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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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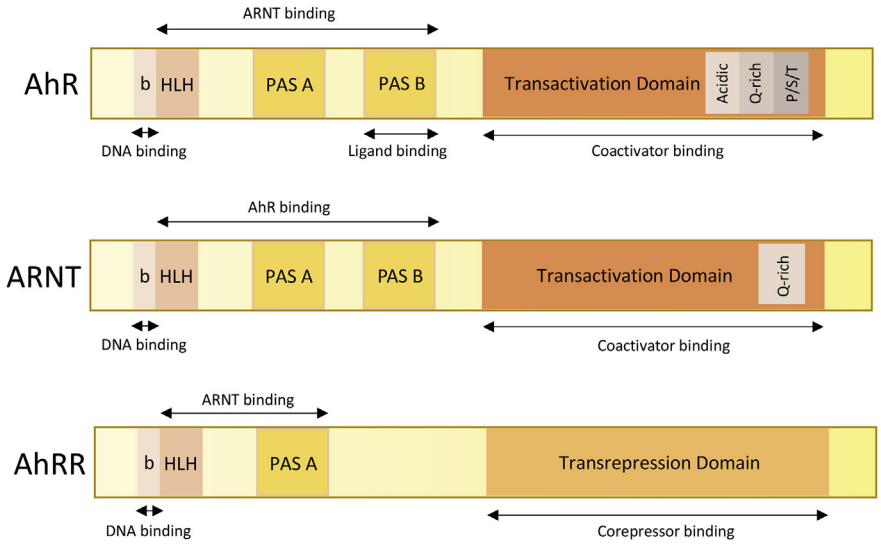

Fig. 1. **The functional domains of the AhR, ARNT and AhRR proteins.** The AhR contains 1) a bHLH domain that allows the dimerization with its partner ARNT, the binding of DNA and the interactions with chaperones such as Hsp90 (Heat Shock Protein 90); it also contains sequences important for both nuclear 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

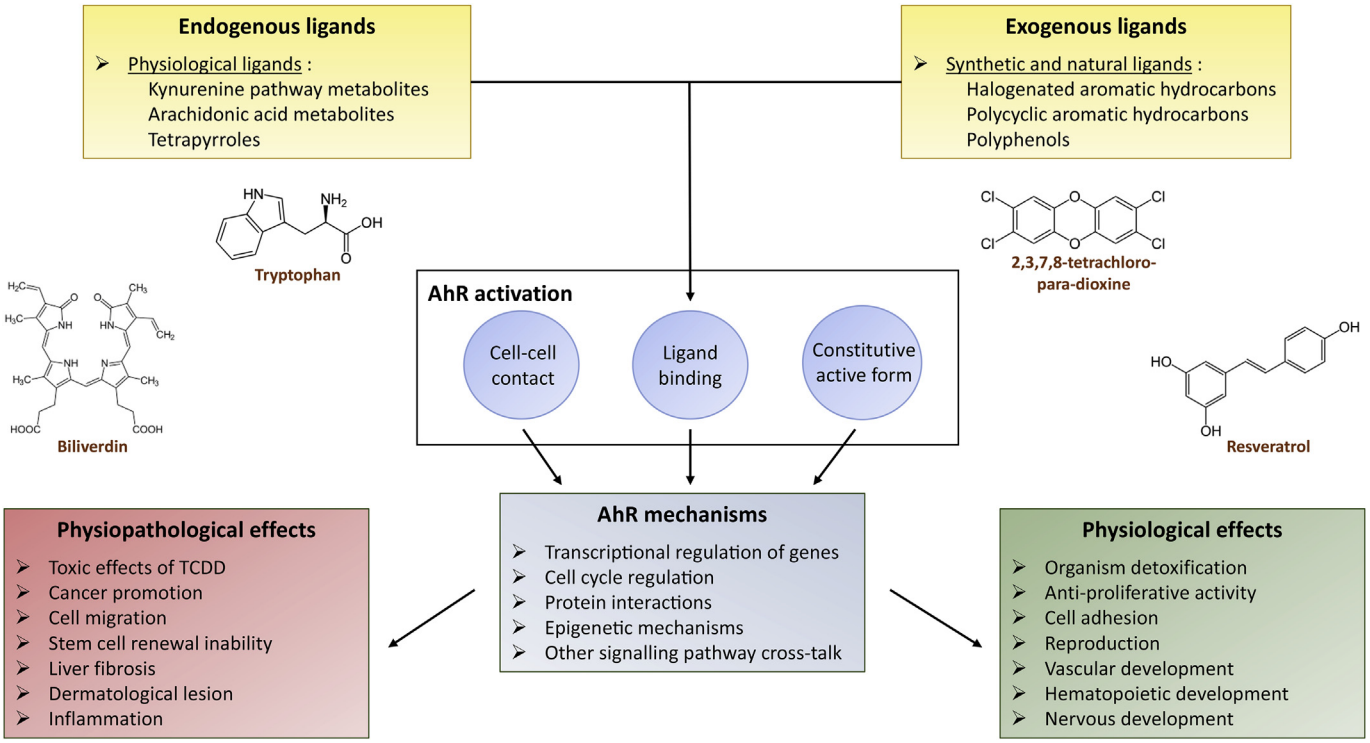

Fig. 2. **The functional relationship between the AhR ligands and the regulatory roles of this receptor in physiology and pathophysiology.** Synthetic ligands such as Halogenated Aromatic Hydrocarbons (HAHs) such as PCBs ("Polychlorobiphenyls") and PCDD (polychlorinateddibenzo-para-dioxins) or PAHs (Polycyclic Aromatic Hydrocarbons) which include benzo (a) pyrene (B(a)P) or 3-methylcholanthrene (3-MC) were among the first molecules to be identified as AhR ligands. These molecules are present in the air or in foods as complex mixtures, they are very stable; some may accumulate in the body (TCDD has a half-life of about seven years in humans) and they are powerful inducers of AhR [80]. Dioxins or PCBs are highly soluble in fats and can, therefore, reach high concentrations in fatty foods such as dairy products, fishes, meats and seafood. **More recently, ligands of natural origins (food and endogenous ligands) such as flavonoids or indole derivatives also have been characterized as AhR ligands.** Flavonoids are found in fruits and vegetables and represent the most abundant class of polyphenols. Among them, quercetin and resveratrol activate the AhR [8,81] and exert both agonist and antagonistic effects. Indoles such as indole-3-carbinol (I3C), which are derived from cruciferous plants such as broccoli or Brussels sprouts, are reported to have anti-cancer properties. Part of the effects of I3C occurs via activation of the AhR [82]. In addition, physiological endogenous ligands of the AhR such as indole amino acid metabolites (tryptophan, tryptamine, indole acetic acid) recently have been characterized. A photoproduct of tryptophan also has been identified through structural and chromatographic studies [83]: FICZ (6-formylindolo [3,2-b] carbazole) [84]. Indirubin and indigo represent another group of indoles [85] which are detected in human urine under normal physiological conditions and, therefore, are present in our organisms, and are strong inducers of the AhR [85,86]. Physiological ligands also include metabolites of arachidonic acid (lipoxin A4, some prostaglandins (PGG2)) [87,88], tetrapyroles (bilirubin, a degradation product), heme and biliverdin [89]).

(PON1) which might allow the detoxication of oxidized lipids and which could explain, partly, the beneficial effects of exposure to resveratrol on the incidence of cardiovascular diseases. This may be due to the binding of the AhR to alternative XREs [15]. Since TCDD does not activate PON1 expression, this suggests that different ligands might activate different gene clusters.

One of the key target genes activated in the AhR genomic pathway is the AhR repressor, AhRR [16–18] (Fig. 1). The AhRR protein is similar to the AhR but it cannot bind ligands due to the absence of the PAS B domain in the N-terminal region [18,19]. Further, the AhRR differs from AhR and ARNT in that the C-terminal domain, which is a transactivation domain in AhR and ARNT, is a transrepression domain in AhRR. It allows the binding of corepressors which are involved in a negative regulatory loop for AhR. Following induction, AhRR suppresses AhR activity by binding to ARNT and XRE (AhRR-ARNT complex) [20,21]. AhRR, thus, is able to modulate the transcription of AhR-dependent genes. This negative regulatory loop and the proteosomal degradation of the receptor protect biological systems from the consequences of overstimulation by agonists and provide a temporal control of the signaling (Fig. 3). In addition to the genomic pathway, several non-genomic pathways have been identified recently (Fig. 4). For instance, following exposure to TCDD, there is a rapid increase in intracellular calcium concentration (from both extracellular and endoplasmic reticulum sources). TCDD also leads to the functional activation of the tyrosine kinase Src by releasing it from the AhR complex [22]. This could be accompanied by the activation of the Focal Adhesion Kinase and by the modification of the adhesion properties of the cell through disruption of focal adhesion points [22,23]. Src activation could be accompanied also very rapidly by the activation of MAP kinases, ERK1 and ERK2. All these processes may converge to regulate pathophysiological processes such as inflammation. Indeed, the calcium influx causes the activation of protein kinase C (PKCα) which phosphorylates a serine residue of a cytosolic enzyme, phospholipase A2 (cPLA2) with

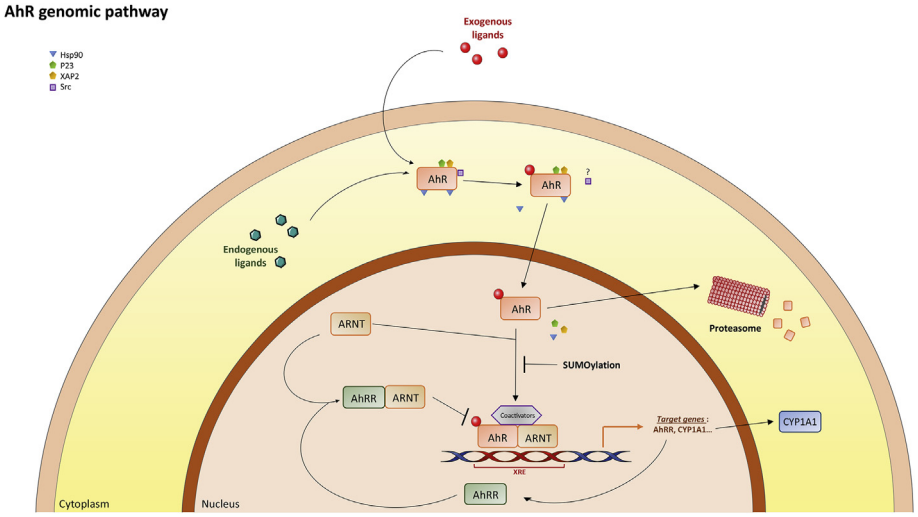

Fig. 3. **The AhR genomic pathway.** When a ligand crosses the plasma membrane (passive diffusion), it binds to the AhR (the PAS B domain). This allows the translocation of the ligand-receptor complex into the nucleus and the dissociation of the receptor complex. In the nucleus, the complex heterodimerizes with its partner ARNT (AhR Nuclear Translocator also called HIF-1β) [90]. The heterodimer binds specific DNA sequences located in the promoter regions of target genes named xenobiotic response elements (XRE, 5′-TA/TGCGTG-3′) [80]. AhR-ARNT induces the transcription of target genes by the recruitment of various components of the transcriptional machinery [91] such as CBP/p300 (cAMP response element-binding protein binding protein) [80–82], SRC-1 (steroid receptor coactivator 1), p160/bHLH-PAS, NCoA2/GRIP1/TIF2 (Nuclear receptor Coactivator 2/Glucocorticoid Receptor Interacting Protein 1/Transcriptional Intermediate Factor 2) and p/CIP (p300/CBP/CoIntegrator-associated Protein) [95] as well as other transcriptional coactivators such as RIP140 (Receptor Interacting Protein 140) [96,97] or ATP-dependent chromatin remodeling components such as BRG-1 (Brahma Related Gene). After being exported out of the nucleus, the AhR is rapidly degraded in the cytoplasmic compartment by the proteasome [12]. Other post-translational modifications such as SUMOylation of the human AhR have been observed [13].

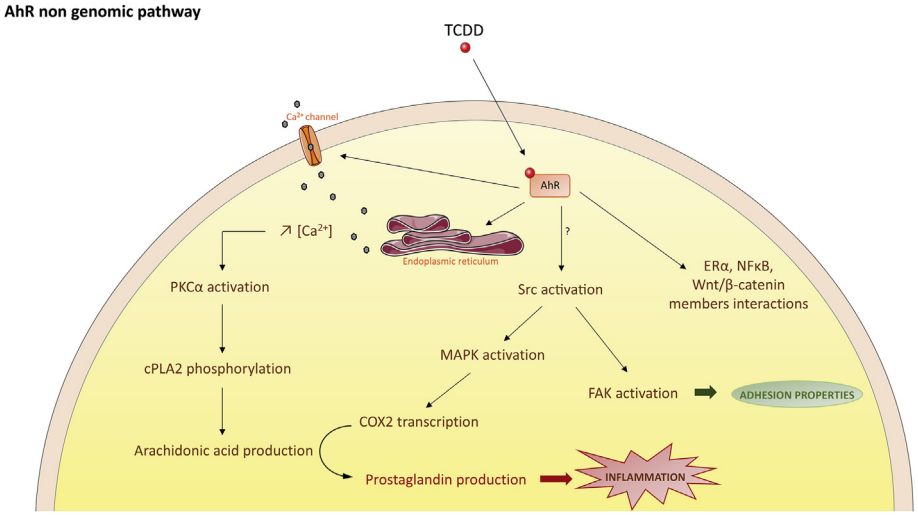

Fig. 4. **The AhR non-genomic pathways.** In recent years, numerous observations indicate that additional AhR pathways can be activated by the AhR. For instance, TCDD rapidly increases intracellular calcium concentrations or the activity of the Src tyrosine kinase and Focal Adhesion Kinase with functional consequences for other pathways (MAPK) or cellular functional properties (adhesion and migration). One outcome of such activations could be inflammation through the subsequent production of arachidonic acid and then prostaglandins. Finally, the AhR is able to interact with several other transcriptional regulators such as β-catenin, NF-kB or the estrogen receptor alpha.

the subsequent production of arachidonic acid. The parallel activation of MAP kinases by Src leads to the transcription of cyclooxygenase 2 (COX2) which uses arachidonic acid to produce prostaglandins that can cause inflammation. Thus, these two signaling pathways, which were initially activated by TCDD, converge towards the stimulation of inflammation [24]. Moreover, the AhR interacts with Wnt/β-catenin, ER-alpha or NF-kB and strongly modulates their actions [25–28]. On the other hand, these transcription factors also impact AhR signaling. For example, β-catenin is now described as a co-activator of this receptor [29].

Finally, after exposure to a ligand, the level of the AhR protein has been found, both *in vitro* and *in vivo*, to decrease rapidly without the level of the messenger RNA being altered [9].

5. Regulation of cellular functions by the AhR

The best-characterized AhR function to date is the establishment of a protective adaptive response to xenobiotics through induction of the synthesis of xenobiotic metabolism enzymes. Aromatic hydrocarbons activate the AhR which induces family 1-P450 cytochromes (1A1, 1A2, 1B1) the functions of which deal mostly with hydrocarbon detoxication. This elegant regulatory loop protects xenobiotic-exposed animals by detecting and then metabolizing these substances. However, the high degree of conservation of this receptor among species [21], its pattern of expression during development and in adult tissues [30] and the phenotypic alterations observed in AhR-deficient mice [31–33] suggest a strong involvement of the AhR in cell physiology which is independent of the metabolism of xenobiotics. The detoxification function of the AhR may have been acquired late in evolution.

5.1. Cell proliferation

One of the most intriguing and exciting aspects of AhR biology is its ability to promote or inhibit cell proliferation. For example, AhR KO mouse embryonic fibroblasts exhibit slow growth and accumulation in the G2/M phase of the cell cycle [34]. In human hepatoma cells (HepG2), AhR-siRNAs block the G1/S transition of the cell cycle and decrease cyclins D1 and E as well as CDK2/4-dependent cyclin kinases. This supports a pro-proliferative role for the receptor [35]. TCDD also can affect the expression of genes involved in cell proliferation (TGF-β, IL-1β and PAI-2), regulation of the cell cycle (JunB and JunD [36]) and inflammation [37–39]. In human breast cancer cells (MCF-7), NF-kB, via its RelA subunit, physically interacts with AhR [25] which results in transactivation of the c-myc proto-oncogene. With respect to the cell cycle, the expression of JunD and subsequently cyclin A, which blocks cell contact inhibition and favors proliferation [36], is triggered by TCDD-activated AhR via a novel ARNT-independent pathway. The role of AhR as a cancer promoter has been demonstrated in murine models which overexpress a constitutively active form of the AhR [40,41]. All these results suggest that the AhR favors cell proliferation. However, other studies have revealed an anti-proliferative activity of the AhR. AhR stimulates the transcription of the tumor suppressor gene, p27Kip1, in non-proliferative hepatoma cells or in the fetal thymus [42,43]. The AhR also regulates the function of the pro-proliferative factor E2F (E2F factors can be inhibited by direct interaction with retinoblastoma protein, pRb, and their function also depends on the presence of co-activators p300) in 3 different ways: 1) TCDD activates the physical interaction between the AhR and pRb which promotes its binding to E2F and stops the cell cycle [44], 2) in addition, TCDD stimulates the interaction between AhR and p300, which leads to displacement of p300 from E2F sites [45], 3) finally, a direct inhibitory interaction was detected between the AhR and E2F with potential implications for stem cell renewal [46,47].

Overall, the activity of the AhR on cell proliferation is probably dependent on the cell type, the timing of the cell cycle (and the expression of interacting partners such as RelA or pRb), the developmental period (if considering an animal model). Therefore, any specific action which would include the use of an AhR ligand to control the cell cycle, needs to be carefully evaluated in regard to these parameters.

5.2. Adhesion and cell migration

The contribution of the AhR in adhesion processes, which involve cell-cell and cell-extracellular matrix interactions, has recently emerged. Cell density also influences the compartmentalization of the AhR and low densities lead to a nuclear localization of the AhR [48]. These interactions are also very important for metastatic processes.

Knock-out models seem to confirm this involvement of the AhR in cell migration. Immortalized mammary fibroblasts derived from AhR KO mice, display decreased migration which is associated with an increased formation of cytoskeleton stress fibers and a reduction in the formation of lamellipods [49]. Signaling pathways which regulate cell migration are also inhibited in AhR-deficient cells which exhibit weaker activation of focal adhesion kinase (FAK), PKB/Akt (protein kinase B), ERK1 (extracellular signal-regulated kinase 1) and Rac-1 (Ras-related C3 botulinum toxin substrate 1). In addition, these fibroblasts induce fewer tumors *in vivo* in immune-deficient NOD-SCID mice (non-obese diabetic/severe combined immunodeficiency) than in wild-type mice [49].

The involvement of AhR in mobility and cellular plasticity also has been demonstrated by studies based on xenobiotic treatments. Exposure of human MCF-7 or HepG2 cells to TCDD causes morphological changes such as the appearance of lamellipodia, which cause greater cell adhesion and motility. This is associated with a reorganization of the cytoskeleton mainly due to a redistribution of actin and vinculin and to the activation of the FAK and Src kinases (Fig. 4) [23]. These cellular effects are accompanied by changes in the expression of certain genes such as E-cadherin and by the activation of JNKs [23]. E-Cadherin downregulation is a hallmark of epithelial-mesenchymal transition which is triggered by transcription factors such as Slug, a direct AhR target gene [50,51].

6. Physiological roles of the Ah receptor

AhR KO mice display developmental abnormalities which highlight the roles of the receptor in female fertility [52], perinatal growth [18,31], regulation of blood pressure, production of peripheral lymphocyte counts [31,32,53] and increased susceptibility to colitis [54]. Recently, it has been shown in a mouse model of induced-colitis, that FICZ (a high-affinity endogenous AhR ligand) prevents intestinal barrier function via AhR activation by suppressing IL-6 and claudin-2 expression [55].

Depending upon the model, AhR KO mice develop cardiac hypertrophy [56], dermatological lesions, portal vascular hypertrophy [32] and pyloric hyperplasia of the gastrointestinal tract [56]. One of the most common phenotypes to all AhR KO

models is vascular. The mice exhibit a systematic persistence of ductus venosus [57], a porto-fetal shunt of the developing liver, which normally closes immediately after birth [58,59]. These abnormalities result in reduced liver size associated with portal fibrosis and early lipid accumulation [60,61]. A candidate gene that could explain this liver phenotype is Transforming Growth Factor ß (TGF-β). The AhR KO mouse livers have increased levels of TGF-β in the portal space [62] which could contribute to the development of fibrosis and to a low proliferative capacity as a result of the pro-fibrogenic and anti-proliferative activities of this cytokine. Additional studies have shown that this elevation of TGF-β is related to the accumulation of retinoic acid and to a reduction in retinoic acid metabolism, which lead to a decrease in CYP2C39 [63]. Other vascular abnormalities have been observed in these mice, such as the persistence of the hyaloid artery and an impairment of limbic vascularization in the developing eye [57]. The AhR KO mice also develop an ocular pathology which consists of a horizontal pendular nystagmus which is associated with myelin defects of the optic nerve and a local inflammation [64]. Similar myelin defects also have been identified recently in the peripheral nervous system [65]. Moreover, the AhR is involved in neuroendocrine pathways such as those that control the brain-pituitary-interrenal and gonadal axes. Treatment of rainbow trout with β-naphtoflavone and resveratrol, agonist and antagonist of AhR, respectively, has elucidated the role of the receptor in the disruption of steroid production after PCB exposure [66].

Studies in KO models suggest that AhR ligands activate AhR-independent pathways but these results require thoughtful interpretation as to the mechanisms involved. For example, in AhR KO rats, treatment with alpha-naphtoflavone (an AhR antagonist) causes an increase in the rate of ovulation and in follicular growth [67]. Abnormalities in the immune system also have been explored. After administration of TCDD, AhR KO rats displayed changes in immune phenotypes such as a decrease in $CD8^+$ T cells and $CD11^+$ but an increase in NKT cells [68].

Although similar consequences frequently are found in different species (such as the insensitivity to the effects of TCDD in AhR-deficient animals as compared to the wild-type), some AhR KO phenotypes are species-specific, such as the differences that occur between mice and rats [69,70]. For example, vascular phenotypes that are found in AhR KO mice, such as the persistent ductus venosus of the liver or hyaloid artery in the eye, are not observed in AhR KO rats. Or, alterations of the urinary tract (renal dilatation or degenerative changes and ureter dilatation) have been identified in AhR KO rats, but not in AhR KO mice.

7. Conclusion

In recent years, new functions of the AhR have been identified both in vertebrate and invertebrate models. In vertebrates, the AhR regulates the functions of transposable elements (including retrotransposons) which are suspected to regulate a large number of gene expression patterns [71,72], chromatin functions (insulators) and also epigenetic mechanisms through the regulation of SIRT1 activity or miR expression [5]. This could have potential impacts in terms of evolution. The AhR is also a protein whose functions have been modified throughout evolution. In invertebrates, no ligand for the AhR has been identified to present [73−75]. This suggests that the protein has acquired detoxication functions over time.

Conflict of interest

There is no conflict of interest for all authors.

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