Ahr-mediated signal transduction pathway. A review.

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Polychlorodibenzo-p-dioxins (PCDDs), polychlorodibenzofurans (PCDFs) and organochlorinated compounds sharing a chemical structure and electronic distribution similar to PCDDs and PCDFs, show similar physicochemical characteristics. They all possess a high hydrophobicity together with high physical and chemical resistance to degradation, what make them be able to be very widespread in the environment. They also have in common a high toxicity, being the most toxic one of this group of compounds the 2,3,7,8-tetrachlorosibenzo-p-dioxin, commonly named as TCDD or dioxin. The main way, and also the most studied, to exhibit their toxic effect, is through the interaction with the Aryl hydrocarbon receptor (AhR) also known as dioxin receptor.

The TCDD-AhR, or more generally pollutant-AhR, complex, plays a pivotal role in mediating a broad range of distinct toxic responses[1] such as immune suppression, thymic involution, endocrine disruption, wasting syndrome, chloracne, birth defects, and carcinogenesis[2].

The extensive study of the mechanism of how these dioxin-like compounds share their toxic effect, have led to propose a preliminary signal cascade beginning with the interaction of TCDD and AhR. This signal transduction is represented in Fig 1.

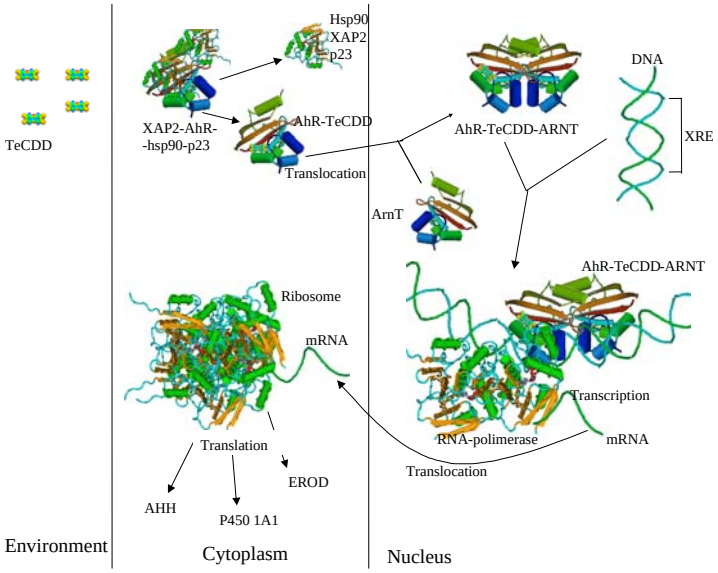

Figure 1. TCDD-AhR interaction and signal transduction.

In the absence of ligand, the non-activated dioxin receptor is associated with the molecular chaperone hsp90[3], the co-chaperone p23[4,5], and the immunophilin-like protein XAP2[6,7,8]. Upon ligand binding the dioxin receptor accumulates in the cell nucleus where it forms a transcriptionally active complex with the transcription factor Arnt, which in turn, induces release of hsp90 from the receptor[5,9,10]. The dioxin AhR-Arnt heterodimer activates transcription of target genes by specifically binding to dioxin inducible transcriptional control elements, XREs having as consensus sequence 5'T-GCGTG3' [11], which are located in regulatory regions of a network of genes encoding drug-metabolizing enzymes, such as cytochrome P-450 1A1, glutathione S-transferase Ya and quinone oxidoreductase.

The transcription of several genes regulated by AhR-Arnt complex (CYP1A1 and CYP1A2) is also regulated by cytokines[12]. It has been reported that TNF-α and NF-κB are able to modify CYP1A1 and CYP1A2 levels in human primary hepatocytes. It has been demonstrated[13] that the two pathways, AhR-Arnt and cytokines, interacts by physical association of their respective critical components, RelA and AhR, and that this interaction is associated with mutual functional modulation of gene expression controlled by the AhR and NF-κB.

All these works focused to study this AhR mediated signal transduction, have led to a higher knowledge at a molecular level of each one of the proteins involved in this mechanism.

Aryl hydrocarbon receptor (AhR) and Aryl hydrocarbon nuclear translocator (Arnt): The AhR belongs to the basic helix-loop-helix (bHLH)/Per-Arnt-Sim domains (PAS) family of transcription factors. These proteins (PAS family proteins) are characterized by two conserved domains, consisting of: i) bHLH: basic aminoacids followed by a helix-loop-helix structure common with other transcription factors. This region is responsible of DNA XRE binding and protein dimerization ii) PAS domains: are degenerate repeated sequences involved in protein dimerization. Figure 2 shows the position of the different motifs in the AhR sequence together with their activity.

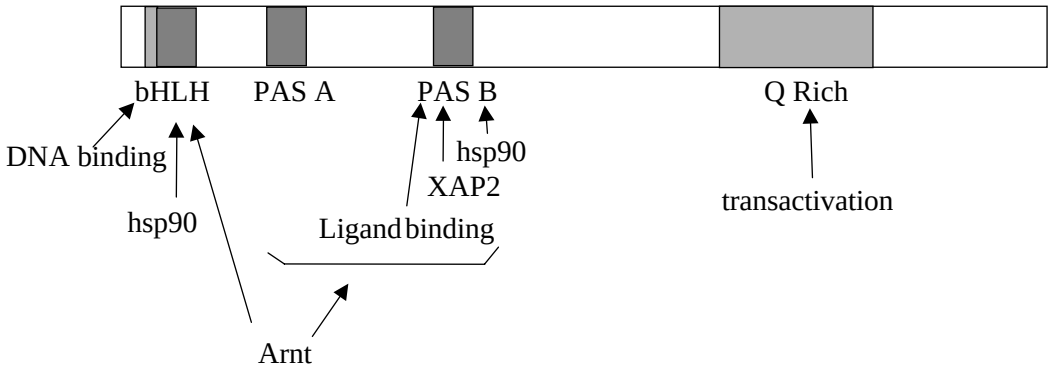

Fig 2. Functional domains of AhR.

Arnt also belongs to the bHLH/PAS family being the main difference with AhR that Arnt do not posses ligand binding activity, and that the DNA sequence recognized by the basic region is different form the recognized by the basic region of AhR.

Hsp90 and its co-chaperone p23: Hsp90 interacts with two spatially distinct motifs of the dioxin receptor, the ligand-binding PAS-B domain and the bHLH domain[14]. This molecular chaperone seems to be required to maintain a high affinity ligand binding conformation of the receptor[15].

The hsp90-associated molecular co-chaperone p23 is a protein generally ligated to hsp90 and appears to play a role in stabilizing dioxin-receptor-hsp90 interaction[5].

XAP2: Another hsp90-binding protein is the 38 kD immunophilin-like protein XAP2. This protein was originally identified as the hepatitis B virus protein X-associated protein in yeast two-hybrid studies[16], and later this protein has been characterized as a constituent of the non-activated dioxin receptor complex[6,7,8]. The C-terminal portion of the PAS B domain of the dioxin receptor[17,18] mediates XAP2-AhR interaction. XAP2 presents regions of homology with other immunophilins such as FKBP12 and FKBP52 present if other steroid hormone receptor complexes[6,7,8]. These regions of homology are the tetratricopeptide repeats (TPRs) which plays a role in mediating protein-protein interactions[19]. XAP2 has a stabilizing effect on dioxin receptor protein levels and has a role in regulation of the intercellular localization of the dioxin receptor by an uncharacterized cytoplasmic retention mechanism[17,18].

TPR domains
Protein interaction

Fig 3. Functional domains of XAP2

Too much work has been done to understand how the TCDD and other dioxin-like compounds share their toxic effect in the organism, but it is only the beginning. There is still too much work to be done to understand the AhR-mediated signal transduction, and its interaction with other signal transduction pathways.

Recently the work is not being focused in looking for new interacting proteins with AhR, but it is being focused on other parameter affecting the activation o deactivation of the AhR cytoplamatic and nuclear complexes, cellular localization, etc, such as PKC phosphorilation[20], cAMP induced phosphorilation...

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