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"Suppressor of Cytokine Signalling" Molecules in Infection and Inflammation

Berit Carow and Martin E. Rottenberg
Dept. of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm Sweden

1. Introduction

Cytokines are messengers that coordinate the development and function of leukocytes and therefore are indispensable for the initiation, maintenance and termination of all types of immune responses. A tight control of cytokine functions is crucial for both, the control of infections and the prevention of infection-associated immunopathology. Different intracellular mechanisms of cytokine signal inhibition are involved in the regulation of innate and adaptive immune responses. Among these, the family of suppressor of cytokine signalling (SOCS) proteins identified more than a decade ago (Endo *et al.* 1997; Naka *et al.* 1997; Starr *et al.* 1997) are non-redundant negative feedback inhibitors of both pro-inflammatory but also of anti-inflammatory cytokine responses (Kubo *et al.* 2003; Yoshimura *et al.* 2007).

Type I and type II cytokine receptors do not possess a cytoplasmic kinase activity and therefore are dependent on associated Janus kinases (JAKs). JAKs conduct the signal of many cytokines including many interleukins (IL), all interferons (IFN) and hemopoietins. Activated JAKs cross-phosphorylate themselves and phosphorylate the associated cytokine receptor creating binding sites for proteins that contain phosphotyrosine binding SH2 domains. The SH2 domain of signal transducers and activators of transcription (STATs) then binds to the phosphorylated receptors. Recruited STATs get phosphorylated by the adjacent JAKs, and act as binding sites for the SH2 domain of another STATs, which also will be phosphorylated. The STAT dimer translocates into the nucleus where it acts as a transcription factor activating the transcription of specific genes. The diversity of STAT-mediated intracellular pathways is due to the presence of 7 STATs, activated by different receptors. Moreover, activated STAT dimers act as homo- or heterodimers, which increases the diversity of target promoters and thereby of gene patterns that can be activated.

The JAK-STAT pathway can be negatively regulated at different stages: protein tyrosine phosphatases remove phosphates from cytokine receptors and activated STATs, whereas PIAS (protein inhibitors of activated STATs) act in the nucleus (Leonard & O'Shea 1998; Krebs & Hilton 2001; Hebenstreit *et al.* 2005; Shuai 2006). In this chapter we will focus on the role of another inhibitor of the JAK-STAT pathway, the SOCS proteins. The importance of these proteins is evidenced by the fact that mice deficient for some of the SOCS proteins demonstrated a non-redundant role of SOCS proteins in regulating the immune system (Alexander 2002).

SOCS proteins play a role in balancing immune functions at different levels, including the differentiation of immune cell populations and their activation by environmental stimuli. Both deletion and over-expression of SOCS proteins in animal models provided insights into their importance of regulating the responsiveness to cytokines. Accumulated today's knowledge on the immunobiology of SOCS proteins convert them into new potential targets for treatment of inflammatory diseases but might also help to improve infection control.

2. SOCS at the molecular level

The family of SOCS proteins consists of 8 members (cytokine inducible SH2 protein, CIS, SOCS1-7), which share a central modulator organization with a SH2 domain, a C-terminal SOCS box and an amino-terminal domain of variable length (fig. 1). The SOCS-box was shown to interact with elongin A and B, cullin 5 and ring box. This complex acts as an E3 ubiquitin ligase, initiating ubiquitination in other words the covalent binding of ubiquitin to target proteins, which is followed by the proteosomal degradation of bound signalling complexes as JAKs and cytokine receptors (Verdier *et al.* 1998; Kamura *et al.* 2004; Piessevaux *et al.* 2008). The SH2 domain of SOCS proteins determines the specificity of the SOCS and CIS proteins for the respective cytokine receptors (Endo *et al.* 1997; Nicholson *et al.* 2000).
So far, SOCS1 and SOCS3 are the most studied SOCS proteins. They both contain a N-terminal kinase inhibitory region (KIR) that is absent in other SOCS proteins (fig. 1). The KIRs of SOCS1 and SOCS3 can directly inhibit JAK tyrosine kinase activity, acting as pseudo-substrates, and by that can block the interaction of JAKs with their substrate STAT molecules. JAK inhibition by SOCS1 and 3 takes place even in the absence of the SOCS box (Yasukawa *et al.* 1999; Zhang *et al.* 2001). SOCS1 can bind to the catalytic domain of JAK2 and to Tyk2 a molecule of the JAK family that mediates IFN-α/β signalling. SOCS1 has also been shown to bind directly to type I IFN receptors (IFNar1) (Fenner *et al.* 2006) and to the IFN-γ receptor inhibiting efficiently STAT1-mediated signalling (Kubo *et al.* 2003; Qing *et al.* 2005; Fenner *et al.* 2006). Furthermore, SOCS1 can bind to the insulin receptor (Mooney *et al.* 2001; Rui *et al.* 2002) and to the glucocorticoid receptor via its SH2 domain (Haffner *et al.* 2008). Besides JAK2, SOCS3 binds to a variety of receptors as the common IL-6 family co-receptor gp130 at the phosphorylated tyrosine 757, erythropoietin receptor, granulocyte colony stimulating factor (GCSF) receptor, growth hormone receptor (Hansen *et al.* 1999;

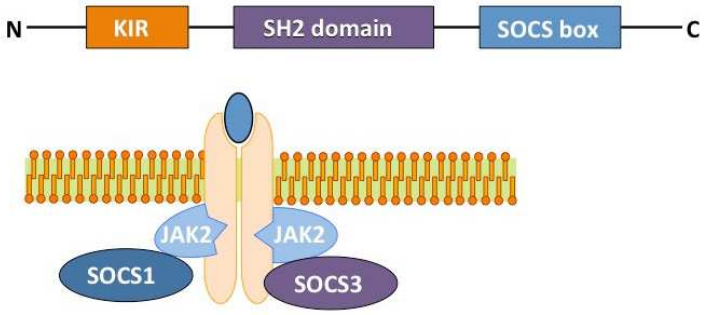

Fig. 1. Schematic structure of SOCS1 and SOCS3 proteins shown in upper panel, SOCS1 and SOCS3 as negative regulators of JAK/STAT signalling in lower panel. SOCS1 preferably binds directly to the JAK activation loop while the SH2 domain of SOCS3 binds to the cytokine receptor.

Nicholson *et al.* 2000; Sasaki *et al.* 2000; Hortner *et al.* 2002a; Hortner *et al.* 2002b) and cytokine receptors IL2Rβ and IL-12Rβ1(Cohney *et al.* 1999; Yamamoto *et al.* 2003). Possible interactions of SOCS1 and SOCS3 with Toll-like Receptor (TLR) signalling have been described and will be discussed later.

3. SOCS1

SOCS1 is expressed constitutively in the thymus, spleen, lung and testes of mice. SOCS1 mRNA expression can be rapidly induced by many cytokines, especially IFNs, and serves as a classical feed back loop inhibiting its inducing pathway (Naka *et al.* 1997; Starr *et al.* 1997). Importantly, SOCS1 mRNA expression increases even in response to microbial molecules such as LPS, Pam_3Cys and CpG oligonucleotides that signal via TLR (Dalpke *et al.* 2001; Alexander 2002; Fujimoto & Naka 2003; Dennis *et al.* 2006). Furthermore, hormones like insulin (Emanuelli *et al.* 2000), cardiotrophin (Hamanaka *et al.* 2001) or glucocorticoids (Bhattacharyya *et al.* 2011) have been shown to stimulate SOCS1 expression.

$SOCS1^{-/-}$ animals die within 3 weeks after birth due to fatty degeneration and necrosis of the liver (Naka *et al.* 1998; Starr *et al.* 1998). These mice show retarded growth, lymphopenia and multi-organ haematopoietic infiltrates. At least in part, the spontaneous inflammatory disease is thought to be due to IFN-γ hyper-responsiveness of SOCS1-deficient tissue, because $SOCS1^{-/-}$-$IFN\text{-}\gamma^{-/-}$ as well as $SOCS1^{-/-}$-$STAT1^{-/-}$ mice survive healthy until adulthood (Alexander *et al.* 1999; Marine *et al.* 1999b). The importance of IFN-γ was further apparent in mice heterozygous for IFN-γ and lacking SOCS1 that survived until 5 month of age before succumbing with myocardis and polymyositis (Metcalf *et al.* 2000). SOCS1 mice, treated with neutralizing antibodies from birth, died of the same phenotype reaching adulthood (Bullen *et al.* 2001). A similar expected protection from lethality was observed in $SOCS1^{-/-}$ crossed with $IFN\text{-}\gamma R^{-/-}$ and $STAT1^{-/-}$ mice. Furthermore, $RAG2^{-/-}$-$SOCS1^{-/-}$ are healthy to at least 3 month of age, implicating that IFN-γ secreted by T and/ or NKT cells might be responsible for the tremendous inflammation observed (Marine *et al.* 1999b). In fact, depletion of NKT cell by antibody-treatment significantly increased the survival of mice. Surprisingly, mice with a conditional knock down for SOCS1 in T and NKT cells did not display any of the $SOCS1^{-/-}$ pathologies, indicating that a deletion of SOCS1 in T and NKT cells is not sufficient for the hyper-inflammation but that this was due an uncontrolled response of myeloid cells together with an excessive neonatal IFN-γ release (Chong *et al.* 2003). The fact that myeloid cells are involved was demonstrated by the lethality of chimeric mice, which received $SOCS1^{-/-}$ bone marrow after irradiation (Metcalf *et al.* 2003). On the other hand, T cells were also required for SOCS1-mediated lethality since $SOCS1^{-/-}$ mice with a SOCS1 transgene expressed only by T cells survived. Interestingly, the survival of $SOCS1^{-/-}$ mice also increased when back-crossed to $IFNar1^{-/-}$ mice (lacking one of the IFN-α/β R subunits) indicating that even type I IFNs in part contribute to the lethal inflammation of SOCS1 deficient animals. Altogether, SOCS1 lethality is mainly due to both an exacerbated secretion of IFN-γ by T and NKT cells during the neonatal period and to a hyper-response of myeloid cells to IFN-γ, but IFN-γ-independent immune responses such as type I IFN and others discussed below are also likely to contribute to it.

The use of conditional knock down mice, as well as in vitro experiments with different cell populations allowed a more precise definition of the role of SOCS1 in different cell lineages. A combination of SOCS1 conditional knock downs in hematopoetic cells using the cre-lox technology confirmed that SOCS1 deficiency in both T cells and macrophages

is critical to result in lethal inflammation (Chong *et al.* 2005). SOCS1$^{fl/-}$ LysM-cre mice deficient for SOCS1 in myeloid cells showed signs of morbidity starting from 50 days of age with splenomegaly as the most prominent feature. Moribund SOCS1$^{lox/-}$ LysM-cre mice showed aberrantly activated T cells and elevated serum levels of IFN-γ, TNF-α and IL-12 p40. SOCS1$^{fl/fl}$ Lck-cre mice, deleted for SOCS1 in T- and NKT-cell compartment did not develop lethal multi-organ inflammation but developed multiple lymphoid abnormalities, including enhanced differentiation of thymocytes toward CD8 T cells and very high percentages of peripheral CD8 T cells with a memory phenotype (Chong *et al.* 2005).

SOCS1$^{-/-}$ mice could also be partially protected from neonatal lethality when crossed with STAT1$^{-/-}$, STAT4$^{-/-}$ or STAT6$^{-/-}$ mice but nevertheless showed a chronic inflammation with aberrant T cell activation (Metcalf *et al.* 2000; Naka *et al.* 2001; Eyles *et al.* 2002). STAT6 and STAT4 are two STAT family members that specifically mediate signals that emanate from the IL-4/ IL-13 and IL-12 receptors, respectively (Wurster *et al.* 2000). IL-4/ IL-13 and IL-12 are cytokines that are important regulators of the proliferation, differentiation and functional capacity of lymphocytes. Although the impact of genetic deletion of STAT4 and STAT6 genes in the survival of SOCS1 deficient animals is lower than that of STAT1, this demonstrates that SOCS1 also regulates IL-4 and IL-12 signalling. Uncontrolled responses to IL-12, an inflammatory cytokine, could contribute to increased IFN-γ secretion by T cells production and, as indicated above, to the development of inflammatory disease in SOCS1$^{-/-}$ mice (Eyles *et al.* 2002). IL-4, like IFN-γ, induces de novo expression of SOCS-1 in primary macrophages. Induction of SOCS1 gene expression by IL-4 is STAT6-dependent and SOCS1 feedback inhibits expression of STAT6-responsive genes. Upon binding to their ligand the IL-4 and IL-12 receptors induce tyrosine phosphorylation of the JAK2 protein kinase (Wurster *et al.* 2000). In relation, SOCS1 deletion in T cells resulted in an elevated production of both IFN-γ and IL-4, which might indicate an enhanced function of Th2 populations in addition to Th1 cells. Overexpression of SOCS1 in Th2 cells has been shown to repress STAT6 activation and inhibit IL-4-induced proliferation, while depletion of SOCS1 by an anti-sense SOCS1 enhanced cell proliferation and induced activation of STAT6 in Th2 cells (Yu *et al.* 2004). On the other hand, the role of SOCS1 in a Th2 skewed immune responses has been suggested (Lee *et al.* 2009), in relation to the fact that SOCS1 expression is 5-fold higher in Th1 than in Th2 cells (Egwuagu *et al.* 2002).

Dendritic cells (DCs) play a critical role in initiating and regulating adaptive immune responses. Silencing of SOCS1 in DCs broke self-tolerance to tumor antigens and increased the magnitude of antigen-presentation (Shen *et al.* 2004; Evel-Kabler *et al.* 2006). Moreover, the increased responses of SOCS1$^{-/-}$ T and NK cells to IL-12 (Eyles *et al.* 2002), and the IFN-γ-mediated inflammatory disease in mice deficient for SOCS1 in regulatory T (Treg) cells (Lu *et al.* 2009; Lu *et al.* 2010) showed a SOCS1-mediated control of Treg cell function, but also highlights the relevance of SOCS1 as target molecule in these diseases. In Treg cells specific microRNA regulated SOCS1 expression.

SOCS1 has also been shown to inhibit B cell proliferation in vitro and autoantibody production in vivo, through suppression of BAFF/BLyS a B cell growth and differentiation factor, that has been implicated in systemic autoimmune diseases (Hanada *et al.* 2003).

Taken together, several findings indicate that SOCS1 is involved in the regulation of Th1 responses by modulating the responses of different immune cells, such as macrophages, DCs, Th1 and Treg cells.

3.1 Role of SOCS1 in infectious diseases and inflammation

SOCS1 deficient mice are hypersensitive to LPS-induced endotoxic shock, associated with increased levels of IL-12 and TNF-α (Kinjyo *et al.* 2002). Surprisingly, even though IFN-γR$^{-/-}$ mice are very resistant to endotoxic shock (Car *et al.* 1994), additional knock-out of IFN-γ or STAT1 did not rescue SOCS1$^{-/-}$ mice from lethal LPS injection, demonstrating that SOCS1 attenuates IFN-independent mechanisms that mediate septic lethal shock (Car *et al.* 1994; Kinjyo *et al.* 2002; Nakagawa *et al.* 2002). Furthermore, elevated sensitivity to endotoxin shock was observed in SOCS1$^{fl/fl}$ LysM-cre mice lacking SOCS1 in macrophages and neutrophils (Hashimoto *et al.* 2009b). Another contributing factor to the elevated sensitivity might be that SOCS1 mediates the protective effect of cardiotrophin-1 in sepsis-induced cardiomyocyte depression (Tanimoto *et al.* 2005).

These findings suggest an interaction of SOCS1 with components of TLR signalling underlying the role of SOCS1 in protection against septic shock. In fact, binding of SOCS1 to IRAK1 and the p65 subunit of NFκB has been shown to destabilize and limit NFκB activation (Kinjyo *et al.* 2002; Nakagawa *et al.* 2002; Ryo *et al.* 2003; Maine *et al.* 2007). Others demonstrated that SOCS1 might also bind to apoptosis signal-regulating kinase 1 (ASK1) and regulate mitogen-activated protein kinases JNK and p38 (He *et al.* 2006). Furthermore, SOCS1 was shown to mediate the degradation of the adaptor protein Mal, involved in TLR2 and TLR4 signalling (Mansell *et al.* 2006). However, results from other investigators could not confirm a direct effect of SOCS1 on TLR signalling (Baetz *et al.* 2004; Gingras *et al.* 2004) . SOCS1 over-expression did not affect TLR signalling, instead the inhibition of IFN-α/β-mediated STAT1 activation by SOCS1 has been suggested to account for the observed sensitivity to LPS in IFN-γ$^{-/-}$/SOCS1$^{-/-}$ mice (Baetz *et al.* 2004; Gingras *et al.* 2004). Thus, further work is required to clarify whether SOCS1 is directly involved in the regulation of TLR signalling.

A wide range of pathogens including parasites, bacteria and viruses are potent stimulators of SOCS1 expression in the host. Despite obvious differences in the immunobiology and in the type of protective or deleterious immune responses elicited, for most intracellular infections studied, SOCS1 expression is apparently facilitating pathogen replication. But by hampering inflammatory reactions SOCS1 may also improve the pathological outcome of infections and thereby reduce morbidity. In this respect, manipulation of the immune system by SOCS1 conveys an adaptive advantage to pathogens. Microbes replicating in macrophages can be thought of hijacking the host SOCS system as an immune evasion mechanism.

To unravel the role of SOCS1 different infection models knock out and conditional knock down mouse strains have been applied. Other tools, such as lentiviruses encoding SOCS1 siRNA and treatment with small molecules inhibiting or mimicking SOCS1 action have also been used. Altogether, targeting SOCS1 may serve as a tool to improve the control of different infections and their pathological outcomes.

3.1.1 Viral infections

Several viruses including Herpes Simplex Virus (HSV)(Frey *et al.* 2009), human respiratory syncytial virus (RSV) (Hashimoto *et al.* 2009a), hepatitis C (HCV)(Yao *et al.* 2011), Ebola (Okumura *et al.* 2010) and human-immunodeficiency (HIV)(Yadav *et al.* 2009) virus were found to up regulate SOCS1 (Yang *et al.* 2008; Frey *et al.* 2009; Hashimoto *et al.* 2009a;

Hashimoto *et al.* 2009b; Okumura *et al.* 2010; Yao *et al.* 2011). Since SOCS1 is interfering with the type I IFN signalling, a role for SOCS1 in incrementing susceptibility to viral infection could be expected.

SOCS1$^{-/-}$/IFN-γ$^{-/-}$ mice outlived Semliki Forest virus (SFV)-infected control mice substantially (Alexander *et al.* 1999). Even though serum levels of IFN-α/β were lower in infected SOCS1$^{-/-}$ mice than in controls, an increased sensitivity to IFN-α/β was associated to resistance. The IFN-ar1 chain of the IFN-α/β receptor was shown to interact with SOCS1 and therefore inhibited efficient host responses (Fenner *et al.* 2006).

In another model, human T cell lymphotropic virus (HTLV) replication in peripheral blood mononuclear cells correlated with induction of SOCS1 and inhibition of IFN-α/β and IFN-stimulated gene expression (Oliere *et al.* 2010). These authors also showed that HTLV infection-induced SOCS1 mediated proteosomal degradation of IRF3, the blockade of IFN-gene expression and enhanced viral load. Of importance, SOCS1 did not only inhibit type I IFN-mediated viral defences but was found to impair efficient IFN-α stimulated anti-tumoral defences in mice (Zitzmann *et al.* 2007).

In vivo, injection of dnSOCS1 construct into the hearts of coxsackievirus-infected mice attenuated both virus replication and cardiomyocyte damage, protecting the heart from viral infection, suggesting that SOCS1 is a relevant therapeutic target (Yasukawa *et al.* 2003b).

Recently, specific microRNAs were found to regulate IFN-α/β responses. Infection with vesicular stromatitis virus (VSV), was shown to stimulate miR-155 expression that, by inhibition of SOCS1, positively regulated host antiviral innate immune response by promoting IFN-α/β responses (Wang *et al.* 2010). Thus, while SOCS1 is up-regulated during inflammatory IFN-mediated responses, miRNA might be a new mechanism by which the host can fine-tune its antiviral state.

Besides type I IFNs, responses to IFN-γ can be an essential component of control of some viral infections. The HSV-infection in keratinocytes, stimulated SOCS1 expression and made them refractory to IFN-γ, whereas HSV infected fibroblasts did not increase SOCS1 levels and developed an antiviral state after IFN-γ stimulation (Frey *et al.* 2009). Treatment of cells with a SOCS1 antagonist peptide as well as silencing SOCS1 with siRNA protected keratinocytes from HSV-1 infection and restored responsiveness to IFN-γ.

In contrast to suppression of IFN-mediated protective responses by SOCS1, in other virus infections unrestrained immune responses can cause damaging immunopathology. In these cases impairment of cytokine responses with SOCS1 may prevent inflammatory damage. Thus, in a vaccinia virus infection model, the administration of a small tyrosine inhibitor peptide that binds to JAK2 and inhibits STAT1 phosphorylation as well as a peptide mimicking the SOCS1 KIR region protected mice against lethal virus infection (Ahmed *et al.* 2009).

Clinical studies showed T cell exhaustion in chronically HCV-infected individuals. Interestingly, the expression of programmed death receptor 1 (PD1) and SOCS1 was increased in T cells and macrophages (Frazier *et al.* 2010; Zhang *et al.* 2011). In both cell types, blocking of PD1 signalling reduced SOCS1 expression and led to improved T cell proliferation and IL-12 secretion by macrophages respectively.

Studies on HIV progressor patients showed that SOCS1 expression was elevated in CD4 T cells displaying reduced IRF1 expression after IFN-γ stimulation in comparison to healthy controls (Yadav *et al.* 2009). Furthermore, SOCS1 was found to bind to HIV gag protein

improving production and stability of HIV-1 particles (Ryo et al. 2008). In a HIV vaccination model in mice, silencing of SOCS1 in DC using siRNA increased the secretion of IL-12 and other pro-inflammatory cytokines resulting in enhanced memory humoral and cellular immune responses (Song *et al.* 2006). Recently, it was shown that treatment of DCs from HIV patients with SOCS1 siRNA augmented the frequency of polyfunctional cytotoxic T cells (T cells secreting IL-2, TNF-α and IFN-γ are associated with protection)(Subramanya *et al.* 2010), suggesting that silencing SOCS1 in DCs may contribute to improved HIV-vaccination.
Taken together, SOCS1 induction is a successful tool of various viruses to diminish antiviral IFN responses, leading in many of the infections to impaired control of infection.

3.1.2 Bacterial infections

Studies on the role of SOCS1 have been focussed on intracellular bacterial infections in which IFN-γ usually plays a major protective role. Research from our laboratory showed that *Chlamydia pneumoniae* infection of macrophages induced SOCS1 expression in a STAT-1 and IFN-α/β dependent manner (Yang *et al.* 2008). Infected SOCS1$^{-/-}$ macrophages displayed lower bacterial titers and higher levels of IFN-regulated genes as iNOS (inducible nitric oxide synthase) and IDO (indoleamine dioxygenase), that participate in the control of intracellular bacteria. RAG1$^{-/-}$/SOCS1$^{-/-}$ mice showed 10-fold lower bacteria numbers in lungs than controls 6 days after infection. However, RAG1$^{-/-}$/SOCS1$^{-/-}$ mice died within seven days after infection with *C. pneumoniae* showing a severe pulmonary inflammation, whereas RAG1$^{-/-}$ mice survived for more than 60 days. Thus, SOCS1 has a crucial role in preventing lethal inflammation in *C. pneumoniae* infection.
Tuberculosis is another disease in which IFN-γ plays a critical role in containing bacterial levels and in the maintenance of the latent asymptomatic disease in infected individuals. Infection with different mycobacterial species such as *Mycobacterium bovis* (Imai *et al.* 2003), *M. avium* (Vazquez *et al.* 2006) and *M. tuberculosis* have been shown to stimulate SOCS1 in macrophages (Imai *et al.* 2003; Vazquez *et al.* 2006; Srivastava *et al.* 2009; Carow *et al.* 2011). Different innate immune receptors including TLR, NLR and DC-SIGN were found to mediate SOCS1 stimulation in mycobacterial infected myeloid cells (Srivastava *et al.* 2009).
Experiments from our laboratory and others, showed improved *M. tuberculosis* control in SOCS1 deficient macrophages and DCs (Srivastava *et al.* 2009; Carow *et al.* 2011). SOCS1$^{-/-}$ infected macrophages expressed higher levels of IFN-γ-responsive genes but also higher levels of IFN-γ itself than infected control cells. In agreement, SOCS1$^{-/-}$ macrophages secreted higher amounts of IFN-γ in response to IL-12, and although levels of IL-12 were not altered, SOCS1$^{-/-}$ macrophages displayed increased IL-12Rβ1 expression (Fig. 2). Of importance, the improved control of *M. tuberculosis* or *M. bovis* BCG by SOCS1$^{-/-}$ was lost in IFN-γ$^{-/-}$/SOCS1$^{-/-}$ macrophages, indicating that IFN-γ secretion mediates the improved mycobacterial control by SOCS1$^{-/-}$ macrophages. Moreover, despite SOCS1 expression, *M. tuberculosis*-infected macrophages were unimpaired in their response to IFN-γ. Altogether, as depicted in fig. 2, this suggests that SOCS1 regulates the secretion of rather than the response to IFN-γ, via controlling responses to IL-12 and that this causes mycobacterial resistance of macrophages. As stated above, SOCS1 regulates STAT4 activation in response to IL-12, which probably accounts for this mechanism (Eyles *et al.* 2002) (Fig. 2).

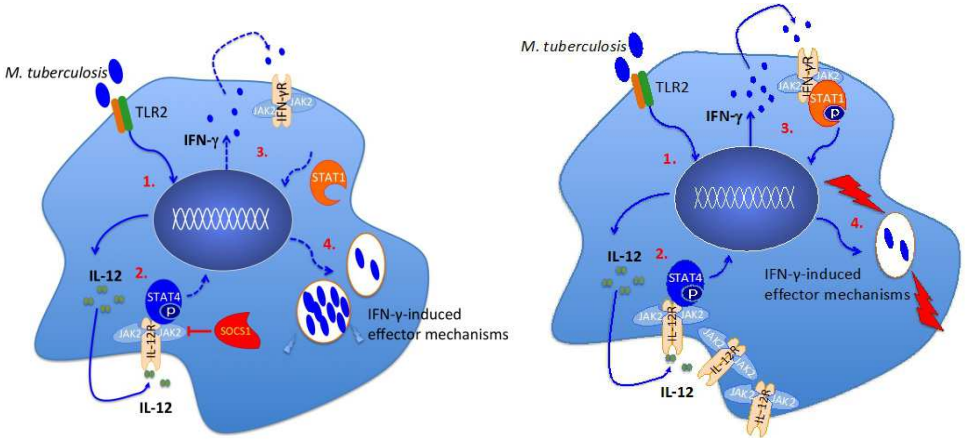

Fig. 2. SOCS1 in *M. tuberculosis*-infected macrophages

Macrophage responses and control of *M. tuberculosis* infection in absence (left panel) or presence (right panel) of SOCS1 regulating IFN-γ mediated genes.

RAG1$^{-/-}$SOCS1$^{-/-}$ as well as SOCS1$^{fl/fl}$ LysM-cre mice displayed lower bacterial loads in the lungs early after aerosol infection with *M. tuberculosis*, indicating that SOCS1 expression by macrophages facilitates *M. tuberculosis* infection. However, RAG1$^{-/-}$/SOCS1$^{-/-}$ and IFN-γ$^{-/-}$/SOCS1$^{-/-}$ mice showed a dramatic pulmonary inflammation from 3 weeks after *M. tuberculosis* infection without reduced bacteria numbers in different organs. This inflammatory response was caused by SOCS1-deficiency in non-macrophage cells, since it was not observed in *M. tuberculosis*-infected SOCS1$^{fl/fl}$ LysM-cre mice. Overall, *M. tuberculosis* infection induces SOCS1 that by diminishing IL-12 responses impairs IFN-γ secretion by macrophages. This results in lower levels of IFN-γ-regulated genes and in increased pulmonary bacterial levels at early time points. Later during infection, SOCS1 in non-macrophages cells protects mice from severe inflammation. At these later time points, macrophages containing bacteria are able to respond to IFN-γ and reduce bacterial levels, despite SOCS1 expression. Thus, SOCS1 does not mediate resistance to infection at late time points (fig. 3).

A role of SOCS1 in T cells during *M. tuberculosis* has been envisaged (Srivastava *et al.* 2011). However, SOCS1$^{fl/fl}$ Lck-cre mice deficient for SOCS1 in T cells showed no reduction in *M. tuberculosis* numbers in the lung (unpublished observation).

We have also analysed the expression of SOCS1 in tuberculosis patients. We found higher SOCS1 mRNA levels in blood samples from pulmonary tuberculosis patients than in endemic controls (Srivastava *et al.* 2009; Masood *et al.* submitted). Furthermore, SOCS1 transcripts were raised in T cells of patients with far advanced as compared with those showing a moderately advanced disease (Masood *et al.* submitted). This confirmed studies describing an over-representation of SOCS1 (as well as other interferon-induced genes) in active tuberculosis patients compared to latent patients (Berry *et al.* 2010).

In summary, SOCS1 possesses two roles during infection: on the one hand it suppresses protective immune responses but on the other hand also prevents the development of detrimental inflammation. Therefore, it clearly depends on the stage of infection, but also on

the type of the infection and the genetics of the host whether SOCS1 improves or worsens the outcome of infection.

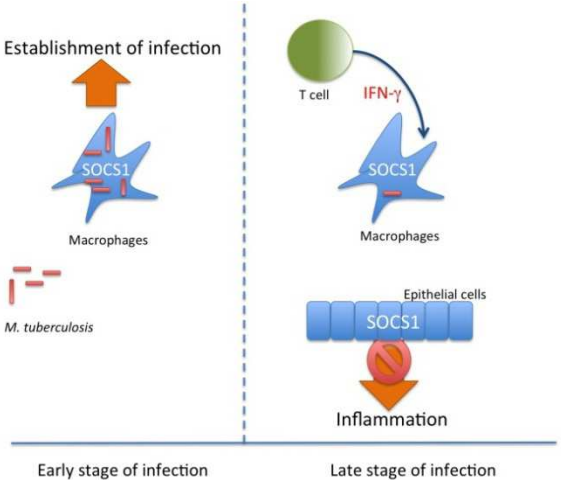

Fig. 3. Role of SOCS1 during different stages of M. tuberculosis infection

3.1.3 Parasite infections

The role of SOCS1 was also studied in a limited number of infections with parasites. SOCS1$^{-/-}$ mice were resistant to development of cerebral malaria after infection with *Plasmodium berghei*. This is surprising since IFN-γ mediates cerebral malaria in this model (Bullen *et al.* 2003b). However, the underlying mechanisms were not revealed.

SOCS1$^{-/-}$ macrophages were capable of killing *Leishmania major* at a 100-fold lower IFN-γ concentration than WT macrophages (Alexander *et al.* 1999). However, SOCS1$^{+/-}$ *L. major*-infected mice showed a worsened infection immunopathology, with larger dermal lesions but without reduction of parasites (Bullen *et al.* 2003a).

Another parasite, *Toxoplasma gondii* induced *SOCS1* expression in macrophages. SOCS1 over-expressing macrophages were unable to control parasite growth in response to IFN-γ whereas SOCS1$^{-/-}$ macrophages were restored in their ability to induce IFN-γ responsive genes after *T. gondii* infection (Zimmermann *et al.* 2006).

Moreover, recent data show that implantation of the parasite *Brugia malayi*, a causative agent of lymphatic filariasis, generated Th2 responses associated with development of M2 macrophages in mice. Expression of SOCS1 not only controlled the secretion of pro-inflammatory cytokines in M1 macrophages but was involved in maintaining M2 differentiation (Whyte *et al.* 2011). In line, patients with filariasis showed increased Th2 and impaired Th1 antigen-specific responses, which was associated with increased T cell expression by SOCS1 (Babu *et al.* 2005). Altogether, the function of SOCS1 during infections with parasites resembles that in bacterial infections, balancing anti-pathogen responses and the severity of inflammation.

4. SOCS3

SOCS3 is an important endogenous inhibitor of STAT3-mediated cytokine signalling. SOCS3 has been shown to be induced by different hormones including ciliary neutrophilic factor,

leptin, prolactin and growth hormones (Adams *et al.* 1998; Bjorbaek *et al.* 1998; Bjorbaek *et al.* 1999; Pezet *et al.* 1999) and cytokines like leukemia inhibitory factor, IL-11, IL-10, IL-2, IL-27 and IL-6 (Starr *et al.* 1997; Auernhammer & Melmed 1999; Bousquet *et al.* 1999; Cassatella *et al.* 1999; Cohney *et al.* 1999) but also by microbial molecular patterns as LPS or CpG (Stoiber *et al.* 1999; Dalpke *et al.* 2001).

Among these, the role SOCS3 in regulation of IL-6 responses has been studied in detail. IL-6 is a pro-inflammatory cytokine that has been found to play a role in many inflammatory diseases, while IL-10 is a potent anti-inflammatory cytokine, which suppresses gene activation through TLR signalling pathways, but can also inhibit Th1 responses at different levels. While it is known that STAT3 is essential for the biological actions of both IL-6 and IL-10, it was unclear for many years how these two cytokines could have exactly opposing functions.

Interestingly, an inhibitory role for SOCS3 could only be shown for cytokines binding to the IL-6 receptor whereas the signalling of IL-10 that also stimulates STAT3-activation was unaffected by SOCS3 (Song & Shuai 1998; Lang *et al.* 2003; Yasukawa *et al.* 2003a; Kimura *et al.* 2004; Shuai 2006). This is explained by the ability of SOCS3 to bind to the IL-6 receptor subunit gp130 (Tyr 759) but not to the IL-10 receptor (Nicholson *et al.* 2000; Lehmann *et al.* 2003; Yasukawa *et al.* 2003a). STAT3 activation in response to IL-6 is prolonged in absence of SOCS3. It has been proposed that the sustained activation of STAT3 is essential for the anti-inflammatory effect, while transient activation of STAT3 promotes inflammation (Yasukawa *et al.* 2003a).

Gp130 is a promiscuous cytokine receptor subunit that mediates signalling by IL-6 and other cytokines such as IL-11, IL-27, leukemia inhibitory factor (LIF) and cardiotrophin-1 (Taga & Kishimoto 1997). Gp130 is present on hematopoietic and nonhematopoietic cells, and its expression can vary depending on the cell's activation status (Andersson *et al.* 1978). Gp130 itself does not bind to cytokines but acts as a co-receptor. When the cytokine (for example IL-6) binds to the IL-6Ra, it triggers a heterodimeric association with gp130 to form a signalling complex (Silver & Hunter 2010). SOCS3 also modulates signalling of gp-130-dependent cytokines. Moreover, the mutation of SOCS3 binding site on the gp130 receptor increased STAT3 activation in response to IL-6 and stimulated IL-10-like anti-inflammatory responses (Ohtani *et al.* 2000; Croker *et al.* 2003; Lang *et al.* 2003; Yasukawa *et al.* 2003a). Such anti-inflammatory responses are abolished when the gp130 Y759 mutated mice possessed a monoallelic deletion of STAT3 (McLoughlin *et al.* 2005; Yoshimura *et al.* 2007). As already mentioned above, SOCS3 inhibits also signalling via non gp130 containing cytokine and hormone receptors such as GCSF, leptin, IL-12 and even IFNs (Song & Shuai 1998; Bousquet *et al.* 1999; Bjorbak *et al.* 2000; Shen *et al.* 2000; Hortner *et al.* 2002b).

SOCS3 knock out mice die during embryonic life due to placental defects (Marine *et al.* 1999a; Roberts *et al.* 2001). The early death is caused by enhanced LIF signalling, since SOCS3$^{-/-}$ mice showed altered trophoblast differentiation. Animals, in which the SOCS3 deletion in the placenta was rescued by a tetraploid rescue method, showed extended embryonic life. However, rescued SOCS3$^{-/-}$ embryos died due to cardiac hypertrophy (Takahashi *et al.* 2003).

4.1 SOCS3 in myeloid cells/granulopoiesis

Mice with a conditional knock down of SOCS3 in myeloid cells demonstrated the role of SOCS3 in suppression of IL-6/gp130 signalling. SOCS3-deficient macrophages stimulated with IL-6 displayed an increased magnitude and duration of STAT1 and STAT3 activation in comparison to controls (Croker *et al.* 2003; Lang *et al.* 2003; Yasukawa *et al.* 2003a).

Mice deficient for SOCS3 in myeloid cells are resistant to LPS-induced endotoxic shock whereas STAT3 deficient mice are highly sensitive (Takeda *et al.* 1999; Yasukawa *et al.* 2003a). Thus, STAT3 activation mediates anti-inflammatory IL-10 signalling and in the absence of SOCS3, similar anti-inflammatory properties in response to IL-6 (Johnston & O'Shea 2003). Furthermore, macrophages lacking SOCS3 were shown to secrete reduced levels of TNF-α and IL-12 after IL-6 and LPS stimulation (Yasukawa *et al.* 2003a).
In a similar manner, DCs deficient for STAT3 contributed to T cell hyper-activation while in the absence of SOCS3, DCs induced a selective expansion of regulatory T cells (Cheng *et al.* 2003; Matsumura *et al.* 2007). An overexpression of SOCS3 in DCs resulted a reduction of expression of co-stimulatory molecules and IL-12. Moreover, SOCS3-deficient and overexpressing DCs had the capacity to suppress EAE development (Li *et al.* 2006; Matsumura *et al.* 2007).
Croker et al. (2003) and Lang et al (2003) on the other hand, using SOCS3 deficient macrophages found an increased STAT1 activation and elevated levels of IFN-γ-regulated genes in response to IL-6.

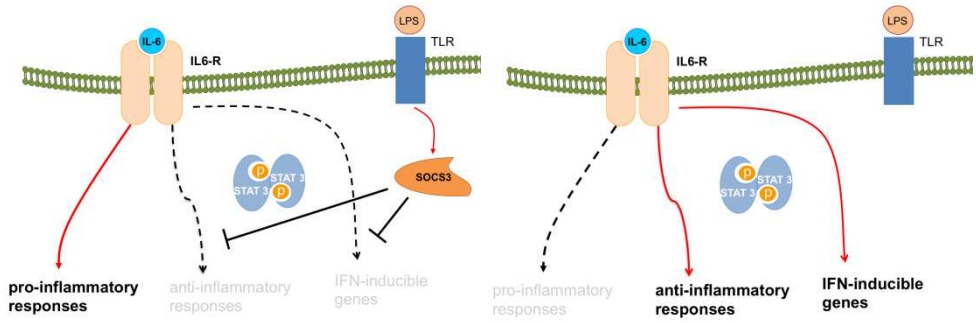

Fig. 4. SOCS3 inhibits anti-inflammatory and IFN-inducible genes in response to IL-6. Adapted from (Johnston & O'Shea 2003)

Other molecular targets of SOCS3 have been reported: SOCS3 inhibited the activation of TNF-receptor-associated factor 6 (TRAF6) and TGF-β-activated kinase 1 (TAK1), essential for both TLR– and IL-1-induced responses (Frobose *et al.* 2006). Prele et al. (2006) found no differences in LPS responses of SOCS3 transfected human macrophages. Thus, further studies are required to determine whether there is a direct role for SOCS3 in TLR signalling.
Upon over-expression, SOCS3 was found to bind to the GCSF receptor and reduced STAT3 activation in response to GCSF (Hortner *et al.* 2002b; Hermans *et al.* 2003). In agreement, deletion of SOCS3 in the myeloid or hematopoietic cells increased numbers of neutrophils, which showed increased survival and proliferative capacity (Croker *et al.* 2004; Kimura *et al.* 2004). Following GCSF injection SOCS3-deficient mice developed neutrophilia, and a spectrum of inflammatory pathologies, characterised by neutrophil infiltration in multiples tissues (Croker *et al.* 2008). Overall, SOCS3 regulates survival, growth and activation of neutrophils and an inhibition of SOCS3 may enhance the essential neutrophil recovery after chemotherapy or neutropenia.

4.1.1 SOCS3 in T cells

T cell development in the thymus is unaffected by SOCS3 (Chen *et al.* 2006). However, SOCS3 might play an active role in T cell proliferation and differentiation.

The proliferation of T cells was found to be regulated by SOCS3. T cells overexpressing SOCS3 showed reduced proliferation to mitogens and anti-CD28 (Banerjee *et al.* 2002; Matsumoto *et al.* 2003). On the other hand, SOCS3-deficient CD8 T cells also showed enhanced anti-CD3-induced proliferation. Neutralization of IL-27 also limited T cell proliferation indicating that IL-27 responses are impaired by SOCS3 and account for diminished T cell proliferation (Brender *et al.* 2007).

There is a reciprocal relation between SOCS1 and SOCS3 expression levels in T cells, with high SOCS1 and low SOCS3 expression in Th1 cells whereas high SOCS3 and low SOCS1 expression was found in Th2 cells (Egwuagu *et al.* 2002; Seki *et al.* 2003). However, there are conflicting results whether levels of SOCS3 actively influences the Th1/Th2 balance. Overexpression of SOCS3 in murine T cells resulted in elevated Th2 and decreased Th1 responses during allergy. Furthermore, a reduced Th2 response characterized by decreased IL-4 and increased IFN-γ production was shown in $SOCS3^{+/-}$ mice (Seki *et al.* 2003). A SOCS3 mediated regulation of STAT5 activation was reported to account for the altered Th1/Th2 balance. Another explanation for reduced Th2 responses was suggested by Kinjyo et al. (2006) using Lck $SOCS3^{fl/fl}$ mice, in which Th3-like T cells with higher IL-10 and TGF-β levels were found. These cytokines may then suppress Th1 responses accounting for the decreased Th1/Th2 ratio in SOCS3 deficient mice. However this observation was not confirmed by others: mice with a specific deletion of SOCS3 in the lymphoid cells were reported to have an unaltered Th1 and Th2 cell differentiation (Chen *et al.* 2006). Instead, loss of SOCS3 resulted in enhanced Th17 generation and enhanced STAT3 activation in response to IL-23. Th17 is a T cell subset that produces IL-17 and plays a key role in different autoimmune diseases and in the defense against fungal infections. STAT3 interacted with the *IL17A* and *IL-17F* promoter (Kinjyo *et al.* 2006). TGF-β-mediated the inhibition of SOCS3 expression and therefore prolonged STAT3 activation promoting Th17 development (Qin *et al.* 2009).

The importance of SOCS3 in impairing Th17 development was further confirmed in a study of an atherosclerosis model in mice with a T cell specific SOCS3 knock down and in a rheumatoid arthritis model in mice lacking SOCS3 in hematopoietic and endothelial cells (Wong *et al.* 2006; Taleb *et al.* 2009).

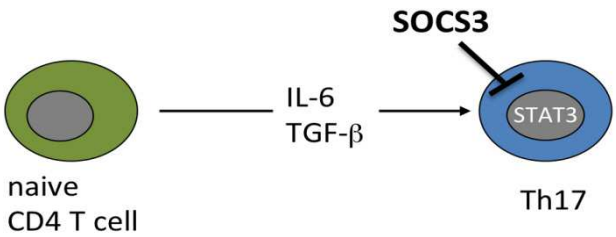

Fig. 5. SOCS3 hampers Th17 cell development

Regulatory T cells, a subset of CD4 T cells that suppress T cell-mediated immune responses and maintain tolerance to self-antigens, were found to be deficient for SOCS3 protein expression (Pillemer *et al.* 2007). Over-expression of SOCS3 in T regs impaired their

proliferation and suppressive function. The role of SOCS3 on T cell differentiation is still not completely understood but it seems likely that SOCS3 impedes both T reg function (and thereby increasing immune responses) and Th17 differentiation (impairing inflammatory responses, fig. 5).
SOCS3 has also been shown to modulate B cell development by affecting the lodging of precursor B cells to the bone marrow, via the regulation of responses to CXCL12 (Le *et al.* 2007).

4.1.2 SOCS3 in leptin and insulin resistance

Infections are accompanied by tissue insulin resistance, as manifested by worsening of metabolic control in diabetic patients and decreased glucose tolerance in non-diabetic subjects. A propensity towards glucose intolerance and diabetes has been documented in patients with chronic HCV infection. Diabetes patients are more susceptible to infections such as tuberculosis or candidiasis. These associated diseases could be linked to SOCS expressin. As stated below pathogen molecules can stimulate SOCS3 expression. SOCS3 binds to the leptin and insulin receptor and inhibits STAT3 activation in response to leptin and insulin respectively (Clement *et al.* 1998; Bjorbak *et al.* 2000; Emanuelli *et al.* 2000; Eyckerman *et al.* 2000; Chen *et al.* 2006). Leptin is an adipocyte-derived hormone that regulates food intake and energy homeostasis (Flier 2004). Leptin-resistance, common in human obesity and in acquired obesity in rodents, may be regulated by SOCS3 (Bjorbaek *et al.* 1998). High fat diet fed $SOCS3^{+/-}$ mice as well as neural cell-specific SOCS3- knock-down mice showed reduced diet-induced obesity, together with increased leptin and insulin sensitivity (Howard *et al.* 2004; Mori *et al.* 2004; Kievit *et al.* 2006). Furthermore, SOCS3 deficient adipocytes were protected from TNF-α-induced insulin resistance (Shi *et al.* 2004). However, mice with a knock down of SOCS3 in hepatocytes displayed increased insulin sensitivity in the liver but developed obesity and systemic insulin resistance with age (Torisu *et al.* 2007). This insulin resistance was accounted by increased inflammatory responses due to the lack of SOCS3. Accordingly, overexpression of SOCS3 in the liver of mice induced insulin resistance, whereas silencing of SOCS3 with antisense oligonucleotides in obese diabetic mice improved insulin sensitivity (Ueki *et al.* 2004a; Ueki *et al.* 2004b). The consistency of the effect of SOCS3 in different approaches on both leptin and insulin resistance indicates SOCS3 as a unique mediator of both obesity and insulin resistance.

4.2 Role of SOCS3 in infectious diseases and inflammation

Similar to SOCS1, SOCS3 expression can be stimulated by both cytokines but also TLR agonists. Additionally, several pathogens including viruses, bacteria and parasites have been shown to stimulate SOCS3 expression. But due to multiple binding partners of SOCS3, it is hard to predict the role of SOCS3 in different infections.

4.2.1 Viral infections

SOCS3 was found to inhibit type I IFN signalling although SOCS3 was less effective than SOCS1 (Song & Shuai 1998; Shen *et al.* 2000). Infection with several viruses induced SOCS3 expression that correlated with reduced STAT1 activation in response to IFN-α/β. HSV stimulated SOCS3 in different human cell lines but not in the B-cell line AKATA. In contrast to SOCS3-expressing cell lines, infected AKATA cells showed no impaired IFN-α/β

mediated STAT1 activation during HSV infection. Silencing of SOCS3 using anti-sense nucleotides significantly hampered replication of HSV (Yokota *et al.* 2005). Similar observations were done during Influenza A, HCV and Epstein Barr virus infections indicating that SOCS3 expression facilitates viral infections (Bode *et al.* 2003; Le Goffic *et al.* 2007; Pothlichet *et al.* 2008; Michaud *et al.* 2010).

Interestingly, mice with a T cell-specific SOCS3 deletion showed increased T cell activation and viral clearance without development of immunopathology during the infection with lymphocytic chriomeningitis virus (LCMV) (Pellegrini *et al.* 2011). Treatment of LCMV-infected mice with IL-7 repressed SOCS3 expression and promoted IL-6 production resulting in enhanced T cell effector functions, numbers and viral clearance. However, the deletion of SOCS3 in all hematopoietic cells induced neutrophilia and early lethality in LCMV-infected mice (Pellegrini *et al.* 2011).

Patients with genotype 1 HCV infection tend to have higher levels of SOCS3 expression, providing a rationale for their propensity toward a lack of therapeutic response (Kim *et al.* 2009). Moreover, one SOCS3 genotype (–4874 AA) expressed SOCS3 at elevated levels and showed a poorer response to therapy (Persico *et al.* 2008).

4.2.2 Bacterial infections

The infection of macrophages with *Salmonella enterica* has been shown to increment SOCS3 but not SOCS1 expression (Uchiya & Nikai 2005). SOCS3 stimulation was dependent on the *Salmonella* pathogenicity island 2 important for bacterial virulence. Infected macrophages showed impaired STAT1 and STAT3 activation in response to IL-6 or IFN-γ respectively, which might prevent effective bacterial killing.

Infection of macrophages with *Mycobacterium avium* or *M. bovis* raised SOCS1 and SOCS3 levels in a TLR2-NOTCH1 dependent pathway (Imai *et al.* 2003; Vazquez *et al.* 2006; Narayana & Balaji 2008).

Patients with active tuberculosis were found to have higher SOCS3 expression levels in whole blood and T cells in comparison to latently infected controls or to patients after chemotherapy (Mistry *et al.* 2007; Jacobsen *et al.* 2010). We observed that SOCS3 expression in blood non-T cells from patients with TB was negatively associated with severity of disease (Masood *et al*, 2011). Atogether the role of SOCS3 in bacterial infections is far from clear.

4.2.3 Parasites

Little is known about the role of SOCS3 in parasites. Infection of macrophages with the parasite *Leishmania dovani* was shown to stimulate SOCS3 expression. SOCS3 levels associated with reduced STAT1 activation after IFN-γ stimulation and therefore with reduced protection (Bertholet *et al.* 2003).

On the contrary, mice lacking SOCS3 in T cells were more susceptible to *Leishmania major* infections. SOCS3-deficiency in T cells led to increased anti-inflammatory TGF-β and IL-10 secretion by T cells and reduced immunoglobulin levels (Kinjyo *et al.* 2006).

Mice bearing a mutation in the SOCS3 binding site of the gp130 receptor displayed increased susceptibility to *Toxoplasma gondii*. A decreased IL-12 production by DCs resulted in reduced IFN-γ secretion by NK cells of these mice. Addition of IL-12 as well as neutralization of IL-6 could restore the wild type phenotype indicating that an altered IL-6 signalling was responsible for increased susceptibility (Silver *et al.* 2011).

	pathogen	mechanism	pathology	pathogen control
SOCS1	SFV	↓ IFN-α/β signalling		worsened
	HTLV-1	↓ IFN-α/β signalling.		worsened
	VSV	↓ IFN-α/β signalling.		worsened
	HSV-1	↓ IFN-γ signalling.		worsened
	Vaccinia Virus	↓immune responses	improved	improved
	HIV-1	Ubiquitination of HIVgag		worsened
	C. pneumoniae	↓IFN-γ signalling	improved	worsened
	M. tuberculosis – M. bovis BCG	↓ IL-12 signalling	improved	worsened
	P. berghi ANKA	???	worsened	worsened
	L. major	↓ IFN-γ signalling	improved	worsened
	T. gondii	↓ IFN-γ signalling		worsened
	B. malayi	Th1/Th2 ratio		worsened
SOCS3	HSV-1	↓IFN-α/β signalling.		worsened
	RSV	↓IFN-α/β signalling.		
	HIV-1	↓IFN-α/β signalling		
	Influenza A Virus	↓IFN-α/β signalling		worsened
	LCMV	↓T cell activation	worsened	worsened
	L. major	↓TGF-β IL-10 production by T cells	?	improved
	T. gondii (gp130 mutation)	↑IL-12 induction in dendritic cells	improved	improved

Table 1. Role of SOCS molecules during microbial infections.

5. Conclusion

SOCS expression is tightly regulated to prevent inflammation while maintaining protective anti-microbial responses. Pathogens are able to potently stimulate SOCS1 and 3 protein expression following infection and hijack SOCS function promoting their survival. In most infections studied, the stimulation of SOCS1 and SOCS3 expression by infectious agents resulted in a worsened pathogen control even though the nature of immune inhibition by the SOCS proteins differed. Thus, SOCS proteins can be manipulated to increase innate immune mechanisms, but also the triggering and the magnitude of adaptive immune responses. This converts SOCS proteins into very attractive therapeutic targets. However manipulation of SOCS levels always bears the risk of increased inflammatory responses. A better understanding of the role of SOCS in infections is required to better gauge SOCS manipulation leading to potentially new therapies.

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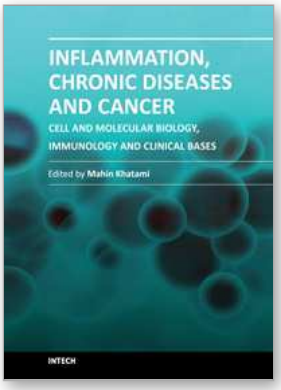

Inflammation, Chronic Diseases and Cancer - Cell and Molecular Biology, Immunology and Clinical Bases

Edited by Dr Mahin Khatami

ISBN 978-953-51-0102-4
Hard cover, 430 pages
Publisher InTech
Published online 09, March, 2012
Published in print edition March, 2012

This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Berit Carow and Martin E. Rottenberg (2012). “Suppressor of Cytokine Signalling” Molecules in Infection and Inflammation, Inflammation, Chronic Diseases and Cancer - Cell and Molecular Biology, Immunology and Clinical Bases, Dr Mahin Khatami (Ed.), ISBN: 978-953-51-0102-4, InTech, Available from: http://www.intechopen.com/books/inflammation-chronic-diseases-and-cancer-cell-and-molecular-biology-immunology-and-clinical-bases/socs-molecules-in-infection-and-inflammation

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Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821