Subcellular Localization of the Aryl Hydrocarbon Receptor Is Modulated by the Immunophilin Homolog Hepatitis B Virus X-associated Protein 2*

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The hepatitis B virus X-associated protein 2 (XAP2) is an immunophilin homolog and core component of the aryl hydrocarbon receptor (AhR). Immunophilins are components of many steroid receptor complexes, serving a largely unknown function. Transiently expressed AhR-YFP (yellow fluorescent protein) localized to the nuclei of COS-1 and NIH-3T3 cells. Co-expression of AhR-YFP with XAP2 restored cytoplasmic localization, which was reversed by 2,3,7,8-tetrachlorodibenzo-p-dioxin treatment (TCDD). The effect of XAP2 on AhR localization was specific involving a nuclear localization signal-mediated pathway. Examination of the ratio of AhR to XAP2 in the AhR complex revealed that −25% of transiently expressed AhR was associated with XAP2, in contrast with +100% when the AhR and XAP2 were co-expressed. Strikingly, TCDD did not influence these ratios, suggesting that ligand binding initiates nuclear translocation prior to complex dissociation. Analysis of endogenous AhR in Hepa-1 cells revealed that −40% of the AhR complex was associated with XAP2, predicting observed AhR localization to cytoplasm and nuclei. This study reveals a novel functional role for the immunophilin-like component of a soluble receptor complex and provides new insight into the mechanism of AhR-mediated signal transduction, demonstrating the existence of two structurally distinct and possibly functionally unique forms of the AhR.

Immunophilins are a family of proteins whose biological importance is rapidly becoming apparent. Immunophilins bind to and mediate the effects of immunosuppressant drugs (1), are involved in neural regeneration (2), and are found as components of many steroid receptor complexes (3). The functional role of immunophilins in receptor complexes is largely unknown. The immunophilin homolog hepatitis B virus X-associated protein 2 (XAP2)† also ARA9 or AIP, does not appear to bind immunosuppressant drugs (4), and is therefore not strictly an immunophilin. It does, however, share significant homology with immunophilins, particularly FKBP12 and FKBP52 (5, 6). XAP2 is a core component of the inactive, cytosolic, aryl hydrocarbon receptor (AhR) complex, together with the AhR (ligand-binding subunit), and a dimer of hsp90 (5, 6, 7).

The AhR is a ligand-activated member of the bHLH-PAS (basic helix-loop-helix Per-Arnt-Sim) transcription factor family (8). In response to ligand binding, the AhR translocates to the nucleus. Two views exist as to the path taken at this stage. (i) The AhR complex may dissociate in the cytoplasm with free AhR translocating to the nucleus and heterodimerizing with ARNT (AhR nuclear translocator), or (ii) ligand binding may initiate nuclear translocation of the intact complex where hsp90 and XAP2 dissociate prior to, or in concert with, dimerization with ARNT. The AhR/ARNT heterodimer binds to dioxin responsive elements (DRE) in the enhancer regions of genes such as CYP1A1, CYP1A2, CYP1B1, and NADPH quinone oxidoreductase and mediates transcriptional up-regulation (9, 10).

In cells, XAP2 appears to be largely bound to hsp90 and thus may act as a chaperone complex for a variety of proteins. XAP2 overexpression in cells has been shown to enhance cytoplasmic AhR levels, suggesting that the amount of XAP2 available to interact with the AhR may limit AhR steady-state levels (11, 12). In this report, the role of XAP2 levels in modulating the subcellular localization of the AhR was examined. The presence of a sufficient pool of XAP2 in the cell is necessary to maintain the AhR in the cytoplasm, which appears to require the presence of XAP2 in the AhR core complex. TCDD treatment does not affect AhR/XAP2 core complex ratios under conditions that result in near complete nuclear translocation, strongly suggesting that XAP2 does not dissociate from the AhR in the cytoplasm following ligand binding. Examination of endogenous AhR core complex ratios, sedimentation profile, and subcellular localization in Hepa-1 cells strongly supports the hypotheses that XAP2 mediates cytoplasmic localization of the AhR and that the liganded complex undergoes nuclear translocation prior to dissociation and heterodimerization with ARNT.

EXPERIMENTAL PROCEDURES

Construction and Sources of Expression Vectors—pcDNA3−βmAhR was used for expression of the AhR (13). pcI-FKBP52 was obtained from David Smith. pEYFP-N1 and pEYFP-Nuc were obtained from CLONTECH (Palo Alto, CA). pcI-XAP2-FLAG and pcI-XAP2-G272D-FLAG were previously prepared in our laboratory (14, 15). pEYFP-AhR was constructed by inserting the mAhR (amplified by

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† The abbreviations used are: XAP2, hepatitis B virus X-associated protein 2; AhR, aryl hydrocarbon receptor; AIP, AhR interacting protein; ARA9, AhR-associated protein 9; ARNT, AhR nuclear translocator; CYP, cytochrome P450; DRE, dioxin responsive enhancer; FKBP52, 52-kDa FK506-binding protein; Hsp90, 90-kDa heat shock protein; MAb, monoclonal antibody; NLS, nuclear localization signal; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TPR, tetratricopeptide repeat motif; YFP, yellow fluorescent protein; PVDF, polyvinylidene difluoride; PAGE, polyacrylamide gel electrophoresis; SDGC, sucrose density gradient centrifugation; TSDS, Tricine SDS.
polymerase chain reaction from pcDNA3-βmAhR with XhoI and XbaI sites added to ligate in frame with YFP) into the XhoI and XbaI restriction sites in the multiple cloning site of pEYFP-N1. The NLS sites added to ligate in frame with YFP) into the DRE-driven luciferase reporter vector (total DNA 800 ng/well made up with pcDNA3) in 12-well culture plates. Approximately 18 h after transfection, cells were treated with 10 nM TCDD or Me2SO (vehicle) for 6 h, following in which luciferase activity was assayed. Values were corrected for protein content as determined by BCA assay.

** Luciferase Reporter Gene Assay—** COS-1 cells grown in 6-well culture dishes were transfected with LipofectAMINE (Life Technologies, Inc., Gaithersburg, MD) at 37 °C in 94% air, 6% CO2.

**Immunoprecipitations—** FLAG-tagged proteins were immunoprecipitated using anti-FLAG monoclonal Ab M2 affinity gel (Sigma, St. Louis, MO). AhR-YFP and AhR-K13A-YFP were immunoprecipitated using anti-AhR mouse monoclonal Ab RPT9 (16) bound to protein G-Sepharose. Immunoprecipitations were carried out in IP buffer (MENG with 20 mM MOPS, pH 7.5, 1 mM MgCl, 2 mM dithiothreitol, 2 mg/ml ovalbumin), resolved by SDS-PAGE and blotted to PVDF membrane (Millipore, Bedford, MA) as described previously (15). Bands were visualized by Western blot analysis using for AhR, RPT1 MAb (16); for hsp90, anti-hsp90/86 rabbit polyclonal Abs (17); for XAP2, anti-FLAG rabbit polyclonal Abs; or where noted, anti-XAP2 MAb (Novus Biologicals, Littleton, CO). Primary antibodies were detected with peroxidase-conjugated goat anti-mouse IgG (GAP) or donkey anti-rabbit polyclonal Abs (DAR-P) (Jackson ImmunoResearch, West Grove, PA) and visualized using the Vector VIP substrate kit (Vector Laboratories Inc., Burlingame, CA).

**Characterization of AhR and XAP2 Monoclonal Antibodies—** AhRFlag and XAP2 were in vitro translated together with [35S]methionine using the TNT kit (Promega). The translation mixture (5 μl) was resolved by SDS-PAGE and blotted to PVDF membrane as described previously (15). AhR and XAP2 bands were quantitated by phosphorimage analysis, and the signals were corrected for the abundance of methionine molecules in each to give a measure of their relative amounts. The membrane was then analyzed by Western blot with PTM1 (anti-AhR MAb) and anti-ARA9 (anti-XAP2 MAb; Novus Biologicals) primary antibodies, and 125I-labeled goat anti-mouse IgG (PerkinElmer Life Sciences) secondary Ab. Bands were visualized by autoradiography, excised, and quantitated by γ-counting. The signal was corrected for the relative amount of each protein giving a measure of the relative sensitivity of each MAb.

**Results**

**Characterization of AhR-YFP and AhR-K13A-FLAG—** To confirm that the AhR-YFP fusion and AhR-K13A-FLAG point mutation resulted in no loss of function, each was transiently expressed in COS-1 cells. Cytosol was isolated and incubated with anti-AhR MAb RPT9 bound to protein G-Sepharose (AhR-YFP), or anti-FLAG M2 MAb affinity gel (AhR-K13A-FLAG). Immunoprecipitates were resolved by SDS-PAGE, electroblotted onto PVDF membrane and visualized by Western blot with RPT1/antibiotin-goat anti-mouse IgG/125I-streptavidin system.

**Discussion**

**Determination of AhR and XAP2 Complex Ratios—** COS-1 cells grown in 100-mm culture dishes were transfected at ~70% confluence with LipofectAMINE according to the manufacturer’s instructions (Me2SO/TCDD treatments were for 1 h prior to harvest). Cell cytosome was prepared as previously (15). Each immunoprecipitation, 400 μg of cytosolic protein was incubated for 1 h on ice with 35 μl of packed 2 μl anti-FLAG affinity resin (RPT9 conjugated to protein G-Sepharose for Hepa-1 AhR) in IP buffer (MENG + 20 mM Na2MoO4, 100 mM NaCl, 2 μg/ml BSA, 2 μg/ml ovalbumin). Immunoprecipitates were washed 3X with IP buffer and 2X with MENG (+ 20 mM Na2MoO4, 100 mM NaCl). Samples were heated with equal volumes of 2X TSB buffer and resolved by SDS-PAGE, blotted to PVDF membrane, and analyzed by Western blot as described above. Bands were quantitated by both phosphor image analysis, and γ-counting (results were comparable), and relative ratios of AhR and XAP2 were determined.

**Sucrose Density Gradient Centrifugation—** TCDD-treated Hepa-1 cytosome extracts were prepared and analyzed by SDGC as described previously (19). For protein levels, fractions were separated by SDS-PAGE, blotted to PVDF membrane, and bands visualized by Western blot using RPT1/biotin-goat anti-mouse IgG/125I-streptavidin system.

**Results**

**Characterization of AhR-YFP and AhR-K13A-FLAG—** To confirm that the AhR-YFP fusion and AhR-K13A-FLAG point mutation resulted in no loss of function, each was transiently expressed in COS-1 cells. Cytosol was isolated and incubated with anti-AhR MAb RPT9 bound to protein G-Sepharose (AhR-YFP), or anti-FLAG M2 MAb affinity gel (AhR-K13A-FLAG). Immunoprecipitates were resolved by SDS-PAGE, electroblotted onto PVDF membrane and visualized by Western blot (Fig. 1A and B). The AhR, AhR-YFP, AhR-FLAG, and AhR-K13A-FLAG each co-immunoprecipitated hsp90 and XAP2 indicating their co-expression and assembly into a complex analogous to that of the AhR. Further confirmation of the functionality of AhR-YFP was obtained by examining its ability to activate a DRE-driven luciferase reporter plasmid. COS-1 cells grown in 6-well culture dishes were transfected with pGudLuc 6.1 (DRE-driven luciferase reporter construct) and either pcDNA3 (control), pcDNA3-βmAhR, or pEYFP-AhR. Cells were treated with 10 nM TCDD or Me2SO (vehicle) for 6 h, followed by an assay for luciferase activity (Fig. 1C). AhR-YFP
demonstrated activation of the luciferase reporter construct similar to the AhR.

AhR-YFP Localization in COS-1 and NIH-3T3 Cells Is Specifically Modulated by XAP2—NIH-3T3 and COS-1 cells grown on glass coverslips in 6-well culture dishes. Cells were transfected with either pEYFP-AhR (500 ng), pEYFP-AhR (500 ng) + pCI-XAP2 (1 μg), pEYFP-AhR (500 ng) + pCI-XAP2-G272D (1 μg), or pEYFP-AhR (500 ng) + pCI-FKBPS2 (1 μg). Cells were treated with either 10 nM TCDD or Me2SO (DMSO) for 1 h prior to visualization where indicated.

Localization of YFP and YFP-Nuc Are Unaffected by Co-expression of XAP2 and TCDD Treatment—COS-1 cells were grown on glass coverslips and transfected with either pEYFP or pEYFP-Nuc (containing three tandem repeats of the nuclear localization signal of the simian virus 40 large T-antigen fused to its C terminus) (CLONTECH, Palo Alto, CA). YFP localized throughout the cell, whereas YFP-Nuc was visible only in the nuclei (Fig. 3A). The localization of YFP and YFP-Nuc was unaffected by treatment with 10 nM TCDD for 1 h. COS-1 cells were co-transfected with either pEYFP or pEYFP-Nuc and pCI-XAP2 or pCI (control) (Fig. 3B). In both cases, XAP2 had no effect on localization, further demonstrating that the effect of XAP2 on AhR localization is specific and is not an artifact of altered nuclear import.

AhR-K13A-YFP Localizes to Cytoplasm and Is Unable to Undergo Ligand-dependent Nuclear Translocation—To determine whether the subcellular localization of AhR-YFP was mediated by the nuclear localization signal (NLS) of the AhR, a point mutation was made in the NLS, to yield AhR-K13A-YFP, which has been previously shown to abolish nuclear translocation (20). In both NIH-3T3 (Fig. 3C) and COS-1 cells (Fig. 3D), AhR-K13A-YFP localized to cytoplasm and did not undergo detectable nuclear translocation following treatment with 10 nM TCDD for 1 h, confirming that AhR-YFP localization in both COS-1 and NIH-3T3 cells is mediated by the NLS of the AhR.

XAP2 Stoichiometry in the AhR Core Complex Transiently Expressed in COS-1 Cells—The stoichiometry of the interaction of the AhR with XAP2 was examined by first calibrating the relative sensitivities of MAbs to each protein (Fig. 4). The anti-ARA9 MAb was determined to have a sensitivity of 0.95 relative to the anti-AhR MAb RPT1. COS-1 cells were transfected with pcDNA3/pCI (control), pCI-XAP2 alone (control), pcDNA3-βAhR-FLAG alone, and pCI-XAP2 + pcDNA3-βAhR-FLAG. Cytosol was prepared, immunoprecipitated with M2 anti-FLAG resin, resolved by SDS-PAGE, and blotted to PVDF membrane. AhR and XAP2 bands were visualized with the appropriate primary and 125I-labeled secondary antibodies and quantitated by γ-counting (Fig. 4B). Values were corrected for nonspecific association with the affinity resin and the sensitivity correction factor to determine the ratio of XAP2 to AhR (Fig. 4C). Transient expression of AhR alone resulted in an AhRXAP2 ratio of 4:1, whereas co-expression of AhR with XAP2 resulted in a ratio of 1:1.

Examination of Endogenous AhR in Hepa-1 Cells—Hepa-1 cells, fixed with paraformaldehyde, were incubated with affinity purified anti-AhR MAb RPT9 (500 μg/ml) and subsequently with goat anti-mouse IgG conjugated to lissamine-rhodamine sulfonyl chloride (LSRC). The AhR localized throughout cytoplasm and nuclei, and demonstrated near complete nuclear localization following treatment with TCDD (Fig. 5A). Fractionation of cells treated with TCDD revealed that the majority of liganded AhR was present in the cytosolic fraction, an apparent artifact of leaching during fractionation, as immunofluorescence microscopy revealed near complete nuclear localization (Fig. 5B). SDS analysis revealed the liganded AhR to be exclusively in the 9 S, oligomeric form (Fig. 5C), demonstrating the presence of intact AhR complex in Hepa-1 nuclei following TCDD treatment. Analysis of total cytosolic levels and AhRXAP2 core complex ratios demonstrated a 1.5-fold excess of AhR over XAP2 in Hepa-1 cytosol and the presence of XAP2 ≈40% of the immunoprecipitated AhR complexes.

DISCUSSION

An AhR-YFP fusion protein was constructed and biochemically characterized to demonstrate the validity of using it to model the AhR (Fig. 1, A and C). Transient expression of AhR-YFP in NIH-3T3 and COS-1 cells (Fig. 2) resulted in nuclear localization of AhR-YFP, in the presence and absence of TCDD. One hypothesis to explain our observations is that transiently expressed AhR-YFP may overwhelm endogenous levels of a factor required for cytoplasmic localization. Two obvious candidates for this factor were hsp90 and XAP2. Co-expression of AhR-YFP with hsp90 had no effect (data not shown), however XAP2 co-expression resulted in a clear redistribution of AhR-YFP to the cytoplasm (Fig. 2). The relocalized, cytoplasmic AhR-YFP was responsive to TCDD, undergoing near complete nuclear translocation following treatment for 1 h. These data suggest that XAP2 modulates the subcellular localization of AhR-YFP and that transiently expressed AhR appears to be functionally distinct from endogenous AhR. Localization of transiently expressed AhR to the nucleus (and

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restoration of cytoplasmic localization by co-expression of XAP2 has been previously observed in COS-1 cells by indirect immunofluorescence microscopy (12). Histological studies of AhR localization in tissue slices have shown time and tissue specific nuclear, perinuclear, and cytoplasmic staining (16, 21), suggesting that AhR localization may be regulated in a tissue-specific manner, possibly through regulation of XAP2 expression. The specificity of the effect of XAP2 on AhR localization was confirmed by co-expression with the immunophilin FKBP52, and XAP2-G272D-FLAG. No effect was seen in either case, demonstrating the specific requirement for functional XAP2.

The effects of TCDD treatment and transient XAP2 expression on NLS-mediated nuclear uptake were examined by transiently expressing YFP and YFP-Nuc in COS-1 cells. YFP localized diffusely throughout cytoplasm and nuclei, whereas YFP-Nuc localized exclusively to nuclei (Fig. 3). TCDD treatment did not alter localization of either protein. To examine for a possible modulation of NLS-mediated nuclear import by XAP2, COS-1 cells were co-transfected with either pEYFP or pEYFP-Nuc and pCI-XAP2. XAP2 did not alter localization in the presence or absence of TCDD (Fig. 3B), demonstrating that neither XAP2 nor TCDD appear to modulate nuclear import pathways in our system. The possibility that transiently expressed AhR-YFP may bypass NLS-mediated nuclear uptake pathways was examined using pEYFP-AhR-K13A. AhR-K13A-YFP localized exclusively to the cytoplasm of both NIH-3T3 and COS-1 cells in the presence and absence of TCDD (Fig. 3, C and D), suggesting that acquisition of nuclear AhR-YFP through a mechanism other than NLS-mediated import is unlikely, thus localization of AhR-YFP is mediated through the NLS of the AhR and is modulated by XAP2.

Modulation of AhR-YFP localization by XAP2 was further explored by determination of ratios of AhR/XAP2 in the AhR core complex. AhR and XAP2 Mabs were calibrated to determine their relative sensitivities to quantitatively determine the ratio of XAP2 to AhR in the AhR core complex (Fig. 4). Western blot analysis revealed that only 25% of transiently expressed AhR in COS-1 cells was associated with XAP2, in contrast with 100% association when the AhR was co-expressed with XAP2. Strikingly, TCDD had no detectable effect on AhR/XAP2 ratios, lending strong support to the hypothesis that ligand binding initiates nuclear translocation of the intact AhR core complex prior to complex dissociation and dimerization with ARNT. In terms of the role of XAP2 in the subcellular localization of the AhR, transient expression of the AhR appears to overwhelm the limited pool of XAP2 that is in equilibrium with the AhR. In vitro translated AhR complexes that lack XAP2 are functional (22), however, in cells XAP2 appears to mediate the subcellular localization of the unliganded AhR. To complement these studies, localization and XAP2 stoichiometry were examined for endogenously expressed AhR in Hepa-1 cells. Indirect immu-
nuclear export of the AhR, leading to apparent cytoplasmic localization (29). The mechanism by which XAP2 modulates the subcellular localization of the AhR is unknown, but may result from a number of possible scenarios. These include the following: 1) XAP2 may physically mask the NLS of the AhR, thereby inhibiting nuclear translocation pending a ligand-induced conformational change that results in exposure of the NLS and subsequent nuclear export of the AhR, leading to apparent cytoplasmic localization. Several of these possibilities are currently under investigation to fully elucidate the mechanism by which XAP2 modulates the subcellular localization of the AhR.

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REFERENCES
1. Armistead, D. M., and Harding, M. W. (1993) Annu. Rev. Med. Chem. 28, 207–215
2. Sabatini, D. M., Lai, M. M., and Snyder, S. H. (1997) Mol. Neurobiol. 15, 223–239
3. Pratt, W. B., and Tuft, D. O. (1997) Endocr. Rev. 18, 306–360
4. Carver, L. A., LaPres, J. J., Jain, S., Dunham, E. E., and Bradfield, C. A. (1998) J. Biol. Chem. 273, 35580–35587
5. Carver, L. A., and Bradfield, C. A. (1997) J. Biol. Chem. 272, 11452–11456

FIG. 5. Examination of AhR localization and AhRXAP2 stoichiometry in Hepa-1 cells. A, laser scanning confocal micrographs of AhR in control and 1 nM TCDD-treated Hepa-1 cells visualized with anti-AhR MAb RPT9 and goat anti-mouse IgG conjugated to lissamine-rhodamine sulfonyl chloride, Me$_2$SO (i), 30 min (ii), 1 h (iii), 2 h (iv). B, relative amount of AhR in Hepa-1 cytosolic fraction compared with total AhR (cytosolic + nuclear). Cells were treated with 1 nM TCDD for 2 h, harvested, homogenized, and centrifuged to obtain nuclear pellet and crude cytosol (resusp to obtain cytoplasm). Nuclear pellet was extracted with MENG (+500 mM NaCl), and soluble extract collected. Aliquots of cytosolic and nuclear extracts were resolved by SDS-PAGE, blotted to PVDF membrane, and visualized using the RPT1/biotin-goat anti-mouse IgG/125I-labeled streptavidin system. C, sedimentation profile of AhR from cytosolic extract of Hepa-1 cells treated with 1 nM TCDD for 2 h. Extracts were applied to 10–30% sucrose gradient in MENG and fractionated. Fractions were acetone precipitated and analyzed by SDS-PAGE, visualized as in panel B, and bands excised and quantitated in a gamma counter. D, ratios of AhR to XAP2 in Hepa-1 cells in cytosolic extracts (cytosol) and in the immunoprecipitated 9 S AhR (complex).
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6. Meyer, B. K., Pray-Grant, M. G., Vanden Heuvel, J. P., and Perdew, G. H. (1998) Mol. Cell. Biol. 18, 978–988
7. Ma, Q., and Whitelaw, M. L., Jr. (1997) J. Biol. Chem. 272, 8878–8884
8. Gu, Y-Z., Hogenesch, J. B., and Bradfield, C. A. (2000) Annu. Rev. Pharmacol. Toxicol. 40, 519–561
9. Denison, M. S., Phelan, D., and Elferink, C. J. (1998) in Toxicant-Receptor Interactions (Denison, M. S., and Helferich, W. G., eds) pp. 3–33, Taylor and Francis, Philadelphia, PA
10. Dogra, S. C., Whitelaw, M. L., and May, B. K. (1998) Clin. Exp. Pharmacol. Physiol. 25, 1–9
11. Meyer, B. K., and Perdew, G. H. (1999) Biochemistry. 38, 8907–8917
12. LaPres, J. J., Glover, E., Dunham, E. E., Bunger, M. K., and Bradfield, C. A. (2000) J. Biol. Chem. 275, 6153–6159
13. Fukunaga, B. N., and Hankinson, O. (1996) J. Biol. Chem. 271, 3743–3749
14. Meyer, B. K., and Perdew, G. H. (1999) Biochemistry. 38, 8907–8917
15. Meyer, B. K., Petrulis, J. R., and Perdew, G. H. (2000) Cell Stress Chaperones 5, 243–254
16. Perdew, G. H., Abbott, B., and Stanker, L. H. (1995) Hybridoma 14, 279–283
17. Perdew, G. H, Nord, N., Hollenback, C. E., and Welsh, M. J. (1993) Exp. Cell Res. 209, 350–356
18. Singh, S. S., Hord, N. G., and Perdew, G. H. (1996) Arch. Biochem. Biophys. 329, 47–55
19. Perdew, G. H. (1991) Arch. Biochem. Biophys. 291, 284–290
20. Ikuta, T., Eguchi, H., Tachibana, T., Yoneda, Y., and Kawajiri, K. (1998) J. Biol. Chem. 273, 2895–2904
21. Abbott, B. D., Birnbaum, L. S., and Perdew, G. H. (1995) Dev. Dyn. 204, 133–143
22. Dolwick, K. M., Swanson, H. L., and Bradfield, C. A. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 8566–8570
23. Pollenz, R. S., Sattler, C. A., and Poland, A. (1994) Mol. Pharmacol. 45, 428–438
24. Chen, H-S., Singh, S. S., and Perdew, G. H. (1997) Arch. Biochem. Biophys. 348, 190–198
25. Wilhelmsen, A., Cuthill, S., Denis, M., Wikstrom, A-C., Gustafsson, J-Å., and Puellinger, L. (1990) EMBO J. 9, 69–76
26. Lees, M., and Whitelaw, M. L. (1999) Mol. Cell. Biol. 19, 5811–5822
27. Heid, S. E., Pollenz, R. S., and Swanson, H. L. (2000) Mol. Pharmacol. 57, 82–92
28. Fu, H., Subramanian, R. R., and Masters, S. C. (2000) Annu. Rev. Pharmacol. Toxicol. 40, 607–647
29. Yang, J., Winkler, K., Yoshida, M., and Kornbluth, S. (1999) EMBO J. 18, 2174–2183