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Aryl Hydrocarbon Receptor: linking environment to immunity

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Abstract

Mucosal and barrier tissues are unique in that they mediate crosstalk between the host and the surrounding environment, which contains many potentially harmful factors. Therefore, it is critical that cell types present at barrier and mucosal surfaces are equipped with mechanisms to sense changes in the environment and to calibrate their responses accordingly. Aryl Hydrocarbon Receptor (AHR) is a ligand dependent transcription factor well known to generate biological responses to environmental pollutants, such as benzo{a}pyrene and halogenated dioxins. Surprisingly, in the last few years a large body of evidence has shown that AHR is also involved in maintaining homeostasis or in triggering pathology by modulating the biological responses of critical cell types at the barrier and mucosal interfaces. Here, we will review progresses in this field and discuss how targeting AHR activation may impact disease.

Keywords

Aryl Hydrocarbon Receptor; IL-22; Mucosal tissues; Innate Lymphoid Cells

1. Introduction

Organs at barrier surfaces such as lung, skin, gut, oral and genital mucosae and eyes are critical to maintain the integrity of the host. They must constantly survey for surrounding signals and carefully discriminate between harmless and harmful events. This discrimination is vital to allow the host to grow, extract nutrients from the environment, control and take advantage of symbiotic organisms and, at the same time, mount proper defenses to the challenge of threatening occurrences.

The Pern-Arnt-Sim (PAS) superfamily of transcription factors is an ancient and highly conserved pathway that regulates communications between the host and the environment and promotes “environmental adaptation” [1, 2]. The PAS superfamily contains proteins that are involved in chemical sensing (AHR), in regulation of circadian rhythm due to light-dark

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cycles (BMAL1 and BMAL2) and in the detection of variations in oxygen tension or redox potentials (HIF-1α, HIF-2α and HIF-3α). PAS superfamily members, such as the Drosophila SIM, a regulator of midline cell lineage [3], are also involved in organ development suggesting that developmental signals may be perceived similarly to environmental stresses.

2. AHR and its ligands

AHR is one of the initial PAS transcription factors identified [4]. AHR is normally present in the cytoplasm of cells bound to chaperones, such as Hsp90, which maintain it in an inactive state. Upon ligand binding, chaperones are released and AHR translocates to the nucleus. Here, it dimerizes with its homolog, AHR-Nuclear Translocator (AHRNT) and the resulting heterodimer binds to Dioxin Responsive Elements (DRE) on promoters to drive the transcription of target genes [5]. These target genes include Xenobiotic Metabolizing Enzymes (XME); among them, and most prominently, the microsomal cytochrome P450-dependent monooxygenases CYP1A1 and CYP1A2 [2]. These enzymes are induced in the attempt to metabolize and inactivate toxic pollutants that bind AHR, such as the polyphenols benzo{a}pyrene, 3-methylcolantrene and the infamous 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which in 1976 was released following an industrial accident in the small city of Seveso, Italy, and led to many cases of chloracne [6].

While pollutants are well-established ligands of AHR, the precise identity of other physiological exogenous and endogenous ligands is still matter of debate [7]. Dietary ligands of AHR have been reported. Among them is the glucobrassicin derivative Indole-3-Carbinol (IC3), a chemical found in high concentrations in vegetables of the Brassica genus, including broccoli, cauliflower, Brussel sprouts and cabbages [8]. IC3 in the acidic environment of the stomach undergo dimerization and generates diindolylmethane (DIM) as well as other metabolites, such as indolylcarbazole (ICZ), that activate AHR. Other described dietary ligands of AHR are natural flavonoids present in fruits and vegetables, such as galangin, genystein, chrysin, apigenin and quercetin [9]. Resveratrol, which is abundant in red wine, has also been reported to bind AHR [7]. Ginsenoides extracted from ginseng, a perennial plant frequently utilized by traditional Chinese medicine, can also bind and activate AHR [10]. However, it is still unclear which, if any, dietary or naturally occurring ligands of AHR have direct agonistic activity or whether these compounds compete with environmental polyphenols, thus mediating an antagonist effect.

Known endogenous ligands of AHR are derivatives of the essential amino acid tryptophan. UV light-mediated degradation of tryptophan generates 6-formylindolo{3,2-b}carbazole (FICZ), which is a potent activator of AHR [11]. L-kynurenine, a catabolic metabolite of tryptophan formed along the pathway to generate niacin, is also a high-affinity AHR ligand [12]. Kynurenine can be generated by the enzyme Trypthophan2,3-dioxigenase (TDO) or the enzymes Indoleamine2,3-dyoxigenase (IDO1 and IDO2), and these enzymes have different roles in different biological scenarios, as discussed later.

Interestingly, bacteria, including commensals such as *B. subtilis*, also produce tryptophan and can regulate tryptophan synthesis by sensing tryptophan concentrations due to dietary

intake [13]. Bacteria and fungi can also metabolize tryptophan into ligands that can activate AHR. *Malassezia furfur*, a fungus common causative agent of pytiriasis versicolor of the skin, secretes several ligands including malassezin, ICZ and FICZ that engage AHR [14]. Several species of lactobacilli, including *Lactobacillus bulgaricus* [15] and *Lactobacillus reuteri* [16] produce AHR ligands, such as indole-3-aldehyde (IAid), and modulate mucosal immune response. Importantly, pathogens such as *Mycobacterium tuberculosis* (*Mtb*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) produce pigmented virulence factors that activate AHR [17]. Specifically, phenazines from *P. aeruginosa* and naphthoquinone phthiocol (Pht) from *Mtb* bind AHR and induce the detoxification enzymes CYP1A1 and CYP1B1 that inactivate these compounds, while instructing an innate immune defense pathway that counteracts and contains infection in hematopoietic and epithelial cells [17]. These findings highlight a new role for AHR as an unexpected pattern recognition receptor (PRR). As phenazynes and naphtoquinones have a broad distribution among prokaryotes present at mucosal barriers and in the environment, recognition of these products by AHR, once again, emphasizes that AHR represents a central node for chemical communication between the environment and the host.

3. AHR in immune responses: cellular targets and cell type specific effects

AHR is expressed by many cell types in the body and therefore exerts pleiotropic effects by integrating with other signaling pathways, such as sex hormones receptors and the Wnt-β catenin network [18]. For instance, AHR in keratinocytes, but not hematopoietic cells, curbs inflammation in a model of imiquimod-induced psoriasis [19]. The initial generation of AHR null mice by two distinct groups also highlighted a role for AHR in normal development. AHR deficient mice frequently died after birth or displayed a slower growth rate in the first few weeks of life [20, 21]. In addition, they developed hepatic anomalies, such as bile duct fibrosis, transient hepatic steatosis and abnormal retinoic acid metabolism in the liver [20-22]. One group also reported reduced spleen and lymph node cellularity [20], which was not noticed by the other group that generated AHR null mice [21]. AHR-deficient animals were resistant to TCDD, but their immune responses were not examined in detail. Emerging findings in the last few years have indicated that AHR signaling shapes a number of immune responses from different cell types and this has profound influences on host-commensal and host-pathogen interactions. AHR plays an especially critical role at mucosal interfaces where the host deals with other living entities and environmental agents, which possess the ability to engage AHR.

4. AHR and Dendritic Cells

It was originally shown that the AHR agonist VAF347 promotes *in vivo* allograft tolerance in a model of islet transplantation via a DC-mediated mechanism [23]. The same compound inhibited the production of inflammatory cytokines and the upregulation of costimulatory molecules on human monocyte-derived DCs stimulated by anti-CD40 and TNF-α [24] and reduced differentiation of $CD34^+$ hematopoietic precursor cells to DCs and Langerhans cells (LCs) *in vitro* [25]. Accordingly, a small molecule purine derivative that acts as AHR antagonist, StemRegenin 1, greatly increased expansion of human $CD34^+$ cells and enhanced their engraft into immune deficient mice *in vivo* [26]. StemRegenin 1 also

supported differentiation of $CD34^+$ precursors to myeloid and plasmacytoid DCs [27, 28]. AHR deficient LCs exhibited impaired maturation *in vivo*, resulting in diminished contact hypersensitivity [29]. In addition, AHR activation in DCs induced expression of the enzymes IDO1 and IDO2 [30] and consequent production of the tryptophan degradation product kynurenine [31], which skews T cell differentiation from Th17 to $Foxp3^+$Treg, promoting immune tolerance. Similarly, the natural AHR ligand 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), originally purified from lung [32], directly acted on DCs inducing tolerogenic properties that promoted Treg differentiation in a retinoic acid-dependent process and, ultimately, suppressed autoimmunity in EAE, a mouse model of human Multiple Sclerosis [33]. TLR agonists, such as LPS, upregulate AHR expression in DCs and other myeloid cells via a RelA/p50-mediated activation of the AHR promoter [34]. Moreover, AHR is involved in LPS response [35] and LPS tolerance [36]. The primary response to LPS is mitigated by activation of AHR upon generation of the endogenous ligand kynurenine by TDO. Accordingly, AHR and TDO2 deficient mice are highly susceptible to primary LPS challenge. However, LPS tolerance induction upon secondary challenge requires the combined action of AHR, IDO1 and TGFβ. In this context, AHR activation results in Src-mediated phosphorylation of IDO1 followed by TGFβ production by IDO1 competent DCs, a sequence of events that eventually prevents systemic inflammation and immunopathology [36]. Importantly, kynurenine is a very abundant AHR ligand generated by tumor cells via the TDO pathway [37]. In tumors kinurenyne promotes clonogenic tumor cell survival but also acts on infiltrating immune cells to prevent immune rejection. Moreover, TDO blockade restores immune–mediated tumor rejection [38], indicating that targeting the TDO pathway may be an effective strategy for cancer treatment.

Altogether, these findings suggest that AHR and its ligands act in a highly integrated “disease tolerance system” that may prevent autoimmunity and excessive immune responses to pathogens, but may be maliciously hijacked by tumor cells to their own advantage.

5. AHR and T cells

It was long known that dioxin exerts an immunosuppressive effects and a single treatment of laboratory mice with low amount of TCDD causes profound defects in humoral and cellular responses. However, the exact mechanisms that led to this immunosuppression were poorly understood. In 2005 Funatake and colleagues showed that TCDD induces $CD4^+$ T cells with regulatory potential, which effectively suppress an acute graft-versus-host response [39]. In spite of this, it was only in 2008 that AHR finally took a central stage in T cell biology and T cell helper differentiation. Two ground-breaking studies showed that AHR plays a critical role in Th17 biology and controls IL-22 production by Th17 T cells [40, 41], suggesting that environmental clues can modulate autoimmune diseases and immune pathology. Interestingly, these studies pointed out that AHR ligands of different origin and, most likely, different affinities differentially impact the outcome of Th17-mediated autoimmune diseases. While TCDD and ITE are potent inducers of Treg differentiation and suppress EAE [41], FICZ enhances Th17 differentiation and increases severity of disease [40, 41]. Moreover, it became evident that the presence of AHR ligands in culture media strongly affects Th17 differentiation and IL-22 production *in vitro* [42, 43]. AHR signaling is particularly relevant for IL-22 production when TGFβ is present [44]. Notch signaling in

$CD4^+$ T cells also induces AHR ligands that boost IL-22 expression [45]. Paradoxically, however, *in vivo* AHR-deficient mice have exaggerated responses to Segmented Filamentous Bacteria (SFB) [46, 47], which selectively drive an antigen-specific Th17 response in small intestinal lamina propria (LP) [48-50].

In addition to having a central role in Th17 differentiation, AHR is also critical for generation of mouse Tr1 T cells, which suppress autoimmunity by secreting IL-10 [51, 52]. AHR is induced by IL-27 and binds to the transcription factor c-Maf. AHR and c-Maf cooperatively transactivate the IL-10 and IL-21 promoters [51]. Similarly, AHR is necessary for generation of human Tr1 T cells [53]. On human $CD4^+$ T cells AHR ligands promote induction of $Foxp3^-$ Tr1-like cells that suppress via granzyme B and secrete IL-10. In addition, in the presence of TGFβ, AHR ligands induce Foxp3 Treg that suppress via the ectonucleoside triphosphate diphosphohydrolase CD39, which hydrolyzes ATP to AMP. Mechanistically, AHR ligands and TGFβ induce SMAD1, which binds to Foxp3 enhancer and promotes Foxp3 expression. AHR ligands and TGFβ also induce expression of Aiolos [54], which binds to Foxp3 to silence IL-2 expression [53]. AHR is further involved in Th17 to Tr1 trans-differentiation, as AHR agonists promote this process [55]. Moreover, AHR controls the metabolism of Tr1 cells at late stages, when Hif-1α is not longer expressed [56].

In addition to Th17 and Tr1 cells, AHR has also a critical role in the generation of IL-6-dependent Th22 cells, which produce IL-22 and mediate protection from entheropathogenic bacteria [57, 58].

Beyond CD4 T cells, AHR modulates antigen specific CD8 T cell responses. During influenza virus infection, AHR deficiency impacts the primary CD8 T cell response in a cell-extrinsic manner [59]. In the absence of AHR, antigen-specific CD8 T cells display altered DNA methylation patterns and a transcriptional profile reminiscent of exhausted CD8 T cells [60]. Similarly, AHR controls retention and/or survival of tissue resident memory CD8 T cells in the skin [61].

AHR is central to γδT cell biology, as well. Innate-like γδ T cells that produce IL-17 [62, 63] express AHR, and AHR is key for IL-22 production by these cells [64]. AHR signaling is crucially required to maintain skin-resident $V\gamma3^+$ γδ T cells, also known as Dendritic Epidermal γδ T cells (DECT), which derive from thymic precursors that migrate to the skin early on during life [65, 66]. Moreover, AHR ligands present in the diet are necessary for survival and maintenance of intraepithelial lymphocytes in small intestinal LP, including both $V\gamma5^+$ γδ T cells and $CD8\alpha\alpha^+$ $TCR\alpha\beta^+$ cells [65].

Altogether these findings corroborate the idea that AHR is uniquely positioned to control the function of many T cell subsets that constantly deal with environmental triggers at mucosal sites and that may generate pathological responses when inappropriately instructed.

6. AHR and Innate Lymphoid Cells

Innate lymphoid Cells (ILCs) are an emerging family of lymphocytes that fulfill the definition of “cytokine-responding by cytokine-producing” lymphocytes [67-71]. ILCs are preferentially distributed at mucosal sites, where they can sense changes in the surrounding

microenvironment primarily through cytokine receptors signaling. ILCs produce signature cytokines that mirror adaptive Th1, Th2 and Th17/Th22 Thelper cells. ILC3s, which are the innate counterpart of Th17/Th22 cells, express high levels of AHR and are exquisitely sensitive to AHR signaling. AHR is not only required for IL-22 production by ILC3s, but is necessary for their development and/or maintenance [72-74]. AHR deficient mice have highly decreased numbers of ILC3s in small intestine LP and in Peyer's patches (PP) and rapidly succumb to *C. rodentium* infection. In addition, AHR-null mice lack “postnatally imprinted” cryptopatches (CPs) and isolated lymphoid follicles (ILFs) while “prenatally imprinted” PP are conserved. Mechanistically, AHR can promote expression of Notch, which is also required for NKp46^{+} ILC3 development [72], or can stabilize c-kit expression, as the c-kit promoter contains XRE binding sites [73]. Lack of AHR in ILC3s results in reduced innate-driven IL-22 production that may favor expansion of SFB leading to exaggerated Th17 responses that cause colitis [46, 47]. In human, AHR antagonism promotes differentiation of IL-22-producing ILC3s to IFN-γ-producing NK cells [75], further implying that AHR plays a key role in ILC3 biology and modulation of their plasticity [76].

Conceivably, AHR ligands present in the diet may contribute to ongoing AHR signaling and regulate the size of small intestinal LP ILC3s and other IELs [65, 73]. However and alternatively, endogenous AHR ligands, such as kynurenine and other tryptophan derivatives, may be more important than diet-derived ligands or may compete with them. On the contrary, AHR ligands generated by bacteria seem to be dispensable, as ILC3s are conserved in germ free mice [72], and germ free mice have normal CPs, despite reduced size of ILFs [77]. Nevertheless, under dietary conditions that provide unrestricted tryptophan availability, microbial-derived AHR ligands may become important to boost ILC3 responses and restrict the colonization and expansion of certain pathogens, such as *C. albicans* [16].

In addition to regulating ILC3 function, some reports suggest that AHR signaling is relevant to conventional NK cells function, the prototype of ILC1 cells. AHR ligands promote NK cytotoxic activity and IFNγ production; thus AHR deficient mice have defective NK cell-mediated antitumor activity i*n vivo* [78]. Moreover, AHR in conventional NK cells is important to trigger IL-10 production during infection with *Toxoplasma gondii (T. gondii).* IL-12 and AHR are required for optimal IL-10 production, with IL-12 increasing AHR expression. AHR null mice have defective NK cell-derived IL-10 production during *T. gondii* infection and are more resistant to this pathogen, as IFNγ responses in the absence of IL-10 promote clearance of *T. gondii* [79].

Altogether these findings draw attention to the central role played by AHR in instructing ILC responses at mucosal interfaces. Moreover, they indicate that AHR signaling has a broad impact on several innate lymphocytes, as it modulates some aspects of conventional NK cells, which affect their responses to tumors or pathogens.

7. Concluding remarks

Despite the fact that AHR was cloned over 20 years ago there is still much that we need to learn about its function in health and diseases. Work done in the last years clearly indicates

that AHR has a fundamental role in immune responses that goes well beyond simple recognition of pollutants. However, the crystal structure of AHR remains to be solved, and the interplay between environmental, dietary, bacterial-derived and endogenous ligands is still poorly understood.

Although multiple lines of evidence indicate that the AHR pathway could be an effective targeting strategy for diseases such as multiple sclerosis, inflammatory bowel diseases, psoriasis, cancer and stem cell transplantation, caution is necessary. Most likely, AHR activation must be tightly controlled in order to obtain the desired effects. For example, AHR-mediated IL-22 production from adaptive and innate cells normally drives protection from bacterial infections and wound healing. However, sustained and dysregulated IL-22 production becomes pathogenic and induce colitis and cancer [80, 81]. Similar exquisite regulation is likely important in many biological processes controlled by AHR.

Overall, the AHR pathway seems to integrate signals from different sources to ensure that host responses carefully reflect and adjust to continuous changes in the environment, a process that is integral to adaptation.

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Highlights

- AHR links environmental clues to host immune responses.
- AHR is activated by exogenous and endogenous ligands; their interplay is still poorly understood.
- Different AHR ligands may differentially influence autoimmune diseases.
- AHR signaling affects multiple immune cell types, including dendritic cells, T cells and Innate Lymphoid Cells.

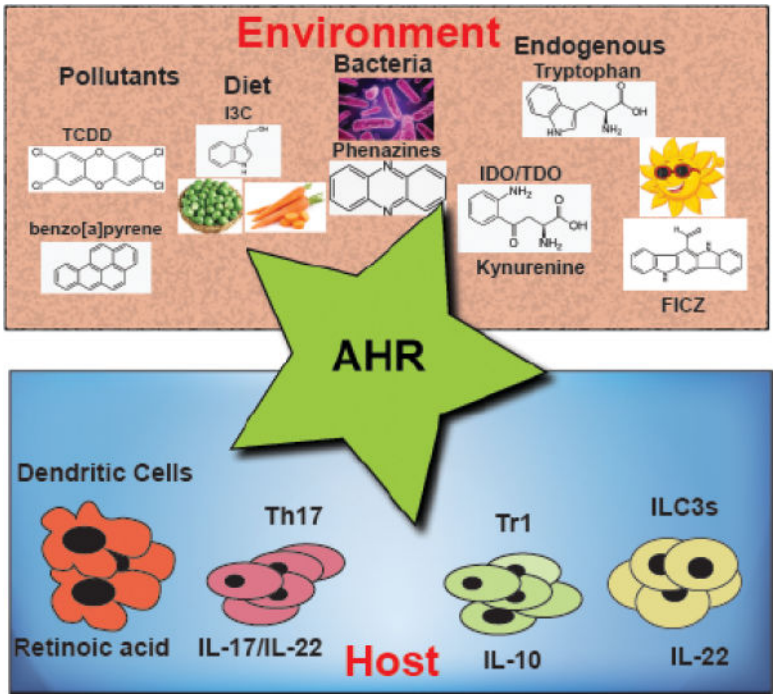

Fig. 1.

AHR integrates responses from environmental and endogenous ligands to mount appropriate immune responses at barrier organs.