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The aryl hydrocarbon receptor cross-talks with multiple signal transduction pathways

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ABSTRACT

Exposure to toxic polycyclic aromatic hydrocarbons raises a number of toxic and carcinogenic responses in experimental animals and humans mediated for the most part by the aryl hydrocarbon – or dioxin – receptor (AHR). The AHR is a ligand-activated transcription factor whose central role in the induction of drug-metabolizing enzymes has long been recognized. For quite some time now, it has become clear that the AHR also functions in pathways outside of its role in detoxification and that perturbation of these pathways by xenobiotic ligands may be an important part of the toxicity of these compounds. AHR activation by some of its ligands participates among others in pathways critical to cell cycle regulation, mitogen-activated protein kinase cascades, immediate-early gene induction, cross-talk within the RB/E2F axis and mobilization of crucial calcium stores. Ultimately, the effect of a particular AHR ligand may depend as much on the adaptive interactions that it established with pathways and proteins expressed in a specific cell or tissue as on the toxic responses that it raises.

1. Introduction

The aryl hydrocarbon (dioxin) receptor (AHR) is a cytosolic ligand-activated transcription factor that mediates many toxic and carcinogenic effects in animals and possibly in humans [1,2]. It is generally accepted that its activation in vertebrates causes the toxic and carcinogenic effects of a wide variety of environmental contaminants such as dioxin (TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin), coplanar polychlorinated biphenyls (PCBs) and polycyclic or halogenated aromatic hydrocarbons (PAHs or HAHs). As a consequence of AHR activation, many detoxification genes are transcriptionally induced, including those coding for the Phase I xenobiotic-metabolizing cytochrome P450 enzymes CYP1A1, CYP1A2, CYP1B1, and CYP2S1, and the phase II enzymes UDP-glucuronosyl transferase UGT1A6, NAD(P)H-dependent quinone oxydoreductase-1 NQO1, the aldehyde dehydrogenase ALDH3A1, and several glutathione-S-transferases. AHR is a member of the bHLH/PAS family of heterodimeric transcriptional regulators (basic-region helix-loop-helix/Period [PER]-Aryl hydrocarbon receptor nuclear translocator [ARNT]-single minded [SIM]) [3,4] involved in regulation of development [5] and in control of circadian rhythm, neurogenesis, metabolism and stress response to hypoxia. Evidence from AHR knockout mice, however, points to functions of the receptor beyond xenobiotic metabolism at several physiologic roles that may contribute to the toxic response. Ablation of the *Ahr* gene in mice leads to cardiovascular disease, hepatic fibrosis, reduced liver size, spleen T-cell deficiency, dermal fibrosis, liver retinoid accumulation and shortening of life span (reviewed

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in [6]), suggesting that it has biological functions other than xenobiotic detoxification that likely contribute to the overall toxic response resulting from its activation.

The AHR is widely expressed in practically all mouse tissues [7], and in humans expression is high in lung, thymus, kidney and liver. In the absence of ligand, the AHR exists as part of a cytosolic protein complex containing two HSP90 chaperone molecules, the HSP90-interacting protein p23 and the immunophilin-like protein XAP2 (also AIP or ARA9) [8–10]. Activation by ligand is followed by translocation of the complex into the nucleus, dissociation from the chaperone proteins and heterodimerization with ARNT. This AHR-ARNT heterodimer interacts with several histone acetyltransferases and chromatin remodeling factors [11–15], and the resulting complex binds to consensus regulatory sequences termed AhREs (aryl hydrocarbon response elements; also XREs or DREs), located in the promoters of target genes, and by mechanisms not yet well characterized, recruits RNA polymerase II to initiate transcription. The activated AHR is quickly exported to the cytosol where it is degraded by the 26S proteasome [16], hence preventing constitutive receptor activity.

Activation of the AHR by high-affinity HAH or PAH ligands results in a wide range of cell cycle perturbations, including G_0/G_1 and G_2/M arrest, diminished capacity for DNA replication, and inhibition of cell proliferation. These alternative functions of the AHR are often accomplished in the absence of an exogenous ligand, but the underlying molecular mechanisms governing these processes remain elusive in part because no definitive endogenous ligands have been identified (reviewed in [17]). At present, all available evidence indicates that the AHR can trigger signal transduction pathways involved in proliferation, differentiation or apoptosis by mechanisms dependent on xenobiotic ligands or on endogenous activities that may be ligand mediated or completely ligand independent. These functions of the AHR coexist with its well-characterized toxicological functions involving the induction of Phase I and Phase II genes for the detoxification of foreign compounds.

In this review, we will address novel experimental evidence relating to these less orthodox AHR functions, focusing on new data appearing since our previous review of this subject [17] dealing with the role of the AHR in the activation of mitogen-activated protein kinases, cell cycle regulation, apoptosis and cell differentiation, with a focus on the cross-talk between AHR signaling pathways and the effectors, regulatory events and cell cycle checkpoints responsible for normal cellular functions. Key steps in the activation of AHR signaling are schematically shown in Fig. 1.

2. Cross-talk between cellular kinases and the Ah receptor

Post-translation modifications such as phosphorylation play a major role in the regulation of gene expression and function in

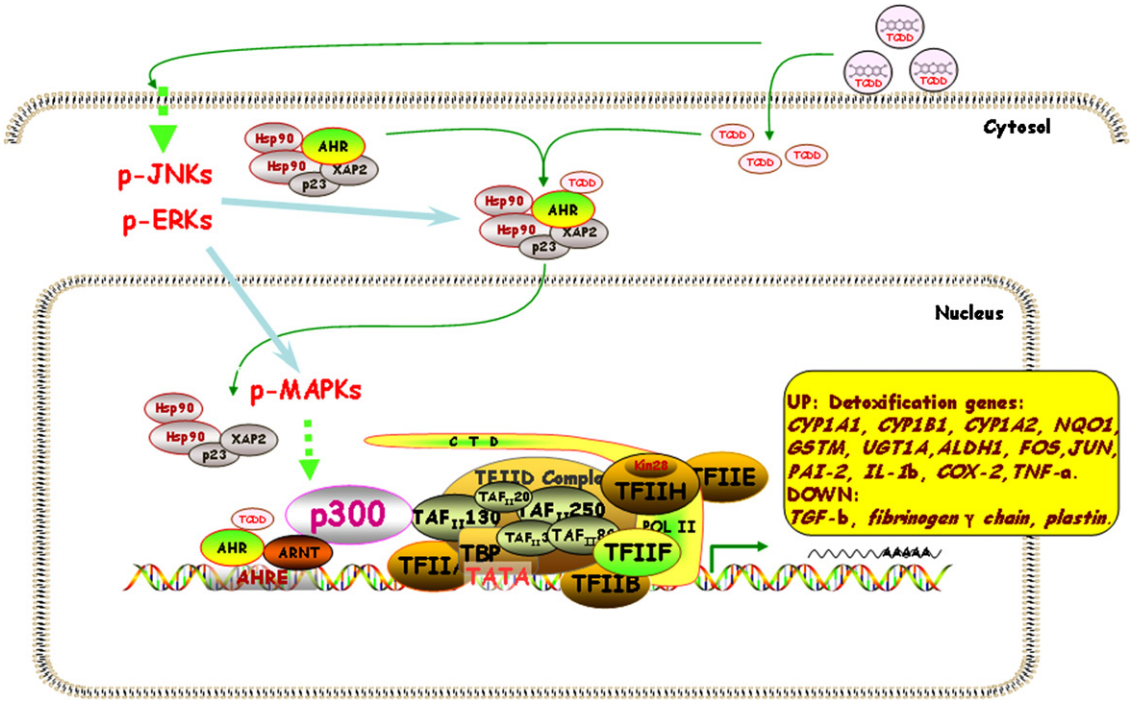

Fig. 1 – *AHR signaling*. Shown are the key events in signaling through the Ah receptor. Entry of ligand (TCDD in the figure) through the cell membrane leads to binding to the receptor followed by translocation of the cytosolic heat-shock chaperone complex to the nucleus. Various MAP kinases are involved in this step. Once in the nucleus, the AHR dissociates from the heat-shock complex, and forms a complex with ARNT that recruits p300 and binds to the cognate sites in DNA. Probably through a DNA-looping step, the complex recruits the basal transcription factors and RNA pol II needed for initiation of transcription. Not shown in the scheme is the obligatory removal of a HDAC1-DNMT1 complex bound in the proximity of the TATA box that blocks RNA pol II recruitment and effectively maintains the gene in a silent state.