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Review

# Cross-talk of dioxin and estrogen receptor signals through the ubiquitin system☆

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ABSTRACT

The arylhydrocarbon receptor (AhR) is a ligand-dependent transcription factor mediating the adverse effects of dioxins. Although cross-talk of dioxins with estrogen and androgen signaling pathways are well described, the underlying molecular mechanisms have been largely elusive. Recent studies showed that modulation of estrogen/androgen signaling by dioxins is exerted in part through direct association of AhR with estrogen (ER) or androgen (AR) receptors. Agonist-bound AhR and ERα work as a functional unit to regulate expression of target genes. In addition to such genomic actions, AhR mediates non-genomic actions of AhR-ligands through the assembly of a CUL4B-based ubiquitin ligase complex and promotes the degradation of ERα and AR. These findings reveal the roles of the ubiquitin system in sensing and biological response to environmental chemicals, in which AhR acts as a ubiquitin ligase component to enhance the destruction of specific substrates.



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## 1. Introduction

Environmental pollutants are becoming a threat to the health of diverse species including humans. The adverse effects of these chemicals are exerted in part through modulation of specific signal transduction pathways. Target molecules of environmental chemicals include receptors for physiological chemicals, or hormones, and sensors for extracellular stresses, as well as non-specific biosubstances such as DNA and proteins. Dioxins, such as tetrachloro-dibenzo-*p*-dioxin (TCDD), are prototypical environmental contaminants that exert a variety of toxic effects [1]. Most of the toxicological effects of dioxins are mediated through the arylhydrocarbon receptor (AhR), or the dioxin receptor. Environmental polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene also serve as ligands for AhR. The AhR is a ligand-dependent transcription factor belonging to the basic helix-loop-helix/Per-Arnt-Sim (bHLH/PAS) family [2–5]. AhR is activated by the binding of ligands, including dioxins and PAHs, after which AhR induces gene expression of drug-metabolizing enzymes such as *CYP1A1* and *CYP1B1*. Therefore, a prototypical view is that AhR is a sensor for endogenous or exogenous toxic chemicals and promotes metabolic clearance.

However, the actions of the direct target genes of AhR alone do not fully explain its toxicological and physiological effects. Accumulating evidence suggests that the AhR exhibits its regulatory functions by modulating the functions of other transcription factors [5–7], including estrogen (ERα and ERβ) [8–12] and androgen (AR) [11,12] receptors. AhR recently has been shown to promote proteasomal degradation of ERs and AR by assembling a ubiquitin ligase complex, $CUL4B^{AhR}$ [11,12]. The role of AhR as a ubiquitin ligase mediates a non-classical pathway for environmental chemicals. In this review, we will summarize molecular mecha-

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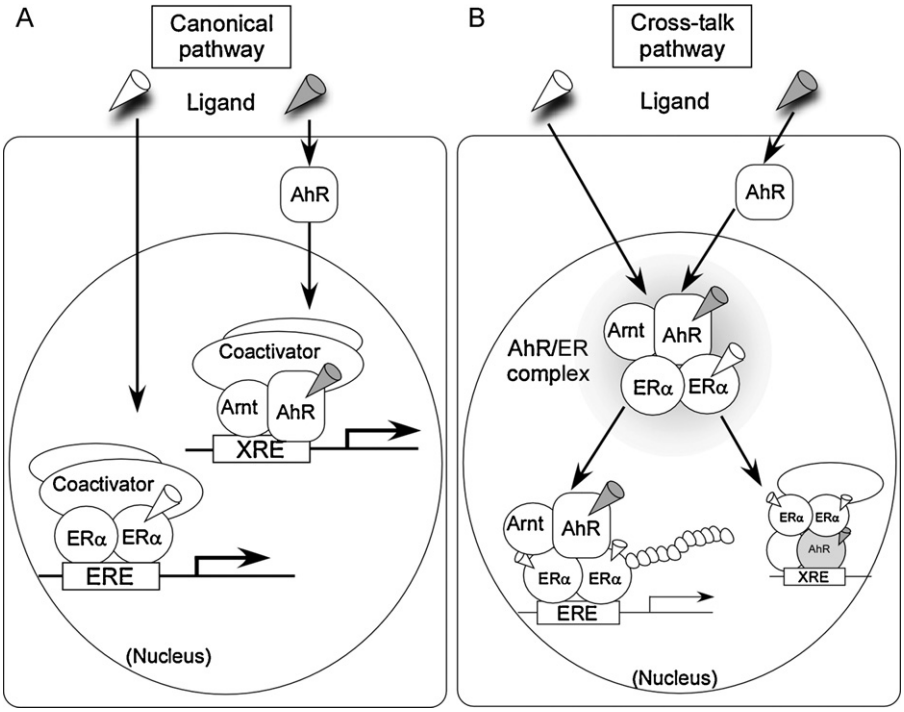


**Fig. 1.** Cross-talk of dioxins with estrogen and androgen signals. (A) Ligand-dependent regulation of gene expression through AhR or ERα. AhR and ERα act as ligand-dependent transcription factors by recruiting transcriptional co-regulator complexes. (B) Cross-talk of AhR and ERα signaling pathways through direct association of AhR with ERα. AhR-ligands induce association of AhR with ERα, and they act as a functional unit to regulate transcription.

nisms of cross-talk between AhR and ER through the ubiquitin system.

## 2. Cross-talk of dioxins with estrogen and androgen signals

AhR and ER/AR are transcription factors belonging to different classes. AhR is a mediator of the toxicological effects of dioxins and also plays a physiological role in various tissues such as the reproductive and immune systems. The transcriptional activity of AhR is regulated by direct binding of its ligands [13,14] (Fig. 1A). The unliganded AhR is sequestered in the cytosol by interacting with the Hsp90/XAP2 chaperon complex [2–5]. The binding of a ligand to AhR induces conformational changes and subsequent translocation of the AhR complex to the nucleus. AhR then dimerizes with the AhR nuclear translocator (Arnt) and activates transcription through the xenobiotic responsive element (XRE) [2–4] (Fig. 1A). On the other hand, ERs and AR belong to the nuclear receptor (NR) superfamily of transcription factors [15–17] (Fig. 1A). Dioxins exert both estrogen- and androgen-related effects [1,6]. AhR appears to modulate estrogen/androgen signaling both positively and negatively depending on the cellular context. Anti-estrogenic effects of dioxins, such as the inhibition of estrogen-induced uterine enlargement, MCF-7 cell growth, and target-gene induction are well described [18,19]. Dioxins have also been shown to have estrogenic effects including the stimulation of uterine enlargement [20], and the induction of estrogen-responsive genes [21]. In addition, AhR-deficient mice exhibit impaired ovarian follicle maturation [22]. Similarly, dioxins are reported to exert both androgenic and anti-androgenic effects on prostate development in an age-specific manner [23]. Despite the fact that some endocrine-disrupting chemicals target ER or AR as agonists or antagonists, dioxins do not serve as their direct ligand. Therefore, the underlying mechanism for dioxins' estrogen/androgen-disrupting actions has been elusive.

During the past two decades, the molecular mechanism of transcription has been extensively elucidated in light of histone modification and chromatin rearrangement. Activated transcription factors recruit a number of transcriptional co-regulators to the target gene promoters [16,17]. The amino-terminal tails of histones are subjected to various covalent modifications such as acetylation, methylation, phosphorylation, and ubiquitylation by specific histone-modifying enzymes. These post-translational histone modifications fine-tune the transcriptional state through chromatin structure rearrangement [24]. Chromatin remodeling complexes rearrange nucleosomal arrays in a non-covalent manner and support the accessibility of co-regulator complexes and transcription factors to specific promoter regions. In addition, ubiquitin ligases and proteasomal subunits also serve as co-regulators, presumably through regulating cyclic recruitment of transcription factors and/or co-regulators [25]. Thus, transcription factors primarily serve as specific adaptors that connect co-regulator complexes to specific promoter regions in a signal- or context-dependent manner. Moreover, cross-talk of signal transduction through the association of different classes of transcription factors has been described [17]. Given the ability of co-regulator complexes to modify chromatin, differential recruitment of co-regulator complexes may underlie cross-talk of transcription factors.

From these notions, we speculated that cross-talk of AhR with ER mediates functional interactions that regulate transcription. Therefore, we investigated molecular mechanism of AhR-ER cross-talk, and found that ligand-activated AhR/Arnt associates with ERα and ERβ through the N-terminal A/B region within ERs [8–11] (Fig. 1B). By means of this association, liganded AhR potentiates the transactivation function of 17β-estradiol ($E_2$)-unbound ERα, while it represses $E_2$-bound ERα-mediated transcription upon the estrogen-responsive element (ERE) [8]. Importantly, AhR-ligand-induced AhR-ERα cross-talk was retained in the presence of a partial ERα-antagonist, tamoxifen, but was abolished by a full antagonist, ICI 182,780, which induces degradation of ERα. This confirmed that AhR-ligand-induced AhR-ERα cross-talk required ERα protein, but not the active conformation of ERα for co-activator recruitment [8]. Ligand-activated AhR forms a complex with ER and a co-activator p300/CBP. Moreover, AhR/ERα cross-talk in

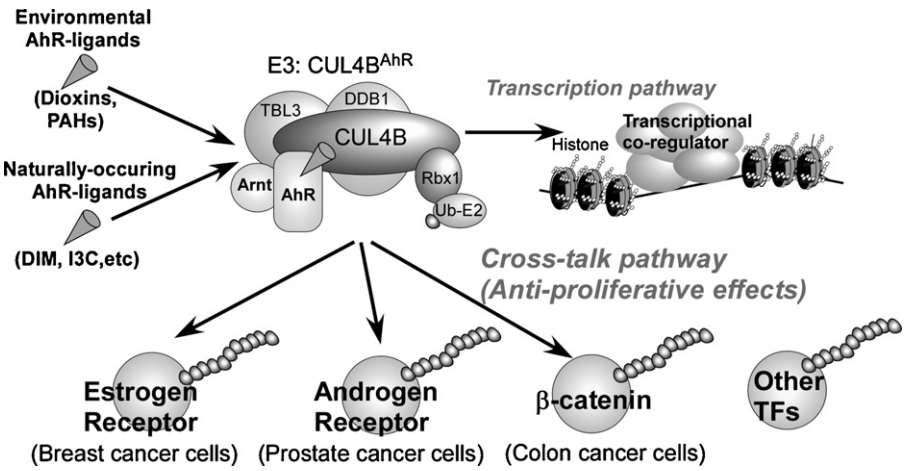


**Fig. 2.** AhR promotes ubiquitylation and degradation of ERα/AR and β-catenin. Various AhR-ligands, including environmental toxins and naturally occurring compounds, induce assembly of AhR ubiquitin ligase complex with CUL4B-type components. $CUL4B^{AhR}$ promotes ubiquitylation and proteasomal degradation of ERα, AR, and β-catenin to repress cell proliferation.

the transcriptional regulation of ERα-responsive genes is abolished in AhR-deficient mice [4,22], confirming the specificity of the molecular pathway *in vivo* [8]. Reciprocally, $E_2$-bound ERα associates with XRE-bound AhR to either potentiate [9] or repress [10] AhR-mediated transcription. Considered together, the AhR/ERα complex may be able to bind to either XRE or ERE through the attachment functions of AhR or ERα, respectively. Alternatively, different complex subtypes that contain AhR/ERα may control promoter selectivity (Fig. 1B). Recent genome-wide analysis showed that the AhR/ER complex appears to regulate both XRE and ERE-driven transcription in a manner dependent on the AhR-ligand [26], confirming our model of AhR-ligand-induced AhR/ER complex formation.

## 3. Ubiquitin ligase activity of AhR for promotion of ERα degradation

A targeted protein degradation system enables down-regulation of specific proteins in response to cellular contexts, including defense against extracellular stresses. The ubiquitin–proteasome system regulates cellular protein degradation and plays a pivotal role in cellular homeostasis [27–29]. Ubiquitylation of proteins is catalyzed by sequential reactions involving ubiquitin activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin protein ligases (E3). Among E1, E2, and E3 enzymes, the E3 ubiquitin ligases are the most diverse and therefore possess substrate specificity. E3 acts as a bridge between E2 and the substrate. E2 then conjugates ubiquitin to the substrate either directly (RING or U-box type E3) or via conjugation to E3 (HECT-type E3) [27,28].

There are multiprotein complex-type E3s, in which substrate-specific adapter components are integrated into core catalytic E3 complexes. Therefore, any protein binding to E3 core components can potentially act in a manner similar to substrate-recognition subunits. An example is Hsp70, which acts as an atypical substrate-specific adapter within the CHIP E3 complex in response to heat shock stress [30]. Hsp70 interacts with misfolded proteins and promotes their degradation. It later undergoes autocatalytic degradation through CHIP [30]. More interestingly, several substrate-specific components can be functionally regulated by extracellular signals and stresses. Although post-translational modifications of substrates, such as phosphorylation, typically serve as signals for recruiting E3s, accumulating evidence suggest that some E3s also sense the extracellular signals to promote ubiquitylation of specific substrates.

When we explored the cross-talk of AhR with ER/AR, we unexpectedly found that activation of AhR induced down-regulation of protein levels of endogenous ERα, ERβ, and AR [12] (Fig. 2). Agonist-enhanced degradation of sex steroid receptors is attenuated in the presence of the proteasome inhibitor MG132, and AhR-ligands enhanced poly-ubiquitylation of ERα. In addition, AhR immunoprecipitated complexes exert a self-ubiquitylation activity in an E1/E2 enzyme-dependent manner *in vitro*. AhR-ligand-dependent recognition of ER and AR by AhR [8] appears to induce ubiquitylation of ER/AR. Moreover, degradation of AhR itself is accelerated upon activated degradation of sex steroid receptors, which is a typical sign of self-ubiquitylation of the E3 component [31]. Taken together, these properties of AhR resemble that of classical adapter components of the E3 ubiquitin ligase complex such as F-box proteins in the SCF complex [28,31,32], DDB2/CSA in the CUL4A complex [33], and VHL in the CUL2 complex [34]. Therefore, we reasoned that activated AhR may serve as an E3 ubiquitin ligase component. The AhR-associating ubiquitin ligase complex includes cullin 4B (CUL4B) [28,35], damaged-DNA binding protein 1 (DDB1) [33,36], and Rbx1 [28] together with subunits of the 19S regulatory particle of the 26S proteasome (Fig. 2). Knock-down of CUL4B or DDB1 by siRNA impaired AhR-ligand-dependent degradation and functional repression of ERα, indicating that CUL4B/DDB1/Rbx1 core E3 components mediate E3 activity of AhR. The core complex appears to constitute a CRL-type E3 ligase, and therefore is referred to as $CUL4B^{AhR}$. We showed that AhR has E3 ubiquitin ligase activity towards ERα both *in vitro* and *in vivo*. Within the complex, AhR serves as a substrate-specific adapter component to recognize ERα as a substrate of the CUL4B E3 complex. The anti-estrogenic effects of AhR-ligands on estrogen-dependent uterine cell proliferation [8] appear to be mediated by the E3 ubiquitin ligase activity of AhR. Taken together, these results indicate that liganded AhR assembles a CUL4B-based ubiquitin ligase complex to target ER and AR for proteasomal degradation and thereby repress their activities. Thus, it appears that AhR acts both as a transcription factor and as a ubiquitin ligase component to mediate different signaling pathways.

## 4. Activation mechanism of the AhR-ER cross-talk pathway

While studying the cross-talk of AhR-ER, we found that the interaction of AhR/ER was induced by different AhR-ligands, such as TCDD, 3-methylcholanthrene (3MC), and β-naphthoflavone (βNF). To gain stronger evidence that activation of AhR led directly to AhR-ER cross-talk, we characterized AhR-ER cross-talk by using a constitutively active AhR mutant (CA-AhR) [13]. CA-AhR lacks

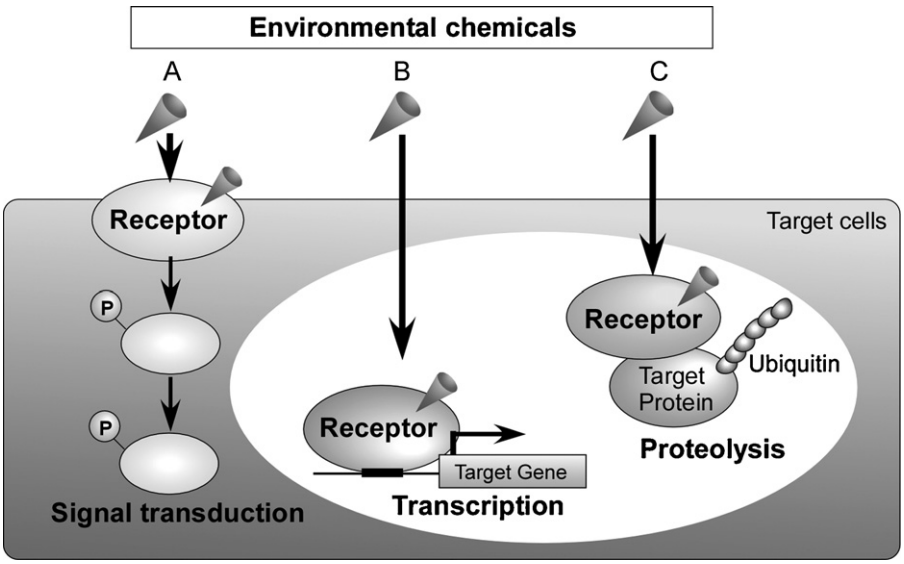


**Fig. 3.** Ubiquitin ligase-based sensing of environmental stresses. The adverse effects of environmental chemicals are exerted in part through modulation of specific signal transduction pathways. This figure shows three representative signaling pathways responsible for actions of environmental chemicals. Based on the finding that AhR serves as a component of E3 ubiquitin ligase, E3 ubiquitin ligase-based sensing of environmental stresses might be widespread.

the ligand-binding PAS-B region and exhibits constitutive activity without ligand stimulation. We found that CA-AhR modulates ERα function in the absence of AhR-ligand [12]. This suggested that activation of AhR is sufficient for interaction with ERα, and that the cross-talk of AhR with ERα is initiated primarily through stimulation of AhR. Similarly, transcriptional activity of AR is also regulated by CA-AhR in the presence of ligand. More importantly, mutants of ERα or AR which lack ligand-binding domains are also activated by CA-AhR. This result strongly suggests that cross-talk of AhR with ERα/AR does not mediate ligand-binding to ERα or to AR. After release from α-amanitin-mediated transcriptional inhibition, CA-AhR and ERα are recruited to target gene promoters with similar time courses. In addition, proteasomal degradation of ERα was induced by expression of CA-AhR, suggesting that ubiquitin system-mediated cross-talk of AhR-ER is also directly regulated by activation of AhR [12].

## 5. Liganded AhR promotes ubiquitylation and degradation of β-catenin

Based on the finding that AhR assembles a ubiquitin ligase complex, it was suggested that the E3 ubiquitin ligase activity of AhR and the transcriptional activity of AhR were responsible for a distinct set of biological events. Therefore, identification of other $CUL4B^{AhR}$ substrate proteins might reveal new molecular links between AhR-mediated signaling and other signaling pathways. As one such substrate for AhR E3 ligase, β-catenin was recently found to be ubiquitylated by activated AhR [37] (Fig. 2). β-catenin is a transcription factor downstream from the Wnt signaling pathway and has many profound functions in various tissues. β-catenin is generally degraded through the APC/Axin system in the absence of Wnt signaling. Kawajiri et al. found that activated AhR causes proteasomal degradation of β-catenin in colon tumor cell lines [37]. Activated AhR associates with β-catenin and promotes its ubiquitylation, and represses the transcriptional activity of β-catenin [37]. Reflecting these observations, AhR-deficient mice frequently develop colon tumors with abnormal accumulation of β-catenin protein. These findings suggest that β-catenin is another degradation substrate for $CUL4B^{AhR}$ ubiquitin ligase (Fig. 2).

It was noted that ER, AR, and β-catenin promote cellular proliferation in their target tissues. Therefore, one biological role of the ubiquitin ligase function of AhR could be to decrease proliferative activity through the degradation of those transcription factors (Fig. 2). This raises the possibility that AhR ligands that selectively affect ubiquitin ligase function (and which do not induce its transcriptional activity) might be useful for cancer therapy. Supporting this idea, administration of AhR-ligands efficiently suppressed colon cancer in $APC^{Min/+}$ mice, an established mouse model of familial adenomatous polyposis [37]. Thus, the selectivity of AhR-ligands towards ubiquitin ligase activity vs. transcriptional activity might be important for potential therapeutic approach. We found that, in addition to typical AhR ligands (TCDD, βNF, and 3MC), the transcriptional partial antagonist 3,3′-diindolylmethane (DIM) also induced ubiquitin ligase activity of $CUL4B^{AhR}$ [11]. This result was supported by the report that DIM administration suppressed colon cancer in mice [37]. A naturally occurring AhR-ligand, indole-3-carbinol (I3C), was recently shown to activate AhR-mediated ubiquitylation and degradation of ERα [38]. I3C activates AhR to enhance AhR-mediated ubiquitylation and proteasomal degradation of ERα. GATA3 was identified as a down-stream target of ERα. Although the receptor for plant hormone auxin is an adapter component of the E3 ubiquitin ligase [39,40], such hormone-dependent E3 ubiquitin ligase has not been identified in animals. In this regard, identification of endogenous AhR-ligands which regulate E3 ubiquitin ligase activity of AhR might be an interesting field to explore.

## 6. Ubiquitin ligase-based sensing of environmental stresses

Based on the finding that AhR serves as a component of E3 ubiquitin ligase, E3 components that respond to environmental stresses may be more diverse than initially believed. It is suggested that activation of atypical E3 complexes may be a strategy by which environmental stress sensors could respond to those stresses (Fig. 3). Nrf2 is a transcription factor regulating phase II of drug metabolism [41]. Activation of Nrf2 is reported to be regulated by a signal-dependent E3 ubiquitin ligase component, Keap1. Similar to $CUL4B^{AhR}$, Keap1 assembles a CUL3-based ubiquitin ligase complex to promote degradation of Nrf2 in the absence of a stressor [41]. Upon addition of a stressor such as oxidative stress-causing chemicals, Keap1 is modified by these chemicals at specific cysteine residues. This releases Nrf2 from the CUL3 complex which subsequently translocates into the nucleus. Thus, the phase I regulator

AhR and the phase II regulator Keap1 both act as signal-dependent components of E3 ubiquitin ligase.

In this regard, it is noteworthy that thalidomide, another prototypical toxin that originates from human industrial activity, was recently reported to target an E3 ubiquitin ligase component. Ito et al. identified Cereblon (CRBN) as a thalidomide-interacting protein in affinity purification [42]. Surprisingly, CRBN forms a complex with CUL4A and DDB1, indicating that CRBN is an adapter component of the CUL4A/CUL4B-type E3 complex. Importantly, thalidomide was found to bind to and directly inhibit CRBN E3 activity. Although the substrate(s) of CRBN is currently unknown, it appears that CRBN regulates morphological development through E3 activity and thalidomide disrupts its normal activity to cause teratogenicity.

In conclusion, E3 ubiquitin ligase-based sensing of environmental stresses might be widespread (Fig. 3). The discovery of $CUL4B^{AhR}$ suggests that the adverse effects of AhR ligands are, at least in part, attributable to the enhanced degradation of substrate proteins such as ER/AR and β-catenin through the E3 ubiquitin ligase activity of AhR [11,12]. In fact, studies have found that various environmental chemicals act as ligands of nuclear receptors and therefore affect transcriptional regulation. Thus, systematic exploration of the ubiquitin system as a target of environmental agents might lead to greater understanding of their mechanisms of actions.

## Competing interest

The authors declare no competing financial interests.

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