. Viruses evade immune responses using a variety of strategic interventions. DNA and RNA viruses often inhibit IFN-induced anti-viral responses by blocking the JAK/STAT pathway [83–86]. Induction of SOCS3 by viruses such as herpes simplex virus type 1 (HSV-1), HCV and HIV-1, suggests a key role for SOCS3 in suppressing anti-viral signal transduction [87–89].

HSV-1 is estimated to infect ~3.7 billion people under 50 years of age (WHO, 2012). The virus rapidly induces SOCS3 expression via STAT3 activation, which consequently attenuates anti-viral IFN JAK/STAT signalling, thus enhancing HSV-1 replication [89, 90].

HCV infection represents another global health problem, with ~180 million of the world's population currently infected. ~70–80 % of these patients develop chronic infection, with a risk for progressive liver fibrosis and hepatocellular carcinoma [91]. HCV core protein is thought to inhibit IFN-mediated STAT1 activation via increased SOCS3 expression, which may, at least in part, explain the lack of therapeutic responsiveness to IFN-α treatment [88]. In fact, hepatic SOCS3 expression is strongly associated with resistance to IFN-α therapy [87, 91]. Furthermore, Zhu et al., showed that IFN-α resistant HCV replicons produced higher levels of SOCS3 than their IFN-sensitive counterparts [92]. Recently, we reported that peripheral blood mononuclear cells from HCV-infected patients have elevated SOCS3 expression, compared to healthy controls, and that HCV overexpression in Huh7 hepatocytes induced SOCS3, which inhibited TNF-α signalling [29]. Interestingly, while Shao et al., also showed overexpression of SOCS3 inhibited IFN-induced STAT1 phosphorylation, it reduced HCV replication, suggesting that in this context, the anti-viral actions of SOCS3 are mediated through a JAK/STAT-independent pathway [93].

HIV is also a major health problem, infecting ~34 million individuals worldwide (WHO, 2013). SOCS1 and SOCS3 have been found to be increased upon HIV-1 infection and responsible for reduced IFN responsiveness and, in the case of SOCS1, regulation of HIV-1 Gag trafficking and assembly [94, 95]. IFN-β transiently suppresses viral replication within macrophages of the central nervous system (CNS) upon HIV-1 infection [96], but the virus overcomes this protective innate immune response via the induction of SOCS3, which inhibits IFN-β-mediated JAK/STAT signalling [96]. In contrast to these studies, Miller et al., reported that HIV-1 downregulates SOCS3 and SOCS1, which results in sustained activation of STAT proteins. The authors conclude that SOCS3- and SOCS1-mediated interference of HIV infection drives immune activation, thereby favouring HIV replication [97].

Influenza A virus triggers contagious acute respiratory disease that infects 5–10 % of the adult population each year (WHO, 2016) [98]. Overexpression of Influenza NS1 protein in HeLa cells upregulated SOCS1 and SOCS3 and inhibited STAT1-3 signalling, demonstrating an immune evasion strategy that ensures anti-viral responses to IFNs are blocked [99]. Pauli et al., also reported that Influenza A virus inhibited type I IFN signalling through induction of SOCS3, in an NF-κB-dependent manner. Additionally, SOCS3-deficient murine embryonic fibroblasts (MEFs) or SOCS3 knockdown cells showed sustained phosphorylation of STAT1, correlating with elevated expression of type I IFN-dependent genes and reduced viral titres [100].

RSV causes severe respiratory tract illness in infants and the elderly. RSV regulates IFN signalling via SOCS1, SOCS3 and CIS induction [101–103]. RSV also interferes with type I IFN signalling by mediating proteasomal degradation of STAT2, which demonstrates the broad anti-viral immune evasion strategies of this virus [104].

These findings collectively demonstrate the important role for SOCS3 in regulating type I IFN responses during viral infection and show how a number of viruses, including HSV-1, HCV, Influenza and RSV, all induce SOCS3 expression in several cell types. This immune evasion strategy has been shown to actively dampen host anti-viral responses, thus promoting the ability of the virus to replicate. Together these reports may suggest that, as with inflammatory disorders, therapeutic manipulation of SOCS3 expression could be a useful tool in restoring the anti-viral immune responses.

SOCS3 and bacterial infection

SOCS3 plays a critical role in restraining inflammation and, in doing so, generates optimal levels of protective immune responses against bacterial infection. Induction of SOCS3 by LPS indicates its important role in immune responses against bacteria [105], and has paved the way for

analysis into SOCS3-induction via a plethora of specific bacterial species including *Anaplasma phagocytophilum*, the causative agent of tick-borne human granulocytic anaplasmosis (HGA) [106], *Brucella* species (*B. melitensis*, *B. neotomae* and *B. ovis*) [107], *Lactobacillus rhamnosus* GG and *Streptococcus thermophilus* [108].

Borrelia burgdorferi or its lipidated outer surface protein A (L-OspA) amplified IL-10-induced SOCS1 and SOCS3 mRNA and protein expression in murine J774 macrophages [109]; *Helicobacter pylori* in a Korean isolate (HP99), induced the expression of SOCS3 in rat gastric mucosal cells (RGM-1) [110]; *Mycobacterium bovis Bacille Calmette-Guérin* (*M. bovis* BCG) up-regulated and activated NOTCH1 signalling, leading to the expression of SOCS3 [111], all suggesting a conserved bacterial immune evasion strategy. *Salmonella typhimurium* increased TLR4-mediated SOCS3 expression in draining lymph nodes (DLNs) and blocked Smad3 (small mothers against decapentaplegic homolog-3)-mediated production of CCL21. The reduction in CCL21 is thought to disrupt lymph node architecture and cell trafficking and thus enhance *S. typhimurium* virulence [112].

There is also an increasing body of evidence implicating SOCS3 as having a crucial role in *Mycobacterium tuberculosis* (TB) infection and disease severity. Using DNA array and RT-PCR technology, Mistry et al., found elevated SOCS3 expression in whole blood from TB patients as well as patients with recurrent TB, when compared to healthy donors with latent *M. tuberculosis* infection (LTBIs) [113]. Given that SOCS3 overexpression in mice leads to immune polarisation, promoting generation of Th2 cells [51] and suppression of Th17 responses [52], the modulation of SOCS3 in T cells is an important immune polarising process during *M. tuberculosis* infection.

A later study by Nair et al., showed that the PPE18 protein of *M. tuberculosis* upregulates the expression, as well as tyrosine phosphorylation, of SOCS3, which directly leads to inhibition of LPS-induced IL-12 and TNF-α production by blocking nuclear translocation of p50, p65 NF-κB, and c-rel transcription factors [114]. A separate study found that SOCS3 expression in either lymphoid or myeloid cells generates resistance to *M. tuberculosis* via SOCS3's regulation of IL-6/STAT3 signalling, which prevented IL-6-mediated inhibition of TNF and IL-12 secretion. In this way, SOCS3 contributed to IFN-γ expression in $CD4^+$ T cells and attenuated the secretion of IL-17 by γδ T cells, in response to infection [115]. Further studies have demonstrated that SOCS3 expression correlates with severity of disease, with SOCS3 mRNA accumulation significantly reduced in advanced pulmonary TB, compared with endemic controls [116, 117].

This data highlights the broad spectrum of bacterial pathogens that harness our immune responses via SOCS3 and further identify it as a target to improve the control of infection, or enhance the efficiency of novel vaccination strategies against bacteria.

SOCS3 and cancer

SOCS3 exhibits clear tumour suppressor activity, which is thought to be mediated via both the JAK/STAT pathway and focal adhesion kinase (FAK) signalling [80, 118–124]. FAK is a ubiquitously expressed, non-receptor, protein tyrosine kinase that plays a crucial role in many cellular processes including cell survival, proliferation and motility [125–127]. SOCS3 binds to FAK, inhibits its kinase activity and induces its degradation via the proteasome, thereby effecting cell migration and tumour invasion [118]. Aberrant methylation in the promoter region of the SOCS3 gene frequently occurs in several types of human malignancy, and its transcriptional silencing is associated with malignant tumour behaviour [80, 128]. Decreased SOCS3 expression was found in adenocarcinoma human alveolar epithelial cells (A549), induced by SOCS3 methylation. Reactivation of SOCS3, using a demethylation agent, attenuated proline-rich tyrosine kinase 2 (PYK2) expression and phosphorylation, resulting in reduced cell migration [129]. In addition, SOCS3 methylation has been reported in hepatocellular carcinoma (HCC) cells, with restoration of SOCS3 via demethylation, leading to suppressed STAT3 phosphorylation and cell growth in HCC cells [121]. Constitutive activation (by tyrosine phosphorylation) of STAT3 and STAT5, both of which are SOCS3-regulated, has been connected to cancer development [130, 131]. STAT3 is a substrate for the breast tumour kinase (Brk), a tyrosine kinase expressed in breast carcinoma, which has been linked to tumour progression [132]. Knockdown of Brk in breast cancer cells (T47D and BT474), decreased the phosphorylation of STAT3 and inhibited T47D cell migration, indicating that blocking Brk activity could have a profound effect in treating breast cancer [132]. Recently, Gao et al., demonstrated that SOCS3 binds to Brk and inhibits its kinase activity. SOCS3 associates with Brk via its SH2 domain, but its main inhibitory effect is mediated by the KIR domain [133]. In addition, the C-terminal SOCS box domain of SOCS3 has a modest effect on promoting Brk degradation [133]. The authors reported that, as SOCS3 is the only known inhibitor of Brk, it is a potential therapeutic target for blocking Brk activity and inhibiting cancer progression [133]. In T47D breast cancer cells, SOCS3

also suppressed STAT3 expression and abrogated STAT5 phosphorylation, decreasing cell proliferation [134]. Overexpression of SOCS3 in the head and neck squamous cell carcinoma (HNSCC) cell line again inhibited proliferation, migration and invasion, clearly identifying SOCS3 as an effective tumour suppressor gene [135].

Th17 cells produce pro-inflammatory mediators such as IL-17A, IL-17F, IL-21, and TNF-α, but their overproduction is linked to autoimmunity and cancer [136, 137]. The fish oil, docosahexaenoic acid (DHA), is suggested to be an effective adjuvant for anti-cancer drugs, with several intracellular targets, including NF-κB and peroxisome proliferator-activated receptor gamma (PPARγ) [138]. Interestingly, DHA reduces STAT3 phosphorylation, thereby interfering with Th17 cell differentiation. This effect was associated with DHA-induced SOCS3 expression, in a PPARγ-dependent manner. Silencing of SOCS3 in T cells blunted the capacity of DHA to restrain IL-17 expression. In addition, DHA prevented tumour outgrowth in an IL-17-dependent manner, as measured by cell viability assay [139]. Leptin JAK/STAT signalling is involved in gastric cancer [140]. Murine gastrointestinal epithelial cells, containing a SOCS3 deletion, developed gastric tumours, with mice demonstrating an increase in the cell damage-, cell cycle- and apoptosis-related molecules, p53, p21 and Bcl-xL. Furthermore, enhanced STAT3 phosphorylation, induced by deletion of SOCS3, led to increased leptin production, possibly acting through the zinc finger transcription factor, specificity protein 1 (Sp1). These SOCS3-deficient mice developed tumours in the stomach within 2 months and died within 6 months, demonstrating SOCS3's role in regulating this tumourigenic pathway [140]. Sp1 and STAT3 regulate both distinct and overlapping groups of genes during tumourigenesis. These two transcription factors function in cooperation to activate target genes in cancer progression [141, 142].

While SOCS3 can inhibit activation of STAT3 of several cytokine receptors, including gp130 [143, 144], granulocyte-colony stimulating factor receptor [145], leptin receptor [146] and IL-12Rβ [38], it does not inhibit STAT3 activation in the IL-10 receptor pathway, suggesting a broad regulatory capacity for IL-10-induced SOCS3 [46, 147].

Altogether, these data explicitly illustrate the anti-tumour activity of SOCS3, which acts by limiting the production of a plethora of genes involved in cell survival, proliferation and motility, culminating in limited tumour growth. Indeed, new immune-related anti-cancer therapies may benefit by exploring SOCS3 as a potential target for treatment of specific malignancies.

Therapeutic implications of SOCS3

The broad regulatory properties of SOCS3 and its direct involvement in inflammatory disorders, diabetes, cancer and both bacterial and viral infection, highlights it as a strong therapeutic target. On the other hand, SOCS3 is induced by a number of cytokines with both pro- and anti-inflammatory functions, including IL-6 [46] and IL-10 [148], respectively. Furthermore, SOCS3 differentially regulates inflammation depending on the cell type, presenting obvious therapeutic challenges that must be addressed through specific cell targeting [8, 149]. For this reason, the transient nature of SOCS3 expression is being addressed to ensure therapeutic effectiveness [150]. For example, cell-penetrating (CP) forms of SOCS3 have been established in cell cultures and mice, effectively blocking signal transduction and protecting against inflammation and organ failure during bacterial challenge [151]. Also, overexpression of SOCS3, using a recombinant adenovirus cDNA, reduced inflammatory RA development in mice [61], further demonstrating the therapeutic potential of SOCS3.

Interestingly, HCV upregulates SOCS3 in both hepatocytes [93] and immune cells [29], and since SOCS3 regulates the IFN-α pathway, it makes its suppression an obvious target for enhancing the response to therapeutic IFN-α. However, as with artificial induction of SOCS3, its reduction may also be challenging. MicroRNAs are increasingly being identified as regulators of SOCS expression [152]. This is demonstrated in the repression of microRNA-122, which inhibits SOCS3 expression (via enhanced promoter methylation) and was postulated as a promising alternative to treat HCV [153–155]. We have also shown miR19a expression to suppress SOCS3, both at the mRNA and protein level [156], identifying another possible method of silencing SOCS3.

By suppressing the tumour-promoting activity of STATs, SOCS3 could also be a useful tool in the treatment of cancer; in fact, SOCS3 overexpression has already been shown to inhibit growth of non-small lung cancer cells and adenoviral transfer of SOCS3 enhanced the radio-sensitivity of non-small lung cancer cells [157]. Infection of liver tumour cells with oncolytic adenovirus CN305 (AdCN305)-SOCS3 and AdCN305-cell-penetrating peptides-SOCS3 resulted in dramatic cytotoxicity of liver tumour cells. However, the cytotoxic effects were not observed in normal cells infected with these vectors. Infection of liver tumour cells with AdCN305-SOCS3 and AdCN305-cpp-SOCS3 resulted in almost complete inhibition of STAT3 phosphorylation, demonstrating that the transfer of SOCS3 via an oncolytic adenovirus represents a useful approach to be explored further in the treatment of

cancer [158, 159]. Furthermore, SOCS3 overexpression suppressed the growth of the malignant fibrous histiocytoma (MFH) cell line by inhibiting STAT3 and IL-6 production, adding to the growing body of evidence pointing towards SOCS3 as an effective tumour suppressor [160]. Upregulation of SOCS3 by platelet factor 4 (PF4) may also be a therapeutic target for cancer. PF4 is an angiostatic chemokine that suppresses tumour growth and metastasis [161]. Recently, PF4 was found to induce SOCS3, thereby inhibiting STAT3 activation, angiogenesis, growth and induced apoptosis in myeloma cells [161]. Silencing of SOCS3 abolished PF4's ability to inhibit STAT3 activation, suggesting a critical role of SOCS3 in PF4-induced STAT3 inhibition and indicating that PF4 may be a potential new targeting agent for the treatment of myeloma [161].

Expression of SOCS3 is also closely associated with the severity of allergic asthma and dermatitis, making it a target for therapeutic intervention in allergic disease [50, 162]. Heterozygous deletion of SOCS3 and overexpression of a dominant negative form of SOCS3 were both proven to be effective in prevention of early and late-phase responses of allergic conjunctivitis, a common allergic eye disease [162]. However, another study showed that defective SOCS3 expression causes inflammatory skin disease [163]. Keratinocyte-specific deletion of SOCS3 caused severe skin inflammation, with inflamed skin showing constitutive STAT3 activation and upregulation of IL-6 [163]. This SOCS3-mediated homeostatic function in skin inflammation is supported by other reports showing that a specific microRNA, miR203, is highly expressed in human psoriatic skin and inhibits the expression of SOCS3 [164]. Together, these studies confirm the therapeutic potential of SOCS3 in development, diagnoses and treatment of human disorders; thus manipulation of SOCS3 could be a novel therapeutic approach and methods of artificially regulating its expression may be a solution for many diseases.

Conclusion

The discovery of SOCS proteins has provided new insight into cytokine regulation and immune responses. SOCS3 plays a significant role in regulating different signal transduction pathways, with the classical JAK/STAT regulation being the target of its effects. SOCS3 expression is shown to be associated with many inflammatory, immunological, infectious and oncogenic disorders. The vast body of evidence which has accumulated over the past two decades indicates that the regulation of SOCS3 expression may be a powerful therapeutic tool to treat various human diseases such as RA, pathogenic infection, diabetes and cancer. The role of SOCS3 in several signalling pathways is becoming evident and, therefore, further investigation into its regulation of cascades, such as MAPK and NF-κB, may reveal even more intricate roles for SOCS3 in human disease. However, it is already clear that regulatory peptides, overexpression constructs or microRNA may be useful tools in enhancing or suppressing SOCS3 levels and could represent new and exciting approaches in treating disease.

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