

## Aryl hydrocarbon receptor as a new therapeutic target for cancer and immune disorders

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the role of the aryl hydrocarbon receptor (AhR) in cell proliferation and immune responses, and to highlight the potential for AhR to serve as a therapeutic target for cancer and immune diseases.

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### Abstract

The aryl hydrocarbon receptor (AhR) was discovered more than three decades ago, and initially was characterized as a transcription factor with a role in xenobiotic metabolism. However, based on subsequent observations that AhR remains active under physiological conditions, exhibits constitutive expression during development, and has a high degree of conservation among species, it was hypothesized that AhR is responsible for functions in addition to its role in detoxification. Correspondingly, recent studies have elucidated novel physiological roles for this ligand-dependent transcription factor that link it to several pathways associated with disease development. In this review, studies are presented that support a role for AhR in cell proliferation, apoptosis, and immune homeostasis, thereby highlighting the therapeutic potential of this receptor for cancer and immune disorders.

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**Key words:** Aryl hydrocarbon receptor; Cell proliferation; Apoptosis; Immunity; Cancer

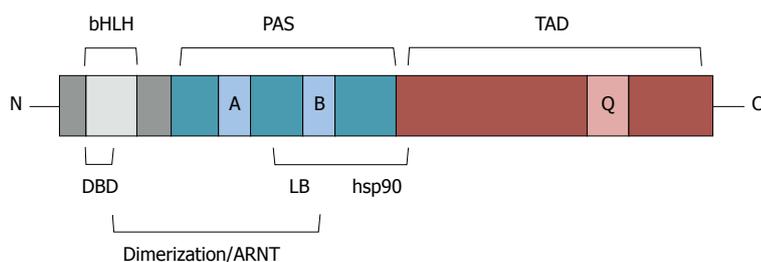
**Core tip:** The goal of the present review was to discuss

### INTRODUCTION

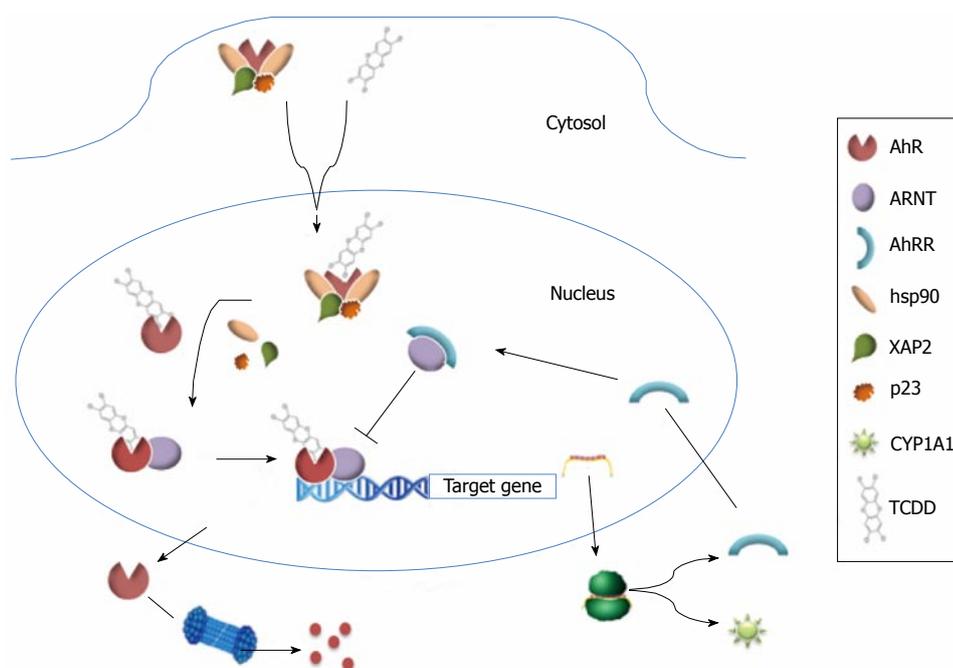
Discovery of the aryl hydrocarbon receptor (AhR) was the result of several efforts to understand the mechanism by which polycyclic aromatic hydrocarbons induce their own metabolism *via* aryl hydrocarbon hydroxylase (AHH) activity (now known to be mediated by CYP1A1). In addition, variations in the inducibility of AHH between mouse strains<sup>[1]</sup>, as well as mutations present in mouse hepatoma cells<sup>[2]</sup>, led to the discovery of the gene that encodes AhR<sup>[3]</sup>.

AhR is a member of the basic helix-loop-helix-Per-Arnt-Sim transcription factor family. The basic helix-loop-helix (bHLH) motif is located at the N-terminus of AhR, with two amphipathic  $\alpha$  helices separated by a loop. This region is required for DNA binding and for protein dimerization. The Per-Arnt-Sim (PAS) domain is located at the C-terminus of the bHLH region. It functions as a docking region for other PAS proteins such as AhR nuclear translocator (ARNT) and mediates binding of ligands and hsp90. Nuclear localization signal (NLS) and a nuclear export signal were located at the N-terminal region, while the C-terminal region of AhR contains a glutamine-rich transactivation domain recognized by several co-activators (Figure 1).

In its inactive form, AhR localizes to the cytoplasm where it can form a multiprotein complex with two



**Figure 1 Schematic representation of the functional domains of aryl hydrocarbon receptor.** bHLH: Basic helix loop helix; PAS: Per-Arnt-Sim; TAD: Transcription activation domain; Q: Glutamine-rich region; DBD: DNA binding domain; LB: Ligand binding domain; ARNT: AhR nuclear translocator.



**Figure 2 Model of the aryl hydrocarbon receptor signaling pathway.** Upon binding of a ligand to aryl hydrocarbon receptor (AhR) [such as 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin(TCDD)], the nuclear localization signal of AhR is then exposed, and AhR is translocated to the nucleus where dimerizes with AhR nuclear-translocator (ARNT) protein and dissociates from a chaperone complex composed of X-associated protein (XAP2), hsp90, and p23. Then it binds xenobiotic-responsive elements, and up regulates expression of its target genes. AhR subsequently dissociates from ARNT and translocates to the cytosol where it undergoes proteasome-mediated degradation. AhRR: AhR repressor.

molecules of hsp90, the co-chaperone protein, p23, and X-associated protein 2. However, upon binding of its ligands, the NLS of AhR is exposed and induces the translocation of AhR to the nucleus where it dimerizes with ARNT. The ligand-AhR-ARNT complex then binds dioxin-responsive elements, also known as xenobiotic-responsive elements, which contain the core sequence, 5'-GCGTG-3'. As a result, target genes of AhR are up-regulated. Since dimerization of ARNT and AhR repressor (AhRR, also a bHLH protein) is competitive, AhR is negatively regulated. In addition, AhR is subject to degradation by the ubiquitin-proteasome 26S system (Figure 2).

AhR is highly conserved from invertebrates to vertebrates, and has three forms: AhR1, AhR2, and AhRR. Phylogenetic studies suggest that AhR emerged approximately 550 million years ago<sup>[4]</sup>. In mammals, AhR1 is the form expressed, and it has been found primarily in liver and lung tissues. Although, it has also been detected in several tissues and cell types, including brain, heart, kidney, muscle, placenta, thymus, spleen, macrophage, and lymphocytes.

Initially, AhR was studied as part of an adaptive chemical response since it mediates the toxic effects of environmental contaminants such as halogenated aromatic hydrocarbons (HAHs) and polycyclic aromatic hydrocarbons (PAHs). The prototype ligand for AhR is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which has the highest affinity for AhR and is the most potent of these compounds. However, based on the high degree of conservation across species and its constitutive expression, it is hypothesized the AhR may have additional roles in the cell. Indeed, in the recent years, several studies have elucidated novel physiological roles for this transcription factor in cell development<sup>[5]</sup>, cell proliferation and apoptosis<sup>[6]</sup>, circadian rhythmicity<sup>[7]</sup>, cholesterol and glucose metabolism<sup>[8]</sup>, immune system homeostasis<sup>[9]</sup>, and more recently, in the ubiquitin-proteasome system<sup>[10,11]</sup>.

Therefore, the goal of this review was to discuss the role of AhR in cell proliferation and immune responses, and to highlight the potential for AhR to serve as a therapeutic target for cancer and immune diseases.

## ARYL HYDROCARBON RECEPTOR AND CANCER

AhR has been shown to mediate the toxic effects of HAHs and PAHs, including their carcinogenic forms. These compounds bind and activate AhR by inducing the expression of metabolizing enzymes, thereby promoting their own metabolism. In particular, PAHs such as benzo[*a*]pyrene are converted into highly mutagenic and carcinogenic metabolites by cytochrome P4501A1 and 1B1. The carcinogenic AhR dependent action of PAHs has been demonstrated using an AhR knockout mouse (AhR-null). Topical application of benzo[*a*]pyrene was found to produce skin tumors in wild-type mice, yet tumors did not develop in AhR-null mice that received the same application<sup>[12]</sup>. A clinical association between AhR and cancer has also been described as a result of accidental or occupational exposure to HAHs such as dioxins. In a follow-up study of a population accidentally exposed to dioxin, exposure to this compound increased the rates of mortality due to cancer<sup>[13,14]</sup>. Similarly, a cohort study reported that workers exposed to dioxins presented a higher risk for developing cancer<sup>[15]</sup>. Although the carcinogenicity of dioxins is AhR-dependent, these compounds are rarely metabolized, and their mechanism(s) of action remain unknown.

In the last few years, a large number of studies have indicated that AhR, in addition to its xenobiotic-metabolizing function, has important roles in mediating cell proliferation and regulating apoptosis. In particular, AhR has been identified as a potential oncogene and tumor suppressor.

### AhR as an oncogene

Overexpression of AhR has been detected in various types of human cancers, including pancreatic cancer<sup>[16]</sup>, lung carcinoma<sup>[17]</sup>, gastric cancer<sup>[17]</sup>, and prostate cancer<sup>[18]</sup>. Similar results have been observed in rodent models. Expression of a constitutively active AhR in transgenic mice was found to induce stomach tumors<sup>[19]</sup>, and to enhance the oncogenic potential of N-nitrosodiethylamine<sup>[20]</sup>. *In vitro*, overexpression of AhR in A549 cells was found to accelerate cell proliferation<sup>[21]</sup>. Activation of AhR in transformed cells in the absence of exogenous ligands has also been observed, with higher levels of AhR detected in nuclear fractions of HeLa cells<sup>[22]</sup>. However, in HaCaT cells, AhR localization appears to be influenced by cell density, with nuclear localization observed for AhR at low cell densities, and cytoplasmic localization observed when cells are confluent<sup>[23]</sup>. Taken together, these results support a role for AhR overexpression in tumor development.

Activation of AhR by exogenous ligands has also been shown to increase cell proliferation. For example, treatment of human mammary epithelial cells with benzo[*a*]pyrene increases intracellular levels of Ca<sup>2+</sup>, thereby accelerating cell proliferation<sup>[24]</sup>. The authors hypothesize that this effect may be mediated by epidermal growth factor receptor (EGFR), and the combination

of these changes promote human breast cancer. Similarly, activation of AhR by TCDD in colon cancer cells induces EGFR phosphorylation and cell proliferation, and small interfering RNA targeting AhR abolished this effect<sup>[25]</sup>. Consequently, these data suggest that AhR may promote cell proliferation *via* activation of EGFR.

AhR also stimulates cell proliferation by interacting with other transcription factors. In particular, NF- $\kappa$ B-RelA/AhR interaction transactivates *c-myc* gene promoter by binding at a novel NF- $\kappa$ B-RelA/AhR response element<sup>[26]</sup>. Induction of *c-myc* then enhances cell proliferation of mammary epithelial cells, which has the potential to affect the tumorigenic process. In contrast, others studies have shown that inactivation of AhR inhibits cell proliferation. AhR-defective mutant cells (Hepa c1c12) derived from Hepa1c17 mouse hepatoma cells exhibit a prolonged doubling time and a higher percentage of cells in the G<sub>0</sub>/G<sub>1</sub> phase compared to wild-type cells<sup>[27]</sup>. However, when AhR cDNA was introduced, the doubling time of Hepa1c12 cells was restored similar to that of wild-type cells. Consistent with these results, silencing of AhR in HepG2 and MCF-7 cells resulted in cell arrest and an increase in the percentage of cells in the G<sub>0</sub>/G<sub>1</sub> phase<sup>[28]</sup>. On the other hand, primary hepatocytes and embryonic fibroblasts obtained from an AhR-null mouse exhibit lower cell proliferation rates and increased levels of apoptosis compared to wild-type cells<sup>[29]</sup>. In both cases, higher levels of transforming growth factor (TGF) were detected in conditioned medium obtained from AhR-null cell cultures<sup>[30]</sup>. It was subsequently hypothesized that higher levels of the proliferation inhibitor TGF are due to a decrease in retinoic acid metabolism<sup>[6,31]</sup>.

While it has been demonstrated that AhR acts as a positive regulator of cell proliferation, deregulation of apoptosis may also be important. This was showed in an initiation-promotion rat model. TCDD treatment was found to enhance hepatocellular proliferation and to reduce levels of apoptosis<sup>[32]</sup>. *In vitro*, TCDD inhibits the death of HepG2 cells by an etoposide-induced mechanism<sup>[33]</sup>. Similar results were reported when MCF10A and Huh-7 cell cultures were irradiated with UVC light<sup>[34,35]</sup>. Interestingly, in both treatment-induced apoptosis models, lower levels of the well-studied tumor suppressor, p53, were detected. P53 is a protein that promotes DNA repair and/or apoptosis, and the loss of its function has observed in several human cancers. Pääjärvi *et al.*<sup>[36]</sup> have proposed a mechanism by which TCDD and PAHs decrease levels of p53, in which TCDD activates the ubiquitin ligase, Mdm2, which in turn degrades p53. More recently, we have shown that activation of AhR increases levels of Ube2l3, an ubiquitin-conjugating enzyme, thereby enhancing ubiquitination and degradation of p53 and attenuating apoptosis<sup>[11]</sup>.

### AhR as a tumor suppressor

In contrast with the above reports, AhR has also been identified as a negative regulator of cell proliferation. For

**Table 1** Immune cell types that are regulated by aryl hydrocarbon receptor

Cell type	AhR-dependent effect	Ref.
Th	Absence of AhR increases secretion of inflammatory cytokines (IFN- $\gamma$ , IL-12)	[71]
T <sub>reg</sub>	Activation of AhR by TCDD increases their proliferation	[58]
Tr1	IL-27-induces AhR activity, which in combination with c-Maf, suppresses their differentiation	[72]
B cells	TCDD enhances IgM secretion and inhibits the differentiation of plasma cells	[73]
DCs	TCDD reduces the number of splenic DCs	[74]
Macrophage	AhR-STAT1 interactions suppress the activation and differentiation of macrophage, and induces the IgA receptor Fc $\alpha$ RI. TCDD reduces CD11a expression.	[49,75] [76]

AhR: Aryl hydrocarbon receptor; Th: T helper lymphocytes; T<sub>reg</sub>: T regulatory lymphocytes; Tr1: T regulatory 1 lymphocyte; DCs: Dendritic cells; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin.

example, treatment of 5L hepatoma cells with TCDD leads to the arrest of cells in the S phase<sup>[37]</sup>. However, when AhR deficient variants were used, an inhibition of cell growth by TCDD was not observed, suggesting that this effect is mediated by AhR<sup>[38]</sup>. Similar results were reported when MCF-7 cells were treated with TCDD<sup>[39]</sup>. More recently, Laiosa *et al.*<sup>[40]</sup> observed an increase in the numbers of thymocytes in the G1 phase following TCDD treatment. Negative regulation of cell proliferation by AhR has also been observed in the absence of exogenous ligands. Overexpression of AhR was found to inhibit the growth of Jurkat T cells by arresting cells in the G1 phase and increasing levels of apoptosis<sup>[41]</sup>.

Regarding the anti-proliferative activity of AhR, it appears to be mediated by its function as a transcription factor and by its capacity to interact with other proteins. In particular, in 5L cells, activation of AhR induces the transcription and translation of the cell cycle inhibitor p27<sup>Kip1</sup><sup>[42]</sup>. A similar result was obtained in human neuronal cells, where TCDD treatment induced p27<sup>Kip1</sup> expression and led to an inhibition of cell proliferation and hypophosphorylation of retinoblastoma (pRb) protein<sup>[43]</sup>. Alternatively, when AhR directly interacts with other proteins, it can modulate several cell processes as well. Puga *et al.*<sup>[44]</sup> showed that, when AhR interacts with the tumor suppressor protein, pRb, the ability of pRb to inhibit the transcriptional activity of E2F is enhanced, thereby leading to an arrest of the cell cycle in the G<sub>1</sub> phase.

## ARYL HYDROCARBON RECEPTOR AND THE IMMUNE SYSTEM

When investigating the mechanisms that mediate cancer development, it can be difficult to separate genetic factors from immunological factors, particularly regarding the involvement of AhR which has the ability to regulate both events independently. As previously discussed, AhR has the capacity to regulate the cell cycle and induce apoptosis, while also affecting both the induction and re-

pression of carcinogenesis. During the carcinogenic process, the response of the immune system towards tumor cells is an important component, in addition to the role of the transformed cells themselves. The immune response can also vary from individual to individual. AhR has been shown to regulate many aspects of immune cell responses to tumor development<sup>[45,46]</sup>, and a list of relevant studies are provided in Table 1.

Many authors consider that AhR regulates the immune system mainly by balancing levels of Th17 and T<sub>reg</sub> cells. For example, AhR signalling influences the differentiation of T<sub>reg</sub> cells by activating the TGF- signalling pathway<sup>[47]</sup>. In this case, the presence of TGF-induces T<sub>reg</sub> cells, and in combination with the presence of IL-6 in the microenvironment, differentiation of Th17 cells is favored<sup>[48]</sup>. Another pathway involves the interaction of AhR with the signal transduction activator transcriptional factor (STAT)-1, which can modify the activation and differentiation of macrophage depending on the microenvironment of the responsive cells<sup>[49]</sup>. Consequently, differentiation of Th17/T<sub>reg</sub> cells is affected<sup>[50]</sup>. Another aspect of the immune response that is affected by AhR involves interaction between AhR and RelB, a transcription factor necessary for the differentiation and function of dendritic cells (DCs)<sup>[51]</sup>. AhR also participates in regulating NF- $\kappa$ B (reviewed in<sup>[52]</sup>), a ubiquitous transcription factor that regulates many chemical mediators of the immune system. Consequently, NF- $\kappa$ B can affect different outcomes when an immune response is elicited. There is also evidence to indicate that a regulatory loop of AhR can control cytokine production, and these cytokines can modulate the expression of some CYPs<sup>[53]</sup>, thereby affecting the outcome of an immune response.

Despite the complex interactions that exist between the immune system and AhR, some researchers have also identified AhR as an immune regulator that modulates the development of cancer as a result of AhR-independent processes. The endogenous ligand, kynurenine (kyn), which is produced from tryptophan by cancer cells, can act on AhR to facilitate the evasion of brain tumors from immune surveillance<sup>[54]</sup>. In a different, yet related, strategy, AhR is required to induce the expression of indoleamine 2,3-dioxygenase (IDO), an immunosuppressive enzyme that metabolizes tryptophan into Kyn in DCs<sup>[55]</sup>. As a result of this interaction, an immunosuppressive microenvironment is created which facilitates tumor evasion.

The ability of AhR to modulate an immune response to tumor cells mostly depends on the type of ligand that engages AhR, as well as the physiological conditions of individuals<sup>[56,57]</sup>. The duration of AhR stimulation is also a factor, and can determine the outcome of the immune response generated. This has been observed with FICZ (6-formylindolo (3, 2-b) carbazole) and TCDD ligands<sup>[58]</sup>, and also among endogenous ligands such as Lipoxin A<sub>4</sub> and bilirubin, which can lead to opposite effects in the same disease model<sup>[59,60]</sup>.

A dual role for AhR in the outcome of infection dis-

**Table 2** Degenerative diseases modified by aryl hydrocarbon receptor

Degenerative disease	AhR-dependent effect	Ref.
Experimental autoimmune encephalomyelitis	TCDD suppresses the disease by inducing T reg cells	[58]
GVHD	FICZ exacerbates the disease	
	TCDD prevents the disease by generating T reg cells	[46]
Colitis	FICZ exacerbates disease	[77]
Collagen-induced arthritis	AhR exacerbates the diseases	[78]
Autoimmune uveoretinitis	TCDD suppresses the disease	[79]
Spontaneous autoimmune diabetes	TCDD suppresses the disease	[80]
Experimental multiple sclerosis	AhR activation reduces inflammation <i>via</i> Tr1 induction	[72]
Experimental lupus	Induction of Tr1 by AhR activation stops the inflammatory process	[81]
Rheumatoid arthritis	AhR activation by TCDD exacerbates the disease	[82]

AhR: Aryl hydrocarbon receptor; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin.

eases has also been observed in several experimental models. Just the presence of AhR can control inflammation in parasitic diseases such as experimental Toxoplasmosis<sup>[61]</sup> and experimental Leishmaniasis<sup>[62]</sup>, as well as in bacterial infections such as *Citrobacter rodentium*<sup>[63]</sup> and *Streptococcus pneumoniae*<sup>[64]</sup>. In other models, activation of AhR has been shown to induce inflammation and a more rapid clearance of infection, as observed in an animal model infected with *Listeria monocytogenes*<sup>[65]</sup>. Regarding viruses, AhR also plays a key role in the outcome of the infection. Activation of AhR by TCDD was found to decrease the survival rate of animals already infected with influenza virus<sup>[66]</sup>, it increased the viral burden of human cytomegalovirus<sup>[67]</sup>, and it increased the replication rate of immunodeficiency virus type 1<sup>[68]</sup>.

With AhR able to control the balance of inflammation and immune suppression by modulating levels of Th17/Th22 subpopulations, AhR also influences the outcome of certain degenerative disease models, particularly autoimmune-based diseases. Specific immune microenvironments are also dependent on levels of TGF and IL-6, thus, the balance of Th17/T<sub>reg</sub> cells can be affected (Table 2).

## CONCLUSION

Several studies have established that AhR mediates functions in addition to xenobiotic detoxification. In this review, the ability of AhR to regulate cell proliferation and homeostasis of the immune system were described, thereby supporting the link between AhR and cancer and inflammation. In addition, the molecular mechanisms associated with, or predicted for, the actions of AhR suggest that this receptor is a potential target for the treatment of cancer and immune disorders. However, further research is needed to more completely characterize this

protein. In particular, it remains unclear what determines whether AhR will behave as an oncogene or a tumor suppressor, or as a pro-inflammatory or anti-inflammatory factor. Furthermore, endogenous ligands of AhR remain to be identified, and this will facilitate the development of novel AhR ligands, agonists, and antagonists that do not have toxic side effects. Currently, there are several drugs (approved for use by the United States FDA) that present agonist or antagonist activity towards AhR. These include omeprazole and mexiletine, which may be useful as therapeutic drugs for pathologies where AhR has been shown to have a role. Omeprazole has been found to be a potent inhibitor of migrating breast cancer cells, and this effect is AhR-dependent<sup>[69]</sup>.

Finally, it is worth noting that the transactivation domain sequence of human AhR (hAhR) and mouse AhR (mAHR) share 58% similarity, and hAhR exhibits a 10 fold lower affinity for TCDD compared with mAHR. However, the opposite result is observed for endogenous ligands such as indirubin<sup>[70]</sup>, that have higher affinity to hAhR than to mAHR. These observations are relevant for the development of pharmacological drugs that target AhR, a receptor whose relevance to human disease continues to be elucidated.

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