Mechanism of Suppression of Cytochrome P-450 1A1 Expression by Tumor Necrosis Factor-α and Lipopolysaccharide*

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Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin-1β, and lipopolysaccharides (LPS), suppress the gene expression of cytochrome P-450 1A1 (cyp1a1). The mechanism of the suppression is not well understood. In present study, we show that activation of nuclear factor-κB (NF-κB) is a critical event leading to the suppression of cyp1a1 gene expression, thus providing an underlying mechanism for the TNF-α- and LPS-induced cyp1a1 suppression. We demonstrated that: (i) inducible RelA expression down-regulated aryl hydrocarbon receptor (AhR) activated reporter gene; (ii) the suppressive effects of LPS and TNF-α on the AhR-activated reporter gene could be blocked by pyrrolidine dithiocarbamate, which is known to inhibit NF-κB action; and (iii) TNF-α and LPS-imposed repression could be reversed by the NF-κB super repressor (SRIκBα), thus demonstrating the specific involvement of NF-κB. Furthermore, nuclear receptor co-activators p300/CBP and steroid receptor coactivator-1 act individually as well as cooperatively to reverse the suppressive effects by NF-κB on the AhR-activated reporter gene, suggesting that these transcriptional co-activators serve as the common integrators for the two pathways, thereby mediating the cross-interactions between AhR and NF-κB. Finally, using the chromatin immunoprecipitation assay, we demonstrated that AhR ligand induces histone H4 acetylation at the cyp1a1 promoter region containing the TATA box, whereas TNF-α inhibits this acetylation, suggesting that AhR/NF-κB interaction converges at level of transcription involving chromatin remodeling.

The cytochrome P-450 1A1 (cyp1a1) is a member of the cytochrome P-450 monoxygenase superfamily, which plays an important role in xenobiotic metabolism as well as in carcinogenesis (1, 2). Gene expression of cyp1a1 is highly regulated by development, tissue-specific factors, hormonal influences, xenobiotics, and pathophysiological mechanisms. In particular, it has been demonstrated that cyp1a1 expression is suppressed by LPS and TNF-α as well as other inflammatory cytokines (3–5). The mechanisms of the observed down-regulation of cyp1a1 by TNF-α and LPS are not well understood.

cyp1a1 gene expression is transcriptionally regulated by the aryl hydrocarbon receptor (AhR) (reviewed in Ref. 6). The AhR is a ligand-activated basic-helix-loop-helix/Per-ARNT-Sim (bHLH-PAS) transcription factor (7, 8). The ligands for the AhR include polycyclic aromatic hydrocarbons, such as 3-methylcholanthrene, benzo(a)pyrene, polyhalogenated aromatic hydrocarbons, such as the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and certain congeners of polyhalogenated biphenyls. The AhR resides in the cytoplasm in association with Hsp90 (9, 10) and a 38-kDa immunophilin-like protein (11–13). Upon ligand activation, the AhR translocates into the nucleus and binds to another basic helix-loop-helix PAS protein called the AhR nuclear translocator (ARNT) (14). The heterodimeric protein complex then binds to the enhancer sequence (xenobiotic response element (XRE)) located in the promoter region of AhR-controlled genes, such as cyp1a1 (15). Receptor binding to the XREs results in conformational changes in the chromatin structure in the cyp1a1 promoter leading to the subsequent transcriptional events (6).

LPS and proinflammatory cytokines such as TNF-α and interleukin-1β are known to induce NF-κB. NF-κB is a pleiotropic transcription factor playing an important role in regulation of physiological processes including immune responses, inflammatory reactions, cell proliferation, apoptosis, and developmental processes (reviewed in Ref. 16). 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 transcription activation. We have recently demonstrated a mutually inhibitory interaction between the AhR and NF-κB signaling pathways (17). These led us to hypothesize that the NF-κB plays an important role in mediating the suppression of cyp1a1 expression by inflammatory agents. In this study, we demonstrated that NF-κB plays a direct role in TNF-α- and LPS-induced down-regulation of cyp1a1 expression. Furthermore, our results suggest that the steroid receptor coactivator-1 (SRC-1) (18) and the transcription coactivator p300/CBP (19, 20) are common coactivators shared by the NF-κB and AhR pathways. These coactivators are known to...
have histone acetyl transferase (HAT) activity that contributes to activation of transcription of target genes. In support of the role of coactivators SRC-1 and p300 in mediating AhR/NF-κB interaction, we demonstrated by using the chromatin immunoprecipitation assay that NF-κB induced suppression of cyp1a1 expression by inhibiting ligand-induced histone H4 acetylation at the promoter region of cyp1a1. These results thus provide a mechanistic explanation for the long standing observation that the proinflammatory cytokines and bacterial endotoxin cause down-regulation of the expression of cytochromes P-450 1A1/1A2 and alter xenobiotic metabolism.

MATERIALS AND METHODS

Plasmids—pTIPGFP-RelA-GST was created by subcloning the RelA fragment into the BglII and NarI sites of the pTIPGFP-GST vectors (21). The RelA fragment was created by PCR amplification using a 685 bp plasmid (22) as the template. The primers used in the reaction were YE1 (GGGGCTATCCGACCATGGAGGACTCCGTC and YE2 (GGGCCCTGGAGA-TTAGGCTGCTGTGACTGACGAG). pGudLuc-6.1, a reporter plasmid containing the firefly luciferase gene under control of four XRE sequences, was kindly provided by M. A. Denison (23). SRiBe, which contains serine to alanine mutation in amino acid 322 and abolishes previous transcriptional activity, was cloned into pSG5 vector and SRiBe was cloned into the pcDNA vector (Invitrogen). Plasmid DNAs used for transfection were purified using the Qiagen Maxi-Prep DNA isolation system (Qiagen).

Cell Culture, Transient, and Stable Transfection—The cells were maintained in α-minimum essential medium supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 100 μg/ml streptomycin, and 250 μg/ml amphotericin B (Life Technologies, Inc.), 5% CO₂ at 37 °C. For transient transfection, Hepa1c1c7 cells were seeded in 6-cm dishes, and transfection was performed using LipofectAMINE (Life Technologies, Inc.) when cell density reached 80% confluency. pSv-β-galactosidase control plasmid (Promega) was used for normalization of transfection efficiency. Six hours after transfection, the cells were treated with AhR ligands (TCDD) or MeSO (solvent control) for 18 h before harvest for determination of luciferase activity. For stable transfection to create the tetracycline-inducible RelA expression cells, the HeLa Tet-On cells (CLONTECH Laboratories) were transiently transfected with the pTIPGFP-RelA-GST by lipofection. The transfected cells were then grown under the selection of puromycin (1 μg/ml). Selected colonies were picked and expanded in the presence of puromycin.

RNA Isolation and RT-PCR—For RNA purification, total cellular RNA was isolated with Trizol reagent (Life Technologies, Inc.) when cell density reached 80% confluence. pSV-CYP1A1/1A2 (Refs. 3 and 4; reviewed in Ref. 29). A common de-
NF-κB. To investigate the role of NF-κB in cyp1a1 regulation, we tested the effects of TNF-α and LPS on cyp1a1 expression. For this purpose, the murine hepatoma cells (Hepa1c1c7) were transiently transfected with pGudLuc6.1 through lipofection with LipofectAMINE. Six hours after the transfection, the cells were treated with either TNF-α or LPS for 12 h, and the luciferase activity was determined with a luminometer. All data are the means ± S.D. of triplicate transfections from a single representative experiment. C, Hepa1c1c7 cells were maintained in 6-well plates, and when growth reached 80% confluency, cells were treated with TCDD (10 nM), TNF-α, and LPS as shown. LPS was added to the medium 6 h prior to the addition of TCDD, whereas TNF-α was added together with TCDD. Twelve hours after TCDD treatment, the cells were harvested with Trizol (Life Technologies, Inc.) for the RT-PCR assay.

Controlled Expression of RelA Suppresses the cyp1a1—To further test the specific suppressive effects of RelA subunit of NF-κB on the cyp1a1 promoter, we created a controlled expression system by inserting RelA into the expression vector pTiPGF-GST-EGFP. This vector allows the inserted RelA to be expressed as a fusion protein (GST-RelA-EGFP) under the control of the tetracycline-responsive promoter and contains a puromycin-resistant gene (21). HeLa cells stably transfected with the pTiPGF-GST-RelA-EGFP were selected with puromycin. The HeLa cells were then transiently transfected with pGudLuc 6.1, and the transfected cells were treated with TCDD. The addition of doxycycline to the cell culture medium caused a dose-dependent increase of the expressed fusion protein (Fig. 2A) with concomitant decreases in the pGudLuc6.1 reporter gene activity (Fig. 2B). Expression of GST-EGFP alone did not affect the pGudLuc6.1 reporter gene activity, indicating that the suppressive effects are due to the RelA moiety of the fusion protein (Fig. 2A).

NF-κB RelA Plays a Major Role in TNF-α- and LPS-induced Down-regulation of cyp1a1 Expression—To demonstrate that NF-κB is directly involved in the cyp1a1 suppression by TNF-α and LPS, we first treated pGudLuc 6.1 transfected Hepa1c1c7 cells with TNF-α or LPS, and pyrrolidine dithiocarbamate (PDTC). PDTC is an antioxidant that has been widely used as a chemical inhibitor of NF-κB (30). In transient transfection assays with Hepa1c1c7 cells, PDTC treatment reversed the LPS-induced suppression of the pGudLuc6.1 reporter gene activity and significantly attenuated TNF-α-induced suppression of the reporter gene activity (Fig. 3), suggesting that NF-κB plays an important role in the suppression of cyp1a1 expression by TNF-α and LPS.
Suppression of cyp1a1 Expression by NF-κB

FIG. 3. PDTC reverses the TNF-α and LPS-induced suppression of pGudLuc 6.1. Hepa1c1c7 cells were transiently transfected with the pGudLuc 6.1 reporter gene by lipofection. The transfected reporter gene was allowed to express for 6 h, and the cells were cotreated with either PDTC + TNF-α or PDTC + LPS at the indicated dosage for 18 h, and then the luciferase activity was determined. The data are the means ± S.D. of triplicate transfections from three independent experiments.

mutation at residues 32 and 36. These mutations render the SRiXBa unable to be phosphorylated at serines 32 and 36 and resistant to degradation through the proteosome pathway, thereby causing constitutive inhibition of NF-κB (24, 25). In transient transfection assays, Hepa1c1c7 cells were cotransfected with pGudLuc 6.1 and increasing amounts of SRiXBa expression plasmid. Activation of NF-κB by either TNF-α or cotransfection of RelA expression plasmid caused suppression of the reporter gene activity. However, the TNF-α- or RelA-induced suppression of pGudLuc 6.1 was reversed by coexpression of SRiXBa (Fig. 4). As can be observed in Fig. 4, expression of SRiXBa actually enhanced the TCDD-induced pGudLuc 6.1 reporter gene activity. We believe that this is due to the suppression of the AhR by the endogenous level of NF-κB activity. Endogenous NF-κB activity is readily observable in untreated Hepa1c1c7 cells by EMSA (Fig. 5A, lane 1). These results taken together with those of the PDTC experiment indicate that NF-κB is an important factor in the TNF-α-induced suppression of cyp1a1 gene expression.

Activation of NF-κB by TNF-α and LPS Has No Direct Effect on In Vitro AhR-XRE Binding—One of the potential mechanisms for NF-κB-induced suppression of cyp1a1 transcription is for AhR and NF-κB to form an inactive complex, incapable of binding to the XRE sequences. To test this hypothesis, we performed an EMSA assay using nuclear extracts of TCDD-, TNF-α-, and LPS-treated Hepa1c1c7 cells. NF-κB activities were markedly induced by TNF-α and LPS as determined by EMSA with radiolabeled κB probe (Fig. 5A). The activated NF-κB proteins were the p65/50 heterodimer and p50/50 homodimer as determined by the EMSA supershift experiments (Fig. 5B). However, despite the strong activation of NF-κB, the binding of AhR-ARNT to the XRE consensus sequence was not affected by either TNF-α or LPS treatment at 2 h (Fig. 5C). These observations are in interesting contrast with the results of transient transfection results and RT-PCR, showing TNF-α and LPS significantly suppressed the AhR-driven luciferase gene activity (Fig. 1), suggesting that TNF-α and LPS suppress cyp1a1 transcription at step(s) downstream from AhR-XRE binding.

SRC-1 and p300/CBP Are Coactivators for the AhR and Act Cooperatively to Reduce the NF-κB-instigated Repression of cyp1a1 Promoter Activity—The transcriptional activity of the AhR and NF-κB are known to be modulated by transcriptional coactivators. Among the coactivators, p300/CBP and SRC-1 are known to be involved in the transcriptional activity of NF-κB. p300/CBP has been shown to be able to coactivate the AhR pathway (31). Using transient transfection assays, we tested the effects of p300/CBP and SRC-1 on the AhR/NF-κB interactions. Transient expressions of either SRC-1 (Fig. 6A) or p300 (Fig. 6B) caused enhancement of pGulLuc 6.1 reporter gene activity in Hepa1c1c7 cells, which is consistent with the coactivator functions of transcriptional coregulators (31, 32). We further tested the effects of these coactivations on the NF-κB-induced suppression of AhR driven reporter gene activity. In transient transfection assays, cotransfection of p65 with pGudLuc6.1 caused suppression of TCDD-induced reporter gene activity. Cotransfection of p300 and SRC-1 individually attenuated the suppressive effects of p65, and when transfected in combination, p300 and SRC-1 completely overcame the p65-induced suppression of pGudLuc6.1 reporter gene activity (Fig. 6C).
EMSA. To detect AhR binding to XRE, end-labeled XRE probes were used in EMSA. A, to detect activation of NF-κB, radiolabeled XRE probes in EMSA. B, EMSA supershift experiment to identify the p65/p50 heterodimer and p50/50 homodimer that bind to XRE probe. A, antibodies against p65, p50, and ARNT. C, to detect AhR binding to XRE, end-labeled XRE probes were used in EMSA. The double arrows indicate the specific binding of AhR complex to XRE. N.S., nonspecific binding. For both A and C, to show binding specificity, 200-fold of the unlabeled probes of wild type sequence (wt) and mutated sequence (mt) were used to compete with the radiolabeled probes in EMSA.

p300/CBP and SRC-1 are known to possess intrinsic HAT activity that is involved in chromatin remodeling and leads to gene activation. Their involvement in AhR/NF-κB interactions strongly suggests that NF-κB activation affects the chromatin remodeling of the cyp1a1 promoter. To investigate this potential effect, we used the ChIP assay to test the effects of TNF-α treatment on the TCDD-induced AhR binding on the cyp1a1 promoter and to study the acetylation of histones in native chromatin of the cyp1a1 promoter in Hepa1c1c7 cells. In these experiments, we found that ligand (TCDD) treatment induced AhR binding to the –821 to –343 region of cyp1a1 gene, which contains XRE sequences (33) (Fig. 7A). AhR binding to this region was associated with a concomitant increase in histone H4 acetylation (Fig. 7A). Histone acetylation is even more pronounced in the region containing the TATA box (Fig. 7B), suggesting that active chromatin remodeling activity is also occurring in this region. Consistent with the EMSA results, the effects of AhR binding to –821 to –343 is not affected by TNF treatment. Strikingly, TNF-α treatment inhibits the TCDD-induced H4 acetylation in the –821 to –343 region of the cyp1a1 gene, and the suppressive effect is most clearly observed in the region containing the TATA box (–285 to +66) (Fig. 7B).

**DISCUSSION**

Alteration of expression of cytochromes P-450 by proinflammatory cytokines, LPS, and double-stranded RNA (from certain viral infections) has important physiological implications as the metabolism of many drugs, xenobiotic detoxification, as well as homeostasis maintained by endogenous steroid hormones all depend on cytochromes P-450 action. Although there are some cytochromes P-450 that have been reported to be induced by TNF-α and LPS, the recurring findings are that inflammatory cytokines and LPS predominantly suppress the gene expression of cytochromes P-450 (reviewed in Ref. 29). The results of this study suggest a mechanistic explanation for the long standing observation that inflammatory cytokines and LPS suppress the expression of the gene encoding cytochrome P-450 1A1 (cyp1a1). Based on the results of our earlier studies, which show a direct interaction between the AhR and NF-κB pathways, we postulated that the inducers of NF-κB would down-regulate the cyp1a1 expression. Most of the reports have been largely consistent with this hypothesis. Indeed, it has recently been shown that H2O2 treatment suppresses cyp1a1 expression (34, 35). Although the investigators suggested that H2O2-induced cyp1a1 suppression is due to down-regulation of NF-κB, based on the fact that H2O2 is well known to induce NF-κB expression. (*, statistically significant difference (p < 0.01) compared with control; **, control. All data are the means ± S.D. from three triplicate transfection representatives of three independent experiments.)

**FIG. 5.** TNF-α and LPS treatments activate NF-κB but do not alter the binding of AhR to XRE. Hepa1c1c7 cells were treated with TNF-α (1 and 5 ng/ml), LPS (1 and 5 μg/ml), and TCDD (10 nm) for 2 h. Nuclear extracts from these treated cells were used for detection of activations of NF-κB and AhR by EMSA. A, to detect activation of NF-κB, radiolabeled XRE probe was used in EMSA. B, EMSA supershift experiment to identify the p65/p50 heterodimer and p50/50 homodimer that bind to XRE probe. A, antibodies against p65, p50, and ARNT. C, to detect AhR binding to XRE, end-labeled XRE probes were used in EMSA.

**FIG. 6.** SRC-1 and p300 act individually as well as cooperatively to reverse the NF-κB-induced suppression of pGudLud6.1 reporter gene activity. A and B, coactivation of the AhR-driven luciferase reporter gene by SRC-1 and p300, respectively. Hepa1c1c7 cells were transiently cotransfected with pGudLud6.1 and increasing amounts of either SRC-1 (A) or p300 (B) expression plasmids. After 6 h, the cells were treated with TCDD (1 nm) for 18 h before harvest for determination of luciferase activity. C, in transient transfection assay with Hepa1c1c7 as described in A and B above, coexpression with p65, SRC-1, or p300 attenuated the suppressive effects of RelA on the pGudLud6.1 reporter gene activity. Coexpression of SRC-1 and p300 together with p65 caused complete reversal of the RelA-imposed suppression of the AhR-driven luciferase gene activity. *, statistically significant difference (p < 0.01) compared with control; **, control. All data are the means ± S.D. from three triplicate transfections representatives of three independent experiments.

In our current studies, the important role of NF-κB in suppression of cyp1a1 expression is demonstrated based on the following results: (i) AhR activated luciferase reporter gene is down-regulated by RelA subunit of NF-κB under the control of tetracycline-regulated expression system; (ii) the suppressive effects of LPS and TNF-α on the AhR-activated reporter gene can be blocked by PDTC, which is known to inhibit NF-κB action; and (iii) TNF-α and LPS-imposed repression of cyp1a1 promoter activity could be reversed by the NF-κB super repressor (SRIκBα), thus demonstrating the specific involvement of NF-κB.

The results of the above experiments establish the role of...
NF-κB in suppression of cyp1a1 expression. To further investigate the mechanism of NF-κB-induced cyp1a1 suppression, we studied the roles of common transcriptional coactivators in mediating the suppression. It is known that transcriptional coregulators such as the p300/CBP and SRC-1 function as coactivators for both the AhR and NF-κB pathways. These coactivators have been shown to possess HAT activity (36–38). HAT activity is involved in the chromatin remodeling, which is a key step in transcriptional activation (39–41). Because p300/CBP and SRC-1 are found to be the coregulators for both AhR and NF-κB pathways, it is conceivable that there may be a competition such that when one pathway is activated, the other pathway will be repressed through competition for coactivator availability: a “squelching” mechanism. The results of this study support this hypothesis. As shown in Fig. 6C, expression of p300/CBP or SRC-1 alleviates the suppression imposed by activation of NF-κB. Coexpression of p300 and SRC-1 totally abolished the suppressive effect of NF-κB on the AhR-mediated reporter gene.

We have previously demonstrated a physical association between the AhR and the RelA subunit of NF-κB. It is intriguing to speculate about how this association causes the observed down-regulation of cyp1a1 expression. One possibility is that the AhR and RelA form an inactive complex, thereby preventing the AhR from binding to the enhancer sequences. We do not believe that this is the explanation, however, because we observed that activation of NF-κB by either TNF-α or LPS does not hinder the AhR-ARNT complex from binding to the XRE DNA sequences (Fig. 5C). Furthermore, the results of ChIP assays demonstrated that TCCD treatment causes binding of the AhR to the regions of the cyp1a1 gene containing XREs in 2 h and that cotreatment with TNF-α has no effects on the binding of AhR to this region (Fig. 7A). These results are in agreement with the in vitro EMSA results (Fig. 5C). In interesting contrast to the lack of effects of TNF-α to AhR binding to XRE, histone H4 acetylation is markedly inhibited by TNF-α treatment especially at the promoter region around TATA box within 2 h of TNF-α treatment (Fig. 7). These results suggest that ligand-induced activation of cyp1a1 expression is a series of interconnected yet distinct events. The activator (AhR) binding to the enhancer sequences is separable from the subsequent assembly of the preinitiation complex, which includes the recruitment of coactivators bearing HAT activities. These observations also imply that binding by an activator to an enhancer sequence is necessary but not sufficient for transcriptional activation. Our results are consistent with the two-stage model of steroid receptor gene activation proposed by Jenster et al. (42).

The involvement of p300/CBP and SRC-1 in the AhR/NF-κB functional interactions suggest an important role for histone acetylation in the AhR-mediated gene regulation. This view is clearly supported by the results in this study. We demonstrated, by using ChIP and EMSA, that activation of AhR with ligand causes AhR-ARNT complex to bind to the XRE sequences with concomitant increase in the histone H4 acetylation in the TATA box region of cyp1a1. Histone acetylation is associated with transcriptional activation (41). TNF-α treatment abolishes the acetylation of H4. Histone acetylation of the chromatin is an important initial step for gene activation, followed by the assembly of the preinitiation complex. Hypoacetylated chromatin is silenced in gene transcription. Therefore, TNF-α-induced inhibition of histone acetylation suggests inactivation of the cyp1a1 promoter. It is noteworthy that the status of histone acetylation is an outcome of two opposing processes, i.e. acetylation and deacetylation; therefore the observed inhibition of H4 acetylation at the cyp1a1 promoter could be the result of either the reduced HAT activity or increased deacetylation brought about by histone deacetylases.

In summary, we have demonstrated that NF-κB plays an important role in cyp1a1 suppression caused by TNF-α and LPS. We further demonstrated that p300/CBP and SRC-1 act individually, as well as cooperatively, to reverse the suppressive effects by TNF-α and LPS on the AhR-activated reporter gene. These observations suggest that these transcriptional coactivators serve as the common integrators for the two pathways, thereby mediating the cross-interactions between AhR and NF-κB. By using ChIP assay, we demonstrated the NF-κB/AhR interaction converges at the level of transcription, in that TNF-α activation suppresses cyp1a1 expression by inhibiting histone H4 acetylation at cyp1a1 promoter. Whether the inhibited histone acetylation at cyp1a1 promoter is brought about by reduced HAT or increased histone deacetylase activity or both remains to be investigated.

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