Signal transduction via the interferon-γ (IFN-γ) receptor requires the tyrosine phosphorylation of signal transducers and activators of transcription (Stats). Whereas tyrosine phosphorylation of Stat1 occurs in all cells, activation of Stat5 by IFN-γ is cell type-restricted. Here we investigated the mechanism of Stat5 activation by the IFN-γ receptor. In transfection assays both Stat5 isoforms, Stat5a and Stat5b, were phosphorylated on tyrosine in response to IFN-γ. Stat5 activation required the presence of tyrosine 420 (Tyr-420) in the murine IFNGR1 receptor chain, which also serves as the Stat1 binding site. Moreover, a peptide including Tyr-440, the Stat1 binding site of the human IFNGR1 chain, conferred the ability upon a synthetic receptor to activate Stat5. Suppressor of cytokine signaling 3 (SOCS3) inhibited the activation of Stat5 by the IFN-γ receptor, and the Tyr-440-containing peptide stretch was sufficient for repression. SOCS3 expression had little effect on the activity of Jak kinases not associated with cytokine receptors. In IFN-γ-treated, Stat1-deficient fibroblasts Stat5 was inefficient in inducing transcription of a Stat1-dependent reporter gene, suggesting it does not per se make a major contribution to the expression of IFN-γ-responsive genes.

Interferon-γ (IFN-γ) is a cytokine with pleiotropic effects on both innate and adaptive immune responses. It activates macrophages for enhanced antibacterial performance and contributes to tumor surveillance and antiviral immunity (1). The IFN-γR is composed of two different chains, IFNGR1 and IFNGR2, that bind, respectively, the Jak1 and Jak2 tyrosine kinases (2). Binding of IFN-γ to its receptor stimulates the activity of the Jak kinases, which phosphorylate Tyr-440 in the IFNGR1 receptor chain (3–6). The phosphorylated tyrosine serves as a docking site for signal transducer and activator of transcription 1 (Stat1), an SH2 domain-containing transcription factor. Tyrosine phosphorylation of the receptor-associated Stat1 by the Jak3 kinases is followed by the translocation of the dimerized protein to the cell nucleus where it binds to GAS promoter sequences and induces the transcription of IFN-γ-responsive genes (7, 8). The essential character of Stat1 in the biology of IFN-γ was demonstrated by targeted disruption of its gene in mice, which resulted in severely compromised innate immunity and adverse effects on the regulation of Th cell generation and function (9, 10), reviewed in Levy (11).

The ability of the IFN-γR to activate Stats is not restricted to Stat1. Stat3 or Stat5 tyrosine phosphorylation has been reported to occur in a number of cell types upon treatment with IFN-γ (12, 13). In the case of Stat5, preferential activation of only one of two Stat5 isoforms, Stat5a, was noted (12). The molecular basis for Stat5 activation by the IFN-γR is not known, and there are at present no explanations for isoform selectivity or cell type specificity of its activation. Moreover, the biological implications of deploying Stat5 in response to IFN-γ are unclear. Mice with a targeted disruption of the Stat5a and/or Stat5b isoforms have not been analyzed for defects in IFN responses, and these investigations might be hampered by the fact that such animals develop defective T cell immunity that obscures any effects of Stat5 deficiency on the IFN-γ response (14–17).

The suppressors of cytokine signaling (SOCS) genes are induced by activated Stats, and SOCS exert feedback inhibition on cytokine receptor signaling (reviewed in Refs. 18–20). Different members of the SOCS family appear to apply different modes of repressing Stat activation. For example, SOCS1 (or JAb) efficiently binds to the phosphorylated activation loop of Jak and obstructs their ability to bind and phosphorylate substrates (21). By contrast, the ability of SOCS3 to inhibit Jaks directly is controversial (22, 23). It appears that SOCS3 is a more potent inhibitor when bound to a cytokine receptor chain either by competing for Stat binding or through an increased inhibitory activity on Jak activity (24–27). SOCS3 inhibits Stat5 activation in a number of cytokine responses, and it also inhibits tyrosine phosphorylation of Stat1 by the IFN-γ receptor (28, 29). The ability of SOCS3 to inhibit Stat5 activation in the context of IFN responses has not been investigated.

Our study addresses the mechanism of Stat5 activation by the IFN-γR and of its inhibition by SOCS3. We report a crucial role of the peptide motif containing Tyr-440 (or Tyr-420 in the murine receptor) for both processes.

EXPERIMENTAL PROCEDURES

Cells, Transfection of Cells, Cytokines—COS7, COSN31 cells (30), 293HEK, and murine Stat1-deficient fibroblasts (31) were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum. COS7 and COSN31 cells were transfected with indicated amounts of plasmids by electroporation. 293HEK cells and Stat1-deficient fibroblasts were transfected by lipofection using, respectively, Superfect or Effectene reagents (Qiagen) and the manufacturer’s in-
Structures. Where indicated, cells were treated with 5 ng/ml murine recombinant IFN-γ (a kind gift of Dr. Günther Adolf, Boehringer Ingelheim, Austria, Vienna) or 7 units/ml human recombinant erythropoietin (Epo; a kind gift of Dr. Martin Willeim, Institute of Experimental Pathology, Vienna General Hospital).

Plasmids—Plasmids expressing the murine IFN-γR chains and the IFNGRIY420F chain were kindly provided by Dr. Robert Schreiber (Washington University, St. Louis, MO), Dr. Silvio Hemmi (University of Zurich), and Dr. Michel Aguet (Institute of Experimental Cancer Research, Lausanne) (30, 32). The DNAs were kindly provided by Dr. Peter Heinrich (BTH, Aachen) and Dr. Friedemann Horn (Max Bürger Research Center, University of Leipzig). A plasmid expressing murine SOCS3 under the control of the EF1α promoter was received from Dr. Akihiko Yoshimura (Institute of Life Sciences, Kurume University).

Antibodies—We have recently described rabbit antibodies recognizing the Stat1α C terminus (40) and a monoclonal antibody against SOCS3 (41). Antibodies raised in rabbits against a C-terminal Stat5α peptide (α-Stat5α) or a Stat5 fusion protein (α-Stat5b) are published elsewhere (42). Antibodies specifically reacting with Stat5b (α-Stat5b) were raised in rabbits against a peptide representing its 24 C-terminal amino acids. A polyclonal antibody recognizing tyrosine-phosphorylated Stat5α and Stat5b was purchased from Upstate Biotechnology (Lake Placid, NY).

Electrophoretic Mobility Shift Assay (EMSA)—We have recently described this assay using an oligonucleotide with the GAS sequence of the rat β-casein promoter (42) and references therein.

Western Blot—Western blots using the antibodies to Stat1α, Stat5α, or SOCS3 were carried out as described recently (40, 41).

Luciferase Assay—Luciferase activity in whole cell extracts were determined by standard procedures (43).

RESULTS

Activation of Both Stat5 Isoforms by the IFN-γR—To determine whether the isoform-specific activation of Stat5 in the IFN-γ response of macrophage progenitor cells results from an intrinsic ability of the IFN-γR to discriminate between Stat5α and Stat5b, we transfected the murine IFNGR2 chain into COSN31 cells, which stably express the murine IFNGR1 chain (30), along with either Stat5α or Stat5b. The transfected cells were treated with murine IFN-γ, which binds specifically to the murine IFN-γR of transfected cells. Cellular extracts were analyzed by EMSA and EMSA supershift. Fig. 1A shows that IFN-γ caused activation of Stat5α and Stat5b to a similar extent. Stat5α is expressed at very low levels in COS cells. Activation of the endogenous protein by the transfected IFN-γ receptor was below the level of detection. To confirm that the IFN-γR similarly activates both Stat5α isoforms, 293HEK fibroblasts were transfected with both chains of the murine IFN-γR and either Stat5α or Stat5b. In each case half of the transfected cells were treated with murine IFN-γ and Stat5 expression, and tyrosine phosphorylation was analyzed by Western blot. Fig. 1B shows low but similar levels of tyrosine phosphorylation for Stat5α and Stat5b.

The Stat1 Binding Site of the IFNGR1 Mediates Stat5 Activation by IFN-γ—To investigate the importance of receptor association for Stat5 tyrosine phosphorylation, co-transfection experiments were carried out in COS7 cells with murine IFNGR2, Stat5α, and either the wt or Y420F-mutated murine IFNGR1 chain. Activation of the endogenous Stat1 served as an internal control for these experiments. Compared with the wt receptor chain, the Y420F-mutated receptor caused no activation of Stat1 and very little activation of Stat5α (Fig. 2A). To confirm this result we tested the Y420F mutation in a competition assay. Different amounts of mutated receptor chain were transfected to compete for Stat activation by the transgenic receptor chain in COSN31 cells. Fig. 2B shows that at 30 μg of transfected plasmid, the mutated chain efficiently repressed activation of both Stat5α and Stat1 by the IFN-γR. By contrast, 30 μg of transfected wtIFNGR1 as a control did not affect Stat activation.

To obtain further evidence for the ability of the Tyr-440-containing peptide motif of the human IFN-γ receptor to mediate Stat5 tyrosine phosphorylation, we made use of synthetic receptors. These are composed of the external and transmembrane domains of the EpoR, the juxtamembrane region of gp130 that associates with the Jak kinases Jak1, Jak2, or Tyk2, and a C-terminal region containing a 7-amino acid stretch including either Tyr-440 from the IFN-γR or, as controls, receptors, with the Stat5 binding sites from the EpoR (Tyr-343), the GM-CSFR (Tyr-882), or without a Stat binding motif (ΔBR) (Refs. 37–39; Figs. 3A). These receptors were transfected into HEK293 cells together with Stat5α, and half of the cells were treated with Epo for 20 min. Fig. 3A shows that very little activation of Stat5α by Epo was observed in the absence of a Stat binding site (ΔBR). The presence of the IFN-γR peptide including Tyr-440 clearly enhanced Stat5α activation, confirming the intrinsic ability of these amino acids to associate with Stat5. As expected, the strong binding sites of the EpoR and GM-CSFR were more efficient in mediating Stat5 tyrosine phosphorylation. Epo-mediated activation of endogenous Stats was below the detection limit, as shown in the control experiment of Fig. 3C.
To directly test the promiscuity of the IFN-γR motif in activating Stat1 and Stat5, we co-transfected the synthetic receptor with different ratios of Stat1 and Stat5 expression plasmids. Fig. 4A shows the activation of both Stats in a dose-dependent manner. By contrast, the Stat binding module from the EpoR was absolutely specific for Stat5 (Fig. 4B).

Inhibition of Stat5 Activation by SOCS3—To test whether Stat5 activation by the synthetic receptors can be suppressed by SOCS3 or whether this requires the presence of additional receptor sequences, we transfected a SOCS3 expression plasmid into HEK293 cells along with the synthetic receptors and Stat5a. SOCS3 expression efficiently inhibited the activation of Stat5a by receptors containing the IFN-γR, EpoR, or GM-CSFR modules (Fig. 3B). Thus, unlike the interleukin-6 response, where SOCS3 inhibition of Stat3 tyrosine phosphorylation requires a gp130 tyrosine residue that is not one of the Stat3 binding sites (44), the Stat1 and Jak binding sites of the synthetic IFN-γR are sufficient to mediate inhibition by SOCS3.

**FIG. 3.** Stat5 activation by synthetic receptors and inhibition by SOCS3. A, schematic drawing of the receptors employed in this study as adapted from May et al. (39). The tyrosine-based Stat activation motifs and the Box1,2 motifs for Jak association are indicated. The solid triangle depicts a C-terminal flag tag. B, 293HEK cells were transfected as described above with 10 or 30 μg of the Y420F-mutated IFNGR1 expression plasmid, which competes for IFN-γ binding with the wt chain expressed by COSN31. As a control, identical amounts of the wt IFNGR1 chain were transfected. Stat activation by recombinant murine IFN-γ (muIFN-γ) was analyzed as described for panel A.

**FIG. 2.** Tyr-420 of the murine IFNGR1 chain is required for Stat5 activation. A, COS7 cells were transfected by electroporation with plasmids expressing the murine IFNGR2 chain, Stat5a, and either wt or Y420F-mutated IFNGR1 chain. Half of the transfected cells were treated with recombinant murine IFN-γ (muIFN-γ), and Stat activation was monitored by EMSA and EMSA supershift analysis with antibodies against Stat5a. B, COSN31 cells were transfected as described above with 10 or 30 μg of the Y420F-mutated IFNGR1 expression plasmid, which competes for IFN-γ binding with the wt chain expressed by COSN31. As a control, identical amounts of the wt IFNGR1 chain were transfected. Stat activation by recombinant murine IFN-γ (muIFN-γ) was analyzed as described for panel A.
Stat1 activation by the synthetic receptor containing Tyr-440 of the IFN-γR was similarly suppressed (Fig. 5). Transfection of 1 μg of SOCS3 expression plasmid was enough to cause full inhibition of Stat activation by the synthetic receptors in our experimental set-up, and repression was maintained at 2, 3, and 4 μg of transfected plasmid (Fig. 5 and data not shown).

To determine whether the suppressive effect of SOCS3 transfection reflected a direct inhibitory activity on the Jaks, further transfection experiments were performed. Because the gp130 Jak binding site of the synthetic receptors has the potential to associate with Jak1, Jak2, and Tyk2, expression plasmids for all three tyrosine kinases were co-transfected into 293 cells together with Stat5a and different amounts of SOCS3 expression plasmid. Fig. 6 demonstrates the efficient activation of Stat5a by the co-transfected kinases. In the case of Jak2 and Tyk2, SOCS3 expression caused about 50% inhibition of Stat5 tyrosine phosphorylation at 2 μg of transfected SOCS3 plasmid, and this could not be increased by higher plasmid amounts. An unexpected dose dependence was noted in the case of Jak1. Low amounts of SOCS3 caused efficient inhibition, but the inhibitory effect was abolished by increasing the amount of transfected SOCS3 in a highly reproducible manner. Importantly, none of the tested kinases showed the same dose dependence of inhibition by SOCS3 as was observed in the case of receptor-mediated Stat5 activation. This suggests that mechanisms other than direct binding to Jaks contribute to the SOCS3-mediated inhibition of Stat activation by the synthetic cytokine receptors.

**Transcriptional Activity of Stat5 in the IFN-γ Response**—Having demonstrated the potential of the IFN-γR to activate Stat5, we sought to determine the effect of IFN-γ-activated Stat5 on gene expression. To this end, we transfected Stat5a into Stat1-deficient fibroblasts along with the IFN-γ-responsive IFP53 reporter plasmid. The IFP53 promoter contains a GAS sequence that associates Stat1 as well as Stat5 (12, 45). Fig. 7A shows poor transactivation of the reporter by the trans-
fected Stat5. Stat5b was superior to Stat5a, and chicken Stat5 (cStat5), with features of both mammalian isoforms (35), displayed transcriptional activity between that of the mammalian proteins. Importantly, transfection of Stat1 under otherwise identical conditions stimulated reporter gene expression more than 40-fold (not shown).

Transcriptional responses via the endogenous IFN-γ/R could be mimicked with the synthetic receptor containing the Tyr-440 peptide (Fig. 7B). In the case of the mammalian Stats, the transcriptional response could not be enhanced with the EpoR or GM-CSF receptor binding sites despite their superior ability to generate Stat5 dimers. Moreover, reporter gene activation by the synthetic EpoR was very similar to that of the authentic EpoR. In an independent experiment, the EpoR and co-transfected Stat5b stimulated the IFP53 reporter gene 4.1-fold, whereas a 4.8-fold stimulation was seen using the synthetic receptor with the EpoRY343 peptide. Together the data suggest a requirement for additional factors to achieve high levels of Stat5-dependent transcription.

**DISCUSSION**

The binding of cytokines to their receptors frequently causes the activation of several different Stats. Despite this, studies in gene-targeted mice suggest that only one of these mediates the predominant biological effects of the activating cytokine (11). IFN-γ causes tyrosine phosphorylation of Stat1 and, in a cell-type-restricted manner, that of Stat3 and Stat5. Stat1 deficiency alone abolishes the major immunological functions of IFN-γ like the activation of macrophages or the regulation of the adaptive immune response (9, 10). However, IFN-γ is a pleiotropic cytokine exerting a plethora of effects on the activation, growth, and differentiation of cells (46, 47). Importantly, some of the biological effects of IFN-γ, like those on the growth and differentiation of hematopoietic cells, may be redundant with other cytokines, whereas others, like the activation of macrophages, are not. Thus, one might argue that effects of Stat5 or Stat3 deficiency on the IFN-γ response are not readily overt because other cytokines compensate. Moreover, the absence of Stat3/5 in an IFN-γ response might cause only minor alterations that are hard to detect, particularly if analyzed against a background of more severe phenotypes caused by tissue-restricted Stat3 ablation (48) or Stat5a/b deficiency (16, 17).

In this paper we show that Stat5 activation by the IFN-γ receptor results from a promiscuity of the amino acids surrounding Tyr-420 and Tyr-440 of, respectively, the murine and human IFNGR1 chains for Stat1 and Stat5. The binding of cytokines to their receptors frequently causes the activation of several different Stats. Despite this, studies in gene-targeted mice suggest that only one of these mediates the predominant biological effects of the activating cytokine (11). IFN-γ causes tyrosine phosphorylation of Stat1 and, in a cell-type-restricted manner, that of Stat3 and Stat5. Stat1 deficiency alone abolishes the major immunological functions of IFN-γ like the activation of macrophages or the regulation of
and Stat3 can bind to the same phosphorylated tyrosine (49), or the interleukin-9 receptor, where a single tyrosine residue was shown to cause activation of Stats 1, 3, and 5 (50). Some ability to activate Stat5 was retained by IFN-γ/H9253 receptors containing the Y420F mutant of the IFNGR1 chain or by the H9004 synthetic receptor without a Stat binding site. Our previous studies suggest this may be because of a direct interaction between the Jak kinase domain and Stat5 (51).

Our studies further show that the IFN-γ/H9253 receptor has no intrinsic ability to distinguish between the Stat5a and Stat5b isoforms. This possibility was suggested by our earlier finding in hematopoietic progenitor cells where IFN-γ/H9253 treatment resulted in the tyrosine phosphorylation of Stat5a but not of Stat5b despite expression of both proteins (12). One possible explanation is that Stat5 activation by the IFN-γR is determined by threshold levels of expression that may in some cells be exceeded by Stat5a but not Stat5b. Alternatively, ancillary proteins may form complexes with Stat5a in some cells and create increased affinity for the IFN-γR complex.

Compared with Stat1, Stat5, activated by the IFN-γR, displayed very little ability to support transcription of a transfected reporter gene. Similar observations were made with Stat5 in the case of GM-CSF or Epo-treated cells (12, 52). The exact contribution of Stat5 to the Epo response in vivo is still controversial (16, 53), but the protein clearly affects the generation of monocytes/macrophages in response to GM-CSF (35). Consistent with studies on its transactivation domain (54), Stat5 may not per se be a potent transcription factor but, rather, may require interaction with other DNA-binding proteins to stimulate gene expression. Another important activity of Stat5 may lie in its ability to mediate gene repression. This assumption emerged from both studies in cultured cells (55) and the analysis of knock-out mice (16), which suggested a role for Stat5 in suppressing the expression of the testosterone 15α-hydroxylase gene in male mice.

SOCS3 inhibited both Stat1 and Stat5 tyrosine phosphorylation by the synthetic Tyr-440 receptor with similar efficiency, suggesting that the mechanism of inhibition may be the same in both cases. In agreement with the results by others (22), our findings suggest that SOCS3 inhibition of Stat1 or Stat5 activation cannot be explained entirely by the effect of the protein on Jak kinases. The gp130 Jak binding site of the synthetic receptor was shown to associate with Jak1, Jak2, and Tyk2 (56, 57). Cytoplasmic Jak2 and Tyk2 could not be efficiently inhibited by even high amounts of co-transfected SOCS3. Surprisingly, Jak1 was inhibited by low amounts of SOCS3, but inhibition was lost with increasing SOCS3 expression. We have no explanation for this dose effect, but comparison to the dose response of Stat inhibition by the complete synthetic receptor rules out the possibility that our results are entirely due to a direct interaction between SOCS3 and Jak1. We propose that Jak inhibition by SOCS3 might be more efficient when Jaks are associated with receptors. Possibly receptor chains stabilize the Jak-SOCS complex, as has been suggested for the interleukin-2 receptor β-chain (24) and/or increase the ability of SOCS3 to inhibit Jaks (26). Alternatively or additionally, SOCS3 might

**FIG. 7. Transcriptional activity of Stat5 in Stat1-deficient cells.** A, Stat1-deficient fibroblasts were transfected with an IFN-γ-responsive reporter gene (IFP53-Luc) and mammalian Stat5a or Stat5b or with chicken Stat5 that contains features of both mammalian Stat5 isoforms. Half of each transfected culture was treated with IFN-γ for 6 h followed by determination of luciferase activity. Data are expressed as inducibility, i.e. the ratio of luciferase activity from IFN-γ-treated and untreated cells. Inducibility in a control experiment with transfected Stat1 was 40-fold. B, the same experiment as in panel A was performed by transfecting the indicated synthetic receptors along with the reporter gene and Stat5.
itself bind to the phosphorylated Tyr-440 of the synthetic receptor via its SH2 domain and compete for Stat binding. This mode of action has been suggested in the case of Epo receptor Tyr-401, which also associates with Stat5 (26), and for the insulin receptor (27).

In conclusion, our studies show that promiscuity of a receptor binding site is the basis of Stat5 activation by IFN-γ and that this phosphorylated tyrosine suffices to mediate inhibition by SOCS3 in the case of both Stat1 and Stat5. We suggest that tissue-restricted Stat5 activation by the IFN-γ/H9253 can be confirmed in future studies. We thank Robert Schreiber, Silvio Hemmi and Michel Aguet for cDNAs encoding wt or mutant IFN-γR chains. We also thank Peter Heinrich and Friedemann Horn for providing plasmids encoding synthetic cytokine receptors. We thank Manuela Baccarini and Pavel Kovarik for reading and providing critical comments on this manuscript.

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The Stat1 Binding Motif of the Interferon-γ Receptor Is Sufficient to Mediate Stat5 Activation and Its Repression by SOCS3
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