Identification of a Domain in the β Subunit of the Type I Interferon (IFN) Receptor That Exhibits a Negative Regulatory Effect in the Growth Inhibitory Action of Type I IFNs*

(Received for publication, August 26, 1997, and in revised form, December 19, 1997)

Leonidas C. Platianias‡, Paul Domanski§, Owen W. Nadeau§, Taolin Yi‡, Shahab Uddin‡, Eleanor Fish, Benjamin G. Neel**, and Oscar R. Colamonici†‡‡

From the ‡Section of Hematology/Oncology, University of Illinois at Chicago, and West Side Veterans Affairs Hospital, Chicago, Illinois 60607, the §Department of Pathology, University of Tennessee, Memphis, Tennessee 38163, the ¶Department of Cancer Biology, The Cleveland Clinic Foundation Research Institute, Cleveland, Ohio 44195, the ¶¶Department of Medical Genetics and Microbiology, University of Toronto, Toronto, Ontario M55 IA8, Canada, and the ‡‡Cancer Biology Program, Division of Hematology-Oncology, Department of Medicine, Beth Israel Hospital, Boston, Massachusetts 02215

Expression of human α and long form of the β (βL) subunits of type I interferon receptor (IFN-R) in mouse cells is sufficient to activate the Jak-Stat pathway and to elicit an antiviral state in response to human IFNα2 and IFNβ. We demonstrate herein, however, that these cells respond to the antiproliferative effects of murine IFNαβ but not human type I IFNs. These results suggest that an unknown species-specific component is required for the antiproliferative effect of human type I IFNs. The absence of this component can be complemented by expressing the human βL chain truncated at amino acid 346. Thus, the distal region of the βL chain appears to function as a negative regulator of the growth inhibitory effects of type I IFNs. Further studies looking for possible targets of the βL regulatory domain demonstrated that this region associates with a tyrosine phosphatase. These results suggest that a protein associated with the negative regulatory domain of βL, likely a tyrosine phosphatase, plays a role in regulating the growth inhibitory effects of human type I IFNs.

The most prominent effects of type I interferons (IFN)† are the antiviral and antiproliferative actions (1). These effects are mediated through binding to the type I interferon receptor (IFN-R or IFNαR), which is composed of two subunits termed α, or IFNAR1, and β, or IFNAR2 (2–10). The genes encoding the different subunits of the type I IFN-R are clustered in the q22.1 region of human chromosome 21 (6, 7, 11–16). This region also harbors an orphan class II cytokine receptor, the CRFB-4 gene, which is encoded on human chromosome 21 between the genes for the βL chain of the IFNαR and the β subunit of the IFNγR (10, 17). Expression of the human α and long form of the β chain (βL) subunits in mouse L-929 cells fully reconstitutes the activation of the Jak-Stat pathway and the induction of an antiviral state in response to HuIFNα2 and HuIFNβ (9). Furthermore, only the first 82 amino acids of the cytoplasmic domain of the βL chain are required to activate the Jak-Stat pathway and induce the antiviral effect in response to IFNα2 (18).

The α and β subunits of the type I IFN-R associate with protein tyrosine kinases of the Jak family (4, 8, 18). The α subunit interacts with Tyk2 (4, 19, 20) while the cytoplasmic domain of the βL contains a docking site for Jak1 (18). Binding of type I IFNs to their receptor triggers rapid tyrosine phosphorylation of Tyk2 and Jak1 kinases, type I IFN-R subunits (21–25), and Stat factors (reviewed in Refs. 26–28). Regulation of tyrosine kinase activity is mediated in most cytokine systems by protein tyrosine phosphatases (PTPs). For example, SHP1 (also named SHP, SHPTP1, HCP, FTP1C, Ref. 29), a predominantly hematopoietic tyrosine phosphatase that regulates the activity of the erythropoietin and IL-3 systems (30–35), has also been implicated in IFNα signaling in hematopoietic cells (36, 37). However, the role of SHP1 in other cell types is not clear since this PTP is mainly expressed in hematopoietic cells, whereas the IFN system functions in almost all, if not all, cell lineages.

Mouse L-929 cells that coexpress wild-type human α and β subunits respond to the antiviral effects of human type I IFNs, demonstrating the presence of functional human type I IFN-R (9). We therefore decided to test these cells for their ability to respond to the antiproliferative effects of type I IFNs. Human IFNα and IFNβ induced only a minimal antiproliferative response, whereas murine type I IFNs produced a marked inhibition of cell proliferation. These data indicate that (i) induction of the antiproliferative and antiviral responses occurs through partially divergent pathways and (ii) that a novel species-specific signaling component is required, in addition to the α and βL chains, for the growth inhibitory effect. Surprisingly, the antiproliferative response was observed in cells that express the human βL chain truncated at amino acid 346. Thus, the distal part of the βL chain apparently contains a negative regulatory domain that controls the growth inhibitory effects of type I IFNs. Further characterization of this negative regulatory domain revealed that it interacts with a PTP that appears to be distinct from SHP1 and SHP2. The data herein suggest that a novel species-specific component is required for the growth inhibitory effect and that this effect is regulated by a distal region corresponding to amino acids 346–417 on the β subunit.
Interaction of IFNaRβp2 with PTP Regulates Cell Proliferation

MATERIALS AND METHODS

IFNs and Antibodies—Human recombinant IFNo2 was kindly provided by Drs. M. Brunda (Hoffmann-La Roche) and Paul Trotta (Schering-Plough). The anti-phosphotyrosine antibody (4G10) was obtained from UBI (Lake Placid, NY). The polyclonal antibodies against the α (αα513-577, IFNaRC-1), β2 (IFNaRC-2), and β1 (β1205-513, and β1375-513) subunits of the type I IFN-R, as well as the rabbit sera anti-Tyk2 had been previously described (4, 38, 39). The anti-SHP1 and -SHP2 sera used for immunoprecipitations and Western blotting were purchased from UBI, Santa Cruz Biotechnologies, and Transduction Laboratories. The anti-JAK1 sera was kindly provided by Dr. J. N. Ihle (St. Jude’s Children’s Hospital, Memphis, TN).

Constructions and Expression of the Human Type I IFN-R Subunits in Mouse L-929 Cells—Mouse L-929 cells lines expressing different constructs of the human α and β subunits LpZRaβ226, LpZRaβ724, LpZRaβ477, LpZRaβ548, and LpZRaβ2300 were described previously (9, 18). The L-929 transfectants stably coexpressing mutations of tyrosine 466 and truncation at amino acid 511 of the α subunit (designated as αY1F511) with either wild type or truncation 346 of the β subunit (LpZRaY1F531P531, and LpZRaY1F531P548 respectively), as well as co-expressing wild-type α chain and β subunit carrying a mutation of tyrosine 411 to phenylalanine, are described elsewhere.2

Cell Proliferation Assays—Cell proliferation was assessed by performing MTT assays (7, 40) and cell counts after treatment with the indicated amount of human and mouse IFNs. Briefly, cells were seeded at 6,000 cells/well in 24-well plates in a final volume of 0.6 ml and treated with the indicated concentrations of IFNs. The numbers of cells per well were determined by trypsinization and counting of duplicate wells in a hemocytometer. Experiments were performed at least twice with two independent clones carrying the same mutation.

Immunoblotting—Cells were treated with different concentrations of the indicated IFNs for 15 min, rapidly centrifuged at 2000 × g for 30 s in an Eppendorf microfuge, and subsequently solubilized in lysis buffer. Immunoprecipitation and immunoblotting were performed as described previously (4).

Phosphatase Assays—For protein phosphatase assays, cells expressing wild-type α chain and the β subunit truncated at the indicated amino acids were treated with or without IFNa2 for 10 min at 37 °C and lysed in lysis buffer as described previously (4). The β subunit was precipitated using a polyclonal serum raised against a GST fusion protein encoding the entire cytoplasmic domain (β1205-513) (39), immunoprecipitates were washed three times in cold phosphatase buffer to remove phosphatase inhibitors. The phosphatase activity of the immunocomplexes was determined using pNPP (Sigma) as a substrate. The phosphatase assay was carried out at 37 °C for 0.5 h in 50 ml of reaction mixture (100 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM EDTA, 1 mM dithiothreitol, 10 mM pNPP). The reaction was terminated by adding 950 μl of 1 M NaOH. The reaction product, p-nitrophenolate, was quantified by measuring absorbance at 405 nm.

RESULTS

Expression of the Human α and β Subunits of the Type I IFN-R Is Not Sufficient to Reconstitute the Antiproliferative Response—Mouse L-929 cells transfected with the human α and β chains, LpZRaβ126, activate the Jak-Stat pathway and are highly responsive to the antiviral effects of HuIFNo2 and HuIFNβ (9). To characterize the antiproliferative effect of type I IFNs in these cells, we first performed MTT proliferation assays using L-929 cells stably transfected with wild-type human α and β subunits (LpZRaβ126). Fig. 1A shows that high doses of HuIFNo2 (100,000 units/ml) had little effect on cell proliferation. However, treatment with MuIFNβ or MuIFNβ at doses between 1,000 and 10,000 units/ml induced a significant antiproliferative effect. To confirm the results obtained with MTT assays, we performed similar experiments in which cell numbers were assessed. Fig. 1B shows that treatment of LpZRaβ126 cells (Fig. 1B, αβ2 cells) with MuIFNβ reduced cell proliferation more than 95% over a period of 6 days, whereas HuIFNo2 produced a minimal response (20%, from 545,000 cells/well to 445,000 cells/well in control and HuIFNo2-treated cells, respectively). Similar results were observed when MuIFNβ and HuIFNβ were used (data not shown). These results indicate that the endogenous mouse type I IFN-R expressed in L-929 cells can trigger a complete antiproliferative effect in response to mouse IFNs. Thus, in contrast to the antiviral effect, reconstitution of the human receptor with the α and β chains in these cells is not sufficient to trigger an antiproliferative effect in response to human type I IFNs, suggesting that an additional human signaling component is required for this effect.

It has been reported that human/rodent somatic cell hybrids carrying human chromosome 21 acquire the ability to respond to the antiviral effect and induction of HLA class I antigens by human type I IFNs (7, 11–16, 41–45). This is in part due to the fact that the human type I IFNs in these cells can trigger an antiproliferative effect in response to mouse IFNs. Thus, in contrast to the antiviral effect, reconstitution of the human receptor with the α and β chains in these cells is not sufficient to trigger an antiproliferative effect in response to human type I IFNs, suggesting that an additional human signaling component is required for this effect.

2 Domanski and Colamonici, manuscript in preparation.
growth inhibitory response. Since human/rodent somatic cell hybrids carrying human chromosome 21, including A9+21 cells, have been shown to develop an antiviral state and induce HLA class I antigens in response to human type I IFNs (7, 11–16, 41–45), the inability of these cells to respond to the antiproliferative effects of human type I IFNs further suggests that an additional species-specific signaling component is required. Moreover, it is unlikely that this signaling element is encoded by any genes present on human chromosome 21.

Deletion of a Negative Regulatory Region of the β2 Chain Promotes the Growth Inhibitory Effects of Human Type I IFNs—Since deletion of the distal region of the α chain produces an increase in HLA class I response induced by human IFNα2 (48), we wished to determine whether the antiproliferative response could be induced by human IFNs in L-929 cells that express α and β2 subunits with deletions of various regions of their cytoplasmic domains. Cells that express the β2 chain truncated at amino acid 417 are more responsive to MuIFNαβ than to HuIFNα2 (Fig. 2A, panel A). These results parallel our findings for L-929 or A9+21 cells, which express wild-type receptor subunits (Fig. 1, B and C). By direct contrast, L-929 cells coexpressing both the wild-type α and β2 chain truncated at amino acid 346 (Fig. 2, panels B, αβL346,2 cells), responded to the growth inhibitory effects of human type I IFNs. Truncation of the cytoplasmic domain of β2 at amino acid 300, which removes the Jak1 binding site (18), abolished the antiproliferative response to human type I IFNs but did not affect the antiproliferative response to MuIFNαβ (Fig. 2C), demonstrating that the mouse signaling machinery is intact in these cells. We also studied L-929 transfectants expressing wild-type β2 chain and an α chain with a deletion of the negative regulatory domain (truncation at amino acid 511 and tyrosine 466 mutated to phenylalanine; Fig. 2, panel D, αY1FβL11,11 cells) (48). These cells showed a significant response to MuIFNαβ, whereas human type I IFNs induced only a partial antiproliferative effect, which was similar to that observed in cells expressing wild-type receptors. This result suggests that the negative regulatory region of the α subunit does not control cell proliferation (48). However, L-929 cells coexpressing the same mutations of the α subunit and β2 truncated at amino acid 346 (Fig. 2, panel E, αY1F31FβL346,3) were extremely sensitive to the antiproliferative effect of human and mouse type I IFNs. Similar results were obtained with two independent clones carrying the same mutation (data not shown). These data strongly suggest that a region corresponding to amino acids 346–417 in the β2 chain contains a negative regulatory domain and may be a possible target for mouse regulatory proteins. Thus, removal of this negative regulatory domain appears to complement the absence of an unknown species-specific component required for the antiproliferative effect (see “Discussion”).

The β2 Subunit of the Type I IFN-R Associates with a Phosphatase—Tyrosine phosphorylation plays a central role in IFN and cytokine signaling. Therefore, to determine if the negative regulatory domain of β2 was associated with a PTP, we performed in vitro phosphatase assays after immunoprecipitation with anti-β2 sera. As a source of β2 chain, we used cell lysates obtained from mouse L-929 cells cotransfected with the wild-type α subunit and truncations of the β2 chain at amino acids 346, 417, or 462, respectively. Cells were treated with IFNα2 for 10 min, cell lysates were immunoprecipitated with an antibody that recognizes all truncated forms of the β2 chain, and in vitro phosphatase assays were performed on the immunoprecipitates. Fig. 3 shows that significant phosphatase activity is associated with β2Y462 and β2Y417, but not with β2Y346 after IFNα2 treatment, indicating that the 346–417 region of β2 associates with a PTP. Since the increase in phosphatase activity associated with the 346–417 region of β2 is observed only after IFNα2 treatment, we could not elucidate whether the β2-associated PTP is recruited to the receptor complex after IFNα2 stimulation or is constitutively associated with the β2 chain and activated by IFNα2 stimulation.

Deletion of the Negative Regulatory Domain of the β2 Subunit at Amino Acid 346 Results in Strong and Prolonged Tyrosine Phosphorylation of Jak1—We next sought to test if deletion of the 346–417 region of the β2 chain and, consequently, removal of the phosphatase interaction site had an effect on tyrosine phosphorylation. We performed time course and dose response experiments with mouse L-929 cells stably cotransfected with wild-type α chain and β2 truncated at amino acids 346 and 417, respectively. Fig. 4A shows that more intense phosphorylation of Jak1 was observed at lower doses of IFNα2 in cells expressing the β2L subunit truncated at amino acid 346, as compared with the β2L chain truncated at residue 417. Moreover, deletions distal to amino acid 346, but not at amino acid 417, prolonged...
phatases, we studied the effect of a phenylalanine mutation of tyrosine 411 on cell proliferation. Panel F (Fig. 2) shows that mutation of tyrosine 411 to phenylalanine does not reconstitute the antiproliferative effect of type I IFNs. Similar results were also obtained with different clones carrying the same mutations (data not shown). Therefore, tyrosine 411 is not critical for induction of the negative regulatory effect and is presumably not a docking site for SH2-containing phosphatases.

**DISCUSSION**

The type I IFNs have multiple biological actions, including antiviral and antiproliferative effects, which are the most prominent of these cellular responses (1). Binding of human type I IFNs to mouse L-292 cells that express human α and βL chains is sufficient to trigger activation of the Jak-Stat pathway and to produce a full antiviral response, which demonstrates the presence of functional human type I IFN-R subunits (9). We therefore tested these cells for their ability to respond to the antiproliferative actions of human type I IFNs. Although these cells were able to respond to the full growth inhibitory effects of MuIFNβL, only a minimal response was observed for human type I IFNs. Thus, the antiproliferative pathway is intact in these cells but not fully activated via the human receptors. Similar results were also observed for different clones of mouse A9–21 cells that carry several copies of human chromosome 21, which is thought to contain the type I IFN-R cluster (7, 11–16, 41–45) and an uncharacterized signaling component (46, 47). Altogether, these data indicate that (i) induction of the antiproliferative and antiviral responses occurs through partially divergent pathways and (ii) that a novel species-specific signaling component is required, in addition to the α and βL chains, for the growth inhibitory effect.

It has been reported that elements of the cytoplasmic domains of cytokine receptors have a negative regulatory role in signaling. For example, removal of the docking site for SHP1 in EPO-R results in hypersensitivity to EPO and prolonged phosphorylation of Jak2 (31). Similarly, deletion of the distal region of the α subunit of the IFNαR in increased sensitivity to induction of HLA class I antigens by IFNα2 (48). Correspondingly, removal of the distal region (346–417) of the cytoplasmic domain of βL resulted in a gain in response to the growth inhibitory effects of IFNo, indicating that this region encodes a negative regulatory domain. The effect of the negative regulatory domain of βL is specific, as demonstrated by the finding that deletion of a homologous region of the α chain did not have an effect on cell proliferation (Fig. 2, aY1IF511βL cells). The negative regulatory domain of βL interacts with a PTP as indicated by detection of phosphatase activity associated with the 346–417 region of βL and the finding that deletion of this region resulted in prolonged phosphorylation of Jak1 in mouse cells. Mutation of the only tyrosine in the negative regulatory domain (Tyr–411) did not have the same effect on the antiproliferative response as deletion of the 346–417 region, indicating that the putative phosphatase is not docked to βL through an SH2 domain. Moreover, immunoprecipitation with antibodies against the α and βL chains, and pull-down experiments with GST fusion proteins encoding the cytoplasmic domain of the α and βL chains failed to precipitate SHP1 or SHP2 (data not shown). Taken together, these data indicate that the 346–417 region of βL functions as a negative regulator for the antiproliferative effect of IFNs, possibly by recruiting a regulatory phosphatase through an SH2-independent mechanism. Consistently with the finding in mouse cells, immunoprecipitations with anti-βL antibodies also revealed phosphatase activity specifically associated with the βL subunit expressed in human cells (data not shown). It should be noted, however, that in human cells no conclusive data have been using

---

**Fig. 3.** IFNo2-induced phosphatase activity associated with the βL subunit of the type I IFN-R. Phosphatase activity associated with the indicated truncations of the βL subunit antisera were present in all lanes. (A) Phosphatase activity (alanine 346 (αL346), 346 (αL346) or 417 (αL417) were treated with the indicated doses of IFNo2 for 8 min at 37 °C. Cells were lysed and immunoprecipitated with anti-βL sera followed by sequential immunoblotting with the anti-phosphotyrosine antibody (top panel) followed by stripping and reprobing of the filters with an anti-Jak1 monoclonal antibody (bottom panel) to demonstrate that similar amounts of proteins were present in all lanes. B, kinetics of Jak1 phosphorylation. αL346, and αL417, cells were treated with 20,000 units/ml of IFNo2 for the indicated periods of time. Cells were lysed, and the Jak1 antibody was immunoprecipitated with anti-βL sera followed by sequential immunoblotting with anti-phosphotyrosine (top panel) and -Jak1 (bottom panel) antibodies.

**Fig. 4.** Truncation of the βL subunit of the type I IFN-R at amino acid 346 results in increased tyrosine phosphorylation of Jak1. A, dose response experiment. Cells coexpressing the α chain and truncation mutants of the βL chain at amino acids 346 (αL346) or 417 (αL417) were treated with the indicated doses of IFNo2 for 8 min at 37 °C. Cells were lysed and immunoprecipitated with anti-βL sera as described under “Materials and Methods.” Immunoblotting was first performed with anti-phosphotyrosine antibody (top panel) followed by stripping and reprobing of the filters with an anti-Jak1 monoclonal antibody (bottom panel) to demonstrate that similar amounts of proteins were present in all lanes. B, kinetics of Jak1 phosphorylation. αL346, and αL417, cells were treated with 20,000 units/ml of IFNo2 for the indicated periods of time. Cells were lysed, and the Jak1 antibody was immunoprecipitated with anti-βL sera followed by sequential immunoblotting with anti-phosphotyrosine (top panel) and -Jak1 (bottom panel) antibodies.
GSTβ1 fusion proteins.

Since mouse IFNs completely inhibit proliferation of cells expressing human α and β1 chains, we can conclude that the mouse receptor couples the signal induced by murine IFNs with the intracellular proteins responsible for antiproliferative pathway in these cells. Consequently, the inability of LpZRαβL and A9+21 cells to respond to the growth inhibitory effect of human IFNs centers the defect at the level of the human receptor. One possibility is that the intracellular domains of the human α and/or β1 chains, which are responsible for activation of the antiproliferative pathway, are not homologous to their murine counterparts. However, this possibility is highly unlikely, based on two primary observations. First, deletion of the negative regulatory domain of β1 allows a full human IFNβ-induced antiproliferative effect, indicating that the human receptor subunits are capable of interacting with the appropriate mouse signaling proteins. Second, these transfectants respond to the antiviral effect of IFNs. Another possibility is that the missing species-specific component corresponds to a third receptor subunit. In this scenario, the antiproliferative response requires the assembly of a receptor composed of three subunits; in this complex, the third receptor subunit regulates the activity of a protein associated with the negative regulatory domain of β1 presumably a PTP. If, in fact, a phosphatase is involved, the third receptor subunit may delay activation of the PTP or release the PTP from the complex, resulting in prolonged activation of Jak1 and generation of the antiproliferative response. Thus, deletion of the negative regulatory domain of β1 has the same outcome as activating the third receptor subunit, blocking the action of the PTP or an unknown protein that associates with this region.

Acknowledgments—We thank Dr. J. N. Ihle for providing the Jak1 antisera.

REFERENCES

1. Pestka, S., Langer, J. A., Zoon, K. C., and Samuel, C. E. (1987) Annu. Rev. Biochem. 56, 727–777
2. Uze, G., Lutfalla, G., and Gresser, I. (1990) Cell 60, 225–234
3. Colamonici, O. R., D’Alessandro, F., Diaz, M. O., Gregory, S. A., Neckers, L. M., and Nordan, R. (1990) Proc. Natl. Acad. Sci. U. S. A. 87, 7230–7234
4. Colamonici, O. R., Yan, H., Domanski, P., Handa, R., Smalley, D., Mullersman, J., Witte, M., Krishnan, K., and Krolewski, J. (1994) Mol. Cell. Biol. 14, 8133–8142
5. Uze, G., Lutfalla, G., Bandu, M. T., Proudhon, D., and Megens, K. E. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 4774–4778
6. Lutfalla, G., Gardiner, K., Proudhon, D., Megens, K. E. (1992) EMBO J. 11, 5100–5108
7. Tan, Y. H., Schneider, E. L., Tischfeld, J., Epstein, C. J., and Ruddle, F. H. (1974) Science 186, 61–63
8. Revel, M., Bash, D., and Ruddle, F. H. (1976) Nature 260, 139–141
9. Tan, Y. H. (1976) Nature 260, 141–143
10. Epstein, C. J., McManus, N. H., Epstein, L. B., Branca, A. A., D’Alessandro, S. B., and Baglioni, C. (1982) Biochem. Biophys. Res. Commun. 107, 1060–1066
11. Langer, J. A., Rashidbaigi, A., Lai, L.-W., Patterson, D., and Jones, C. (1990) Somatic Cell Mol. Genet. 16, 231–240
12. Cleary, C. M., Donnelly, R. J., Sch, J., Mariano, T. M., and Pestka, S. (1994) J. Biol. Chem. 269, 18747–18749
13. Lutfalla, G., Gardiner, K., and Uze, G. (1993) Genomics 16, 366–373
14. Domanski, P., Fish, E., Nadeau O. W., Witte, M., Platianias, L. C., Yan, H., Krolewski, J., Pitha, P., and Colamonici, O. R. (1997) J. Biol. Chem. 272, 26388–26393
15. Colamonici, O. R., Uytendaele, H., Domanski, P., Yan, H., and Krolewski, J. J. (1994) J. Biol. Chem. 269, 3518–3522
16. Yan, H., Krishnan, K., Lim, J. T. E., Contillo, L. G., Schindler, C. W., and Krolewski, J. J. (1996) Mol. Cell. Biol. 16, 2074–2082
17. Platianias, L. C., and Colamonici, O. R. (1992) J. Biol. Chem. 267, 24053–24057
18. Platianias, L. C., Uddin, S., and Colamonici, O. R. (1994) J. Biol. Chem. 269, 17761–17764
19. Abramovich, C., Shulman, L. M., Ratovitski, E., Harrsch, S., Tovey, M., Eid, P., and Revel, M. (1994) EMBO J. 13, 5871–5877
20. Platianias, L. C., Uddin, S., Yetter, A., Sun, X.-J., and White, M. F. (1996) J. Biol. Chem. 271, 278–282
21. Constantinescu, S. N., Croze, E., Wang, C., Murti, A., Basu, L., Mullersman, J. E., and Pfeffer, L. M. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 9602–9606
22. Ihle, J. N. (1995) Nature 337, 591–594
23. Schindler, S., and Darnell, J. J. E. (1995) Annu. Rev. Biochem. 64, 621–651
24. Taga, T., and Kishimoto, T. (1992) FASEB J. 6, 3387–3396
25. Adachi, M., Fischer, E. D., Ihle, J., Imai, K., Jirik, F., Neel, B., Pawson, P., Shen, S.-H., Thomas, M., Ullrich, A., and Zhao, Z. (1996) Cell 85, 15
26. Tanaka, K., and Neel, B. G. (1996) Cell 87, 365–368
27. Klingmüller, U., Lorenz, U., Cantley, L. C., Neel, B. G., and Lodish, H. F. (1995) Cell 80, 729–738
28. Yi, T., Zhang, J., Miuara, O., and Ihle, J. N. (1995) Blood 85, 87–95
29. Yi, T., Miu, L. F., Krystal, G., and Ihle, J. N. (1993) Mol. Cell. Biol. 13, 7577–7586
30. Yi, T., and Ihle, J. N. (1993) Mol. Cell. Biol. 13, 3350–3358
31. You, S., and You, J. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 5834–5838
32. Taga, T., and Watanabe, K. (1994) Mol. Cell. Biol. 14, 23630–23633
33. Taga, T., and Watanabe, K. (1994) Mol. Cell. Biol. 14, 23630–23633
34. Taga, T., and Watanabe, K. (1994) Mol. Cell. Biol. 14, 23630–23633
35. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
36. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
37. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
38. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
39. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
40. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
41. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
42. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
43. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
44. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
45. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
46. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
47. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
48. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633
49. Yi, T., and You, J. (1994) Mol. Cell. Biol. 14, 23630–23633