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Title: Aryl Hydrocarbon Receptor and Its Diverse Ligands and Functions: an exposome receptor

Authors: Lucie Larigot^{1,3,#}, Louise Benoit^{1,2,3,#}, Meriem Koual^{1,2,3}, Céline Tomkiewicz^{1,3}, Robert Barouki^{1,2,3}, Xavier Coumoul^{1,3}

Affiliations :

¹ INSERM UMR-S1124, T3S, Toxicologie Environnementale, Cibles thérapeutiques, Signalisation cellulaire et Biomarqueurs

² Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges-Pompidou, Service de Chirurgie Cancérologique Gynécologique et du Sein, Paris, France

³ Université de Paris, 45 rue des Saints-Pères, 75006 Paris-France

E-mails : luciole271@gmail.com; louise.am.benoit@gmail.com; meriemkoual@hotmail.com; celine.tomkiewicz@inserm.fr; robert.barouki@parisdescartes.fr; xavier.coumoul@u-paris.fr

Corresponding author: Xavier Coumoul, xavier.coumoul@u-paris.fr, +33 1 42 86 33 59

#: both authors contribute equally to this work

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List of abbreviations

3MC: 3-methylcholanthrene
ABCC3: ATP Binding Cassette Subfamily C Member 3
AhR: Aryl hydrocarbon Receptor
AIP: AhR-Interacting Protein
ALDH: ALdehyde DeHydrogenase
ARNT: Aryl hydrocarbon Receptor Nuclear Translocator
 β -NF: β -Naphthoflavone
bHLH: basic Helix Loop Helix
BRCA1: BReast CAncer 1
CCND1: cyclin D1 protein
CD: Cluster of Differentiation
CDK: Cyclin-Dependant Kinase
CHDF: 6-CycloHexyl-1,3,8-trichloroDibenzoFuran
CKD: Chronic Kidney Disease
CNS: Central Nervous System
COPD: Chronic Obstructive Pulmonary Disease
COX2: CycloOXygenase 2
cPLA2: cytosolic PhosphoLipase A2
c-Src: cellular-Sarcoma
CUL4B: Cullin 4B
CYP450: CYtochrome P450
CYP1A1: CYtochrome P450 1A1 (family)
CYP1B1: CYtochrome P450 1B1 (family)
DC: Dendritic Cell
DEAB: N,N-diethylaminobenzaldehyde
DEN: Diaethylnitrosamin
DIM: 3,3'-Diindolylmethane
DMBA: dimethylbenz[a]anthracene
E2: β -Estradiol
EMT: Epithelial-Mesenchymal Transition
ER α : Estrogen Receptor alpha
ERE: Estrogen Responsive Element
ET-1 : Endothelin-1
FAK: Focal Adhesion Kinase
FICZ: 6-formylindolo [3,2-b] carbazole
GTPase: Guanosine TriPhosphate (GTP)ase
HAH: Halogenated Aromatic Hydrocarbon
HER2: Human Epidermal Growth Factor Receptor-2
HIF-1 α : Hypoxia Inducible Factor-1 alpha

Hsp90: Heat Shock Protein 90
IAA: indole-3-acetic acid
IDG: indoxyl- β -D glucuronide
IDO1: Indoleamine 2,3-Dioxygenase 1
IECs: Intestinal Epithelial Cells
IELs: IntraEpithelial Lymphocytes
IL-X: interleukin-X (X : number)
ILCs: Innate lymphoid cells
IS : Indoxyl Sulfate
Kd: dissociation constant
KLF6: Kruppel Like Factor 6
KO: Knock-Out
Kyn: Kynurenine
LDL: Low-density lipoprotein
MAPK: Mitogen-Activated Protein Kinases
MCDF: 6-methyl-1,3,8-trichlorodibenzofuran
MCF-7: Michigan Cancer Foundation-7
MCP-1: Monocyte Chemoattractant Protein 1
MMP: Matrix MetalloProteinase
MuSCs: Muscle Stem Cells
NF- κ B: Nuclear Factor-kappa B
NLS: Nuclear Localization Signal
nM: nanoMolar
ox-LDL: oxidized Low-Density Lipoprotein
PAH: Polycyclic Aromatic Hydrocarbons
PAS: Per ARNT Sim
PAX: PAired boX protein
PKC: Protein Kinase C
pRB (or RB): RetinoBlastoma protein
ROS: Reactive Oxygen Species
SAhRM: Selective AhR Modulators
SARS-CoV-2: Severe Acute Respiratory Syndrome-CoronaVirus-2
Sox: SRY-related HMG-box genes
SR1: StemRegenin 1
STAT: Signal Transducer and Activators of Transcription
TCDD: 2,3,7,8-TetraChloroDibenzo-*p*-Dioxin
TDO: Tryptophane 2,3-Dioxygenase
TGF- β (or Tgfb): Transforming Growth Factor β
Th17: T helper 17 lymphocyte
TNF-alpha: Tumor Necrosis Factor-alpha

TR1: Type 1 Regulatory cells

Treg: regulatory T cells

Trp: Tryptophan

UTC: Urinary Tract Cancers

Vav3: Vav guanine nucleotide exchange factor 3

VCAM-1: Vascular Cell Adhesion Molecule 1

Vim: Vimentin

XAP2: X-associated protein 2

XRE: Xenobiotic Responsive Element

Wnt: Wingless (Wg) integration site (Int)

Abstract

The Aryl hydrocarbon Receptor (AhR) is a transcriptional factor which regulates multiple functions following its activation by a variety of ligands including xenobiotics, natural products, microbiome metabolites, endogenous molecules. Because of this diversity, it constitutes an exposome receptor. One of its main functions is to regulate several lines of defense against chemical insults and bacterial infections. Indeed, in addition to its well-established detoxication function, it has several functions at physiological barriers, and it plays a critical role in immunomodulation. It is also involved in the development of several organs and their homeostatic maintenance. Its activity is dependent on the type of ligand and on the timeframe of the receptor activation, which can be either sustained or transient, leading in some cases to opposite modes of regulations as illustrated in the regulation of different cancer pathways. The development of selective modulators and their pharmacological characterization are important areas of research.

Introduction: the discovery of the AhR signaling pathway and the detoxication functions

A complex detoxification system allows living organisms to be resistant to exposure to xenobiotics. A great deal of research has been carried out to better understand how this detoxification system works and has led to the identification and characterization of its components.

In the late 1950s, the first enzymes involved in the metabolism of xenobiotics were discovered and were later identified as hemoproteins and named cytochrome P450 (CYP450). They were firstly characterized as enzymes involved in the oxidation of exogenous compounds (1). The existence of the Aryl hydrocarbon Receptor (AhR) was suspected in 1976 by Poland, who described a set of genes capable of controlling the induction of enzymes with aryl-hydroxylase activity (2).

The AhR is a basic Helix Loop Helix/Period ARNT Single-minded (bHLH/PAS) transcription factor. In its inactive basal state, the receptor is part of a complex consisting of different partners, sequestering the receptor in the cytoplasm of cells: two Hsp90 chaperons, XAP2 (also known as AIP/ARA9), the c-Src kinase and the co-chaperon p23. Both Hsp90 interact with the AhR; XAP2 interact with both AhR and Hsp90 proteins. p23 is a co-chaperon as it does not directly interact with the AhR but with one Hsp90. c-Src is part of the cytoplasmic complex. When a ligand binds to the AhR, it induces the release of one Hsp90 and exposed the Nuclear Localization Signal (NLS in the N-terminal region). c-Src is also released. The AhR can then translocate into the nucleus, in which the dissociation of the other chaperons and co-chaperons (XAP2, the other Hsp90 and p23) leads to its dimerization with its partner the AhR Nuclear Translocator (ARNT). The AhR/ARNT heterodimer can bind to specific response elements called Xenobiotic Responsive Elements (XRE), located in the target gene regulatory sequences. XREs have consensus sequence 5'-TNGCGTG-3': the AhR recognizes the half-site "TNGC" and ARNT the part "GTG" (3).

The most famous exogenous synthetic ligands are Halogenated Aromatic Hydrocarbons (HAH) including 2,3,7,8-TetraChloroDibenzo-*p*-Dioxin (TCDD) and Polycyclic Aromatic Hydrocarbons (PAH) such as 3-methylcholanthrene and benzo(a)pyrene (4, 5). All these molecules have a strong affinity for AhR, with dissociation constant (K_d) from pM to nM for HAH and from nM to μM for PAH. Most of these pollutants cause toxic effects. For example, acute exposure to dioxins causes skin damage such as chloracne, while long-term exposure leads to developmental and reproductive abnormalities, immunotoxicity or thyroid disruption.

The sequence of events we described is named the genomic pathway. However, the binding of a ligand to the AhR also modulates its ability to interact with other proteins including Maf and KLF6, kinases, pRB or CUL4B (E3-ubiquitin ligase) (6–8). These interactions activate potential non-genomic pathways. For example, in rats, after exposure to TCDD, the intracellular concentration of Ca²⁺ increases rapidly, resulting in the activation of Protein Kinase C (PKC) (9, 10). The phosphorylation of phospholipase A2 (cPLA2) by PKC subsequently leads to the production of arachidonic acid. The dissociation of the cytoplasmic AhR complex also activate kinases: c-Src which belongs to this complex is released upon binding of a ligand and leads to the activation of MAP kinases, resulting in the transcription of the cyclooxygenase 2 (COX2) mRNA. The corresponding protein uses arachidonic acid to produce prostaglandins, thus causing inflammation (11). Activation of c-Src also results in the activation of FAK that modifies the cellular adhesion, disrupting the focal adhesion points (12). Finally,

interactions with NF κ B subunits (13, 14), the estrogen receptor-alpha ER α (15, 16) and β -catenin (17)(18) have been described, impacting these key signaling pathways.

The inputs of the AhR knock-out models in vertebrates and invertebrates

Beside its functions in the regulation of xenobiotic metabolism, the AhR also modulates endogenous functions although less characterized.

The AhR is expressed early during embryogenesis, especially during organogenesis in the neuroepithelium and heart in mice between 9 and 13 days of gestation (19). The expression of the AhR then increases in the liver, kidneys, lungs, muscles, and epidermis but also in the retina (20, 21). In adult humans, it is highly expressed in the placenta, lungs, heart, pancreas, and liver, and to a lesser extent the kidney, brain, and muscle (22).

In case of AhR deficiency, mice fertility and growth are altered (23–25). In addition, AhR KO mice develop both cardiac and vascular hypertrophies (24, 26) (27–29). The gastrointestinal tract is impacted in both rats (increased susceptibility to colitis) and mice (pyloric hyperplasia) (30). Overall, AhR deficiency accelerates aging in mice (31).

The toxicity of TCDD in mice mediated by the AhR reveals also important endogenous functions of the receptor, suggesting interference with important developmental and physiological functions related to reproduction, nervous and immune systems or tumor promotion (32).

Non-mammalian models were also explored to identify endogenous functions of AhR orthologs; in vertebrates, orthologs are found in reptiles, birds or fish and are able to bind TCDD (33, 34). In invertebrates, AhR orthologs have similarities in structure and signaling pathway but are unable to bind prototypical ligands of vertebrates such as TCDD or alpha-naphthoflavone. However, the AhR is involved in the regulation of development (e.g., of the nervous system) in *Caenorhabditis elegans* and *Drosophila melanogaster* (35)(36, 37) suggesting that it can be activated without exogenous ligands; in vertebrates, this is the case of the cell cycle regulation (38–40). These studies suggest that the AhR can be either activated by endogenous ligands or can have ligand-independent functions. Thus, a likely hypothesis is that the ancestral function of the AhR could be the regulation of developmental functions, while its role in xenobiotic metabolism could be an adaptive functional evolution which appeared later in evolution in vertebrates.

The discovery of a broad diversity of ligands

Three dimensional structural studies have been carried out to better understand the molecular functions of the AhR. These studies allowed a better understanding of the DNA-binding domain structure of the AhR, but none allowed to precisely characterize its ligand binding domain, which is a critical part of the receptor activity. For example in mice, an alanine to valine mutation in position 375 (PAS B domain) may result in altered binding affinity (41), whereas a deletion of part of this domain may cause a constitutive activity of AhR without ligand binding (42). In addition, despite a high degree of homology

and identity among the organisms studied, there are many amino acid variations in the PAS domain, resulting in differences in specificity and affinity between species (43).

In mammals, a multitude of AhR ligands have been identified and can be classified into different categories:

- Exogenous ligands generally linked to anthropic activities.
- Natural molecules from our diet can activate the AhR, although most of them are ligands of low affinity. For example, polyphenols such as flavonoids (quercetin) activate the AhR and induce genes that are either similar to those induced by TCDD, e.g. the CYP1A1 gene (44) , or a set of genes that are not induced by classical exogenous ligands, e.g. the paraoxonase 1 gene (45). Resveratrol, a stilbene polyphenol, is a weak AhR activator capable of competing with TCDD by reducing the transactivation of traditional AhR target genes (46) but it also induces other sets of genes (45). Indoles, such as indole-3-carbinol or one of its secondary metabolites, 3-3'-Diindolylmethane, are degradation products found in cruciferous vegetables and characterized as AhR ligands (47, 48); they are also inducers of the human and rat CYP1A1 (49, 50).
- Endogenous molecules can also act as AhR ligands. This hypothesis of endogenous activation of the receptor has emerged in studies in AhR KO mice. Endogenous ligands include indoles (also present in our diet) such as tryptophan and its derivatives like tryptamine, indole acetic acid, or kynurenine that are able to activate the AhR (51–53). Tryptophan is indeed metabolized through the kynurenine pathway (Kyn, 95%) by the enzymes Trp 2,3-dioxygenase (TDO, highly expressed in the liver) and indoleamine 2,3-dioxygenases (IDO1, expressed in many tissues and IDO2). FICZ (6-formylindolo[3,2-b]carbazole) is also a derivative of tryptophan, produced by ultraviolet radiation in the skin. FICZ is the most potent AhR ligand known to date: it has a stronger affinity than TCDD for the human AhR (TCDD $K_d=0.48$ nM/FICZ $K_d=0.07$ nM) (4, 54). Some of these tryptophan metabolites are microbiome-derived and are agonists or antagonists of AhR activity (indole, indole-3-acetate or tryptamine) (55)(56). Other compounds from bacteria are also known as AhR ligands such as virulence factors (phenazine or pyocyanin from *Pseudomonas aeruginosa* (57) or modulators such as the lipopolysaccharide from *Escherichia coli* (58). Indigo or indirubin are also able to activate the AhR (59, 60). Other molecules including leukotrienes or heme metabolites (bilirubin and biliverdin) have also been identified as AhR ligands (61).

One key dimension to consider regarding the nature of the AhR is the chemical diversity of ligands; most of them, while chemically different, increase the expression of CYP -although to different extents- which could potentially metabolize them quickly. However, several ligands are resistant to this enzymatic process, leading to their persistence in organisms (e.g., dioxins). This is an important dimension to consider because this impacts the nature of AhR activation (transient vs chronic). Another

factor that could trigger a chronic activation of the AhR, is a persistent exposure. We believe that the time frame of AhR activation is a critical determinant which might lead to very different outcomes.

The AhR: an exposome receptor at the barriers

As mentioned, the AhR is highly expressed at several important physiological barriers such as the placenta, lung, gastrointestinal system, and liver (22, 62)(63). In these tissues, the AhR is involved in both detoxication processes involving xenobiotic metabolizing enzymes such as cytochromes P450, and in immune functions translating chemical signals into immune defense pathways.

The gut barrier illustrates the central role of the AhR in the interactions that occur between the microbiota, the immune system, and the intestinal physiology: first, the AhR KO leads to disruption of epithelial tight junctions and increases susceptibility to infections. The AhR also regulates the proliferation of intestinal stem cells by repressing the Wnt signaling pathway (64). Second, FICZ, a tryptophan derivative and high-affinity ligand of the AhR plays a central role in these homeostatic processes by maintaining high production of interleukin 22 (IL-22) by innate group 3 lymphoid cells (65). IL-22 enhances the function of the intestinal epithelial barrier against various pathogens. FICZ also favors the differentiation of goblet cells enhancing mucin-2 expression, leading to maintenance of the mucus and alleviation of infection (65). However, FICZ is rapidly metabolized by CYP1A1, an enzyme whose activity can be increased by microbial derivatives such as butyrate (a short-chain fatty acid which promotes histone acetylation of the CYP1A1 promoter and also an AhR ligand (66)). Cyclic variations in the levels of FICZ and IL-22 appear to maintain intestinal homeostasis. AhR ligands produced by the microbiota (phenazines, indole-3-aldehyde, short-chain fatty acids), which are also subject to cyclic variations, regulate the microbiome composition and functions (67, 68). On the contrary, a chronic activation of the AhR (due to the presence of persistent ligands in the food or insufficient catabolism of tryptophan metabolites by CYP1A1) could lead to deleterious effects in the gut, for example due to over-activity of IL-22 which is proinflammatory (65).

The lung constitutes another barrier exposed to components of air pollution such as particles and hydrocarbons (air pollution, cigarette smoke). The AhR detects such hydrocarbons and protects the pulmonary cells from their deleterious effects through metabolization. Indeed, the involvement of the receptor in different lung pathologies has been documented: the most telling example is COPD (Chronic Obstructive Pulmonary Disease), which is associated with exposure to cigarette smoke; the AhR counteracts the development of COPD by reducing the lung inflammation induced by the components of cigarette smoke, as well as oxidative stress. It limits the breakdown of the lung epithelium and limits bacterial infections (69). AhR KO models show that the receptor promotes the survival of lung cells (anti-apoptotic effect). However, its sustained activity or expression has been described as deleterious in other lung pathologies (cancer, see below) (70).

In the skin, AhR deficiency favors bacterial infection with a skin tissue which displays a delaminated appearance. Similarly, some AhR antagonists impair the barrier functions while FICZ improves them, reducing the local inflammation through involvement of OVO-like proteins. On the contrary, chronic AhR activation (for example by TCDD) leads to epidermal hyperplasia and sustained inflammation (71).

At these barriers, **immune regulation** is a key factor (72): as already mentioned, **inflammatory processes** maintain the integrity of epithelia or the recruitment of protective cells but in case of excessive inflammation, these processes can be deleterious. The interaction of the AhR with NF- κ B proteins has been largely documented: its interaction with RelA (p65), 1) blocks the transcriptional activity of the receptor, 2) suppresses the inhibition of NF- κ B by I κ B (73); conversely, the AhR-RelA dimer regulates the transcription of key inflammatory genes such as interleukin 6 (73–75). The expression of the AhR itself also depends on IL-6 which activates the transcriptional regulator STAT3 (76); STAT3 binds to the promoters of the AhR (77) and to one of its targets, the indoleamine-2,3-dioxygenase (IDO1) gene. According to the nature of the stimuli (persistent vs non-persistent ligands) and its duration, the outcome can largely vary. For example, in a tumorigenic context or under chronic exposure to hydrocarbons (cigarette smoke), the proinflammatory environment with high expression of IL-6 promotes its own maintenance through: 1) activation of STAT3, 2) STAT3-dependant stimulation of IDO1 and AhR expression, 3) production of KYN (by IDO1), 4) activation of the AhR (by KYN), 5) transcriptional activation of IL-6 (by the AhR) (78).

Similarly, **dendritic cells (DC)**, involved in the presentation of antigens and the differentiation of immune cells, represent a target population to AhR ligands (79)(80). The nature of these ligands could also influence the type of response triggered by DC. While most studies report an anti-inflammatory role mediated by the AhR in DC, few studies have shown that ligands such as TCDD triggers a pro-inflammatory profile (71).

Moreover, in the gut, **intestinal epithelial cells (IECs)**, **intraepithelial lymphocytes (IELs)** or **innate lymphoid cells (ILCs)** display specific functions regulated by the AhR (71). **IECs** control bacterial infection, a process disrupted by AhR deficiency. The receptor appears to favor the differentiation of stem cells into IEC and their sensitivity to a pro-inflammatory environment. **IELs** stimulated by a variety of AhR ligands, display an immunoregulatory role and can communicate with distant organs such as the Central Nervous System. Finally, the AhR controls the function of a specific subtype of **ILC**, ILC3, which limits opportunistic infections. The disruption of AhR signaling in these 3 types of cells, is suspected to play a role in the disruption of the microbiota together with the development of infectious, autoimmune, and tumorigenic diseases.

The emerging roles of the AhR in physiology and pathophysiology

Several recent studies indicate that the AhR and its ligands may regulate the development and homeostasis of several organs and tissues.

AhR KO models have shown that the receptor regulates the heart and vasculature development and functions (including blood pressure) (81, 82). Disruption of these functions impair other organs (e.g.,

eye, nervous system) but they can also result from the functional disruption of other tissues (e.g., kidney).

Indeed, the AhR regulates the development and homeostasis of **muscles** with a significant number of studies on the **heart** (cardiac hypertrophy, reduced cardiac ejection fraction).

- AhR overactivation (with TCDD) impacts the function of muscle satellite cells (MuSCs), the quiescent stem cells required for the repair of adult skeletal muscles, altering the populations of cells expressing the transcription factors PAX3 and PAX7 (83, 84). Chronic activation of the AhR (with dioxin) also alters the function of cardiomyocytes, promoting fibrosis through disruption of the WNT pathway (85)(86).

In addition, alteration of the AhR leads to **endothelial dysregulation**

- AhR deficiency elevates the levels of endothelin-1 (ET-1), a vasoconstrictive factor and lowers the expression of Vav3, a GTPase activator leading to an overactive renin-angiotensin system (87); the persistent ductus venosus (the most common deficit of the vasculature observed in AhR KO mice) is observed in the liver leading to the development of liver steatosis (88). Moreover, hyaloid arteries in the eye also persist in AhR KO mice.
- A chronic activation of the AhR by repeated exposure to polycyclic aromatic hydrocarbons (PAHs) present in combustion products (automobile exhaust gases, cigarette smoke, etc.) induces the formation of oxidized low-density lipoproteins (LDL), which promote the formation of foam cells, markers of atherosclerosis and inflammation of endothelial vascular cells (89). Moreover, modified LDL are known to activate the AhR, suggesting the existence of a regulatory loop (90). These processes could be due to the stimulation of VCAM-1 by the AhR-NF- κ B pathway, promoting macrophage chemotaxis, the absorption of oxidized lipoproteins (ox-LDL) by these macrophages and the proliferation of endothelial smooth muscle cells (91–93).

The heart and the vasculature can also be impacted by other organs: indeed, uremic toxins derive from Trp and can cause cardiac toxicity. For example, in chronic **kidney** disease (CKD), serum Trp levels decrease while metabolites of the Kyn pathway increase (94). Trp can also enter the serotonin-producing or the indole pathways: indeed, the intestinal microbiota converts Trp into indoles which, when absorbed, can serve as precursors of uremic toxins such as IS, indole-3-acetic acid (IAA) or indoxyl- β -D glucuronide (IDG), three AhR ligands (95–97). IS is a cardiovascular and renal risk factor causing oxidative stress, blocking repair processes of the vasculature, and limiting endothelial proliferation: in the kidney, through AhR activation, IS disrupts the renal glomeruli (98), affects iron metabolism via the regulation of hepcidin (99), increases the expression of MCP-1 (Monocyte Chemoattractant Protein-1) (100) contributing to the attraction of macrophages. IAA activates the AhR/NF- κ B pathway, stimulating the expression of cyclooxygenase 2 (COX2) & the production of reactive oxygen derivatives (ROS) (101).

One study shows that the AhR is activated in patients with CKD (102) and in experimental models (mice). In patients with CKD, the serum levels of IS and IAA are significantly higher and there is a correlation between serum IS levels and the AhR activity in patients with end-stage renal disease

(103); chronic activation of the AhR by IS causes an increase in TNF-alpha expression (104). AhR is also suspected to be activated in diabetic nephropathy (105), in the regulation of the renin-angiotensin system via the AhR/STAT3 pathway (106), or in urinary tract cancers (UTC) (107); in UTC, the AhR activity increases the expression of metalloproteases (MMP1-2-9) and decreases E-Cadherin suggesting the occurrence of an epithelial-mesenchymal transition (EMT)(108).

Interestingly, in AhR KO mice, an alteration of the renal architecture (hydronephrosis, tubular and uroepithelial degeneration) is observed (109). Similar phenotypes are observed in rats where AhR deficiency leads to hydronephrosis, hydroureter, secondary medullary tubular and uroepithelial degenerative changes.

Recent studies have significantly increased the number of data linking the AhR to the development of the **nervous systems** in vertebrates which could have been anticipated by the phenotypes described in *C. elegans* and *D. melanogaster*.

The AhR is expressed in the retina (110) and other parts of the **central nervous system**, as its deficiency impairs visual-processes and leads to a horizontal nystagmus due to the demyelination of the optic nerve and downregulation of myelin-associated glycoprotein expression in oligodendrocytes (111). The occurrence of a nystagmus has been subsequently diagnosed in humans bearing a AhR mutation (112, 113). The demyelination in the CNS is also observed in the **peripheral nervous system**, potentially due to an altered Wnt/ β -catenin signaling (114). More generally, AhR deficiency alters hippocampus-related memory and learning functions and the formation of functional synapses in newborns; the Wnt/ β -catenin signaling is also suspected to be involved in this process (115). The functions of the blood–brain barrier could also be altered upon AhR deficiency as the receptor regulates the expression of xenobiotic-metabolizing enzymes such as multidrug resistance protein 1 (116). As mentioned, neurodevelopmental alterations are also observed in invertebrates suggesting conservative processes in the evolution (35).

Finally, the alterations in the populations of cells in these tissues (muscle satellite cells, oligodendrocytes, ...) are also observed for blood and immune cells (T cells, B cells, NK cells, macrophages, and dendritic cells, (1)(117)) in either case of AhR deficiency or AhR overactivation: one of the most significant example is the differentiation of both Treg and Th17 cell populations, two subset of Th cell subsets. Th17 cells regulate processes counteracting bacterial infections while Treg cells mediate immunosuppression involved in peripheral tolerance. FICZ and other AhR agonists favors the occurrence of Th17 subsets and subsequently worsens in vivo autoimmune diseases including MS. However, this might be highly dependent on the environment of the tissue (primarily the presence of the pro-Th17 interleukin, IL-23), as some AhR ligands ultimately lead to the conversion of these Th17 cells into anti-inflammatory TR1 cells (71).

This regulatory effect on blood cells of the AhR, balancing different related cell types, can be extended to the **megakaryocytes** and their precursors; indeed, StemRegenin 1 (SR1), an antagonist of the AhR increases the human population of CD34⁺CD41^{low} cells, a fraction of very efficient precursors of proplatelets (118).

The AhR is clearly involved in the development and homeostasis of numerous barriers and organs without binding to xenobiotics. Any long alteration of its expression or activity impairs the balance of cell populations, leading to significant outcomes (autoimmunity, demyelination...) Moreover, at first sight, the convergence of disrupted phenotypes in models of AhR deficiency vs AhR activation, shed the light recently on the importance of the nature of the stimuli (persistent vs non-persistent). This is not the only controversial issue related to the AhR field.

The case of AhR functions in cancer

A significant number of studies have been published linking the AhR to cancer processes leading to a controversial debate on the pro-tumorigenic vs anti-tumorigenic role of the receptor (119)

Many studies have described the AhR pathway as *pro-tumorigenic*. Firstly, compared to non-invasive tissues, the AhR is often overexpressed in different cell lines of tumors such as breast, leukemia, lung, liver, stomach, head and neck cervix, ovarian cancer (120)(121, 122)(123)(124)(125)(126)(127)(128). However, only few studies have investigated the role of the AhR in promoting cancer in non-malignant cells (120) (126) (129). In human mammary benign cells, Brooks et al. noted that a high level of AhR was associated with a modified cell cycle (with a 50% increase in population doubling time in cells expressing the AhR by more than 3-fold) and EMT including increased cell migration (129). They therefore hypothesized that the AhR could induce a malignant profile in normal cell lines. Likewise, *in vivo*, only few studies evaluated the spontaneous tumor formation after AhR activation (130). Moenniks et al found striking results with 55% of chemically-induced liver tumors in mice with constitutively active AhR versus 6% in wild type mice (131). After feeding mice with 7,12-dimethylbenz[a]anthracene (DMBA) for 20 weeks, Currier et al. found that 75% initiated mammary tumors (132) associated with an increased AhR expression level (132) (133). The expression of the AhR was also correlated to the stage of the disease (normal, pre-cancerous, cancerous) (120)(134)(135). In clinical studies, high AhR levels were associated with pathological tumor stage, histological grade, lymph node involvement and even survival in different cancers such as clear cell carcinoma, urothelial cancer and hepatocellular carcinoma (125)(136)(108). More specifically, in Her2+ aggressive breast cancer, a correlation has been found between high AhR levels and Her2+ expression (137)(138).

In addition to the expression of the AhR, its localization is however of paramount importance. It is accepted, that the AhR remains cytosolic until ligand-activation and then translocates into the nucleus. However, constitutive nuclear localization of the AhR had been noted and was associated with a more negative prognosis (136).

The AhR pathway has also been associated with different pro-metastatic features such as: resistance to apoptosis, invasiveness, modified cell cycle (S- → G2/M phases), migration and proliferation. Knockdown (siRNA), inhibition (CH22319, CB7993113 and DEAB) or activation of the AhR (TCDD, indirubine, FICZ, β -naphthoflavone (β -NF), DMBA) has helped elucidate these mechanisms in breast, renal, lung, head and neck, urothelial cancer (120) (139) (136) (108) (123) (140) (141) (142) (128). An important process regulated in the AhR pathway seems to be the EMT (120). Several EMT

markers were increased in different *in vivo* and *in vitro* models following AhR activation (Slug, E-cadherine) (74) (143) (140) which also favors stemness properties. Stanford et al studied triple negative inflammatory breast cancer lines and noted the development of cancer stem like cells after over-expression of the AhR (ALDH1 high, Sox2, Snai1, Twist 1, Twist2, Tgfb1, and Vim) (123) (128).

Likewise, the importance of the role of the micro-environment in tumor progression and dissemination is increasing and some studies focused on AhR expression and significance in tumor micro-environment. High levels of AhR in tumor-infiltrating lymphocytes could be associated with pathological tumor stage, histological grade and even disease specific survival in clear cell carcinoma (136). AhR could promote a pro-inflammatory tumor environment through the secretion of IL-6 and IL-22 (144). *In vivo*, mice treated by an AhR agonist (DMBA) presented breast tumors with high levels of active nuclear AhR in tumors but also in their surrounding stromal cells (133). When introducing AhR+ mammary fibroblasts in mice, Mulero et al induced larger and more subcutaneous tumors (92% versus 25%) than in AhR- fibroblasts (145).

The AhR could also promote resistance to chemotherapy (128)(123). After AhR KO, Goode et al. found an increase in radiation-induced apoptosis and an enhanced response to paclitaxel in triple negative breast cancer, a cancer particularly difficult to treat (139). Indeed, genes involved in drug-resistance (ABCC3) were down-regulated after KO of the AhR (146). *In vivo*, over-expressing the AhR promoted invasiveness whereas knockouts decreased metastasis in mice in breast cancer (120)(139)(123)(133). Similar mechanisms were found such as cell migration, angiogenesis and invasion (145). Stanford et al even found an increased survival in mice treated with an AhR inhibitor (CB7993113) in oral squamous cell carcinoma (83% survival versus 25% at 26 days) (128).

The exact mechanism of the “pro-cancer” effect of the AhR remains unclear and several hypothesis can be drawn in addition to the EMT. Some have studied the role of hypermethylation (120) and suppression of BRCA1 transcription in breast cancer (147). The kynurenine pathway is often explored in the activation of the pro-tumor effect of the AhR pathway (148)(149)(150) (146) (151); indeed, in breast cancer, TDO produces AhR ligands derived from the kynurenine pathway (148) (149), which activate the receptor that in turn activates the expression of IL-6 in breast and head and neck cancer (150). It has also been suggested that this pathway could activate the AhR through a stromal secretion of IDO, underlying the potential role of the tumor micro-environment in this activation (74).

On the other hand, several authors have shown that the AhR could relay an **anti-tumorigenic effect**. Indeed, several reports did not associate an enhanced expression of the AhR with aggressiveness of the tumor (tumor grade) (152)(153)(154). Regarding its activity (activation with exogenous agonists such as β -NF, 3MC, TCDD, MCDF, Omeprazole, Tranilast, DIM), studies have found a decrease in tumor invasiveness, proliferation, cell cycle and migration in breast (Her2+ and triple negative) and pancreatic cancer (155)(156)(157)(158)(159)(160)(152)(161)(162). Prud'homme et al even found that over-activation of the AhR by Tranilast was more effective in reducing the number of mammospheres in breast cancer than paclitaxel or etoposide (158). Furthermore, promoting the AhR pathway could diminish stemness through a decrease of notably, ALDH, Notch1, Notch3 and β -catenin

(155)(158). Likewise, one report suggests a decrease of EMT markers following AhR overexpression (vimentine) (159). Moreover, translat favors an anti-inflammatory tumor micro-environment (inhibits the production of TGF- β , interferon- γ , IL-6, IL-10, and IL-17) (159) (163).

The AhR can relay the activity of endocrine disruptors with anti-tumor effects: in breast cancer, the AhR represses E2-dependant induction of genes (152) with a clear anti-estrogenic influence (164). After treatment of MCF-7 cells by AhR agonists, Ohtake *et al* found a decreased ERE-mediated transcription due to a direct inhibiting interaction of the AhR with ER- α and ER- β (165). Likewise, McDouglas *et al.*, suggested to reduce mammary tumor growth and also prevent uterine cancer, using the synergistic effects of an AhR agonist (6-MCDF, a furan) with tamoxifen (166).

In vivo, similar results were found with lower lymph node metastasis and visceral metastasis in mice with an enhanced AhR pathway in several cancers (prostate, breast) (167) (156) (157) (158) (159) (161). Fan *et al* found different results from those of Moenniks (163)(131): induction of liver adenomas with DEN was increased in AhR KO mice compared to wild-type mice (only found in male animals). In a clinical study, high expression of AhR in pancreatic cancer was associated with a longer disease-free survival according to Jin *et al.* (162).

A complex concept dependent on the context. To understand the discrepancies in the AhR role in cancer, several parameters must be taken in account:

First, the type of cancer needs to be considered (168). Indeed, the expression of the AhR is variable from one tissue to another (135)(162)(169)(153)(170). There is also a strong variability of AhR expression from one individual to another depending on the genetic and environmental status (171). For instance, the smoking status influenced the association between the AhR and CYP1A1, but not between the AhR and CYP1B1 in lung cancer (135).

Second, in the first long-term study on the effects of oral TCDD on mice, it was found that the oncologic outcome depended on species, sex and timing of the exposure (172). The heterogeneity of experimental data: type of cell lines, protocols, type of AhR activators or repressors or *in vivo models* used are important limitations. The presence of an exogenous or endogenous ligand is paramount: Barhoover *et al* found that in the absence of exogenous ligands, the AhR interacted with CDK4 and CCND1 and facilitated cell progression. However, treatment by TCDD, induced G1 cell cycle arrest through RB1 dephosphorylation (173). In pancreatic cancer, high basal levels of AhR were found only in malignant cells, yet exogenous activation (TCDD, 6-MCDF, DIM, 8-MCDF, 6-CHDF) decreased cell growth in a dose dependent- manner (134). Similar results were found by Wang *et al.* in ovarian cancer in the presence of an endogenous AhR ligand (2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester) (174). In breast cancer, Korzeniewski found a different action on the AhR depending on whether the ligand was endogenous or exogenous (154). Endogenous stimulation promoted centrosome amplification through cyclin E. However, in the presence of an AhR agonist (indirubine), centriole overduplication was inhibited. Endogenous ligands have, in general, pro-proliferative and tumor-promoting properties, whereas exogenously activated AhR could have anti-proliferative activities.

The nature of the activation (transient vs sustained) is also a key factor to consider as shown in melanoma (175).

Third, the model used must be extrapolated with caution to the human being (153). For instance, Narasimhan et al. found that suppression of the AhR pathway had a pro-tumorigenic effect *in vitro* (EMT, tumor migration) in triple negative breast cancer. However, AhR suppression *in vivo* decreased the formation of metastasis in a zebrafish larvae model. Moreover, treatment by AhR agonists in these fishes, also decreased metastasis formation (176). It is important to note that tumorigenesis and the metastatic cascade are complex processes that involve several signaling pathways and the same ligand can activate one pathway while inhibiting another.

In conclusion, targeting the AhR pathway could be very useful for treating cancers, notably cancers that lack therapeutic options such as triple negative cancer but with a high need to precisely characterize the functions of the receptor for each patient. Considering these findings, two main solutions have been proposed: AhR modulators and personalized medicine. The best perspective would be the development of selective AhR modulators that would have different actions depending on the tissue (177). An AhR modulator, acting similarly to tamoxifen, could be a great therapeutic advance. A personalized approach, depending on the level of AhR expression and individual response, could also be a step in using this Janus-faced AhR pathway, as a novel therapy. Therefore, the development of SAhRM (Selective AhR modulators) has been initiated in the field of cancer but now finds potential new applications in other medical fields.

Conclusion: the potential of AhR pathways as therapeutic targets

The discovery of the adaptative AhR-XME pathway during the 90s strengthened the idea that the sole function of the receptor was linked to xenobiotic metabolism. The use of KO models and omics technologies at the beginning of this century led to the first hypotheses that the AhR could regulate physiological processes and bind to an endogenous ligand. In fact, several additional signaling pathways (NF- κ B, ER, Wnt/ β -catenin signaling, c-Src, FAK, HIF-1 α), numerous ligands including xenobiotics, natural xeno-products and endogenous molecules (including ones from the microbiota) and multiple physiological functions have now been attributed to the AhR.

The outcomes linked to several regulatory pathways modulated by the AhR appear to be dependent on the mode of exposure and the persistence of the ligand (acute vs chronic activation, persistent vs non-persistent). This concept was also strengthened by the observation that AhR deficiency and chronic AhR activation could lead to similar phenotypes such as liver steatosis and/or fibrosis observed in AhR KO mice and Kyn- or TCDD-treated mice (88, 178–181). Subsequently, SAhRM are now considered to treat pathologies related to a deficiency or an overactivation of the receptor. Another option is to modulate the concentrations of the ligands with current clinical trials inhibiting the synthesis of kynurenine (IDO1 or TDO inhibitors) but with potential secondary effects (increased concentration of Trp, and secondary microbiota metabolites). The use of probiotics (*Lactobacillus reuteri*) which produce AhR ligands is also proposed to counteract pro-inflammatory processes.

Several ligands of very different nature and origin share the property of alleviating the symptoms of experimental arthritis. These ligands have obvious therapeutic contraindications (179) but tapinarof is currently in Phase II for the treatment of psoriasis and atopic dermatitis (182)(183). Other candidate molecules have been proposed: tetrandine (184), norisoboldine (185), berberine (186), simomenin (187), 3,3'-diindolylmethane (188), indole-3-carbinol (189), resveratrol (45), curcumin (190), coal tar (191). Some specific effects of these molecules have been characterized such as the blockade of Th17 differentiation by tetrandine, berberine, indole-3-carbinol, resveratrol, the formation of Treg by sinomenin, the decreased production of pro-inflammatory cytokines by 3,3'-diindolylmethane.

As a result, and despite their low oral bioavailability, these molecules constitute ligands of interest (for the development of more pharmacologically stable derivatives) to target other immune pathologies such as induced colitis (192), lupus erythematosus (193), multiple sclerosis (71), Type I diabetes (194), experimental autoimmune encephalomyelitis (195) and more recently viral infection such as ZIKA and SARS-CoV-2 (196, 197).

Legends of figures (Created with BioRender.com)

Figure 1: the AhR signaling pathways. The AhR belongs to a cytoplasmic complex composed of two Hsp90 chaperons, AIP/XAP2/ARA9, the co-chaperon p23 and additional partners including the c-Src kinase. Upon binding to a ligand, the complex dissociates leading to the potential activation of several pathways: the genomic pathway with its nuclear partner ARNT, regulating the transcription of target genes (containing in their promoters, xenobiotic response elements, XREs). Among them, xenobiotic metabolism enzymes (such as cytochromes P450) ensure the detoxicating function of the AhR metabolizing the ligands into metabolites which can be easily eliminated from the body. The dissociation of the cytoplasmic complex leads potentially to the interaction of the AhR with NF- κ B members (RelA), beta-catenin, or nuclear receptors (e.g., estrogen receptor); several outcomes are then modulated including cell proliferation, differentiation, or inflammation. Endocrine disruption can also occur. Other members of the cytoplasmic complex such as c-Src could trigger alternative pathways: activated focal adhesion kinase (FAK) or MAPK may participate in the regulation of adhesion or proliferation processes.

Figure 2: the multiple roles of the AhR at physiological barriers and for organ development and homeostasis. The AhR regulates common and specific processes in different organs and tissues. Some of them are critical barriers against chemical insults or bacterial infections (gut, skin, lung), and the nature of AhR activity depends on the type of ligand and on the timeframe of the receptor activation, which can be either sustained or transient. Immune processes including inflammation and dendritic cell function play a significant role for the development and the maintenance of these barriers or organs. AhR deficiency or chronical AhR activation can therefore trigger pathophysiological processes.

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Figure 1

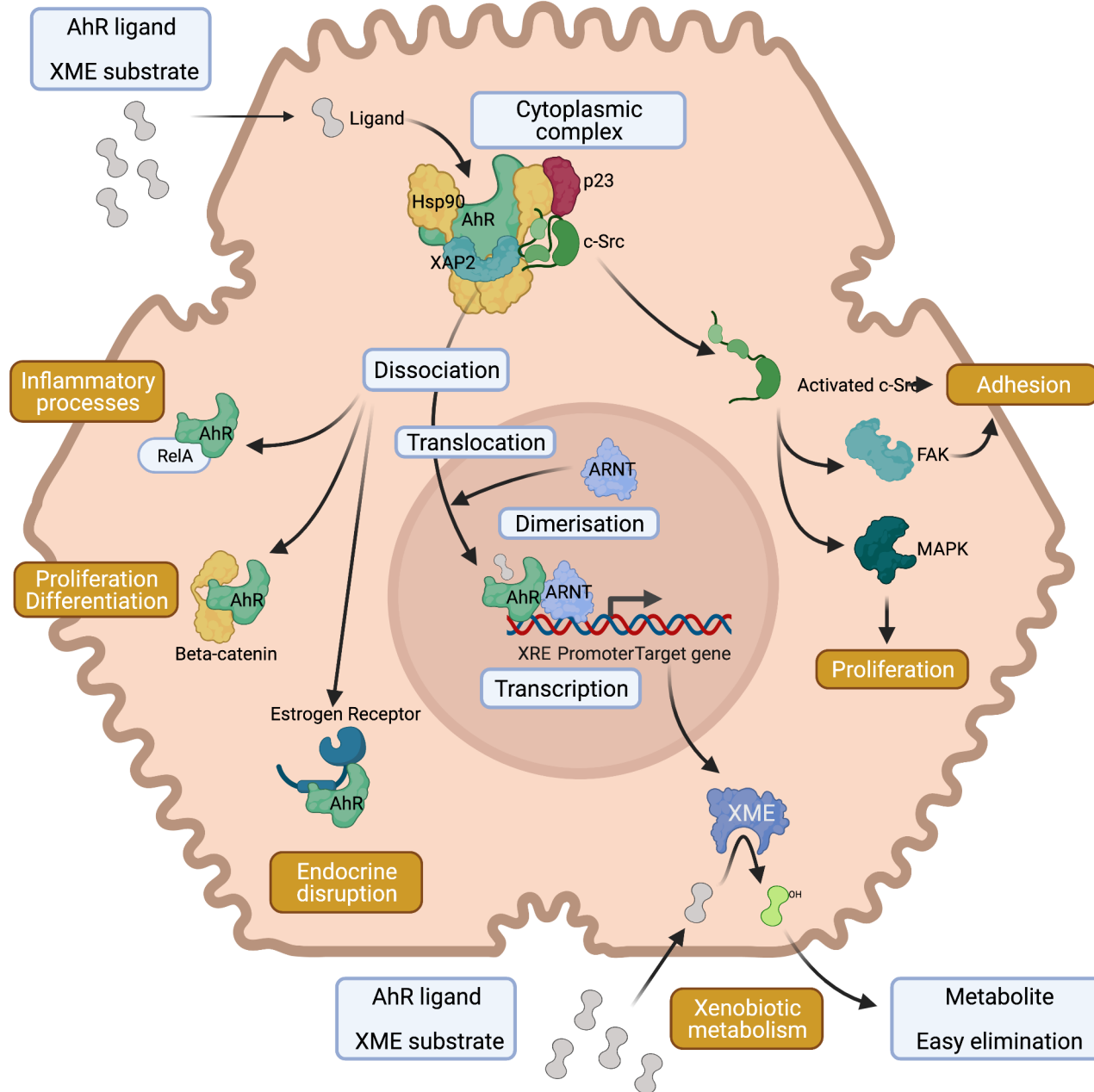


Figure 2

