Cytosolic Tyrosine Dephosphorylation of STAT5
POTENTIAL ROLE OF SHP-2 IN STAT5 REGULATION*

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STAT5, a member of the signal transducers and activators of transcription (STATs), is important in modulating T cell functions through interleukin-2 (IL-2) receptors. Like other STAT proteins, STAT5 undergoes a rapid activation and inactivation cycle upon cytokine stimulation. Tyrosine phosphorylation and dephosphorylation are critical in regulating STAT5 activity. A number of protein tyrosine kinases have been shown to phosphorylate STAT5; however, the phosphatases responsible for STAT5 dephosphorylation remain unidentified. Using CTLL-2 as a model system, we provide evidence that tyrosine dephosphorylation of STAT5 subsequent to IL-2-induced phosphorylation occurs in the absence of STAT5 nuclear translocation and new protein synthesis. Nevertheless, down-regulation of the upstream Janus kinase activity during the deactivation cycle of IL-2-induced signaling does involve new protein synthesis. These findings point to the constitutive presence of STAT5 tyrosine phosphatase activity in the cytosolic compartment. We further demonstrate that SHP-2, but not SHP-1, directly dephosphorylates STAT5 in an in vitro tyrosine phosphatase assay with purified proteins. Furthermore, tyrosine-phosphorylated STAT5 associates with the substrate-trapping mutant (Cys→Ser) of SHP-2 but not SHP-1. These results suggest a potential role for cytoplasmic protein-tyrosine phosphatases in directly dephosphorylating STAT5 proteins and in maintaining a basal steady state level of STAT activity.

Signal transducers and activators of transcription (STATs)
are latent cytoplasmic transcription factors that, upon activation by tyrosine phosphorylation, dimerize, translocate to the nucleus and bind to specific regulatory elements that control gene expression (1–4). STAT5, a STAT family member, was first characterized as a mammary gland transcription factor (18–20). (iv) STAT5 activity may also be attenuated through direct interaction with other cellular proteins (22, 23). (v) In some early hematopoietic progenitors, nuclear protease activity can cleave full-length STAT5 to generate carboxyl-truncated STAT5 isoforms, which may function as dominant-negative proteins (22, 23).

The transient kinetics of STAT5 tyrosine phosphorylation following cytokine stimulation (15) strongly suggests tyrosine dephosphorylation as a critical mechanism in down-regulating STAT5 activity. In contrast to protein-tyrosine kinases phosphorylating STAT5, the subcellular localization and the identity of protein-tyrosine phosphatase(s) in dephosphorylating STAT5, as well as other STAT proteins, remain largely unknown. In this report, we examine STAT5 regulation in response to IL-2 using an IL-2-dependent CTLL-20 cell line as a model system. By blocking nuclear transport, we are able to specifically analyze the regulation of cytoplasmic STAT5 proteins. Furthermore, we establish an in vitro system to characterize potential STAT5 protein-tyrosine phosphatases.

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‡ The abbreviations used are: STAT, signal transducer and activator of transcription; IL, interleukin; Jak, Janus kinase; GST, glutathione S-transferase; GTPyS, guanosine 5′-3-O-(thio)triphosphate.
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**RESULTS**

**STAT5 Tyrosine Dephosphorylation in the Absence of Nuclear Translocation**—To determine the time course of the IL-2-induced STAT5 activation and inactivation cycle, IL-2-deprived CTLL-20 cells were stimulated with IL-2 for 5 min, 15 min, 30 min, and 1 h. As shown in Fig. 1, IL-2 induced rapid tyrosine phosphorylation of cytosolic STAT5 within 5 min, and the levels of tyrosine phosphorylation returned to base line after 1 h. Like other cytokine-mediated STAT activation (27), however, IL-2 also induced rapid and transient nuclear translocation of STAT5 (data not shown; also see Fig. 2B). Therefore, to address the possibility that STAT5 may be dephosphorylated in the cytoplasm, we decided to specifically examine the regulation of cytoplasmic STAT5 by blocking STAT5 nuclear translocation.

It is known that GTP hydrolysis is essential for active nuclear import of macromolecules (28). Indeed, we observed that pretreatment with the nonhydrolyzable GTP analog, GTPγS, blocked STAT5 nuclear translocation upon stimulation of CTLL-20 cells with IL-2 for 15 min to 1 h (Fig. 2B, compare lanes 2 and 3–5). Therefore, GTPγS blocks STAT5 nuclear import instead of simply delaying the time course of STAT5 nuclear translocation. Nevertheless, IL-2-induced STAT5 tyrosine phosphorylation and, most importantly, the subsequent dephosphorylation of STAT5 occurred without nuclear translocation (Fig. 2A). For controls, cytosolic and nuclear fractions prepared from cells with or without permeabilization and GTPγS treatment were analyzed by immunoblotting for Eps15, a cytosolic marker, and Sp1, a nuclear marker (29). As shown in Fig. 2, C and D, there was very little cross-contamination from either fraction, indicating that the nuclear membranes were still intact after permeabilization. These results suggest that nuclear translocation is not a prerequisite for STAT5 tyrosine dephosphorylation. They also point to the existence of a cytosolic protein-tyrosine phosphatase(s) capable of dephosphorylating STAT5.

**STAT5 Tyrosine Dephosphorylation Does Not Require New Protein Synthesis in the Presence of Protein Kinase Inhibitors**—Mitogen-induced expression of protein phosphatase has been shown to function as a negative feedback control mechanism (30). To determine if STAT5 tyrosine phosphatase activity needs to be induced by cytokines, we examined the kinetics of...
IL-2-induced STAT5 tyrosine phosphorylation and subsequent dephosphorylation in the absence of new protein synthesis and continuous kinase activity. IL-2-deprived CTLL-20 cells were first pretreated with cycloheximide to block new protein synthesis (Fig. 3A). Cells were either left unstimulated (lane 1) or stimulated with IL-2 for 15 min to accumulate a pool of tyrosine-phosphorylated STAT5 (lane 2). Genistein, staurosporine, or Me₂SO carrier control were then added to block further kinase activity that would phosphorylate STAT5 on tyrosine residues. Without protein kinase inhibitors, IL-2-induced STAT5 tyrosine phosphorylation was sustained in CTLL-20 pretreated with cycloheximide (lanes 3-6). In contrast, in the presence of genistein (lanes 7-10) or staurosporine (lanes 11-14), STAT5 was rapidly tyrosine-dephosphorylated.

To further confirm the presence of protein-tyrosine phosphatase activity in cycloheximide-treated cells, pervanadate was used to inhibit phosphatase activity before IL-2 stimulation of CTLL-20 cells. As shown in Fig. 3B, IL-2-induced tyrosine phosphorylation of STAT5 was sustained without continuous kinase and phosphatase activities (lanes 3-6). These results suggest that STAT5 tyrosine phosphatase(s) is constitutively present, and the steady state level of STAT5 tyrosine phosphorylation is predominantly determined by the upstream kinase activity. Therefore, the negative feedback control mechanisms regulating STAT activity are directed mostly at preventing further STAT phosphorylation, as described in other studies (18–20).

Down-regulation of Jak Kinases Subsequent to IL-2-induced Activation Involves New Protein Synthesis—In response to IL-2 stimulation, Jak1 and Jak3 are the two major protein-tyrosine kinases in phosphorylating STAT5 proteins (15). To address the possibility that Jak1 and Jak3 contribute to sustained IL-2-induced STAT5 phosphorylation in the presence of cycloheximide (Fig. 3A, lanes 2–6), we examined the kinetics of IL-2-induced tyrosine phosphorylation of Jak1 and Jak3. As described previously, Jak1 and Jak3 are rapidly and transiently phosphorylated on tyrosines upon IL-2 stimulation (Fig. 4, panels A and B, respectively, lanes 1–7). In the absence of new protein synthesis, however, IL-2-induced tyrosine phosphorylation of Jak1 and Jak3 was prolonged (Fig. 4, panels A and B, respectively, lanes 8–14). This is consistent with the reported negative feedback control mechanisms in down-modulating Jak kinase activity (19). Furthermore, these results suggest that, upon IL-2 stimulation of cycloheximide-pretreated cells, sustained elevation of Jak kinase activity is involved in maintaining a high steady state level of STAT5 tyrosine phosphorylation.

Tyrosine Dephosphorylation of Cytosolic STAT5 in Vitro—To further identify the cytosolic STAT5 tyrosine phosphatase, we analyzed tyrosine dephosphorylation of STAT5 within a purified cytoplasmic fraction in vitro. Consistent with the existence of constitutive STAT5 tyrosine phosphatase activity in the cytoplasm, Fig. 5 demonstrates that tyrosine-phosphorylated STAT5 in the cytosolic fraction prepared from IL-2-stimulated CTLL-20 could be dephosphorylated in vitro in the absence of nuclei. Sodium orthovanadate completely inhibited STAT5 tyrosine dephosphorylation (compare lanes 5 and 6), confirming the involvement of protein-tyrosine phosphatases. No further enhancement of STAT5 tyrosine phosphorylation was observed in the presence of sodium orthovanadate (compare lanes 1 and 6), suggesting that protein-tyrosine kinases capable of phosphorylating STAT5 were not active under these conditions. Not only soluble STAT5, but STAT5 immunoprecipitates on protein A-Sepharose could also be tyrosine dephosphorylated when mixed with cytosol prepared from CTLL-20 or other T cell lines, although to a lesser extent (data not shown). It is possible that the tyrosine residues on immunobilized STAT5 were not completely accessible to protein-tyrosine phosphatases.

Tyrosine-phosphorylated STAT5 Is a Direct Substrate of SHP-2—Cytosolic protein-tyrosine phosphatases SHP-1 and SHP-2 have both been implicated in the regulation of
Jak-STAT-signaling pathways (4). To determine if SHP-1 or
SHP-2 can directly dephosphorylate STAT5 on tyrosines,
STAT5 immunoprecipitates prepared from IL-2-stimulated
CTRL-20 were incubated with purified GST-SHP-1 or GST-
SHP-2 fusion proteins from 30 min to 2 h. As shown in Fig. 6A,
GST-SHP-2 dephosphorylated immobilized STAT5 within 30
min (lanes 7–10). In contrast, there was no detectable tyrosine
dephosphorylation of STAT5 immunoprecipitates by GST-
SHP-1 throughout the time course (lanes 3–6). As a control,
immobilized STAT5 did not undergo tyrosine dephosphoryl-
ation in the absence of exogenously added phosphatases, indi-
cating that no phosphatase activity was co-immunoprecipi-
tated with STAT5 (lane 2). Quantification of properly exposed
films, after normalization to the amount of STAT5 proteins,
revealed a 5-fold reduction on the levels of STAT5 tyrosine
phosphorylation by GST-SHP-2 as compared with buffer con-
trol and GST-SHP-1.

To determine whether SHP-2 can dephosphorylate the crit-
ical tyrosine residues of STAT5 proteins, an antibody against
STAT5 phosphorylated on Tyr-694/Tyr-699 was used in immu-
noblotting after the in vitro phosphatase assay. As shown in
Fig. 6B, dephosphorylation of Tyr-694/Tyr-699 by SHP-2 oc-
curred within 5 min. The observation that dephosphorylation
of Tyr-694/Tyr-699 by SHP-2 (Fig. 6B) was less than overall ty-
rosine dephosphorylation of STAT5 by SHP-2 (Fig. 6A) raises
the possibility that SHP-2 may dephosphorylate other tyrosine
residues of STAT5 proteins. The inability to completely dephos-
phorylate STAT5 under these conditions could be due to limited
accessibility of the tyrosine residues on immobilized STAT5 as
described above.

To confirm that GST-SHP-1 is functional, we examined its
phosphatase activity toward Lck, a known substrate of SHP-1
(31). Fig. 6C shows that GST-SHP-1 rapidly dephosphorylated
Lck immunoprecipitates prepared from LSTRA cells express-
ing high levels of tyrosine-phosphorylated Lck (13) (lane 3).
Tyrosine dephosphorylation of Lck by GST-SHP-2, on the other
hand, was much weaker (lane 4). As a control, there was no
phosphatase activity co-immunoprecipitated with Lck (lane 2).
Therefore, under the in vitro conditions described here, puri-
fied GST-SHP-1 and GST-SHP-2 preferentially dephosphoryl-
ate Lck and STAT5, respectively.

Substrate-trapping Mutant of SHP-2 Associates with Tyro-
sine-phosphorylated STAT5—We did not observe the associa-
tion of SHP-2 and STAT5 in IL-2-stimulated CTRL-20 cells (not
shown). This is consistent with the finding that no phosphatase
activity was co-immunoprecipitated with STAT5 from IL-2-
stimulated cells as described above. One possible explanation
is that this enzyme-substrate interaction is not stable. Therefore,
we used a substrate-trapping mutant (Cys → Ser) to stabilize
the interaction between SHP-2 and STAT5. As shown by glu-
thathione pull-down experiments (Fig. 7), a GST-SHP-2 sub-
strate-trapping mutant stably associated with tyrosine-phos-
phorylated STAT5 from IL-2-stimulated CTRL-20 cytosol
(compare lanes 2 and 5). Consistent with the inability of SHP-1
to dephosphorylate STAT5, there was no significant association
of the GST-SHP-1 substrate-trapping mutant (Cys → Ser) with
tyrosine-phosphorylated STAT5 (lane 6). As a control, GST
alone did not associate with STAT5 proteins (lanes 1 and 3).
These results further establish that STAT5 can be a direct
substrate of SHP-2.

**DISCUSSION**

Although the mechanisms whereby STAT proteins become
activated are being delineated, much less is known about their
subsequent nucleocytoplasmic trafficking and deactivation (4).
Nuclear transport of a large number of cellular proteins, in-
cluding transcription factors, involves the Ran/importin active
transport system (28). Active nuclear transport requires the
interaction between importin and nuclear localization se-
quences on the target protein and is mediated by the GTPase
activity of Ran. We show here that nuclear translocation of
STAT5 following IL-2 stimulation can be inhibited by a nonhy-
drolyzable GTP analog (Fig. 2). Consistent with our finding,
we observed that the involvement of Ran/importin in interfer-
ron-γ-dependent nuclear import of STAT1 (32, 33). It is,
therefore, very likely that nuclear translocation of other
STAT family members also requires GTP hydrolysis. However,
there is no discernible nuclear localization sequences found on
STAT proteins, and the precise mechanism underlying nuclear
import of STAT remains unclear (4).

Deactivation of tyrosine-phosphorylated nuclear STAT pro-
tiens involves both tyrosine dephosphorylation and nuclear
export back to the cytoplasm for a subsequent cycle of activa-
tion/inactivation (34). The concomitant tyrosine dephosphory-
lation and export of nuclear STAT proteins makes it very dif-
cult to determine their sequential order. Using chimeric STAT1
with the amino-terminal sequences from STAT2 or STAT5,
Strehlow and Schindler (35) showed a correlation between a
defect in nuclear translocation and prolonged activation of the
chimeric STAT proteins. However, a causal relationship cannot
be established because the chimeric STAT mutants are intrin-
sically deficient for tyrosine dephosphorylation. This is consis-
tent with the important role of the amino-terminal domain of
STAT1 in regulating its tyrosine dephosphorylation (36). In
contrast, by analyzing endogenous wild-type STATs both in
vitro (Fig. 2) and in vitro (Fig. 5), we clearly demonstrate the
existence of cytosolic protein-tyrosine phosphatases in dephos-
phorylating STAT5 and possibly other STAT family members.

Our results indicate that nuclear translocation of STAT5 is
not essential for its tyrosine dephosphorylation (Fig. 2). It
should be emphasized, however, that our data do not exclude
the possible role of a nuclear protein-tyrosine phosphatase in
STAT5 regulation. Cyttoplasmic and nuclear protein-tyrosine
phosphatases may cooperatively contribute to constitutive
STAT5 dephosphorylation in their respective subcellular com-
partments. Alternatively, protein-tyrosine phosphatases may
shuttle between cytoplasm and nucleus. It has been proposed
that nuclear translocation of STAT family members may in-
volve other cellular proteins, such as cytokine receptor com-
plexes, as chaperones (37). It is possible that cytosolic phospha-
tase translocates to the nucleus with the associated STAT
proteins (38). However, we have not been able to detect signif-

Among all known cytoplasmic protein-tyrosine phosphatases, SHP-1 and SHP-2 are widely implicated in modulating the Jak-STAT pathway. SHP-1 and SHP-2 have been shown to negatively (38) and positively (39, 40) regulate STAT5 activity, respectively. However, there are also reports demonstrating the opposite effects (41–43). Furthermore, because both SHP-1 and SHP-2 have been shown to modulate tyrosine phosphorylation of Jak kinases (4), which regulate downstream STAT proteins, it is difficult to evaluate the direct effects of SHP-1 and SHP-2 on STAT5. By using purified SHP-1 and SHP-2 proteins, we demonstrate here that SHP-2, but not SHP-1, directly dephosphorylates STAT5 in vitro. Additionally, our results indicate that there is substrate specificity for protein-tyrosine phosphatases, and our in vitro system can be used to identify other potential STAT5 tyrosine phosphatases.

Our finding that cycloheximide pretreatment stabilizes IL-2-induced STAT5 tyrosine phosphorylation (Fig. 3) supports the involvement of a negative feedback loop in down-regulating Jak-STAT signaling, such as the induction of Jak-binding protein or cytokine-inducible SH2-containing proteins (18–20). The inability to induce Jak-binding protein and cytokine-inducible SH2-containing protein expression could result in constitutive Jak kinase activity and continuous recruitment of STAT5 to the IL-2 receptor complex, where the constitutive Jak kinase resides. Consistent with this hypothesis, we observed prolonged IL-2-induced tyrosine phosphorylation of Jak1 and Jak3 in the presence of cycloheximide (Fig. 4). It is unlikely, however, that STAT5 tyrosine phosphatase is part of the negative feedback control because tyrosine dephosphorylation of STAT5 does not require new protein synthesis (Fig. 3). This is consistent with the constitutive presence of SHP-2 in the cells before or after cytokine stimulation (44).

Our data suggest that SHP-2 may be one of the protein-tyrosine phosphatases that contribute to constitutive dephosphorylation of cytosolic STAT5. Consistent with the constitutive presence of active phosphatases, previous studies have shown that pervanadate treatment alone could induce STAT activation in resting cells (45, 46). Following IL-2 stimulation, however, the highly induced kinase activity of Jak1 and Jak3 overcomes the phosphatase activity. This shift of balance results in the accumulation of tyrosine-phosphorylated STAT5, nuclear translocation, and regulation of gene expression. Subsequently, inhibition of Jak kinase activity through negative feedback control and other mechanisms allows the phosphatase activity to become predominant and reduce the steady state of STAT5 phosphorylation to basal level. The observation that STAT activity is controlled by the duration and intensity of upstream Jak kinase activity over the background of constitutive dephosphorylation is not restricted to IL-2-dependent STAT5 regulation. Similar results have been reported for interferon-stimulated gene factor 3 and STAT5 in response to interferon-α and growth hormone, respectively (47, 48). Therefore, the delicate balance between kinase and phosphatase activity could be the key determinants in defining steady state activity of various STAT family members.
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