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Review

Molecular mechanisms of AhR functions in the regulation of *cytochrome P450* genes

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Abstract

AhR, a ligand-activated transcription factor, mediates xenobiotic signaling to enhance the expression of target genes, including drug-metabolizing cytochrome P450s. The recent development of several new techniques, including chromatin immunoprecipitation and RNA interference, has expanded and deepened our knowledge of AhR function in the xenobiotic signal transduction. In this review, we briefly summarize our current understanding of the activation and inactivation of AhR activities and discuss the future directions of AhR research.

Keywords: Aryl hydrocarbon receptor; Cytochrome P450; Transcription factor; Coactivator; Gene regulation

Cytochrome P450 (CYP) is a superfamily of hemoproteins, composed of more than 3000 molecules and distributed across species ranging from bacteria to vertebrates. These proteins catalyze the monooxygenation of various endogenous and exogenous substrates [1,2]. Superfamily members are classified according to the similarity of their primary structures; members of families 1, 2, 3, and 4 are mainly involved in the metabolism of exogenous chemicals, including drugs, food additives, and environmental pollutants. CYPs are typically inducible; specific forms of CYPs are induced in response to the administration of certain chemicals [3–5].

Recently, the molecular mechanisms governing the inducible expression of CYPs have been successfully elucidated, including the inducers, *cis*-acting DNA elements, cognate transcription factors, and coactivators. The inducible expression of the CYP1 family is regulated by a heterodimer of the aryl hydrocarbon receptor (AhR or dioxin receptor) and the aryl hydrocarbon receptor nuclear translocator (Arnt), which contain a bHLH-PAS structural motif [5,6]. Expressions of the CYP2, 3, and 4 family members are controlled by other transcription factors (CAR, PXR, and PPAR) of the nuclear receptor (NR) superfamily, which have a characteristic zinc finger motif different from that in AhR [3–5].

The specific involvement of these receptor-type transcription factors in the induction of certain CYPs has been confirmed by gene-engineering technology, including gene-knockout methods [3,6–8]. The recent development of new techniques, including small interference RNA (siRNA) and chromatin immunoprecipitation (Chip) analyses, has greatly expanded our knowledge of the molecular mechanisms controlling the inducible expression of drug-metabolizing CYPs [9]. In this short review, we summarize the recent advances in the study of AhR activation and inducible expression of CYP1 and some other CYP families. The mechanisms of NR-related inducible expression of CYP2, 3, and 4 families are addressed in a number of excellent review articles [10–12].

Activation of AhR

Normally, AhR exists in a dormant state within the cytoplasm in association with a complex of HSP90, XAP2, and p23. Upon ligand binding, AhR in the complex is activated by a conformation change that exposes a

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nuclear localization signal(s) (NLS). The ligand-activated AhR in the complex translocates into the nucleus and forms a heterodimer with the closely related Arnt protein already present in the nucleus by dissociating from the complex [5,6].

Structure–activity relationship studies examining the binding activity of AhR ligands using a large number of halogenated aromatic hydrocarbons (HAHs) and polycyclic aromatic hydrocarbons (PAHs) suggest that the presumed AhR binding pocket accepts planar ligands with maximal van der Waal's dimensions of $14 \times 12 \times 5$ Å [13,14] (Fig. 1). Some electronic and thermodynamic properties of ligands appear to be important for a high binding affinity, although formulation of the exact structure necessary has yet to be defined [14]. 2′,3′,7′,8′-Tetrachlorodibenzo-*p*-dioxin (TCDD) and indolo[2,3-*b*]carbazole (ICZ) are the most potent inducers of CYP1 expression. AhR, which is well conserved from invertebrates like *Caenorhabditis elegans* and *Drosophila melanogaster* to vertebrates [15], mediates the majority of pharmacological and toxicological effects on host animals elicited by those xenobiotics. This high degree of evolutionary conservation among species suggests that AhR plays an important physiological role in homeostasis and/or development. In support of this hypothesis, many endogenous compounds with chemical properties different from those of the known high affinity xenobiotic ligands, such as tryptamine and indole acetic acid [16], bilirubin and biliverdin [17], and lipoxin A4 [18], have been isolated as potential natural ligands of AhR (Fig. 1). These compounds have relatively low binding affinities for AhR in comparison to those of TCDD, 2,3,7,8-tetrachlorodibenzofuran (TCDF), and ICZ. Of the tryptophan-derived natural AhR ligands like indirubin and indigo, 6-formylindolo[3,2-*b*]carbazole (FICZ), a tryptophan photoproduct, has a very high affinity for AhR, comparable to that of TCDD (Fig. 1). FICZ is formed in cell culture medium exposed to light in the presence of riboflavin [19]. Identification of all these compounds as active ligands for AhR was conducted by examining their ability to induce *CYP1A1* gene expression in cultured cells or by measuring their xenobiotic response element (XRE)-binding activity by gel mobility shift assay (GMSA). Although these chemicals have the potential to activate AhR activity, identification of a true physiological ligand for AhR would require to clarify how the activation of AhR by these naturally occurring ligands is associated with specific physiological functions.

Recently, a number of papers have reported that AhR is activated in the absence of obvious ligands in Hepa 1clc7 cells [20], human keratinocytes [21], 10T1/2 fibroblasts [22], and HaCaT cells [23] grown under specific culture conditions. When Hepa-1 cells and human keratinocytes were grown in suspension, CYP1A1 mRNA was induced without the addition of AhR ligands in an AhR-dependent manner at levels similar to that seen following TCDD treatment [20,21]. Suspension cultures of several C3H10T1/2 fibroblast clonal sub-lines that contain an integrated AhR-responsive reporter gene exhibited a time-course and levels of reporter activation and endogenous CYP1B1 induction that paralleled TCDD stimulation in confluent monolayer culture. Loss of cell–cell contacts at low culture densities also activated the expression of the

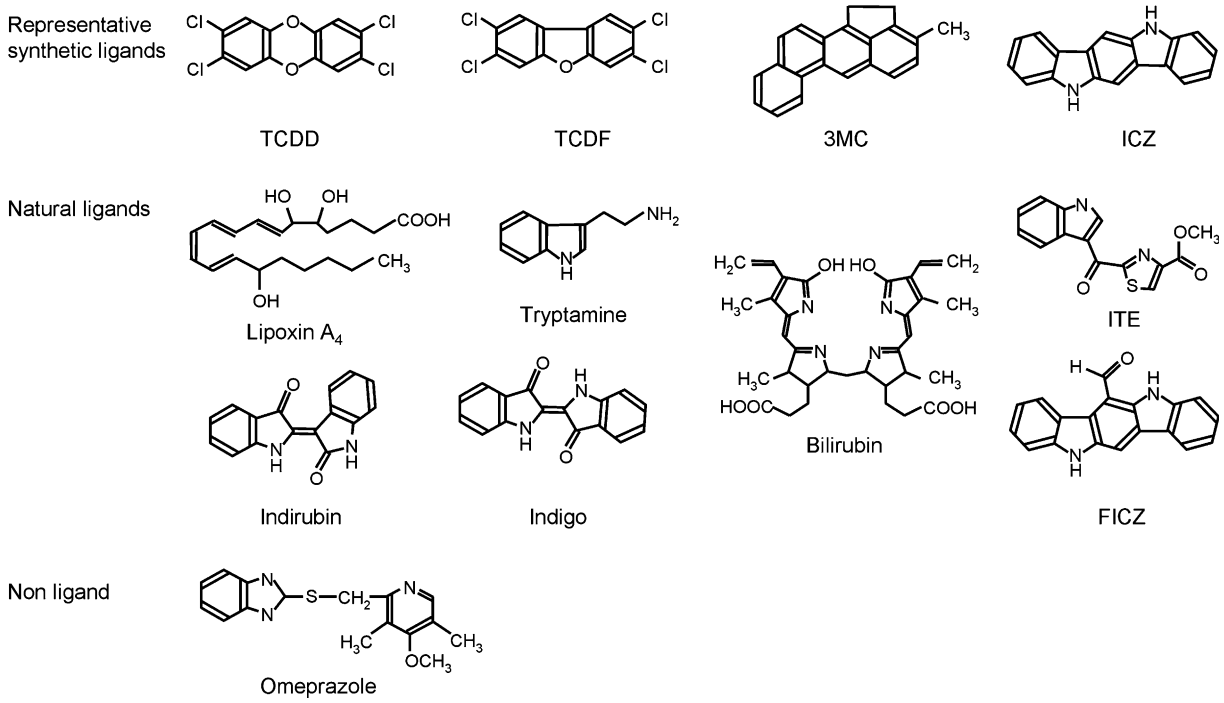

Fig. 1. Chemical activators of AhR. TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDF: 2,3,7,8-tetrachlorodibenzofuran, 3MC: 3-methylcholanthrene, ICZ: indro[3,2-*b*]carbazole, ITE: 2-(1′*H*-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester, FICZ: 6-formylindolo[3,2-*b*]carbazole.

reporter at levels comparable to TCDD stimulation of confluent cells in a manner independent of cell cycle changes. Suspension culture and TCDD treatment induced comparable AhR nuclear translocation and AhR/Arnt complex formation [22]. Culture of a keratinocyte cell line, HaCaT, at low cell densities or at confluence in Ca^{2+}-deficient S-MEM induces the nuclear accumulation of AhR in association with enhanced expression of a reporter gene whose expression is driven by XRE sequences [23]. These findings suggest that disruption of cell–cell contacts or cell–cell interactions stimulates the nuclear localization and transcriptional activity of AhR via a signal transduction pathway. The nuclear accumulation of AhR is regulated by the phosphorylation of Ser68 within the nuclear export sequence (NES) of AhR. Use of specific kinase inhibitors has suggested that this phosphorylation event is catalyzed by p38 MAPK [23]. An increasing number of reports have described that phosphorylation regulates AhR activity in the physiological signaling pathway regulating cell cycle progression as well as the xenobiotic signal transduction pathway [24]. Omeprazole induces CYP1A1 in an AhR-dependent manner without binding directly to AhR [25,26]. Tyrosine kinase inhibitors, tyrphostins AG17 and AG879, selectively inhibited omeprazole-mediated AhR signaling, but did not affect TCDD-mediated induction of CYP1A1. Mutational analysis provided evidence that a Tyr320Phe mutation abolished omeprazole-dependent AhR activation, while the TCDD-dependent activation of *CYP1A1* transcription was only minimally affected. These results suggest that Tyr320 is a putative phosphorylation site on AhR activated by omeprazole in a ligand-independent manner via a signal transduction pathway that involves protein tyrosine kinases. This pathway is independent from that induced by high-affinity ligands, such as TCDD [26]. Although the protein kinases involved remain unclear, AhR can be activated in a ligand-independent manner.

Cis-acting DNA elements

The regulatory DNA elements responsible for the induction of CYP1 by polyaromatic hydrocarbons like TCDD, called XREs, were first identified by transient DNA transfection experiments using a reporter gene, whose expression was driven by the *CYP1A1* promoter [27]. Later, additional experiments introducing a variety of mutations at this locus defined the consensus sequence and designated this sequence the DRE or AhRE [5,28]. All *CYP* genes whose expression are induced by PAH or HAH, including CYP1A1, 1A2 [6,27,28], 1B1 [29], 2A8 [30], and 19 [31] (Fig. 2), carry XRE sequences within their promoters. The human *CYP1A1* and *1A2* genes, found on chromosome 15q23 [32], are arranged in head to head orientation at a distance of approximate 23 kb apart. A similar chromosomal arrangement is reported for the mouse *Cyp1A1* and *1A2* genes on chromosome 9B, the syntenic chromosome to human Ch15q23. Although both genes are similarly inducible by PAH or HAH and share a common 5′ flanking region, the regulatory mechanisms governing the expression of each are quite different. Under normal conditions, CYP1A2 is expressed at basal levels in the liver, while no basal expression of CYP1A1 is observed in this

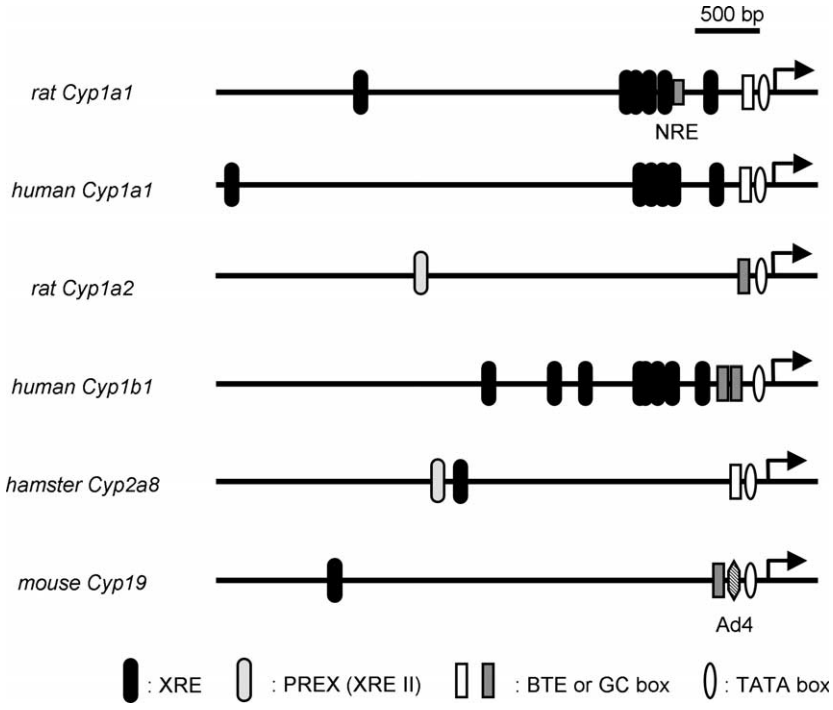

Fig. 2. Schematic representation of regulatory elements in the promoter of *CYP*s.

organ. Expression of CYP1A1 could be upregulated in multiple tissues in response to inducers, while that of CYP1A2 is restricted to the liver. In AhR-deficient mice, CYP1A1 expression is completely abolished; in these animals, although basal expression of CYP1A2 was retained in the liver, inducible expression was lost [33]. These findings clearly indicate that the expression of CYP1A1 and 1A2 is differently regulated, despite a common 5′ upstream sequence. Recently, a DNA element responsive to 3MC (XRE2: CATGN$_6$ CTTG), which is similar to a consensus DNA-binding sequence [CNRG-N$_{5\sim6}$-CNR(G/C)] recognized by the LBP-1 family, was discovered in the proximal promoter of the *CYP1A2* gene [34]. A putative factor (X) binding to this sequence was suggested by GMSA. Ligand-activated AhR/Arnt bound to the X factor as a coactivator is likely conferring inducibility of the *CYP1A2* gene in response to the inducer [34]. Coactivator-like functions of AhR/Arnt have already been reported [35,36]. An analogous sequence, designated PREX, was also identified within the promoter of the *CYP2A8* gene. This sequence acted as an inducible enhancer that cooperated with the XRE sequence in the *CYP2A8* promoter. The factor binding to PREX was identified as NF2d9 (LBP-1a) [37]. Less is known of the regulatory mechanisms governing the inducible expression of CYP1A2. In addition to the XRE sequence, a BTE (basic transcription element) sequence, which is a GC box sequence localized in the proximal promoter of *CYP1A1*, is also important to achieve a high level of CYP1A1 [38] and 2A8 [30] inducible expression. The XRE and GC box sequences frequently coexist in the promoters of xenobiotic-inducible genes, suggesting that these elements cooperatively enhance the inducible expression of these genes (Figs. 2 and 3). Another putative NF-1 binding site has also been reported within the proximal promoter of the *CYP1A1* gene [9], but no experimental evidence has addressed its functional significance. Two regulatory DNA elements are found in the promoter of *CYP19* gene, XRE and Ad4/SF-1, whose cognate binding factors, AhR and Ad4BP/SF-1, interact on the chromosomal DNA to enhance gene expression synergistically [31].

Trans-acting factor for XRE

Mouse genetics initially implicated the existence of a mediator of the xenobiotic signaling, leading to the induction of CYP1A1 expression. This mediator was later identified as a factor binding to xenobiotics, which was designated the aryl hydrocarbon receptor or AhR [39]. This factor was also dubbed the dioxin receptor (DR), due to the high avidity with which it bound TCDD. Approximately a decade later, GMSA revealed that a factor that bound the XRE sequence in a TCDD-dependent manner contained a factor which also bound TCDD directly. This XRE-binding factor behaved like AhR; both the cytoplasmic localization under normal conditions and the induction of nuclear translocation by TCDD treatment mimicked the patterns seen for AhR [40]. cDNA cloning of this XRE-binding factor revealed its molecular structure to be a DNA-binding tran-

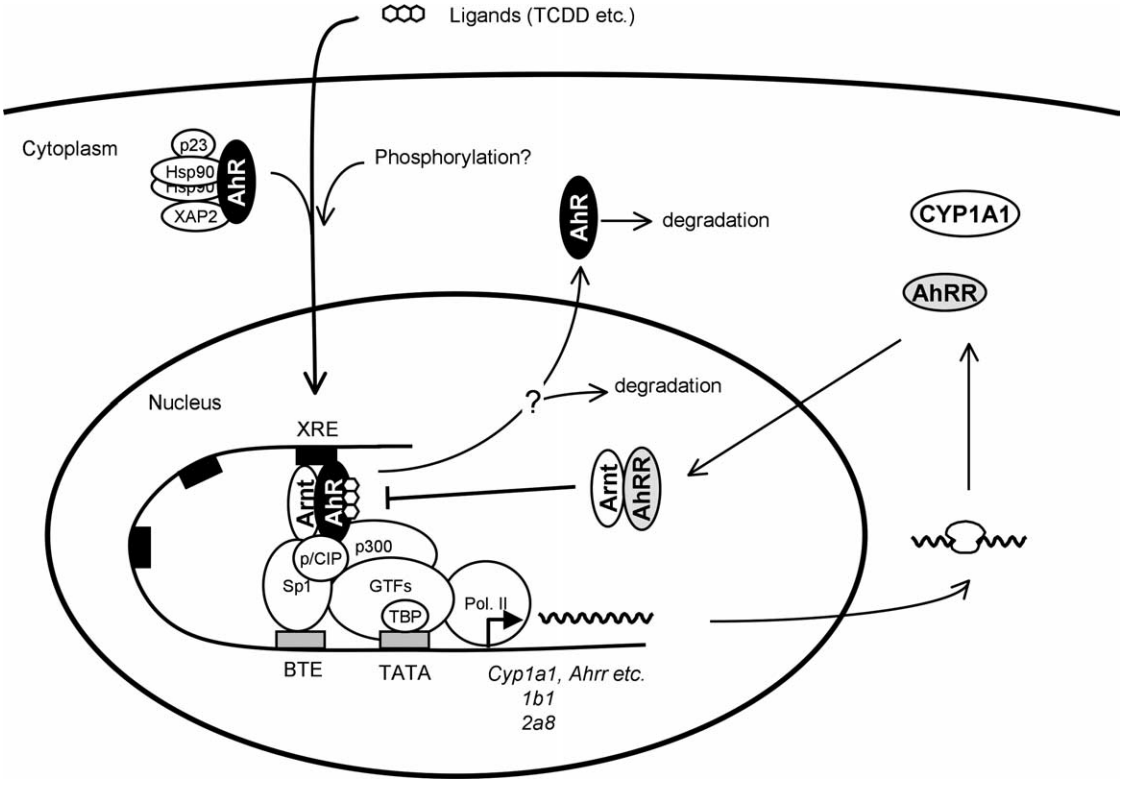

Fig. 3. A model of AhR signaling pathway.

scription factor with a bHLH motif similar to that seen for cMyc and MyoD [41,42]. Expression experiments demonstrated that AhR exogenously expressed from cDNA could be activated by TCDD or 3MC to form a heterodimer with Arnt, resulting in activation of XRE binding and transactivating activities. DNA footprint analysis and GMSA revealed that binding of Sp1 to the BTE facilitated the binding of the AhR/Arnt heterodimer to the XRE by physical interaction and vice versa, cooperatively enhancing expression of the *CYP1A1* gene [38]. The AhR/Arnt heterodimer bound to the XRE sequence and, in turn recruited CBP or P300, a HAT coactivator, to the C-terminal activation domain of Arnt [43]. Transient DNA transfection assays using a XRE-driven reporter gene demonstrated that the coactivators SRC-1 and RIP-140, the retinoblastoma protein Rb, PML, and Nedd8 interact with AhR to enhance reporter gene expression [9]. ChIP assay confirmed and extended the involvement of these coactivators in the inducible expression of *Cyp1A1*. These studies determined that the related HAT coactivators, SRC-1, NCoA-2, and p/CIP, all associate with the *Cyp1A1* enhancer region in Hepa-1 cells in a TCDD-dependent manner [44,45]. Injection of anti-SRC-1 or anti-p/CIP Abs into Hepa-1 cells abolished the TCDD-mediated induction of the reporter gene, clearly demonstrating that these factors function in AhR-mediated xenobiotic signal transduction as coactivators [45]. Overexpression of these cofactors revealed that SRC-1 and NCoA-2, but not p/CIP, interact with Arnt, while AhR interact with all three coactivators. In contrast to the interaction with CBP, the helix 2 domain of Arnt interacts with SRC-1 [9,45].

Typically, genomic DNA is closely packed into the unique units of chromosomal structure, called nucleosomes. These structures consist of 146 bp of DNA wound around a core of histone proteins, containing two molecules each of H2A, H2B, H3, and H4. Neighboring nucleosomes are associated through a short stretch of DNA covered by a H1 histone linker. Assembly of this fundamental chromosomal structure prevents the transcriptional machinery from gaining access to the genes involved. Experiments using micrococcal nuclease revealed that, in the absence of inducers, the 5′ upstream regulatory and coding regions of *CYP1A1* exist in a silent nucleosomal configuration. A nucleosome at the proximal promoter exists in a fixed position approximately −60 to −120 bp from the *CYP1A1* transcription start site, while the other nucleosomes are positioned randomly throughout the gene. TCDD treatment disrupts nucleosomes in the promoter and the transcribed portions of the gene, relieving nucleosomal repression [46].

In association with the chromosomal remodeling that occurs during drug induction, transient DNA transfection and ChIP analysis indicated the involvement of BRG1, a component of a subset of SWI/SNF ATP-dependent chromatin-remodeling complexes, in the enhancement of *Cyp1A1* gene expression by TCDD. Exogenous expression of BRG1 potentiated AhR/Arnt-mediated reporter gene expression in a TCDD-dependent fashion in Hepa-1 cells. Upon co-transfection with SRC-1, BRG1 restored the inducible expression of the endogenous *Cyp1A1* gene in the BRG-1- and hBrm-deficient SW13 and C33 cell lines in response to the inducer. An ATPase-deficient mutant of BRG-1, however, was unable to do so. ChIP analysis demonstrated that BRG-1 associates with the enhancer region of the *Cyp1A1* gene in vivo in a TCDD- and Arnt-dependent manner, suggesting the specific recruitment of BRG-1 by the AhR/Arnt heterodimer. These results indicate the importance of ATP-dependent chromatin remodeling in the inducible gene expression mediated by the AhR/Arnt heterodimer [47].

The recruitment of the Mediator/TRAP/DRIP/ARC multisubunit complex to the *Cyp1A1* promoter is also important for the transduction of xenobiotic signals that activate target gene expression, as revealed by ChIP analysis, DNA transfection, and RNAi experiments. ChIP kinetic analysis of recruitment of Med220 and CDK8 (subunits of Mediator/TRAP/DRIP/ARC) demonstrated that these factors associate with the enhancer XRE sequence rapidly and persistently after TCDD treatment. These kinetics followed shortly after those seen for binding of AhR and p/CIP coactivators to the XRE sequence. In contrast, *Pol*II bound to the promoter, but not to the enhancer. Depletion of Med220 from HepG2 cells by RNAi substantially reduced Med220 protein levels and inhibited endogenous AhR-mediated transcription from the *Cyp1A1* gene. Treatment of Hepa-1 cells with TCDD induced the binding of AhR and p/CIP to the enhancer sequence within 10 min. The binding of p300 and Med220 to the enhancer and the binding of *Pol*II to the promoter were detected after 15 min. After binding reached maximal value at 15–30 min, the degree of binding of each protein remained constant until 2 h after treatment [6,48]. Although a relatively large number of coactivators and mediators have been identified to be involved in AhR-dependent induction of CYP1A1 (Fig. 3), it seems likely that additional coactivators are also involved. As CYP1A1 is strongly induced by PAHs and HAHs, such as TCDD, and a considerable amount of information has been accumulated in regard to the transcription and chromatin remodeling factors involved, *CYP1A1* induction continues to be a good model in which to elucidate the precise mechanisms of gene regulation, including the temporal and spatial recruitment of mediators, the interactions between transcription factors, and the modification of nucleosomal structures (Fig. 3).

Degradation of the AhR

To understand the mechanisms of gene regulation, it is important to investigate both the upregulation and termination phases of inducible transcription. Recent reports have suggested that AhR is rapidly downregulated following ligand binding by degradation [49]. Experiments using the proteasome inhibitor MG132 suggested that the downregulation of AhR is mediated by the proteasome. The concentrations of AhR proteins in the nuclear frac-

tions of cultured cells are highest after 1–2 h of TCDD treatment, and then, rapidly decline with increasing time. In the presence of MG132 or lactacystin, a 26S proteasome inhibitor, TCDD treatment elicited even higher levels of AhR and Arnt proteins within nuclei at as late as 8 h. The high levels of nuclear AhR and Arnt detected in cells treated with proteasome inhibitors included increased amount of the AhR and Arnt heterodimer that is capable of binding the XRE sequence. Cells treated with a combination of TCDD and MG132 induced reporter gene expression more rapidly at a greater magnitude than cells treated with TCDD alone. The luciferase activity increased linearly throughout the 8 h time course in cells treated with TCDD and MG132, peaking at approximately a 1300-fold induction. In cells treated with TCDD alone, inducible reporter expression peaked at 5 h, with only a 100-fold induction that gradually decreased thereafter [49,50].

A number of reports investigated the subcellular location of AhR degradation. LMB is a specific inhibitor of CRM-1-mediated nuclear export. Following LMB treatment, AhR remained predominantly in the nuclei. Treatment with this inhibitor abrogated the degradation of ligand-activated AhR in the culture cells, HepG2 or Hepa-1. GMSA demonstrated that AhR in the nuclei of LMB- and TCDD-treated cells were capable of binding to the XRE sequence. These results suggest that AhR must be exported from the nucleus to be degraded [50]. A recent study using a constitutively nuclear AhR (termed DR-NLS), which contains two NLS, revealed that AhR (DR-NLS) was degraded within nuclear compartments in a 26S proteasome-dependent manner. Although the degradation of the modified AhR (DR-NLS) may differ from that of native AhR, these results suggest that AhR can be degraded within the nucleus [51,52]. Future experiment will need to address whether the AhR and Arnt heterodimer bound to the XRE sequence is degraded by proteasome while bound to the DNA or after release from the XRE sequence. The AhR repressor AhRR, whose expression is enhanced by AhR, forms a heterodimer with Arnt to replace the AhR/Arnt complex in association with the XRE sequence [53]. AhRR may play a role in releasing the AhR/Arnt heterodimer from the XRE sequence, facilitating its degradation. As the degradation of AhR is important for the regulation of AhR activity, determination of the physiological location of AhR degradation remains important for future research.

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