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Commentary

From dioxin toxicity to putative physiologic functions of the human Ah receptor in homeostasis of stem/progenitor cells

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2,3,7,8-Tetrachlorodibenzo-p-dioxin = TCDD (PubChem CID 15625
6-Formylindolo[3,2-b]carbazole = FICZ (PubChem CID 1863)
StemRegenin 1 (PubChem CID 46199207)
Tranilast (PubChem CID 5282230)
VAF347 (PubChem CID 10172275)
3,3′-Diindolylmethane, DIM (PubChem CID 3071)

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ABSTRACT

Despite decades of intensive research physiologic Ah receptor (AHR) functions are not yet elucidated. Challenges include marked species differences and dependence of AHR function on the cell type and cellular context. Hints to physiologic functions may be derived (i) from feedback loops between endogenous ligands and substrates of major target enzymes such as CYP1A1 and UGT1A1, and (ii) from dioxin toxicity in human individuals. For example, dioxin-mediated chloracne is probably due to dysregulated homeostasis of sebocyte stem/progenitor cells. Dioxin-mediated inflammatory responses may be due to complex dysregulation of hematopoiesis. Comparison of AHR functions with those of PXR and its target enzyme CYP3A4 may be helpful to emphasize AHR functions in specialized cells: PXR is known to be mainly involved in regulation of systemic metabolism of endo- and xenobiotics. However, AHR may be mostly controlling local homeostasis of signals in specialized cells such as stem/progenitor cells. Accumulating evidence suggests that knowledge about physiologic AHR functions may stimulate drug development.

1. Introduction

Ah receptor (AHR) is a multifunctional transcription factor of the PAS (Per-Arnt-Sim) superfamily [1–4]. It is the only ligand-activated member of this family. However, ligand-activated transcription factors are frequent in the hormone receptor family, including PXR, a key transcription factor in the drug-metabolizing enzyme system [5–7]. A comparison between AHR and PXR may be helpful to emphasize particular AHR functions. Notably, direct and indirect regulatory mechanisms have to be distinguished [8]. The present discussion is focused on direct mechanisms.

AHR has been discovered in studies of the metabolism of aryl hydrocarbons and as mediator of dioxin toxicity [9]. Dioxin stands here for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Although dioxin toxicity remains challenging, present investigations are mainly focused on identification of physiologic AHR ligands and functions. Despite decades of intensive research physiologic AHR functions are not fully understood. Major difficulties are the marked species differences as well as cell- and cell context-dependent AHR functions.

Hints on physiologic AHR functions in humans may be obtained (i) from elucidation of feedback loops between endogenous AHR ligands and substrates of target enzymes including CYP1A1 and UGT1A1 [10], as well as (ii) from symptoms of dioxin poisoning in exposed individuals [11,12]. Accumulating evidence suggests that the AHR may be involved in control of the cell cycle [13] and in self-renewal and differentiation of stem/progenitor cells [14–16]. AHR functions are known to modulate the immune system [17–19] and microbial defence [20]. In a previous commentary dealing with the mechanism of dioxin-mediated chloracne [12], it has been emphasized that it may be useful to first identify the target cell and thereafter the transcription factors cooperating with

Abbreviations: AhR, aryl hydrocarbon receptor; PXR, pregnane-X-receptor; CYP, cytochrome P450; UGT, UDP-glucuronosyltranswferase; FICZ, 6-formylindolo[3,2-b]carbazole; ICZ, indolo[3,2-b]carbazole; ITE, 2-(1H--indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

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AHR. In the present commentary this concept is substantiated and extended to dioxin-mediated modulation of the hematopoietic system and inflammatory reactions.

2. Ah receptor ligands and feedback loops with substrates of CYP1A1 and UGT1A1

A number of endogenous AhR ligands are currently discussed including FICZ, bilirubin and eicosanoids (Table 1) [18,21–24]. FICZ is believed to be a physiologic AHR agonist [22–24]. Chemically-related phytochemicals such as indole-3-carbinol and its products 3,3′-diindolylmethane (DIM) and indolo[3,2-b]carbazole (ICZ) are generated from vegetables and fruit, which may have important functions in the development of the postnatal immune system (discussed in Section 3.3). A number of AHR agonists and antagonists are presently developed as therapeutic drugs (discussed in Section 4). Metabolism of endogenous AHR ligands leads to important feedback loops, discussed subsequently using CYP1A1 and UGT1A1 as examples (Fig. 1).

2.1. AhR-CYP1A1-FICZ axis

The tryptophan photoproduct FICZ is believed to be a physiologic AHR agonist. It is generated by both UVB radiation and reactive oxygen species (ROS) via indole-3-acetaldehyde suggesting that FICZ is likely to be formed systemically [24]. FICZ is as potent as TCDD. In contrast to TCDD, FICZ is efficiently metabolized by CYP1A1, allowing transient AHR activation. This may be necessary for AHR functions in cell cycle regulation [13]. It is conceivable that AHR links intrinsic and external control of stem/progenitor cell fate in the stem cell microenvironment or niche (discussed in Section 3).

2.2. Bilirubin homeostasis

The heme metabolite bilirubin has been characterized as low affinity AhR agonist and substrate of UGT1A1. Hyperbilirubinemia is neurotoxic in the newborn. Absence of UGT1A1 activity in Crigler–Najjar syndrome, type 1, is fatal [25]. On the other hand, bilirubin also exhibits important antioxidant properties. Hence, the bilirubin serum level has to be homeostatically controlled [10]. One example for a function of AHR in this process is the observation that UVB radiation of human UGT1 transgenic mice leads, probably via generation of the potent AHR agonist FICZ, to reduction of the serum bilirubin level ([72], legend to Fig. 1). In addition to regulation by the AHR, UGT1A1 expression is known to be controlled by CAR and PXR. Treatment of newborns with the CAR activator phenobarbital has been used to reduce hyperbilirubinemia in the newborn [10,25]. Interestingly, UGT1A1 expression is controlled by an evolutionary-conserved 290-base pair cluster of response elements for six transcription factors (AhR, Nrf2, PXR, CAR, PPARα and glucocorticoid receptor) ([26]

Table 1
Overview on ligands of AHR and PXR. References are given in [6,10,18,21] and are included for putative drugs. *AhR antagonist.

Transcription factor	Ligand		
	Endobiotic	Phytochemical	Xenobiotic
Ah-receptor (AhR)	Tryptophan metabolites: FICZ Indolyl sulfate Indirubin Kynurenin ITE Heme metabolites: Bilirubin Eicosanoids: Lipoxin A 12-HETE	Indole-3-carbinol ICZ 3,3′-Diindolyl- methane (DIM) Malassezin Tryptanthrine Quercetin	Toxins: TCDD Benzo[a]pyrene Drugs: StemRegenin1*[50,52] Tranilast [38,39,54] VAF347 [38,39,55] ITE in nanoparticles [18,48] Omeprazol [49]
PXR	Cholesterol metabolites: Lithocholic acid Heme metabolites: Bilirubin	Hyperforin	Rifampicin [7] Dexamethason [7] Phenobarbital [7]

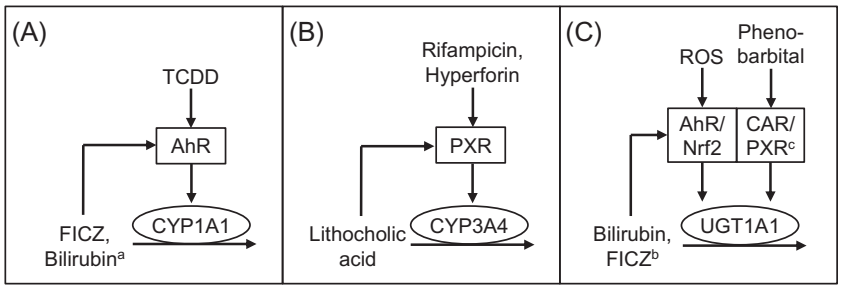

Fig. 1. Feedback loops between endogenous receptor ligands of AHR and PXR and substrates of catabolic enzymes. (A) Transient CYP1A1 induction by FICZ. (B) CYP3A4 induction by lithocholic acid. (C) Bilirubin-mediated UGT1A1 induction by AHR/Nrf2 and CAR/PXR. In addition to endobiotics, the discussed transcription factors are also activated by xenobiotics. [a]High concentrations of bilirubin induce CYP1A1 [71]. [b]Evidence for FICZ-mediated UGT1A1 induction in skin has been indirectly obtained [69]. [c]In the absence of ligand, PXR may act as repressor of UGT1A1 expression [70].