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SOCS proteins in T helper cell differentiation: implications for allergic disorders?

Hiromasa Inoue and Masato Kubo

Asthma, allergic rhinitis and atopic dermatitis are allergic immune disorders characterised by a predominance of T helper 2 (Th2) cells, the resulting elevation of allergen-specific IgE, and mast-cell- and basophil-associated inflammation. The cytokine environment at the site of the initial antigen stimulation determines the direction of Th-cell differentiation into Th1 or Th2 cells. The SOCS (suppressor of cytokine signalling) proteins are implicated in the control of the balance between Th1 and Th2 cells in this process. SOCS3 is predominantly expressed in Th2 cells and inhibits Th1 differentiation; conversely, SOCS5 is expressed predominantly in Th1 cells and inhibits Th2 differentiation. Here, we discuss the role of SOCS proteins in Th-cell differentiation and explore the potential of SOCS proteins as targets for therapeutic strategies in allergic disorders.

Bronchial asthma, allergic rhinitis (hay fever) and atopic dermatitis (eczema) have become major public health problems over the past two decades. These allergic immune disorders are characterised by an elevation of total and specific IgE antibodies and infiltration of mast cells and basophils, resulting in mast-cell- and eosinophil-associated inflammation (Refs 1, 2, 3). A complex interplay of multiple genetic and environmental factors contributes to the onset and maintenance of atopic and allergic immune diseases (Refs 4, 5), but, mechanistically, T helper 2 (Th2) cells are known to have an important role (Ref. 1).

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Th cells exhibit cytokine expression patterns that divide them into at least two functionally distinct subsets: Th1 and Th2. Th1 cells secrete interleukin (IL)-2, interferon (IFN)-γ and tumour necrosis factor (TNF)-α, which promote cellular immune responses against intracellular pathogens and viruses, mediate delayed-type hypersensitivity responses and might be associated with organ-specific autoimmune diseases. Th2 cells produce IL-4, IL-5, IL-6, IL-10 and IL-13, which promote humoral immune responses, mainly against extracellular pathogens. However, cytokines such as IL-4, IL-5 and IL-13 secreted from Th2 cells play a pivotal role in the pathophysiology of allergic diseases (Ref. 1). IL-4 and IL-13 are potent activators of B-cell antibody production, particularly IgE, and IL-13 appears to act directly on the airway epithelial cells to produce the pathological features of asthma (Ref. 6). IL-5 plays a critical role in eosinophil differentiation and maturation.

The cytokine environment at the site of the initial antigenic activation determines the direction of $CD4^+$ T-cell differentiation towards either Th1 or Th2 cells, and thereby the generation of distinct immune responses. It is well documented that the presence of IL-4 in the induction phase promotes the predominance of Th2 cells (Refs 7, 8, 9), whereas IL-12 and IFN-γ are critical cytokines for Th1 differentiation (Ref. 10). To maintain the Th1–Th2 dichotomy, cytokines that are secreted from Th1 cells inhibit Th2 responses, whereas those secreted from Th2 cells inhibit Th1 responses. However, the mechanism of how Th1 and Th2 cytokines crossregulate is mostly unclear. Epidemiological studies strongly suggest that the increase in allergy prevalence has resulted from improved hygiene and a reduction in the frequency of infections inducing Th1-mediated inflammatory responses. These observations indicate that inhibition of Th2 development by Th1-derived cytokines might be a strategy to treat allergic disorders (Ref. 8).

The suppressor of cytokine signalling (SOCS) proteins are a new family of molecules that act as negative regulators of cytokine signalling (Refs 11, 12), and are known to be involved in the pathogenesis of many inflammatory diseases. The discovery of the SOCS proteins has provided new insight into how Th1 and Th2 cytokines might regulate the Th1 and Th2 immune responses. Here, we discuss the role of the SOCS proteins in Th1 and Th2 differentiation and allergic diseases. We also consider the possibility that SOCS proteins might be novel therapeutic targets for the treatment of these diseases.

Cytokine signalling

Cytokines, including ILs, IFNs and haemopoietins, play important roles in the regulation of cellular growth and differentiation in immune responses. Interaction of these extracellular ligands with their cell-surface receptors results in the activation of intracellular molecules: the Janus family kinases (JAK1, JAK2, JAK3 and TYK2), and 'signal transducer and activator of transcription' proteins (STAT1–6) (Refs 7, 8). Specifically, ligand-induced receptor dimerisation results in reciprocal tyrosine phosphorylation of receptor-associated JAKs and JAK-mediated tyrosine phosphorylation of the cytoplasmic domain of the receptor. The SH2-domain-containing STATs can then dock to the tyrosine-phosphorylated receptor, and are themselves activated following tyrosine phosphorylation by JAKs. STATs then dimerise and translocate to the nucleus where they regulate gene expression through specific DNA binding. Immune responses require both activating and inhibiting pathways, and the SOCS proteins play a role as negative regulators for the JAK–STAT signalling pathway.

The SOCS protein family

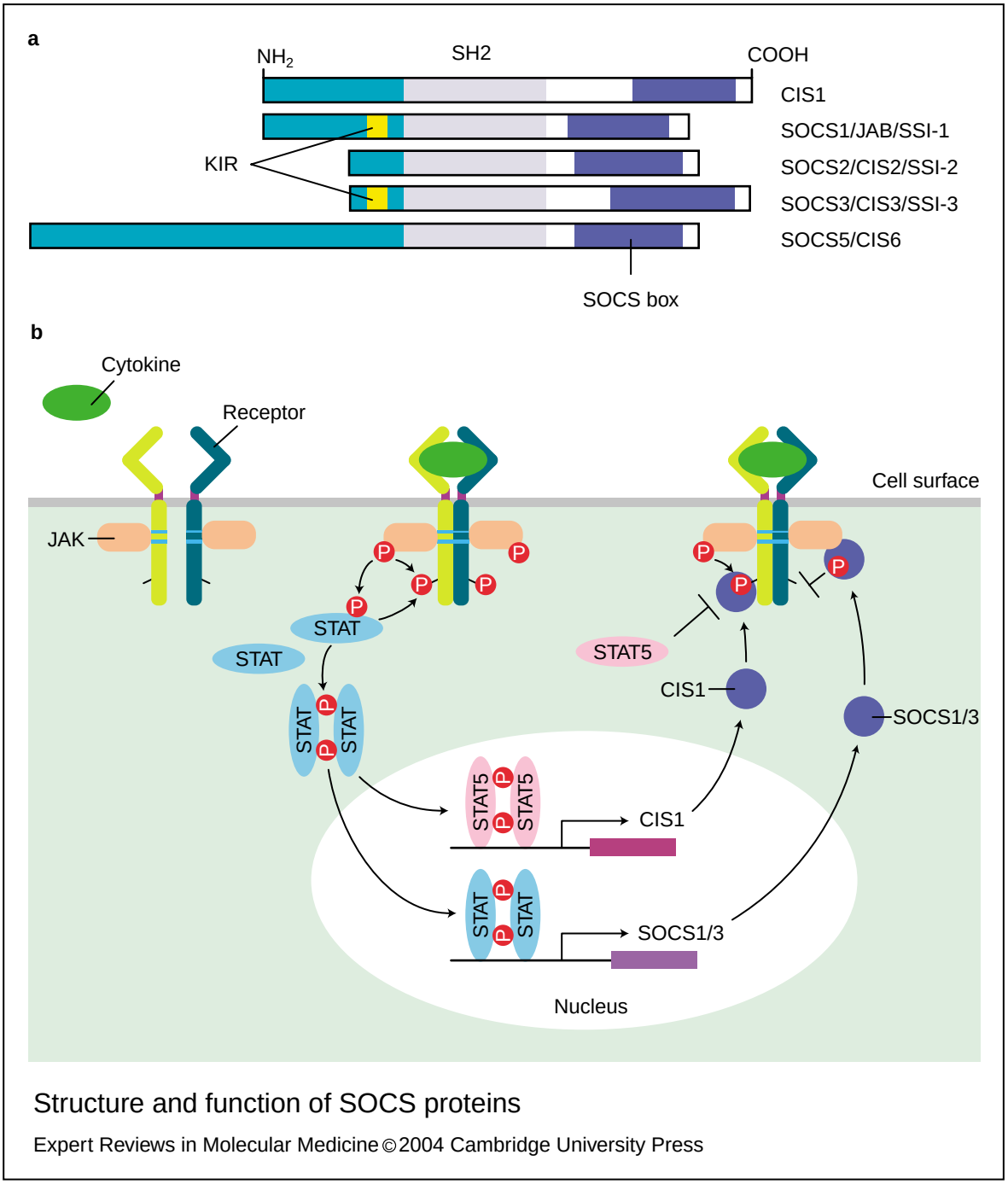
Eight members of the SOCS protein family have been identified: cytokine-inducible SH2-containing protein (CIS) and SOCS1–7. SOCS proteins are characterised by possession of a central SH2 domain and conserved C-terminus (the SOCS box) (Refs 9, 11, 12) (Fig. 1a). CIS, SOCS1 and SOCS3 are the best studied, and they act in a classical negative-feedback loop to inhibit cytokine signal transduction (Fig. 1b).

CIS was identified as an immediate-early activation gene induced in response to several cytokines. It binds to phosphorylated tyrosine residues on cytokine receptors that also serve as docking sites for STAT5 (Ref. 13); thus, competition or sterical hindrance for the binding sites of STAT5 has been proposed as the mechanism for CIS inhibition of cytokine signalling (Ref. 14).

Subsequently, SOCS1 was identified independently by three groups as a Src homology 2 (SH2)-domain-containing JAK-binding protein (Refs 15, 16, 17), and SOCS3 was identified by sequence similarity to SOCS1 (Ref. 9). SOCS1 and SOCS3 bind to

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Structure and function of SOCS proteins

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Figure 1. Structure and function of SOCS proteins. (a) Domain organisation of SOCS (suppressor of cytokine signalling) family members. All SOCS proteins have a central SH2 domain and relatively well-preserved amino acid sequences that form the SOCS box or CIS homology (CH) domain. SOCS1 and SOCS3 also have unique 30 amino acid residues at the N-terminal side of the SH2 domain, named the kinase inhibitory region (KIR). SOCS4, SOCS6 and SOCS7 are less well studied and are not shown here. (b) Inhibitory mechanisms of SOCS proteins. Cytokine signalling induces the expression of SOCS proteins through the JAK–STAT signalling pathway. The induced SOCS proteins block the interaction of STATs with receptors by steric hindrance or competition via SH2-domain-mediated binding to JAKs and cytokine receptors, or inhibit the catalytic activity of JAKs though binding via the KIR and SH2 region. Abbreviations: CIS, cytokine-inducible SH2-containing protein; JAB, JAK-binding protein; SSI, STAT-induced STAT inhibitor.

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phosphorylated tyrosine on JAKs via their SH2 domains. In addition, both SOCS1 and SOCS3 can inhibit JAK tyrosine kinase activity via a kinase inhibitory region (KIR) in their N-terminal domains, which probably functions as a pseudosubstrate (Refs 18, 19); thus, both the KIR and SH2 domains are required for inhibition. SOCS3 also binds directly to Tyr759 of gp130 (the signal-transducing subunit of the IL-6 receptor), and with lower affinity to Tyr985 of the leptin receptor, and Tyr401 of the erythropoietin receptor (Refs 20, 21, 22, 23, 24).

The C-terminal SOCS box of SOCS proteins functions in the recruitment of the ubiquitin transferase system, by binding to the elongin B and C complex, and thus might mediate degradation of proteins associated with the N-terminal regions of the SOCS proteins (Refs 25, 26). The functional importance of the SOCS box was shown by SOCS1-mediated suppression of the transforming potential of the fusion protein TEL–JAK2; suppression involved proteasomal degradation of TEL–JAK2, which was shown by mutational analysis to require the SOCS box (Refs 27, 28). The phenotypes of SOCS-box-deficient SOCS1 knock-in mice also suggest the requirement of the SOCS box for full SOCS1 activity (Ref. 29).

Taken together, these findings indicate that the SH2 domain conserved in all SOCS family members is required for the association with phosphorylated JAKs and receptors in a tyrosine-based interaction. The SOCS box might regulate the stability of JAKs and receptors associated with the SH2 domains and the N-terminal regions of the SOCS proteins.

Roles for SOCS proteins

It is possible that SOCS proteins regulate the response to cytokines at various inflammatory sites (Refs 30, 31). Many reports have indicated that SOCS1 and SOCS3 are induced by several inflammatory and anti-inflammatory cytokines, such as IL-2, IL-4, IL-6 and IFNs, and that they negatively regulate those cytokine actions (Refs 31, 32, 33, 34, 35) (Table 1). Studies of SOCS3 expression in chronic inflammatory disease showed high levels in colon epithelial cells in a mouse model of intestinal bowel disease as well as in patients with ulcerative colitis and Crohn's disease (Refs 36, 37). SOCS1 expression during the early stages of enterovirus infections in the heart attenuates antiviral defence by inhibiting IFNs, thus promoting cardiac injury (Ref. 38). In the following sections we briefly discuss roles for distinct SOCS proteins in Th1 and Th2 immune responses.

SOCS1

Regulation of IFN-γ-mediated signalling

The physiological role of SOCS1 has been addressed by studies in knockout mice. SOCS1-deficient mice die by 3 weeks of age with severe lymphopaenia, activation of peripheral T cells, liver degeneration, and macrophage infiltration in several organs (Refs 39, 40, 41). Removal of IFN-γ-producing T and natural killer T (NKT) cells significantly extends the lifespans of such mice (Refs 41, 42, 74), indicating an important role for SOCS1 in controlling IFN-γ-mediated signalling. The lifespan of SOCS1-deficient mice is also increased when SOCS1 expression is restored in lymphocytes, or in the absence of CD28, but at older ages these mice developed systemic lupus erythematosus (SLE)-like autoimmune diseases along with polycystic kidneys, pneumonia, chronic skin ulcers, and chronic granulomas in the gut and various other organs (Ref. 43). Therefore, the disease induced by SOCS1 deficiency is a complex syndrome consisting of acute and chronic inflammatory diseases and autoimmune-like diseases (Refs 44, 45). The chronic inflammatory diseases arise as a result of accumulation of activated dendritic cells (DCs) that secrete high levels of BAFF/BLysS, which has been newly identified as a B-cell growth and differentiation factor associated with the generation of autoreactive B cells. SOCS1-deficient mice exhibit an aberrant expansion of abnormal $CD8^+$, $CD11c^{lo}$, $CD11b^-$ and $B220^-$ DC populations that highly express IFN-γ and BAFF/BLysS (M. Kubo et al., unpublished).

Studies of the signalling pathways that regulate, or are targets of, SOCS1 have given further insight into its roles. SOCS1 is induced by various cytokines acting via JAK–STAT signalling and strongly inhibits this pathway by binding to all JAK family members (Table 1). SOCS1 expression is also induced by pathogen-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharides (LPS) and CpGs, in macrophages (Ref. 46) and Toll-like receptor (TLR) signalling cascades, and can suppress these pathways (Table 1): overexpression of SOCS1 in a macrophage cell line suppressed TLR signalling via NF-κB activation (Refs 47, 48). This is consistent with the finding that SOCS1-deficient mice were hyper-responsive to LPS, and that macrophages from these mice produced increased levels of TNF-α and IL-12 (Ref. 47).

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Table 1. Regulators and targets of SOCS family members

SOCS family member[a]	Factors inducing SOCS expression	Signalling inhibited by SOCS	Refs
CIS	IL-2, IL-3, IL-6, IL-9, IFN-α,TNF-α EPO, TSLP GH, prolactin	IL-2, IL-3 EPO GH, prolactin	13, 14
SOCS1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-13, IFN-α/β, IFN-γ, LIF, TNF-α EPO, TSLP, G-CSF, GM-CSF, M-CSF GH, prolactin, insulin, CNTF, cardiotropin, TSH LPS, CpG DNA	IL-2, IL-4, IL-6, IL-7, IL-12, IL-15, IFN-α/β, IFN-γ, LIF, TNF-α EPO, TSLP GH, prolactin, insulin, leptin LPS, CpG	9, 11, 31, 45, 47
SOCS2	IL-6, IFN-α, IFN-γ, LIF GH, prolacin, insulin, CNTF, cardiotropin	IL-6 GH, IGF-1	45
SOCS3	IL-1, IL-2, IL-4, IL-6, IL-9, IL-10, IL-13, IFN-α, IFN-γ, LIF EPO, GM-CSF GH, prolactin, insulin, leptin, CNTF LPS, CpG DNA	IL-2, IL-4, IL-6, IL-9, IL-11, IL-12, IFN-α/β, IFN-γ, LIF EPO GH, prolactin, insulin, leptin	9, 11, 31, 32, 62
SOCS5	IL-6, IL-12	IL-4, IL-6	32, 51

[a]Regulators and targets of SOCS4, SOCS6 and SOCS7 have been less well studied.

Abbreviations: EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GH, growth hormone; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; LIF, leukaemia-inhibitory factor; LPS, lipopolysaccharide; M-CSF, macrophage colony-stimulating factor; SOCS, suppressor of cytokine signalling; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin; TSH, thyroid-stimulating hormone.

Control of Th-cell differentiation by SOCS1?

During Th-cell differentiation, IFN-γ (induced by IL-12) and IL-4 are known to inhibit Th2 and Th1 development, respectively (Refs 42, 49), and SOCS1 has been proposed as an important molecule in these events. In the absence of SOCS1, the mutual regulation was abrogated (Ref. 50): SOCS1-deficient T cells exhibit sustained phosphorylation of STAT6 or STAT4 when cells were stimulated with IL-4 or IL-12, respectively, which subsequently resulted in those T cells differentiating excessively towards Th2 or Th1 cells. These results support the notion that SOCS1 regulates both Th1 and Th2 polarisation through the inhibition of cytokine signalling, including IL-12 and IL-4 (Fig. 2). The SOCS1-deficient T cells are constitutively activated and exhibit massive IFN-γ production, indicating that the SOCS1-deficient environment generates a Th1-dominant situation (Ref. 39). However, SOCS1 is equally expressed in Th1 and Th2 cells derived from ovalbumin (OVA)-specific T-cell receptor transgenic mouse (TCR Tg) $CD4^+$ T cells (Ref. 51), indicating that Th1 differentiation normally occurs even in the presence of SOCS1. Thus, the role of SOCS1 in Th1/Th2 differentiation is still contentious.

SOCS-1$^{-/-}$*IFN-γ*$^{-/-}$ double knockout mice are more sensitive to Th1-type arthritis inflammatory responses than wild-type mice (Ref. 52). Since SOCS1 inhibits IFN-γ and IL-12 signalling, Th1 skewing in SOCS1-deficient $CD4^+$ T cells might simply be explained by a hypersensitivity to IL-12 (Ref. 53). Therefore, in this case, SOCS1 seems to selectively inhibit IFN-γ and IL-12 signalling. Similarly, IL-6-induced SOCS1 expression might be involved in inhibiting Th1 responses (Ref. 54). Under Th2 skewing conditions, IL-6 derived from Th2 cells would induce SOCS1 expression,

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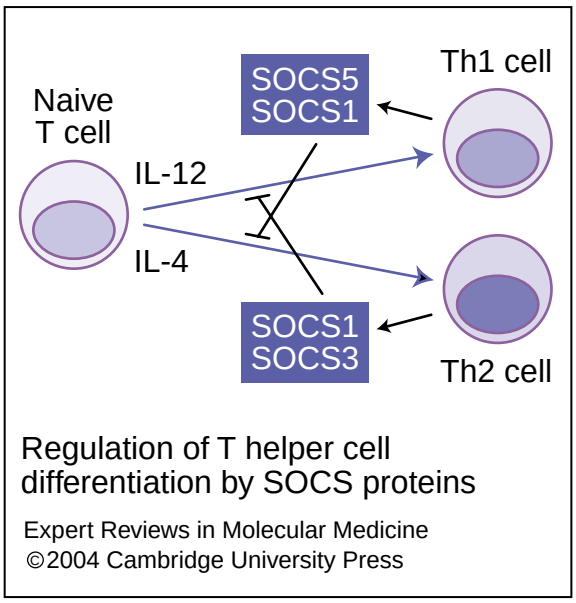


Figure 2. Regulation of T helper cell differentiation by SOCS proteins. Interleukin (IL)-12 induces SOCS5 expression in T helper (Th) 1 cells, whereas IL-4 induces expression of SOCS3 in Th2 cells. These SOCS proteins reciprocally inhibit the counterpart Th differentiation process. SOCS1 expression seems to be differently regulated in Th1 and Th2 cells, depending on the antigen, and SOCS1 inhibits both Th1 and Th2 development. SOCS, suppressor of cytokine signalling.

resulting in the blocking of the IFN-γ signalling pathway and acceleration of Th2 differentiation (Ref. 54). However, SOCS1 is predominantly expressed in Th1 cells derived from hen-egg-lysozyme-specific TCR Tg $CD4^+$ T cells (Ref. 55), leading to an alternative possibility that SOCS1 selectively inhibits Th2 differentiation via the inhibition of IL-4-mediated signalling. Therefore, the question of whether the expression of SOCS1 in T cells is a key factor in regulating the direction of Th-cell differentiation remains unresolved. Another significant possibility is that a high level of IFN-γ production by an abnormal $CD8^+$ DC population contributes to the Th1-dominant situation in the SOCS1-deficient mice, since $CD4^+$ T cells seem to develop normally in T-cell-specific SOCS1-deficient mice (Ref. 56).

SOCS5

Negative regulation of Th2 development?

Activation of STAT6 by IL-4, the key cytokine promoting Th2 development, is selectively impaired in Th1 cells, although the expression levels of components in the IL-4–STAT6 signalling cascade, such as the IL-4 receptor (R) α-chain, JAK1, JAK3 and STAT6, are not significantly different between Th1 and Th2 cells (Refs 57, 58). It is possible that SOCS5 inhibits IL-4-induced STAT6 activation, and thereby enhances Th1 polarisation.

SOCS5 binds to the cytoplasmic domain of the IL-4R α-chain in a non-tyrosine-based interaction (Ref. 51), and structurally interferes with the interaction between JAK1 and IL-4R. The binding of SOCS5 to IL-4R occurs via the N-terminal region of SOCS5; like SOCS4 and SOCS6, SOCS5 has a long and unique N-terminal region in comparison with CIS and SOCS1–3 (Ref. 59) (Fig. 1a), suggesting that this region regulates target specificity (Ref. 51). Expression data are consistent with a role for SOCS5 in inhibiting Th2 development: SOCS5 is exclusively expressed in committed Th1 cells, but not in Th2 cells, and SOCS5 expression seems to be regulated by the Th1-driving cytokine IL-12 (Ref. 51). The findings that T cells from transgenic mice constitutively expressing SOCS5 exhibited a reduction of IL-4-mediated Th2 development also support the idea that SOCS5 might be a specific negative regulator of IL-4-dependent signalling in the control of Th2 differentiation (Ref. 51) (Fig. 2). Thus, the selective induction of SOCS5 during initial T-cell activation might play a role in regulating the direction of Th-cell differentiation. However, a drastic positive effect on Th2 polarisation has not been found in SOCS5-deficient mice (Ref. 60). The in vivo role of SOCS5 in Th-cell differentiation thus remains to be clarified.

Transgenic mice expressing SOCS5 in various organs exhibit marginal growth retardation, suggesting an alternative role of SOCS5. In addition, the expression of SOCS5 is induced in the M1 cell line in response to stimulation with IL-6, and the expressed SOCS5 marginally inhibits IL-6 signalling (Ref. 61). Clearly more work is required to understand further the in vivo functions of SOCS5.

SOCS3

Negative regulation of Th1 development?

A variety of evidence implicates SOCS3 in inhibiting Th1-cell differentiation. SOCS3 is induced by a Th2 cytokine environment, including IL-4, IL-6 and IL-10, during Th-cell development, leading to selective expression in both mouse and human Th2 cells (Refs 55, 62).

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T-cell-specific forced expression of SOCS3 resulted in increased Th2 development, whereas Th1 development was consistently reduced (Ref. 62) (Fig. 2). Conversely, inhibition of SOCS3 function by using a dominant negative mutant SOCS3 or reduction in expression in SOCS3$^{+/-}$ mice reversed this Th-cell polarisation (Ref. 62). In vitro studies showed that SOCS3 can specifically bind to the cytoplasmic region of IL-12Rβ (Tyr800) and inhibit STAT4 activation in T cells mediated by IL-12, the key Th1-promoting cytokine (Refs 62, 63). Moreover, SOCS3 inhibited the activation of IL-12-controlled genes such as the IL-12Rβ2 and the T-bet gene (Ref. 62).

Other SOCS3 functions

SOCS3 also influences T-cell function by negatively regulating IL-2 signalling (Ref. 32) and inhibiting the TCR and CD28 signalling pathways (Refs 64, 65). SOCS3 binds calcineurin (a calmodulin-dependent protein serine/threonine phosphatase), which regulates the translocation of NF-AT into nuclei, and thereby inhibits TCR-mediated NF-AT functions (Ref. 65). In addition, competitive binding of SOCS3 to the phosphatidylinositol 3-kinase-binding site on the costimulatory molecule CD28 downregulates CD28-costimulation-mediated IL-2 production in initial T-cell activation (Ref. 64). Thus, SOCS3 might play an important role in regulating T-cell development and activation by multiple mechanisms.

SOCS3 has also been implicated in regulating inflammation by inhibiting IL-6 signalling. IL-6 induces gene transcription resulting in inflammatory responses, such as expression of acute-phase protein in liver. As mentioned above, SOCS3 binds to a phosphorylated tyrosine residue (Tyr759) of gp130 (of IL-6R) with high affinity (Ref. 66). In macrophages, SOCS3 specifically binds to gp130 and inhibits IL-6-mediated STAT3 activation (Refs 66, 67, 68). LPS and IL-10 induce high-level expression of SOCS3 in macrophages, suggesting SOCS3 might be an essential component of the anti-inflammatory effect mediated by IL-10 (Ref. 69). The phosphorylation of STAT3 is drastically prolonged in macrophages derived from conditional SOCS3-deficient mice on stimulation with IL-6, but not IL-10, indicating that LPS- and IL-10-induced SOCS3 specifically attenuates signalling mediated by IL-6 and gp130 (Refs 66, 67, 68).

SOCS3-deficient mice die as a result of placental defects during embryonic development (Refs 70, 71, 72). Embryonic lethality can be remedied by restoration of wild-type placental function, demonstrating an essential role for SOCS3 in placental development and a nonessential function in embryonic development. Rescued SOCS3-deficient mice show a prenatal lethality with cardiac hypertrophy. The leukaemia inhibitory factor (LIF) receptor deficiency rescues the SOCS3-related placental defect and embryonic lethality, suggesting that SOCS3 is an essential regulator of LIF receptor signalling in trophoblast differentiation (Ref. 72).

Regulation of allergic responses by SOCS3

The data on SOCS3 in Th-cell differentiation suggest that SOCS3 might influence the development of allergic diseases through the inhibition of IL-12-mediated Th1 development. SOCS3 is predominantly expressed in induced Th2 cells in vitro. SOCS3 expression in peripheral CD3^{+} T cells from patients with Th2-type diseases, such as atopic asthma and dermatitis, tightly correlates with the severity of the disease (Refs 62, 73). Serum IgE concentrations were also increased in individuals with high SOCS3 expression. Asthma is characterised by a variable degree of airflow obstruction, airway hyper-responsiveness (AHR; defined by an enhanced airflow obstruction in response to nonspecific stimuli), mucus overproduction, and chronic airway inflammation with eosinophil and lymphocyte infiltrates. AHR was markedly enhanced in transgenic mice in which T cells constitutively expressed SOCS3 in an OVA-induced asthma model (Ref. 62). The amounts of serum IgE, the production of Th2 cytokines (IL-4, IL-5 and IL-13) in the airway, and airway eosinophilia were also enhanced in the SOCS3-transgenic mice when compared with control mice. Therefore, high SOCS3 expression skews Th-cell differentiation towards Th2 cells and might contribute to the pathogenesis of asthma. Thus, SOCS3 expression in T cells could be a pathological marker for allergic diseases.

SOCS proteins in the treatment of allergic diseases

The implication of SOCS proteins in the regulation of Th1–Th2 balance and asthma phenotypes suggests a range of new therapeutic strategies that might reduce Th2-induced inflammation and its

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consequences in the airways and skin. For example, in asthma, SOCS function could be modulated to inhibit different points in the inflammatory cascade: Th2 differentiation; activation of Th2 cells; and effects of the Th2 cytokines. As discussed, SOCS3 blockade by overexpression of a dominant-negative mutant inhibited Th2-cell induction (Ref. 62). Thus, a new mode of asthma therapy could be targeting SOCS3 by using pharmacological, antisense, or DNA vaccine approaches to inhibit the Th2 response. Alternatively, increasing levels of SOCS5 in Th2 cells might shift the Th1–Th2 balance towards Th1 and reduce the number of Th2 cells. Thus, SOCS proteins could be novel therapeutic targets for the treatment of allergic diseases. However, these immunomodulatory approaches have the potential to disrupt the appropriate balance of the immune system, and their possible value in controlling allergic responses needs to be tested further.

Concluding remarks

Following the discovery of SOCS family proteins, research has focused on their functions. The presence of IL-12 or IL-4 in the initial antigen stimulation determines the direction of Th-cell differentiation into Th1 or Th2 cells, and preferential expression of SOCS5 and SOCS3, respectively. SOCS5 and SOCS3 inhibit Th2 and Th1 differentiation, respectively, implicating them in allergic immune responses and suggesting them as targets for therapeutic strategies in allergic disorders. SOCS1 is also a potential therapeutic target as a regulator of DC development. The functions of other members of the SOCS family require further characterisation. Future studies of SOCS proteins are expected to give important new insights into the pathophysiology and therapeutic strategies of allergic disorders.

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Features associated with this article

Figures

Figure 1. Structure and function of SOCS proteins.
Figure 2. Regulation of T helper cell differentiation by SOCS proteins.

Table

Table 1. Regulators and targets of SOCS family members.

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