Nuclear Export of Retinoid X Receptor α in Response to Interleukin-1β-mediated Cell Signaling

ROLES FOR JNK AND SER260*

Received for publication, August 28, 2005, and in revised form, March 6, 2006. Published, JBC Papers in Press, March 21, 2006, DOI 10.1074/jbc.M508277200

Tracy L. Zimmerman, Sundararajah Thevananther, Romi Ghose, Alan R. Burns, and Saul J. Karpen

From the Texas Children’s Liver Center, Department of Pediatrics, Baylor College of Medicine, Houston, Texas 77030

As the obligate heterodimer partner to class II nuclear receptors, the retinoid X receptor α (RXRα) plays a vital physiological role in the regulation of multiple hepatic functions, including bile formation, intermediary metabolism, and endobiotic/xenobiotic detoxification. Many RXRα-regulated genes are themselves suppressed in inflamed liver via unknown mechanisms, which constitute a substantial component of the negative hepatic acute phase response. In this study we show that RXRα, generally considered a stable nuclear resident protein, undergoes rapid nuclear export in response to signals initiated by the pro-inflammatory cytokine interleukin-1β (IL-1β), a central activator of the acute phase response. Within 30 min of exposure to IL-1β, nuclear levels of RXRα are markedly suppressed in human liver-derived HepG2 cells, temporally coinciding with its appearance in the cytoplasm. The nuclear residence of RXRα is maintained by inhibiting c-jun N-terminal kinase (JNK, curcumin or SP600125) or CRM-1-mediated nuclear export (Leptomycin B). Pretreatment with the proteasome inhibitor MG132 blocks IL-1β-mediated reductions in nuclear RXRα levels while increasing accumulation in the cytoplasm. Mutational studies identify one residue, serine 260, a JNK phosphoacceptor site whose phosphorylation status had an unknown role in RXRα function, as critical for IL-1β-mediated nuclear export of transfected human RXRα-green fluorescent fusion constructs. These findings indicate that inflammation-mediated cell signaling leads to rapid and profound reductions in nuclear RXRα levels, via a multistep, JNK-dependent mechanism involving Ser260, nuclear export, and proteasomal degradation. Thus, inflammation-mediated cell signaling targets RXRα for nuclear export and degradation; a potential mechanism that explains the broad suppression of RXRα-dependent gene expression in the inflamed liver.

After injury or infection, the liver participates in a program of modified gene expression known collectively as the acute phase response (APR)2 (1). A wide variety of hepatic functions are altered during the APR, much of which occurs by cytokine-mediated activation or suppression of target gene transcription. Among the principal hepatic physiologic processes inhibited during the negative hepatic APR are genes involved in endobiotic/xenobiotic metabolism, glucose homeostasis, and bile formation, which then leads to cholestasis. Activation of the negative hepatic APR leads to cholestasis by decreasing bile salt synthesis (2), reducing canaliculn bile salt export (3), and suppressing bile salt import, the latter of which occurs primarily by transcriptional down-regulation of the sodium-dependent taurocholate co-transporting polypeptide (Slc10A1) (4, 5). Recent evidence suggests that cytokine-mediated activation of cell signaling pathways during the APR leads to this coordinated response (6). One possibility is targeted repression of the essential heterodimer partner for type II nuclear receptor, RXRα (NR2B1), which is an attractive mechanism to explain the suppression of many hepatic genes during the APR. Recent studies from multiple groups, including our own, support the involvement of inflammation-based cell signaling pathways as a suppressor of RXRα-dependent gene expression, although the underlying mechanisms are unknown (7–11). One cytokine in particular, interleukin-1β, (IL-1β) appears to be a major player in mediating these effects, both in vivo and in vitro (10, 12). How IL-1β-activated pathways ultimately leads to reduced RXRα heterodimer DNA binding in the nucleus is not known.

In this study we sought to investigate the hypothesis that IL-1β-mediated activation of c-jun N-terminal kinase (JNK) cell signaling reduces RXRα function by inducing its export from the nucleus and initiating proteasome-mediated degradation. We found that the subcellular localization of RXRα is responsive to IL-1β signaling, whereby it undergoes a rapid JNK-mediated, CRM-1-dependent nuclear export, leading to decreased nuclear RXRα levels and subsequent reduced nuclear DNA binding activity. Using green fluorescent protein (GFP) technology, we show that JNK-mediated RXRα-GFP is exported out of the nucleus like native RXRα and that nuclear export involves the JNK phosphoacceptor site, serine 260. Finally, IL-1β-induced cell signaling leads to rapid proteasome-mediated degradation of RXRα, suggesting that JNK-mediated nuclear export is the first and critical step that results in reduced nuclear levels of RXRα. Taken together, these studies reveal that RXRα is a target for pro-inflammatory cytokine cell signaling and provide a novel molecular mechanism for the broad and significant reduction of hepatic RXRα-regulated gene expression in the inflamed liver.

EXPERIMENTAL PROCEDURES

Materials—HepG2 cells were obtained from the American Type Culture Collection (ATCC, Rockville, MD). Cell culture reagents were purchased from Invitrogen, human recombinant IL-1β was purchased from R&D Systems Inc. (Minneapolis, MN), Curcumin and SP600125 were from Calbiochem, MG132 was from Biomol (Plymouth Meeting, PA), and Leptomycin B was from Sigma-Aldrich. FuGENE 6 was purchased from Roche Applied Science. Subcloning and mutation reagents were obtained from Stratagene (La Jolla, CA). Antibodies for JNK (num-
JNK-mediated Nuclear Export of RXRα

IL-1β Induces a Rapid Shift in RXRα Subcellular Localization—We first sought to determine the effects of IL-1β on RXRα protein levels and localization in the human liver-derived cell line, HepG2, a well studied model of IL-1β modulation of RXRα-regulated hepatic gene expression (9, 12). Within 30 min of exposure to IL-1β, nuclear levels of RXRα fell significantly (Fig. 1, A and B) and return to baseline levels within 16 h after treatment. Correspondingly, within 30 min, RXRα protein is readily detectable in cytoplasmic fractions from IL-1β-treated cells. Importantly, nuclear and cytoplasmic levels of two transcription factors, the heterodimer partner of RXRα, namely NRRA and RXRβ, were significantly affected by IL-1β treatment (Fig. 1, compare C and D). In contrast, nuclear levels of RXRα were not significantly affected by IL-1β treatment (Fig. 1, compare E and F), demonstrating that the effects of IL-1β on RXRα protein subcellular localization are specific. Notably, slower migrating RXRα species were present in the nuclear fractions obtained 30–60 min after cytokine treatment (Fig. 1, A and B), coincident with a decrease in nuclear RXRα protein. IL-1β treatment leads to a rapid and profound reduction in nuclear RXRα, coincident with a relocalization of RXRα from the nucleus to cytoplasm.
Electrophoretic mobility shift assays (Fig. 1I) performed on nuclear extracts from IL-1β-treated HepG2 cells show decreased binding of nuclear proteins to a typical RXRα/RARα heterodimer binding site (DR2), with a timeline that corresponds to the rapid and sustained depletion of nuclear RXRα (Fig. 1, compare I with B). Because activation of JNK is involved in IL-1β-mediated suppression of RXRα:RARα activation of the sodium-dependent taurocholate co-transporting polypeptide DR2 element, it was important to determine whether there is a temporal link between JNK activation and subcellular relocalization of RXRα (12). As seen in Fig. 1J, the timeline of IL-1β-JNK activation (as phospho-JNK) is not only consistent with previous reports (15) but coincides with the peak subcellular relocalization of RXRα (Fig. 1I).

IL-1β-mediated RXRα Nucleocytoplasmic Relocalization Is Critically Dependent upon JNK—JNK can phosphorylate RXRα at several sites, yet the physiological consequences are controversial (16). Nor is there a known role for IL-1β-mediated effects on RXRα nucleocytoplasmic relocalization, although results in Fig. 1 support this possibility (14). To investigate the role of JNK in IL-1β modulation of RXRα subcellular localization, we utilized two potent inhibitors of JNK activity, curcumin, the yellow pigment derived from the spice turmeric (12, 17), and SP600125 (18). As seen in Figs. 2, A–D, pretreatment with either agent potently inhibits the effects of IL-1β on the subcellular localization of RXRα. These findings clearly support a critical role for IL-1β-activated JNK in determining the subcellular localization of RXRα.

**FIGURE 1.** Altered nuclear and cytoplasmic levels of RXRα after exposure to IL-1β. A, HepG2 cells were treated with either saline for 30 min or 10 ng/ml IL-1β for 30–90 min. Nuclear (left) or cytoplasmic (right) protein extracts were analyzed via SDS-PAGE and immunoblotting techniques for RXRα, RARα, or Oct-1 protein levels. * denotes slower migrating species. B, densitometric analysis of RXRα protein levels in HepG2 cells treated as in A for 0.5–16 h (n = 3). * = p < 0.05 relative to saline treatment. C–H, Immunofluorescence of fluorescein isothiocyanate-labeled antibody detecting RXRα (C and D, green), DAPI nuclear staining (E and F, blue), and overlay (G and H) in HepG2 cells after saline (C, E, and G) or IL-1β (D, F, and H) treatments for 30 min. I, Electrophoretic mobility shift analysis of HepG2 nuclear extract binding activity to the DR2 element. HepG2 cells were treated with either saline for 2 h or 10 ng/ml IL-1β for 2–16 h before isolation of nuclear extracts and analysis by EMSA as described. (Sp and Nsp, specific and nonspecific cold double stranded-oligo competition of 16-h time point, respectively). J, Immunoblot analysis of phosphorylated JNK (P-JNK) and total JNK levels in whole cell protein extracts from HepG2 cells treated with saline for 30 min or 10 ng/ml IL-1β for 15–180 min.
RXRa in the cytoplasm (see Fig. 1C (19, 20)) we considered the former possibility to be less likely than the latter. HepG2 cells were pretreated with either vehicle or leptomycin B (LMB), a potent inhibitor of CRM-1 (chromosome region maintenance-1)-dependent nuclear export, prior to IL-1β treatments (21). In extracts from IL-1β-treated cells, nuclear RXRa levels were modestly, but insignificantly, reduced when pretreated with LMB (Fig. 3), whereas cytoplasmic RXRa levels remained essentially undetectable. Inhibition of newly translated RXRa import into the nucleus was unlikely to be a major component of the actions of IL-1β, because pretreatment with the protein synthesis inhibitor cycloheximide had no discernible effect on either nuclear or cytoplasmic RXRa levels in response to IL-1β (data not shown). Taken together, these findings indicate that the rapid reduction in nuclear RXRa, accompanied by its appearance in the cytoplasm in response to IL-1β-induced signaling, is because of nuclear export of resident nuclear RXRa protein and not via an impairment in nuclear import of newly synthesized RXRa.

**IL-1β Induces GFP-tagged RXRa Export from the Nucleus**—To further elucidate the molecular mechanisms of RXRa nuclear export in response to IL-1β, a RXRa C-terminally tagged GFP construct was made and expressed in transiently transfected HepG2 cells. The RXRa-GFP fusion protein construct transactivated a reporter gene to a similar extent as transfected RXRa, indicating that the GFP tag had no significant effect on the transcriptional activity of RXRa (data not shown). HepG2 cells were transiently transfected with RXRa-GFP and analyzed in a blinded fashion by categorizing the subcellular location of GFP in individual transfected GFP-positive cells as either exclusively nuclear (N), or both nuclear and cytoplasmic (N+C). Between 68 and 73% of transfected cells express the RXRa-GFP protein exclusively in the nuclear compartment (vehicle treatments, Fig. 4 and 5), whereas the remaining 27–32% of transfected cells showed RXRa-GFP expression throughout the cell (N+C). When treated with IL-1β for 60 min, only 25–30% of transfected cells exhibited exclusive nuclear RXRa-GFP localization (≈70% reduction, Figs. 4 and 5), similar to the response of endogenous RXRa protein to IL-1β seen in immunoblot and immunocytochemical analyses (Fig. 1).

**The Response of RXRa-GFP to IL-1β Is Curcumin- and LMB-sensitive**—To test the role of JNK phosphorylation and CRM-1-dependent nuclear export, we followed the response of RXRa-GFP to IL-1β after a short pretreatment period with either curcumin or LMB. A 30-min pretreatment with the JNK inhibitor curcumin completely blocked the export of RXRa in response to IL-1β treatment (Fig. 4A), similar to that seen for native RXRa (Fig. 2, A and B). One hour of LMB pretreatment blocked the ability of IL-1β to cause a decrease in

---

**FIGURE 2. JNK inhibitors block the appearance of cytoplasmic RXRa after exposure to IL-1β.** A and B, HepG2 cells were pretreated for 30 min with either MeSO or 25 μM curcumin prior to a 30 min exposure to 10 ng/ml IL-1β or saline vehicle. A, representative immunoblot detecting RXRa protein, B, densitometric analysis of A (n = 4). C and D, HepG2 cells were pretreated for 30 min with either a MeSO or 30 μM SP600125 prior to treatment with IL-1β or saline vehicle for 30 min. C, representative immunoblot detecting RXRa protein. D, densitometric analysis of C (n = 3). Loading controls for nuclear (N, Oct1) and cytoplasmic (C, β-actin) proteins are shown. Bar graphs depict mean ± S.D.

**FIGURE 3. Leptomycin B blocks IL-1β-induced nuclear export of RXRa.** HepG2 cells were pretreated for 1 h with either methanol vehicle (MeOH) or 1 nM leptomycin B, followed by treatment with IL-1β or saline vehicle for 30 min. A, representative immunoblot detecting RXRa protein. B, densitometric analysis of A (n = 3). Loading controls for nuclear (N, Oct1) and cytoplasmic (C, β-actin) proteins are shown. Bar graphs depict mean ± S.D.
nuclear levels of RXRa-GFP (Fig. 4B). In concert with the immunoblot analyses (Figs. 2 and 3), these findings support critical and integral roles for JNK and CRM-1 in IL-1β-induced nuclear export of both native and GFP-tagged, RXRa, and that C-terminally tagged RXRa-GFP faithfully models the response of native RXRa to IL-1β.

Ser260 Is Critically Involved in RXRa-GFP Nuclear Export—Several amino acid residues in RXRa, including Ser260, have been identified as JNK phosphorylation sites (14), although the functional consequences related to the phosphorylation status of these sites are uncertain (22). An analysis of the potential JNK sites in RXRa led us to first explore a role for Ser260 in IL-1β-mediated nuclear export by creating RXRaS260A-GFP, where Ala is substituted for Ser260. Upon IL-1β treatment, nuclear export of RXRaS260A-GFP was significantly attenuated in comparison to wild type RXRa-GFP (Fig. 5, G–L, compared with A–F). After IL-1β treatment, 52% of cells transfected with RXRaS260A-GFP still retained exclusive nuclear residence (Fig. 5M), significantly higher than 25% of cells transfected with wild type RXRa-GFP (Fig. 5M). Transfected cells expressing either RXRa-GFP or RXRaS260A-GFP showed no significant difference in the predominantly nuclear localization of the fusion protein (73 and 71%, respectively; see Fig. 5, A, G, and M), nor in trans-activating ability (data not shown). This indicates that Ser260 is not required for either the native nuclear localization or function of RXRa but is required for full nuclear export in response to IL-1β.

IL-1β Induces Proteasome-mediated Degradation of RXRa—IL-1β induces prolonged suppression of nuclear RXRa levels, suggesting that the modified and exported RXRa, once in the cytoplasm, may be highly susceptible to degradation, rather than acting as a substrate for remodification and reimportation back into the nucleus. Thirty minutes after exposure to IL-1β, we isolated nuclear and cytoplasmic extracts from cultures pretreated for 1 h with vehicle (Me2SO) or the 26S proteasome inhibitor, 1 MG132 (Fig. 6). Both nuclear and cytoplasmic concentrations of RXRa were increased by preincubation with MG132 at baseline (time 0), consistent with an inhibition of ongoing proteasomal degradation during the preincubation period by MG132. Importantly, there is clearly an accumulation of RXRa in both compartments in extracts prepared from cells pretreated with MG132 before exposure to IL-1β (30-min samples). These data support critical roles for proteasome-mediated degradation of RXRa in...
response to IL-1β signaling, while still allowing for the processes of modification and export to continue.

**DISCUSSION**

In previous studies, we have identified inflammation-mediated suppression of hepatobiliary transporter gene expression via involvement of IL-1β-induced JNK activation and subsequent reduction of nuclear RXRα-containing heterodimer binding capacity and function (12). However, the consequences and roles of JNK on RXRα function or subcellular relocalization were unknown. In this report, we sought to determine the underlying molecular mechanisms and provide evidence to support the hypothesis that the reduction in RXRα nuclear binding activity is because of the rapid and specific JNK-dependent modification and nuclear export of RXRα. In addition, RXRα nucleocytoplasmic translocation is LMB-sensitive and therefore exported from the nucleus via a CRM-1/exportin-1 dependent mechanism. We identify one residue, Ser260, a known JNK phosphorylation site whose functional importance was previously unknown, as critical to IL-1β-mediated RXRα nuclear export. Finally, exported RXRα undergoes proteasome-mediated degradation, linking IL-1β cell signaling pathways to reductions in nuclear RXRα levels. These studies provide an explanation for the suppression of RXRα-dependent gene expression by IL-1β (12). Taken together, this is the first description of a direct molecular link between activation of cell signaling pathways and alteration of the nuclear residence of the central type II nuclear receptor heterodimer partner, RXRα.

Understanding the mechanisms of the hepatic response to inflammation is clinically relevant, because inflammation is a major component of both acute and chronic liver diseases, and RXRα-regulated genes are essential to multiple physiological processes in liver (23–25). Moreover, Geier et al. (10) recently showed that IL-1β is a critical mediator of JNK-mediated phosphorylation sites in RXRα, which included three sites in the N-terminal region, as well as Ser260 in the ligand binding domain, but did not describe any role for phosphorylation of these sites in directing subcellular location. Combining the present and previous

**FIGURE 7.** Model proposing roles for IL-1β-induced JNK activation that lead to the nuclear export and proteasomal degradation of RXRα. Kupffer cells (KC) are the resident hepatic macrophage and are considered the primary cytokine source in inflamed livers. Hepatocytes respond to local release of IL-1β by activating a variety of cell signaling pathways, including JNK. In this model, activated JNK phosphorylates RXRα, at several sites including Ser260, which is a necessary step before nuclear export, ubiquitination, and proteasome-mediated destruction. Sites of action for curcumin, SP600125, leptomycin B, and MG132 are shown. There may be a component of proteasome-mediated degradation in the nucleus. LPS, lipopolysaccharide; C, canalculus.
studies on the effects of IL-1β, it is clear that IL-1β-induced cell signaling rapidly and reproducibly reduces nuclear RXRα levels and function via a JNK-dependent pathway (12); however, a direct role for JNK-dependent phosphorylation of Ser260 as a critical component of IL-1β-mediated nuclear export of RXRα remains to be proven.

Linking IL-1β-Induced Signaling to Phosphorylation, Nuclear Export, and Proteasome-mediated Degradation of RXRα—Several lines of evidence support this novel pathway of regulating the nuclear residence of RXRα: 1) IL-1β-induced JNK activation is central to RXRα nuclear export, 2) IL-1β-activated JNK directly phosphorylates RXRα (12), 3) Ser260 is necessary for IL-1β induced nuclear export, 4) inhibition of CRM-1-dependent nuclear export maintains nuclear RXRα levels, 5) proteasome inhibition maintains whole cell RXRα levels, and 6) immunoblot analyses suggest a transient higher molecular weight species of RXRα (Fig. 1A, *) consistent with phosphorylated RXRα (14, 32, 34). It is unlikely that a significant contribution is made from JNK-mediated phosphorylation in each subcellular compartment. Future experiments are needed to help determine the broad suppression of multiple hepatic physiological processes (Fig. 7). It is likely that prolonged suppression of RXRα-regulated pathways plays a prominent role in the progression of liver injury in chronic liver diseases, most all of which invoke inflammation as a major pathophysiological factor or cofactor. The pathophysiological mechanisms provided in this study points to several new therapeutic targets for treating altered hepatic gene function in acute and chronic liver diseases by addressing cell signaling effects on RXRα.

REFERENCES

1. Baumann, H., and Gasparde, J. (1994) Immunol. Today 15, 74–80
2. Feingold, K. R., Spady, D. K., Pollock, A. S., Moser, A. H., and Grunfeld, C. (1996) J. Lipid Res. 37, 223–228
3. Hartmann, G., Cheung, A. K., and Piquette-Miller, M. (2002) J. Pharmacol. Exp. Ther. 303, 273–281
4. Karpen, S. J., Sun, A. Q., Kudith, B., Hagenbuch, B., Meier, P. J., Ananthanarayanan, M., and Suchy, F. J. (1996) J. Biol. Chem. 271, 15211–15221
5. Trauner, M., Arrese, M., Lee, H., Boyer, J. L., and Karpen, S. J. (1998) J. Clin. Investig. 101, 2092–2102
6. Mosbah, H. (1997) J. Pathol. 181, 257–266
7. Morgan, E. T. (1997) Drug Metab. Rev. 29, 1129–1188
8. Beigneux, A. P., Moser, A. H., Shigemura, K. J., Grunfeld, C., and Feingold, K. R. (2000) J. Biol. Chem. 275, 16390–16399
9. Denson, L. A., Auld, K. L., Schiek, D. S., McClure, M. H., Mangelsdorf, D. J., and Karpen, S. J. (2000) J. Biol. Chem. 275, 8835–8843
10. Geier, A., Dietrich, C. G., Voigt, S., Kim, S. K., Gerloff, T., Kullak-Ublick, G. A., Lorenzen, J., Matern, S., and Gurtug, C. (2003) Hepatology 38, 345–354
11. Ghose, R., Zimmerman, T. L., Thevananthar, S., and Karpen, S. J. (2004) Neur. Recept. 2, 4
12. Li, D., Zimmerman, T. L., Thevananthar, S., Lee, H. Y., Kurie, J. M., and Karpen, S. J. (2002) J. Biol. Chem. 277, 31416–31422
13. Itoh, M., Adachi, M., Yasui, H., Takekawa, M., Tanaka, H., and Imai, K. (2002) Mol. Endocrinol. 16, 2382–2392
14. Adam-Statham, S., Penna, L., Chambon, P., and Rochette-Egly, C. (1999) J. Biol. Chem. 274, 18932–18941
15. Poulois, J. E., Weber, J. D., Bellocco, J. M., Di Bisceglie, A. M., Britton, R. S., Bacon, B. R., and Baldassare, J. J. (1997) Ann. J. Physiol. 273, G804–G811
16. Rochette-Egly, C. (2003) Cell. Signal. 15, 355–366
17. Chen, Y. R., and Tan, T. H. (1998) Oncogene 17, 173–178
18. Han, Z., Boyle, D. L., Chang, L., Bennett, B., Karin, M., Yang, L., Manning, A. M., and Firestein, G. S. (2003) J. Clin. Investig. 108, 73–81
19. Prufer, K., and Barsony, J. (2002) Mol. Endocrinol. 16, 1738–1751
20. Rastinejad, F. (2001) Curr. Opin. Struct. Biol. 11, 33–38
21. Kudo, N., Wolff, B., Sekimoto, T., Schreiner, E. P., Yoneda, Y., Yanagida, M., Horinouchi, S., and Yoshida, M. (1998) Exp. Cell Res. 242, 540–547
22. Matsushima-Nishiwaki, R., Okuno, M., Adachi, S., Sano, T., Akita, K., Moriwaki, H., Friedmann, S. L., and Kojima, S. (2001) Cancer Res. 61, 7675–7682
23. Wan, Y. J., An, D., Cai, Y., Bepa, J. J., Hung-Po Chen, T., Flores, M., Postic, C., Magnuson, M. A., Chen, J., Chien, K. R., French, S., Mangelsdorf, D. J., and Sucov, H. M. (2000) Mol. Cell. Biol. 20, 4436–4444
24. Karpen, S. J. (2002) J. Hepatol. 36, 832–850
25. Moseley, R. H. (2004) Clin. Liver Dis. 8, 83–94
26. Xie, W., Radomsinska-Pandya, A., Shi, Y., Simon, C. M., Nelson, M. C., Ong, E. S., Waxman, D. J., and Evans, R. M. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 3375–3380
27. Staudinger, J. L., Goodwin, B., Jones, S. A., Hawkins-Brown, D., MacKenzie, K. I., LaTour, A., Liu, Y., Klaassen, C. D., Brown, K. K., Reinhard, J., Willson, T. M., Koller, B. H., and Kliwer, S. A. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 3369–3374
28. Kopf, E., Plassat, J. L., Vivat, V., de The, H., Chambon, P., and Rochette-Egly, C. (2000) J. Biol. Chem. 275, 33280–33288
29. Lefebvre, P., Gaub, M. D., Tahayato, A., Rochette-Egly, C., and Formstecher, P. (1995) J. Biol. Chem. 270, 10806–10816
30. Lee, H. Y., Suh, Y. A., Robinson, M. J., Clifford, J. L., Hong, W. K., Woodgett, J. R., Cobb, M. H., Mangelsdorf, D. J., and Kurie, J. M. (2000) J. Biol. Chem. 275, 32193–32199
31. Matkovits, T., and Christakos, S. (1995) Mol. Endocrinol. 9, 232–242
32. Sinivas, H., Jurosek, D. M., Kalyankrishna, S., Cody, D. D., Price, R. E., Xu, X. C., Narayanan, R., Weigel, N. L., and Kurie, J. M. (2005) Mol. Cell. Biol. 25, 1054–1069
33. Cao, X., Liu, W., Lin, F., Li, H., Kolluri, S. K., Lin, B., Han, Y. H., Dawson, M. I., and Zhang, X. K. (2004) Mol. Cell. Biol. 24, 9705–9725
34. Bruck, N., Bastien, J., Bour, G., Tarrade, A., Plassat, J. L., Bauer, A., Adam-Statham, S., and Rochette-Egly, C. (2005) Cell Signal 17, 1229–1239