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The aryl hydrocarbon receptor in the crossroad of signalling networks with therapeutic value

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ABSTRACT

The aryl hydrocarbon receptor (AhR) is well-known for its major contributions to the cellular responses against environmental toxins and carcinogens. Notably, AhR has also emerged as a key transcription factor controlling many physiological processes including cell proliferation and apoptosis, differentiation, adhesion and migration, pluripotency and stemness. These novel functions have broadened our understanding of the signalling pathways and molecular intermediates interacting with AhR under both homeostatic and pathological conditions. Recent discoveries link AhR with the function of essential organs such as liver, skin and gonads, and with complex organismal structures including the immune and cardiovascular systems. The identification of potential endogenous ligands able to regulate AhR activity, opens the possibility of designing *ad hoc* molecules with pharmacological and/or therapeutic value to treat human diseases in which AhR may have a causal role. Integration of experimental data from *in vitro* and *in vivo* studies with "*omic*" analyses of human patients affected with cancer, immune diseases, inflammation or neurological disorders will likely contribute to validate the clinical relevance of AhR and the possible benefits of modulating its activity by pharmacologically-driven strategies. In this review, we will highlight signalling pathways involved in human diseases that could be targetable by AhR modulators and discuss the feasibility of using such molecules in therapy. The *pros* and *cons* of AhR-aimed approaches will be also mentioned.

1. Introduction

Since the discovery of the intracellular receptor responsible for the aryl hydrocarbon hydroxylase activity in TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin)-treated mouse liver (Poland, Glover, & Kende, 1976), and the cloning and characterization of its cDNA in humans (Dolwick, Schmidt, Carver, Swanson, & Bradfield, 1993) and mice (Burbach, Poland, & Bradfield, 1992; Ema et al., 1992), the aryl hydrocarbon/dioxin receptor (AhR) has been extensively studied as a ligand-activated transcription factor mediating the cellular responses against environmental toxicants. In recent years, AhR has been confirmed as an important signalling molecule needed to maintain homeostasis in different tissues and cell types (Bock, 2017; Esser & Rannug, 2015; Mulero-Navarro & Fernandez-Salguero, 2016; Nebert, 2017; Pohjanvirta, 2012; Puga, Ma, & Marlowe, 2009). It has been thoroughly described that the AhR protein has basic-helix-loop-helix-PAS (bHLH-PAS) functional domains shared by other members of the same family of transcriptional regulators (Pohjanvirta, 2012), although AhR has the specific property of being activated by a wide array of chemicals among which TCDD is considered its prototype exogenous agonist (Mimura & Fujii-Kuriyama, 2003; Pohjanvirta, 2012; Pohjanvirta & Tuomisto, 1994). From a functional point of view, *in vitro* work has shown that, upon ligand binding (*e.g.* TCDD binding), cytosolic AhR translocates to the nuclear compartment to bind its transcriptional partner Aryl hydrocarbon receptor nuclear translocator also known as Hypoxia inducible factor 1β (ARNT/HIF1β) (Nebert & Dalton, 2006; Swanson & Bradfield, 1993; Swanson, Chan, & Bradfield, 1995). AhR/ARNT heterodimers interact with a partially characterized set of co-activators and the resulting transcriptional complex then binds to a consensus XRE (xenobiotic responsive element) sequence (5′-GCGTG-3′) located in the regulatory region of target genes such as *CYP1A1* (Hankinson, 1995, 2005; Whitlock, 1999). Target gene expression is ended by the release of AhR-ARNT complexes from the DNA and by proteosomal-dependent degradation of the receptor in the cytosol (Davarinos & Pollenz, 1999;

Abbreviations: AhR, aryl hydrocarbon/dioxin receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; EGF, Epidermal growth factor; FICZ, 6,12-diformylindolo[3,2-*b*]carbazole; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor

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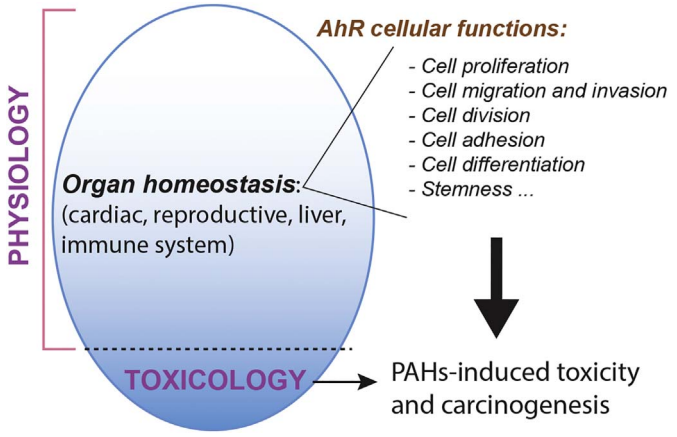

Fig. 1. AhR integrates physiological and toxicological cellular functions. AhR has a major role in toxicology contributing to the metabolism and elimination of toxic and carcinogenic compounds present in the environment. Studies over the years have also demonstrated the many physiological functions of this receptor that integrates its signalling pathway in organ homeostasis and in the maintenance of critical cellular functions. Overall, it is considered that the toxicological activities of AhR may represent an exacerbated cellular response of its endogenous roles.

Ma & Baldwin, 2000; Santiago-Josefat, Pozo-Guisado, Mulero-Navarro, & Fernandez-Salguero, 2001).

A recurring open question in the field is the existence of an endogenous ligand(-s) with agonistic or antagonistic activity able to modulate homeostatic AhR functions. Since the relevance of AhR in controlling development and physiology is now clearly established (Fig. 1), it is reasonable that certain molecules generated by the cellular metabolism could act as ligands for this receptor (Pohjanvirta, 2012). An increasing number of molecules are now considered endogenous AhR ligands with different potential for receptor activation including indigo and indirubin, arachidonic acid-derived molecules, heme metabolites and dietary compounds such as indol-3-carbinol and flavonoids (reviewed in (Nguyen & Bradfield, 2008)). Tryptophan metabolites produced by the endogenous cellular metabolism (Heath-Pagliuso et al., 1998) or by UV-induced transformation of tryptophan to 6-formylindolo[3,2-*b*]carbazole (FICZ) (Rannug et al., 1987, 1995; Wincent et al., 2012) are currently considered potent AhR ligands detectable in human liver and likely substrates of CYP1 enzymes (Wincent et al., 2009). Despite the fact that AhR may be activated in absence of putative endogenous ligands by alternative molecular mechanisms, it is assumed that pharmacological AhR modulation could have promising therapeutic value for the treatment of human disease. Although attractive, such approach should take into consideration that AhR has cell-type specific effects on known cellular processes, a property that would require the design of either agonistic or antagonistic molecules. In addition, data obtained from immortalized or primary cells *in vitro* and from genetically-modified animal models, should be interpreted with caution if intended to design AhR modulators aimed to rescue the normal activity of signalling pathways whose cell- and tissue-specific alteration causes human disease.

In this review, we will analyze the potential use of AhR as a pharmacological and therapeutic target for treatment of human disease. For that, we will describe disease-associated signalling pathways with which AhR can functionally interact, the possible impact of epigenetics in modulating AhR activity under a therapeutic context, and how restoring physiological levels of AhR activity by selective modulators could represent a novel strategy to control altered cellular functioning.

2. AhR interacts with signalling networks having therapeutic value

Several previous reviews have addressed the implication of AhR in cell cycle, cell proliferation, differentiation, cell survival and migration.

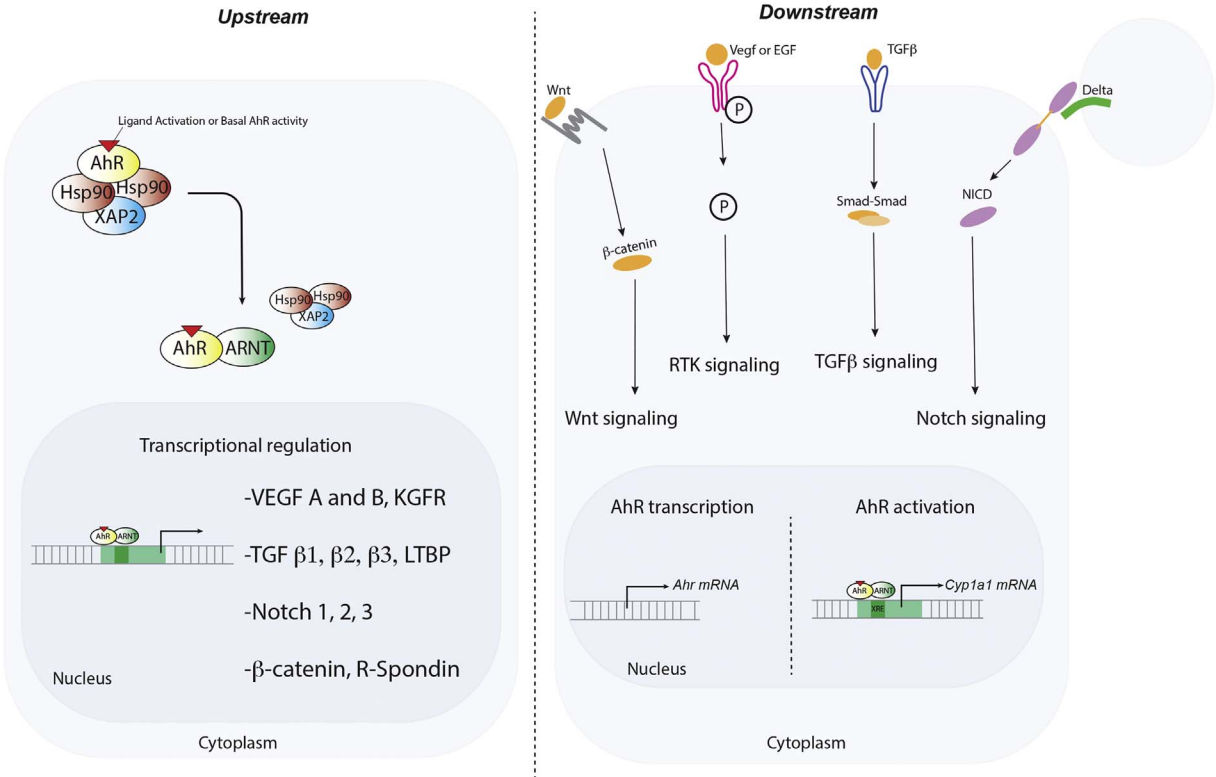

Fig. 2. Upstream and downstream functions of AhR. (Left) AhR following its activation by exogenous or endogenous molecules releases chaperone molecules and translocates to the nucleus. Dimerization with ARNT forms a transcriptional complex that binds to a DRE consensus sequence and modulates the transcription of target genes. (Right) AhR expression can be regulated by different interacting signalling pathways that will ultimately modulate both nuclear AhR levels and AhR-dependent transcription of target genes.