Review Article

Role of SOCS proteins in inflammation and autoimmune diseases

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Various cytokines are involved in the regulation of the immune system and inflammation. Dysregulation of cytokine signaling can cause a variety of diseases, including allergies, autoimmune diseases, inflammation, and cancer. Most cytokines utilize the so-called Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway. This pathway is negatively regulated by suppressors of cytokine signaling (SOCS) proteins. SOCS proteins bind to JAK or certain cytokine receptors, thereby suppressing further signaling events. Studies using conditional knockout mice have shown that SOCS proteins are key physiological pathological regulators of inflammation as well as immune homeostasis. Recent studies have also demonstrated that SOCS1 and SOCS3 are important regulators of adaptive immunity, especially helper T cell differentiation.

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The JAK/STAT pathway and SOCS proteins

Cytokines play several essential roles in the development, differentiation, and function of myeloid and lymphoid cells. Some of them, including interleukins, interferons (IFNs), and hematopoietic growth factors, activate the Janus kinase (JAK)-signal transducers and activators of the transcription (STAT) pathway[1,2)]. In this pathway, cytokine binding results in receptor oligomerization, which initiates the activation of JAK kinases (JAK1, JAK2, JAK3, and Tyk2). The activated JAKs phosphorylate the receptor cytoplasmic domains, which creates docking sites for SH2-containing signaling proteins, including STATs. It is now known that a large number of cytokines, growth factors, and hormonal factors activate JAK and/or STAT proteins. For example, pro-inflammatory cytokine IL-6 binds to the complex of the IL-6 receptor α chain and gp130, which mainly activate JAK1 and STAT3. IFNγ receptors utilize JAK1 and JAK2, then mainly activate STAT1. Interestingly, the anti-inflammatory cytokine IL-10 also activates STAT3. IL-6- or IL-23-mediated STAT3 activation, IL-12-mediated STAT4, and IL-4-mediated

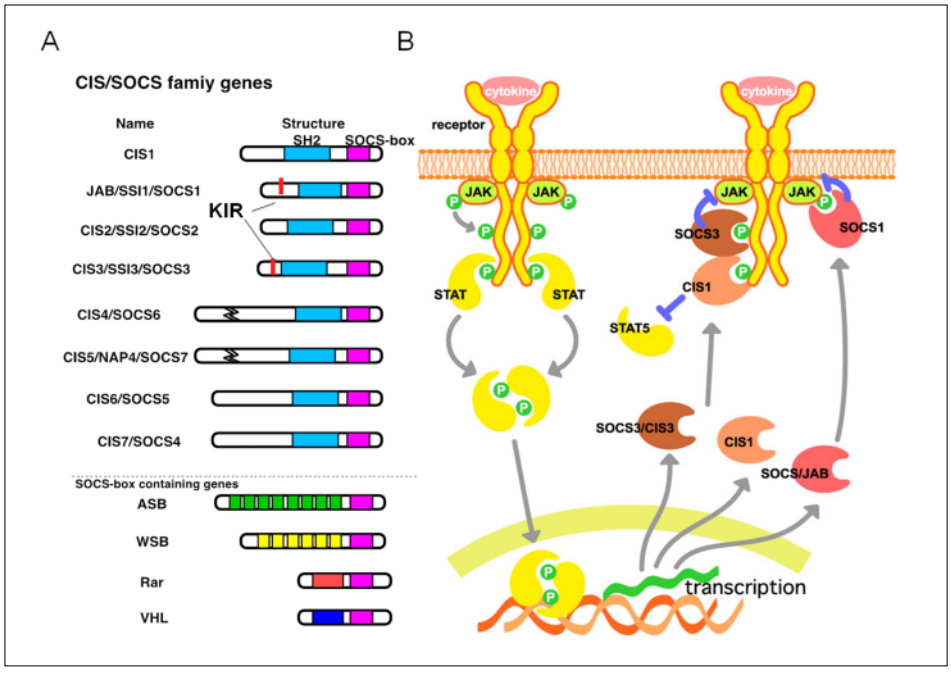

Fig.1 The structure and function of SOCS proteins

(A) Schematic structure of the CIS/SOCS family proteins. The SOCS box is conserved in all CIS/SOCS family proteins. SOCS1 and SOCS3 contain a unique kinase inhibitory region (KIR) immediately upstream of the central SH2 domain, which is proposed to function as a pseudosubstrate. Other SOCS box-containing proteins are illustrated.

(B) Mechanism of suppression by CIS, SOCS1, and SOCS3. All of these are induced by cytokine stimulation. CIS binds to the STAT5 activating receptors, thereby suppressing further activation of STAT5 and inducing degradation of the receptor. SOCS1 binds to JAKs, and SOCS3 binds to the receptor through the SH2 domain, but both inhibit JAK activity through KIR. These complexes may be degraded by ubiquitination and proteasomal degradation recruited through the SOCS box.

STAT6 activation have been demonstrated to be essential for Th17, Th1, and Th2 differentiation, respectively[3]. IL-2-mediated STAT5 activation is essential for T cell proliferation as well as regulatory T cell (Treg) development[4]. The action of STAT5 also appears to be very direct, as STAT5 binds the *Foxp3* gene, which is the master regulator of Tregs (see Fig.2). IL-6/STAT3 and IL-4/STAT6 inhibits *Foxp3* gene expression, although the mechanism remains controversial[5, 6].

Although our understanding of the intracellular signaling molecules that mediate the functional outcome of cytokine-receptor activation in the immune system has increased significantly, recent research has placed increasing emphasis on the mechanisms for the termination of signals and cross-talks with other signaling pathways. The CIS/SOCS family of proteins is one of the major mechanisms for such regulations[7-9]. At the time of their discovery, the SOCS proteins were recognized as an important mechanism in the negative regulation of the cytokine-JAK-STAT pathway, but recent studies using gene-disrupted mice have revealed that they play additional unexpected and important roles in many immunological processes[10-13], atherosclerosis[14], metabolism[15, 16], and cancer[13, 17-19]. In this review, we will focus on the recent progress of SOCS studies on inflammation and helper T cell differentiation.

The CIS/SOCS family

The suppressor of cytokine signaling (SOCS) proteins and cytokine-inducible SH2-containing (CIS; also known as CISH) protein molecules comprise a family of intracellular proteins[7, 11, 20]. There are eight CIS/SOCS family proteins: CIS, SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6, and SOCS7, each of which has a central SH2 domain, an amino-terminal domain of variable length and sequence, and a carboxy-terminal 40-amino-acid

module known as the SOCS box (Fig.1A)[21]. The SOCS box is also found in other miscellaneous proteins. The SOCS box interacts with elongin B and elongin C, Cullins, and the RING-finger-domain-only protein RBX2 (which recruits E2 ubiquitin-transferase)[22, 23]. VHL (von Hippel-Lindau) gene product, whose gene product is the principal negative regulator of hypoxia-inducible factor has been shown to bind to SOCS1 and induces the degradation of Jak2. Chuvash polycythemia-associated VHL mutants have altered affinity for SOCS1 and do not engage with and degrade phosphorylated JAK2[24]. These results indicate that CIS/SOCS family proteins, as well as other SOCS box-containing molecules, function as E3 ubiquitin ligases and mediate the degradation of proteins that are associated with these family members through their N-terminal regions (Fig.1A).

The central SH2 domain determines the target of each SOCS and CIS protein. The SH2 domain of SOCS1 directly binds to the activation loop of JAKs[25]. The SH2 domains of CIS, SOCS2, and SOCS3 bind to phosphorylated tyrosine residues on activated cytokine receptors[8]. SOCS3 binds to gp130-related cytokine receptors, including the phosphorylated tyrosine 757 (Tyr757) residue of gp130, the Tyr800 residue of IL-12 receptor β2, and Tyr985 of the leptin receptor[26-30]. Thus, SOCS3 in the brain has been implicated in leptin-resistance[15, 31]. SOCS molecules bind to several tyrosine phosphorylated proteins, including Mal (TLR signaling)[32] and IRS1/2 (insulin signaling)[16]. Thus, SOCS proteins generally induce the degradation of the target molecules by binding through the SH2 domain and ubiquitination through the SOCS box (Fig.1B).

In addition, both SOCS1 and SOCS3 can inhibit JAK tyrosine kinase activity directly through their kinase inhibitory region (KIR). KIR has been proposed to function as a pseudosubstrate that is essential for the suppression of cytokine signals[25]. The SH2 domain of SOCS3 does not have a high affinity to the activation loop of JAKs yet the KIR of SOCS3 has a higher affinity to the kinase domain of JAK2 than that of SOCS1[33]. Because the receptors to which SOCS3 binds mostly activate STAT3, SOCS3 is an inhibitor that is relatively specific to STAT3. SOCS3 also inhibits STAT4, which is activated by IL-12[29]. However, because SOCS3 does not bind to the IL-10 receptor, SOCS3 cannot inhibit IL-10 signaling. Therefore, IL-10 induces a robust and prolonged STAT3 activation, whereas IL-6-mediated STAT3 activation is transient in macrophages. This is an important mechanism to distinguish the anti-inflammatory activity of IL-10 and inflammatory activity of IL-6[20].

SOCS1 and inflammation

Although *SOCS1* knockout (KO) mice are normal at birth, they exhibit stunted growth and die within 3 weeks of birth, with activation of peripheral T cells, necrosis of the liver, and macrophage infiltration of major organs[34]. The neonatal defects exhibited by SOCS1$^{-/-}$ mice appear to occur primarily as a result of unbridled IFNγ signaling, since SOCS1$^{-/-}$ mice that also lack the IFNγ gene or the IFNγ receptor gene do not die neonatally. Since SOCS1/Rag2-double knockout (DKO) mice survived much longer, SOCS1 has been thought to be an important negative regulator of Th1. This is confirmed by generating T cell-specific SOCS1-conditional KO (cKO) mice[35].

In addition, SOCS1 has been demonstrated to be involved in the suppression of inflammation by regulating innate immune cells and nonimmune cells. Using liver-specific SOCS1-cKO mice, we demonstrated that SOCS1 deletion in hepatocytes enhanced concanavalin A (ConA)-induced hepatitis, because pro-apoptotic signals, including STAT1 and JNK activation, were enhanced in SOCS1-deficient liver[36]. SOCS1 deletion in NKT cells also enhanced sensitivity to ConA-induced hepatitis. However, the number of iNKT cells was drastically decreased but that of type II NKT cells was increased by SOCS1 deficiency[37]. This mechanism remains to be clarified. Deficiency of SOCS1 in macrophages cells resulted in hyper-responses to lipopolysaccaride (LPS)[38-40] and SOCS1-deficient dendritic cells (DCs) promoted hyperactivation of Th1, lupus-like autoimmune diseases, and anti-tumor immunity[41, 42].

SOCS1 has been implicated in the mechanism of glucocorticoid-mediated STAT1 suppression[43, 44]. SOCS1 is also highly upregulated by M. tuberculosis infection and reduced responses to IL-12, resulting in an impaired IFN-γ secretion by macrophages that in turn accounts for deteriorated intracellular mycobacterial control. Thus, SOCS1 expression by macrophages hampered *M. tuberculosis* clearance early after infection *in vivo* in an IFN-γ -dependent manner. On the other hand, at later time points, SOCS1 expression by non-macrophage cells protected the host from infection-induced detrimental inflammation[45]. We have demonstrated that SOCS1 plays an essential role in intestinal immune homeostasis by regulating prostaglandin E2 (PGE2)-mediated DC and macrophage suppression[12]. Although SOCS1/Rag2 DKO mice did not die neonatally, these mice developed severe colitis at 2 to 6 months of age, mostly due to impairment of the PGE2-mediated anti-inflammatory mechanism[46].

SOCS3 and inflammation

In contrast to SOCS1, the role of SOCS3 in innate inflamma-

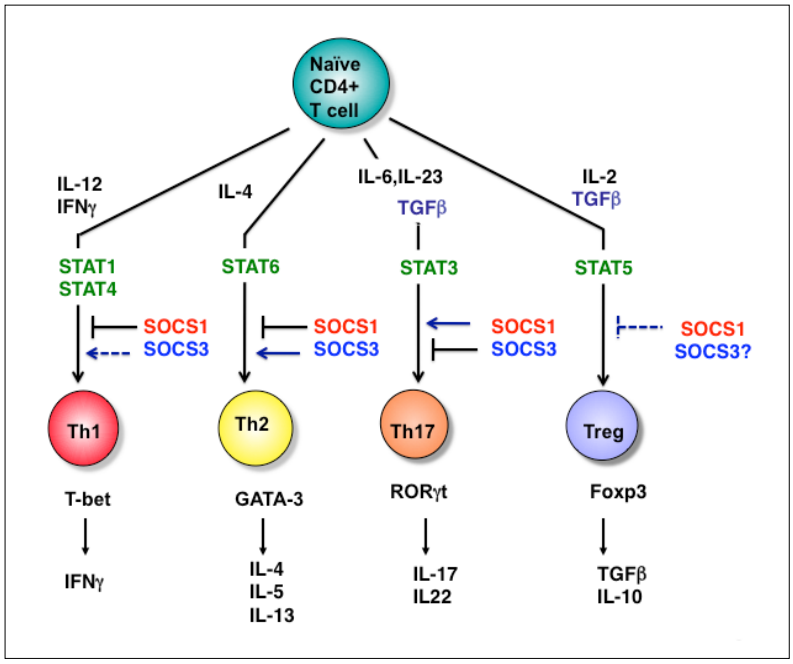

Fig.2 Role of STATs and SOCS proteins in helper T cell differentiation

T cell differentiation from naïve cells into the various functional subtypes (e.g., Th1, Th2, Th17, and Treg cells) primarily depends on the action of cytokines as indicated. SOCS1 and SOCS3 regulate the cytokine pathways indicated, and thereby dictate $CD4^+$ T cell differentiation. Note that SOCS3 inhibits Th1 through overexpression by suppressing IL-12-mediated STAT4 activation. However, SOCS3 deletion also inhibits Th1 by promoting the production of IL-10 and TGF-β. In Tregs, SOCS1 deletion promotes Treg expansion; however, these are functionally impaired. Thus, SOCS1 negatively regulates the Treg number, but is necessary for the function of Tregs. The role of SOCS3 in Tregs has not yet been clarified. For Th17, RORγt induction by TGF-β has been demonstrated to be independent of Smad2/3/4.

tion is complex. SOCS3 deficiency in macrophages protects mice from endoroxemia, because of the reduced production of inflammatory cytokines, which is due to the enhanced anti-inflammatory effect of STAT3[20]. Furthermore, macrophage-specific SOCS3-cKO mice have reduced IL-12 responses and succumb to toxoplasmosis. In the absence of SOCS3, macrophages are hypersensitive to the anti-inflammatory properties of IL-6. Thus, SOCS3 plays a critical role in suppressing IL-6 signals and promoting immune responses to control *T. gondii* infection[47]. Macrophage-specific SOCS3-cKO mice exhibited resistance to the tumor transplantation model because of reduced tumor-promoting cytokines such as TNFα and IL-6 and enhanced production of anti-tumorigenic chemokine MCP2/CCL8[13]. Thus, SOCS3 is an important modulator of macrophage phase and functions.

SOCS3$^{-/-}$ DCs exhibited constitutive activation of STAT3 and expressed low levels of MHC class II molecules, co-stimulatory molecules, and IL-12[48]. Adoptive transfer of *SOCS3*$^{-/-}$ DCs suppressed EAE. *SOCS3*$^{-/-}$ DCs produced a higher amount of TGF-β than WT DCs, resulting in a selective expansion of forkhead box P3 (FoxP3)-positive regulatory T cells (Tregs). However, SOCS3-transduced DCs also expressed low levels of MHC class II and CD86 molecules and produced high levels of IL-10 but low levels of IL-12, IFNγ, and IL-23 p19[49]. STAT3 activation was suppressed by SOCS3 overexpression. Although the mechanism has not yet been clarified, SOCS3-transduced DCs efficiently induced Th2-cell differentiation and suppressed Th17 *in vitro* and *in vivo* and the adoptive transfer of *Socs3*$^{-/-}$ DCs suppressed EAE, just like SOCS3-Tg DCs[49]. These results suggest

that the status of STAT3 activation levels may determine the balance between Th2 and Tregs induced by DCs.

In certain situations, SOCS3 suppresses inflammatory reactions by inhibiting STAT3. STAT3 activation is found in epithelial and lamina propria cells in the colon of mice with intestinal bowel disease (IBD), as well as in human ulcerative colitis and Crohn's disease patients[50] and in synovial fibroblasts of RA patients[51]. Forced expression of either SOCS3 or a dominant negative form of STAT3 in mouse arthritis models suppressed the induction/development of the disease, indicating that SOCS3 in non-immune cells is probably anti-inflammatory[51]. These findings are consistent with the idea that the IL-6- and IL-6-related cytokines-STAT3 pathway promotes chronic disease progression and SOCS3 is part of this negative-feedback loop. This idea is supported by a recent finding that the JAK inhibitor CP-690550 is a potent therapeutic agent for the autoimmune arthritis model by suppressing the IL-6/STAT3 amplification[52]. However, if STAT3 plays a protective role, such as in ConA-induced hepatitis, deletion of SOCS3 is anti-inflammatory[18].

In addition, SOCS3 is an important negative regulator of granulopoiesis because SOCS3 negatively regulates the G-CSF receptor signaling[53, 54]. Mice in which the SOCS3 gene was deleted in all hematopoietic cells developed a spectrum of inflammatory pathologies with hyper-neutrophilia. SOCS3-deficient mice developed inflammatory neutrophil infiltration into multiple tissues and consequent hind-leg paresis[55].

Overview of helper T cell differentiation

Helper T cells play essential roles in adaptive immune responses and chronic inflammation. After emigrating from the bone marrow, thymocyte progenitors enter the thymus. Following positive selection, single positive ($CD4^+$ or $CD8^+$ SP) cells migrate to the periphery as naïve T cells. Naturally occurring $CD4^+CD25^+$ $Foxp3^+$regulatory T cells (nTregs) also develop in the thymus from immature $CD4^+$ T cells. After exiting the thymus, naïve T cells are activated by antigen-presenting cells (APCs), and develop specialized properties and effector functions, Th1, Th2, and Th17 (Fig.2)[56].

Th1 cells, which evolved to enhance the eradication of intracellular pathogens (e.g., intracellular bacteria, viruses, and some protozoa), are characterized by their production of IFNγ a potent activator of cell-mediated immunity. IL-12 is an inducer of Th1. Immune pathogenesis that results from dysregulated Th1 responses to self or commensal floral antigens can promote tissue destruction and chronic inflammation, macrophage activation, and granuloma. Th2 cells, which evolved to enhance the elimination of parasitic infections (e.g., helminths), are characterized by the production of interleukin (IL)-4, IL-5, and IL-13, which are potent activators of B-cell immunoglobulin (Ig)E production, eosinophil recruitment, and mucosal expulsion mechanisms (mucous production and hypermotility). IL-4 is necessary to induce Th2. Dysregulated Th2 responses can cause allergies and asthma. Th17 cells secrete a distinctive set of immunoregulatory cytokines, including IL-17A, IL-17F, IL-22, and IL-21. These cytokines collectively play roles in inflammation and autoimmunity and in the elimination of extracellular bacterial and fungal pathogens. Th17 cells have been demonstrated to play essential roles in autoimmune models, such as experimental autoimmune encephalitis (EAE) and collagen-induced arthritis (CIA). The Th17 differentiation of naïve T cells is initiated by IL-6 and TGF-β. In addition, IL-23, as well as IL-21, is thought to be a key cytokine for the maturation and/or maintenance of Th17 cells. IL-6, IL-21, and IL-23 all activate STAT3, which is thought to be essential for Th17 differentiation[57, 58]. It has also been reported that STAT3 plays a critical role in the induction of the orphan nuclear receptor, RORγt, which directs Th17 cell differentiation by inducing the IL-23 receptor[59]. TGF-β also induces the differentiation of naïve T cells into $Foxp3^+$ Tregs (iTregs) in the peripheral immune compartment, and iTreg and Th17 are reciprocally regulated[60, 61] (Fig.2).

SOCS1 and helper T cell differentiation and functions

We have recently demonstrated that SOCS1 is an essential regulator for helper T cell differentiation. Most $SOCS1^{-/-}CD4$ naïve T cells differentiated into Th1, even under Th2 or Th17 skewing conditions, whereas Th17 differentiation was strongly suppressed[35]. This was also dependent on IFNγ, because Th17 was normally developed in $SOCS1^{-/-}IFN\gamma^{-/-}$ T cells. As a result, T cell-specific SOCS1-deficient mice developed autoimmune inflammatory diseases with age[10] and were very sensitive to dextran sulfate sodium (DSS)-induced colitis[62] and ConA-induced hepatitis (Th1 type disease)[37], but were resistant to experimental autoimmune encephalomyelitis (EAE), a typical Th17 type disease[35].

Th17 suppression by SOCS1 deficiency is probably due to the hyperproduction and signal transduction of IFNγ. Indeed, STAT1 activation in $SOCS1^{-/-}$ T cells was upregulated and strong Th1 skewing was corrected under $STAT1^{+/-}$ conditions[35](and unpublished data). Interestingly, STAT3 activation was reduced in SOCS1-deficient T cells, mostly due to the upregulation of SOCS3 gene expression, which can account for reduced IL-6

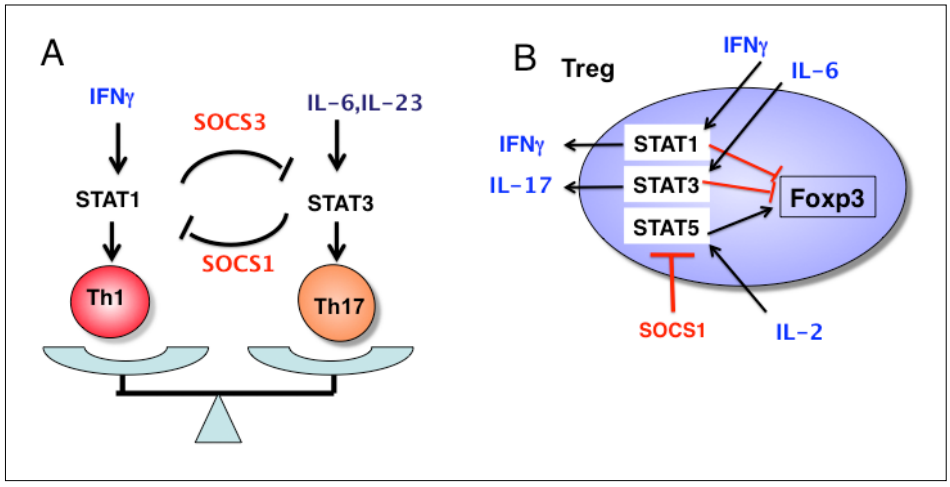

Fig.3 Role of SOCS1 and SOCS3 in Th1/Th17 balance (A) and in nTreg integrity (B)

(A) In Th1 conditions, activated STAT1 induces SOCS3 expression, which in turn inhibits STAT3 activity, thereby suppressing Th17 development. In Th17 conditions, SOCS1 is highly expressed and inhibits IFNγ-mediated Th1 development.

(B) In nTregs, the SOCS1 level is constantly high, and suppresses STAT1, STAT3, and STAT5 in inflammatory conditions (high levels of cytokines such as IL-2, IL-6, and IFNγ). The higher activation of STAT5 results in an increase in the number of Tregs, because STAT5 directly upregulates Foxp3 expression. The higher activation of STAT1 and STAT3 induces loss of Foxp3 expression by unknown mechanisms and promotes IFNγ and IL-17 production, respectively. Thus, SOCS1 is a "guardian" of Tregs.

responses and Th17 differentiation. Indeed, SOCS3-tg mice were resistant to EAE, and Th17 differentiation of SOCS3-tg T cells was suppressed. The reciprocal regulation of Th1 and Th17 by SOCS1 and SOCS3 is illustrated in Fig.3A. In addition, SOCS1$^{-/-}$ T cells were less responsive to TGF-β, although the mechanism has not yet been clarified. Reduced STAT3 activation and TGF-β signaling may explain the suppression of Th17 differentiation in SOCS1-deficient T cells. Our microarray analysis revealed that T-bet, Eomesodermin, and Gfi-1 were upregulated in SOCS1-deficeint Th17 cells, all of which have been reported to suppress Th17 differentiation[63, 64].

SOCS1 also plays an important role in the regulation of regulatory T cells. Higher numbers of Tregs are observed in the thymus and spleen of T cell-specific SOCS1-deficient mice[65]. This is probably due to higher IL-2 responses, because IL-2 enhances the proliferation of Tregs (Fig.3B). Importantly, SOCS1 has been shown to be a target of miRNA-155 in Tregs[65]. During thymic differentiation, the upregulation of Foxp3 drives the high expression of miR-155, which in turn promotes the expansion of Treg cells by targeting SOCS1.

However, SOCS1 has recently been found to play more important functional roles in Tregs. Various studies have suggested that Tregs may become harmful effector T cells in inflammatory conditions. Lu et al. observed that SOCS1 deletion specifically in Tregs induced the development of spontaneous dermatitis, splenomegaly, and lymphoadenopathy, suggesting a defective Treg function in these mice[66]. The defective suppression activity of SOCS1-deficient Tregs was confirmed through the failure to suppress colitis in *Rag2*$^{-/-}$ mice by the co-transfer of naïve T cells and Tregs[10]. In the absence of SOCS1, Tregs easily lost Foxp3 expression, and became pathogenic T cells that induced severe colitis[66]. In addition, SOCS1 plays an important role in preventing inflammatory cytokine production from Tregs. Normally, Tregs do not secrete inflammatory cytokines even in inflammatory conditions. In the absence of SOCS1, Tregs secrete IFNγ and IL-17 by hyperactivation of STAT1 and STAT3, respectively[10]. Thus, SOCS1 is a "guardian" of Tregs, since SOCS1 inhibits loss of Foxp3 and conversion of Tregs to Th1- or Th17-like cells (Fig.3B).

Role of SOCS3 in helper T cells

The degree to which SOCS3 expression in T cells is increased is correlated to the severity of human allergic diseases such as asthma and atopic dermatitis[67]. The enhanced action of SOCS3 may promote allergic responses, since transgenic SOCS3 expression in T cells inhibits Th1 development and promotes Th2 development[67]. Enhanced Th2 development may be due to the suppression of Th1 because IL-12 mediated Th1 differentiation by SOCS3 overexpression. Therefore, SOCS3-tg mice were sensitive to *L. Major* infection, where Th1 is necessary for eradication of this microbe[68]. As described before, SOCS3-expressing T cells differentiated into Th17 cells less efficiently than WT T cells[35]. In contrast, mice lacking SOCS3 in T cells result in reduced allergen-induced eosinophilia in the airways[69](Fig.3A). SOCS3 silencing with small interfering RNA (siRNA) in primary $CD4^+$ T cells attenuated the Th2 response *in vitro* and *in vivo*[70]. SOCS3 deficiency promoted Th17 differentiation in T cells[71]. Using VavCre-SOCS3 conditional KO mice, Wong et al. reported that the IL-1-induced inflammatory joint disease model was severely deteriorated in the absence of SOCS3 accompanying the enhanced IL-17 production from $CD4^+$ T cells[55]. SOCS3 deficiency in T cells reduced atherosclerotic lesion development and vascular inflammation, which was dependent on IL-17, whereas the overexpression of SOCS3 in T cells reduced IL-17 and accelerated atherosclerosis[14]. The absence of SOCS-3 in helper T cells therefore generally inhibits Th1 and Th2 by producing IL-10 and TGF-β, but had dramatic pro-inflammatory effects under Th17 conditions[11]. The paradoxical effect of SOCS3 on T cell regulation is mostly due to the dual function of STAT3; it promotes the production of both inflammatory IL-17 and anti-inflammatory IL-10 and TGF-β.

In the LCMC clone 13 infection model, SOCS3 is highly induced in T cells, and T cell-specific SOCS3-deficient mice exhibit a profound augmentation of immunity and are protected from severe organ pathology, with an increase in the number of virus-specific $CD8^+$T cells and an increase in the ability of $CD4^+$T cells to secrete TNF-α and IL-17. This T cell-intrinsic SOCS3 induction has been implicated as a major factor contributing to immunological failure in the setting of chronic active infection[72].

SOCS and human inflammatory diseases

It has been estimated that more than 20% of all malignancies are initiated or exacerbated by inflammation; for example, most human hepatocellular carcinomas (HCCs) are a consequence of hepatitis C virus (HCV) infection[73]. The expression of *SOCS1* is often silenced in these tumors by hypermethylation of CpG islands including HCCs. We found that silencing of *SOCS1* was frequently observed even in pre-malignant HCV-infected patients[19]. Liver injury is associated with hyperactivation of STAT1 and reduced activation of STAT3. Therefore, the reduced expression of SOCS1 may enhance tissue injury and inflammation through the hyperactivation of STAT1, promoting the turnover of epithelial cells and enhancing their susceptibility to oncogenesis. Therefore, SOCS1 is a unique anti-oncogene that prevents carcinogenesis by suppressing chronic inflammation[36, 74].

SOCS3 may also be involved in the development and progression of malignancies. SOCS3 expression levels were reduced in tumor areas of patients infected with HCV compared with non-tumor regions[18]. Hyperactivation of STAT3 by SOCS3 repression may contribute to tumorigenesis by inducing multiple tumor-promoting genes[17].

As mentioned before, levels of SOCS3 in T cells are correlated to allergic diseases[67]. Several genomic SNPs in the human *SOCS1* gene were found to be associated with serum IgE levels[75], asthma[76], and leukemia[77]. SOCS1 mutations were found in human lymphomas[78].

Concluding remarks

Over the past decade, following the discovery of the SOCS protein families, we have extended our understanding of the structure and function of these proteins. SOCS proteins act as simple negative-feedback regulators, and they also play a part in the fine tuning of the immune response and inflammation. Therapeutic trials using SOCS anti-sense oligonucleotides, shRNA, and peptide mimetics are currently underway in animal models. SOCS1 and SOCS3 are ideal therapeutic targets for autoimmune diseases and inflammatory diseases, including cancer.

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Disclosure

We have no conflicts of interest.

References

1) O'Shea JJ, Gadina M, Schreiber RD: Cytokine signaling in 2002: new surprises in the Jak/Stat pathway. Cell. 2002; 109 Suppl: S121-S131.

2) Adamson AS, Collins K, Laurence A, O'Shea JJ: The Current STATus of lymphocyte signaling: new roles for old players. Curr Opin Immunol. 2009; 21: 161-166.
3) O'Shea JJ, Lahesmaa R, Vahedi G, Laurence A, Kanno Y: Genomic views of STAT function in CD4+ T helper cell differentiation. Nat Rev Immunol. 2011; 11: 239-250.
4) Cheng G, Yu A, Malek TR: T-cell tolerance and the multifunctional role of IL-2R signaling in T-regulatory cells. Immunol Rev. 2011; 241: 63-76.
5) Takaki H, Ichiyama K, Koga K, Chinen T, Takaesu G, Sugiyama Y, Kato S, Yoshimura A, Kobayashi T: STAT6 Inhibits TGF-beta1-mediated Foxp3 induction through direct binding to the Foxp3 promoter, which is reverted by retinoic acid receptor. J Biol Chem. 2008; 283: 14955-14962.
6) Elias KM, Laurence A, Davidson TS, Stephens G, Kanno Y, Shevach EM, O'Shea JJ: Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway. Blood. 2008; 111: 1013-1020.
7) Yoshimura A, Naka T, Kubo M: SOCS proteins, cytokine signalling and immune regulation. Nat Rev Immunol. 2007; 7: 454-465.
8) Kubo M, Hanada T, Yoshimura A: Suppressors of cytokine signaling and immunity. Nat Immunol. 2003; 4: 1169-1176.
9) Endo TA, Masuhara M, Yokouchi M, Suzuki R, Sakamoto H, Mitsui K, Matsumoto A, Tanimura S, Ohtsubo M, Misawa H, et al: A new protein containing an SH2 domain that inhibits JAK kinases. Nature. 1997; 387: 921-924.
10) Takahashi R, Nishimoto S, Muto G, Sekiya T, Tamiya T, Kimura A, Morita R, Asakawa M, Chinen T, Yoshimura A: SOCS1 is essential for regulatory T cell functions by preventing loss of Foxp3 expression as well as IFN-{gamma} and IL-17A production. J Exp Med. 2011; 208: 2055-2067.
11) Tamiya T, Kashiwagi I, Takahashi R, Yasukawa H, Yoshimura A: Suppressors of cytokine signaling (SOCS) proteins and JAK/STAT pathways: regulation of T-cell inflammation by SOCS1 and SOCS3. Arterioscler Thromb Vasc Biol. 2011; 31: 980-985.
12) Chinen T, Komai K, Muto G, Morita R, Inoue N, Yoshida H, Sekiya T, Yoshida R, Nakamura K, Takayanagi R, et al: Prostaglandin E2 and SOCS1 have a role in intestinal immune tolerance. Nat Commun. 2011; 2: 190.
13) Hiwatashi K, Tamiya T, Hasegawa E, Fukaya T, Hashimoto M, Kakoi K, Kashiwagi I, Kimura A, Inoue N, Morita R, et al: Suppression of SOCS3 in macrophages prevents cancer metastasis by modifying macrophage phase and MCP2/CCL8 induction. Cancer Lett. 2011; 308: 172-180.
14) Taleb S, Romain M, Ramkhelawon B, Uyttenhove C, Pasterkamp G, Herbin O, Esposito B, Perez N, Yasukawa H, Van Snick J, et al: Loss of SOCS3 expression in T cells reveals a regulatory role for interleukin-17 in atherosclerosis. J Exp Med. 2009; 206: 2067-2077.
15) Mori H, Hanada R, Hanada T, Aki D, Mashima R, Nishinakamura H, Torisu T, Chien KR, Yasukawa H, Yoshimura A: Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. Nat Med. 2004; 10: 739-743.
16) Torisu T, Sato N, Yoshiga D, Kobayashi T, Yoshioka T, Mori H, Iida M, Yoshimura A: The dual function of hepatic SOCS3 in insulin resistance in vivo. Genes Cells. 2007; 12: 143-154.
17) Ogata H, Chinen T, Yoshida T, Kinjyo I, Takaesu G, Shiraishi H, Iida M, Kobayashi T, Yoshimura A: Loss of SOCS3 in the liver promotes fibrosis by enhancing STAT3-mediated TGF-beta1 production. Oncogene. 2006; 25: 2520-2530.
18) Ogata H, Kobayashi T, Chinen T, Takaki H, Sanada T, Minoda Y, Koga K, Takaesu G, Maehara Y, Iida M, et al: Deletion of the SOCS3 gene in liver parenchymal cells promotes hepatitis-induced hepatocarcinogenesis. Gastroenterology. 2006; 131: 179-193.
19) Yoshida T, Ogata H, Kamio M, Joo A, Shiraishi H, Tokunaga Y, Sata M, Nagai H, Yoshimura A: SOCS1 is a suppressor of liver fibrosis and hepatitis-induced carcinogenesis. J Exp Med. 2004; 199: 1701-1707.
20) Yasukawa H, Ohishi M, Mori H, Murakami M, Chinen T, Aki D, Hanada T, Takeda K, Akira S, Hoshijima M, et al: IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. Nat Immunol. 2003; 4: 551-556.
21) Masuhara M, Sakamoto H, Matsumoto A, Suzuki R, Yasukawa H, Mitsui K, Wakioka T, Tanimura S, Sasaki A, Misawa H, et al: Cloning and characterization of novel CIS family genes. Biochem Biophys Res Commun. 1997; 239: 439-446.
22) Kamizono S, Hanada T, Yasukawa H, Minoguchi S, Kato R, Minoguchi M, Hattori K, Hatakeyama S, Yada M, Morita S, et al: The SOCS box of SOCS-1 accelerates ubiquitin-dependent proteolysis of TEL-JAK2. J Biol Chem. 2001; 276: 12530-12538.
23) Kamura T, Maenaka K, Kotoshiba S, Matsumoto M, Kohda D, Conaway RC, Conaway JW, Nakayama KI: VHL-box and SOCS-box domains determine binding specificity for

Cul2-Rbx1 and Cul5-Rbx2 modules of ubiquitin ligases. Genes Dev. 2004; 18: 3055-3065.

24) Russell RC, Sufan RI, Zhou B, Heir P, Bunda S, Sybingco SS, Greer SN, Roche O, Heathcote SA, Chow VW, et al: Loss of JAK2 regulation via a heterodimeric VHL-SOCS1 E3 ubiquitin ligase underlies Chuvash polycythemia. Nat Med. 2011; 17: 845-853.

25) Yasukawa H, Misawa H, Sakamoto H, Masuhara M, Sasaki A, Wakioka T, Ohtsuka S, Imaizumi T, Matsuda T, Ihle JN, et al: The JAK-binding protein JAB inhibits Janus tyrosine kinase activity through binding in the activation loop. Embo J. 1999; 18: 1309-1320.

26) Sasaki A, Yasukawa H, Shouda T, Kitamura T, Dikic I, Yoshimura A: CIS3/SOCS-3 suppresses erythropoietin (EPO) signaling by binding the EPO receptor and JAK2. J Biol Chem. 2000; 275: 29338-29347.

27) Schmitz J, Weissenbach M, Haan S, Heinrich PC, Schaper F: SOCS3 exerts its inhibitory function on interleukin-6 signal transduction through the SHP2 recruitment site of gp130. J Biol Chem. 2000; 275: 12848-12856.

28) Lehmann U, Schmitz J, Weissenbach M, Sobota RM, Hortner M, Friederichs K, Behrmann I, Tsiaris W, Sasaki A, Schneider-Mergener J, et al: SHP2 and SOCS3 contribute to Tyr-759-dependent attenuation of interleukin-6 signaling through gp130. J Biol Chem. 2003; 278: 661-671.

29) Yamamoto K, Yamaguchi M, Miyasaka N, Miura O: SOCS-3 inhibits IL-12-induced STAT4 activation by binding through its SH2 domain to the STAT4 docking site in the IL-12 receptor beta2 subunit. Biochem Biophys Res Commun. 2003; 310: 1188-1193.

30) Bjorbak C, Lavery HJ, Bates SH, Olson RK, Davis SM, Flier JS, Myers MG Jr: SOCS3 mediates feedback inhibition of the leptin receptor via Tyr985. J Biol Chem. 2000; 275: 40649-40657.

31) Zhang R, Dhillon H, Yin H, Yoshimura A, Lowell BB, Maratos-Flier E, Flier JS: Selective inactivation of Socs3 in SF1 neurons improves glucose homeostasis without affecting body weight. Endocrinology. 2008; 149: 5654-5661.

32) Kobayashi T, Takaesu G, Yoshimura A: Mal-function of TLRs by SOCS. Nat Immunol. 2006; 7: 123-124.

33) Sasaki A, Yasukawa H, Suzuki A, Kamizono S, Syoda T, Kinjyo I, Sasaki M, Johnston JA, Yoshimura A: Cytokine-inducible SH2 protein-3 (CIS3/SOCS3) inhibits Janus tyrosine kinase by binding through the N-terminal kinase inhibitory region as well as SH2 domain. Genes Cells. 1999; 4: 339-351.

34) Marine JC, Topham DJ, McKay C, Wang D, Parganas E, Stravopodis D, Yoshimura A, Ihle JN: SOCS1 deficiency causes a lymphocyte-dependent perinatal lethality. Cell. 1999; 98: 609-616.

35) Tanaka K, Ichiyama K, Hashimoto M, Yoshida H, Takimoto T, Takaesu G, Torisu T, Hanada T, Yasukawa H, Fukuyama S, et al: Loss of suppressor of cytokine signaling 1 in helper T cells leads to defective Th17 differentiation by enhancing antagonistic effects of IFN-gamma on STAT3 and Smads. J Immunol. 2008; 180: 3746-3756.

36) Torisu T, Nakaya M, Watanabe S, Hashimoto M, Yoshida H, Chinen T, Yoshida R, Okamoto F, Hanada T, Torisu K, et al: Suppressor of cytokine signaling 1 protects mice against concanavalin A-induced hepatitis by inhibiting apoptosis. Hepatology. 2008; 47: 1644-1654.

37) Hashimoto M, Hiwatashi K, Ichiyama K, Morita R, Sekiya T, Kimura A, Sugiyama Y, Sibata T, Kuroda K, Takahashi R, et al: SOCS1 regulates type I/type II NKT cell balance by regulating IFNgamma signaling. Int Immunol. 2011; 23: 165-176.

38) Hashimoto M, Ayada T, Kinjyo I, Hiwatashi K, Yoshida H, Okada Y, Kobayashi T, Yoshimura A: Silencing of SOCS1 in macrophages suppresses tumor development by enhancing antitumor inflammation. Cancer Sci. 2009; 100: 730-736.

39) Kinjyo I, Hanada T, Inagaki-Ohara K, Mori H, Aki D, Ohishi M, Yoshida H, Kubo M, Yoshimura A: SOCS1/JAB is a negative regulator of LPS-induced macrophage activation. Immunity. 2002; 17: 583-591.

40) Sachithanandan N, Graham KL, Galic S, Honeyman JE, Fynch SL, Hewitt KA, Steinberg GR, Kay TW: Macrophage deletion of SOCS1 increases sensitivity to LPS and palmitic acid and results in systemic inflammation and hepatic insulin resistance. Diabetes. 2011; 60: 2023-2031.

41) Hanada T, Yoshida H, Kato S, Tanaka K, Masutani K, Tsukada J, Nomura Y, Mimata H, Kubo M, Yoshimura A: Suppressor of cytokine signaling-1 is essential for suppressing dendritic cell activation and systemic autoimmunity. Immunity. 2003; 19: 437-450.

42) Hanada T, Tanaka K, Matsumura Y, Yamauchi M, Nishinakamura H, Aburatani H, Mashima R, Kubo M, Kobayashi T, Yoshimura A: Induction of hyper Th1 cell-type immune responses by dendritic cells lacking the suppressor of cytokine signaling-1 gene. J Immunol. 2005; 174: 4325-4332.

43) Bhattacharyya S, Zhao Y, Kay TW, Muglia LJ: Glucocorticoids target suppressor of cytokine signaling 1 (SOCS1) and

type 1 interferons to regulate Toll-like receptor-induced STAT1 activation. Proc Natl Acad Sci USA. 2011; 108: 9554-9559.

44) Haffner MC, Jurgeit A, Berlato C, Geley S, Parajuli N, Yoshimura A, Doppler W: Interaction and functional interference of glucocorticoid receptor and SOCS1. J Biol Chem. 2008; 283: 22089-22096.

45) Carow B, Ye X, Gavier-Widen D, Bhuju S, Oehlmann W, Singh M, Skold M, Ignatowicz L, Yoshimura A, Wigzell H, et al: Silencing suppressor of cytokine signaling-1 (SOCS1) in macrophages improves Mycobacterium tuberculosis control in an interferon-gamma (IFN-gamma)-dependent manner. J Biol Chem. 2011; 286: 26873-26887.

46) Koga K, Takaesu G, Yoshida R, Nakaya M, Kobayashi T, Kinjyo I, Yoshimura A: Cyclic adenosine monophosphate suppresses the transcription of proinflammatory cytokines via the phosphorylated c-Fos protein. Immunity. 2009; 30: 372-383.

47) Whitmarsh RJ, Gray CM, Gregg B, Christian DA, May MJ, Murray PJ, Hunter CA: A Critical Role for SOCS3 in Innate Resistance to Toxoplasma gondii. Cell Host Microbe. 2011; 10: 224-236.

48) Matsumura Y, Kobayashi T, Ichiyama K, Yoshida R, Hashimoto M, Takimoto T, Tanaka K, Chinen T, Shichita T, Wyss-Coray T, et al: Selective expansion of foxp3-positive regulatory T cells and immunosuppression by suppressors of cytokine signaling 3-deficient dendritic cells. J Immunol. 2007; 179: 2170-2179.

49) Li Y, Chu N, Rostami A, Zhang GX: Dendritic cells transduced with SOCS-3 exhibit a tolerogenic/DC2 phenotype that directs type 2 Th cell differentiation in vitro and in vivo. J Immunol. 2006; 177: 1679-1688.

50) Suzuki A, Hanada T, Mitsuyama K, Yoshida T, Kamizono S, Hoshino T, Kubo M, Yamashita A, Okabe M, Takeda K, et al: CIS3/SOCS3/SSI3 plays a negative regulatory role in STAT3 activation and intestinal inflammation. J Exp Med. 2001; 193: 471-481.

51) Shouda T, Yoshida T, Hanada T, Wakioka T, Oishi M, Miyoshi K, Komiya S, Kosai K, Hanakawa Y, Hashimoto K, et al: Induction of the cytokine signal regulator SOCS3/CIS3 as a therapeutic strategy for treating inflammatory arthritis. J Clin Invest. 2001; 108: 1781-1788.

52) Mori T, Miyamoto T, Yoshida H, Asakawa M, Kawasumi M, Kobayashi T, Morioka H, Chiba K, Toyama Y, Yoshimura A: IL-1{beta} and TNF{alpha}-initiated IL-6-STAT3 pathway is critical in mediating inflammatory cytokines and RANKL expression in inflammatory arthritis. Int Immunol. 2011; in press

53) Kimura A, Kinjyo I, Matsumura Y, Mori H, Mashima R, Harada M, Chien KR, Yasukawa H, Yoshimura A: SOCS3 is a physiological negative regulator for granulopoiesis and granulocyte colony-stimulating factor receptor signaling. J Biol Chem. 2004; 279: 6905-6910.

54) Croker BA, Metcalf D, Robb L, Wei W, Mifsud S, DiRago L, Cluse LA, Sutherland KD, Hartley L, Williams E, et al: SOCS3 is a critical physiological negative regulator of G-CSF signaling and emergency granulopoiesis. Immunity. 2004, 20: 153-165.

55) Wong PK, Egan PJ, Croker BA, O□Donnell K, Sims NA, Drake S, Kiu H, McManus EJ, Alexander WS, Roberts AW, et al: SOCS-3 negatively regulates innate and adaptive immune mechanisms in acute IL-1-dependent inflammatory arthritis. J Clin Invest. 2006; 116: 1571-1581.

56) Yoshimura A, Wakabayashi Y, Mori T: Cellular and molecular basis for the regulation of inflammation by TGF-beta. J Biochem. 2010; 147: 781-792.

57) Yang XO, Panopoulos AD, Nurieva R, Chang SH, Wang D, Watowich SS, Dong C: STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. J Biol Chem. 2007; 282: 9358-9363.

58. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, et al: Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008; 452: 773-776.

59) Ivanov, II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR: The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17^{+} T helper cells. Cell. 2006; 126: 1121-1133.

60) Ichiyama K, Yoshida H, Wakabayashi Y, Chinen T, Saeki K, Nakaya M, Takaesu G, Hori S, Yoshimura A, Kobayashi T: Foxp3 inhibits RORgammat-mediated IL-17A mRNA transcription through direct interaction with RORgammat. J Biol Chem. 2008; 283: 17003-17008.

61) Takimoto T, Wakabayashi Y, Sekiya T, Inoue N, Morita R, Ichiyama K, Takahashi R, Asakawa M, Muto G, Mori T, et al: Smad2 and Smad3 are redundantly essential for the TGF-beta-mediated regulation of regulatory T plasticity and Th1 development. J Immunol. 2010; 185: 842-855.

62) Horino J, Fujimoto M, Terabe F, Serada S, Takahashi T, Soma Y, Tanaka K, Chinen T, Yoshimura A, Nomura S, et

al: Suppressor of cytokine signaling-1 ameliorates dextran sulfate sodium-induced colitis in mice. Int Immunol. 2008; 20: 753-762.

63) Ichiyama K, Sekiya T, Inoue N, Tamiya T, Kashiwagi I, Kimura A, Morita R, Muto G, Shichita T, Takahashi R, et al: Transcription factor Smad-independent T helper 17 cell induction by transforming-growth factor-beta is mediated by suppression of eomesodermin. Immunity. 2011; 34: 741-754.

64) Ichiyama K, Hashimoto M, Sekiya T, Nakagawa R, Wakabayashi Y, Sugiyama Y, Komai K, Saba I, Moroy T, Yoshimura A: Gfi1 negatively regulates T(h)17 differentiation by inhibiting RORgammat activity. Int Immunol. 2009; 21: 881-889.

65) Lu LF, Thai TH, Calado DP, Chaudhry A, Kubo M, Tanaka K, Loeb GB, Lee H, Yoshimura A, Rajewsky K, et al: Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity. 2009; 30: 80-91.

66) Lu LF, Boldin MP, Chaudhry A, Lin LL, Taganov KD, Hanada T, Yoshimura A, Baltimore D, Rudensky AY: Function of miR-146a in controlling Treg cell-mediated regulation of Th1 responses. Cell. 2010; 142: 914-929.

67) Seki Y, Inoue H, Nagata N, Hayashi K, Fukuyama S, Matsumoto K, Komine O, Hamano S, Himeno K, Inagaki-Ohara K, et al: SOCS-3 regulates onset and maintenance of T(H)2-mediated allergic responses. Nat Med. 2003; 9: 1047-1054.

68) Nakaya M, Hamano S, Kawasumi M, Yoshida H, Yoshimura A, Kobayashi T: Aberrant IL-4 production by SOCS3-over-expressing T cells during infection with Leishmania major exacerbates disease manifestations. Int Immunol. 2011; 23: 195-202.

69) Kinjyo I, Inoue H, Hamano S, Fukuyama S, Yoshimura T, Koga K, Takaki H, Himeno K, Takaesu G, Kobayashi T, et al: Loss of SOCS3 in T helper cells resulted in reduced immune responses and hyperproduction of interleukin 10 and transforming growth factor-beta 1. J Exp Med. 2006; 203: 1021-1031.

70) Moriwaki A, Inoue H, Nakano T, Matsunaga Y, Matsuno Y, Matsumoto T, Fukuyama S, Kan OK, Matsumoto K, Tsuda-Eguchi M, et al: T cell treatment with small interfering RNA for suppressor of cytokine signaling 3 modulates allergic airway responses in a murine model of asthma. Am J Respir Cell Mol Biol. 2011; 44: 448-455.

71) Chen Z, Laurence A, Kanno Y, Pacher-Zavisin M, Zhu BM, Tato C, Yoshimura A, Hennighausen L, O'Shea JJ: Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. Proc Natl Acad Sci USA. 2006; 103: 8137-8142.

72) Pellegrini M, Calzascia T, Toe JG, Preston SP, Lin AE, Elford AR, Shahinian A, Lang PA, Lang KS, Morre M, et al: IL-7 engages multiple mechanisms to overcome chronic viral infection and limit organ pathology. Cell. 2011; 144: 601-613.

73) Yoshimura A: Signal transduction of inflammatory cytokines and tumor development. Cancer Sci. 2006; 97: 439-447.

74) Hanada T, Kobayashi T, Chinen T, Saeki K, Takaki H, Koga K, Minoda Y, Sanada T, Yoshioka T, Mimata H, et al: IFNgamma-dependent, spontaneous development of colorectal carcinomas in SOCS1-deficient mice. J Exp Med. 2006; 203: 1391-1397.

75) Mostecki J, Cassel SL, Klimecki WT, Stern DA, Knisz J, Iwashita S, Graves P, Miller RL, van Peer M, Halonen M, et al: A SOCS-1 Promoter Variant Is Associated with Total Serum IgE Levels. J Immunol. 2011; 187: 2794-2802.

76) Harada M, Nakashima K, Hirota T, Shimizu M, Doi S, Fujita K, Shirakawa T, Enomoto T, Yoshikawa M, Moriyama H, et al: Functional polymorphism in the suppressor of cytokine signaling 1 gene associated with adult asthma. Am J Respir Cell Mol Biol. 2007; 36: 491-496.

77) Guillem V, Amat P, Cervantes F, Alvarez-Larrán A, Cervera J, Maffioli M, Bellosillo B, Collado M, Marugán I, Martinez-Ruiz F, et al: Functional polymorphisms in SOCS1 and PTPN22 genes correlate with the response to imatinib treatment in newly diagnosed chronic-phase chronic myeloid leukemia. Leuk Res. 2011; in press

78) Mottok A, Renne C, Seifert M, Oppermann E, Bechstein W, Hansmann ML, Kuppers R, Brauninger A: Inactivating SOCS1 mutations are caused by aberrant somatic hypermutation and restricted to a subset of B-cell lymphoma entities. Blood. 2009; 114: 4503-4506.