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Graphical Biochemical Review

AhR signaling pathways and regulatory functions

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Abstract

Animals and humans are exposed each day to a multitude of chemicals in the air, water and food. They have developed a battery of enzymes and transporters that facilitate the biotransformation and elimination of these compounds. Moreover, a majority of these enzymes and transporters are inducible due to the activation of xenobiotic receptors which act as transcription factors for the regulation of their target genes (such as xenobiotic metabolizing enzymes, see below §4 for the AhR). These receptors include several members of the nuclear/steroid receptor family (CAR for Constitutive Androstane Receptor, PXR for Pregnane X Receptor) but also the Aryl hydrocarbon Receptor or AhR, a member of the bHLH-PAS family (basic Helix-Loop-Helix - Period/ARNT/Single minded). In addition to the regulation of xenobiotic metabolism, numerous alternative functions have been characterized for the AhR since its discovery. These alternative functions will be described in this review along with its endogenous functions as revealed by experiments performed on knock-out animals.

Keywords: AhR; ARNT; AhRR; Dioxins; Src; Cytochromes P450

1. Introduction

Animals and humans are exposed each day to a multitude of chemicals in the air, water and food. They have developed a battery of enzymes and transporters that facilitate the biotransformation and elimination of these compounds [1,2]. Moreover, a majority of these enzymes and transporters are inducible due to the activation of xenobiotic receptors which act as transcription factors for the regulation of their target genes (such as xenobiotic metabolizing enzymes, see below §4 for the AhR) [3]. These receptors include several members of the nuclear/steroid receptor family (CAR for Constitutive Androstane Receptor, PXR for Pregnane X Receptor) [4] but also the Aryl hydrocarbon Receptor or AhR, a member of the bHLH-PAS family (basic Helix-Loop-Helix − Period/ARNT/Single minded) (Fig. 1). In addition to the regulation of xenobiotic metabolism, numerous alternative functions have been characterized for the AhR since its discovery. These alternative functions will be described in this review along with its endogenous functions as revealed by experiments performed on knock-out animals [5].

2. The AhR ligands

Numerous ligands (Fig. 2) for the AhR have been described. Xenobiotics, which are mostly aromatic hydrocarbons (including dioxins or PCBs “polychlorinated biphenyls”) were the first ligands discovered. The main source of human exposure (>90%) to aromatic hydrocarbons is through contaminated food. Acute exposure to high doses of dioxins in the workplace or due to industrial accidents can cause skin lesions such as chloracne. Long-term environmental exposure results in more extensive toxic

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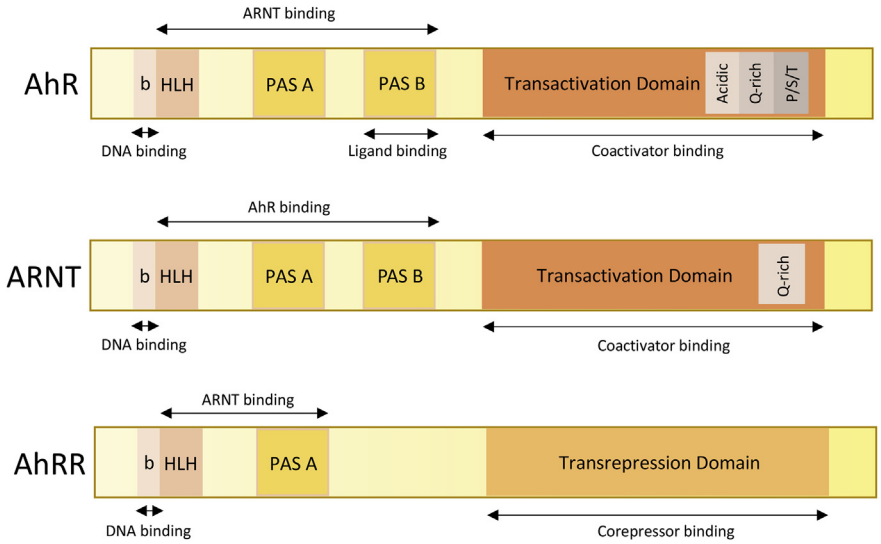

Fig. 1. **The functional domains of the AhR, ARNT and AhRR proteins.** The AhR contains 1) a bHLH domain that allows the dimerization with its partner ARNT, the binding of DNA and the interactions with chaperones such as Hsp90 (Heat Shock Protein 90); it also contains sequences important for both nuclear import and export [76]; 2) a PAS domain which comprises two structural repeats A and B which are also involved in the dimerization with ARNT (PAS A) but which also allows the ligand binding (PAS B); 3) a C-terminal domain which contains three subdomains: one subdomain which is enriched with acidic residues (glutamate/aspartate), another one which is enriched with glutamine (Q-rich) and a third one which is enriched with serine, threonine & proline (S/T/P). Coactivators and co-repressors interact with the AhR via this domain [77,78]. ARNT has a structure similar to AhR: The bHLH and PAS A domains are involved in the dimerization with AhR or AhRR and in DNA-binding. But in spite of the presence of a PAS B domain, ARNT is not able to bind ligands. AhRR also contains a DNA-binding domain (bHLH) and a dimerization domain (PAS A). The absence of the PAS B domain leads to its inability to bind ligands [79].

effects among which are immunotoxicity, neurodevelopmental abnormalities, thyroid dysfunction, disruption of steroid hormones and reproductive functions. Experiments in animals have demonstrated carcinogenicity, with multiple cancer sites, in a large number of species (recent epidemiological studies on occupationally exposed persons are in agreement with these findings). The International Agency for Research on Cancer (IARC) has classified TCDD in group 1 (carcinogenic to humans) whereas PCBs are classified in an intermediate group, 2A (probably carcinogenic to humans). Recently, natural compounds which are found in food have been characterized as AhR ligands. Flavonoids such as quercetin and resveratrol, the most abundant class of polyphenols, are found in fruits and vegetables. Indoles such as indole-3-carbinol (I3C) are derived from cruciferous vegetables such as broccoli or Brussels sprouts. Finally, molecules in the body which are formed by endogenous metabolism, such as FICZ (formylindolo [3,2-b] carbazole), indirubin, indigo, metabolites of arachidonic acid or kynurenine pathway metabolites, also have been described as AhR ligands. In the central nervous system, the catabolism of tryptophan leads to the production of NAD^+, neuroactive metabolites such as kynurenic acid, glutamatergic agonists (NMDA) or neurotoxins (quinolinic acid). In mammals, three enzymes catalyze the first limiting step of catabolism of tryptophan to N-formyl-kynurenine: TDO2 ("tryptophan-2,3-dioxygenase") and IDO1 and 2 ("indoleamine-2,3-dioxygenases") [6].

3. The AhR complex

The non-activated form of the AhR is cytoplasmic and it forms a complex with several chaperones [7] among which are two HSP90 (Heat Shock Protein 90), a co-chaperone p23, a XAP-molecule 2 (hepatitis B Virus X-associated protein 2). Some studies suggest that the Src tyrosine kinase also is a member of the complex. These proteins maintain the correct folding of the AhR, allow a proper recognition of the ligand by the receptor and, subsequently, ensure indirectly an efficient transcriptional effect [8].

4. Activation and modulation of the AhR

Several signaling pathways can be activated by the AhR. The first pathway to be described was the genomic pathway (Fig. 3) and it is now well-characterized. After a ligand is bound, the AhR translocates into the nucleus and it binds to ARNT to form an active heterodimer. This heterodimer modulates the expression of targets by binding to xenobiotic responsive elements (XRE) and coregulators. The amount of protein expressed from targeted genes is reduced by 80–95% in many cell culture models within 4 h of treatment by a ligand [9–11]. After being exported out of the nucleus, the AhR is rapidly degraded in the cytoplasmic compartment by the proteasome [12]. Proteasomal degradation of the AhR involves its binding of ubiquitin covalently. Other post-translational modifications of the AhR have been observed. SUMOylation enhances AhR stability through inhibition of its ubiquitinylation. However, this may suppresses its trans-activating activity [13, 14]. The different ligands of the AhR may activate the receptor differentially. We have shown that resveratrol does not strongly activate the expression of CYP1A1 in a human hepatocellular cell line. However, resveratrol does activate the expression of paraoxonase 1