Estrogen receptor and aryl hydrocarbon receptor signaling pathways

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Estrogen receptors (ERs) and the aryl hydrocarbon receptor (AhR) are ligand activated transcription factors and members of the nuclear receptor and bHLH-PAS superfamilies, respectively. AhR is involved in xenobiotic metabolism and in mediating the toxic effects of dioxin-like compounds. Crosstalk has been observed among AhR and nuclear receptors, but has been most well studied with respect to ER signaling. Activated AhR inhibits ER activity through a number of different mechanisms, whereas ERα has been reported to have a positive role in AhR signaling. Here we will discuss recent data revealing that dioxin bound AhR recruits ERα to AhR regulated genes. We will also consider the implications of ER recruitment to AhR target genes on ER and AhR signaling.

Received December 12th, 2005; Accepted April 3rd, 2006; Published July 7th, 2006 | Abbreviations: AF1: activation function 1; AhR: aryl hydrocarbon receptor; ARNT: aryl hydrocarbon receptor nuclear translocator; bHLH-PAS: basic-helix-loop-helix Per (Period)–ARNT–SIM (single minded); CYP1A1: cytochrome P4501A1; DMBA: 7,2-dimethylbenz[a]anthracene; E2: 17β-estradiol; ER: estrogen receptor; shRNA: short hairpin RNA; TCDD: 2,3,7,8-tetrachlorodibenzo-[p]-dioxin. Copyright © 2006, Matthews and Gustafsson. This is an open-access article distributed under the terms of the Creative Commons Non-Commercial Attribution License, which permits unrestricted non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.

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Introduction

Estrogen receptor α (ERα) and ERβ, and related steroid hormone receptors mediate the signals of small hydrophobic molecules by acting as ligand-dependent transcription factors. Ligand binding induces receptor homodimerization, DNA binding to estrogen response elements in the promoter regions of target genes, recruitment of coregulators and changes in transcription. Although ligand binding is an important mechanism of nuclear receptor activation, many receptors, including ERα and ERβ, are activated by growth hormones, kinases, and other hormone-bound steroid receptors and transcription factors [Kato et al., 1995; Kousteni et al., 2001]. The aryl hydrocarbon receptor (AhR) is a member of the basic-helix-loop-helix Per (Period)–ARNT (aryl hydrocarbon nuclear translocator)–SIM (single minded) (bHLH-PAS) family [Gu et al., 2000]. Upon ligand binding, the AhR translocates from the cytoplasm to the nucleus where it binds its dimerization partner ARNT. The activated AhR/ARNT heterodimer complex binds to its cognate DNA sequences, termed xenobiotic response elements (XREs), and activates the expression of AhR target genes, such as cytochrome P4501A1 (CYP1A1) and CYP1B1 [Hankinson, 1995]. AhR null animals reveal that the AhR mediates most, if not all, of the toxic effects of 2,3,7,8-tetrachlorodibenzo-[p]-dioxin (TCDD) [Lahvis and Bradfield, 1998]. Although its physiological role is unknown, the AhR has been shown to play an important role in liver development and female reproduction [Baba et al., 2005; Schmidt et al., 1996].

Inhibitory crosstalk between AhR and ER signaling

Inhibitory crosstalk between the AhR and ER signaling was suggested by early experiments examining the long-term effects of TCDD treatment in Sprague Dawley rats [Kociba et al., 1978]. Among the findings, were the observations that the incidences of both mammary and uterine tumors were decreased in female rats [Kociba et al., 1978], which were supported by other reports demonstrating that TCDD inhibits the formation of 7,2-dimethylbenz[a]anthracene (DMBA) induced mammary tumors [Holcomb and Safe, 1994]. Several studies have since reported that activated AhR inhibits the expression of E2 induced genes [Safe and Wormke, 2003]. The precise molecular mechanisms for this crosstalk are unclear, and may be a combination of several different mechanisms (Figure 1).

AhR agonist dependent recruitment of ERα to AhR regulated promoters

Recent data from our group reveals that in the absence of 17β-estradiol (E2) TCDD bound AhR recruits ERα to AhR regulated genes, CYP1A1 and CYP1B1 [Matthews et al., 2005]. This recruitment most likely occurs through direct protein/protein interactions between ERα and AhR [Beischlag and Perdew, 2005; Ohtake et al., 2003]. Promoter occupancy by ERα at CYP1A1 was increased by cotreatment with TCDD and E2; however, E2 treatment only enhanced TCDD-induced CYP1A1 regulated reporter gene activity and not endogenous CYP1A1 mRNA levels. The molecular mechanisms governing the increase in recruitment of ERα by cotreatment of TCDD and E2 are unclear, but may be a combination of E2-induced homodimerization resulting in recruitment of ERα homodimer rather than the monomer and that the conformational change of ERα induced by E2 better exposes the epitope interaction surfaces allowing improved antibody interaction. Our data support the novel scenario that active AhR can redirect ER from ER target genes to AhR target genes, suggesting that AhR can
AhR has been reported to inhibit ER activity through a combination of several different mechanisms: direct inhibition by the activated AhR/ARNT heterodimer through binding to inhibitory XRE (iXRE) present in ER target genes; squelching of shared coactivators, including ARNT; synthesis of an unknown inhibitory protein; increased proteasomal degradation of ER; and altered estrogen synthesis/metabolism through increase in aromatase, cytochromeP450 1A1 and 1B1 expression. Modified from Safe and Wormke, 2003.

Regulate ERα protein levels and consequently estrogenic responses [Matthews et al., 2005]. For example, TCDD treatment is known to reduce the protein levels of ERα, which are dependent on proteasome activity [Wormke et al., 2003]; the recruitment of ERα to the AhR complex, away from ER regulated genes may serve as a mechanism to regulate ERα protein levels (Figure 2). The signals that recruit ERα to the activated AhR complex are unknown, and may include the activation of other signaling pathways, such as kinases, since the ERα AF1 is needed for recruitment to and interaction with the AhR complex [Ohtake et al., 2003] (Wihlén et al., in preparation).

Is AhR a coregulator of ER-dependent transcription?

3-Methylcholanthrene, a polycyclic aromatic hydrocarbon (PAH) AhR agonist has been reported to activate AhR such that it interacts with unliganded ERα and the entire AhR/ERα complex is recruited to estrogen responsive genes, suggesting that ER signaling is modulated by co-regulatory-like functions of AhR [Ohtake et al., 2003]. However, PAHs can be metabolized to relatively potent estrogenic compounds and independent studies have reported estrogenic effects of 3MC and other AhR agonists in the absence of AhR [Pearce et al., 2004; Shipley and Waxman, 2005]. AhR agonists, such as 3MC, have recently been shown to directly activate ERα, and are suggested to represent a new class of mixed AhR/ER agonists [Abdelrahim et al., 2006]. Moreover, ARNT directly interacts with ERs and has been shown by transient transfection to coactivate ER-dependent gene expression [Brunnberg et al., 2003].

ERα is a ligand activated modulator of AhR-dependent transcription

Our studies confirm a proposed “hijacking” of ERα by activated AhR [Brosens and Parker, 2003], but we and others observe ERα to be present at AhR target genes [Abdelrahim et al., 2006; Beischlag and Perdew, 2005; Matthews et al., 2005]. As we have suggested above this recruitment could have important consequences on ER signaling, but also reveals an important role for ERα in AhR-dependent transcription. There are conflicting reports on the effect of E2 on TCDD-induced expression of AhR target genes. Some studies report an inhibition [Beischlag and Perdew, 2005; Kharat and Saatcioglu, 1996], whereas we and others observe a slight activation or no
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