Cooperative Interaction between AhR·Arnt and Sp1 for the Drug-Inducible Expression of CYP1A1 Gene*

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Expression of CYP1A1 gene is regulated in a substrate-inducible manner through at least two kinds of regulatory DNA elements in addition to the TATA sequence, XRE (xenobiotic responsive element), and BTE (basic transcription element), a GC box sequence. The trans-acting factor on the XRE is a heterodimer consisting of arylhydrocarbon receptor (AhR) and AhR nuclear translocator (Arnt), while Sp1 acts as a regulatory factor on the BTE. We have investigated how these factors interact with one another to induce expression of the CYP1A1 gene. Both in vivo transfection assays using Drosophila Schneider line 2 (SL2) cells, which is devoid of endogenous Sp1, AhR, and Arnt, and in vitro transcription assays using baculovirus-expressed AhR, Arnt, and Sp1 proteins revealed that these factors enhanced synergistically expression of the reporter genes driven by a model CYP1A1 promoter, consisting of four repeated XRE sequences and a BTE sequence, in agreement with previous observation (Yanagida, A., Sogawa, K., Yasumoto, K., and Fujii-Kuriyama, Y. (1990) Mol. Cell. Biol. 10, 1470–1475). We have proved by coinunpreci-
pitation assays and DNase I footprinting that both AhR and Arnt interact with the zinc finger domain of Sp1 via their basic HLH/PAS domains. When either the AhR·Arnt heterodimer or Sp1 was bound to its cognate DNA element, DNA binding of the second factor was facilitated. Survey of DNA sequences in the promoter region shows that the XRE and GC box elements are commonly found in the genes whose expressions are induced by polycyclic aromatic hydrocarbons, suggesting that the two regulatory DNA elements and their cognate trans-acting factors constitute a common mechanism for induction of a group of drug-metabolizing enzymes.

Transcriptional activation of eukaryotic genes in response to exogenous or endogenous signals is accomplished by multiple sequence-specific protein/DNA and protein/protein interactions. DNA-binding proteins that recognize the appropriate DNA sequences in the promoter of a gene can interact with other transcription factors to transmit transcription-enhancing effects on the basic transcription machinery, commonly including transcription factor IID and RNA polymerase II. Transcription of the CYP1A1 (cytochrome P-450c) gene, which encodes a drug-metabolizing enzyme, is induced by polycyclic aromatic hydrocarbons such as 3-methylcholanthrene and TCDD1 (1, 2). The analysis of CYP1A1 gene regulation by the DNA transfer experiments in transient transfection assays revealed that a high level of inducible expression required at least two regulatory DNA sequences, designated XRE (xenobiotic responsive element) and BTE (basic transcription element, a GC box sequence) (3–6). The regulatory factor on the XRE is a heterodimer complex consisting of AhR (aryl hydrocarbon receptor; Refs. 7 and 8) and Arnt (AhR nuclear translocator; Ref. 9) (10–12), while Sp1 is a regulatory factor acting on the BTE. Like steroid hormone receptors, AhR exists in the cytoplasm of normal cells in association with hsp90 (13–16). As soon as an inducer is taken up in cells, it is recognized and bound by AhR. The resultant inducer-bound AhR was stimulated to be disso-
ciated from hsp90 and translocate to the nucleus, where it forms a transcriptionally active complex with Arnt to activate the CYP1A1 gene via binding to the XRE. In DNA transfer experiments, deletion of either the XRE or BTE element in a fusion gene consisting of the CYP1A1 promoter and the CAT (chloramphenicol acetyltransferase) structural gene resulted in a remarkable reduction in CAT expression (6). The fusion gene lacking the BTE sequence in the promoter exhibited only a low inducible expression of CAT activity in response to the inducer, because of the decreased constitutive expression, while the gene deleted of the XRE showed only a constitutive CAT expression even in the presence of the inducer. These results suggest a cooperative interaction between the factors acting on the XRE and BTE sequences to enhance the expression of the gene. Recently, we and other groups have isolated cDNA clones for these regulatory factors (7–9), and we have now investigat-
ged how these factors interact with each other on their cognate DNA elements.

In this paper, we describe the several lines of evidence for physical interaction between the AhR·Arnt complex and Sp1 by in vivo DNA transfer experiment, in vitro transcription assay, coinunprecipitation methods, and DNase I footprinting. Experiments introducing a variety of deletional mutations into these factors demonstrated that the interaction between AhR·Arnt and Sp1 is accomplished through the basic HLH/PAS domains of AhR·Arnt and zinc finger domain of Sp1. Survey of the sequence data base shows that both the XRE and the GC box are present in promoter regions of a group of drug-metabolizing enzyme genes, suggesting that the two DNA elements

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1 The abbreviations used are: TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; AhR, arylhydrocarbon receptor; Arnt, AhR nuclear translocator; hsp, heat shock protein; BTE, basic transcription element; CAT, chlor-amphenicol acetyltransferase; CYP, cytochrome P450; DTT, dithiothre-
itol; PMSF, phenylmethylsulfonyl fluoride; GST, glutathione S-trans-
ferase; HLH, helix-loop-helix; PAS, Per-Arnt-AhR-Sim; PAGE, polyacrylamide gel electrophoresis; XRE, xenobiotic responsive ele-
ment; PCR, polymerase chain reaction; bp, base pair(s); kbp, kilobase pair(s); 3-MC, 3-methylcholanthrene.
and their cognate DNA binding factors constitute a common mechanism for the inducible expression of this class of genes.

**EXPERIMENTAL PROCEDURES**

**Plasmid Construction of Expression Vectors**

Expression Plasmids of Sp1, AhR, and Arnt in Drosophila SL2 cells—pGEMAct-Sp1 was constructed by inserting a full Sp1 cDNA fragment derived from pRSV-Sp1 into the XhoI site in pGEMAct-2 (a kind gift from Dr. I. Nishida and M. Yoo (Aichi Cancer Center)). pGEMAct-hAhR and pGEMAct-Arnt were constructed by inserting 2.5-kbp Asp718 fragment and 2.5-kbp NcoI/XhoI fragment from pBSK-hAhR (described below) and pBKS-Arnt (10), respectively, into pGEMAct-2 which had been digested with XhoI and treated with Klenow fragment.

In Vitro Expression Vector of Sp1—pSP-Sp1 as Sp1 expression plasmid was made by inserting a cDNA fragment (nucleotides 31–2475) (17) containing a full coding sequence for rat Sp1 into pSP72 (Promega). CAC755 and CAC649 were generated by inserting an XbaI linker into the Ncol and ApaI sites in pSP-Sp1 for creating a termination codon, respectively. To produce ΔAB, pSP-Sp1 was digested with BsmI and PFiMI for deletion of the 1200-bp BsmI/PFiMI fragment, treated with T4 DNA polymerase, and then ligated intramolecularly with a Smal linker (10 mer). Zf was generated as follows: ΔAB was digested with PvuI and BglII. The resulting 1200-bp BglII/PvuI fragment, containing 800-bp and 2500-bp fragments were ligated intermolecularly. Zf1D was generated by inserting an XbaI linker into the Ncol site in Zf.

**Baculovirus Expression System**

Wild type baculovirus genomic DNA was used for cotransfection with pVL1393H6hAhR, pVL1393H6hArnt, and pVLH6rSp1 into SF9 cells (23). Infected cells were identified by plaque assays, and subsequently the virus was plaque-purified to homogeneity as described (18).

**Purification of the Recombinant Proteins**

SF21 cells in 50 flasks (75-cm²) that expressed AhR, Arnt, and Sp1 were harvested at a maximal expression time and were washed with cold phosphate-buffered saline, followed by resuspension in 20 ml of buffer D (20 mM HEPES (pH 7.9), 500 mM KCl, 20% glycerol, 1 mM DTT, 1 mM PMSF, 5 mM NaF). The cells were homogenized by a glass homogenizer or mild sonication and were centrifuged at 25,000 × g for 30 min at 4°C. The supernatants were brought to 5 mM imidazole (pH 7.9) and applied to the ProBond™ resin (Invitrogen) that had been pre-equilibrated with the same buffer containing 5 mM imidazole. The column was washed with 5 column volumes of the same buffer followed by 20-column volume of the buffer containing 40 mM imidazole and then the recombinant protein was eluted with 5 column volumes of buffer D containing 150 mM imidazole. Silver staining and immunoblot analysis using 7.5% SDS-PAGE were used to determine the purity of the proteins. Their purities were approximately 90%, 90%, and 10% for Sp1, Arnt, and AhR, respectively (Fig. 2). The purification of AhR in an active state was difficult because of its low solubility and instability, and only a partially purified sample was used for the subsequent experiments.

For the in vitro transcription assay, the DNase I footprinting analysis, the eluate was subject to the PD-10 column (Pharmacia) for change of the KCl concentration to 100 mM KCl.

**In Vitro Transcription Assays**

Nuclear extracts were prepared from SF9 cells as described by Dingwall et al. (24). Reactions were performed in 30 µl containing 800 ng of template DNA and 200 ng of pml10404(180) as an internal control. Final concentration of the reaction constituents were 11 mM HEPES (pH 7.9), 11% (v/v) glycerol, 57 mM KCl, 0.1 mM EDTA, 0.28 mM PMSF, 0.56 mM DTT, 8 mM MgCl₂, 4 units of RNasin (Promega), 1 μM 3-MC, Sp1 (20 ng), AhR (20 ng), Arnt (20 ng), and nuclear extracts (10 μl, final concentration of about 2 mg of protein/ml). For competition assay, the XRE-1 or mutated XRE oligonucleotides (25-fold) (10) were added in the reaction mixtures. Reaction mixtures were preincubated for 25 min at 30°C. After transcription was initiated by the addition of nucleotides (final concentration of 600 μM for each of ATP and CTP, 25 μM UTP, 300 μM 3'-O-methyl-GTP, and [α-32P]UTP (3000 Ci/mmol)), reaction mixtures were incubated for 45 min at 30°C, followed by the addition of RNAse A (20 units) and further incubated for 15 min at 30°C. Reactions were terminated by the addition of a stop buffer (0.5% SDS, 10 mM EDTA, 100 mM sodium acetate (pH 5.2), 1 μg of RNA/ml; Boehringer Mannheim) and were extracted once with 1:1 phenol/chloroform. An aqueous phase was precipitated with ethanol, rinsed with 80% ethanol, and dried in vacuo. RNA samples were resuspended in a dye solution (98% formamide, 1% each xylene cyanol and bromphenol blue) and electrophoresed on 8% urea, 6% polyacrylamide gel in 0.5 x TBE buffer (45 mM Tris, 45 mM borate, 1.25 mM EDTA (pH 8.2)). Autoradiography and quantification were carried out by exposure to Fuji RX film or with an Imaging analyzer (Fuji film, BAS100).

**Commonprecipitation Assay and in Vitro Binding Assay**

Commonprecipitation assay was performed as described (18). In vitro binding assay by GST-Arnt fusion proteins were performed as follows. Glutathione S-transferase fusion proteins were isolated from Escherichia coli strain PT-TxBL21DE3 (a kind gift from Dr. S Ishii, 2 M. Erna, manuscript in preparation.)
Synergistic Transactivation of CYP1A1 Promoter in SL2 Cells by AhR, Arnt, and Sp1—By the transient expression system using Hepa-1 cell culture, we identified two regulatory elements in the promoter of the CYP1A1 gene, XRE and BTE (a GC box element), both of which were essential for a high level of drug-inducible transcription (6). To further investigate whether and how the transcription factors acting on these DNA elements activate the CYP1A1 gene transcription in response to the inducer, we examined the transcriptional activity in an in vitro transient expression system using Drosophila SL2 cells, which are known to be devoid of mammalian transcription factor AhR, Arnt, and Sp1-related proteins. We constructed a model reporter plasmid by fusing the CYP1A1 gene promoter with the CAT structural gene (Fig. 1A). As a control experiment, only addition of an inducer could not induce the CAT expression in SL2 cells transfected with the reporter plasmid (Fig. 1B, lanes 1 and 2). The transfection of Sp1 could only activate marginally the transcription of the CAT gene (lanes 3 and 4). Likewise, transfection with either the AhR or Arnt expression plasmid had essentially no effect on transactivation of the CAT fusion gene even in the presence of Sp1 (data not shown). In contrast, while the expression plasmids both AhR and Arnt in the absence of Sp1 in the SL2 cells transfected with the CAT expression plasmid enhanced the CAT expression from p53-ICAT plasmid by about 8-fold (compare lanes 5 and 6), cotransfection of the AhR and the Arnt expression plasmids together with the Sp1 plasmid remarkably enhanced the CAT expression by about 15-fold in the response to the added inducer (compare lanes 7 and 8). Since a complete supply of AhR, Arnt, and Sp1 already enhanced the CAT expression about 3-fold above the background level in the absence of the inducer (lanes 5 and 7), the fully enhanced CAT expression in response to the inducer amounted to about 50-fold above the background levels (lanes 5 and 8). These results further strengthen the previous evidence for the synergistic effects of the XRE and BTE sequences on the CYP1A1 gene expression.

Results

Synergistic Transactivation of CYP1A1 Promoter in SL2 Cells by AhR, Arnt, and Sp1

To further investigate the mechanism of the CYP1A1 gene transcription, we examined effects of partial purified AhR, Arnt, and Sp1 on the transcriptional activity in an in vitro transcription assay system (Figs. 2 and 3). We also constructed model genes from the CYP1A1 gene promoter and the G-free cassette template (Fig. 3A). p53-IC2AT was produced by placing four copies of the XRE on the −53-bp promoter of the CYP1A1 gene linked to the G-free cassette. Deletion of the GC box sequence from p53-IC2AT made p44-IC2AT. We used SF9 cell nuclear extract which is known to be devoid of endogenous mammalian Sp1-related proteins and AhR-Arnt, as a source of basal transcription factors and RNA.
polymerase. Purified Sp1 stimulated the transcription about 3-fold over background levels on p53-IC2AT, while AhR and/or polymerase. Purified Sp1 stimulated the transcription about 7-fold above background. Addition of an excessive amount of the XRE sequence to the reaction mixture reduced the transcription to a level of the Sp1-dependent transcriptional activity (Fig. 3B, lane 7), while the mutated XRE fragment had essentially no effect (lane 8). The enhancement by AhR-Arnt in the presence of Sp1 was not observed with p44-IC2AT, which is devoid of the GC box (Fig. 3C, lane 6). In these experiments, partially purified AhR was already activated for the most part to form a heterodimer with Arnt, which was able to bind the XRE sequence without the inducer. Purification procedures probably changed the conformation of AhR in the AhR-hsp90 complex or released AhR from its complex to form a heterodimer with Arnt as described previously (25). Therefore, addition of AhR and Arnt preparations along with Sp1 enhanced the in vitro transcription even without inducers. Addition of the inducer enhanced only and additional 10% increase in the transcription activity without it. To show full transcription activity, we presented the results in the presence of the inducer (Fig. 3). These results showed that the in vitro transcription activities depend on AhR-Arnt, Sp1, and their cognate binding sequence and suggest that the enhanced transcription resulted from a synergistic effect between the AhR-Arnt complex and Sp1, which confirms the results of in vivo DNA transfer experiments using Hepa-l cells (6) and SL2 cells (Fig. 1), although it was not so marked as that observed in the in vivo transient transfection system.

Sites for Interaction of Sp1 with AhR and Arnt—To examine whether Sp1 physically interacts with AhR and/or Arnt, we performed commounprecipitation experiments using anti-AhR and anti-Arnt antibodies. Sp1 was synthesized in the presence of [35S]Met in the in vitro reticulocyte lysate system and used in incubations with AhR or Arnt produced by the baculovirus expression system. Sp1 was incubated with AhR or Arnt, and then the incubation mixture was subsequently immunoprecipitated with anti-AhR or Arnt antibodies. As shown in Fig. 4, Sp1 incubated with AhR was commounprecipitated by anti-AhR antibodies and likewise, incubation of Sp1 with Arnt lead to commounprecipitation by anti-Arnt antibodies. In control experiments of incubations without AhR or Arnt, neither of the antibodies could precipitate Sp1 (lanes 4 and 7).

To examine functional domains of Sp1 responsible for association with AhR and Arnt, we tested the interaction of a series of Sp1 deletion mutants with AhR and Arnt. Fig. 5A illustrates several deletion constructs of Sp1 and a summary of their interaction with AhR and Arnt. The experimental data are presented in Fig. 5B. Removal of the zinc finger motifs (CA649 and CA353) abolished association of Sp1 with AhR and Arnt (Fig. 5, A and B). In contrast, removal of most of the sequence N-terminal (ΔAB and Zf) or C-terminal (CA755) to the zinc finger had essentially no effect on the binding activity.
Only the zinc finger motifs (ZfAD) retained an adequate capacity for the association with AhR and Arnt. It was reported that the region immediately C-terminal to the zinc finger domain, designated the D region (26), is necessary for homologous interaction of Sp1, but this region is not necessary for interaction with AhR or Arnt. Subdivision of the zinc finger domain for the interaction activity remains to be investigated.

Interaction Site of AhR and Arnt with Sp1—As reciprocal experiments, we examined interaction sites of AhR and Arnt with Sp1. Figs. 6A and 7A show the structures of AhR, Arnt, and their derivatives with functional domains, which were elucidated by previous studies (27–29). For AhR, we synthesized 35S-labeled AhR and a series of deletion mutants in the presence of [35S]Met in the in vitro reticulocyte lysate system, and used these proteins for incubation with Sp1 produced in the baculovirus expression system. The incubation mixtures were treated with anti-Sp1 antibodies, and the resultant immunoprecipitates were electrophoresed in a polyacrylamide gel. Deletion of the HLH region reduced only slightly the binding activity to Sp1, while deletion of the PAS reduced it markedly. When both of the regions were deleted simultaneously, the binding activity was almost completely abolished. For the assay of interaction with Arnt, GST fusion protein of Arnt and various deletion mutants were bacterially expressed and purified. The GST-fusion proteins were incubated with [35S]Met-labeled Sp1, and then glutathione-bound beads were added to the incubation mixture. Following centrifugation, the 35S-labeled Sp1 that bound the GST fusion proteins was eluted and analyzed by gel electrophoresis. As shown in Fig. 7 (A and B), 35S-labeled Sp1 was found associated with both HLH and PAS regions of Arnt. Association of Sp1 with the HLH region appeared to be more stable than that with the PAS, somewhat different from the case of AhR. In any event, the HLH and PAS domains of AhR and Arnt appear to cooperatively interact with the zinc finger of Sp1.
on their recognition sequences (lines 3-5 and lines 9-11) in dose-dependent manners. On the other hand, when both of them were incubated simultaneously with the DNA sequence, the DNase I footprinting pattern was not entirely the sum of the two footprints exhibited by separate incubations with Sp1 and AhR-Arnt. For instance, the bands indicated by arrowheads 1 and 3 were protected at lower concentrations of each one of Sp1 and AhR-Arnt when each factor was incubated in the presence of the other, and a new hypersensitive band (arrowhead 2) appeared in the GC box region upon incubation of Sp1 and AhR-Arnt together. These results suggest that the two transcription factors interacted with each other on their cognate DNA binding sites and consequently changed their mode of binding to the recognition sites. These data also suggest that binding of one of the two factors to its DNA site facilitates binding of the other to its cognate site.

**DISCUSSION**

In our previous study on gene regulation of CYP1A1 by DNA transfer experiments, the two DNA elements, XRE and BTE, together with the TATA sequence are necessary for a high level of inducible expression of the CYP1A1 gene in response to inducers such as TCDD and 3-MC. Lack of one of the two elements in the promoter region reduced markedly the expression of the gene, suggesting a synergistic effect of the two elements on the CYP1A1 gene expression. In line with this observation, we further demonstrated the synergistic transactivation by AhR-Arnt and Sp1 through an in vitro DNA transfer experiment using SL2 cells and an in vitro transcription assay system. Since SL2 cells is known to be devoid of Sp1 or its highly related factors and AhR-Arnt, in vivo DNA transfer experiments showed that a high level of inducible CAT expression in response to the inducer was clearly dependent on the simultaneous transfection of the expression plasmids of AhR, Arnt and Sp1 into SL2 cells. On the other hand, transcription of either Sp1 plasmid or AhR and Arnt plasmids alone resulted in only a low level of the CAT expression. The synergistic enhancing effect on the transcription between Sp1 and AhR-Arnt was also observed in the in vitro transcription system using Sf9 cell lysates, which lack Sp1 and AhR-Arnt, although it was not so marked as in the in vivo transient transfection system. It was revealed that an optimal transcription driven by a model CYP1A1 promoter requires Sp1, AhR-Arnt, and their cognate recognition sequences. When one of the factors or the DNA elements was missing in this in vitro system, the transcription activity was markedly reduced, consistent with a synergistic effect of the XRE and BTE sequences on the transcription of the CYP1A1 gene in vivo. Survey of the promoter regions of the genes, whose expressions are known to be induced in response to aromatic inducers such as TCDD and 3-MC, reveals that most, if not all, of the genes carry these two regulatory DNA elements (Fig. 9; Refs. 5 and 30–33). Although its presence was not reported, there is an apparent GC box sequence in the promoter region of the glutathione S-transferase gene. These results suggest that the XRE and GC box sequences and their cognate binding factors constitute a com-
mon mechanism for drug induction of a group of drug-metabolizing enzymes. Immunoprecipitation assay and GST-fusion protein binding assay demonstrated that Sp1 and AhR-Arnt physically interact with each other. The experiments using deletion mutants of various parts of the three proteins clearly demonstrated that the interaction was mediated by the zinc finger domain of Sp1 and the HLH/PAS domains of AhR and Arnt proteins. Recently Sp1 has been reported to interact with itself or with other transcription factors such as NF-κB, GATA-1, and YY-1 to synergistically enhance the transcription driven by the promoter containing the GC box and the corresponding factor binding sequences (34–37). Interestingly, the interaction of Sp1 with these regulatory factors including AhR-Arnt is always mediated through its zinc finger domain. Since there is apparently no common sequence among these partner factors, it is interesting to investigate whether various parts of the zinc finger of Sp1 interact with respective partner molecules or whether a common part of the zinc finger is used for interaction with these factors in an adaptive manner. Alternatively, it is possible that apparently different primary structures, resulting in interaction with a common part of the zinc finger domain of Sp1. In any event, it is important to track down the interactive sequence of Sp1 into a small portion of the molecule for each of the partner proteins. In DNase I footprint analysis, while separate addition of AhR-Arnt and Sp1 protected their respective DNA recognition sequences against digestion by DNase I, the simultaneous presence of the two transcription factors caused unique alterations in the combination of the two DNase I footprint patterns (indicated by arrowheads in Fig. 8), suggesting physical interaction between AhR-Arnt and Sp1 bound on their DNA elements. In addition, judging from the intensity of the protected bands, it appeared that the extent of protection by one factor was increased in the presence of the other. These results suggest that binding of one of the two factors to its recognition sequence facilitates the other to bind its cognate DNA element. This cooperative DNA binding of the two transcription factors could result in synergistic enhancement of transcription of the CYP1A1 gene.

Although the N-terminal region of Sp1 is known to interact with TAF110 to enhance basal transcription (38), AhR and Arnt have potent transcriptional activation domains in the C-terminal regions (27, 28). It remains to be studied how the physical interaction between AhR-Arnt and Sp1 leads to synergistic enhancing effect on transcription of the CYP1A1 gene. In this study, we used a model promoter of the CYP1A1 gene constructed by placing XRE sequences on the −53-bp segment of the CYP1A1 gene, which carries a GC box sequence on the 5′ end. Therefore, the XRE sequences are brought in such close proximity to the GC box that the two transcription factors may interact efficiently with each other. It is generally envisioned that chromosomal looping may bring together complexes of Sp1 bound on the GC box sequence and AhR-Arnt on the XREs in the promoter of CYP1A1 gene.

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