Inhibition and Restoration of Prolactin Signal Transduction by Suppressors of Cytokine Signaling*

Alain Pezet, Hélène Favre, Paul A. Kelly, and Marc Edery‡

From the INSERM U344, Faculté de Médecine Necker, 156 rue de Vaugirard, 75730 Paris Cedex 15, France

Prolactin (PRL) has been shown to activate the cytoplasmic tyrosine kinase Janus kinase 2 (Jak2) and the subsequent recruitment of various signaling molecules including members of the signal transducer and activator of transcription family of transcription factors. Recently, an expanding family of cytokine-inducible inhibitors of signaling has been identified that initially included four members: suppressor of cytokine signaling (SOCS)-1, SOCS-2, SOCS-3, and cytokine-inducible src homology domain 2 (SH-2) proteins. The present study analyzes the role of these members in PRL signaling. Constitutive expression of SOCS-1 and SOCS-3 suppressed PRL-induced signal transducer and activator of transcription 5-dependent gene transcription, and Jak2 tyrosine kinase activity was greatly reduced in the presence of SOCS-1 or SOCS-3. SOCS-1 was shown to associate with Jak2, whereas SOCS-2 was associated with the prolactin receptor. Co-transfection studies were conducted to further analyze the interactions of SOCS proteins. SOCS-3 was shown to suppress the inhibitory effect of SOCS-1 by restoring Jak2 kinase activity but did not affect the inhibitory effect of SOCS-3 on PRL signaling. Northern blot analysis revealed that SOCS-3 and SOCS-1 genes were transiently expressed in response to PRL, both in vivo and in vitro, whereas the expression of SOCS-2 and CIS genes was still elevated 24 h after hormonal stimulation. We thus propose that the early expressed SOCS genes (SOCS-1 and SOCS-3) switch off PRL signaling and that the later expressed SOCS-2 gene can restore the sensitivity of cells to PRL, partly by suppressing the SOCS-1 inhibitory effect.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

* The abbreviations used are: PRL, prolactin; PRLR, prolactin receptor; LHRE, lactogenic hormone-responsive element; SH-2 protein; Jak2, Janus kinase 2; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; CIS, cytokine-inducible SH-2 protein; Jak2, Janus kinase 2; STAT, signal transducer and activator of transcription; LHRE, lactogenic hormone-responsive element; oPRL, ovine prolactin; GH, growth hormone; TK, thymidine kinase.

** From the INSERM U344, Faculté de Médecine Necker, 156 rue de Vaugirard, 75730 Paris Cedex 15, France. Tel.: 33-1-40-61-53-10; Fax: 33-1-43-06-43-43; E-mail: marc.edery@necker.fr.

† To whom correspondence should be addressed: INSERM U344, Endocrinologie Moléculaire, Faculté de Médecine Enfants Malades, 156 rue de Vaugirard, 75730 Paris Cedex 15, France. Tel.: 33-1-40-61-53-10; Fax: 33-1-43-06-43-43; E-mail: marc.edery@necker.fr.

‡ The abbreviations used are: PRL, prolactin; PRLR, prolactin receptor; SOCS, suppressor of cytokine signaling; CIS, cytokine-inducible SH-2 protein; Jak2, Janus kinase 2; STAT, signal transducer and activator of transcription; LHRE, lactogenic hormone-responsive element; oPRL, ovine prolactin; GH, growth hormone; TK, thymidine kinase.

Experimental Procedures

Reagents and Antibodies—Ovine PRL was a gift from the National Hormone and Pituitary/National Institute of Diabetes and Digestive and Kidney Diseases program (Baltimore, MD). Anti-FLAG monoclonal antibody M2 is a product of IBI-Kodak. The anti-phosphotyrosine antibody (αPY) and the anti-Jak2 antibody (αJak2) were purchased from Upstate Biotechnology, Inc.

Cells—T-47D human mammary cancer cells were grown in complete medium consisting of RPMI 1640 medium containing 10% fetal calf serum. Cells were deprived of serum for a 24-h period before the addition of human PRL (1 μg/ml) for different time periods.

Animals—Livers were obtained immediately after death from female 8-week-old C57BL/6 mice that had been injected intraperitoneally with ovine PRL (1 μg/g body weight) for different time periods.

Transient Transfection for LHRE-TK-Luciferase Assay—293 cells were split into 6-well plates before being transiently transfected using the calcium phosphate technique with 0.5 μg of pCH110 (β-galactosidase expression vector from Pharmacia), 0.1 μg of LHRE-TK-luciferase (a fusion gene carrying six copies of the LHRE and the TK minimal promoter linked to the coding region of the luciferase gene; LHRE is a STAT5 binding element of the β-casein promoter), 0.05 μg of plasmid pROCMV containing PRLR cDNA, and increasing concentrations (25–250 ng DNA) of FLAG epitope-tagged SOCS-1, SOCS-2, SOCS-3, or CIS (also referred as CIS1) in pEP-BOS expression vector (4). After 24 h of expression, the cells were incubated in the absence of serum before hormone stimulation (18 nt oPRL for 24 h) using serum-free Dulbecco’s modified Eagle’s medium-F-12 and then lysed, and luciferase and β-galactosidase activities were measured (18, 19). Aliquots of lysates were

This paper is available on line at http://www.jbc.org
were incubated with anti-Jak2 antibody (1:100) prepared from the livers of C57BL/6 mice (left panels) or T-47D cells (right panels) that had been treated with PRL for different time periods were hybridized with the indicated cDNA probes. The integrity of the RNA samples and the efficiency of transfer of RNA samples were monitored by ethidium bromide staining, and the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is included as a loading control. The exposure time is 24 h.

Immunoprecipitation and Western Blotting—Each 100-mm culture dish of 293 cells was co-transfected with 1 μg of PRLR cDNA, 0.5 μg of cDNA encoding the human tyrosine kinase Jak2, and 4 μg of each form of SOCS-encoding plasmid. For co-expression experiments, 1 μg of SOCS-1-encoding plasmid and 10 μg of SOCS-2-encoding plasmid or 2 μg of SOCS-3-encoding plasmid and 20 μg of SOCS-2-encoding plasmid were co-transfected. Cells were stimulated by PRL (18 ng/ml) for 15 min. Cells were subsequently lysed as described previously, and the lysates were incubated with anti-Jak2 antibody (1 μg/ml) or anti-FLAG antibody (0.5 μg/ml) and collected using protein A-agarose or protein G-agarose (15, 20). Immunoprecipitated proteins were separated by SDS-polyacrylamide gel electrophoresis (7%) transferred onto polyvinylidene difluoride transfer membrane (Polyscreen™; NEN Life Science Products); and immunodetected with appropriate antibodies to anti-Jak2 (Upstate Biotechnology, Inc.; 1:10,000), anti-phosphotyrosine (Upstate Biotechnology, Inc.; 1:10,000), anti-FLAG (Kodak; 0.5 μg/ml), and anti-PRLR (monoclonal antibody 5; 1 μg/ml); and visualized by ECF or ECL (Amersham Pharmacia Biotech). The experiments were repeated four to seven times, and a representative blot is shown in the figures.

RNA Preparation and Northern Blot Analysis—The preparation of RNA from cell cultures and liver samples was carried out according to the acidic/phenol/chloroform method. Northern blot analysis was performed essentially as described previously (21) using full-length cDNA inserts encoding SOCS-1, SOCS-2, SOCS-3, or CIS that were radiolabeled by random priming. The membranes were stripped in boiling 0.1% SDS and reprobed with the given probe. Three to four independent experiments were performed, and a representative experiment is shown in the figures.

RESULTS

Expression of SOCS Genes in Mammary and Hepatic Cells—The induction of SOCS-1, SOCS-2, SOCS-3, and CIS gene expression in mouse liver and in T-47D mammary cells upon PRL stimulation is shown in Fig. 1. SOCS-3 and, to a lesser extent, SOCS-1 are transiently expressed in liver and mammary cells, whereas SOCS-2 and CIS have somewhat different kinetics of induction and are still elevated 24 h after hormonal stimulation.

SOCS-1 and SOCS-3 Inhibit the Functional Activity of PRLR—The effect of the constitutive expression of SOCS genes on the response of 293 cells to PRL was investigated using the LHRE construct, for which we obtained a maximal induction of 20.1 ± 0.8 (n = 6)-fold upon PRL stimulation when SOCS plasmids were not transfected. Luciferase activity obtained in dose-response experiments has been normalized to these maximal fold induction values and is expressed as a percentage of these values (19). The constitutive expression of the SOCS-1 gene at increasing concentrations led to inhibition of the activation of transcriptional activity starting with very low doses of transfected cDNA (25 ng/well) (Fig. 2).

SOCS-3 constitutive expression also led to the inability of the PRLR to transmit the transcriptional response; however, this was achieved with higher concentrations of transfected plasmid. Interestingly, expression of SOCS-2 resulted in a partial inhibition in signaling (40%; the mean was statistically different (p < 0.01, Fisher's test) from 0 μg of SOCS-2 transfected plasmid), and this was obtained only with low concentrations of transfected plasmid (25 ng/plate) (Fig. 2). Lowering the concentration of transfected SOCS-2 to 1 ng/plate did not further inhibit signaling (data not shown); higher concentrations actually resulted in a restoration of the responsiveness of the LHRE construct to PRL (Fig. 2). Constitutive expression of CIS had no effect on the activation of gene transcription by PRL.

Immunoblot analysis of 293 cell lysates that were immunoprecipitated with Jak2 antibody revealed that upon constitutive expression of SOCS-1 or SOCS-3, PRL-induced tyrosine phosphorylation of Jak2 was greatly reduced (Fig. 3). Constitutive expression of CIS or SOCS-2 plasmid did not affect Jak2 kinase activity (Fig. 3).

Interactions of SOCS Molecules in PRL Signaling—To further investigate the interactions of SOCS proteins in PRL-mediated activation of gene transcription, cDNAs encoding SOCS proteins were co-transfected together with PRLR and the LHRE-TK-luciferase construct in 293 cells. As shown in Fig. 4A, the constitutive expression of SOCS-1 and SOCS-2 at increasing concentrations resulted in the restoration of transcriptional activity in a dose-dependent manner. Western blot analysis indicates that the level of expression of SOCS-1 is not affected by SOCS-2 co-transfection (Fig. 4B). The same experiments conducted with SOCS-3 and increasing concentrations of transfected SOCS-2 did not show any restoration of PRL signaling (Fig. 4A), indicating that the rescue of signal transduction by SOCS-2 was specific to SOCS-1. Constitutive expression of CIS at increasing concentrations also failed to modify the effects of SOCS-1, SOCS-2, and SOCS-3 on PRL-induced transactivation of the LHRE-TK promoter (Fig. 5).

SOCS-1 Associates with Jak2, and SOCS-2 Associates with the PRLR—To determine which molecules associate with the different SOCSs in PRLR signaling, we conducted an immunoblot analysis of 293 cell lysates immunoprecipitated with the anti-FLAG antibody and further analyzed them by Western blotting using an anti-phosphotyrosine antibody, as indicated in Fig. 6. Upon constitutive expression of SOCS-1, a major band of 130 kDa co-immunoprecipitated with the anti-FLAG antibody and was identified as Jak2 by immunoblotting with an antibody to Jak2. Although SOCS-1 was shown in Fig. 3 to greatly reduce but not completely suppress tyrosine phosphorylation of Jak2, the apparent level of tyrosine phosphorylation of Jak2 in Fig. 6 can be attributed mainly to the use of the anti-FLAG antibody for immunoprecipitation, which co-immunoprecipitates tyrosine-phosphorylated Jak2 through its recruitment to SOCS-1. Upon constitutive expression of SOCS-2, a major band of 92 kDa was co-immunoprecipitated with the anti-FLAG antibody. The PRLR monoclonal antibody revealed the 92-kDa protein, indicating that SOCS-2 associates with the PRLR. The level of tyrosine phosphorylation of the PRLR increased upon PRL stimulation because SOCS-2 did not inhibit Jak2 kinase activity. SOCS-3 constitutive expression did not reveal any major, specific tyrosine-phosphorylated protein co-immunoprecipitating with the anti-FLAG antibody (Fig. 6) and
similarly for CIS constitutive expression; no major, specific tyrosine-phosphorylated protein was co-immunoprecipitated with the anti-FLAG antibody (data not shown). A minor but consistent band of 130 kDa corresponding to Jak2 was observed upon SOCS-3 constitutive expression.

**Mechanism of SOCS-2-induced Restoration of PRL Signaling**—To determine whether Jak2 kinase was involved in the restoration process, cDNAs encoding Jak2, PRLR, SOCS-1, and SOCS-2 were co-transfected. Immunoblot analysis of cell lysates immunoprecipitated with Jak2 antibody revealed that upon co-expression of SOCS-1 and SOCS-2, PRL-induced tyrosine phosphorylation of Jak2, which had been shown to be greatly reduced by SOCS-1 alone, was restored (Fig. 7). However, this was not the case when SOCS-3 and SOCS-2 were co-expressed, in which case no detectable Jak2 activity was observed with or without PRL stimulation (Fig. 7), in agreement with the absence of restoration of activation of gene transcription under these conditions. Immunoblot analysis of cell lysates immunoprecipitated with the anti-FLAG antibody is shown in Fig. 7 and indicates that the major tyrosine-phosphorylated band corresponds to the 92-kDa PRLR and is induced by PRL, although a minor 130-kDa band corresponding to Jak2 is present, and its tyrosine phosphorylation is induced upon PRL stimulation, which is not the case when SOCS-1 alone is transfected (Fig. 6); thus, a large proportion of the PRLR is associated with SOCS-2 during the restoration process. Also, the apparent level of expression of SOCS-1 is not affected by SOCS-2 co-transfection (Fig. 7B) when compared with the transfection of SOCS-1 alone (Fig. 6).

**SOCS-2 Associates with Tyr-309 of the Intracellular Domain of the PRLR**—To investigate the individual role of each tyrosine of the cytoplasmic domain of the PRLR in SOCS-2 recruitment, cDNAs encoding the natural and mutant forms of the PRLR including 9F in which all tyrosines were replaced by phenylalanines and individual substitution of phenylalanine for tyrosines (8F-Ynnn) known to be phosphorylated (18) were co-transfected with SOCS-2-encoding plasmid. Lysates from PRL-stimulated cells were immunoprecipitated with anti-
FLAG antibody and further analyzed by Western blotting using anti-phosphotyrosine antibody. As shown in Fig. 8, a major band of 92 kDa corresponding to the tyrosine-phosphorylated PRLR was co-immunoprecipitated with the anti-FLAG antibody and was present only with wild type PRLR. None of the mutants known to be docking sites for STAT5 and highly tyrosine-phosphorylated (8F-Y580, 8F-Y479, and 8F-Y473) were associated with SOCS-2. Although it was not detectable in the anti-phosphotyrosine blot, the presence of mutant 8F-Y309 was detectable (but to a lesser extent than the wild type) using the anti-PRLR antibody; indeed, this mutant form is known to be weakly tyrosine-phosphorylated (18). These results support the notion of an interaction between SOCS-2 and the PRLR and suggest that Tyr-309 may represent a docking site for SOCS-2.

**DISCUSSION**

Understanding the mechanism by which PRL signaling is switched off requires the identification of novel proteins capable of suppressing PRL signal transduction. Recent reports have identified such proteins for several cytokines; we now assess the role of these proteins in the inhibition of PRL signal transduction pathways.

Both the SOCS-1 and SOCS-3 genes were transiently expressed in mouse liver and T-47D mammary cells and shown to
completely inhibit the activation of gene transcription by PRL. SOCS-1 was more potent an inhibitor at low concentrations of protein than was SOCS-3. This may correlate with the fact that lower levels of SOCS-1 mRNA than SOCS-3 are induced in hepatic cells in response to prolactin and GH (13). Accordingly, the crucial role of SOCS-1 in postnatal growth and survival has been demonstrated recently in mice lacking SOCS-1 (22).

Interaction of SOCS-1 with Jak2 markedly reduced its tyrosine kinase activity upon PRL stimulation, supporting the observation that SOCS-1 interacts with the catalytic region of Jak kinases, thus inhibiting their catalytic activity (5, 6) and, as a result, inhibiting the activation of signaling intermediates such as STATs. SOCS-2 was a partial inhibitor of signal transduction and, interestingly, when high levels of the SOCS-2 gene were constitutively expressed, there was a restoration of signaling by PRL without superinduction, as observed after GH stimulation (13). Although the activity of SOCS-2 appears to differ in regulating PRL and GH signal transduction, in both cases, the enhanced response to cytokine with high levels of SOCS-2 suggests that SOCS-2 itself may regulate the activity of endogenous suppressors such as SOCS-1 or SOCS-3; indeed, co-transfection experiments using SOCS-1 and SOCS-2 indicated that SOCS-2 was able to suppress the inhibitory effect of SOCS-1 by restoring PRL signal transduction; however SOCS-2 did not suppress the inhibitory effect of SOCS-3. This is the first demonstration of a dual effect of SOCS molecules by inhibiting and restoring signaling.

Although CIS gene expression was induced by PRL, the constitutive expression of this gene did not affect the activation of gene transcription by PRL. CIS has been shown to inhibit

**Fig. 6.** Association of PRLR signaling molecules with SOCS proteins. 293 cells expressing PRLR, Jak2, and various SOCS constructs were incubated in the presence (+) or absence (−) of 18 nM oPRL at 37 °C before lysis and immunoprecipitation with αFLAG. Lane U, cells that were not transfected with SOCS plasmids. Lane V, immunoprecipitation with a control antibody (monoclonal antibody 263). Immunoprecipitated proteins were Western blotted with αPY, αJak2, αFLAG, or αPRLR. The positions of Jak2 (130 kDa) and PRLR (92 kDa) are indicated. Molecular masses of the protein standards are indicated on the left in kDa. Because SOCS-1 and SOCS-2 are migrating in the region of immunoglobulin light chains, an enlargement of the blot is shown to better visualize the SOCS-1 and SOCS-2 proteins.

**Fig. 7.** The ability of wild type and mutated PRLR to associate with SOCS-2 in response to PRL. 293 cells expressing various forms of wild type (WT) or mutated PRLR and SOCS-2 were stimulated with 18 nM oPRL for 15 min at 37 °C. Whole cell extracts were immunoprecipitated with anti-FLAG antibody and Western blotted with αPY, αPRLR (7.5% SDS-polyacrylamide gel electrophoresis), or αFLAG antibodies (15% SDS-polyacrylamide gel electrophoresis). Molecular masses of the proteins standard are indicated on the left in kDa. The arrows indicate the migration of the proteins.
Inhibition and Restoration of PRL Signaling by SOCS

cytokine signal transduction by competing with STAT5 or other signaling molecules for docking sites on the receptor (3, 23, 24).

Recently, CIS3, also referred to as SOCS-3, and in addition SOCS-1 but not CIS1 have been shown also to inhibit PRL receptor-mediated STAT5 signaling (16). The present experiments further indicate that CIS does not modify the effects of SOCS-1, SOCS-2, and SOCS-3 on PRL signaling.

Although both SOCS-1 and SOCS-3 inhibited PRL-mediated activation of gene transcription, several differences between the mechanisms of action of SOCS-1 and SOCS-3 were observed: 1) SOCS-1 did associate with Jak2 and inhibited its kinase activity, whereas SOCS-3 was weakly associated with Jak2, 2) SOCS-1 was more potent than SOCS-3 in suppressing PRL signaling, and 3) SOCS-2 appeared to restore PRL signal transduction that had been inhibited by SOCS-1 but did not affect the SOCS-3 inhibitory effect. Similarly, it has been reported that SOCS-3 has a lower Jak2 than SOCS-1, and that SOCS-3 is a weaker inhibitor of interleukin 6 signaling than SOCS-1 (15). Furthermore, it has been shown recently that the inhibitions by SOCS-1 and SOCS-3 of interleukin 6 and leukemia-inhibitory factor-induced macrophage differentiation of M1 cells involve distinct portions of the Jak-STAT pathway, suggesting that the mechanisms of action of SOCS-1 and SOCS-3 in inhibiting signaling are quite different (12).

Interestingly, SOCS-2 was shown to be associated with the PRLR; as such, SOCS-2 has been shown to associate with the insulin-like growth factor I receptor, although the tyrosines involved in this interaction are not known (17). The interaction of SOCS-2 with the PRLR most probably involves Tyr-309 of the intracellular domain of the PRLR, which is the closest phosphorylated tyrosine to Box1 of PRLR, the region of association with Jak2 (25). The potent effect of SOCS-2 in suppressing the inhibitory effect of SOCS-1, which itself associates with Jak2, may result from the proximity of the regions of SOCS-2 and SOCS-1 association, respectively, in the PRLR and in Jak2. Given the fact that the SOCS-1 gene is expressed early as compared with the SOCS-2 gene in mammary cells and hepatic cells in response to PRL stimulation, a possible function of SOCS-2 would be to restore PRL signaling and thus re-sensitize cells to PRL after the initial inhibitory effect of SOCS-1. It will be interesting to test whether this hypothesis can be extended to other members of the expanding family of SOCS and CIS proteins and to other cytokines.

The SH-2 containing tyrosine phosphatases SHP-1 or SHP-2 do not appear to be involved in the inhibition of PRL signaling (2, 26) in contrast to signal transduction pathways activated by GH or other cytokines. The SOCS proteins appear as major regulator of PRL signaling; the complex interaction between the different SOCS molecules in PRL signaling will be further clarified by generation of mice lacking one or multiple members of this family.

Acknowledgments—We thank D. Hilton and R. Starr for the gift of SOCS-pEF-BOS expression vectors and for reading and editing the manuscript. Ovine PRL was kindly provided by the National Hormone and Pituitary Program.

REFERENCES

1. Bole-Feyssot, C., Goffin, V., Edery, M., Binart, N., and Kelly, P. A. (1998) Endocr. Rev. 19, 225–268
2. Ali, S., Chen, Z., Lebrun, J. J., Vogel, W., Khatrienkonov, A., Kelly, P. A., and Ullrich, A. (1996) EMBO J. 15, 135–142
3. Yoshimura, A., Ohkubo, T., Kiuchi, T., Jenkins, N. A., Gilbert, D. J., Copeland, N. G., Harra, T., and Miyajima, A. (1998) EMBO J. 14, 2816–2826
4. Starr, R., Wilson, T. A., Viney, E. M., Murray, L. J., Rayner, J. R., Jenkins, B. J., Gonda, T. J., Alexander, W. S., Metcalf, D., Nicola, N. A., and Hilton, D. J. (1997) Nature 387, 917–921
5. Endo, T. A., Masuhara, M., Yokouchi, M., Suzuki, R., Sakamoto, H., Mitsui, K., Matsumoto, A., Tanimura, S., Obitsu, M., Misawa, H., Miyazaki, T., Leonor, N., Taniguchi, T., Fujita, T., Kanakura, Y., Komiyi, S., and Yoshimura, A. (1997) Nature 387, 921–924
6. Naka, T., Narazaki, M., Hirata, M., Matsumoto, T., Minamoto, S., Azoo, A., Nishimoto, N., Kajita, T., Tags, T., Yoshizaki, K., Akira, S., and Kishimoto, T. (1997) Nature 387, 924–929
7. Ohya, K., Kajigaya, S., Yamasita, Y., Miyazato, A., Hatake, K., Miura, Y., Ikeda, U., Shimada, K., Ozawa, K., and Mano, H. (1997) J. Biol. Chem. 272, 27175–27182
8. Bjorbaek, C., Elmquist, J. K., Frantz, J. D., Shoelson, S. E., and Flier, J. S. (1998) Mol. Cell 1, 619–625
9. Starr, R., and Hilton, D. J. (1998) Int. J. Biochem. Cell Biol. 30, 1081–1085
10. Narazaki, M., Fujimoto, M., Matsumoto, T., Morita, Y., Saito, H., Kajita, T., Yoshizaki, K., Naka, T., and Kishimoto, T. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 13130–13134
11. Yoshimura, A. (1998) Leukemia (Baltimore) 12, 1851–1857
12. Nicholson, S. E., Willson, T. A., Farley, A., Starr, R., Zhang, J. G., Baca, M., Alexander, W. S., Metcalf, D., Hilton, D. J., and Nicola, N. A. (1999) EMBO J. 18, 375–385
13. Adams, T. E., Hansen, J. A., Starr, R., Nicola, N. A., Hilton, D. J., and Billestrup, N. (1998) J. Biol. Chem. 273, 1285–1287
14. Song, M. M., and Shuai, K. (1998) J. Biol. Chem. 273, 35056–35062
15. Suzuki, R., Sakamoto, H., Yasukawa, H., Masuhara, M., Wakioka, T., Sasaki, A., Yuge, K., Komiyi, S., Inoue, A., and Yoshimura, A. (1998) Oncogene 17, 2271–2278
16. Helman, D., Sandowski, Y., Cohen, V., Matsumoto, A., Yoshimura, A., Merchav, S., and Gertler, A. (1998) FEBS Lett. 441, 287–291
17. Dey, B. R., Spence, S. L., Nisley, P., and Furlanetto, R. W. (1998) J. Biol. Chem. 273, 24085–24101
18. Pezet, A., Perrag, F., Kelly, P. A., and Edery, M. (1997) J. Biol. Chem. 272, 25043–25050
19. Goffin, V., Kinet, S., Ferrag, F., Binart, N., Martial, J. A., and Kelly, P. A. (1996) J. Biol. Chem. 271, 16573–16579
20. Berlanga, J. J., Guiulio, O., Buteau, H., Applanat, M., Kelly, P. A., and Edery, M. (1997) J. Biol. Chem. 272, 2050–2052
21. Martini, J. F., Pezet, A., Guezennece, C. Y., Edery, M., Postel-Vinay, M.-C., and Kelly, P. A. (1997) J. Biol. Chem. 272, 18951–18958
22. Starr, R., Metcalf, D., Elefanty, A. G., Blysh, M., Willson, T. A., Nicola, N. A., Hilton, D. J., and Alexander, W. S. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 14395–14399
23. Matsumoto, A., Masuhara, M., Mitsui, K., Yokouchi, M., Obitsu, M., Misawa, H., Miyazaki, T., and Yoshimura, A. (1997) Blood 89, 3148–3154
24. Yoshimura, A. (1998) Cytokine Growth Factor Rev. 9, 197–204
25. Pezet, A., Buteau, H., Kelly, P. A., and Edery, M. (1997) Mol. Cell. Endocrinol. 129, 199–208
26. Berchhold, S., Volarevic, S., Meriggel, R., Mercep, M., and Groner, B. (1998) Mol. Endocrinol. 12, 556–567