Targeted recruitment of histone acetyltransferase (HAT) activities by sequence-specific transcription factors, including the retinoic acid receptors (RARs) and retinoid X receptors (RXRs), has been proposed to lead to destabilization of nucleosomal cores by acetylation of core histones. However, biochemical evidence indicates that destabilization and depletion of linker H1 histones must also occur at the promoter regions of actively transcribing genes. Mechanisms by which nuclear receptors and other transcription factors affect the removal of histone H1 from transcriptionally silent chromatin have not been previously described. In this report, we show that RARs interact in a ligand-dependent manner with HMG-I, which is known to displace histone H1 from chromatin. We further show that HMG-I and a novel related protein, HMG-R, also interact with other transcription factors. Using sense and antisense constructs of HMG-I/R in transient transfection assays with a retinoid responsive reporter, we also demonstrate that HMG-I/R is important for retinoid dependent transcriptional activity of RAR. These findings suggest a step wise mechanism by which RARs and other transcription factors can cause a targeted unfolding of compact chromatin as a first step in transcriptional activation, which would then be followed by recruitment of HAT activity and subsequent events.

Retinoid acid receptors and retinoid X receptors (RAR and RXR α, β, and γ) are sequence-specific, ligand-dependent transcription factors belonging to the superfamily of steroid/thyroid/vitamin D₃ nuclear receptors (1). RAR-RXR heterodimers induce gene expression in a ligand dependent manner through RA responsive elements (RAREs) present in the promoter regions of responsive genes (2). Recently, CBP/p300, Sug1/Trip1, TIF1, SRC-1/N-CoA1, TIF2/GRIP1, and ACTR have been identified as co-factors, which interact with RARs and other nuclear receptors in a ligand-dependent manner (3, 4). Biochemical evidence supports models involving depletion of the nucleosomal core as well as H1 histones at the promoter regions of actively transcribing genes. CBP/p300, its associated protein p/CAF, SRC-1, and ACTR have intrinsic histone acetyltransferase (HAT) activity (5–7). It has been proposed that recruitment of HAT activity by sequence-specific transcription factors leads to acetylation of core histones and a destabilization of the nucleosomal core, thereby facilitating transcriptional activation (8–10). However, an earlier obligatory step in transcriptional activation involves an unfolding of the compact, 30-nm chromatin fiber, which results only from a displacement of the potent transcriptional repressor, histone H1, from chromatin (11, 12). Mechanisms by which nuclear receptors and other transcription factors affect this obligatory removal of histone H1 from transcriptionally silent chromatin have not been described previously. In this report, we provide evidence that RARs interact in a ligand-dependent manner with HMG-I, which is known to displace histone H1 from chromatin (13). Additionally, we identify an HMG-I-related protein, HMG-R, which also interacts with RARs in a ligand-dependent manner. We further show that HMG-I and HMG-R interact with RXRs; PPARγ, c-Jun, and CBP, thus indicating recruitment of HMG-I/R by various transcription factors as a common mechanism for enhancer-dependent transcriptional activation. Finally, using transient transfections, we demonstrate that HMG-I/R is required for retinoid-dependent transactivation of a reporter construct by RAR, thus showing the functional consequences of RAR-HMG-I/R interactions.

MATERIALS AND METHODS

Plasmid Constructions—In yeast two-hybrid screening, the bait (pAS2-RAR-ΔAB) consisted of the Gal4-DBD and the human RARγ coding sequence spanning C–F regions (amino acids 90–454). pAS2-RARγΔAB was constructed by PCR amplification of RARγΔAB from an RARγ expression vector using primer pairs 5'-AGGAATTCCTCGAGTGTGCAATGACAAGT-3' and 5'-AGGGATCCCTCAAGGCTCTGGGACCATTTACGCCG-3' and subsequently cloning the amplified product into EcoRI-BamHI sites of pAS2-1 (CLONTECH). pAS2-RARγ was prepared by PCR amplification of RARγ using primer pairs 5'-AGCCCGAGGATTCGTGGCCACCAATAAGGAGCGG-3' and 5'-TAATTGATCTCTGGTCTAGGCTGGGAGCTT-3' and cloning the amplified product into the EcoRI site of pAS2-1. pGBT-RAR-DEF was prepared by PCR amplification of RARγΔDEF using primer pairs 5'-TCGGAAGTGATCTCTGACAGGAGAGTCGTG-3' and 5'-AAATTGATCTCTGGTCTAGGCTGGGAGCTT-3' and cloning the amplified product into EcoRI-BamHI sites of pGB29. pACT2-Sug1 was isolated during the screening procedure. pAS2-RARΔAB and pAS2-RARΔAB were constructed by PCR amplification of C–F regions of RARα (amino acids 88–462) and RARγ (amino acids 81–448). Primer pairs used for PCR amplification of RARαΔAB were 5'-AGGAATTCCTCGAGTGTGCAATGACAAGT-3' and 5'-AGGGATCCCTCAAGGCTCTGGGACCATTTACGCCG-3'. The amplified product was cloned into Smal-BamHI sites of pAS2-1. pGBT-RXRs was prepared by PCR amplification of RXRα from an expression vector using primer pairs 5'-AGGAATTCCTCGAGTGTGCAATGACAAGT-3' and 5'-AGGGATCCCTCAAGGCTCTGGGACCATTTACGCCG-3' and subsequently subcloning the amplified

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The abbreviations used are: RAR, retinoic acid receptor; RXR, retinoic X receptor; HAT, histone acetyltransferase; HMG, high mobility group protein; RAR, RARE-responsive element; CBP, CREB-binding protein; TIF, transcription intermediary factor; SRC, steroid receptor co-activator; GRIP, glucocorticoid receptor interacting protein; PPAR, peroxisome proliferator-activated receptor; DBD, DNA-binding protein; AD, activation domain; AF, activation function; LBD, ligand binding domain; TTNBP, 4,12-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propanoylbenzoic acid; CAT, chloramphenicol acetyltransferase.

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product into EcoRI-PstI sites of pGBT9 (CLONTECH). pAS2-Jun, pAS2-PPARγ, and pAS2-CBP were constructed by PCR amplification of wild type c-Jun, PPARγ, and 1–840 amino acids of CBP, respectively, and subsequently cloning them into appropriate sites of pAS2-1. Primer pairs used for PCR amplification of c-Jun were 5′-AGGAATTCATGACTGCAAAGATGGAAAGCACC-3′ and 5′-AGGGATCTCCAAATTGTTGCAACTGCTG-3′. The amplified product was cloned into EcoRI-BamHI sites of pAS2-1. Primer pairs used for PCR amplification of PPARγ were 5′-AGCATATGCAATGGTATGGCAGAGACAG-3′ and 5′-AGGCTCGAAGTCC-3′. The amplified product was cloned into HincII sites of pAS2-1. Primer pairs used for PCR amplification of CBP were 5′-AGGAATTCATGACTGCGAGACAGAGATC-3′ and 5′-AGGAATTCATGACTGCGAGACAGAGATC-3′. The amplified product was cloned into HindIII-BamHI sites of pAS2-1. A schematic representation of all the bait constructs is presented in Fig. 1.

For transient transfections, the RA-responsive reporter, RARE3-tk-lacZ, containing three copies of the canonical DR5 motif in pBLCAT5+, was kindly provided by Dr. S. Mader. The HMG-I sense, PHMG-I(Si) and HMG-I antisense (PHMG-I(As)) expression vectors were prepared by PCR amplification of HMG-I cDNA from pACT2-HMG-I using primer pairs 5′-AGGGATCCACCATGAGTGAGTC-3′ and 5′-AGGTACCATGAGTGAGTC-3′ and subsequently cloning the PCR-amplified product into T overhangs of pTarget expression vector. The amplified products were resolved on a NuSieve gel (4%), visualized by ethidium bromide staining, excised, cloned into TA cloning plasmid, and sequenced.

Yeast Strains and Media—The Saccharomyces cerevisiae yeast strain Y190 (MATa, ura 3–52, his 3–200, ade 2–101, lys 2–801, trp 1–901, leu 2–3, 112, GalaΔ, GalαΔ, cyh 2, lys2::GAL1-UAS – His3, URA3::GALI( las) – layers) (CLONTECH Match-maker system II) was grown at 30 °C in either YPD medium or synthetic defined medium II) was grown at 30 °C in either YPD medium or synthetic defined medium (14). HaCaT library was purchased (CLONTECH) and amplified according to the GeneTrapper protocol for semisolid amplification of plasmid cDNA libraries (Life Technologies, Inc.). Approximately, 600,000 double transformants were screened on medium lacking tryptophan, leucine, and histidine (–Trp, –Leu, –His) containing 25 ml of 3-amino-1,2,4-triazole in the presence of retinoid agonist, TTNPB (1 μM). Positive clones were verified for β-galactosidase activity using two different methods.

Yeast Two-hybrid Screening—pAS2-RARγΔAB-transformed yeast strain Y190 was further transformed with a HaCaT keratinocyte cDNA library in pACT2 expressing Gal4-AD chimeras using lithium acetate (14). HaCaT library was purchased (CLONTECH) and amplified according to the GeneTrapper protocol for semisolid amplification of plasmid cDNA libraries (Life Technologies, Inc.). Approximately, 600,000 double transformants were screened on medium lacking tryptophan, leucine, and histidine (–Trp, –Leu, –His) containing 25 ml of 3-amino-1,2,4-triazole in the presence of retinoid agonist, TTNPB (1 μM). Positive clones were tested for β-galactosidase activity using two different methods.

β-Galactosidase Assays—For qualitative evaluation of RAR interaction, β-galactosidase filter lift assays were carried out. Yeast colonies that grew on selective media were streaked on fresh selective plates in the presence of the retinoid for 3 days at 30 °C. Cells were transferred onto Whatman No. 5 paper, submerged in liquid nitrogen for 10 s, placed on a filter paper presoaked in Z buffer (100 mM sodium phos-
phate, pH 7.0, 10 mM KCl, 1 mM MgSO₄) supplemented with 50 mM β-mercaptoethanol and 0.07 mg/ml 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside. Filters were then incubated at 30 °C and checked for the appearance of blue colonies, thus indicating interacting proteins. For quantitative studies, yeast colonies, positive in lift assay, were counted and the β-galactosidase activity was quantified using dual luciferase reporter assay system (Promega). Transfections and CAT Assays—HeLa cells, grown in Dulbecco's modified Eagle's medium containing charcoal-stripped fetal calf serum (10%), were transfected using the GenePORTER transfection procedure (Gene Therapy Systems, San Diego, CA). Cells were plated 18 h before transfection at 40% confluence (40,000 cells/well) in a 24-well plate. The cells were transfected with the RA-responsive reporter, RARE3-tk-CAT along with pACT2-HMG-R and β-galactosidase activity, indicating interaction in vivo, is shown. D, dose-response curve of RARγ and HMG-I/HMG-R interaction. Yeast cells were co-transformed with pGBT-RARγ and pACT2-HMG-I (solid bars) or pACT2-HMG-R (open bars). 

RESULTS AND DISCUSSION

To gain a better understanding of the mechanism of retinoid action, we used a yeast two-hybrid system to identify and characterize proteins that interacted with human RARγ in a ligand dependent manner. RAR is a modular protein containing six functional regions, namely, A through F. A/B region contains a ligand-independent transactivation function, C region contains two zinc fingers and corresponds to the core of the ligand-dependent interaction of wild type RARγ with HMG-I/HMG-R. β-Galactosidase activity of yeast cells transformed with wild type RARγ (pAS2-RARγ) or co-transformed with pAS2-RARγ and pACT2-HMG-IA/pACT2-HMG-R in the absence (open bars) or presence (solid bars) of TTNPB (1 μM) is shown. B and C, RARs interact with HMGs in a ligand-dependent manner. β-Galactosidase activities of yeast cells co-transformed with RAR mutants and either HMG-R (B) or HMG-I (C) in the absence (open bars) or presence (solid bars) of TTNPB (1 μM) in yeast is shown. D, contribution of AF-1 and AF-2 to RAR-HMG interaction. Yeast cells were co-transformed with pGBT-RAR-DEF, pAS2-RARγΔAB, or pAS2-RARγ along with pACT2-HMG-R and β-galactosidase activity, indicating interaction in vivo, is shown. E, dose-response curve of RARγ and HMG-I/HMG-R interaction. Yeast cells were co-transformed with pAS2-RARγ and pACT2-HMG-I (solid bars) or pACT2-HMG-R (open bars). β-Galactosidase activity indicating interaction in the presence of various concentrations of TTNPB is given.
DBD, and E region contains the ligand binding domain (LBD), heterodimerization domain, and ligand-dependent transactivation function. The sequence of RARγ encompassing the C–F regions (amino acids 90–454) was used as bait (Fig. 1) to isolate cDNAs encoding interacting proteins from a HaCaT keratinocyte cDNA library. Thus, the bait construct (pAS2-RARγΔAB) contained both the DBD and the LBD of RAR fused to the Gal4-DBD in an yeast expression vector pAS2-1. A schematic representation of all the bait constructs used herein is presented in Fig. 1. Stably transfected pAS2-RARγΔAB yeast cells were transformed with the second vector that expressed the Gal4-AD fused to HaCaT keratinocyte library cDNAs. In addition to a major amplified fragment of 320 base pairs (HMG-1), another amplified fragment of 250 base pairs (HMG-R) was observed in all the samples (Fig. 2C). The identity of these bands was confirmed by sequencing the TA-cloned PCR fragments. HMG-R is a novel form, which appears to be produced from the HMG-I/Y gene by alternative splicing using noncanonical splice donor and acceptor sites.

To demonstrate that the full-length RARγ also interacts with HMG-I/HMG-R in a ligand-dependent manner in vivo, stably transformed RARγ (pAS2-RARγ) yeast cells were further transformed with pACT2-HMG-I/HMG-R and assayed for β-galactosidase activity in the absence or presence of TTNPB. Full-length RARγ, by virtue of its intrinsic activation functions (2), elicited a low level of β-galactosidase activity in the presence of TTNPB, which was further induced approximately 25-fold in the presence of pACT2-HMG-I and pACT2-HMG-R (Fig. 3A). pACT2-HMG-IR also showed ligand-dependent interaction with RARα and RARβ (Fig. 3, B and C). RARγ full-length protein interacted more avidly with HMG-IR than RARγΔAB (Fig. 3, B and C). To determine the regions of RAR involved in interaction with HMG in vivo, pGBT-RARγΔEF, pAS2-RARγΔAB, and pAS2-RARγ transformed yeast cells were used. pACT2-HMG-R interacted poorly with RARγΔEF and RARγΔAB but interacted strongly with RARγ (Fig. 3D). These results demonstrate that the LBD, which is present in the E region of RAR, alone is not sufficient for interaction with HMG,
but the ligand-independent A/B transactivation function, AF-1 (2), is also required for full interaction. Full-length RAR interacted with both HMG-I and HMG-R in a retinoid dose-dependent manner (Fig. 3A). Similar dose responsiveness has been observed for the retinoid-dependent induction of a number of endogenous RA-responsive genes.

HMG-I/Y proteins are associated with transcription-promoting activity (13). HMG-I/Y proteins are associated with transcriptionally active H1-depleted chromatin (13) and are overexpressed in hyperproliferative cancer cells as compared with normal cells (22–25). In accordance with its role in active transcription, HMG-I has been shown to interact with a number of other transcription factors such as NF-κB, ATF-2, Elf-1, Oct-2, Oct-6/Tst-1, and PU.1 (26–32). In addition to RAR, HMG-I and HMG-R also interacted with RXRα (Fig. 4A), PPARγ (Fig. 4B), c-Jun (Fig. 4C), and CBP (Fig. 4D). Unlike in the case of RARs, the interaction between PPARγ and HMG-I/R was PPARγ agonist-independent (Fig. 4B). These data taken together suggest that transcription factors in general may direct HMG-I to promoter regions of target genes. Since acetylation of HMG would destabilize its interaction with DNA, and RARs associate with HATs, we asked the question whether CBP/p300 could potentially acetylate HMG-I. Our data demonstrate that although HMG-I interacted with CBP, it was not acetylated by either CBP or p300 (Fig. 5A), demonstrating its potential to bind to its DNA site in the context of the RAR-CBP/p300 complex.

To further characterize the RAR-HMG interaction observed in the yeast two-hybrid system, we studied their association in vitro. RAR antibodies were immobilized on protein A- and G-Sepharose beads and used for adsorbing baculovirus-produced RARs. The RAR-bound beads were then mixed with radiolabeled in vitro translated Gal4-HMG-I in the presence or absence of TTNPB (1 μM). RARα and RARγ antibodies specifically immunoprecipitated HMG-I in a ligand-dependent manner (Fig. 5B).

If HMG-I/R proteins are important in nuclear hormone receptor-mediated transcription, then their effects should be quantifiable in transient transfection experiments. Accordingly, we next examined the effect of HMG-I/R on the transcriptional activity of RAR. HeLa cells were transiently transfected with RARE3-tk-CAT, an RA-responsive reporter, with or without HMG-I or HMG-R expression vectors in the presence or absence of TTNPB (1 μM). Transfection

FIG. 6. HMG is required for RAR-dependent transactivation. A, HMG-I/R increases the expression of an RA-responsive reporter. HeLa cells were transfected with the reporter gene RARE3-tk-CAT (1 μg) with or without 0.1 μg of pHMG-I(S) or pHMG-R(S) expression vectors in the presence or absence of TTNPB (1 μM). B, HMG-R antisense inhibits the expression of RA-responsive reporter. Cells were transfected with RARE3-tk-CAT (1 μg) and HAT activities and their targets in chromatin. Step 1 may involve the recruitment of HMG-I/R, thus converting a silent 30 nm chromatin fiber into a relatively open 10-nm fiber. Step 2 may involve the removal of linker histone H1 by HMG-I/R, thus converting a silent 30 nm chromatin fiber into a relatively open 10-nm fiber. Since acetylation of HMG would destabilize its interaction with DNA, and RARs associate with HATs, we asked the question whether CBP/p300 could potentially acetylate HMG-I. Our data demonstrate that although HMG-I interacted with CBP, it was not acetylated by either CBP or p300 (Fig. 5A), demonstrating its potential to bind to its DNA site in the context of the RAR-CBP/p300 complex.

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with either HMG-I or HMG-R sense expression vector resulted in approximately 2-fold induction in the retinoid-dependent expression of RARE3-tk-CAT (Fig. 6A). Since HMG-I is already highly expressed in transformed cells (22–25), the observed modest induction of retinoid-dependent expression of RARE3-tk-CAT by HMG-I/R co-transfection is an expected outcome. In order to abrogate the levels of endogenous HMG-I/R proteins, and the endogenous repertoire of RARs present in HeLa cells, and the reporter, RARE3-tk-CAT, in the presence of TTNPB. As shown in Fig. 6B, TTNPB (1 μM) induced the expression of RARE3-tk-CAT, and this activity was inhibited by co-transfection with pHMG-R(AS) in a dose-dependent manner. Finally, we tested whether co-transfection with pHMG-R(S), the HMG-R sense expression vector, rescues the pHMG-R(AS)-mediated inhibition of RARE3-tk-CAT expression. As shown in Fig. 6C, TTNPB (1 μM) induced the expression of RARE3-tk-CAT through the endogenous repertoire of RARs present in HeLa cells, and this activity was inhibited by approximately 50% by co-transfection with 0.01 μg of pHMG-R(AS). Furthermore, co-transfection with pHMG-R(S) relieved the inhibitory activity of pHMG-R(AS) on RARE3-tk-CAT expression. These results demonstrate that HMG-I/R is involved in RAR-mediated transactivation in cells.

RARs and other nuclear receptors recruit HAT activities to their site of action by interacting with CBP/p300, ACTR, and SRC-1 (3–5). These enzymatic activities would acetylate histones H2A, H2B, H3, and H4 (5) and thus partially release the constrained negative DNA supercoiling of the nucleosomal core. However, these activities should be preceded by removal of the linker histone (H1), which constrains the active 10-nm chromatin fiber containing nucleosomal cores into a compact and transcriptionally silent 30-nm fiber. Histone H1 is not acetylated in its DNA binding N- or C-terminal tails (19), suggesting that its affinity to DNA cannot be reduced by HAT activity and that removal of H1 has to be effected by an alternate mechanism. Our data indicate that RARs and other transcription factors are capable of recruiting the H1 displacing activities of HMG-I/HMG-R in a targeted and ligand-dependent manner (Fig. 7). Since HMG-I protein has 19 putative acetylation sites (lysine residues), including two in the DNA binding A/T hook domain (Fig. 2B), the acetylation of HMG-I by CBP/p300 could potentially decrease its ability to displace H1. However, in accordance with its proposed role as a H1 displacement factor, either CBP or p300 (Fig. 5A) did not acetylate HMG-I.

In order to destabilize compact higher order chromatin structures and to liberate DNA from the nucleosome at the site of active transcription and facilitate RNA polymerase II complex assembly, both linker and chromosomal histones need to be released by transcription factors. Our model predicts that nuclear receptors and other transcription factors may recruit HMG-I/HMG-R and HATs in a targeted step-wise manner, thereby unraveling linker and core histone assembly and facilitating the formation of transcriptionally competent DNA in the promoter regions of target genes.

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REFERENCES

1. Chambon, P. (1994) Semin. Cell Biol. 5, 115–125
2. Nagpal, S., Friant, S., Nakshatri, H., and Chambon, P. (1993) EMBO J. 12, 2549–2560
3. Glass, K. R., Rose, D., and Rosenfeld, M. G. (1997) Curr. Opin. Genet. Dev. 9, 222–232
4. Chen, H., Lin, R. D., Schiltz, R. L., Chakravarti, D., Nash, A., Nagy, L., Privalsky, M., Nakatani, Y., and Evans, R. M. (1997) Cell 90, 569–580
5. Bannister, A., and Kouzaiades, T. (1996) Nature 384, 641–643
6. Yang, X.-J., Ogryzko, V. V., Nishikawa, J.-I., Howard, B. H., and Nakatani, Y. (1996) Nature 382, 319–324
7. Spencer, T. E., Jenuent, G., Burcin, M. M., Allis, C. D., Zhou, J., Mixzen, C. A., McKenna, N. J., Onate, S. A., Tsai, S. Y., Tsai, M. J., and O’Malley, B. W. (1997) Nature 389, 194–198
8. Brownell, J. E., and Allis, C. D. (1996) Curr. Opin. Genet. Dev. 6, 176–184
9. Wolfe, A. P., and Pruss, D. (1996) Cell 86, 817–819
10. Wade, P. A., and Wolfe, A. P. (1997) Curr. Biol. 7, 882–884
11. Croston, G. E., Kerrigan, L. A., Lira, L. M., Marshak, D. R., and Kadonaga, J. T. (1991) Science 251, 643–649
12. Laybourn, P. J., and Kadonaga, J. T. (1991) Science 254, 238–245
13. Zhao, K., Kas, E., Gonzalez, E., and Laemmli, U. K. (1993) EMBO J. 12, 3237–3247
14. Gieta, D., St. Jean, A., Woods, R. A., and Schiestl, R. H. (1992) Nucleic Acids Res. 20, 1425
15. Nagpal, S., Athanikar, J., and Chandraratna, R. A. S. (1995) J. Biol. Chem. 270, 923–927
16. Carlsson, J. R., Mork, E., Hultlund, J., Laland, S. G., and Lund, T. (1988) Biochem. Biophys. Res. Commun. 158, 646–651
17. Reeves, R., and Nissen, M. S. (1990) J. Biol. Chem. 265, 8573–8582
18. Nissen, M. S., and Reeves, R. (1995) J. Biol. Chem. 270, 4353–4360
19. Davies, J. R. (1995) Int. Rev. Cytol. 162A1, 191–259
20. Ericsson, C., Grossbach, U., Bjorkroth, B., and Daneholt, B. (1990) Cell 60, 75–83
21. Kamakaka, R., and Thomas, J. O. (1990) EMBO J. 9, 3997–4006
22. Johnson, K. R., Disney, J. E., Wyatt, C. R., and Reeves, R. (1990) Exp. Cell Res. 187, 69–76
23. Ram, T. G., Reeves, R., and Hosick, H. L. (1993) Cancer Res. 53, 2655–2660
24. Chiapetta, G., Bandiera, A., Berlingeri, M. T., Visconti, R., Maniolfetti, G., Battista, S., Martinez-Tello, F. J., Santoro, M., Giancotti, V., and Fusco, A. (1995) Oncogene 10, 1307–1314
25. Fedele, M., Bandiera, A., Chiapetta, G., Battista, S., Viglietto, G., Maniolfetti, G., Casamassimi, A., Santoro, M., Giancotti, V., and Fusco, A. (1996) Cancer Res. 56, 1986–1991
26. Du, W., Thanos, D., and Maniatis, T. (1993) Cell 74, 887–898
27. John, S., Reeves, R. B., Lin, J. X., Child, R., Leiden, J. M., Thompson, C. B., and Leonard, W. J. (1995) Mol. Cell. Biol. 15, 1786–1796
28. Lewis, H., Kaszubska, W., DeLamarter, J., and Whelan, J. (1994) Mol. Cell. Biol. 14, 5761–5769
29. Du, W., and Maniatis, T. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 11318–11322
30. Nagpal, S., Pongubala, J. M. R., and Atchison, M. L. (1995) J. Immunol. 155, 4330–4338
31. Abdulkadir, B. S. A., et al. (1995) J. Exp. Med. 182, 487–500
32. Leger, H., Sock, E., Renner, K., Grumm, F., and Wegner, M. (1995) Mol. Cell. Biol. 15, 3738–3747