SOCS3 Exerts Its Inhibitory Function on Interleukin-6 Signal Transduction through the SHP2 Recruitment Site of gp130*

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Interleukin-6 is involved in the regulation of many biological activities such as gene expression, cell proliferation, and differentiation. The control of the termination of cytokine signaling is as important as the regulation of initiation of signal transduction pathways. Three families of proteins involved in the down-regulation of cytokine signaling have been described recently: (i) SH2 domain-containing protein-tyrosine phosphatases (SHP), (ii) suppressors of cytokine signaling (SOCS), and (iii) protein inhibitors of activated STATs (PIAS). We have analyzed the interplay of two inhibitors in the signal transduction pathway of interleukin-6 and demonstrate that the tyrosine phosphatase SHP2 and SOCS3 do not act independently but are functionally linked. The activation of one inhibitor modulates the activity of the other; Inhibition of SHP2 activation leads to increased SOCS3-mRNA levels, whereas increased expression of SOCS3 results in a reduction of SHP2 phosphorylation after activation of the interleukin-6 signal transduction pathway. Furthermore, we show that tyrosine 759 in gp130 is essential for both SHP2 and SOCS3 but not for SOCS1 to exert their inhibitory activities on interleukin-6 signal transduction. Besides SHP2, SOCS3 also interacts with the Tyr(P)-759 peptide of gp130. Taken together, our results suggest differences in the function of SOCS1 and SOCS3 and a link between SHP2 and SOCS3.

Interleukin-6 exerts its biological activities through a receptor complex composed of the IL-6-binding subunit gp80 and a dimer of the signal transducing receptor subunit gp130 (for review see Ref. 1). After ligand binding and gp130 dimer formation, constitutively associated kinases of the Janus family Jak1, Jak2, and tyrosine kinase 2 become activated by auto-phosphorylation. gp130, subsequently tyrosine phosphorylated on its cytoplasmic tail, recruits the transcription factors of the family of signal transducers and activators of transcription (STAT1 and STAT3) (2, 3) and the protein-tyrosine phosphatase SHP2 (4) via specific phosphotyrosine-SH2 domain interactions (5, 6). In turn, these signaling components become tyrosine-phosphorylated also. Jak1 has been described to be crucial for the activation of gp130, the STAT factors (7), and SHP2 (8). The tyrosine-phosphorylated STATs form homo- and/or heterodimers (9) and translocate to the nucleus where they bind to enhancer elements of interleukin-6 inducible genes (10).

The Jak/STAT signal transduction pathway is under negative control by several different mechanisms. The presence of a nuclear phosphatase leading to dephosphorylation of activated STAT1 has been proposed by Haspel et al. (11). These authors observed a quantitative recycling of dephosphorylated STAT1 from the nucleus to the cytoplasm implicating a circulation of STAT factors between the cytoplasm and the nucleus. These data contradict those of Kim and Maniatis (12) who demonstrated a proteasome-dependent loss of activated STAT1 in the nucleus. Recently, another group of IL-6 signaling inhibitors has been described, STAT-binding proteins, known as protein inhibitors of activated STATs (PIAS) (13, 14). Although the PIAS do not contain phosphotyrosine binding domains such as SH2 or PTB domains, they associate with activated, tyrosine-phosphorylated STATs, leading to a loss of STAT-DNA binding activity. The mechanism of this highly specific interaction of protein inhibitor of activated STATs with activated STAT factors remains to be elucidated. Another new family of inhibitors of cytokine signaling has been discovered in three different laboratories, recently. These proteins are referred to as suppressors of cytokine signaling (SOCS) (15), Jak-binding proteins (16), or STAT-induced STAT inhibitors (17). The members of this family contain a central SH2 domain as well as a carboxyl-terminal domain called the SOCS box. Depending on the cell type examined, SOCS1, SOCS2, and SOCS3 expression was found to be rapidly induced by IL-6. Because the SOCS proteins inhibit the IL-6-induced phosphorylation of Janus kinases, gp130 and STAT factors, they are regarded as feedback inhibitors of IL-6 signaling. SOCS1 inhibits the kinase activity of the three Janus kinases Jak1, Jak2, and tyrosine kinase 2 involved in IL-6 signaling (15–17). Recently, it has been described that SOCS1 binds to phosphotyrosine 1007 within the kinase domain of activated Jak2 (18). Also, the protein-tyrosine phosphatase SHP2 was found to inhibit IL-6 signal transduction. Activation of the IL-6 receptor complex leads to a recruitment of SHP2 to tyrosine 759 in gp130 and to its subsequent tyrosine phosphorylation (4). SHP2 activation is a crucial event for the induction of the mitogen-activated protein kinase (MAPK) pathway upon IL-6 stimulation (19). Mutation of Tyr-759 in gp130 results in an enhanced and prolonged STAT1 and STAT3 activation and in an increased gene induction (8, 20, 21).

Because SOCS3 is induced by IL-6 (15–17) and SHP2 is simultaneously activated (4), we asked whether these proteins...
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Influence each other in respect to expression (SOCS3) or tyrosine phosphorylation (SHP2). We observed that an inhibition of SHP2 activation led to an enhanced induction of SOCS3 mRNA. On the other hand the expression of the SOCS3 protein decreased the level of tyrosine-phosphorylated SHP2 after IL-6 stimulation. Furthermore, we found that SOCS3, but not SOCS1, requires the SHP2 recruitment site in gp130 to exert its negative function on the IL-6 signal transduction pathway. Finally, it is demonstrated in the present study that both SHP2 and SOCS3 interact with a phosphotyrosine peptide containing the Tyr-759 motif of gp130. Although we demonstrate an SHP2-SOCS3 protein-protein interaction, we were also able to show that binding of SOCS3 to Tyr-759 of gp130 does not depend on the presence of SHP2.

Experimental Procedures

Materials—Restriction enzymes were purchased from Roche Molecular Biochemicals and AGS (Heidelberg, Germany), and oligonucleotides were synthesized by MWG-Biotech (Ebersberg, Germany). Vent polymerase was obtained from New England Biolabs (Beverly, MA). Recombinant p53 was a gift of Dr. B. Birken and K. H. Selliger of Roche Molecular Biochemicals. Peptides were kindly provided by Dr. J. Schneider-Mergener, JERINI (Berlin, Germany). The peptides used had the following amino acid sequences Tyr(P)-683, biotin-β-ASNKDQMPYSIDGNTFD; Tyr-759, biotin-β-ASTTSTQQVYSTVHS; Tyr(P)-759, biotin-β-ASTTSTQQVYSTVHS; Tyr(P)-767, biotin-β-ATVHSQGpYRHQVPS; Tyr(P)-814, biotin-β-ALPRQQYGFKQNCQG; Tyr(P)-905, biotin-β-EGMPKSpYLPQTVRQ, and Tyr(P)-915 biotin-β-APTQVRGpYMPQ. Antibodies to gp130 (B-P4) were gifts from Dr. J. Wijdenes (Besançon, France). Antibodies to the Tyr-759 biotin-EG(YYYY) fusion protein. Cells were lysed by sonication, and purification was accomplished by precipitation with 2.5 M of biotinylated peptides at 4 °C overnight and precipitated with 2 μM of biotinylated peptides at 4 °C overnight and precipitated with 2.5 mg of protein A-Sepharose (Amersham Pharmacia Biotech) or NeutrAvidine-coupled agarose (Pierce), respectively. Immune complexes were analyzed by SDS-polyacrylamide gel electrophoresis and transferred to a polyvinylfluoride membrane. Antibodies were detected by incubation with the appropriate primary antibodies (4G10, 1:1000; anti-SHPI, 1:1000; anti Flag2-biotin, 1:500; anti-GST, 1:1000) and horseradish peroxidase-coupled secondary antibodies (1:2000) (Dako, Hamburg, Germany) or horseradish peroxidase-coupled streptavidine (1:5000) (Pierce). The membranes were developed with an enhanced chemoluminescence kit (Amersham Pharmacia Biotech). To verify application of equal amounts of protein, blots were stripped and reprobed.

Expression of Glutathione S-transferase Fusion Proteins—The expression GST-SOCS3 (23–151) was performed in Escherichia coli (BL21). Bacteria were grown at 37 °C in LB medium with ampicillin to an A600 of 1.2 and treated with isoprropyl-1-thio-β-D-galactopyranoside (1 mM) for 5 h at 26 °C to induce expression to the GST-SOCS3 (23–151) fusion protein. Cells were lysed by sonication, and purification was performed according to the manufacturer’s instructions (Amersham Pharmacia Biotech).

Results

SOCS1 and SOCS3 but Not SOCS2 or CIS Are Potent Inhibitors of Acute Phase Protein Induction by Interleukin-6—To find out which of the IL-6-induced SOCS proteins interfere with the IL-6-stimulated induction of acute phase protein (APP) synthesis in liver cells, we tested whether SOCS1, SOCS2, SOCS3, or CIS expression affects APP gene promoter induction in human HepG2 hepatoma cells (Fig. 1). The respective SOCS or CIS cDNAs were cotransfected together with a reporter gene construct harboring the promoter of the a2-macroglobulin gene linked to the luciferase reporter gene (PGL3cm2-215Luc) and an expression vector for a chimeric receptor containing the extracellular domain of the EpoR and the cytokine receptor domain of gp130 (EG(YYYYY)), which allowed us to study the IL-6 signal transduction pathway independently from endogenous gp130 (25). Stimulation with erythropoietin led to a 20-fold induction of the reporter gene in the transiently transfected cells expressing the chimeric receptor in the absence of SOCS/CIS. Coexpression of SOCS1 or SOCS3 led to a dramatic reduction in
APP gene promoter induction. Even the background level of reporter gene expression was reduced indicating that SOCS1 and SOCS3 also influence basal transcription in unstimulated cells. In contrast, SOCS2 and CIS had only moderate effects. Thus, SOCS1 and SOCS3 but neither SOCS2 nor CIS are potent inhibitors for acute phase protein gene induction by interleukin-6.

Lack of SHP2 Activation Leads to an Enhanced SOCS3 Expression—SHP2 counteracts the IL-6-induced acute phase protein gene induction (8, 20, 25). To study the interplay of the IL-6 signal transduction inhibitors SOCS1, SOCS3, and SHP2, we asked whether SHP2 might also negatively regulate the IL-6-induced expression of SOCS1 and SOCS3 (Fig. 2, A and B). Therefore, IL-6-dependent Ba/F3 cells, which do not express endogenous gp130 (29), were stably transfected with gp130 receptor mutant cDNAs. Receptor surface expression of the transfected Ba/F3 cells was monitored by fluorescence-activated cell sorter analysis with an antibody raised against the extracellular domain of gp130 (29). Stimulation of cells expressing the wild type receptor gp130(YYYYYY) led to a rapid induction of SOCS3 mRNA as determined in Northern blot analysis (Fig. 2A). The data were normalized to glyceraldehyde-3-phosphate dehydrogenase-mRNA levels (Fig. 2B). There was no detectable induction of SOCS1 mRNA in Ba/F3 cells (data not shown). Stimulation of cells carrying a mutation of the SHP2 recruitment site in gp130 by a substitution of Tyr-759 to Phe (gp130(YFFFF)) resulted in increased SOCS3 mRNA levels compared with the wild type receptor. The single tyrosine 759 in the cytoplasmic part of gp130 (gp130(FYYYY)) was not sufficient to mediate induction of the SOCS3 gene. These observations indicate that SHP2 activation counteracts SOCS3 gene expression.

SOCS3 Acts via Tyr-759 of gp130 on the IL-6 Signal Transduction complexes was analyzed by Western blotting (Fig. 3). Coexpression of SOCS3 led to a reduced SHP2 phosphorylation compared with cells not transfected with SOCS3-cDNA. We conclude from these data that SOCS3 also regulates signaling components, which themselves are negative regulators of the
IL-6 signal transduction pathway.

SOCS3 but Not SOCS1 Requires the SHP2 Recruitment Site in gp130 to Exert Its Inhibitory Activity on Acute Phase Protein Gene Induction—SOCS1 interacts with the kinase domain of activated Jak2 (16, 18, 30). On the other hand, only a weak association of Jak2 with SOCS3 has been described by Suzuki et al. (31). Unlike SOCS1, SOCS3 does not inhibit Jak kinase activity in vitro (30). To learn more about the mechanism of action of SOCS3, we tested whether SOCS3 activity depends on the activation of SHP2 and examined the potential of SOCS1 and SOCS3 to inhibit acute phase protein gene induction in the presence or absence of tyrosine 759 in gp130. Therefore, chimeric EpoR/gp130 wild type or mutant receptors were expressed in HepG2 cells together with or without SOCS1/ SOCS3. Reporter gene assays similar to those described above were performed (Fig. 4). Mutation of Tyr-759 in gp130 to Phe led to an enhanced APP promoter/reporter gene induction as expected from previously described experiments (8) (compare YYYYYY with YYYYFY). Both the expression of SOCS1 (Fig. 4A, left part) or SOCS3 (Fig. 4B, left part) led to reduced levels of the reporter luciferase activity upon stimulation of the wild type receptor EG/YYYYYY. Interestingly, unlike SOCS1, SOCS3 was unable to reduce APP gene promoter induction in the absence of Tyr-759 (EG/YYYYFF) (Fig. 4B, right part). Rather a slightly enhanced luciferase activity was measured after expression of SOCS3. Thus, SOCS3 but not SOCS1 requires the SHP2 recruitment site, i.e. Tyr-759 in gp130 to exert its inhibitory effect on acute phase protein gene induction.

The Inhibitory Effect of SOCS3 on STAT3 Activation Is Mediated by Tyrosine 759 in gp130—To further confirm the requirement of Tyr-759 in gp130 for SOCS3 action, we asked whether the SOCS3-mediated reduction of STAT1/STAT3 activation (15–17, 30) depends on Tyr-759 in gp130. Therefore, COS7 cells were transfected with wild type EG/YYYYYY or mutant EG/YYYYFY chimeric receptor-cDNAs together with increasing amounts of SOCS3-cDNA. STAT tyrosine phosphorylation in Western blots (Fig. 5A and B) and DNA binding activity in electrophoretic mobility shift assays (Fig. 5C) were analyzed after receptor stimulation. In these assays, SOCS3 turned out to be more potent in counteracting STAT3 (Fig. 5A) and STAT1 (Fig. 5B) phosphorylation in the presence of YYYYFY) than in the absence (YYYYYY) of Tyr-759 in the cytoplasmic part of gp130. Similar results were obtained with electrophoretic mobility shift assays (Fig. 5C), STAT activation upon stimulation of the wild type cytoplasmic part of gp130 is quite sensitive to SOCS3 expression. In contrast, STAT activation through the YYYYFY receptor mutant was significantly less sensitive to SOCS3 cotransfection. However, transfection of large amounts of SOCS3-cDNA also led to a reduced STAT activation in erythropoietin-stimulated cells expressing the Y759F receptor mutant, probably mediated by a receptor-independent mechanism. For comparison, similar experiments were performed in the presence of SOCS1. Again, increasing amounts of SOCS1-cDNA led to a reduction of STAT3 and STAT1 tyrosine phosphorylation (Fig. 5D). STAT activation (Fig. 5E) and DNA binding activity (Fig. 5F) after stimulation. The potential of SOCS1 to inhibit STAT activation was not affected by a mutation of tyrosine 759 in gp130. From these observations we conclude that the efficient inhibition of STAT1 and STAT3 activation by SOCS3, but not by SOCS1, requires Tyr-759 in gp130.

SOCS3 Binds to SHP2—Because the inhibitory activities of both SHP2 and SOCS3 depend on Tyr-759 in gp130, it was interesting to examine whether SOCS3 interacts with SHP2. For this purpose SHP2 was immunoprecipitated from cellular extracts of COS7 cells transfected with SOCS3-cDNA. Co precipitation of SOCS3 shows the interaction of SHP2 with SOCS3 (Fig. 6, right lane). When the reverse precipitation was performed with antibodies to the Flag-tag of SOCS3 only a very faint band of co-precipitated SHP2 was observed after long exposure times (data not shown). It is likely that the antibody used for the precipitation of SOCS3 interferes with the SOCS3/SHP2 complex formation.

SOCS3 but Not SOCS1 Binds to the Phosphotyrosine Peptides Corresponding to Tyr-759 in gp130—Because SOCS3 con-
FIG. 5. The inhibitory effect of SOCS3 on STAT activation is mediated via tyrosine 759 in gp130. COS7 cells were transfected with 5 μg of pSVL-EG(YYYYY) or pSVL-EG(YFYYYY) and the indicated amount of the SOCS3 encoding expression vector pEF-Flag-I/mSOCS3. The cells were stimulated with 7 units/ml erythropoietin for 15 min as indicated, and nuclear extracts were prepared. Equal amounts of nuclear
transfected with an expression vector for SOCS3 (20 μg), or SHP2 (right lane) antibodies. The precipitates were subjected to SDS-polyacrylamide gel electrophoresis and analyzed for SHP2 and SOCS3 by Western blotting (IB).

SHP2 and SOCS3 by Western blotting (IB). The precipitates were analyzed without antibodies (left lane), with Flag (middle lane), or SHP2 (right lane) antibodies. The amounts of SHP2 and SOCS3 in the SHP2-depleted extract were estimated by a second immunoprecipitation with antibodies against SHP2 (lane 12) and against the Flag-tag of SOCS3 (lane 11) demonstrating the lack of SHP2 and the presence of SOCS3 in the SHP2-depleted extract. Finally, this SHP2-depleted extract was used for the precipitation with the phosphotyrosine peptide 759 of gp130 (lane 13). It is concluded from this experiment that SHP2 is not required for SOCS3 binding to the Tyr(P)-759 peptide. Binding of an SH2-Domain-containing SOCS3 Fragment to the Tyr(P)-759 Peptide of gp130—The specific binding of SOCS3 to the phosphotyrosine peptide Tyr(P)-759 implicates that this interaction is because of the SOCS3-SH2 domain. To examine this interaction in more detail, we expressed a GST-SOCS3 fusion protein comprising the amino acids 23–155 of SOCS3 (GST-SOCS3(23–151)) in E. coli. From structural predictions this part of SOCS3 has been suggested to contain the extended SH2 domain (15–18). The purified fusion protein was incubated with biotin-conjugated peptides corresponding to the Tyr(P)-759 motif of gp130 in phosphorylated or unphosphorylated form. The peptide precipitates were analyzed for GST-SOCS3(23–151) by Western blotting using a GST-specific antibody (Fig. 9). A strong binding of the fusion protein was only observed with the tyrosine-phosphorylated peptide Tyr(P)-759.

**DISCUSSION**

SHP2, SOCS1, and SOCS3 are regulators of cytokine signaling (8, 15–17, 20, 21). In the present study, we have focused on the interplay of these proteins in IL-6 signal transduction. We describe for the first time a physical and functional link between SHP2 and SOCS3 and differences in the mode of action of SOCS1 and SOCS3. The inhibitory action of SHP2 on the IL-6 signal transduction pathway depends on Tyr-759 in gp130 (8, 20, 21). Surprisingly, we found that the presence of Tyr-759 in gp130 is also crucial for the inhibitory function of SOCS3 (Figs. 4 and 5). An exchange of Tyr-759 by Phe impairs the inhibitory activity of SOCS3 on both STAT1 and STAT3 activation (Fig. 5) as well as on acute phase protein gene promoter induction (Fig. 4). The function of SOCS1, however, is not affected by this point mutation in gp130, demonstrating the specific requirement of Tyr-759 for SOCS3 activity. The simplest explanation for this finding is that the inhibitory activity of SOCS3 depends on the interaction of its SH2 domain with Tyr(P)-759 in the receptor protein. Indeed, we were able to demonstrate that SOCS3, but not SOCS1, specifically associates with the phosphopeptide Tyr(P)-759 of gp130. Interestingly, SHP2 also binds to this peptide (Fig. 7). The interaction of SOCS3 with the cytoplasmic tail of gp130 could be direct or via other proteins. We have presented evidence for the existence of SHP2-SOCS3 complexes (Fig. 6), which could reflect an adaptor function of SHP2 for SOCS3. Therefore, we tested whether SOCS3 binds directly or through SHP2 to the Tyr(P)-
The depletion of SHP2 did not impair SOCS3 binding to the Tyr(P)-759 receptor peptide (Fig. 8). Furthermore, we were able to demonstrate that the recombinant GST-SOCS3-(23–151) fusion protein containing the SOCS3-SH2 domain binds to phosphotyrosine Tyr(P)-759 of gp130 (Fig. 9). These results show that SHP2 is not required for binding of SOCS3 to the gp130 receptor motif.

In previous reports it has been described that SHP2 inhibits IL-6-induced acute phase protein gene promoter activation by down-regulation of STAT phosphorylation (8, 20, 21). In the present paper we have shown that SOCS1 and SOCS3, but neither SOCS2 nor CIS, are potent inhibitors of APP gene promoter induction (Fig. 1). This observation is consistent with data of Nicholson et al. (30) who described a powerful inhibitory activity of SOCS1 and SOCS3 on leukemia inhibitory factor (LIF) signaling.

SOCS1 and SOCS3 exhibit similar effects on STAT3 phosphorylation and APP gene induction (18, 30). It has been shown by several investigators that SOCS1 and SOCS3 bind to the kinase domain of activated Jak1 and Jak2 (18, 30, 32). An attractive model for Jak inhibition by SOCS1 suggests that the kinase activation loop of Jak2 interacts with the SH2 domain of SOCS1. This allows SOCS to present its kinase inhibitory region, which is quite homologous to the kinase activation loop, to the pocket in the activation site, which in turn might prevent the access of substrates and/or ATP (18).

However, SOCS1 and SOCS3 seem to exert their feedback inhibitory action on the Jak/STAT pathway by different mechanisms as indicated by our results and the observation that SOCS1, but not SOCS3, inhibits Jak autophosphorylation in an in vitro kinase assay (18, 30). In contrast, Sasaki et al. (32) did not find these differences but a higher affinity of SOCS1 than SOCS3 to bind Jak2. Furthermore, the kinase inhibitory region of SOCS3 was more potent in inhibiting of Jak2 than the kinase inhibitory region of SOCS1 (32).

The novel aspect of the data presented in this paper is the fact that SOCS3, in contrast to SOCS1, has to be recruited to the receptor complex to inhibit IL-6 signal transduction. Thus, the inhibition of IL-6 signaling by SOCS3 could be because of different mechanisms. First, SOCS3 could inhibit Jak activity...
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via binding of the SOCS3-SH2 domain to the activation loop of the kinase. Second, SOCS3 could be recruited to gp130, directly to Tyr(P)-759 or by binding to the receptor-associated SHP2, leading to the inhibition of Jaks through the kinase inhibition region of SOCS3, which is in line with the observation of Sasaki et al. (32).

Because SOCS3 gene expression is induced by IL-6 and because SOCS3 inhibits IL-6-signal transduction, SOCS3 functions as a feedback inhibitor (15–17). We did not observe a significant SOCS1-mRNA induction after stimulation with IL-6-sIL-6R complexes (Fig. 2). However, this does not exclude that SOCS1 also influences IL-6 signaling when induced via another pathway. It has been proposed that SHP2 phosphorylation results in an increase in enzymatic (phosphotyrosine phosphatase) activity (33), which in turn might also negatively influence signal transduction by dephosphorylating signaling components. Interestingly, an impaired SHP2 activation by the mutation of Tyr-759 in the gp130 receptor correlates with an enhanced SOCS3 gene induction (Fig. 2). Furthermore, SOCS3 itself can not act on this receptor mutant as an inhibitor of its own expression. Thus, a reduction in SHP2 activation might be compensated by an increase in SOCS3 expression. On the other hand, an enhanced SOCS3 expression leads to a reduced level of SHP2 phosphorylation (Fig. 3). This might be because of the inhibition of Jaks by SOCS3 or by direct competition of SHP2 and SOCS3 for Tyr(P)-759 of gp130. Therefore, an enhanced expression of SOCS3 might be compensated by a reduced level of phosphorylated SHP2. Further experiments are required to show whether tyrosine phosphorylation of SHP2 modulates SOCS3 activity. It is not yet clear which tyrosine residue(s) in SHP2 are phosphorylated after stimulation of the IL-6-signal transduction pathway.

The MAPK activator phorbol 12-myristate 13-acetate has recently been shown to inhibit the Jak/STAT pathway (34, 35). Work from our laboratory (36) demonstrates that the inhibitory function of MAPK on IL-6-signal transduction also depends on the presence of Tyr-759 in gp130. Mutation of Tyr-759 in gp130 to Phe abolishes the potential of phorbol 12-myristate 13-acetate to inhibit IL-6-induced STAT activation. Because phorbol 12-myristate 13-acetate also induces SOCS3 gene transcription, it is very likely that phorbol 12-myristate 13-acetate exerts its action via SOCS3 whose activity also depends on Tyr(P)-759 in gp130 as described in the present report.

It is intriguing to assume that SHP2 exerts at least part of its negative regulatory function on the Jak/STAT pathway through the recruitment of SOCS3 to the activated receptor complex. To test this idea, experiments are presently in progress.

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