Formation of STAT5-containing DNA Binding Complexes in Response to Colony-stimulating Factor-1 and Platelet-derived Growth Factor*

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Colony-stimulating factor (CSF-1) activates several members belonging to the STAT (signal transducers and activators of transcription) family of transcription factors. We investigated the DNA binding complexes activated by CSF-1 in several cell lines and compared them with complexes activated by platelet-derived growth factor and interleukin 3. Our results indicate that the SIF-A complex activated by CSF-1 and platelet-derived growth factor may contain STAT3/STAT5 heterodimers binding to the high affinity SIF binding site, m67. In addition, both growth factors activate one or several STAT5-containing protein complexes binding to the prolactin-inducible element, PIE. The formation of these complexes was cell type and growth factor specific. Interleukin 3 activated only PIE binding complexes containing STAT5A and STAT5B and did not activate m67 binding complexes. It appears, therefore, that STAT5 cannot bind to m67 as a homodimer, but it can bind if it is dimerized with STAT3, whereas it can bind to the PIE element without being either complexed with STAT3 or any other known STAT protein, possibly as a homodimer or as STAT5A/STAT5B heterodimer. However, in addition, STAT5 may heterodimerize with other proteins and form novel PIE binding complexes.

Over the past several years, a new group of transcription factors has been characterized and cloned (reviewed in Ref. 1). The first members of this family of transcription factors, known as STAT1 proteins (signal transducers and activators of transcription), were identified as the factors mediating the response to IFN-α (2). Subsequently, it has been shown that a wide range of cytokines and growth factors lead to the activation of members of the STAT family. Thus far, six members of the family have been cloned. The STAT5 gene is the only one which has been duplicated (3). The levels of amino acid sequence identity between the different members of the STAT family range between about 50 and 18% (4). However, all known STAT proteins share several features, one SH2 and one SH3-like domain and one C-terminal tyrosine residue, which is phosphorylated upon activation. In addition, several of the STAT proteins require the phosphorylation of a C-terminal serine, located within a well conserved mitogen-activated protein kinase phosphorylation site, for DNA binding, and/or transactivation capacity (5–8). The mitogen-activated protein kinase phosphorylation site is present in STAT1, STAT3, and STAT4; however, the biological requirement for serine phosphorylation has thus far, only been demonstrated for STAT1 and STAT3 (6).

Binding of the STAT proteins to specific DNA sequences on the promoter of regulated genes requires prior dimerization, involving binding of a C-terminal phosphotyrosine of one STAT protein to the SH2 domain of the other. The formation of heterodimeric complexes has been observed, such as STAT1/STAT2 binding to the interferon-α/β response element via p48 (9), and STAT1/STAT3 binding to the sis-inducible element (SIE) (10). The composition of these complexes has been confirmed by the use of specific antibodies in electrophoretic mobility shift assays. In parallel, overexpression of STAT proteins in cell lines and subsequent activation led to the formation of DNA binding protein complexes resembling those observed in untransfected cells. The STAT protein complexes have been shown to bind several related DNA sequences with different affinities. It has further been noted that several of the STAT proteins can be a component of different DNA binding protein complexes. For example, STAT1 can either bind to DNA as a homodimer, or heterodimerize with STAT3 or with STAT2.

STAT5 was first characterized as a prolactin-inducible transcription factor in the mammary gland in sheep (11). Subsequently, STAT5 or related proteins were found to be activated by a wide range of cytokines, including growth hormone, IL-3, IL-5, granulocyte/macrophage-CSF, G-CSF, thrombopoietin, erythropoietin, IL-2, IL-4, IL-7, IL-13, IL-15, INF-γ, epidermal growth factor, and CSF-1 (3, 11–23). The presence of two STAT5 genes and an initial lack of suitable specific antibodies created some difficulties in the interpretation of the results.

We show here that a protein reactive with an antibody raised against the C terminus of STAT5A is a component of the SIF-A complex activated by the growth factors CSF-1 and PDGF, binding to the high affinity binding site m67. Therefore, the SIF-A complex appears to contain a heterodimer composed of STAT3 and either STAT5A or a related protein, similar to a STAT3/STAT5 heterodimer. STAT5A and STAT5B can bind to the prolactin-inducible element as homodimers or heterodimers (3, 11–23). The presence of two STAT5 genes and an initial lack of suitable specific antibodies created some difficulties in the interpretation of the results.

We show here that a protein reactive with an antibody raised against the C terminus of STAT5A and STAT5B can bind to the prolactin-inducible element as homodimers or heterodimers after activation by CSF-1, PDGF, or IL-3.

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‡ The abbreviations used are: STAT, signal transducers and activators of transcription; CSF-1, colony-stimulating factor-1; G-CSF, granulocyte-CSF; SIE, sis-inducible element; SIF, sis-inducible factor; IL, interleukin; PDGF, platelet-derived growth factor; PIE, prolactin-inducible element.
**EXPERIMENTAL PROCEDURES**

Cell Lines and Culture—NFS-60 cells (26) were maintained in Dulbecco's modified Eagle's medium supplemented with 10% bovine fetal serum and 1 ng/ml recombinant human G-CSF (obtained from Amgen Corp.) at 37 °C in 5% CO₂. NIH3T3 cells expressing the wild-type human CSF-1R (T56 cells, a gift from Dr. Martine Roussel, Memphis, Tennessee) and the murine myeloid cell line M1 were maintained in Dulbecco's modified Eagle's medium containing 10% bovine fetal serum. FDC-P1 cells, derived from FDC-P1 cells by retroviral infection with an expression construct of the murine CSF-1 receptor (27), were a gift from Dr. Larry Rohrschneider, Seattle, WA. These cells were maintained in Dulbecco's modified Eagle's medium supplemented with 500 units/ml recombinant murine IL-3 and 10% bovine fetal serum. BAC1.2F5 cells, a murine macrophage cell line, a gift from Dr. Richard Stanley, New York, NY, were maintained in Dulbecco's modified Eagle's medium supplemented with 10,000 units/ml recombinant human CSF-1 (gift from CETUS Corp.) and 10% fetal bovine serum.

Electrophoretic Mobility Shift Assay—This assay was performed as described before (25). Total protein extracts were prepared from cells and used in binding reactions using end-labeled, double-stranded oligonucleotides. The following double-stranded oligonucleotide sequences were used: m67, 5'-GATCGACATTTCCGTAATCG (28); and PIE, 5'-GATCGAGTTTCAAGATCC (11). If required, the following antibodies were added to the binding reactions 15 min prior to the addition of the DNA probe: anti-STAT1 (Transduction Laboratories, Lexington, KY); anti-STAT3 directed against the C-terminal amino acids 750–769 and shown not to cross-react with STAT5 (Refs. 21 and 25; Santa Cruz Biotechnology); anti-STAT5A, raised against a C-terminal peptide, DQQGEFDLDESMDNA, of the murine STAT5A protein, which does not cross-react with STAT5B or STAT1; and anti-STAT5B (Santa Cruz Biotechnology), raised against a C-terminal peptide, DWARRVEELLGPMDSQ, of the murine STAT5B protein. According to the manufacturer's specifications, the anti-STAT5B antibody may cross-react with STAT5A; however, we observed very little cross-reactivity.

Immunoprecipitations and Western Blot Analysis—STAT3 and STAT5A proteins were immunoprecipitated from T56 cells, separated by SDS-polyacrylamide gel electrophoresis, transferred onto Hybond-C membrane (Amersham Corp.), and probed using anti-STAT5 antibodies. After removal of the antibodies, the membrane was reprobed with anti-STAT3 antibodies.

**RESULTS**

Formation of SIE-binding STAT3/STAT5 Heterodimers—We have shown previously that G-CSF activates the formation of complexes containing STAT3 and STAT5A or a STAT5A-related protein capable of binding to the high affinity SIE sequence, m67, in NFS-60 cells (25). To investigate if any other cytokines or any other cell lines promote the formation of this complex with the m67 element, we treated cells with PDGF and CSF-1. These growth factors have been shown previously to activate the SIF complexes A, B, and C, respectively (10). We have described previously that CSF-1 caused the formation of SIF complexes A, B, and C in bone marrow-derived macrophages, BAC1.2SF cells, and in NIH3T3 cells expressing the human STAT1-1 receptor, T56. CSLF-1 has further been demonstrated to activate STAT5 in BAC1.2F5 cells (20). Pretreatment of the protein extracts of CSF-1-treated BAC1.2F5 cells with antibodies to STAT5A or STAT3 led to a reduction of the formation of the SIF-A complex (Fig. 1A). The same effect was observed using proteins of CSF-1-treated FDwtfms cells and T56 cells (Fig. 1, B and C). These results indicate that in response to CSF-1, STAT1, STAT3, and STAT5A become part of SIE-binding protein complexes. A slight reduction of the SIF-A band was observed in some experiments in the presence of the STAT5B antibodies. This is probably due to a weak cross-reactivity of the STAT5B antibodies with STAT5A. The relative amount of activated STAT1 appeared to vary from cell line to cell line, which was most noticeably reflected in the intensity of the SIF-C band observed.

In addition, PDGF, another activator of SIF complexes A, B, and C, activated the formation of SIF-A containing STAT5A reactive protein. A, BAC1.2F5 cells were cultured in the absence of CSF-1 for 16 h. The cells were then incubated for 5 min in the presence of 10,000 units/ml recombinant human CSF-1 prior to the preparation of protein extracts. The protein extracts were used for electrophoretic mobility shift assays with the m67 high affinity SIE probe. Where indicated, the protein extract was pretreated for 15 min with antibodies to STAT1, STAT3, STAT5A, or STAT5B prior to the addition of the probe. B, FDwtfms cells, after incubation for 16 h in the absence of IL-3, were incubated with 10,000 units/ml CSF-1 prior to the preparation of the protein extracts. The assay was performed as in A. C, Same as A but using extracts of T56 cells after incubation with CSF-1. D, Same as C but using extracts of T56 cells after incubation with PDGF.

The specificity of the anti-STAT5A antibodies was verified by probing Western blots of immunoprecipitated STAT3 and STAT5A. After removal of the STAT5 antibodies, the filters were reprobed with antibodies to STAT3. No cross-reactivity of the antibodies was observed (Fig. 2). Similarly, antibodies raised against STAT5B did not react with STAT3 but cross-reacted weakly with STAT5A, as claimed by the manufacturers (data not shown). These results demonstrate that PDGF, which acts by binding

![Figure 1](image-url)
to a specific receptor that is very closely related to the CSF-1 receptor, activates STAT1, STAT3, and STAT5A like CSF-1. The results show as well that the proposed STAT3 homodimeric complex, designated SIF-A, can be composed of a STAT3/STAT5 heterodimer, giving rise to a complex that comigrates with the proposed STAT3 homodimer. It appears, however, that CSF-1 and PDGF did not mediate the formation of a STAT3 homodimeric complex because the antibody to STAT5A abolished the SIF-A band completely.

Another cytokine described to activate STAT3 is IL-6, which signals through the gp130 receptor subunit, which is closely related to the cytoplasmic domain of the G-CSF receptor (29). During the acute phase response in the rat liver, STAT3 and STAT5B are activated, and they have both been demonstrated to bind to the acute phase response element (24). We, therefore, analyzed protein extracts of IL-6-treated M1 cells for the presence of STAT3/STAT5 heterodimers. A complex containing both STAT3 and STAT5 was observed (data not shown).

Activation of STAT5-containing PIE Binding Complexes by CSF-1 and PDGF—It has been recognized before that STAT proteins form specific complexes with several different DNA-binding sequences, and the composition of the protein complexes may vary depending on the DNA binding site. We, therefore, performed DNA binding studies using protein extracts of CSF-1- and PDGF-treated cells and the prolactin-inducible element (PIE) of the bovine casein gene promoter, which was first described as a STAT5 binding site (11). In these binding reactions, we observed three specific complexes, X, Y, and Z, when proteins from CSF-1-treated T56 cells were used (Fig. 3A). The addition of antibodies identified complex Z as containing STAT1. This band comigrated in the gel with the proposed STAT1 homodimeric complex SIF-C binding to the m67 sequence. The formation of complex Y was affected by the addition of antibodies to STAT5B, and complex X contained STAT5A. None of the complexes contained STAT3. In the same cells, PDGF activated only significant levels of the slowest migrating PIE binding complex X, which was confirmed to contain STAT5A (Fig. 3B). The lack of complex Z agrees with our finding of low levels of STAT1 activation by PDGF, as shown in the electrophoretic mobility shift assay using the m67 probe, observed in Fig. 1D.

Incubation of FDwtfms cells with CSF-1 led to the activation of the same m67 binding proteins as observed in T56 cells. However, the complexes binding to the PIE sequence were different from the complexes observed using proteins of T56 cells. Complex Z, containing STAT1, was missing or greatly reduced, and a new PIE binding complex, W, appeared to contain STAT5A. Another complex was observed that comigrated with complex Y observed in the T56 cell extracts and similarly contained STAT5B (Fig. 3C). The slowest migrating complex X observed with extracts of the T56 cells, which migrated significantly slower than the SIF-A complex, was not present in the binding reactions using proteins of FDwtfms cells.

In response to CSF-1, BAC12F5 cells activated two PIE-binding protein complexes, comigrating with complexes X and Y (Fig. 3C). It appeared, however, that the STAT5B antibody not only affected complex Y, as observed previously, but complex X as well. Again, none of the complexes contained STAT3. The antibody to STAT1 gave a faint supershift of a band that was not detectable previously. This could be due to stabilization of weak protein/DNA interactions and is in agreement with the results obtained in Fig. 3A, in which the band supershifted by the STAT1 antibody was significantly stronger than the STAT1-containing band in the absence of the antibody.

We analyzed the complexes formed in response to IL-3, a known activator of STAT5A and STAT5B (3). As expected, FDwtfms cells activated STAT5A and STAT5B after incubation with IL-3 (Fig. 4). We observed the formation of complexes binding to PIE but not to m67 (data not shown). The PIE-binding complexes Y and W contained either STAT5A or STAT5B and apparently no heterodimers between these two proteins (Fig. 4). These complexes, which comigrated with complexes X and W, observed after incubation of these cells with CSF-1, were possibly homodimeric complexes, because no antibody to any other STAT protein appeared to affect their formation (data not shown).

**DISCUSSION**

STAT5 is a transcription factor that is activated by a large range of extracellular stimuli. The first activator described was prolactin found in the mammary gland (11). Others include growth factors, cytokines, hormones, and cell adhesion to laminin. Other members of the STAT family of transcription factors, which are activated in response to cytokines and growth factors, have been shown not to be required for the proliferative response of the cell (30, 31), and mice defective in the STAT1 gene developed normally (32, 33). Indeed, there is mounting evidence that STAT proteins may be required for either cell differentiation or for functions of differentiated cells. For example, the cellular response to IFN-α, at least in a fibroblast line, required the expression and activation of STAT1 and STAT2 (30, 31). Mice that are deficient in STAT1 have a total lack of response to interferons but are otherwise normal (32, 33).

Although STAT5 was shown not to be required for IL-2-mediated proliferation (12), there is evidence that STAT5 is required for the proliferative response of cells to erythropoietin (34) and to IL-3 (35). Our results show clearly that STAT5 can be part of several quite different complexes, which interact with more than one type of recognition sequence, i.e. with a PIE and a SIE sequence. Our data indicate as well that there may be preferences in the choice of STAT5A over STAT5B during the formation of STAT dimers and during the formation of protein-DNA complexes. The biological function of these different dimers is thus far unclear. Contrary to initial observations, the mouse is not the only species in which the STAT5 gene has been duplicated, giving rise to two closely related genes, STAT5A and STAT5B. Recently, it has been demonstrated that the STAT5B gene gives rise to two proteins, a full-length translation product, and another protein lacking the N-terminal 40 amino acids due to differential splicing of the mRNA (24). It is worth noting that this truncated form lacks the binding site for the anti-STAT5B antibody used in our experiments. Similarly, truncated forms of STAT1 and STAT3 have been described as well (36, 37).
plexes containing STAT5 in response to CSF-1, PDGF, IL-3, and IL-6, using several cell lines. CSF-1 has different biological effects in the cell lines under investigation. T56 cells can proliferate in response to CSF-1 but were not required to do so, since they were kept in 10% serum at all times throughout the experiment. They are fibroblasts that do not undergo morphological changes in response to CSF-1. In contrast, BAC1.2F5 cells absolutely require CSF-1 for proliferation. These cells express a range of proteins characteristic for macrophages, such as the CSF-1 receptor and MAC1, and they are capable of internalizing particles by phagocytosis. They are, however, a permanently proliferating cell line, not undergoing terminal differentiation. FDwtfms cells, on the other hand, proliferate in response to IL-3 but can undergo several rounds of cell division, prior to terminal differentiation into macrophages, in response to CSF-1. The signal initiating the differentiation pathway must originate in response to CSF-1 binding to the receptor. There remains the possibility that STAT5 may be an important factor for the differentiation response. It appears obvious, however, that the activation of STAT5 proteins alone by CSF-1 may not be enough to allow any predictions to be made with regard to the subsequent fate of the cells. STAT5 proteins can form several different DNA-binding complexes, thus possibly allowing the regulation of distinct subsets of genes required for different cellular responses. One of the IL-3-activated complexes binding to the PIE sequence, proposed to contain a STAT5B homodimer, comigrated in the electrophoretic mobility shift assay gel with complex Y observed using the CSF-1-activated T56 cell extracts. The other IL-3-activated, PIE-binding complex, W, proposed to contain a STAT5A homodimer, was not observed in T56 cells after activation with CSF-1, but it was activated by CSF-1 in FDwtfms cells (Fig. 3). Instead, in T56 cells CSF-1 led to the formation of a STAT5A-containing complex X, which migrated significantly slower than the supposed STAT5A homodimer. There are at least two alternative explanations for this result. One possibility is that the STAT5A antibody can bind to two proteins, one of which is the known STAT5A and the other a STAT5A related protein, which shares homology with the C terminus of STAT5A, i.e. with the region against which the antibody was raised. Another explanation for the results is that STAT5A can form another heterodimeric complex with an as yet unidentified binding partner, thus giving the slower migrating complex with the PIE sequence in T56 cells.
The STAT5A antibody consistently supershifted complexes formed with the PIE sequences, X and W, whereas it caused abolition of the SIF-A complex formed with the m67 sequence. This indicates that the antibody will interfere with the formation of the dimer between STAT5A and STAT3 or with binding of the proteins to DNA, whereas it does not interfere with the formation of other complexes containing STAT5A binding to STAT3, thus being structurally distinct from other STAT dimers.

Investigations of the significance of the various STAT5-containing complexes activated in these cells by CSF-1 for cellular biological effects in response to the same factors in different cells.

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REFERENCES

1. Schindler, C., and Darnell, J. E., Jr. (1995) Annu. Rev. Biochem. 64, 621–651
2. Fu, X.-Y., Schindler, C., Imotta, T., Aebersold, R., and Darnell, J. E., Jr. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 7840–7843
3. Mui, A. L.-F., Wakao, H., O’Farrell, A.-M., Harada, N., and Miyajima, A. (1995) Mol. Cell. Biol. 15, 2527–2535
4. Hou, J., Schindler, U., Henzel, W. J., Ho, T. C., Brasseur, M., and McKnight, S. L. (1994) Science 265, 1701–1706
5. Eilers, A., Georgelis, D., Klose, B., Schindler, C., Zieniewski, A., Harpur, A. G., Wilks, A. F., and Decker, T. (1995) Mol. Cell. Biol. 15, 3579–3586
6. Weix, Z., Zheng, Z., and Darnell, J. E., Jr. (1995) Cell 82, 241–250
7. Boutron, T. G., Zheng, Z., Wen, Z., Darnell, J. E., Jr., Stahl, N., and Tancopolous, G. D. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 6915–6919
8. David, M., Petrocico, E., Benjamin, C., Pine, R., and Lerner, A. C. (1995) Science 269, 1722–1723
9. Fu, X.-Y., Kessler, D. S., Veals, S. A., Levy, D. E., and Darnell, J. E., Jr. (1990) Proc. Natl. Acad. Sci. U. S. A. 87, 8555–8559
10. Zhong, Z., Zheng, Z., and Darnell, J. E., Jr. (1994) Science 264, 95–98
11. Wakao, H., Gouilleux, F., and Groner, B. (1994) EMBO J. 13, 2182–2191
12. Fuji, H., Nakagawa, Y., Schindler, U., Kawahara, A., Mori, H., Gouilleux, F., Groner, B., Ihle, J. N., Minami, Y., Miyakazi, T., and Tanaguchi, T. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 5482–5486
13. Gouilleux, F., Wakao, H., Mundt, M., and Groner, B. (1994) EMBO J. 13, 4361–4369
14. Gouilleux, F., Moritz, D., Humar, M., Moriggl, R., Berchtold, S., and Groner, B. (1995) Endocrinology 136, 5700–5708
15. Johnston, J. A., Bacon, C. M., Piniflouz, D. S., Rees, R. C., Kaplan, D., Shibuya, K., Ortolano, J. R., Gupta, S., Chen, Y. Q., Giri, J. D., and O’Shea, J. J. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 8705–8709
16. Bacon, C. M., Tortolini, P. J., Shimoseka, A., Rees, R. C., and Longo, D. L. (1995) FEBS Lett. 370, 63–68
17. Pallard, C., Gouilleux, F., Charon, M., Groner, B., Gisselbrecht, S., and Dusanter-Fourt, I. (1995) J. Biol. Chem. 270, 15942–15945
18. Wakao, H., Harada, N., Kitamura, T., Mui, A. C., and Miyajima, A. (1995) EMBO J. 14, 2527–2535
19. Lai, C.-F., Ripperger, J., Morella, K. K., Wang, Y., Gearing, D. P., Horseman, N. D., Campos, S. P., Fey, G. H., and Baumann, H. (1995) J. Biol. Chem. 270, 23254–23257
20. Barahamoud-pour, F., Meinke, A., Eillers, A., Gouilleux, F., Groner, B., and Decke, D. (1995) FEBS Lett. 359, 29–33
21. Gouilleux, F., Pallard, C., Dusanter-Fourt, I., Wakao, H., Haldosen, L.-A., Norstog, G., Levy, D., and Groner, B. (1995) EMBO J. 14, 2005–2013
22. Ruffin-jonison, S., Chenand, K., and Cohen, S. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 4215–4218
23. Novak, U., Harpur, A. G., Paradiso, L., Kanagasundaram, V., Jaworski, A., Wilks, A. F., and Hamilton, J. A. (1995) Blood 86, 2948–2956
24. Rehman, J. A., Fritz, S., Richter, K., Hocke, G. M., Lottsprech, F., and Fey, G. H. (1995) J. Biol. Chem. 270, 29998–30006
25. Novak, U., Ward, A. C., Hertzog, P. J., and Paradiso, L. (1996) Growth Factors in press
26. Weinstein, Y., Ihle, J. N., Lavu, S., and Reddy, E. P. (1986) Proc. Natl. Acad. Sci. U. S. A. 83, 5010–5014
27. Lioubin, M. N., Myles, G. M., Carlborg, K., Bowtell, D., and Rohrschneider, L. R. (1995) Mol. Cell. Biol. 15, 5682–5691
28. Wagner, B. J., Hayes, T. E., Hoban, C. J., and Cochran, B. H. (1990) EMBO J. 9, 4477–4484
29. Fukunaga, R., Ishikawa-Ikeda, E., Pan, C.-X., Seto, Y., and Nagata, S. (1991) EMBO J. 10, 2825–2835
30. Muller, M., Laxton, C., Briscoe, J., Schindler, C., Imotta, T., Darnell, J. E., Jr., Stark, G. R., and Kerr, I. M. (1995) EMBO J. 14, 4221–4228
31. Leung, S., Qureshi, S. A., Kerr, I. M., Darnell, J. E., Jr., and Stark, G. (1995) Mol. Cell. Biol. 15, 1312–1317
32. Durbin, J. E., Hackett, R., Simon, M. C., and Levy, D. E. (1996) Cell 84, 443–450
33. Meraz, M. A., White, M., Sheehan, K. C. F., Bach, E. A., Rodig, S. J., Di Ghe, A. S., Kaplan, D. H., Riley, J. K., Greenland, A. C., Campbell, D., Carver-Moore, K., Dubois, R. N., Clark, R., Aguet, M., and Schreiber, R. D. (1996) Cell 84, 431–442
34. Damen, J. E., Wakao, H., Miyajima, A., Cutter, R. L., and Krystal, G. (1995) EMBO J. 14, 5557–5568
35. Mui, A. C., Wakao, H., Kinoshita, T., Kitamura, T., and Miyajima, A. (1996) EMBO J. 15, 2425–2434
36. Schindler, C., Shuai, K., Preisover, V. R., and Darnell, J. E., Jr. (1992) Science 257, 809–813
37. Schaefer, T. S., Sander, L. K., and Nathans, D. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 9097–9101
38. Bourette, R. P., Myles, G. M., Carlborg, K., Chen, A. R., and Rohrschneider, L. R. (1995) Cell Growth & Differ. 6, 631–645