Suppressor of cytokine signaling 1 (SOCS1) is an obligate negative regulator of cytokine signaling and most importantly in vivo, signaling via the interferon-γ (IFN-γ) receptor. SOCS1, via its Src homology 2 domain, binds to phosphotyrosine residues in its targets, reducing the amplitude of signaling from cytokine receptors. SOCS1 is also implicated in blocking Toll-like receptor (TLR) signaling in macrophages activated by TLR agonists such as lipopolysaccharide (LPS), thus regulating multiple steps in the activation of innate immune responses. To rigorously test this, we isolated macrophages from Socs1−/− mice on multiple genetic backgrounds. We found no evidence that SOCS1 blocked TLR-activated pathways, endotoxin tolerance, or nitric oxide production. However, Socs1−/−;IFN-γ−/− mice were extremely susceptible to LPS challenge, confirming previous findings. Because LPS induces IFN-β production from macrophages, we tested whether SOCS1 regulates IFN-α/β receptor signaling. We find that SOCS1 is required to inhibit IFN-α/β receptor signaling in vitro. Furthermore, the absence of a single allele encoding TYK2, a Jak (Janus kinase) family member essential IFN-α/β receptor signaling, rescued Socs1−/− mice from early lethality, even in the presence of IFN-γ. We conclude that previous reports linking SOCS1 to TLR signaling are most likely due to effects on IFN-α/β receptor signaling.

SOCS1 is a member of a family of proteins that regulate cytokine signaling pathways via inhibition of key tyrosine phosphorylation events on cytokine receptors and signaling molecules such as JAK family members (1). The inhibitory effects of SOCS proteins are mediated by two domains found in all SOCS family members: an SH2 domain that can bind phosphorylated tyrosine residues and the SOCS box that functions as a ubiquitin E3 ligase and thus potentially directs substrate proteins to the protein degradation machinery (1). Although the biochemical events associated with SOCS function are poorly understood, overwhelming genetic evidence has demonstrated multiple members of the SOCS family are essential for the regulation of specific cytokine signal transduction events in vivo.

Mice lacking SOCS1 die 10–20 days after birth (2–4). Dissection of the cellular and molecular mechanisms involved in the death of the Socs1−/− mice has revealed that SOCS1 is essential for the response of cells to IFN-γ and IFN-γ production (2, 3). In the absence of SOCS1, IFN-γ levels rise, as does the responsiveness of cells bearing IFN-γ receptors (e.g. macrophages), causing an overwhelming inflammatory response that has been analyzed in great detail (1). The key pathway involved in this complex pathologic process is the IFN-γ-mediated phosphorylation and activation of STAT1, the central signal transduction molecule required for IFN-γ signaling (3, 5). SOCS1 itself is a target of IFN-γ-induced gene expression and thereby can function to block IFN-γ signaling via a negative feedback loop (1). Analysis of Socs1−/− mice intercrossed with mice bearing mutations in cytokine signaling pathways has additionally revealed that SOCS1 can regulate signaling from receptors other than the IFN-γR including those using the γc chain and the IL-12 receptor (6–10). This stands in contrast to the inhibitory effects of SOCS2 and SOCS3 that function to block a more limited number of cytokine signaling events (1).

A surprising set of results was recently published showing SOCS1 also regulates Toll-like receptor (TLR) signaling (11, 12).TLRs are a group of 10–11 surface transmembrane proteins that contribute to the sensing of conserved microbial structures, such as lipopolysaccharide (LPS), detected by TLR4 or flagellin that signals through TLR5 (13). TLRs function in higher order signaling complexes that lead, in part, to the rapid activation of NF-κB and MAP kinase signaling and the subsequent production of cytokines and chemokines by cells such as macrophages and dendritic cells (13). The activation of TLR signaling is an essential and conserved mechanism to activate the innate immune system. The authors of the aforementioned papers established that the absence of SOCS1 caused increased lethality when mice were exposed to LPS and that TLR-stimulated macrophages from Socs1−/− mice overproduced nitric oxide (NO) compared with controls (11, 12). They further showed that overexpression of SOCS1 in macrophages reduced TLR4 signaling (11, 12). Based on these data, SOCS1 was proposed to inhibit TLR signaling although the protein(s) in the TLR signal transduction cascade targeted by SOCS1 were not identified. However, SOCS proteins are well established to target tyrosine phosphorylation events, while the TLR signaling cascades are regulated predominantly by serine/threonine phosphorylation (13), making the SOCS1-mediated inhibition of TLR signaling conceptually difficult to
reconcile with existing knowledge of the regulatory events that control TLR signaling. In addition, previous studies have established that SOCS1 expression is induced by TLR4 signaling but indirectly via the autocrine/paracrine effects of IFN-α/β (14).

We therefore designed experiments using Socs1−/− mice and macrophages to provide support for the notion that SOCS1 can regulate TLR signaling. The results, however, demonstrate that there is no compelling evidence for such a regulatory role for SOCS1. In contrast, we find that SOCS1 is a physiologically important regulator of IFN-α/β signaling via effects of TYK2, a JAK family member required for IFN-α/β signaling. Since TLR signaling induces IFN-α/β from macrophages challenged with LPS (14, 15), we propose that previous observations linking SOCS1 and TLR signaling are most likely mediated through the regulation of IFN-α/β signaling.

MATERIALS AND METHODS

**Mice—** Socs1−/− mice were generated from heterozygous intercrosses and have been described in detail (2). Socs1−/− mice on IFN-γ−/−, Rag2−/−, or Stat1−/− backgrounds have been described (2, 16). Tyk2−/− mice were a gift of Dr. K. Shimoda (Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan). Mice lacking TYK2, SOCS1, and IFN-γ, in different combinations, were derived by intercrossing to generate Socs1−/− mice with one or two alleles of IFN-γ and Tyk2. All mice were housed in specific pathogen-free facilities and used in accordance with the guidelines of the St. Jude Institutional Animal Care and Use Committee.

**Macrophage Isolation—** Bone marrow-derived macrophages (BMDMs) and peritoneal inflammatory macrophages were isolated and cultured as described (17, 18).

**TLR and Interferon Signaling Studies—** Macrophages were stimulated with various TLR ligands or interferons as described (19). Immunoblotting was performed as described using antibodies described (17, 20).

**Endotoxin Challenges—** Socs1−/−, Socs1+/−, or Socs1+1/+ mice on an IFN-γ−/− background (ages 8–13 weeks) were individually weighed and challenged with Escherichia coli LPS (made to 5 mg/ml in phosphate-buffered saline) at 40 mg/kg by the intraperitoneal route (19). Mice were monitored every 4–6 h over a 96-h period and survival recorded at each time point. Survival data were analyzed using Kaplan-Meier statistics. Stratification based on the sex of the mice yielded equivalent results.

**NO Measurements—** NO levels from activated macrophages were measured using the Griess assay as described (20).

**Endotoxin Tolerance—** Tolerance in purified macrophages was induced according to the protocols described by Vogel and colleagues (21). Cytokine (TNF-α, IL-6, and IL-12) levels were measured in the culture supernatants by ELISA 18 h after the LPS restimulation (22).

**RESULTS**

**TLR Signaling to Activate ERK and IκBa Phosphorylation Is Unaffected in the Absence of SOCS1—** A series of unpublished preliminary studies performed in our laboratory using macrophages from Socs1−/− mice suggested SOCS1 was unlikely to regulate TLR signaling. In response to recent suggestions that the absence of SOCS1 exacerbated TLR signaling, we accordingly established assay systems to systematically test this concept. We measured TLR signaling by first testing the activation, in Socs1−/− macrophages isolated from the bone marrow of 7–9-day-old mice, of two important pathways of TLR activity: the activation of NF-κB through the phosphorylation and degradation of IκBa and the activation of p42/44 ERK phosphorylation. BMDMs from Socs1−/− or Socs1+1/+ macrophages were stimulated with LPS, CpG DNA, or dsRNA, agonists of TLR4, TLR9, and TLR3, respectively. When measured by immunoblotting using antibodies specific for the activated, phosphorylated forms of IκBa or ERK, the absence of SOCS1 had no significant effect on the normal kinetics or qualitative amounts on the phosphorylated forms of either proteins (Fig. 1). We next isolated BMDMs from adult Socs1−/− mice on three different backgrounds to further attempt to establish if there were any differences in TLR signaling in the absence of SOCS1. BMDMs were isolated from Socs1−/− mice on Rag2−/−, IFN-γ−/−, or Stat1−/− backgrounds and stimulated with LPS or CpG. IκBa and ERK phosphorylation was measured as described above (Fig. 2). As we found for Socs1−/− macrophages, there appeared to be insufficient evidence to support the notion that the absence of SOCS1 affected TLR signaling in terms of IκBa or ERK phosphorylation.

**Socs1−/− Mouse Are Extremely Susceptible to Endotoxin Challenge—** Published studies have shown that Socs1−/− mice are highly susceptible to systemic endotoxin challenge (11, 12). In addition, Socs1+1/+IFN-γ−/− mice were also more susceptible than Socs1+1/+IFN-γ−/− mice, suggesting that gene dosage of Socs1 leads to a significant effect in the response of the host to septic challenge. We performed further experiments to test these concepts. In these experiments, we used adult Socs1−/− mice on an IFN-γ−/− background to obviate the need to use mice less than 10–15 days of age, since newborn mice are more sensitive to LPS challenge than adults (19). Groups of male and female mice were accurately weighed and injected with 40 mg/kg LPS and survival monitored over 4 days. A relatively high dose was necessary, since the absence of IFN-γ signaling enhances endotoxin resistance (23). In agreement with previous studies, we found that Socs1−/− IFN-γ−/− mice rapidly died compared with controls (Fig. 5). However, there was no effect of Socs1 heterozygosity in contrast to claims that loss of a single allele of Socs1 on an IFN-γ−/− background increased LPS-induced lethality (11). In contrast to previous experiments that used limited numbers of mice (n = 4), our experiments used 40 Socs1+1/+IFN-γ−/− mice compared with 23 Socs1+1/+IFN-γ−/− mice to establish that
there was no evidence for any effects of Socs1 heterozygosity on the ability to withstand systemic endotoxin challenge.

**SOCS1 Regulates IFN-α/β Signaling**—The extreme susceptibility of Socs1−/−;IFN-γ−/− mice to endotoxin challenge suggested that SOCS1 was essential to negatively regulate a pathway(s) independent of IFN-γ that was crucial in controlling the systemic response to endotoxin. Since compelling evidence for a role of SOCS1 in directly regulating TLR signaling was lacking, we sought to substantiate a role for SOCS1 in regulation of the systemic inflammatory response to LPS by immunoblotting. Membranes were then stripped and reprobed with antibodies to IkBα or ERK. Results were representative of two independent experiments.

SOCS1 Regulates IFN-α/β Signaling in Innate Immunity

**FIG. 1.** SOCS1 does not affect IkBα phosphorylation and degradation or ERK phosphorylation. Bone marrow cells were isolated from Socs1+/+ or Socs1−/− mice at 8 days post-partum and cultured in the presence of CSF-1 to produce BMDMs. Cells were stimulated with LPS (100 ng/ml), CpG (2 μM), or dsRNA (100 ng/ml) for the times indicated and lysates analyzed for phosphorylated IkBα or ERK by immunoblotting. Membranes were then stripped and reprobed with antibodies to IkBα or ERK. Results are representative of two independent experiments.

**FIG. 2.** SOCS1 does not affect IkBα phosphorylation and degradation or ERK phosphorylation on genetic backgrounds that rescue neonatal lethality caused by the absence of SOCS1. Bone marrow cells were isolated from Socs1+/+,Rag2−/−, Socs1−/−; Rag2−/−, Socs1+/+,IFN-γ−/−, Socs1−/−; IFN-γ−/−, Socs1+/+, Stat1−/−, or Socs1−/−;Stat1−/− mice and cultured to produce mature BMDMs. Cells were stimulated with LPS or CpG and analyzed as described in the legend to Fig. 2. Results are representative of two independent experiments.
Two alleles of well over 100 days (Table I). This suggests that loss of one or born with either of these genotypes has survived, some to /H9253 SOCS1, TYK2, and IFN- /H9253 Socs1 /H11001 Socs1 /H11002 /H11002;Rag2 /H11001 /H11002 /H11002 IFN- /H9253 mice to generate mice lacking SOCS1 but were IFN- /H9253 mice that were healthy and fertile. All mice were also /H11002 /H11002 /H11002;Stat1 /H11002 /H11002 mice are all dead at /H9253 /H11001 /H11002 /H11002;Tyk2 /H11002 /H11002 mice were challenged with LPS for 18 h (gray bars) or left untreated (black bars). Cells were washed and then re-stimulated with LPS for a further 18 h and IL-12 in the culture supernatants measured by ELISA. Results are representative of two independent experiments each using two to three mice of each genotype. Two effects of loss of TYK2 on the lethality caused by SOCS1 deficiency were observed in the progeny of these mice (Table I). First, loss of a single allele of Tyk2 rescued Socs1+/− mice that were also IFN-γ+/+. These mice were weaned and still alive 40 days after birth. By comparison, Socs1+/− mice are all dead at the time of weaning, and most die by 10 days after birth. Therefore, Tyk2 heterozygosity is sufficient to overcome the early lethal effects of SOCS1 deficiency. A second effect was observed on mice that lacked SOCS1 but were IFN-γ−/−. These animals die between 30–70 days but from a pathological syndrome distinct from the Socs1−/− mice (26). We could generate Socs1−/−;IFN-γ−/−;Tyk2−/− or Socs1−/−;IFN-γ−/−;Tyk2−/− mice that were healthy and fertile. All mice born with either of these genotypes have survived, some to well over 100 days (Table I). This suggests that loss of one or two alleles of Tyk2 can also inhibit the lethal effects of IFN-γ in the Socs1−/−;IFN-γ−/− background. Taken together, these data suggest that elimination of TYK2 rescues lethality caused by the absence of SOCS1. This suggests that SOCS1 negatively regulates TYK2 signaling and therefore IFN-α/β signaling.

Fig. 3. SOCS1 does not regulate NO production from macrophages. a, bone marrow cells were isolated from Socs1+/+ or Socs1−/− mice at 8 days post-partum and cultured in the presence of CSF-1 to produce BMDMs. Cells were stimulated with LPS (100 ng/ml), CpG (2 μm), or dsRNA (100 ng/ml) in the absence (left panel) or presence of 2 ng/ml IFN-γ for 18 h. Nitrates in the culture supernatants were measured as described under “Materials and Methods.” b, inflammatory peritoneal macrophages were isolated from Socs1+/+;IFN-γ−/− or Socs1−/−;IFN-γ−/− mice and stimulated with LPS or LPS and IFN-γ as described above. c, bone marrow cells were isolated from Socs1+/+;Rag2−/−, Socs1−/−;Rag2−/−, Socs1+/+;IFN-γ−/−, Socs1−/−;IFN-γ−/−, Socs1+/+;Stat1−/−, or Socs1−/−;Stat1−/− mice and cultured to produce mature BMDMs. Cells were stimulated with LPS or CpG with or without IFN-γ and analyzed for nitrate production after 16 h. Results are representative of four independent experiments.

Fig. 4. SOCS1 does not regulate the ability of macrophages to become endotoxin tolerant. BMDMs from Socs1+/+ or Socs1−/− mice were challenged with LPS for 18 h (gray bars) or left untreated (black bars). Cells were washed and then re-stimulated with LPS for a further 18 h and IL-12 in the culture supernatants measured by ELISA. Results are representative of two independent experiments each using two to three mice of each genotype.

**DISCUSSION**

Our results suggest that SOCS1 plays no direct role in TLR signaling. We found no evidence for any effects of the absence of SOCS1 on TLR-induced signaling pathways critical for the establishment of innate immune responses. In performing
these studies, we found an unanticipated role for SOCS1 in regulating IFN-α/β signaling. This pathway most likely accounts for previously observed effects of the absence of SOCS1 in systemic LPS challenges. 

Previous published studies (11, 12) linking SOCS1 to the inhibition of TLR signaling could not be reproduced in our hands. We have applied genetic and biochemical approaches to show that BMDMs isolated from Socs1−/− mice or Socs1−/− mice on three different genetic backgrounds had normal TLR signaling to different TLR agonists. This result was expected, since there was no prior evidence to suggest that TLR signaling, a pathway primarily regulated by serine/threonine phosphorylation, could be inhibited by any SOCS protein, all of which bind tyrosine-phosphorylated substrates via their SH2 domains. Published data purporting a role for SOCS1 in regulating TLR signaling were in part derived from SOCS1 overexpression in macrophages (11, 12). Numerous genetic studies have established that enforced expression of SOCS family members often leads to artifactual effects on many cytokine and other signaling pathways (1). Thus, the effects of SOCS1 overexpression on TLR signaling appear to fulfill a familiar pattern.

![TABLE I](image)

**Effect of a Tyk2 loss-of-function mutation of the survival of Socs1-deficient mice**

Survival of Socs1−/− mice from crosses of Socs1+/-;IFN-γ−/−, Tyk2−/−, or Socs1+/-;IFN-γ−/−, Tyk2−/− intercrosses are shown. A total of 99 mice were born, and all mice Socs1+/− or Socs1+/+ are excluded from the analysis shown. All mice were genotyped at day 8–10.

| Genotype | No. mice born | No. mice surviving to weaning | No. mice surviving to 40 days | No. mice surviving to 100 days |
|----------|---------------|------------------------------|-------------------------------|-------------------------------|
| Socs1−/−;IFN-γ−/−;Tyk2−/− | 8 | 8/8 | 6/6 | 6/6 |
| Socs1−/−;IFN-γ−/−;Tyk2−/− | 2 | 2/2 | 2/2 | 2/2 |
| Socs1−/−;IFN-γ−/−;Tyk2−/− | 5 | 5/5 | 1/1 | 1/1 |
| Socs1−/−;IFN-γ−/−;Tyk2−/− | 0 | 0/0 | 0/0 | 0/0 |
| Socs1−/−;IFN-γ−/−;Tyk2−/− | 2 | 2/2 | 2/2 | 2/2 |
| Socs1−/−;IFN-γ−/−;Tyk2−/− | 4 | 4/4 | 2/2 | 2/2 |

* The total number of mice in each group continuing to each time point.
SOCS1 was also claimed to regulate systemic endotoxin sensitivity (11, 12). We found similar results using a rigorously defined endotoxin challenge protocol. We showed that Socs1−/− mice were highly sensitive to challenge. In contrast to previous data, however, we could find no evidence for any effects of Socs1 gene dosage on endotoxin sensitivity (11). Most likely, this stems from the low numbers of mice used by other investigators and the arbitrary administration of LPS dosage based on sex (12). In contrast, we used large numbers of mice using exact dosages based on animal weight. IFN-γ−/− mice are very resistant to endotoxin challenge suggesting a significant role for IFN-γ signaling in driving the lethal inflammation in sepsis (23). We were thus surprised that Socs1−/− IFN-γ−/− mice were highly susceptible to LPS challenge. This suggested that SOCS1 regulated IFN-γ-independent pathway(s) in the systemic inflammatory response. Mutations other than the loss of IFN-γ or its signaling components can rescue the SOCS1 deficiency, including loss of STAT6 or IFN-γR signaling (11). Most likely, this stems from the low numbers of mice extended life span of Socs1−/− mice reflects effects on IFN-γ homeostasis in the whole animal that enable the mice to escape the excessive inflammatory response that occurs in the absence of SOCS1, in addition to specific effects on IL-12 and IFN-α/β signaling as well as yet undiscovered cytokine receptors that could utilize TYK2.

In conclusion, we find that SOCS1, an SH2-containing protein that binds phosphotyrosines in its targets, does not regulate TLR signaling, a set of pathways regulated largely by serine/threonine phosphorylation. Our data suggest that SOCS1 regulates IFN-α/β signaling through effects on TYK2 and that previous studies attributing effects of SOCS1 on TLR signaling are more likely the result of priming or concurrent stimulation with IFN-α/β induced by TYK2 signaling. This pathway could be a significant target in the search for novel modifiers of the systemic inflammatory response and thereby be a useful target for sepsis therapeutics.

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Re-examination of the Role ofSuppressor of Cytokine Signaling 1 (SOCS1) in the Regulation of Toll-like Receptor Signaling
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