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Review

Is the aryl hydrocarbon receptor another moonlighting protein?

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ABSTRACT

The aryl hydrocarbon receptor (AHR) is traditionally characterized as a transcription factor that mediates mammalian responses to xenobiotics, namely polyaromatic halogenated (PAH) compounds. The receptor has been a focal point of toxicological research for several decades due to its central role in dioxin and other PAH induced toxicity. The resulting body of work depicts a receptor that not only functions as a ligand-activated transcription factor, but also as one that can influence several different signaling pathways and cellular processes through direct protein:protein interaction. In fact, the diverse functions of the AHR suggest it could be classified as a moonlighting protein. Moonlighting proteins are characterized by their multifunctional cellular roles and include glycolytic enzymes and several cytochrome P450 monooxygenases. Here we review the various cellular functions of the AHR, including its ability to influence transcription, directly and indirectly, and its ability to influence immunity, cell cycle and mitochondrial function via protein:protein interaction. These distinct functions imply that the AHR can be identified as a moonlighting protein.

KEYWORDS: aryl hydrocarbon receptor, dioxins, non-traditional transcription, immunity, mitochondria

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INTRODUCTION

Moonlighting proteins are a diverse class of proteins that include transcription factors, enzymes, and chaperones [1]. They are defined as proteins, encoded by a single polypeptide, which is capable of performing at least two distinct functions within the cell [2]. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was one of the first moonlighting proteins characterized and the list now includes diverse members, such as argonaute 4 (AGO4) and cytochrome P450 family members CYP7B1, CYP17, and CYP170A1 [3-5]. Moonlighting proteins are an intricate part of normal cellular function, as well as, having roles in disease states [6, 7]. Here we examine the aryl hydrocarbon receptor (AHR) with emphasis on its "moonlighting" functions and how these functions make the AHR more than just a transcription factor.

The AHR is characterized as a ligand-activated transcription factor and member of the periodicity/aryl hydrocarbon receptor nuclear translocator/single-minded (PAS) superfamily of environmental sensors. The PAS superfamily members are central to an organism's response to environmental signals such as xenobiotic exposure, light/dark cycles, and hypoxia [8, 9]. Xenobiotics, such as 2,3,7,8 tetrachlorodibenzo-ρ-dioxin (TCDD) and other polyaromatic hydrocarbons (PAHs), act as ligands for the AHR and are pervasive environmental contaminants. PAHs, and other synthetic AHR ligands are primarily produced as by-products of industrial processes,

such as sealant production, paper bleaching, herbicide manufacturing, and waste incineration. Decades of research have proven that these environmental pollutants produce a wide variety of toxic responses in mammals. The United States Environmental Protection Agency (US EPA) has classified dioxin as a probable human carcinogen [10]. The World Health Organization (WHO) considers them a highly toxic family of compounds that elicit adverse effects on immunity, reproduction, development, and hormone signaling [10, 11]. This myriad of pathologies associated with exposure to various PAH compounds are attributed to the single genetic locus that encodes the AHR [12-15]. AHR research has demonstrated that the receptor is involved in diverse cellular processes and is a member of a complex signaling network. Here we examine the AHR's traditional transcriptional role, as well as, the receptor's "moonlighting" functions in non-traditional gene expression, hormone signaling, immune response, and metabolic processes.

The aryl-hydrocarbon receptor: The established perspective

AHR biology

The AHR's ability to transcriptionally regulate the expression of genes that encode xenobiotic metabolizing enzymes led to it being one of the earliest characterized PAS proteins [16]. The receptor was first detected in the 1970's, using radiolabeled TCDD [12]. Subsequent observations detected a difference in TCDD-induced toxicity among inbred laboratory mouse strains [17]. Genetic backcrossing and photoaffinity labeling resulted in the characterization of three different high affinity binding *ahr*^{b} alleles of various molecular weights [18, 19]. The different *ahr*^{b} alleles are: *ahr*$^{b\text{-}1}$, which is found in C57BL/6J mice and codes a 95 kDa AHR, the *ahr*$^{b\text{-}2}$ allele was found in C3H/He and BALB/c laboratory mice strains and codes a 104 kDa receptor, and the *ahr*$^{b\text{-}3}$ allele has been identified in non-laboratory mice such as *Mus caroli, spretus* and *Mus musculus molossinus* and codes a 105 kDa receptor [17, 20]. Only a single low affinity *ahr*^{d} allele has been characterized from various "nonresponsive" mouse strains, and it produces a 104 kDa receptor [17, 21, 22].

The AHR consists of several functional domains. At the N-terminus is a classical bHLH domain that is responsible for DNA binding, dimerization, and contains the nuclear localization signal (NLS) (Figure 1). The central part of the protein contains a PAS domain with A and B box repeats [16]. The PAS domain is thought to act as a secondary interaction surface, dictating the specificity of interaction between heterodimeric partners (Figure 1). In addition, the C terminus of the PAS domain, encompassing the B box repeat, and adjacent protein region contains the ligand binding domain (LBD) and an interaction surfaces for at least two of the receptor's cytosolic partners. Finally, a transactivation domain (TAD), in the C terminus of the protein, is responsible for the recruitment of transcriptional machinery [23] (Figure 1). The bHLH and PAS domains of the receptor are highly conserved across species; however, larger sequence variations are observed in the TAD domains.

Sequence alignment comparisons between the mouse *ahr*$^{b\text{-}1}$ protein sequence and nine other

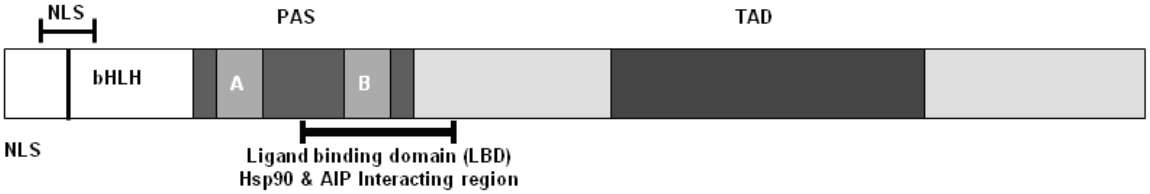

Figure 1. AHR topology. In the N terminus, the nuclear localization signal (NLS) is located at the 5' end of the basic helix-loop-helix (bHLH) domain. Dimerization with its transcription factor partner, the aryl hydrocarbon receptor nuclear translocating (ARNT) protein and DNA binding occur in the bHLH domain. The region also contains the classic A and B boxes found in PAS family members. The C terminus contains the transactivation domain (TAD). This region is highly variable across species.

species demonstrate the variation between these domains. When comparing the bHLH domain, similarity of 85% or greater is found in six out the nine species. The three species that have less than 85% similarity are the chicken (79.8%), monkey (65.8%), and zebrafish (58.8%). A comparison of the PAS domain reveals a greater than 80% similarity between eight out of the nine species; the zebrafish having the lowest similarity (72.4%). Conversely, seven of the nine species have less than 70% similarity to the mouse TAD. The similarity between the rat and the mouse is the greatest at 86.8% and the zebrafish again having the lowest at 20.9%. The variation in the TAD can dictate several aspects of AHR biology such as cellular localization, and gene regulation [24-27] (Figure 2).

In the absence of ligand, the AHR is part of a cytosolic complex. The primary members of this complex are the receptor, a dimer of the 90 kDa chaperone heat shock protein (Hsp90), and the aryl-hydrocarbon receptor interacting protein (AIP) [28-30] (Figure 3). The AIP is also known as the aryl-hydrocarbon receptor interacting protein 9 (ARA9) and X-associated protein 2 (XAP2) [31, 32]. The Hsp90 dimer and AIP are considered the core scaffolding proteins of the cytosolic complex. They function to ensure the

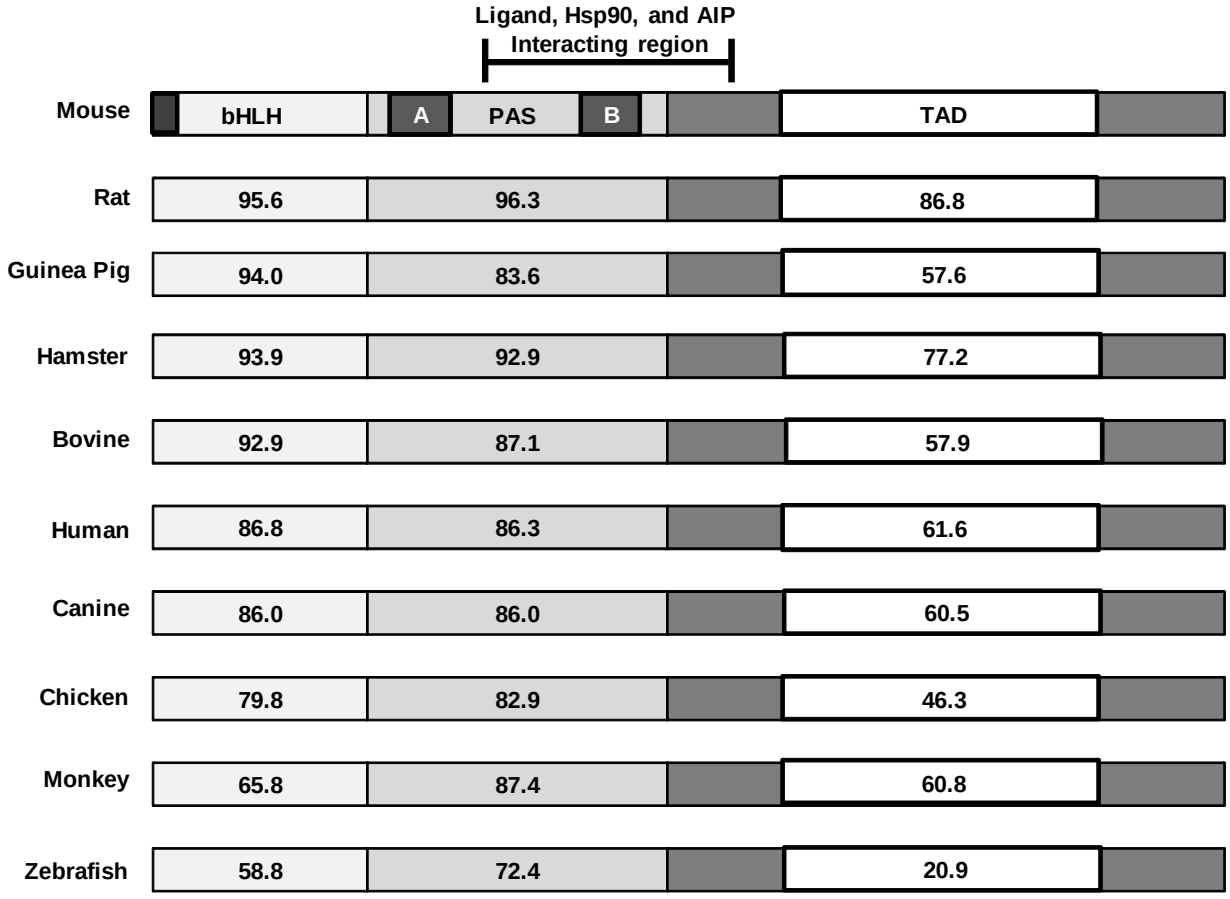

Figure 2. AHR sequence homology comparison. The AHR protein sequence of the basic helix-loop-helix (bHLH), PAS, and transactivation (TAD) domains of ten mammalian species were examined for homology using Lasergene (DNASTAR, Madison, WI). The bHLH and PAS domains are highly conserved across most of these species. The TAD region, however, contains large variation across these species which contributes to the species specific effects of dioxin exposures. Species used for this comparison are: mouse (gi7304873), rat (gi145207984), guinea pig (gi290563759), hamster (gi346227234), bovine (329664848), human (gi4502003), canine (355667647), chicken (gi45383874), monkey (gi355560780), zebrafish (gi67459929).

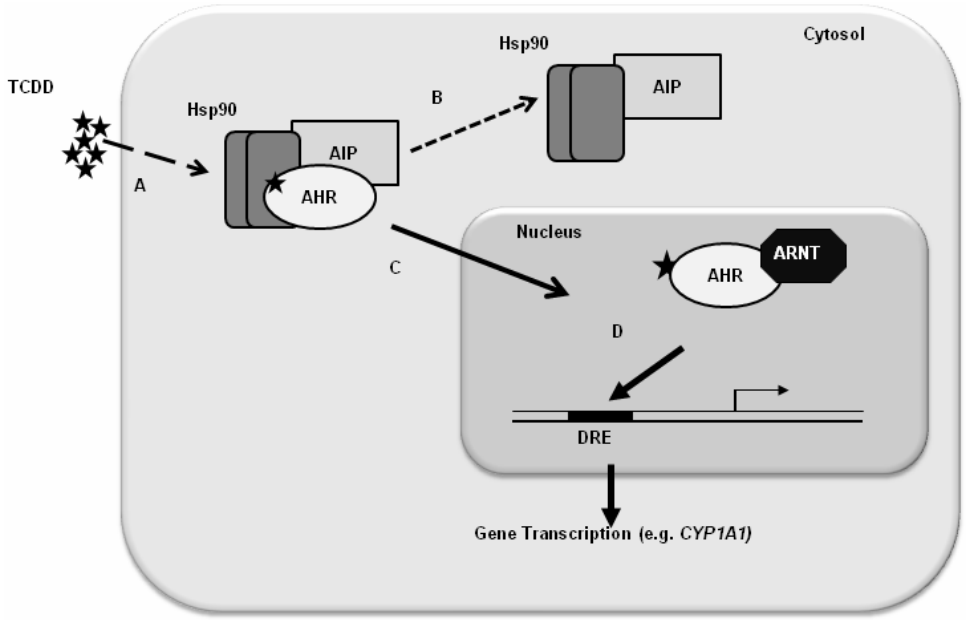

Figure 3. AHR biology. AHR signaling pathway. TCDD is a lipophilic molecule which crosses the plasma membrane and binds the AHR (**A**). Upon ligand binding, the AHR undergoes a conformational change and disassociates from its cytosolic partners (**B**). The ligand bound receptor translocates to the nucleus and heterodimerizes with ARNT (**C**). The AHR/ARNT dimer is an active transcription factor that recognizes dioxin response elements (DREs) within the genome and regulates gene transcription. CYP1A1 is the canonical gene regulated by AHR/ARNT (**D**).

receptor's proper protein folding, maintaining it in a high affinity ligand binding conformational state [31, 33-35]. The co-chaperone protein, p23, has also been shown to be a transient member of this cytosolic complex; however, recent reports have demonstrated it is not required for ligand binding or activation of the receptor [36, 37].

AHR-mediated gene regulation is a dynamic, multi-step process; the first of which is ligand binding. The ligand-bound receptor translocates to the nucleus and forms a heterodimer with the aryl-hydrocarbon nuclear translocator (ARNT) protein [24, 38, 39]. The specificity of the AHR and ARNT dimerization is dictated by the HLH and PAS domains. There is continued debate over the role AHR's cytosolic partners have in the receptor's nuclear translocation and DNA binding abilities. Upon induction of the AHR, a co-localized pool of Hsp90 has been identified in the nucleus, indicating the AHR translocates in a complex with at least one of its cytosolic partners [33, 40]. In contrast, Ikuta *et al.*, demonstrated the AHR's ability for nuclear translocation in the absence of Hsp90 using a receptor with the PAS domain deleted [41]. Hsp90 has been shown to inhibit AHR's ability to heterodimerize with ARNT, thus inhibiting DNA binding and gene regulation events [33, 42]. Given Hsp90 and ARNT interactions with the AHR occur in overlapping regions of the receptor, these findings are not unexpected. A recent study using a conditional knockout mouse model, demonstrated that the AIP was required for TCDD-induced toxicity and the regulation of a subset of the AHR regulated genes [43]. This research indicates that the AHR's cytosolic partners play varied roles in the receptor's transcriptional function.

Upon AHR:ARNT interaction, the complex becomes an active transcription factor [44]. The dimer localizes to genomic DNA at specific sequences known as dioxin response elements (DREs) which contain a core sequence, 5'-GCGTG-3' [45, 46]. A number of nuclear transcription cofactors, including BRG-1, ERAP140, RIP140, CBP, p300, and SRC-1, are recruited to the site of AHR:ARNT:DRE interaction to regulate transcription [39]. The duration of AHR transcriptional activity

is tightly regulated via ubiquitination and subsequent degradation [47, 48]. In addition, the AHR transcriptionally up-regulates its own repressor, the AHR repressor (AHRR). AHRR lacks a TAD and is capable of inhibiting AHR activity in a classic negative feedback loop, primarily via ARNT competition [49]. A 2008 review by Hahn *et al.* provides a comprehensive overview of the multiple mechanisms by which AHRR regulates AHR function [49].

To define the AHR's function, researchers used various AHR knockout and mutant mouse models. AHR null mice exhibit reduced liver size, hepatic fibrosis, and increased splenic weight, but a decreased B cell population thus establishing AHR's developmental role [50-52]. Moreover, these AHR null mice demonstrate resistance to TCDD-induced toxicity. Specifically, characteristic thymic atrophy and aberrant hepatic pathology were not observed in AHR-/- mice upon TCDD exposure [51, 53]. Bunger *et al.* reported on transgenic mice expressing an AHR with a deleted NLS or with the receptor's DNA binding ability ablated [14, 15]. Both of these models presented with similar phenotypes to those described above for the traditional AHR null mouse. Furthermore, TCDD exposure to pregnant dams expressing the mutant receptors did not result in progeny with cleft palate, another hallmark toxic response [14, 15]. These findings demonstrate the central role AHR-mediated gene regulation has in development and toxicity.

Identifying the genes responsible for the TCDD-induced toxicity has been challenging. A transgenic knockout mouse of three AHR regulated cytochrome P450 genes, *Cyp1a1*, *Cyp1a2*, and *Cyp1b1*, was created to investigate what role these prototypical target genes play in dioxin toxicity [54]. *Cyp1a1/1a2/1b1*($^{-/-}$) triple knockout mice exposed to benzo[a]pyrene (BaP) demonstrated increased liver weight and decreased thymus weight, indicating AHR-mediated toxicity in a *Cyp*-independent manner [54]. Moreover, no BaP-induced change was observed in spleen weight or lymphocytes; however an increase in neutrophils was observed in the triple knockouts, indicating these highly inducible AHR regulated genes are not central to AHR-mediated toxicity. This body of research establishes AHR's functions and central role in the complex web of PAH-induced toxicity.

AHR ligands

AHR$^{-/-}$ mice have neural, reproductive, liver, and vascular development abnormalities in the absence of exogenous stimuli, suggesting the receptor does have endogenous functions [15, 55]. The AHR is classified as an orphan receptor, lacking a confirmed endogenous ligand. The identification and characterization of an endogenous AHR ligand(s) is an ongoing area of research [56, 57]. AHR endobiotics primarily fall into three classes; indole derivatives, heme metabolites, and eicosanoids [58]. Indole derivatives, such as 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), indirubin-3-monoxime, and indoxyl-3-sulfate (I3S) are capable of activating the AHR in various tissues and species [59-61]. Recently, Mezrich *et al.* demonstrated AHR activation by kynurenine (Kyn), a tryptophan derivative and proposed endogenous ligand for the receptor, resulted in T_{reg} production [62] (Figure 4A). Two other putative AHR endogenous ligands, the heme metabolites, bilirubin and lipoxinA4, are reported to mediate immune responses in mice [63]. Finally, an arachidonic acid metabolite, 12(R)-hydroxy-5(Z),8(Z),10(E), 14(Z)-eicosatetraenoic acid (12(R)-HETE), does not bind the AHR, but activates the receptor indirectly [64]. It is hypothesized that an unidentified metabolite of 12(R)-HETE is an AHR ligand. The diversity of this group reveals the complex nature of the endogenous AHR ligands and rivals that of the receptor's exogenous ligands.

Exogenous ligands are classified into several sub-groups including benzo-pyrenes and halogenated aromatic hydrocarbons (HAH) [65, 66]. HAH compounds include polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzo-*p*-furans (PCDFs), polybrominated biphenyls (PBBs), and polychlorinated biphenyls (PCBs) [65, 67] (Figure 4B). PCDDs are a family of 75 different congeners and are commonly referred to as 'dioxins' [68]. TCDD is one of the most potent compounds in the dioxin family and the canonical dioxin used in research [69]. The complexity of the AHR exogenous ligands was extensively detailed in a 2002 review by Denison *et al.* [70].

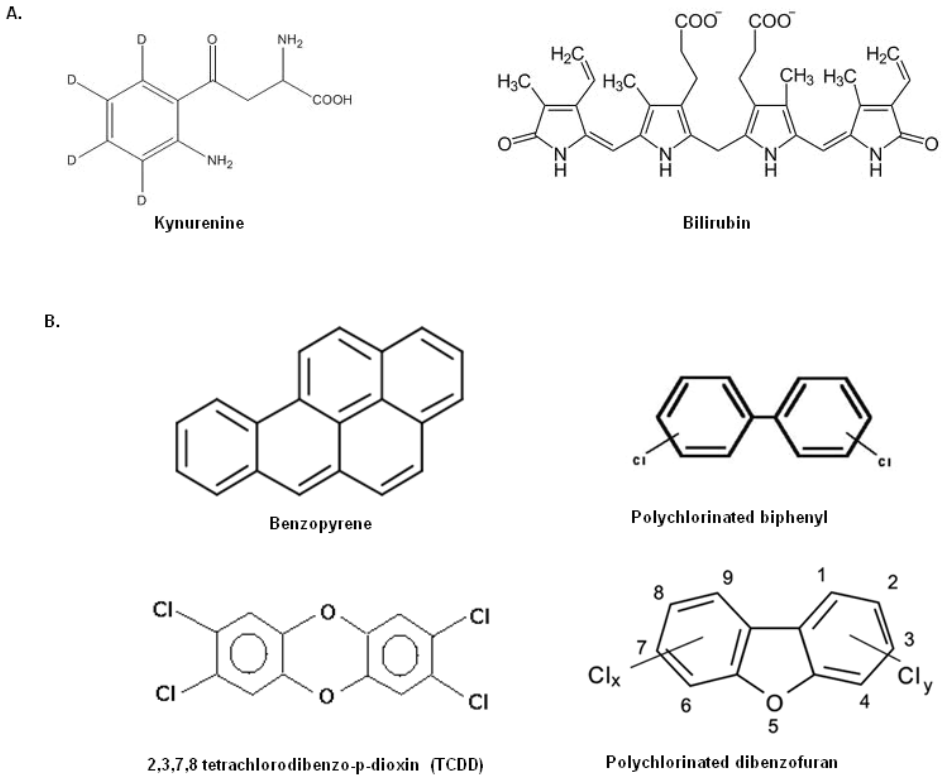

Figure 4. AHR ligands. A) Two examples of endogenous AHR ligands are kynurenine, a tryptophan catabolite, and bilirubin, a heme catabolite. **B)** Four examples of exogenous AHR ligands illustrate the diversity of this group. Benzopyrene is simply an aromatic hydrocarbon, polychlorinated biphenyl is halogenated, polychlorinated dibenzofuran, and 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) are both halogenated and contain oxygen. These exogenous ligands are more stable and less transient than their endogenous counterparts.

AHR-mediated toxicity

PAH exposures result in dynamic tissue, gender, and species-specific toxic responses. TCDD-induced tissue-specific toxicity includes immune system suppression, thymic involution, metabolic dysfunction and wasting syndrome, chloracne, hyperplasia, hypertrophy, and endocrine disruption [65, 71-77]. Increased risk of heart disease, diabetes, reproductive and birth defects, as well as tumor promotion, and cell cycle deregulation have also been linked to dioxin exposure [65, 78-80]. A gender-specific bone phenotype has been observed in mice expressing a constitutively activated AHR (CA-AHR) [81]. CA-AHR female mice presented with ductile bones and bone loss due to inhibited osteoclast differentiation and function, and increased bone resorption. Gender differences are also observed in cases of infertility and incidences of diabetes [80, 82].

Species-specific sensitivity to AHR ligands varies widely among mammals. There is a 5000-fold difference in acute exposure (LD_{50}) to TCDD across tested species, the guinea pig being the most sensitive (LD_{50} = 1 μg/kg) and the hamster being the most resistant species (LD_{50} = 5000 μg/kg) [65]. The variances observed in dioxin exposures between and among species are presented in a review by Pohjanvirta and Tuomisto [83]. Assessing the parameters of harmful dioxin exposure to humans, however, has remained problematic. Deriving an accurate measurement is complex given the variables of age, gender, weight, and total fat body burden in a human population [84, 85]. To further confound matters, the mixtures of dioxin-like compounds in a given exposure, as well as the duration of exposure, are factors for consideration [84, 85]. Acute human exposures to dioxin compounds have not resulted

in any documented human LD_{50} to date [86-88]. Dioxin exposure in humans has been examined in numerous cohort studies with varying results. Long term studies have been conducted on exposure groups from Seveso, Italy, Yucheng, China, and Vietnam veterans. Increased risk of diabetes, carcinogenicity, infertility, birth defects, and cardiovascular disease was observed across these cohort studies [79, 80, 82, 89-93].

Traditional AHR transcriptional regulation

Gene regulation is the canonical function of the AHR. The receptor and the gene battery it regulates have been extensively studied [94, 95]. Recent evidence has suggested that less than 100 genes are targets for direct transcriptional regulation by the AHR [94]. Classic AHR regulated genes include the phase I and II drug metabolizing enzymes. The cytochrome P450 monooxygenases, *CYP1A1*, *1A2* and *1B* were among the first genes shown to be transcriptionally regulated by the AHR [96, 97]. CYP1A1 is considered the biomarker of AHR activation [98, 99]. Phase II enzymes regulated by the AHR include NAD(P)H: quinone oxidoreductase 1 (NQO1), glutathione-S-transferase A2 (GSTA2), carbonyl reductase 3 (CBR3), and members of the UDP-glucuronosyltransferase (UGT) family, (e.g. UGT1A1) [95, 99]. While the regulation of xenobiotic metabolizing enzymes was the original focus of AHR gene regulation studies, the gene battery influenced by receptor activation has proven to be quite complex. Currently, this group includes genes involved in development, differentiation, fatty acid transport, metabolism, cell growth and proliferation, apoptosis, and tumor promotion [95, 100].

The expanded AHR perspective

The wealth of AHR research has proven the AHR has several potential "moonlighting" functions. Today, the receptor is known to influence multiple cellular processes via mechanisms that are not governed by traditional AHR-mediated transcription events. For instance, the AHR has a role in non-traditional transcriptional regulation via crosstalk with other transcription factors, such as hormone receptors and NFkB [101-103]. Still more findings have linked the AHR to kinase signaling pathways and cell cycle regulation [104]. In this section, the AHR's "moonlighting" functions are explored.

AHR, the immune system, and non-traditional transcription function

Immune suppression is a hallmark response of dioxin-induced toxicity [105]. The AHR's role in mechanisms governing immune responses, however, has proven difficult to characterize. Today, research has elucidated several processes by which the AHR functions within the immune system; affecting cytokine levels and T- and B-cell differentiation. The receptor functions through traditional and non-traditional transcription activities, to influence epigenetics and chromatin remodeling, and B- and T- cell activation.

One example of non-traditional transcription function is the AHR's role in NFκB-mediated gene regulation. NFκB is a pleiotropic transcription factor which governs many of the biological processes impacted by dioxin exposure, including the immune system, thymic involution, and carcinogenesis [106, 107]. The mechanism by which AHR activity influences NFκB function is poorly defined. Early studies demonstrated physical interactions between activated AHR and NFκB [108, 109]. From these and other studies, two potential mechanisms for cooperative gene regulation have been proposed [107]. The first mechanism is based on direct protein:protein interaction between the AHR and the RelA subunit of NFκB. It is proposed that the AHR:RelA dimer can influence the transcription mediated by the normal functional complex (i.e. NFκB and AHR:ARNT). The second proposed mechanism is a cooperative DNA binding model between AHR/ARNT and NFκB, leading to a synergistic gene regulation effect. Sulentic *et al.* demonstrated an overlap of DREs and NFκB binding sites upstream of immunoglobulin heavy chain enhancer gene [108]. It is noteworthy, that dioxin exposure can induce NFκB DNA binding in the AHR-deficient BCL1 B-cell line, indicating an AHR-independent mechanism also exists [108]. More recently, an AHR:RelB dimer was shown to bind unique sites in the regulatory region of the IL8 gene [110]. Finally, NFκB-regulated IL6 induction was recently shown to be mediated by AHR's role in histone deacetylase (HDAC) remodeling in tumors, further suggesting

a non-transcriptional role for the receptor in immunity [111]. The AHR has been reported to influence other aspects of the immune system through interactions with other transcription factors such as the signal transducer and activator of transcription (STATs) and C-MAF [62, 112-114]. This pleiotropic effect might have a basis in the AHR's ability to modulate HDAC activity.

The AHR and hormone signaling

One of the most studied non-traditional mechanisms of the AHR which influences cellular processes is its ability to crosstalk with the estrogen receptor (ER) [115-121]. Extensive investigation of the crosstalk between the AHR and ER has revealed the receptors have a dynamic and complex influence on each other's biology. This relationship between these two receptors demonstrates the AHR's ability to influence transcriptional events that do not involve AHR:ARNT:DRE binding.

There are two predominate estrogen receptors, ERα and ERβ, which are ligand-activated members of the steroid receptor superfamily [122]. In the 1970's prolonged TCDD exposure was shown to have an inhibitory effect on the formation of mammary and uterine tumors in Sprague-Dawley rats [123]. Subsequent research demonstrated crosstalk pathway existed between the AHR and ERα. For example, activated AHR and ER can influence each other's ability to regulate target gene expression [117, 124]. The underlying mechanisms of the receptors' crosstalk pathway are varied. First, the receptors are capable of recognizing each other's ligands as agonists [125-127]. Second, the AHR and ERα can co-localize to the other's promoter regions and influence transcriptional output [103, 128, 129]. It should be noted that evidence suggests the ability of the activated ERα to influence AHR-mediated transcription is cell-type specific. Activated ERα has an inhibitory effect on CYP1A1 induction in MEF cell lines while E2 activated ERα enhanced CYP1A1 induction in human breast cancer cell lines [130, 131]. Another study reported no influence of activated ERα on AHR gene regulation events in MCF7 nor Hepa1c1c7 cells [132]. Third, the receptors directly compete for ARNT. ARNT can act as a coactivator for the steroid receptor and ARNT sequestration by the AHR via TCDD exposure can negatively impact ER-mediated transcription [133, 134]. Finally, AHR-mediated CYP genes encode enzymes that metabolize ERα ligands inhibiting the receptor by elimination of its signaling molecule [134-136]. Many of these mechanisms are also involved in the crosstalk between the AHR and androgen receptor (AR) [137]. These functions offer compelling evidence that the receptor's classic transcriptional role is not its only mechanism in cellular homeostasis and disease states. These data strongly suggest that the AHR can influence cellular processes through direct protein:protein interaction.

The AHR and kinase activity

Investigation of AHR biology has demonstrated the receptor's influence on numerous cellular processes, including cell cycle regulation and proliferation, cell motility, intercellular communications and tumor promotion [56, 121, 138-141]. Kinase signaling plays an important role in each of these processes and is another target for AHR crosstalk. For example, TCDD exposure leads to AHR-dependent activation of the tyrosine kinase, Src, in various murine and guinea pig cell lines [142, 143]. Subsequent research using $Src^{-/-}$ mice demonstrated a potential role for the kinase in a subset of TCDD-induced toxic endpoints including thymic involution and loss of adipose tissue [144]. The AHR can also influence the phosphorylation states of different kinases and substrates through traditional and non-traditional regulation. For example, crosstalk between AHR and MAPK pathways is controlled by AHR-mediated expression of c-raf, while growth hormone receptor (GHR) and janus kinase 2 (Jak2) expression are down-regulated when AHR:STAT5 complex binds STAT elements in their upstream gene regions [145, 146].

The AHR can also impact cell cycle progression via its ability to change the phosphorylation state of the retinoblastoma tumor suppressor protein (Rb) [147-151]. The hypophosphorylated form of pRb directly interacts with the AHR and this interaction acts as both a co-activator and co-repressor; influencing expression of cell cycle proteins [147, 148]. Other reports indicate that activation of the AHR leads to the hyper-phosphorylation of Rb and cell cycle progression.

Currier *et al*. reported increased levels of AHR, c-myc, and cyclin D1 (CDK1) in mammary tumors that correlated with hyperphosphorylated RB [152]. In human breast cancer cells, the AHR also interacts with cyclin-dependent kinase 4 (CDK4) and cyclin D1 (CCND1) in the absence of exogenous ligand, thus allowing for cell cycle progression [151]. These results illustrate the AHR can influence cell cycle regulation, kinase pathways, and oncogenesis via its traditional transcription-dependent activity and by direct protein:protein interaction.

The burgeoning AHR perspective

The AHR protein interaction network

AHR-mediated gene regulation has a pivotal role in dioxin toxicity. Traditional AHR-mediated transcriptional regulation, however, may not be the sole mechanism by which toxic responses are induced via the receptor. The ability of the AHR to directly interact with other proteins, such as RelA, Rb, and CDK4, suggest that the receptor can influence cellular processes in the absence of direct transcriptional control. This also raises the possibility that the AHR has more cellular interaction partners. Recently, this possibility was addressed using proteomics analysis of the AHR protein interaction network (AHR-PIN) in Hepa1c1c7 cells. A novel interaction between the AHR and the ATP5α1 subunit of ATP synthase was demonstrated using tandem affinity purification. The ability of the AHR to interact with ATP5α1 suggests that the receptor might be added to the list of potential proteins components of the ATP synthasome [153-156]. Investigation of the functional relevance of the interaction between ATP5α1 and the receptor yielded evidence that the AHR has a role in cellular energetics. TCDD induced an AHR-dependent hyperpolarization of the mitochondrial inner membrane which occurred independently of transcription. Interestingly, the hyperpolarization did not translate into changes in cellular ATP levels, suggesting that the efficiency of the ATP synthase complex is decreased upon TCDD exposure. The hyperpolarization and putative change in ATP synthase efficiency happened concomitantly with a dissociation of the AHR from ATP5α1. It should be noted that the AHR is not the first ligand-activated transcription factor reported to localize to the mitochondria and influence their function. Steroid receptors, such as the estrogen, androgen, thyroid, and glucocorticoid, are known to translocate to mitochondria [157].

These findings open a new area of AHR research regarding the receptor's role in cellular energetics, metabolism, and nuclear-to-mitochondrial stress signaling. In our proposed model the AHR is distributed into cytosolic and mitochondrial pools which have achieved equilibrium (Figure 5A). The demonstrated ability of Hsp90 and AIP to facilitate mitochondrial transport offers a mechanism by which the AHR might enter the organelle [158-162]. When exogenous ligands, such as TCDD, are introduced the cytosolic pool of AHR is activated and translocates to the nucleus, thus disrupting the aforementioned equilibrium. The loss of the cytosolic AHR pool causes the disruption of the AHR:ATP5α1 interaction in the mitochondria possibly by shifting the pool of mitochondrial AHR through mass action (Figure 5B). This model presents a new moonlighting role for the AHR in metabolic function adding it to the growing number of ligand-activated receptors that function in the mitochondria. Given that the AHR null mouse is viable, this interaction and subsequent regulation of energetics is not essential for life, however, it might play an important role in TCDD-induced toxicities, such as wasting syndrome and metabolic dysfunction.

SUMMARY

The AHR was identified more than 30 years ago as the protein responsible for aryl hydrocarbon hydroxylase activation following dioxin exposure. The role the AHR plays in dioxin toxicity was the starting point of investigations that have led to our current understanding of the receptor's biology. Today, the AHR is recognized as a ligand-activated transcription factor that regulates a complex battery of genes. These genes include drug metabolizing enzymes, as well as, genes involved in development and reproduction, fatty acid synthesis, and immune cell response. In addition to transcriptional regulation, the AHR is capable of influencing immunity, cell cycle,

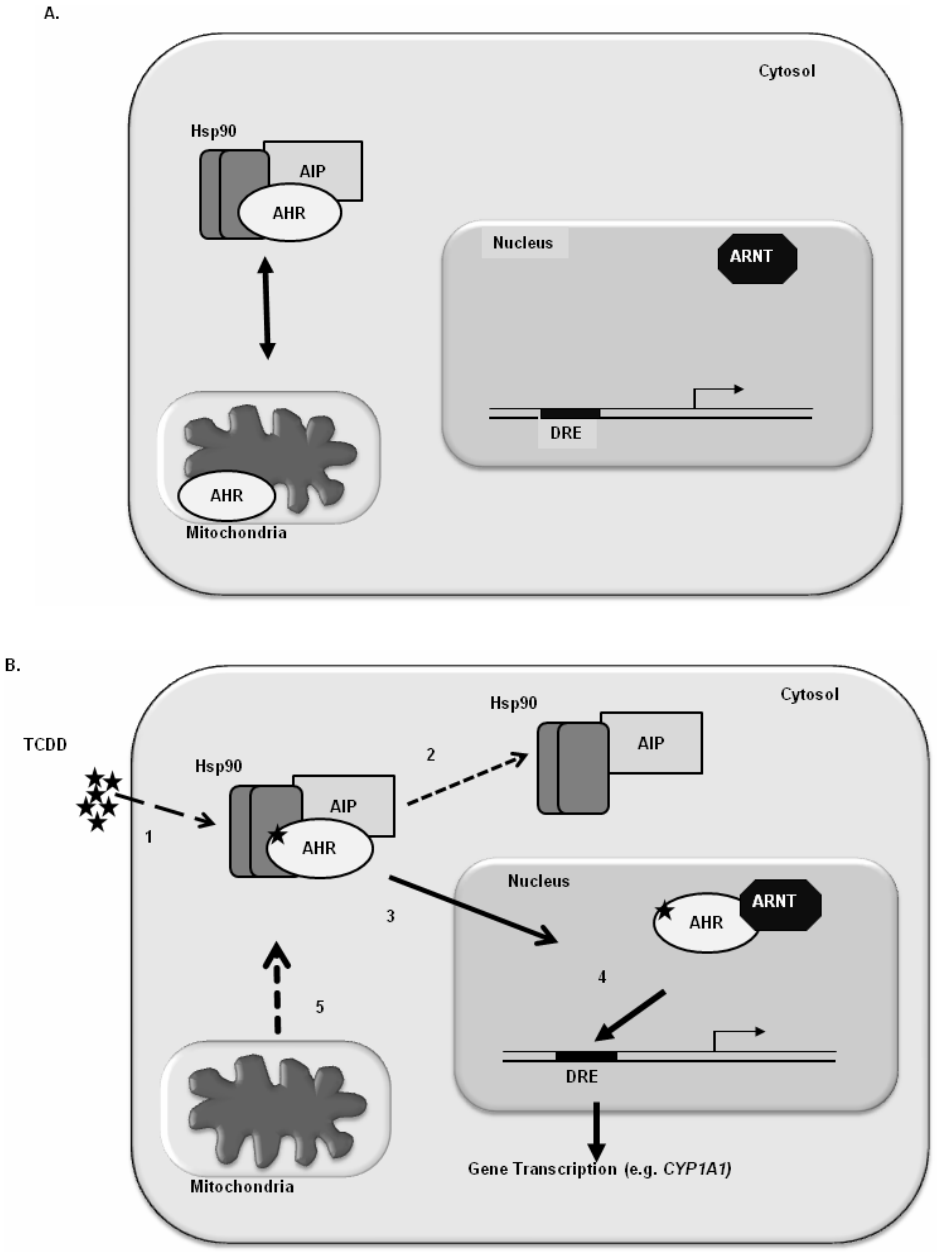

Figure 5. Model of TCDD's influence on AHR's "moonlighting" mitochondrial function. A) AHR cellular localization consists of cytosolic and mitochondrial pools in the absence of exogenous ligand exposure, with the pools being in equilibrium with each other. **B)** Upon exposure to exogenous ligands the cytosolic pool of AHR decreases as the activated protein is shuttled into the nucleus. These events disrupt the AHR cytosolic/mitochondria equilibrium. Through mass action the mitochondrial pool of AHR is depleted. This loss of AHR decreases the efficiency of mitochondrial function.

and mitochondrial function via protein:protein interaction with proteins such as RelA, Rb, CDK4, and ATP5α1 (Figure 6). Though gene regulation has proven to be a central component of the receptor's function and essential for dioxin-induced toxicity, the potential role of protein interaction in modulating AHR-mediated toxicity remains of great interest to researchers. In short, the complexities of the receptor's cellular functions are still not fully elucidated. The characterization

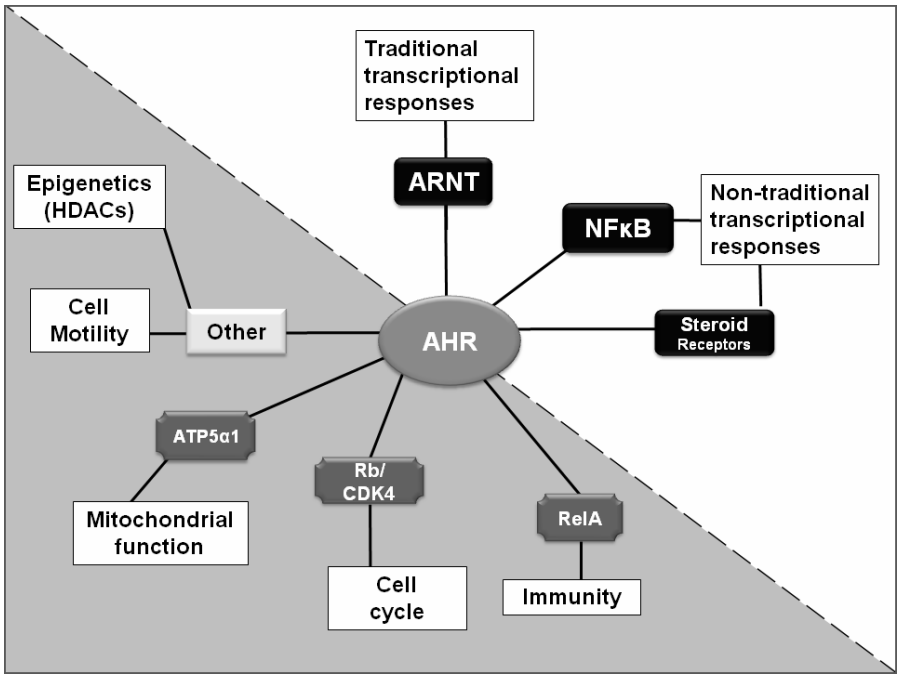

Figure 6. Model of the AHR's cellular roles. The cellular roles of the AHR occur through two modes of action; transcriptional and non-transcriptional protein interactions. The AHR/ARNT dimer serves as a transcription factor in classical gene regulation. The receptor functions in non-traditional transcriptional events when it partners with NFκB and steroid receptors. The AHR also participates in non-traditional protein:protein interactions with RelA, Rb/CDK4, and ATP5α1 to modulate immunity, cell cycle regulation, and mitochondrial function. The receptor is also involved in other cellular functions such as epigenetics and cell motility through, as yet, uncharacterized mechanisms.

of the receptor's ability to directly influence cell cycle, immunity, and mitochondrial parameters has added another layer of information to the growing body of AHR research. It is these unique characteristics of the AHR that make it more than a traditional transcription factor and establish the receptor as new member to the growing family of moonlighting proteins.

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