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AHR toxicity and signaling: Role of TIPARP and ADP-ribosylation

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Abstract

The aryl hydrocarbon receptor is best known for its ability to mediate the toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). However, AHR plays important roles in the immune system, cell growth and numerous other cell functions. Similar to other transcription factors, tight control of AHR activity is necessary to prevent its over-activation. The AHR target gene, TCDD-inducible poly-ADP-ribose polymerase (TIPARP) was recently reported to be part of a new negative feedback loop that regulates AHR activity by ADP-ribosylation. In support of these findings, *Tiparp* deficient mice exhibit an enhanced sensitivity to the toxic effects of TCDD. This review will discuss what is currently known about the role of TIPARP and ADP-ribosylation in AHR signaling and TCDD toxicity.

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Aryl hydrocarbon receptor, 2,3,7,8-Tretrachlorodibenzo-p-dioxin, ADP-ribosylation, TCDD-inducible poly-ADP-ribose polymerase.

Abbreviations

AHR, aryl hydrocarbon receptor; AHRE, AHR response element; ARH, ADP-ribosyl hydrolases; ARNT, AHR nuclear translocator; ARTD, ADP-ribosyltransferase diphtheria toxin-like; bHLH-PAS, basic helix-loop-helix Per-ARNT-Sim; CCCH, cysteine-cysteine-cysteine-histidine; CYP1A1, cytochrome P450 1A1; CYP1B1, cytochrome P450 1B1; IFN, interferon; KYN, kynurenine; LXR, liver X receptors; MACROD1, macrodomain 1; MACROD2, macrodomain 2; NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; PARP, poly-ADP-polymerase; PARG, poly-ADP-ribose glycohydrolase; PCK1, phosphoenolpyruvate carboxykinase 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 α; SIRT1, sirtuin 1; SNPs, single nucleotide polymorphisms; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TIPARP, TCDD-inducible poly-ADP-ribose polymerase; WWE, tryptophan-tryptophan-glutamate.

1. Introduction

The aryl hydrocarbon receptor (AHR) has historically been studied for its ability to mediate the toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD; dioxin) and to regulate the expression of the cytochrome P450 genes, CYP1A1 and CYP1B1. TCDD causes numerous toxic effects in laboratory animals, including a wasting syndrome characterized by altered energy metabolism, body weight loss and death; however, the mechanisms remain unclear [1]. AHR also regulates many biological pathways in the absence of exogenous ligands, including development, cell cycle and the immune response [2,3]. Many of these biological effects are due to the transient activation of AHR by endogenous and/or dietary ligands [4]. However, an important aspect of AHR signaling that is not well understood, and relevant for both its toxic and biological functions, is how AHR activity is controlled. This review focuses on recent findings regarding the role of the AHR target gene, TCDD-inducible poly-ADP-ribose polymerase (TIPARP) and ADP-ribosylation in regulating AHR signaling and TCDD-dependent toxicity.

2. The aryl hydrocarbon receptor mechanism of action

The AHR is a member of the basic helix-loop-helix Per-ARNT-Sim (bHLH-PAS) family, a class of transcription factors that respond to extracellular signals and environmental stresses to alter cell function [5]. The AHR is best known for its ability to bind and mediate the toxic effects of halogenated and polycyclic aromatic hydrocarbons, but it also binds numerous non-toxic dietary, endogenous and gut microbiome derived ligands [6]. The molecular mechanisms of AHR action are diverse and many outcomes are context dependent (reviewed in [7]). The canonical AHR pathway begins with ligand binding to the cytosolic chaperone-bound form of AHR, followed by its nuclear translocation and heterodimerization with the AHR nuclear translocator (ARNT). The AHR:ARNT heterodimer binds to AHR response elements (AHREs) located in proximal regulatory regions, distal enhancers and intronic sequences in an a battery of AHR target genes that are involved in numerous cellular pathways [8,9]. Well-established AHR target genes include CYP1A1, CYP1B1, and AHR repressor (AHRR) and TIPARP (also called PARP7/ARTD14) [10–12]. As with all transcription factors, tight regulation of AHR activity is necessary to prevent its over-activation. However, comparatively little is known about how AHR signaling is controlled. In many cases, AHR activity is attenuated by the induction of CYP1A1/CYP1B1 enzymes that metabolize and inactivate several AHR ligands. Ligand activated AHR is also

proteolytic degraded by the 26s proteasome; however, the level and extent of this degradation varies among cell lines and ligands [13]. In addition, AHR is regulated through a negative feedback loop, where increased AHRR levels inhibit AHR activity through competition with ARNT and/or by tethering to the AHR-ARNT complex [12,14]. Recent studies, indicate that AHRR is a context and tissue-specific negative regulator of AHR, suggesting that there are other mechanisms controlling AHR activity [15,16].

3. AHR mediates TCDD toxicity and wasting syndrome

TCDD causes numerous toxicities in laboratory animals, including teratogenesis, hepatic steatosis, thymic atrophy, immune dysfunction and a lethal wasting syndrome [17]. The dose-dependent sensitivity to TCDD-induced toxicities varies widely among laboratory species and strains [1]. A single dose of TCDD to mice induces a lethal starvation-like syndrome, which includes decreased gluconeogenesis, hepatotoxicity, hepatosteatosis, body weight loss and lethality [1,17]. Reduced serum glucose levels do not correlate with lethality in all species, and total parental feeding prevents body weight loss but not lethality [17]. *Ahr* null and *Ahr DBDmut* mice, which express an AHRE binding deficient mutant of AHR, are resistant to TCDD toxicity [18,19]. Transgenic AHR overexpressing mice develop hepatosteatosis, while *Ahr* null mice and high fat diet fed mice treated with an AHR antagonist as well as *Cyp1b1* deficient mice are protected against obesity and hepatosteatosis [20–22]. This suggests that TCDD toxicity requires the canonical AHR signaling pathway and that AHR has a prominent role in lipid homeostasis. Despite the absolute requirement for AHR, the mechanisms and downstream target genes responsible for these toxic outcomes remain unclear. Male *Cyp1a1* deficient mice are protected against wasting syndrome and some, but not all, TCDD-induced toxicity [23]. However, elimination of AHR-dependent regulation of *Cyp1a1* through deletion of its upstream AHRE region causes a slight increase in sensitivity to TCDD toxicity [24]. *Ahrr* null mice exhibit tissue-specific increases in Cyp1a1 levels and reduced sensitivity to benzo[*a*]pyrene-induced DNA adduct formation in skin [15]. Unfortunately, the sensitivity of *Ahrr* null mice to acute TCDD toxicity has not been reported; however, transgenic overexpression of Ahrr in mice protects then against high dose TCDD-induced lethality [25].

4. TCDD-inducible poly-ADP-ribose polymerase (TIPARP)

TIPARP, a relatively uncharacterized AHR target gene, was recently reported to directly regulate AHR activity and mediate cellular responses downstream of AHR [26,27]. TIPARP (PARP7/ARTD14) is a member of the poly ADP-ribose polymerase (PARP) family also called the ADP-ribosyltransferase diphtheria toxin-like (ARTD) family. PARPs catalyze the transfer of ADP-ribose from nicotinamide adenine dinucleotide (NAD^+) to specific amino acid residues on themselves and on target proteins releasing nicotinamide (NAM). There are 17 PARPs in humans with the majority of them able to catalyze the transfer of one molecule of ADP-ribose (mono-ADP-ribosylation) rather than several ADP-ribose moieties, (poly-ADP-ribosylation) to target proteins [28,29]. ADP-ribosylation profoundly alters target protein activity and plays a role in numerous cellular stress responses, including DNA repair, oxidative stress, immune responses, but also transcription, protein degradation and metabolism [30,31]. NAD^+ is vital for all organisms and a dietary NAD^+-deficiency causes pellagra in humans [32]. The increased enzymatic activity of PARP1, which generates poly-ADP-ribose modifications, during extreme DNA damage results in rapid decreases in cellular NAD^+ levels leading to increased cell death [33]. Whether activation of mono-ADP-ribosyltransferases is sufficient to reduce cellular NAD^+ levels below critical levels is unclear. ADP-ribosylation is dynamically regulated by poly-ADP-ribose glycohydrolase (PARG) and ADP-ribosyl hydrolases (ARHs). Similarly, macrodomain containing proteins, MACROD1, MACROD2, and C6orf130 recognize and hydrolyze mono-ADP-ribose from modified proteins [34,35].

TIPARP was first identified as a TCDD responsive gene in mouse hepatoma cells [11]. It is widely expressed in many tissues and cell lines [11,27]. Both the human and mouse *TIPARP* genes feature a concatemer of AHRE sequences found in well-characterized AHR target genes [36]. A non-coding TIPARP antisense RNA, which lies upstream of exon 1, is also regulated by the same AHRE sequences, but its biological importance is unknown [36]. In addition, TIPARP is regulated by other transcription factors and signaling pathways, including androgen receptor [37], hypoxia factor 1α [38] platelet derived growth factor [39] and interferons [40], suggesting that this enzyme has vast and divergent cellular roles.

Within the PARP family, TIPARP is most evolutionarily conserved with PARP12 (ARTD12) and PARP13 (ARTD13) [27,28,41]. All three proteins contain at least one RNA-type CCCH zinc finger domain, a poly-ADP-ribose binding WWE domain and a PARP catalytic domain (Fig. 1). PARP13 is catalytically inactive, but has a role in antiviral defence by specifically binding to retroviral RNA through its zinc finger domains [42]. TIPARP and PARP12 also inhibit viral replication; however, the mechanism is unknown [40,43]. In addition, TIPARP has been implicated in the maintenance of embryonic stem cell pluripotency and in mitosis, suggesting that it has an important role in development and cell differentiation [41,44]. *Tiparp* null mice are