Ah Receptor and NF-κB Interactions, a Potential Mechanism for Dioxin Toxicity*

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The Ah receptor (AhR) mediates many of the toxic responses induced by polyhalogenated and polycyclic hydrocarbons (PAHs) which are ubiquitous environmental contaminants causing toxic responses in human and wildlife. NF-κB is a pleiotropic transcription factor controlling many physiological functions adversely affected by PAHs, including immune suppression, thymus involution, hyperkeratosis, and carcinogenesis. Here, we show physical interaction and mutual functional repression between AhR and NF-κB. This mutual repression may provide an underlying mechanism for many hitherto poorly understood PAH-induced toxic responses, and may also provide a mechanistic explanation for alteration of xenobiotic metabolism by cytokines and compounds that regulate NF-κB.

The Ah receptor (AhR) is a ligand-activated basic helix-loop-helix transcription factor (bHLH) that plays a pivotal role in mediating a broad range of distinct toxic responses induced by polyhalogenated and polycyclic aromatic hydrocarbons, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and related compounds. These responses include immune suppression, thymic involution, endocrine disruption, wasting syndrome, chloracne (keratinocyte proliferation), birth defects, and carcinogenesis. The mechanism for these AhR-mediated pathophysiological responses is not well understood.

Unliganded AhR is located in the cytoplasm associated with heat shock protein 90 (hsp90) and a 38-kDa, immunoprophillin-related protein (8–10). Upon ligand binding, hsp90 is released from the complex, and the receptor translocates into the nucleus and dimerizes with the aryl hydrocarbon receptor nuclear translocator (ARNT) protein. The heterodimer binds to the xenobiotic response element (XRE) and alters expression of genes controlled by enhancer XREs. XREs, with the conserved core sequences "GGCGTG", are found in the promoter regions of several genes involved in the metabolism of xenobiotics, including cytochromes P-450 (CYP1A1, CYP1A2, and CYP1B1), and related compounds. Studies of the regulation of these genes, especially the regulation of CYP1A1, have provided a basis for understanding the mode of action of dioxin and related compounds.

The transcription of CYP1A1 and CYP1A2 is also regulated by cytokines. It has been reported that TNF-α suppresses CYP1A1 and CYP1A2 levels in human primary hepatocytes, and that 1-LIL-β has been shown to suppress TCDD-mediated induction of P-450A1A1 and P-450A1A2 in hepatocytes. The mechanism(s) of the observed suppression is unknown. It is known, however, that these cytokines induce NF-κB. NF-κB is a pleiotropic transcription factor that participates in many of the physiological responses that have been shown to be affected by xenobiotics, especially TCDD. The classic inducible NF-κB heterodimer typically consists of a p65(ReLa) and a p50(NF-κB-1) subunit, with ReLa being the subunit conferring strong transcriptional activation. We hypothesized that NF-κB may mediate interactions between cytokines and the AhR signaling pathway. In this report, we demonstrate that these two pathways interact by physical association of their respective critical components, i.e. ReLa and the AhR, and that this interaction is associated with mutual functional modulation of gene expression controlled by the AhR and NF-κB.

EXPERIMENTAL PROCEDURES

Cell Culture and Transient Transfection—Cells were maintained in αMEM supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 100 µg/ml streptomycin, and 250 ng/ml amphotericin B (Life Technologies, Inc.), 5% CO₂, and 37 °C. The plasmid constructs used in this study were as follows: human AhR expression plasmid (pAhAR), pNF-κB-Luc (Stratagene), human NF-κB ReLa expression plasmid (pCMV65) (27) and pGudLuc6.1, a reporter plasmid containing the firefly luciferase gene under control of four XRE segments derived from the upstream region of the murine CYP1A1 gene and the mouse mammary tumor virus promoter. This plasmid was generated as described previously (28), except that the Promega vector pGL3 was used instead of pGL2. Plasmid DNAs used were purified using the Qiagen Maxi-Prep DNA Isolation system. For transient transfection, Hepa1c1c7 and COS-7 cells were seeded in 6-cm dishes on day 1, and transfection was performed using LipofectAMINE (Life Technologies, Inc.) when cell density reached 80% confluence. pSV-β-galactosidase Control Vector (Promega) was used for normalization of transfection efficiency. Twelve h after transfection, cells were treated with AhR ligands (TCDD or BNF) or MeSO (solvent control) for 18 h before harvest for determination of luciferase activity or testing in EMSA for DNA-protein binding.

Co-immunoprecipitation/Western Blot Analysis—Mouse hepatoma cells (Hepa1c1c7) were treated with TCDD (10 nM) or MeSO (vehicle control) for 2 h. Before harvest, the cells were washed twice with...
ice-cold phosphate-buffered saline, harvested by scraping, and collected by centrifugation at 1500 × g. The cells were then lysed in lysis buffer (20 mM Hepes, pH 7.4, 125 mM NaCl, 1% Triton X-100, 10 mM EDTA, 2 mM EGTA, 2 mM Na3VO4, 50 mM sodium fluoride, 20 mM ZnCl2, 10 mM sodium pyrophosphate, 1 mM phenylmethylsulfonyl fluoride, 5 μg/ml leupeptin) and centrifuged at 15 min at 12,000 × g, and supernatant fractions were collected. The indicated antisera were added to the lysate, and the binding reactions were performed at 4 °C for 2 h on a rotary shaker, following which 30 μl of GammaBind Plus Sepharose beads (Amersham Pharmacia Biotech) were added to precipitate the antibody-antigen complexes. The beads were washed three times in lysis buffer and boiled in 2 × SDS sample buffer containing dithiothreitol. The proteins were separated by SDS, 8% polyacrylamide gels. Proteins on the gels were transferred to nitrocellulose membranes (Bio-Rad), and the membranes were blocked with 5% bovine serum albumin in TBST buffer (20 mM Tris-HCl, pH 7.6, 137 mM NaCl, 0.5% Tween 20) and incubated with appropriate primary antibodies at 37 °C for 2 h. Blots were then incubated with a 1:2000 dilution of immunofinity purified goat anti-rabbit IgG linked to alkaline phosphatase. Blots were washed three times with TBST with subsequent color development using nitro blue tetrazolium/BCIP (Sigma) as the substrate. **Luciferase Reporter Gene Activity Assay**—Luciferase assays were performed using the Luciferase Assay System (Promega). Briefly, the transfected cells were lysed in the culture dishes with reporter lysis buffer, and the lysates were centrifuged at maximum speed for 10 min in an Eppendorf microfuge. Ten μl of the supernatant fraction was incubated with 100 μl of luciferase substrate, and relative luciferase activity was determined with a luminometer (Turner Designs).

**Preparation of Nuclear Extract and EMS**—Nuclear extracts were prepared using a small scale procedure as described (29). The cytosolic fractions of the extraction were used for the Western blot analysis of the IκBα. Oligonucleotides used for EMSA were commercially synthesized (Life Technologies, Inc.) and included &kappa;B(WT): GCCAGGGGAATTC-CCC and &kappa;B (MT): GCCAGGCTCAATTGAGCT corresponding to a consensus NF-κB binding site (used as the probe for EMSA) and a mutant (used for competition assay in EMSA). These oligonucleotides can self-anneal, and &kappa;B(WT) was labeled with [α-32P]dCTP by using Klenow enzyme (Amersham Pharmacia Biotech). For EMSA assay, 3 μg of nuclear extract protein was incubated in a reaction mixture containing 40 mM KCl, 1 mM MgCl2, 0.1 mM EGTA, 0.5 mM dithiothreitol, 20 mM Hepes, pH 7.9, and 4% Ficoll (400 K) and approximately 30000 cpm of radiolabeled double-stranded oligonucleotide probe. After incubation for 30 min, the reaction mixture was then separated by electrophoresis through a 4.5% nondenaturing polyacrylamide gel.

**RESULTS**

To test the effects of NF-κB on gene expression of CYP1A1, we first investigated the effects of TNF-α treatment on the CYP1A1 promoter activity. For this, we transiently transfected Hepa1c1c7 mouse hepatoma cells, which express wild-type AhR, with a XRE-driven luciferase reporter gene (pGudLuc6.1). Treatment with TNF-α, which is a strong inducer of NF-κB, markedly suppressed TCDD-induced promoter activity as determined by the luciferase reporter gene assay, suggesting that cytokine-induced NF-κB could suppress the activity of AhR (Fig. 1A). To further define the role of NF-κB in the observed suppression, we co-expressed pCMV65, which expresses RelA, with the pGudLuc6.1 reporter gene. Transfection of increasing amounts of the RelA expression plasmid effectively suppressed TCDD-induced XRE-dependent promoter activity (Fig. 1B). These results demonstrated that RelA can suppress AhR-mediated induction of gene expression, suggesting that an underlying mechanism for the observed suppressive effects of cytokines on the CYP1A1 and CYP1A2 expression (20–24) is through the induction of NF-κB.

The NF-κB proteins have been previously shown to interact with several other transcriptional regulators, including several nuclear hormone receptors (30–34), Sp1 (35), and p300/CBP (36, 37), resulting in modulation of different transcriptional regulatory pathways. In several of these cases, direct physical interactions between RelA and other transcription factors have been demonstrated (30–37). We therefore performed co-immunoprecipitation assays to detect possible complex formation between AhR and RelA in vivo (Fig. 2). Hepa1c1c7 cells were lysed with buffer containing Triton X-100. The presence of AhR-RelA complexes was detected by sequential immunoprecipitation and Western blot analysis, initially using an antibody against AhR to immunoprecipitate the complex, and the presence of RelA in the complex was detected by Western blot analysis (Fig. 2A). RelA was detected by Western blot following immunoprecipitation of the Hepa1c1c7 cell lysates with either AhR- or RelA-specific antibodies, but not by immunoprecipitation with control antisera. The association of AhR and RelA was further confirmed with reciprocal immunoprecipitation with an antibody against RelA as the immunoprecipitating
antibody, followed by Western blotting using the antibody directed against the AhR (Fig. 2B). This reciprocal co-immunoprecipitation confirmed the physical association of AhR and RelA. Because the activated AhR is known to associate with the ARNT protein in the nucleus, we tested the possible association of the ARNT with the RelA protein. ARNT is not associated with RelA. The Western blot was stained with an antibody against the ARNT protein.

Because we had previously shown that RelA was capable of inhibiting ligand-induced AhR transcriptional activation, we were interested in assessing the reciprocal effects of AhR activation on NF-κB function. To test the potential suppressive effects of AhR ligands on endogenous NF-κB activity, we treated Hepa1c1c7 cells with BNF and TCDD. BNF, which is an AhR ligand (38–42), is known to cause immune suppression (43). Twelve h later, the transfected cells were treated with 10 nM TCDD. The cells were harvested 18 h later, and the nuclear proteins were extracted and assayed for binding activity to a radiolabeled eB-containing oligonucleotide by EMSA (16). * indicates lanes (11 and 12) in which unlabeled oligonucleotide eB(WT) was included in the reaction as a specific competitor of binding.

**Fig. 2.** Physical association of AhR and RelA. Hepa1c1c7 cells were treated with TCDD (10 nM, 2 h) and lysed with buffer containing Triton X-100. Co-immunoprecipitation/Western blot analysis was performed to detect specific association of AhR and RelA (15). A, immunoprecipitation of RelA with antibody against AhR. Samples of total cell lysates were incubated with rabbit IgG (Sigma) as the negative control, anti-RelA antibody (positive control), and antibody against AhR. The complex was precipitated with protein G coupled to Sepharose beads (GammaBind G Sepharose, Amersham Pharmacia Biotech), and after Western transfer, the blot was probed with antibody against RelA protein (Santa Cruz Biotechnology). IP Abs, immunoprecipitation antibodies. B, immunoprecipitation of AhR with antibody against RelA. The cell lysates were incubated with rabbit IgG (negative control), antibody against AhR (positive control), and antibody against RelA. After Western transfer, the blot was stained with antibody against AhR. C, ARNT is not associated with RelA. The cell lysates were incubated with antibody against RelA, ARNT (positive control), and rabbit IgG (negative control). The Western blot was stained with an antibody against the ARNT protein.

**Fig. 3.** AhR suppresses the NF-κB binding to the κB site. A, suppression of TNF-α-induced NF-κB binding activity by BNF. Hepa1c1c7 cells were treated with BNF (0–10 μM) for 12 h, and then NF-κB activity was induced by TNF-α (1 ng/ml) treatment for 1 h. The NF-κB activity was determined by EMSA. The radiolabeled κB(WT) oligonucleotide was competed with the unlabeled κB(WT) and κB(MT) to demonstrate protein binding specificity. B, suppression of TNF-α-induced NF-κB binding activity by TCDD. Hepa1c1c7 cells were treated with TCDD (20 nM) for 18 h, and NF-κB activity was induced and measured as described in panel A. C, AhR-mediated suppression of NF-κB binding by TCDD. COS-7 cells were transfected with pCMV65 and phuAhR. After 12 h, the transfected cells were treated with 10 μM TCDD. The cells were harvested 18 h later, and the nuclear proteins were extracted and assayed for binding activity to a radiolabeled κB-containing oligonucleotide by EMSA (16). * indicates lanes (11 and 12) in which unlabeled oligonucleotide κB(WT) was included in the reaction as a specific competitor of binding.
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A

COS-7 cells were transiently transfected with pSVsporthuAhR, RelA, and phuAhR (2.0 μg), and 18 h later, the cells were processed for determination of luciferase activity (x1000). Twelve h after transfection, the cells were treated with TCDD for 18 h, and nuclear extracts were prepared and were assayed by EMSA for κB site binding activity. As expected, transfection of pCMVRelA led to readily detectable NF-κB binding (Fig. 3C, lanes 3 and 4) as compared with untransfected cells (lanes 1 and 2). Transfection of increasing amounts of AhR led to suppression of κB binding activity even in the absence of ligand (lanes 5, 7, and 9). At each level of transfected AhR plasmid, treatment with TCDD reduced the levels of NF-κB binding as compared with untreated cells (compare lanes 5, 7, and 9 with 6, 8, and 10, respectively). TCDD treatment coupled with cotransfection of 2 μg of the AhR expression vector (lane 10) resulted in complete repression of NF-κB activity as compared with RelA-transfected cells (lanes 3 and 4). These results demonstrated that activation of the AhR by ligand treatment suppressed NF-κB activity, either because of TNF-α treatment (Fig. 3, A and B) or transfection of RelA (Fig. 3C). It is interesting to note that transfection of low levels of AhR actually increased NF-κB binding in the absence of ligand (lanes 5–8). In an analogous case, Palvimo et al. showed that cotransfection of the androgen receptor increased NF-κB activity in whole cell extracts (31). The reason for the increased NF-κB activity in the presence of low levels of AhR is not known; however, what is clearly demonstrated by these experiments (Fig. 3) is that activation of AhR reduced the binding of NF-κB to its cognate enhancer sequence.

The role of AhR in the suppression of NF-κB-directed promoter activity was demonstrated in a transient transfection study in which transfection of AhR caused suppression of κB-directed promoter activity. Treatment with AhR ligand (BNF) markedly accentuated the suppressive effects (Fig. 4A), consistent with the results from EMSA (Fig. 3C). This transient transfection study (Fig. 4A) also demonstrated that treatment with BNF alone, without exogenously transfected AhR caused suppression of NF-κB activity, suggesting that the COS-7 cells express AhR. We noticed that Hepa1c1c7 cells express high background levels of NF-κB activity. These cells are also known to express wild-type AhR. AhR ligands, TCDD and BNF, both suppressed the endogenous NF-κB activity in the Hepa1c1c7 cells (Fig. 4B). The effects of AhR activation on NF-κB transcriptional activity were further tested in an additional transient transfection assay (Fig. 4C). BNF, as well as α-naphthoflavone (ANF), an isomer and a competitive antagonist of BNF (38–41), were used as the AhR agonist and antagonist, respectively. BNF suppressed the RelA-induced activity of a reporter gene driven by κB enhancer sequences, whereas treatment with the AhR antagonist ANF completely reversed the BNF-induced suppression (Fig. 4C), strongly suggesting that the repression is through an AhR-mediated mechanism. Thus, ligand activation of AhR repressed transcriptional activity by NF-κB as well as binding to the κB motif.

**DISCUSSION**

AhR-mediated gene regulation has been defined by the induction of CYP1A1 in which the ligand-activated AhR translo-
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cates into the nucleus and binds to a promoter containing the XRE sequence, thereby altering gene expression controlled by that promoter. This mode of action limits the regulation of genes by the ligands of the AhR to those containing XRE enhancer sequences or “negative regulatory” sequences (silencers) (44). However, a rich body of literature indicates that ligands of AhR including polyhalogenated and polycyclic aromatic hydrocarbons cause a wide spectrum of toxic responses ranging from apoptosis to cell proliferation, suggesting that AhR is likely to interact with other signaling pathways to cause the observed toxic responses without acting through the XREs. It is now recognized that protein-protein interaction is an important mode of action for transcription factors to increase their regulatory repertoire. For example, it has recently been shown that a DNA-binding deficient glucocorticoid receptor mutant retains its transcriptional transrepression activity without binding to the glucocorticoid response elements (45).

In the present study, we demonstrated that the AhR and NF-κB signaling pathways interact by physical association and functional modulation. Although addition of TCDD did not significantly alter the apparent association between AhR and NF-κB in the in vitro co-immunoprecipitation assay (Fig. 2, A and B), the functional interactions between the AhR and NF-κB are clearly ligand-dependent as shown in the transient transfection assay (Figs. 3 and 4). Our data show that the AhR and RelA proteins have a cognate ability to associate. One model would suggest that unactivated AhR and NF-κB are sequestered in the cytoplasm and kept apart by their respective regulatory mechanisms, i.e. hsp90 associates with AhR and IκBα associate with RelA. This compartmentalization would serve as a regulatory mechanism to keep cellular signaling in order. The AhR and NF-κB subunits would then interact with each other upon provision of their respective activating signals (TCDD and BNF for AhR, and TNF for NF-κB). These signals would cause the dissociation of the hsp90 and IκBα from the AhR and RelA, respectively, allowing the association of AhR and the RelA in vivo. The data presented in Fig. 2, A and B, revealed that AhR and RelA are physically capable of associating with each other within total cell lysates, in which the entire cellular pools of AhR and RelA are exposed to each other, thereby potentially obscuring the effects of ligands. We believe that this specific association of these two proteins underlies the potential functional modulations that were shown in the subsequent transfection assays and EMSA (Figs. 3 and 4).

The mechanism for the observed functional mutual repression is not clear. One possibility is that AhR and NF-κB RelA form an inactive complex, thereby causing mutual repression. Another scenario is that the mutual modulation between the AhR and NF-κB is mediated by a transcription coactivator, such as the p300/CREB. It has been found recently that the transcription coactivator p300/CREB acts as integrator for many signaling pathways (46), ultimately leading to histone acetylation and activation of gene expression. Intriguingly, p300/CREB was found to associate with both RelA (36, 37) and ARNT (47). It is conceivable that the mutual antagonism found between the AhR and NF-κB signaling pathways also converges upon this central transcriptional coactivator. Competition between ligand-AhR/ARNT complexes and RelA for p300/CREB binding could affect the levels of transcriptional activation seen in these two pathways. Some nuclear hormone receptors have also been reported to repress NF-κB activity (30–34), and the effects of the glucocorticoid receptor in this regard have been shown to be mediated at least in part through induction of IκBα (48, 49). In transient transfection, we were unable to observe any alteration of IκBα level by transfected AhR (data not shown), thus at this point, we do not believe that the repressive effects of AhR on NF-κB are mediated through induction of IκBα.

In this study, both TCDD and BNF were used as the ligands for the activation of the AhR. These two ligands have been used interchangeably for binding to the AhR and induction of CYP1A1. Both ligands suppressed NF-κB activity in gel-shift assay (Fig. 3, A and B) as well as transient transfection assays in Hepa1c1c7 cells (Fig. 4B). In a transient transfection assay with COS cells, BNF effectively suppressed the RelA-induced κB enhancer-driven luciferase reporter gene, whereas co-treatment with α-naphthoflavone reversed the suppressive effects of BNF, strongly suggesting that the suppression is mediated by the AhR (Fig. 4C).

In conclusion, we have shown in this study a direct interaction between the AhR and NF-κB signaling pathways. The association between the AhR and RelA provides a physical basis for the functional antagonism, which in turn provides a possible mechanistic explanation for the toxicity of the TCDD. For example, TCDD-induced immune suppression could be a result of AhR-induced suppression of NF-κB activity in a manner somewhat analogous to the immune suppressive effects of glucocorticoids. Recent studies using AhR−/− mice have shown that the AhR is required for thymic toxicity and that cell-autonomous function of the AhR in thymocytes is required for the TCDD toxic effects (3, 50). These results, coupled with our data and the emerging role of NF-κB in inhibition of apoptosis (51–54) suggest a model whereby repression of NF-κB by ligand-AhR interactions could result in enhanced susceptibility of lymphoid cells to apoptotic stimuli, which could contribute to TCDD-mediated immune suppression. Similarly, TCDD-induced skin proliferation could be mediated through inhibition of NF-κB in epidermal cells. A recent report has demonstrated enhanced epidermal hyperplasia in transgenic mice expressing a constitutive IκBα molecule (55). Conversely, the transrepression of AhR activity by NF-κB may be the underlying mechanism for the suppression of CYP1A1 and CYP1A2 by cytokines or other substances, which are capable of inducing NF-κB. Thus, AhR-NF-κB interactions may underlie important aspects of the pathophysiological responses to polyhalogenated and polycyclic aromatic hydrocarbons.

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