The suppressor of cytokine signaling (SOCS) proteins are a family of cytokine-inducible negative regulators of cytokine signaling. Interferon (IFN)-γ treatment induces the expression of SOCS1, SOCS2, and SOCS3 mRNAs. To examine the effect of SOCS proteins on IFN-mediated Janus-activated kinase/signal transducers and activators of transcription (STAT) signaling, HeLa and MCF-7-derived stable cell lines expressing SOCS1, SOCS2, and SOCS3 proteins were established. SOCS1 and SOCS3 but not SOCS2 inhibited the tyrosine phosphorylation and nuclear translocation of STAT1 in response to IFN stimulation. The IFN-mediated antiviral and antiproliferative activities were consistently blocked by the constitutive expression of SOCS1 and SOCS3 but not SOCS2 proteins. The maximum inhibitory activities of SOCS1 and SOCS3 proteins toward the activation of STAT1 were observed at very low levels of SOCS protein expression. In addition, SOCS1 exhibited a much stronger inhibitory activity toward the activation of STAT1 than did SOCS3. These results suggest that SOCS1 and SOCS3 but not SOCS2 are inhibitors of IFN-mediated Janus-activated kinase/STAT signaling pathways.

Interferons (IFNs) have antiviral, immunomodulatory, and antiproliferative activities (1). The binding of IFNs to their cell surface receptors activates receptor-associated Jak tyrosine kinases that then phosphorylate a family of latent cytoplasmic transcription factors named signal transducers and activators of transcription (STATs; Ref. 2). Phosphorylated STAT proteins dimerize and translocate into the nucleus to activate genes. STAT1 and STAT2, which are associated with IFN-dimerize and translocate into the nucleus to activate genes. Phosphorylated STAT proteins then phosphorylate a family of latent cytoplasmic surface receptors activating receptor-associated Jak tyrosine kinases. Although IFN-γ can strongly induce the expression of SOCS1, SOCS2, and SOCS3 mRNAs (21), the biological roles of these SOCS proteins in IFN signaling have not been studied. To determine the effect of SOCS proteins on IFN-mediated Jak/STAT signaling pathways, we generated HeLa (a human cervical cancer cell) and MCF-7 (human breast cancer cell) cell lines expressing SOCS proteins. SOCS1 inhibited the tyrosine phosphorylation and nuclear translocation of STAT1 in response to both IFN-α and IFN-γ. In accord with these results, SOCS1 was found to be able to inhibit the antiviral and antiproliferative activities of IFNs. We further demonstrated that although SOCS3 inhibited IFN signaling, SOCS1 displayed a much stronger inhibitory activity toward the activation of STAT1 in response to IFNs than did SOCS3. The maximum inhibitory activities of SOCS1 and SOCS3 proteins were achieved at very low levels of SOCS protein expression. In contrast, the overexpression of SOCS2 had no effect on the IFN-mediated activation of STAT1 or the antiproliferative activity of IFNs. We conclude that SOCS1 and SOCS3 but not SOCS2 are inhibitors of IFN-mediated Jak/STAT signaling pathways.

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‡ A STAR (Subspecialty Training and Advanced Research) fellow in the Department of Medicine at the University of California, Los Angeles.

¶ To whom correspondence should be addressed: Division of Hematology-Oncology, 11-934 Factor Bldg., 10833 LeConte Ave., Los Angeles, CA 90095-1678. Tel.: 310-206-9168; Fax: 310-825-6192; E-mail: Kshuai@mednet.ucla.edu.

The abbreviations used are: IFN, interferon; SOCS, suppressor of cytokine signaling; Jak, Janus-activated kinase; STAT, signal transducers and activators of transcription; VSV, vesicular stomatitis virus; IL, interleukin; OM, oncostatin M.

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The Suppressor of Cytokine Signaling (SOCS) 1 and SOCS3 but Not SOCS2 Proteins Inhibit Interferon-mediated Antiviral and Antiproliferative Activities*

Mark M. Song‡§ and Ke Shuai‡¶

From the Departments of ‡§Medicine and ¶Biological Chemistry, Molecular Biology Institute, University of California, Los Angeles, California 90095

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**RESULTS**

Inhibition of IFN-activated STAT1 by SOCS1 and SOCS3 but Not SOCS2—SOCS1, SOCS2, and SOCS3 mRNAs are induced in response to IFN-α or IFN-γ for 16 h. Various concentrations of vesicular stomatitis virus (VSV) were added and incubated for 24 or 48 h. Viable cells were detected by crystal violet staining or measured by a methylthiotetrazole assay (25). Data were obtained from four independent experiments.

**DISCUSSION**

The inhibition of IFN-induced STAT1 activation by SOCS1 and SOCS3 suggests a role for SOCS proteins in the regulation of IFN signaling. Further experiments are needed to determine the mechanisms by which SOCS proteins mediate their inhibitory effects on STAT1 phosphorylation and to explore the potential therapeutic implications of these findings.

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functional role of SOCS proteins in IFN signaling, stable MCF-7 cell lines constitutively expressing SOCS1, SOCS2, and SOCS3 were generated. To further analyze the potential effects of SOCS proteins on STAT signaling relative to their levels of expression, we established HeLa cell lines expressing various SOCS proteins by the tetracycline-inducible system. In addition, a common small peptide tag, Flag, was fused to the N termini of all SOCS proteins so that the levels of SOCS protein expression in various stable cell lines could be directly compared.

STAT1 is phosphorylated by Jaks in cells treated with IFN-α or IFN-γ (2). To determine the effect of SOCS proteins on IFN-activated Jak/STAT signaling pathways, we measured the level of STAT1 tyrosine phosphorylation in cell lines expressing various SOCS proteins. Protein extracts from HeLa-SOCS cell lines (in the presence of doxycycline to induce the expression of SOCS proteins) that were untreated or treated with IFN-α or IFN-γ were analyzed by Western blot analysis using the anti-pSTAT1 antibody that specifically recognizes tyrosine phosphorylated STAT1. STAT1 was phosphorylated in control cells (HeLa-hyg) treated with IFNs (Fig. 1A). The band that migrates slightly below STAT1 is probably STAT1β (an alternative splicing product of STAT1 lacking the C-terminal 38 amino acid residues). In contrast, the tyrosine phosphorylation of STAT1 was greatly inhibited in HeLa cells expressing SOCS1 (HeLa-SOCS1) and was inhibited to a lesser extent in HeLa cells expressing SOCS3 (HeLa-SOCS3). The expression of SOCS2 protein in this cell line was comparable with that of SOCS3 and was higher than that of SOCS1 (Fig. 1C). The presence of a similar amount of STAT1 in all samples was confirmed by reprobing the same filter with anti-STAT1 or anti-Flag to detect SOCS protein expression.

Fig. 3. Maximum inhibition of STAT1 activation by low levels of SOCS protein expression. Cells were untreated or treated with various concentrations of doxycycline (0, 0.5, 1, 2, and 4 μg/ml) for 24 h and then stimulated with either IFN-α (500 units/ml) or IFN-γ (5 ng/ml) for 20 min as indicated. The same filters were washed and reprobed with anti-STAT1 or anti-Flag to detect SOCS protein expression. Dox, doxycycline.
SOCS3 but not SOCS2 can inhibit IFN-induced STAT1 activation, and that SOCS1 is a more potent inhibitor than SOCS3 in IFN signaling.

To confirm the observed effects of SOCS proteins on the activation of STAT1 in response to IFN stimulation, we carried out similar experiments in MCF-7 stable cell lines expressing SOCS proteins. Although SOCS1, SOCS2, and SOCS3 were expressed in similar amounts in MCF-7 derived cell lines, SOCS1 and SOCS3 but not SOCS2 inhibited the tyrosine phosphorylation of STAT1 in response to IFN stimulation (Fig. 2). Similarly, SOCS1 displayed a more dramatic inhibitory effect on the activation of STAT1 than did SOCS3 in these cells.

**Maximum Inhibition of STAT1 Activation Can Be Achieved by Very Low Levels of SOCS1 and SOCS3 Expression**—We wanted to examine the inhibitory activities of SOCS proteins relative to their levels of expression in tet-inducible HeLa cells expressing various SOCS proteins. In the absence of doxycycline, very low levels of SOCS protein expression were observed in all three cell lines expressing SOCS1, SOCS2, and SOCS3 due to the leakage of the tet system (Fig. 3; the low level constitutive expression of SOCS2 protein in the absence of doxycycline was observed when the blot was exposed for a longer time (data not shown)). The level of SOCS protein expression increased in response to doxycycline at various concentrations (0–4 μg/ml). The activation of STAT1 in response to IFN-α and IFN-γ was analyzed and compared in these cell lines. STAT1 was phosphorylated in response to IFN-α and IFN-γ in the control cell line detected by anti-phosphoSTAT1 antibody (the identity of a minor band above STAT1 (Fig. 3, upper left panel) is not known, and it did not appear in other experiments (Fig. 1A)). Interestingly, the tyrosine phosphorylation of STAT1 in response to IFNs was inhibited in HeLa-SOCS1 and HeLa-SOCS3 cells in the absence of doxycycline induction (very low levels of SOCS proteins were present at

![Fig. 5. Nuclear translocation of STAT1 tested by immunofluorescence analysis. MCF-7-derived cells expressing various SOCS proteins were untreated or treated with IFN-α for 30 min as indicated. Cells were then stained with anti-STAT1 (final dilution, 1:500).](http://www.jbc.org/Downloaded from)
with IFN-γ. HeLa-derived cell lines expressing various SOCS proteins were treated with IFN-α (0–2000 units/ml) or IFN-γ (0–20 ng/ml) for 4 days. Viable cells were then counted under a microscope. The relative cell numbers, as compared with untreated samples, are shown. The average numbers of viable cells were determined from three independent experiments. 

**Fig. 6. IFN-induced growth inhibition in HeLa-SOCS cells.** HeLa-derived cell lines expressing various SOCS proteins were treated with IFN-α (0–2000 units/ml) or IFN-γ (0–20 ng/ml) for 4 days. Viable cells were then counted under a microscope. The relative cell numbers, as compared with untreated samples, are shown. The average numbers of viable cells were determined from three independent experiments.

IFNs display antiproliferative and antiviral activities in a number of cell lines including HeLa cells. STAT1 has been shown to be required for IFN-mediated antiviral activities in a number of cell lines including HeLa cells. Although SOCS1 and SOCS3 but not SOCS2 inhibited STAT1 phosphorylation in response to IFNs.

**SOCS1 and SOCS3 but Not SOCS2 Inhibited IL-6- and Oncostatin M-induced STAT3 Activation**—Although SOCS2 was shown to inhibit STAT3 activation by the leukemia inhibitory factor in mouse myeloid leukemia M1 cells (23), SOCS2 failed to inhibit the growth hormone-mediated gene activation (22). We examined the effect of SOCS2 protein on other cytokine-mediated activation of the Jak/STAT signaling pathways. The effect of SOCS proteins on the tyrosine phosphorylation of STAT3 induced by IL-6 and OM was analyzed in HeLa-SOCS cell lines (Fig. 4). In control HeLa cells, OM strongly induced the tyrosine phosphorylation of STAT3, whereas IL-6 weakly activated STAT3. The presence of SOCS1 and SOCS3 expression blocked IL-6- and OM-induced tyrosine phosphorylation of STAT3. In contrast, SOCS2 had no effect on STAT3 activation in response to IL-6 or OM.

**SOCS1 and SOCS3 but Not SOCS2 Blocked the Nuclear Translocation of STAT1 in Response to IFN Stimulation**—The nuclear translocation of STAT1 requires phosphorylation on Tyr-701 induced by IFN (8). To confirm the inhibition of SOCS proteins on STAT1 function, we examined the nuclear translocation of STAT1 in the presence of SOCS proteins by immunofluorescence analysis. MCF-7 cells expressing SOCS proteins with or without IFN treatment were analyzed for STAT1 translocation. Whereas STAT1 clearly translocated into the nucleus in response to IFN stimulation in control cells, the presence of SOCS1 and SOCS3 blocked the nuclear translocation of STAT1. In contrast, the expression of SOCS2 had no effect on the nuclear translocation of STAT1 (Fig. 5). These results are in accord with our finding that SOCS1 and SOCS3 but not SOCS2 blocked the tyrosine phosphorylation of STAT1 in response to IFN stimulation.

**Effects of SOCS Proteins on IFN-induced Antiproliferative and Antiviral Activities**—IFNs display antiproliferative and antiviral activities in a number of cell lines including HeLa cells. STAT1 has been shown to be required for IFN-mediated antiproliferative activity (10, 13). We wanted to determine the effect of SOCS proteins on the antiproliferative activity of IFNs. IFN-α and IFN-γ inhibited the proliferation of control HeLa cells (Fig. 6) at various concentrations. In contrast, the IFN-mediated antiproliferative activity was completely inhibited in HeLa-SOCS1 cells. In HeLa-SOCS2 cells, the IFN-α-induced antiproliferative activity was completely blocked (Fig. 6A), whereas the antiproliferative activity of IFN-γ was partially inhibited (Fig. 6B). This partial inhibitory effect of SOCS3 is probably due to the finding that a significant amount of activated STAT1 was present in IFN-γ-treated HeLa-SOCS3 cells (Figs. 1 and 3). In accord with the results from the biochemical characterization of SOCS2, the IFN-induced antiproliferative activity in HeLa-SOCS2 cells was not inhibited.

We next tested the effects of SOCS proteins on IFN-induced antiviral activity. HeLa-SOCS cells were infected with VSV at various concentrations in the presence or absence of IFNs. Viable cells were detected by crystal violet staining. In the control HeLa-Hyg cells, IFN-α or IFN-γ clearly conferred resistance to VSV infection (Fig. 7A, *top left panel*). Similar protective effects of IFNs were observed in HeLa-SOCS2 cells (Fig. 7A, *top right panel*). Similar protective effects of IFNs were observed in HeLa-SOCS2 cells (Fig. 7A, *top right panel*). In contrast, the antiviral activities of IFN-α and IFN-γ were completely blocked in HeLa cells expressing SOCS1 and SOCS3 (Fig. 7A). We further examined the effects of IFNs at various concentrations on VSV infection in HeLa-SOCS cells. The antiviral activity of IFN-α or IFN-γ was completely inhibited in HeLa-SOCS1 and HeLa-SOCS3 cells at the various concentrations of IFNs tested. The expression of SOCS2 protein did not affect the antiviral activity of IFNs (Fig. 7, B and C).
DISCUSSION

IFN-γ induces the expression of SOCS1, SOCS2, and SOCS3 mRNAs (21). In the present study, we have examined and compared the inhibitory effects of SOCS1, SOCS2, and SOCS3 proteins on IFN signaling. We showed that SOCS1 and SOCS3 but not SOCS2 proteins can inhibit IFN-mediated activation of STAT1 as well as the antiproliferative and antiviral activities of IFNs. The maximum inhibitory activity of SOCS1 and SOCS3 proteins toward the activation of STAT1 can be achieved by very low levels of SOCS protein expression, suggesting that SOCS proteins have a high affinity toward Jaks in vivo. SOCS3 appears to be a weaker inhibitor than SOCS1. Although SOCS3 almost completely abolished the activation of STAT1 by IFN-α, the inhibition of IFN-γ-mediated STAT1 activation by SOCS3 was partial and could not be further enhanced, despite an increase in SOCS3 protein expression in the presence of doxycycline (Fig. 3). IFN-α activates Jak1 and Tyk2, whereas IFN-γ activates Jak1 and Jak2. Thus, SOCS3 may have a higher affinity toward Tyk2 as compared with Jak2.

We showed that the overexpression of SOCS2 failed to inhibit the activation of STAT1 in response to IFN stimulation, although the level of SOCS2 overexpression was at least fivefold higher than that at which SOCS1 and SOCS3 exhibited maximum inhibitory activity (Fig. 3). SOCS2 also failed to inhibit the activation of STAT3 in response to IL-6 or OM. Why SOCS2 protein cannot inhibit IFN-, IL-6-, or OM-induced Jak/STAT signaling pathways is not clear. It is possible that SOCS2 may not be able to interact with Jak(s). Alternatively, SOCS2 protein may bind to Jak(s), but the association of SOCS2 with

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**FIG. 7. IFN-induced antiviral activity in HeLa-SOCS cells.** A, 10^4 cells were plated in a single well of a 96-well plate. Cells were untreated or treated with IFN-α (500 units/ml) or IFN-γ (5 ng/ml) for 18 h. Various amounts of VSV (0–10^7 plaque-forming units (pfu)/ml) were then added and incubated for an additional 2 days. Cells were stained with crystal violet. B, methylthiotetrazole assay. 10^4 cells were plated in a single well of a 96-well plate. Cells were treated with various amounts of IFN-α (0–2000 units/ml) for 18 h. VSV (200 pfu/ml) was then added. 36 h after infection, viable cells were measured by the methylthiotetrazole assay to determine the cytopathic effect of VSV. Relative numbers of viable cells were measured by optical density (O.D.) at 540 nm. C, same as B, except that IFN-γ (0–20 ng/ml) was used. □, HeLa-Hyg; ◇, HeLa-SOCS1; ○, HeLa-SOCS2; △, HeLa-SOCS3.
Jak(s) may not prevent the activation of Jak(s) due to the structure of SOCS2. If the latter model is true, SOCS2 should function as a dominant negative inhibitor of SOCS1 or SOCS3. However, our preliminary results suggest that SOCS2 does not affect the inhibitory activity of SOCS1 toward the activation of STAT1 when SOCS1 and SOCS2 are coexpressed. Thus, SOCS2 does not inhibit IFN-, IL-6-, or OM-induced Jak/STAT signaling pathways because of the lack of interaction with Jaks. Interestingly, SOCS2 expression enhanced the antiproiferative activity of IFNs when low concentrations of IFNs were used (Fig. 6). A similar stimulatory effect of SOCS2 on growth hormone-induced gene activation was reported previously (22). The molecular basis for the observed stimulatory effect of SOCS2 is not clear.

We showed in this study that SOCS2 failed to inhibit IFN-, IL-6-, and OM-induced Jak/STAT signaling. Our results are in accord with the previous report that SOCS2 failed to inhibit growth hormone-mediated gene activation (22). Interestingly, it was reported that SOCS2 could inhibit the activation of STAT3 in response to leukemia inhibitory factor in mouse myeloid leukemia M1 cells (23). The discrepancy regarding the ability of SOCS2 to inhibit Jak/STAT signaling pathways is not understood.

Recently, 20 proteins containing a conserved C-terminal SOCS box have been identified (26). It is not known whether other members of the SOCS family can function as inhibitors in cytokine signaling. Although the molecular mechanism of how SOCS proteins may function is not clear, it appears that SOCS proteins can target molecules other than Jaks. Cytokine-inducible SH2-containing protein, the first member of this family, was found to be associated with tyrosine phosphorylated erythropoietin or IL-3 receptors (18). SOCS1 has been shown to bind to and suppress Tec tyrosine kinase (27). It is likely that SOCS proteins may also function in other signaling pathways.

The specificity of SOCS-mediated inhibition of cytokine signaling is poorly understood. Recently, it was reported that leptin induced SOCS3 but not SOCS1 or SOCS2 mRNA in the hypothalamus (28). It was suggested that SOCS3 is the sole protein in the SOCS family that functions as an inhibitor of leptin signaling. Thus, the specificity of the SOCS-mediated inhibitory effect on cytokine signaling can be achieved in part by the pattern of SOCS protein induction in response to cytokine stimulation.

Recently, the PIAS (protein inhibitor of activated STATs) family of proteins has been shown to specifically inhibit STAT signaling (29, 30). Unlike SOCS proteins, which interact with Jaks, PIAS proteins are directly associated with STATs. Thus, the Jak/STAT signaling pathways can be negatively regulated by distinct proteins at different steps.

2. M. M. Song and K. Shuai, unpublished data.

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