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Review article

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The aryl hydrocarbon receptor: a rehabilitated target for therapeutic immune modulation

Carolina M. Polonio[1], Kimberly A. McHale[2], David H. Sherr[3], David Rubenstein[2] & Francisco J. Quintana[1,4,5]

Abstract

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor originally identified as the target mediating the toxic effects of environmental pollutants including polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs) and dioxins. For years, AHR activation was actively avoided during drug development. However, the AHR was later identified as an important physiological regulator of the immune response. These findings triggered a paradigm shift that resulted in identification of the AHR as a regulator of both innate and adaptive immunity and outlined a pathway for its modulation by the diet, commensal flora and metabolism in the context of autoimmunity, cancer and infection. Moreover, the AHR was revealed as a candidate target for the therapeutic modulation of the immune response. Indeed, the first AHR-activating drug (tapinarof) was recently approved for the treatment of psoriasis. Clinical trials are underway to evaluate the effects of tapinarof and other AHR-targeting therapeutics in inflammatory diseases, cancer and infections. This Review outlines the molecular mechanism of AHR action, and describes how it regulates the immune response. We also discuss links to disease and AHR-targeting therapeutics that have been tested in past and ongoing clinical trials.

Sections

[1]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [2]Dermavant Sciences Inc., Morrisville, NC, USA. [3]Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA. [4]Broad Institute of MIT and Harvard, Cambridge, MA, USA. [5]Gene Lay Institute of Immunology and Inflammation, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. e-mail: fquintana@rics.bwh.harvard.edu

Introduction

The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor initially recognized as the mediator of the toxic effects of some environmental pollutants. In 1976, Poland and Glover identified a cytosolic protein that bound specifically to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a highly toxic dioxin[1,2]. They named this protein the aromatic hydrocarbon (Ah) receptor, later identified as the AHR. Further studies revealed that the AHR is a ligand-dependent transcription factor containing a basic helix–loop–helix (bHLH) and a Per–Arnt–Sim (PAS) domain[3–8]. Upon ligand binding, the AHR translocates into the nucleus, where it forms a complex with the AHR nuclear translocator (ARNT; also known as HIF-1β)[9]. This complex then binds to specific DNA sequences known as xenobiotic response elements (XREs) or dioxin response elements (DREs) to regulate the expression of target genes[10].

Historically, AHR agonists were often excluded or discarded during drug development campaigns. This avoidance stemmed from concerns about potential adverse effects and toxicity associated with AHR activation, including developmental abnormalities[2,11,12] and increased cancer risk[13–16]. Activation of the AHR by dioxins is known to be teratogenic, causing developmental abnormalities in fetuses[2]. Exposure to dioxins during critical periods of embryonic development can lead to structural malformations in organs and tissues[12]. Indeed, the AHR contributes to the palate and kidney malformations in mouse embryos that are induced by TCDD[11]. Moreover, prolonged AHR activation by dioxins was also found to promote the development of hepatocellular carcinoma[13] and gastric tumours[14]. In addition, decreased expression of the AHR repressor (AHRR) is detected in human tumours, leading to its proposed role as a tumour suppressor[16]. Conversely, the tumorigenic potential of transformed mammary gland primary fibroblasts is reduced by AHR deficiency[15]. These and other findings raised concerns about the safety of drugs that activate the AHR, particularly in pregnant individuals or those of reproductive age. Thus, drug developers have historically been wary of compounds that could trigger sustained AHR activation, as they might pose long-term health risks for patients.

It was later found that the AHR can also be activated by agonists generated through multiple metabolic pathways and by external sources such as the diet or commensal microorganisms[17–22] (Table 1). The metabolism of tryptophan (Trp) encompasses several biochemical pathways, resulting in the production of multiple AHR agonists. For example, the kynurenine (Kyn) pathway is a major source of AHR agonists, converting Trp into Kyn and other AHR agonists. The conversion of Trp into Kyn involves the enzymes indoleamine 2,3-dioxygenase (IDO1) and tryptophan 2,3-dioxygenase (TDO). However, Trp can also be converted into serotonin and related metabolites bearing AHR agonist activity independently of IDO1 and TDO. Moreover, the microbial metabolism of dietary Trp also produces several AHR agonists, such as tryptamine (TA) and indole-3-acetic acid (IAA).

AHR activation results in the induction of specific transcriptional, epigenetic and metabolic responses with important downstream biologic effects[23,24]. In 2008, it was reported that activation of the AHR by TCDD resulted in the expansion of the functional regulatory T cell (T_{reg} cell) compartment, whereas AHR activation by the Trp-derived agonist 6-formylindolo[3,2-b]carbazole (FICZ) enhanced T helper 17 cell (T_H17 cell)-driven pathogenic responses in the murine experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS)[25,26]. These findings brought attention to the role of the AHR in immune regulation. Most importantly, these studies have paved the way for the development of AHR agonists as potential therapeutic agents for the management of several diseases. For example, 3,5-dihydroxy-4-isopropylstilbene (tapinarof; Dermavant Sciences) was approved for the topical treatment of adult plaque psoriasis and is the first and only therapeutic agent specifically targeting they AHR so far approved by the US Food and Drug Administration (FDA)[27].

This Review describes the mechanisms of AHR-regulated transcription and signal transduction pathways and the capacity of the AHR for modulation of immune responses. We then discuss AHR-targeting strategies for the treatment of inflammation, cancer and infectious diseases, including describing ongoing and historical clinical programmes.

AHR signal transduction pathways

Structure of the AHR protein complex

As a bHLH–PAS transcription factor[28], the AHR contains a bHLH domain at the amino terminus, which is essential for DNA binding, followed by two PAS domains, PAS-A and PAS-B, and a transactivation domain (TAD) at the carboxy terminus[29]. The bHLH domain mediates AHR binding to specific DNA motifs to control the transcriptional activity of target genes[30]; it also facilitates dimerization with ARNT[31]. PAS-A participates in the stabilization of the AHR–ARNT heterodimer[32]. PAS-B harbours a ligand-binding pocket where agonists bind and activate the AHR by inducing a conformational change that exposes a nuclear localization signal, promoting translocation of the AHR into the nucleus[4,33–35]. Once bound to DNA, the C-terminal TAD of AHR interacts with transcriptional regulators and coactivators to activate the expression of target genes[36]. The hinge region between the PAS-A and PAS-B domains is flexible and has a crucial role in ligand-induced conformational changes[37].

Structural studies, including X-ray crystallography and cryo electron microscopy, have been instrumental in advancing our understanding of the molecular mechanisms that regulate AHR activation[38–40]. In its inactive state, the AHR is part of a cytoplasmic protein complex that maintains AHR in a conformation with strong binding affinity for its ligands. This protein complex includes a dimer of the chaperone heat shock protein 90 (HSP90)[41,42], the co-chaperone p23 (refs. 43,44), AHR-interacting protein (AIP; also referred to as XAP2)[45,46] and the c-Src protein kinase[47] (Fig. 1a). One HSP90 molecule binds to the PAS regions of the AHR and the second molecule interacts with the bHLH and PAS domains[48,49], preserving the structural integrity of the inactive AHR[30]. AIP further enhances the stability of the AHR–chaperone complex by directly interacting with both HSP90 and the AHR[45,50]. AIP also promotes the cytoplasmic localization of the AHR by blocking its interaction with the nuclear transport receptor importin-β[51–53]. In addition, co-chaperone p23 ensures AHR cytoplasmic localization and prevents AHR ubiquitination and degradation[54,55]. Finally, the c-Src protein kinase is associated with the cytosolic AHR complex[47,56] and exerts an important role in AHR activation[57].

The rational design of therapeutic small molecules that activate or inhibit the AHR requires a detailed structural understanding of its interactions with ligands[19,37,58]. For example, characterizing the binding modes of endogenous AHR agonists provides a template for designing ligands with desired pharmacological properties[59], such as AHR modulators that selectively target specific biological functions[60]. Cryo electron microscopy structures of AHR–HSP90–XAP2 cytosolic complexes bound to the endogenous AHR agonist indirubin[40] revealed a large ligand-binding cavity that enables interaction with ligands of different sizes. These studies defined a preferential interaction of the AHR with planar compounds, as well as the potential for ligands to differentially interact with residues in the binding pocket resulting in conformational changes that selectively affect the interaction of the

Table 1 | Aryl hydrocarbon receptor (AHR) ligands

Ligand	Origin
Dioxins and dioxin-like	
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	Environmental pollutants
2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)	Environmental pollutants
3-Methylcholanthrene (3-MC)	Environmental pollutants
Benzo[b]fluoranthene	Environmental pollutants
Polycyclic aromatic hydrocarbons (PAHs)	Tobacco smoke and environmental pollutants
Naphthalene	Tobacco smoke and industrial emissions
Polychlorinated biphenyls (PCBs)	Industrial chemicals
Hexachlorobenzene (HCB)	Fungicide and industrial chemical
β-Naphthoflavone (BNF)	Synthetic compound
Tryptophan (Trp) metabolites	
Kynurenine (Kyn)	Host metabolism
Kynurenic acid (KA)	Host metabolism
Trace-extended aromatic condensation products (TEACOPs)	Host metabolism
Indole-3-pyruvate (I3P)	Host metabolism
Indole-3-pyruvic acid (I3PA)	Host metabolism
6-Formylindolo[3,2-b]carbazole (FICZ)	Photo-oxidation
Indole-3-acetic acid (IAA)	Microbiota metabolism
Indole-3-aldehyde (I3A)	Microbiota metabolism
Indole-3-acetaldehyde (IAAId)	Microbiota metabolism
Tryptamine (TA)	Microbiota metabolism
Indoxyl-3-sulfate (I3S)	Microbiota metabolism and host metabolite
Indole metabolites	
Indole metabolites	Dietary metabolite
Indolo[3,3-b]carbazole	Dietary metabolite
2-(Indol-3-ylmethyl)-3,30-diindolylmethane (Ltr-1)	Dietary metabolite
3,30-Diindolylmethane (DIM)	Dietary metabolite
2-(1′*H*-indole-30-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE)	Host metabolism
Dietary	
Quercetin (flavonoid)	Fruits, vegetables and plants
Kaempferol (flavonoid)	Fruits, vegetables and plants
Sulfophane	Cruciferous vegetables
Indole-3-carbinol (I3C)	Cruciferous vegetables
5,11-Diihydroindolo-[3,2-b]carbazole (ICZ)	Cruciferous vegetables
3,3′-Diindolymethane (DIM)	Cruciferous vegetables
Docosahexaenoic acid (DHA)	ω-3 fatty acids derived from fatty fish
Eicosapentaenoic acid (EPA)	ω-3 fatty acids derived from fatty fish
3,5,4′-Trihydroxystilbene (resveratrol)	Fruits, vegetables and plants
Inulin	Dietary fibres
Others	
Bilirubin	Haem-derived metabolism
Biliverdin	Haem-derived metabolism
Indigorubin	Phytochemical
Indigo	Phytochemical
Lipoxin4A	Arachidonic acid metabolites
Prostaglandin G_2 (PGG_2)	Arachidonic acid metabolites
Prostaglandin E_2 (PGE_2)	Arachidonic acid metabolites
Leukotriene B_4 (LTB_4)	Arachidonic acid metabolites
Hydroxyeicosatrienoic acid (12*R*-HETE)	Arachidonic acid metabolites

AHR with individual binding partners. These observations provide important structural insights into the reported ligand-dependent biological effects of AHR activation, and should assist drug developers in refining structure–activity relationships and optimizing drug candidates by using structure-based drug design and virtual screening[61,62]. Based on the structural work of AHR bound to its ligands, the rational design of selective AHR modulators (SAHRMs) is a promising approach to target specific AHR functions while minimizing off-target effects[60]. In this context, although structural information is available on specific AHR domains, an important limitation is the lack of high-quality structural data on the full-length AHR protein.

AHR ligands

AHR agonists include a diverse range of exogenous and endogenous molecules (Table 1). Exogenous ligands primarily consist of environmental pollutants such as dioxins, which are often products of industrial processes and combustion. Endogenous ligands include several metabolic byproducts and natural compounds, such as Trp-derived and microbial metabolites. In this context, it is important to consider pro-ligands — precursor compounds with low affinity for AHR or no agonistic activity, which are converted into AHR agonists in vivo[63]. A well-established example is indole-3-carbinol (I3C), a compound found in cruciferous vegetables. I3C is not itself an AHR ligand, but under acidic conditions in the stomach it is converted into bioactive derivatives, including 3,3′-diindolylmethane (DIM) and 5,11-dihydroindolo-[3,2-b]carbazole (ICZ), which bind to and activate AHR[64–67]. Similarly, the Trp metabolite Kyn is the source of trace-extended aromatic condensation products (TEACOPs), which are highly potent AHR agonists[68]. In addition, several AHR ligands are generated as a result of the action of deaminases on aromatic amino acids. For instance, the enzyme aspartate aminotransferase converts L-Trp into indole-3-pyruvate (I3P), which in aqueous solution spontaneously forms multiple AHR agonists[69]. Moreover, the D-amino acid oxidase (DAAO) enzyme also generates AHR agonists by converting D-Trp into indole-3-pyruvic acid (I3PA), highlighting that multiple enzymatic pathways modulate endogenous AHR activity via the metabolism of amino acids[70]. These enzymatic pathways can be provided by the host or the commensal flora, as exemplified by the conversion of dietary Trp into potent AHR agonist indoles by bacterial tryptophanase[71].

As discussed above, natural AHR ligands can differentially interact with specific residues within the AHR binding site and induce

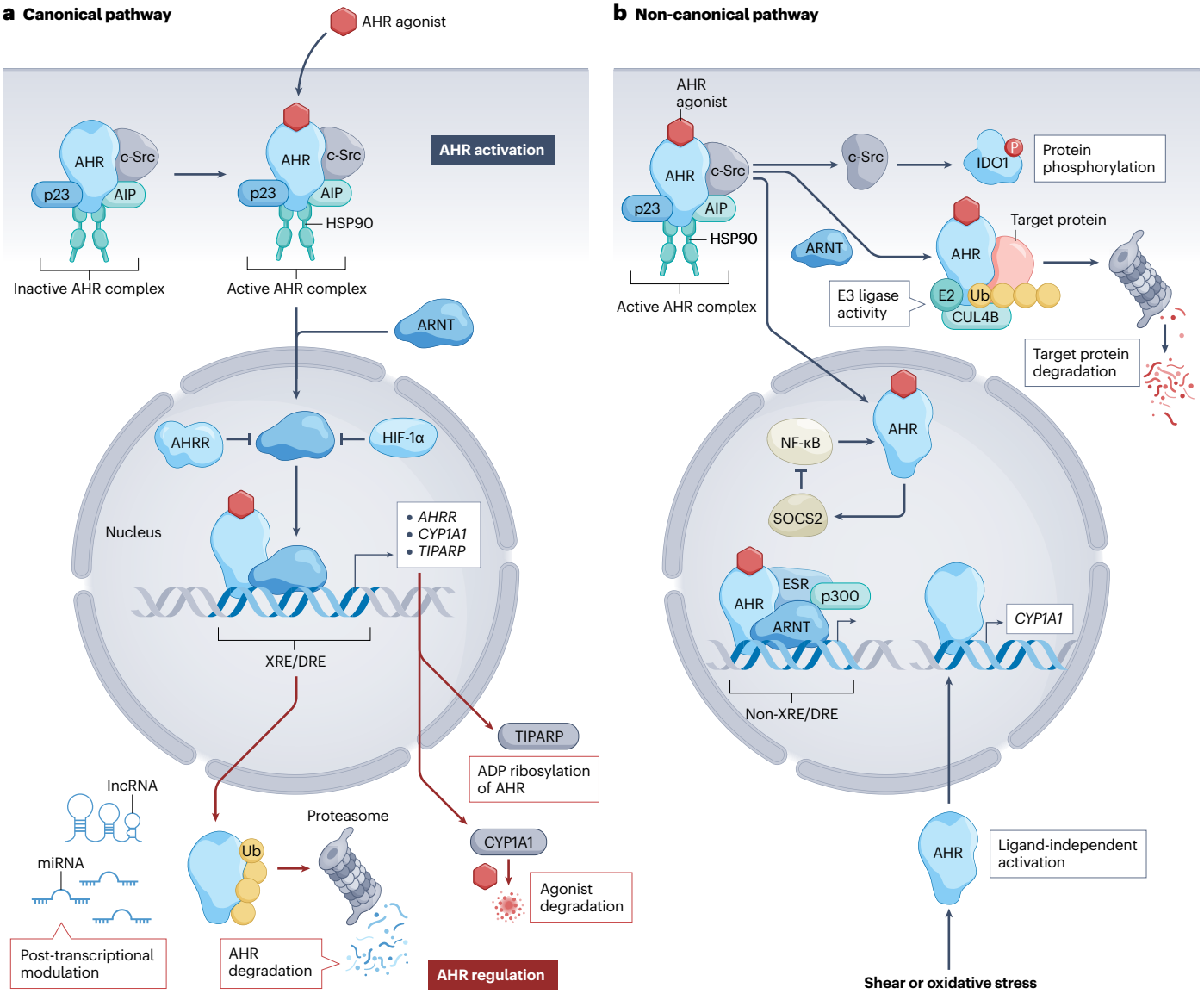


Fig. 1 | Canonical and non-canonical AHR signalling. a, During canonical aryl hydrocarbon receptor (AHR) signalling, the inactive AHR complex containing heat shock protein 90 (HSP90), AHR-interacting protein (AIP), p23 and c-Src is bound by an agonist and translocates from the cytoplasm to the nucleus where it interacts with the AHR nuclear translocator (ARNT). The AHR–ARNT heterodimer binds to DNA sequences with xenobiotic or dioxin response elements (XREs/DREs), leading to transcription of AHR target genes. The regulatory feedback mechanisms that limit AHR activation (red) include post-transcriptional modulation of *AHR* expression by non-coding RNAs such as long non-coding RNAs (lncRNAs) and microRNAs (miRNAs); the ubiquitin-dependent proteasome-mediated degradation of AHR; agonist degradation by CYP1A1; ADP-ribosylation of AHR and/or co-factors by TIPARP; and competition for ARNT binding in the nucleus by hypoxia-inducible factor 1α (HIF-1α) and the AHR repressor (AHRR). **b**, In non-canonical AHR signalling in the cytoplasm, the agonist-activated AHR promotes the phosphorylation of c-Src targets (such as indoleamine 2,3-dioxygenase (IDO1)) or acts as an E3 ubiquitin ligase to promote the degradation of target proteins. In the nucleus, the AHR interacts with other transcription factors such as nuclear factor-κB (NF-κB) to regulate transcription. AHR–ARNT also associates with the oestrogen receptor (ESR) and p300 to activate XRE/DRE-independent target genes. In addition, shear or oxidative stress induce ligand-independent AHR activation and induction of CYP1A1. CUL4B, cullin 4B ubiquitin ligase complex; P, phosphorylation; SOCS2, suppressor of cytokine signalling 2; TIPARP, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)-inducible poly(ADP-ribose) polymerase; Ub, ubiquitylation.

conformational changes and interactions with binding partners[38]. For example, high-affinity ligands such as TCDD induce prolonged AHR activation, which promotes sustained interactions with ARNT and strong transcriptional activation of target genes[28]. By contrast, FICZ and I3C form less stable interactions, leading to transient AHR activation[22,72]. These variations in ligand binding are linked to distinct biological outcomes, which is important to consider in the design of therapeutic SAHRMs.

Upon agonist binding, AHR signalling mechanisms can be broadly categorized into canonical and non-canonical signalling[73]. Importantly,

the diversity of AHR signalling modes enables cells to respond to various stimuli, facilitating adaptation to the cellular environment.

Canonical AHR signalling

The canonical AHR signalling pathway is initiated by agonist binding to the AHR–chaperone complex in the cytoplasm (Fig. 1a). This interaction induces conformational changes of the AHR, which result in the dissociation of AIP from the AHR complex and the exposure of the N-terminal nuclear localization signal[74]. The AHR–agonist complex then interacts with transportin and importin-β, which mediate its nuclear import[75]. Notably, the interaction between importin-β and the AHR is disrupted by the phosphorylation of protein kinase C target sites within the AHR, which serves as a regulatory mechanism to impede nuclear transport[76]. Although the precise details of the conformational changes and translocation of AHR–chaperone complex members to the nucleus are not fully elucidated, in situ proximity ligation assays suggest that HSP90 moves to the nucleus together with the AHR[77].

Once in the nucleus, the AHR–agonist complex heterodimerizes with ARNT[78]. This heterodimerization is a crucial step for the transcriptional activity of the AHR and involves conformational changes in both the AHR and ARNT[79,80]. The AHR–ARNT complex binds to specific DNA sequences harbouring a consensus 5′-TNGCGTG-3′ sequence, where AHR interacts with the 5′-TNGC and ARNT with the GTG-3′ half-sites of the sequence[81–83]. Among the multiple classes of AHR target genes are xenobiotic-metabolizing enzymes, including NAD(P)H-quinone oxidoreductase 1 (NQO1) and members of the cytochrome P450 family (such as CYP1A1, CYP1A2, CYP1B1 (ref. 10)); the cytokines IL-10 and IL-21 (refs. 84–86); and enzymes involved in cell metabolism[87]. Interestingly, the AHR is a potent transcriptional regulator of cytochrome P450 enzymes, and abrogating the delivery of AHR ligands to the liver can avoid potential drug–drug interactions[88].

AHR canonical signalling is subject to negative feedback regulation. For example, the AHRR is expressed from an AHR target gene and competes with the AHR for association with ARNT, limiting AHR-driven gene expression[89,90]. Similarly, hypoxia-inducible factor 1α (HIF-1α) can also compete with the AHR for binding to ARNT[87]. AHR activation also induces the expression of its negative regulator TCDD-inducible poly(ADP-ribose) polymerase (TIPARP). TIPARP inhibits AHR activity by promoting the ADP-ribosylation of AHR and/or its co-factors, thereby limiting AHR signalling[91,92]. In addition, AHR can be degraded by the 26S proteasome[93,94]. Moreover, the AHR target CYP1A1 can promote the metabolic clearance of endogenous AHR agonists[95]. Finally, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) modulate expression of the AHR[96] and its target genes[97–101]. These complementary regulatory mechanisms prevent the development of pathology due to excessive AHR signalling, although they might be less effective at limiting responses induced by metabolically persistent synthetic AHR agonists, such as TCDD.

Non-canonical AHR signalling

Non-canonical AHR signal transduction involves nuclear and/or cytosolic pathways (Fig. 1b). In nuclear mechanisms, the AHR–agonist complex interacts with and regulates the activity of other transcription factors. For example, the AHR controls nuclear factor-κB (NF-κB)[102–105] activity through both direct interactions and indirect mechanisms[106,107]. The AHR directly interacts with RelA and RelB of the NF-κB complex and interferes with transcriptional programmes[102,108]. Furthermore, AHR nuclear translocation induces suppressor of cytokine signalling 2 (SOCS2), which inhibits TLR signalling and NF-κB-dependent expression of cytokines such as IL-6, IL-12a, IL-12b, IL-23a and TNF, thereby indirectly interfering with NF-κB mechanisms[106]. These direct and indirect mechanisms control NF-κB-driven transcriptional programmes in multiple cell types. For example, the AHR interferes with the NF-κB-driven activation of CCAAT/enhancer-binding protein-β (C/EBPβ) in T cells and dendritic cells (DCs), limiting intestinal inflammation[109]. Similarly, the AHR promotes the expression of Krüppel-like factor 4 (KLF4)-driven (ref. 96) and KLF6-driven (ref. 110) transcriptional programmes, whereas it represses signal transducer and activator of transcription (STAT) signalling[111]. The AHR can also act as a transcription co-activator or co-inhibitor, modulating and/or interacting with the retinoic acid receptor (RAR)[112,113], retinoblastoma protein (Rb)[114,115] and promyelocytic leukaemia protein (PML)[116]. Moreover, AHR–ARNT bound to an agonist associates with the oestrogen receptor (ESR), recruiting ESR and the co-activator p300 to oestrogen-responsive DNA elements even in the absence of ESR ligands[117]. Interestingly, p300 controls an epigenetic programme that promotes inflammation driven by non-immune tissue-resident cells[118]. Hence, the AHR could potentially limit the establishment of p300-driven long-lived epigenetic programmes that promote chronic tissue inflammation.

Multiple mechanisms of cytosolic non-canonical signalling have also been described for the AHR. For example, the AHR is reported to act as an E3 ubiquitin protein ligase that targets substrates for ubiquitination and degradation by the proteasome[119]. Specifically, ligand-bound AHR interacts with cullin 4B ubiquitin ligase (CUL4B), triggering the proteasomal degradation of target proteins[119]. It has been postulated that the E3 ligase function of the AHR competes with its transcription factor activity, contingent upon the availability and functionality of ARNT. Consequently, a reduction in ARNT cellular levels results in an augmentation of AHR E3 ligase activity[120].

In addition, by sequestering c-Src in a protein complex, the AHR controls the phosphorylation of c-Src targets that have important roles in cell proliferation, differentiation and survival[47]. For example, during rechallenge with LPS, c-Src is released from its interaction with the AHR complex and phosphorylates IDO1, increasing the availability of AHR ligands and promoting TGFβ production by DCs, which results in long-term regulation of systemic inflammation[121].

Finally, it has been proposed that AHR activation can be triggered in the absence of agonists. For example, shear stress[122] and oxidative stress[123] were shown to induce AHR nuclear translocation and *Cyp1a1* expression. However, it is crucial to explore the significance of this ligand-independent AHR activation in a physiological context.

AHR in adaptive and innate immune responses

The AHR has been identified in the earliest multicellular organisms, including nematodes and placozoans[38,124]. However, the roles of the AHR in the regulation of inflammation appear to have emerged with the evolution of the first vertebrates[124]. The function of AHR signalling in immune cells has been extensively reviewed elsewhere[125–127] so we will provide a brief discussion of these effects, particularly those relevant to targeting AHR therapeutically.

Dendritic cells

DCs are professional antigen-presenting cells, bridging innate and adaptive responses to induce tolerance or immunity[128]. DCs capture endogenous and exogenous antigens, transporting them to secondary lymphoid organs to activate T cells[129]. In this context, AHR regulates DC differentiation and function, impacting T cell activity (Fig. 2).

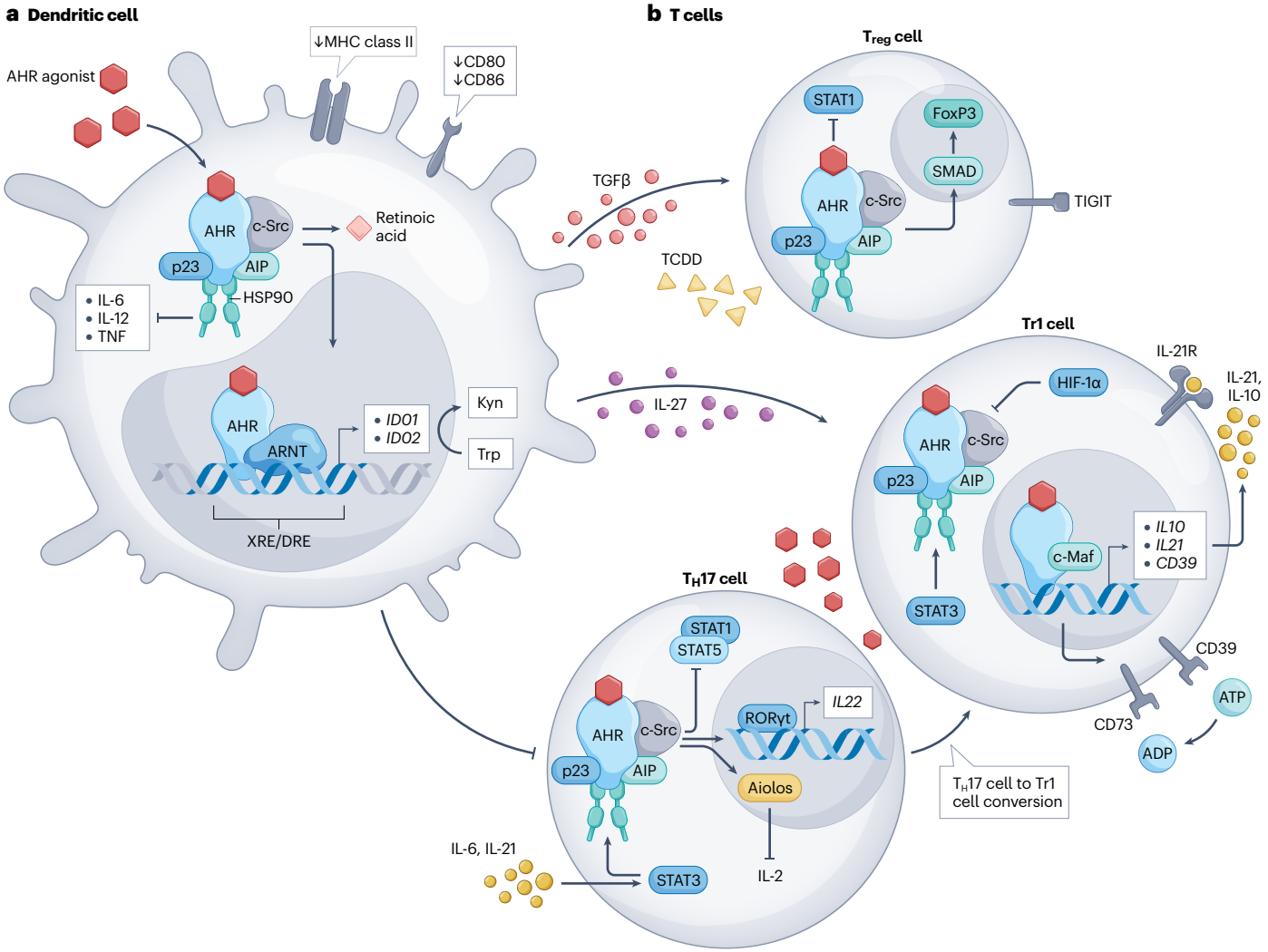


Fig. 2 | The AHR regulates innate and adaptative immunity. a, In dendritic cells (DCs), agonist activation of the aryl hydrocarbon receptor (AHR) reduces the expression of MHC class II antigen presentation molecules and CD80/CD86, reduces the production of pro-inflammatory cytokines IL-6, IL-12 and TNF, and increases retinoic acid production. Additionally, the AHR and AHR nuclear translocator (ARNT) induce expression of IDO1/IDO2, to convert tryptophan (Trp) into kynurenine (Kyn), and increase production of TGFβ and IL-27, thereby indirectly impacting T cell differentiation. Activation of the AHR in DCs induces T regulatory cell (T_{reg} cell) and type 1 regulatory T cells (Tr1 cells) but suppresses T helper 17 cell (T_H17 cell) differentiation. **b**, The AHR directly modulates T cell polarization, controlling the balance between T_{reg} cells and effector T_H17 cells. TGFβ and the AHR agonist 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induce differentiation of T_{reg} cells. Activated AHR impairs signal transducer and activator of transcription 1 (STAT1) activation and induces SMAD1, which enhances expression of Foxp3. AHR expression also increases expression of T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) in T_{reg} cells. IL-27 induces the differentiation of Tr1 cells and STAT3-driven AHR expression. The AHR cooperates with c-MAF to induce expression of IL-10, IL-21 and CD39. IL-21 stabilizes Tr1 cells, whereas IL-10 and CD39 lead to immunosuppression. For example, conversion of extracellular ATP (eATP) into adenosine by CD39 and CD73 contributes to immunosuppressive effects. Hypoxia-inducible factor 1α (HIF-1α) inhibits the AHR in Tr1 cells. In T_H17 cells, IL-6 and IL-21 induce activation of STAT3, which drives AHR expression. AHR expression induces differentiation of T_H17 cells by driving Aiolos expression and inhibiting STAT1 and STAT5 activation; it also promotes RORγt-dependent IL-22 production. AHR expression promotes the conversion of T_H17 cells into Tr1 cells. AIP, AHR-interacting protein; HSP90, heat shock protein 90; IDO, indoleamine 2,3-dioxygenase; XRE/DRE, xenobiotic and dioxin response element.

As an example of modulating DC differentiation and activation, AHR inhibition by the synthetic antagonist StemRegenin 1 (SR1) boosts the differentiation of $CD34^+$ haematopoietic progenitor cells into myeloid and plasmacytoid DCs, which exhibit increased interferon-α (IFNα), IL-12 and TNF secretion along with higher expression of co-stimulatory molecules, inducing potent T cell responses[130]. SR1-driven AHR inhibition also stimulates the differentiation of monocytes into monocyte-derived macrophages, whereas AHR activation by FICZ promotes the generation of monocyte-derived DCs via the induction of IRF4 and BLIMP1 (ref. 131). Therefore, the AHR stimulates the differentiation of monocytes into both DCs and macrophages. Similarly, AHR activation by TCDD promotes the differentiation of

immature DCs into CD11c$^+$MHCII^{high} mature DCs in vitro[132]. The exogenous AHR agonists VAF347, β-naphthoflavone (BNF) and TCDD are also reported to inhibit differentiation of human monocytes into Langerhans DCs[133]. Additionally, oral administration of indoxyl-3-sulfate (I3S) and I3C (Trp-derived metabolites from the diet and microbiota) impaired the differentiation of plasmacytoid DCs that produce type I interferon in mesenteric lymph nodes in response to viral infections[134].

The AHR also impacts antigen presentation in DCs, and hence their ability to activate and polarize T cells. For example, VAF347 inhibits allergic lung inflammation by inducing human tolerogenic DCs that display reduced CD86, HLA-DR and IL-6 expression[135]. Moreover, AHR activation by the agonist 2-(1′*H*-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) in isolated splenic DCs reduced the production of IL-12 for T_H1 cell polarization and IL-6, IL-23 and TGFβ for T_H17 cell polarization[136]. In vivo, ITE administration augmented TGFβ1 and IL-10 production in DCs during EAE, promoting the expansion of Foxp3$^+$ T_{reg} cells and IL-10$^+$ type 1 regulatory T cells (Tr1 cells) to limit central nervous system (CNS) inflammation[136]. Multiple mechanisms contribute to the expansion of Foxp3$^+$ T_{reg} cells and IL-10$^+$ Tr1 cells following AHR activation in DCs. These mechanisms include IL-27 (ref. 137) and retinoic acid[136] production, and also upregulation of IDO1 and its paralogue IDO2, which increases Kyn production[138,139] and results in AHR activation.

AHR signalling in DCs has important consequences for tissue barrier homeostasis. For example, AHR deficiency in DCs impairs Paneth cell function and increases goblet cell differentiation, altering the intestinal epithelial barrier and promoting colitis development[140]. Similarly, environmental chemicals that inhibit AHR worsen inflammation by boosting pro-inflammatory DC and T cell responses[109]. These findings are relevant to multiple mucosal barriers, because mice deprived of dietary AHR ligands also display impaired Langerhans cell migration and exacerbated T cell responses in asthma-like allergic models[141]. Conversely, the adoptive transfer of AHR-induced tolerogenic DCs to a colitis mouse model controls the balance between effector and regulatory T cell responses and ameliorates intestinal inflammation[142].

Although several studies demonstrate an anti-inflammatory role of AHR signalling in DCs, in certain contexts the AHR can participate in pro-inflammatory responses. AHR stimulation of bone marrow-derived dendritic cells (BMDCs) and splenic DCs with TCDD increased MHC class II and CD86 expression, as well as IL-6 and TNF production in vitro[143,144]. In addition, AHR deficiency in Langerhans cells results in the expansion of T_H2 cells and IL-10-producing Tr1 cells upon epicutaneous ovalbumin (OVA) sensitization[145]. Additionally, DC responses can be differentially influenced by various AHR agonists. For example, benzo(a)pyrene — but not FICZ or I3S — downregulates CD83 expression, stabilizing MHC class II expression in the DC membrane. Benzo(a)pyrene-treated DCs exhibit reduced CD80 expression and promote differentiation of Foxp3$^+$ T_{reg} cells[146].

Taken together, these findings suggest that the effects of AHR signalling in DCs involve ligand-specific and context-specific effects. Hence, specific AHR ligands can be designed for the modulation of DC function in vivo, offering therapeutic potential for enhancing immune responses in cancer and infections or reducing reactions in autoimmunity. Designing these ligands requires considering the target, environment and desired outcomes. Understanding AHR signalling in DCs can help identify biomarkers for predicting and monitoring therapy responses.

Innate lymphoid cells

Innate lymphoid cells (ILCs) contribute to immune surveillance and tissue repair, with important functions in autoimmune and infectious diseases[147]. Five ILC subsets have been defined based on the expression of specific transcription factors: T-bet$^+$EOMES$^-$ ILCs (ILC1s), GATA3$^+$ ILCs (ILC2s), RORγt$^+$ ILCs (ILC3s), T-bet$^+$EOMES$^+$ natural killer cells and ID3$^+$ regulatory ILCs[148]. The AHR is crucial for the maintenance and proliferation of CD49a$^+$CD49b$^-$ hepatic ILC1s (refs. 149,150), and human ILC2s express the AHR upon IL-25 and IL-33 stimulation[151], but the functional role of the AHR in ILC1s and ILC2s remains largely unclear. The AHR enhances ILC3 survival by driving the expression of IL-7R, and the anti-apoptotic proteins Bcl-2 and Ki67, thereby controlling cell proliferation[152]. Moreover, the AHR supports NKp46$^+$ IL-22-producing ILC3s by inducing expression of the Notch transcription factor[153]. Finally, the AHR is critical for the capacity of ILC3s to fight off infections. For example, AHR-driven IL-22-producing ILC3s (refs. 154,155) and RORγt$^+$ ILC3s (ref. 156) are essential for clearance of segmented filamentous bacteria and *Citrobacter rodentium*, respectively. Thus, the AHR plays a critical role in the regulation, maintenance and function of ILCs[157].

CD4$^+$ T lymphocytes

T_H cells encompass distinct subsets linked to specific functions and molecular phenotypes[158]. As already mentioned, the AHR influences T cell responses indirectly through the modulation of antigen-presenting cells. In addition, AHR signalling within T cells has important effects on their polarization and function (Fig. 2b). T_H17 cells, T_{reg} cells and Tr1 cells display the highest AHR expression levels[126].

TGFβ in combination with IL-6 or IL-21 (refs. 159–161) prompts the differentiation of RORγt-driven T_H17 cells, which are characterized by the production of IL-17A, IL-17F and IL-22 (refs. 25,26,162) (Fig. 2b). In addition, IL-23 supports the maturation of T_H17 cells and the development of cellular activities relevant to their pathogenic roles in inflammatory autoimmune disorders[163]; for example, the suppression of IL-10 production and expression of GM-CSF[164]. Interestingly, IL-6 and IL-21 induce activation of the STAT3 transcription factor, which drives AHR expression in T_H17 cells[87]. Indeed, the AHR cooperates with STAT3 to drive expression of Aiolos, a transcription factor in the Ikaros family, and suppress IL-2 production, thereby alleviating inhibitory effects of IL-2 on the early stages of T_H17 cell differentiation[165]; the AHR further facilitates T_H17 cell differentiation by inhibiting STAT1 and STAT5 activation[111,166]. In addition, the AHR promotes RORγt recruitment to the *Il22* promoter, inducing IL-22 production[86,167]. Of note, the AHR also cooperates with other transcriptional regulators to drive *Il22* expression in CD4$^+$ T_H22 cells, which do not produce IL-17 and IFNγ and play critical roles in mucosal immunity[168–171].

Tr1 cells are regulatory cells that do not express the transcription factor Foxp3 but produce high levels of IL-10 (ref. 172) (Fig. 2b). Tr1 cell differentiation is induced by IL-27 (refs. 161,173,174), which triggers STAT3-driven AHR expression. The AHR cooperates with the transcription factor c-Maf to promote IL-10, IL-21 (ref. 84) and CD39 (refs. 87,96) expression in Tr1 cells; IL-21 stabilizes Tr1 cells in an autocrine manner[175], whereas IL-10 and CD39 contribute to Tr1 cell immunosuppressive effects. CD39 is an ectonucleotidase that also has an important role in Tr1 cell differentiation[87]. T cell activation triggers the release of ATP to the extracellular medium, and this extracellular ATP (eATP) stabilizes HIF-1α, which promotes AHR degradation by the proteasome[176]. Furthermore, AHR-induced CD39 depletes eATP to facilitate Tr1 cell differentiation, and CD39 also catalyses the degradation

of pro-inflammatory eATP into AMP, which is then used by CD73 to produce anti-inflammatory adenosine[85,87]. Interestingly, the AHR promotes the conversion of T_H17 cells into Tr1 cells[177], probably as part of a mechanism aimed at limiting immunopathology.

AHR activation by TCDD, in the presence of TGFβ, enhances and stabilizes Foxp3 expression in T cells by inducing expression of transcription factors such as SMAD1 and/or Aiolos. Foxp3 and Aiolos inhibit the expression of genes linked to T cell functions, such as IL-2 (ref. 85). AHR signalling also impairs STAT1 activation, facilitating polarization of $Foxp3^+$ T_{reg} cells[111,136]. AHR expression is linked to $Foxp3^+$ T_{reg} cells that co-express the T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), suggesting that it contributes to the regulatory activity of specific $Foxp3^+$ T_{reg} cell subsets[25]. In summary, the AHR acts as a critical regulator of pathogenic and regulatory $CD4^+$ T cell responses.

Other lymphocytes

AHR signalling also controls other lymphocyte populations, such as $CD8^+$ T cells. AHR deficiency increased the abundance of short-lived $CD8^+$ effector T cells ($CD127^-KLRG1^+$) and central memory cells ($CD44^+CD62L^+$), while reducing granzyme-B-producing tissue-resident $CD8^+CD69^+CD103^+$ memory T cells[178]. Indeed, AHR signalling supports memory T cells in the skin to help eliminate microbes[179]. On the other hand, the AHR contributes to the exhaustion of tumour-reactive $CD8^+$ T cells in the tumour microenvironment[180]. Similarly, AHR activation by TCDD suppresses $CD8^+$ T cell responses against influenza virus[181,182]. Future studies should determine whether specific microenvironments or developmental stages are behind these seemingly opposing results.

Finally, the AHR is important for determining the fate of B cells. B cells undergo class-switch recombination, a genetic process enabling alterations in the constant regions of the antibody molecule. These alterations facilitate the production of antibodies across different classes, switching from IgM to IgG, IgA or IgE while maintaining antigen specificity[183]. The AHR negatively regulates class-switch recombination and the differentiation of B cells into plasmablasts and antibody-secreting plasma cells[184]. In addition, the AHR is also essential for the differentiation of IL-10-producing $CD19^+CD21^{hi}CD24^{hi}$ regulatory B cells, which limit inflammation in multiple assays[185]. Based on the success of B cell targeting therapies in autoimmune diseases such as MS[118], the role of the AHR in regulating B cells indicates that it could be targeted for the treatment of T cell-driven autoimmune disorders. However, additional studies are needed to define the effects of AHR modulation on B cell antigen presentation.

Targeting the AHR in inflammatory disorders

The AHR is highly expressed in the immune and stromal cells of epithelial barrier tissues. As a key regulator of immune homeostasis, the AHR can be differentially targeted with specific ligands that either trigger AHR activation and suppress inflammation or, conversely, inhibit the AHR and boost pro-inflammatory immune responses. In the first instance, AHR activators have been demonstrated to suppress various inflammatory conditions in different tissues and organs. Alternatively, AHR inhibition activates immune responses, highlighting therapeutic avenues for neoplastic and infectious diseases[186,187].

Inflammatory skin disease

A critical role for the AHR in inflammatory skin disease was demonstrated by Di Meglio et al.[188]. Imiquimod (IMQ) is a synthetic TLR7 and TLR8 ligand used to treat viral skin infections, but its topical application to the skin in mice induces a T_H17 cell polarized inflammatory dermatosis with features of psoriasis[189]. In this mouse model of psoriasis, AHR deficiency worsened IMQ-induced inflammation. Also, activation of the AHR via topical FICZ application ameliorated IMQ-induced inflammatory changes, whereas topical application of the AHR antagonist CH-223191 worsened inflammation[188]. In another study, difamilast, a phosphodiesterase 4 (PDE4) inhibitor, induced the production of soluble suppression of tumorigenicity 2 protein (sST2) in normal human epidermal keratinocytes through activation of the AHR–NRF2 pathway, thereby suppressing IL-33 activity and reducing symptoms of atopic dermatitis[190].

Tapinarof (also known as DMVT-505, GSK2894512, STI-1001 or WBI-1001) is a naturally identified stilbene compound with AHR agonist activity[191] that was developed by Dermavant Sciences and approved by the FDA in 2022 for the treatment of plaque psoriasis in adults. From the observation that insect larva infected by nematodes failed to undergo putrefaction, tapinarof was identified as a natural metabolite produced by the symbiotic gram-negative bacteria *Photorhabdus luminescens*[192]. Tapinarof was purified and shown to have anti-inflammatory properties in preclinical models, leading to its initial development by Welichem Biotech as a topical medicine for inflammatory skin disease. Early-stage clinical studies demonstrated the efficacy of topical 1% tapinarof cream (WBI-1001) in both psoriasis[193] and atopic dermatitis[194,195]. Tapinarof subsequently underwent additional formulation work by GlaxoSmithKline to yield a physically and chemically stable topical cream formulation (GSK2894512). The drug successfully progressed through phase IIb studies for both psoriasis and atopic dermatitis indications[196,197].

In exploring the mechanism of action of tapinarof, its pharmacological similarity to FICZ was detected using BioMap analyses. This technique characterizes the pharmacologic cellular activity of a compound against a large number of potential targets and compares this activity with the profile of a large library of known compounds[191]. Subsequent work confirmed tapinarof to be an AHR agonist that bound directly to AHR–ARNT heterodimers. It induced the expression of CYP1A1 and the skin barrier components hornerin, filaggrin, involucrin and loricrin in keratinocytes[191] as well as ceramide lipid components of the epidermal barrier[198], and suppressed expression of pro-inflammatory cytokines, including IL-17A and IL-17F, in T cells. In the IMQ mouse model of psoriasis, topical administration of tapinarof suppressed clinical disease as well as IL-17A and IL-17F expression; these effects of tapinarof were lost in AHR-deficient mice, confirming the central role of the AHR in the clinical benefits of tapinarof. Additional work using in vitro and in vivo models demonstrated that tapinarof downregulated the expression of additional pro-inflammatory cytokines, including IL-4, IL-5, IL-6, IL-13, IL-31 and eotaxin. Tapinarof also has direct chemical antioxidant activity and stimulates the Nrf2 transcription factor to drive the production of antioxidative enzymes[191]. Indeed, oxidative stress contributes to inflammation; recent observations demonstrate reduced Nrf2 activity in atopic dermatitis lesioned skin[199]. Collectively, these observations suggest that tapinarof exerts its effects in human psoriasis and atopic dermatitis through an AHR-dependent mechanism.

A cream formulation of tapinarof was progressed through phase III trials by Dermavant Sciences for the treatment of adult plaque psoriasis. The topical drug demonstrated clinically meaningful and statistically significant superiority compared with vehicle control[200]. In addition, a durable effect with continued usage and a remittive effect (that is, continued disease control after treatment discontinuation) have also been observed[201]. In a long-term extension study (PSOARING 3), 41% of patients treated with tapinarof achieved complete clearance of their disease and were able to maintain disease control after therapy

withdrawal for a median time of 4 months. In agreement with the role of the AHR in memory T cell differentiation and function[178], tapinarof inhibited the generation, activity and persistence of memory T cells in vitro[202]; these effects might contribute to the remission observed in clinical studies. Tapinarof systemic absorption was minimal[203] and was generally found to be safe and well tolerated. Tapinarof cream 1% was approved by the FDA for the topical treatment of adult mild, moderate and severe plaque psoriasis. Recently, tapinarof also demonstrated efficacy and safety in plaque psoriasis in Japanese patients in a phase III, double-blind trial (ZBA4-1) and over 52 weeks in an open-label trial (ZBA4-2)[204].

Tapinarof cream is also under development for the topical treatment of atopic dermatitis. ADORING 1 (NCT05014568) and ADORING 2 (NTC05032859) were two identical, double-blind, randomized, vehicle-controlled phase III studies that evaluated its efficacy and safety in adults and paediatric patients with moderate to severe atopic dermatitis. In these studies, tapinarof demonstrated clinically meaningful and statistically significant superiority compared with the vehicle[205,206]. ADORING 3 (NTC05142774) was an open-label, long-term extension study to evaluate the safety and efficacy of tapinarof cream in patients with atopic dermatitis for up to 48 weeks. A supplementary new drug application (sNDA) for the treatment of atopic dermatitis in adults and paediatric patients was submitted to the FDA in 2024.

Multiple sclerosis and experimental autoimmune encephalomyelitis

MS is a chronic autoimmune disease of the CNS, characterized by episodes of demyelination caused by T cells reactive with antigens in myelin and other CNS proteins[207]. As previously discussed, the AHR in $CD4^+$ T cells modulates anti-inflammatory and pro-inflammatory responses[177]. Interestingly, patients with MS show reduced levels of microbiome-derived AHR agonists[208]. Moreover, several AHR agonists have been shown to suppress neuroinflammation and EAE development[25,136,209].

CNS-resident cells play important roles in MS pathophysiology, particularly during the progressive phase of the disease[210]. Astrocytes and microglia are abundant glial cells of the CNS, with important roles in tissue development, homeostasis and repair[211–213]. AHR expression in CNS-resident cells is upregulated during neuroinflammation[214]. Interestingly, the specific deletion of the AHR in astrocytes[215] or microglia[216] results in their exacerbated pro-inflammatory responses and the worsening of EAE. Indeed, AHR activation in astrocytes and microglia was shown to suppress NF-κB-driven pro-inflammatory responses[215,216]. Therefore, AHR signalling participates in MS pathology not only by regulating the autoimmune T cell response but also via the regulation of CNS-resident cells, offering an attractive target for the therapeutic management of multiple disease stages.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by dysregulated immune responses and driven by pathogenic T cell–B cell interactions resulting in chronic inflammation and multi-organ damage[217]. A key pathogenic feature is the expansion of $CD4^+$ T cells into $CXCL13^+$ T follicular helper cells and T peripheral helper cells. The AHR is a critical negative regulator of CXCL13 production, a key chemokine for B cell recruitment. Together with the AP-1 transcription factor JUN, the AHR inhibits the differentiation of $CD4^+$ T cells into T follicular helper cells and T peripheral helper cells, while promoting their differentiation into IL-22-producing T_H22 cells, thereby attenuating SLE severity[218]. In addition, TLR9 signalling driven by DNA from apoptotic cells activates the AHR in phagocytes leading to IL-10 production, which regulates immune tolerance and modulates the progression and severity of SLE in mice and humans[219]. In macrophages from patients with SLE, AHR activation by its agonist I3C promotes an anti-inflammatory M2 phenotype, balancing pro-inflammatory and anti-inflammatory cytokine expression, and highlighting the AHR as a potential therapeutic target for SLE[220]. The ratio of AHR expression in T_H17 cells to that in T_{reg} cells might represent a potential biomarker for predicting skin lesions in SLE, as an elevated ratio is correlated with heightened disease activity and increased risk of skin injury[221]. Therefore, these findings suggest a role for the AHR not only in the control of immune-driven SLE pathology but also as a prognostic biomarker.

Inflammatory bowel disease

The AHR is widely expressed by immune and non-immune cells of the gastrointestinal tract, where it participates in immune and epithelium homeostasis. AHR activation by a diverse set of ligands suppresses inflammation, enhances immune regulatory mechanisms (including by increasing levels of IL-10, IL-22 and T_{reg} cells), upregulates antimicrobial peptides and restores epithelial cell integrity[222]. Interestingly, it was reported that environmental chemicals that promote intestinal inflammation interfere with the immunoregulatory activities of the AHR[109].

The regulation of the levels of endogenous and exogenous AHR ligands has an important role in intestinal homeostasis. CYP1A1 is a direct transcriptional target of the AHR that can catalyse the degradation of physiological AHR agonists[95]. Indeed, the constitutive overexpression of CYP1A1 depletes physiologic AHR agonists, resulting in the loss of AHR-dependent intestinal ILCs and T_H17 cells in mice, and increasing susceptibility to infection. Conversely, the pharmacologic inhibition of CYP1A1 decreases AHR agonist clearance, resulting in enhanced AHR agonist activation and increased IL-22 production by T_H17 cells[223]. In addition to its role in gut barrier homeostasis[224], AHR-driven IL-22 is required for the initiation of the DNA damage response, limiting genotoxic stress and neoplastic transformation at the intestinal epithelial barrier[225].

Preclinical work in animal models further supports a role for the AHR in gastrointestinal homeostasis and its potential as a therapeutic target for inflammatory bowel disease (IBD). For example, in the dextran sodium sulfate (DSS)-induced colitis mouse model, AHR deficiency results in increased colon inflammation[226]. In addition, CARD9 mutations linked to IBD alter the intestinal microbiome, decreasing the abundance of commensal bacteria which produce AHR agonists[227]. Conversely, the AHR agonist FICZ attenuates 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice[228]. Moreover, human T_{reg} cells induced by treatment with the AHR agonist ITE[229] ameliorate TNBS-induced colitis in humanized mice[230]. Interestingly, environmental chemicals were found to worsen intestinal inflammation via AHR-dependent mechanisms operating in DCs and T cells, resembling similar observations made in inflammatory skin disease[109]. Other natural compounds derived from plants termed indigoids are also potent AHR agonists. For example, administration of indigo naturalis (Qing-Dai) showed promising results for treating ulcerative colitis (UMIN000019103)[231]. Also, the combination of curcumin and indigo naturalis induced remission in patients with active ulcerative colitis (NCT03720002). These studies highlight the AHR pathway as a candidate therapeutic target in ulcerative colitis.

In summary, the AHR represents an attractive target for IBD management. An AHR agonist would avoid the immunosuppressive side effects of the oral corticosteroids used as the current standard of care. For example, an AHR agonist formulated as an oral colonic drug delivery system using a pH trigger for immediate drug release in the colon and/or small intestine would have the potential to provide target engagement and efficacy while minimizing systemic exposure and adverse events. Moreover, activating AHR-driven transcriptional programmes might help regulate memory T cells and repair the intestinal epithelial barrier.

Asthma and chronic obstructive pulmonary disease

Preclinical animal models have shown a role for the AHR in the pathophysiology of asthma. In the OVA-induced mouse model of asthma[232], AHR deficiency is associated with increased eosinophil and lymphocyte influx to airways and increased IL-4 and IL-5 production in airways[233]. In the cockroach allergen-induced mouse model of asthma, AHR deficiency is also associated with exacerbated lung inflammation, and ligand-induced AHR activation suppressed inflammation[234].

There is an unmet need for non-steroidal options and therapies to address multiple disease endotypes in asthma[235]. AHR agonists developed as dry powder inhalants have the potential to provide a non-steroidal anti-inflammatory option for inflammatory lung disease, avoiding the side effects linked to inhalant corticosteroid use such as cough, sore throat, oral thrush, growth retardation in children and weight gain. In addition, AHR modulators have the potential to target multiple asthma endotypes. For example, AHR agonist-driven suppression of both T_H2 cells and T_H17 cells would target steroid-responsive and steroid-unresponsive asthma.

Similar to cutaneous atopic disease[236–239], air pollution exacerbates respiratory atopic disease. For example, the AHR agonist indeno[1,2,3-cd]pyrene (IP), a component of particulate matter ($PM_{2.5}$), increased allergic airway inflammation, T_H2 cytokines, eosinophil numbers and OVA-specific IgE via an AHR-dependent mechanism in the OVA-induced mouse model[240]. These pro-inflammatory effects of IP were abrogated in mice expressing a mutant AHR in DCs[240]. Thus, lung inflammation can be promoted or suppressed via the AHR in a ligand-specific manner. These observations identify the AHR as a potential target for the management of respiratory atopic disease.

Chronic obstructive pulmonary disease (COPD) offers another therapeutic opportunity for AHR-targeting drugs. In COPD, chronic exposure to airway irritants, including those in air pollution and cigarette smoke, leads to obstructive airflow changes in the lung; AHR agonists in air pollution and cigarette smoke increase inflammation and mucus production[241]. Neutrophils contribute to the pathophysiology of COPD; neutrophilic proteases, including the serine proteinase human neutrophil elastase, promote the progressive destruction of lung tissue[242]. The reported roles of the AHR in the control of T cell-driven and B cell-driven inflammation, but also of neutrophil chemotaxis[243], suggest therapeutic opportunities for AHR modulators in COPD.

Targeting the AHR in infectious diseases and cancer

We and others have postulated that the AHR functions as a key regulator of homeostasis that participates in a negative feedback loop to limit immunopathology during viral infections[116,244]. These regulatory mechanisms are exploited by pathogens and tumours to evade host immunity. Indeed, targeting the AHR offers a promising therapy for infectious diseases and cancer due to its role in immune regulation and evasion.

Infectious diseases

Given the central role of the AHR in immune regulation, it is not surprising that pathogens activate AHR signalling to evade protective immunity. Therefore, pharmacologic modulation of the AHR might help manage infectious pathologies. AHR activation is detected in multiple infection models, including Zika virus (ZIKV), SARS-CoV-2 and influenza. Using AHR-deficient murine embryonic fibroblasts, Yamada et al. reported that AHR signalling limits type I interferon production induced by various viral pathogens including vesicular stomatitis virus, influenza and herpes simplex virus type 1 (ref. 245). The AHR agonists Kyn and FICZ suppressed type I interferon production, whereas inhibitors of IDO1 and TDO (enzymes that catalyse the generation of Trp-derived AHR agonists) enhanced the antiviral response. Furthermore, pharmacologic inhibition of the AHR with the antagonist CH-223191 upregulated the antiviral type I interferon response. These observations suggest that AHR signalling is activated by viruses to downregulate the host antiviral type I interferon response. Indeed, the AHR activates TIPARP, which subsequently inhibits the serine/threonine kinase TANK binding kinase 1 (TBK1), likely by ADP-ribosylation of the kinase domain, and suppresses type I interferon production. This negative feedback loop might have been evolutionarily selected to limit immunopathology but is hijacked by viruses to promote viral replication and infectivity. Thus, both the AHR and TIPARP are potential targets for treating viral infections[245].

Similarly, ZIKV has also been shown to limit type I interferon responses via the AHR. Indeed, pharmacologic inhibition of the AHR using HP163 suppressed ZIKV infection and developmental abnormalities, including intrauterine growth retardation and microcephaly, in a mouse model of congenital Zika syndrome[116]. Similar antiviral effects were detected following pharmacologic AHR inhibition in dengue virus-infected human cell cultures[116]. More recently, a similar role for the AHR in coronavirus infection was reported. AHR activity is increased in SARS-CoV-2-infected cells, including in lung tissue from patients infected with SARS-CoV-2. The AHR antagonist CH-223191 suppressed the in vitro replication of several coronaviruses, including HCoV-229E and SARS-CoV-2 (ref. 246). Collectively, these observations support the potential of AHR inhibition as a therapeutic strategy in viral infections.

Cancer

The AHR is overexpressed and chronically activated in different types of cancer, including glioblastoma[96,247], breast cancer[248], and oral and gastric cancers[14]. Chronic AHR activation can suppress tumour-specific immunity and trigger stem-like cancer cell formation, driving tumour migration, proliferation and metastasis[249–252]. Cancer cells express high levels of IDO1 and TDO2, generating Trp-derived AHR agonists that suppress protective antitumour immune responses[253–255]. For example, we showed that glioblastoma cells activate the AHR in tumour-associated macrophages. AHR activation in tumour-associated macrophages promotes KLF4 expression, suppressing NF-κB activation while driving the expression of CD39, which promotes $CD8^+$ T cell dysfunction[96]. In addition, IFNγ induces cancer cell apoptosis via STAT1; however, stem-like cancer cells that express high levels of AHR and IDO1 develop resistance to cell death[256]. Moreover, the AHR–IDO1 axis upregulates exhaustion pathways in tumour-infiltrating T cells, suppressing immunity during oral squamous cell carcinoma[257]. In addition, IL-2 signalling

contributes to CD8$^+$ T cell exhaustion in tumour microenvironments via an AHR-dependent mechanism[180]. Finally, a pathway induced by IL-4-induced 1 (IL4I1) generates AHR-activating indole metabolites and kynurenic acid (KA)[258].

Based on these and other findings, preventing AHR activation constitutes a promising approach to revert tumour immunosuppression[259–261]. Indeed, the suppression of AHR activity, either pharmacologically or by genetic deletion, reduced tumour growth by increasing IFNγ$^+$CD8$^+$ T cells within tumours[257]. Interestingly, gut commensal *Lactobacilli* generate Trp-derived AHR agonists. Ampicillin treatment to decrease *Lactobacilli*, or the removal of dietary Trp, promoted the intratumour accumulation of CD8$^+$ T cells and reduced the tumour size[262]. In complementary studies, probiotics targeting AHR signalling were used to improve the immune response against tumour cells. In particular, indole-3-carboxylic acid (ICA) produced by *Lactobacillus gallinarum* can reduce T_{reg} cell differentiation and increase the response of CD8$^+$ T cells to PD1 immune checkpoint blockade in colorectal cancer[263]. Mechanistically, ICA inhibits IDO1, decreasing levels of Kyn available for T_{reg} cell differentiation[263]. Thus, synthetic or microbiome-produced small molecules targeting AHR signalling have the potential to be used in cancer immunotherapy approaches.

AHR antagonists are being clinically evaluated. BAY2416964 is a small molecule designed to inhibit the AHR, with the goal of boosting the immune response to cancer. A phase I clinical trial is determining the highest tolerable dose of BAY2416964 in patients with advanced cancer (NCT04069026). Additionally, BAY2416964 is being administered in combination with the anti-PD1 immune checkpoint inhibitor pembrolizumab in patients with advanced solid cancers, such as head and neck cancer, lung cancer and bladder cancer (NCT04999202). Similarly, another AHR antagonist named IK-175 (Ikena Oncology) is being evaluated in early-stage trials as a single agent and in combination with nivolumab, a humanized anti-PD1 antibody, for individuals with advanced or metastatic solid tumours, including urothelial carcinoma (NCT04200963).

By contrast, an anti-tumorigenic role of the AHR has been described in recent studies. IL-6 and AHR activation in CD8$^+$ T cells drives the differentiation of an IL-22-producing subset of cells, termed Tc22 cells, which exhibit potent cytolytic activity and robust tumour control, and are associated with improved recurrence-free survival in ovarian cancer[264]. In addition, the probiotic *Lactobacillus reuteri* is reported to migrate to melanoma, where it secretes the AHR agonist indole-3-aldehyde (I3A), enhancing antitumour immunity by stimulating IFNγ-producing CD8$^+$ T cells within the tumour microenvironment[265]. Future research should address these seemingly contradictory roles of the AHR in tumour-specific immunity.

Other small molecules targeting the AHR

As well as the clinical trials with Tapinarof discussed above, 20 other clinical trials have either been completed or are underway to interrogate the clinical effects of AHR modulation, using endogenous and dietary ligands as well as synthetic small molecules (Table 2). Among endogenous ligands, supplementation with L-Trp, an amino acid metabolized into AHR agonists[126], is being evaluated in individuals with biopsy-confirmed coeliac disease who do not respond to a gluten-free diet (NCT05576038). Another study evaluates the discriminatory potential of endogenous agonists of AHR, such as Kyn, in identifying individuals with hypertension associated with obstructive sleep apnoea (NCT04646902). Inulin is a dietary fibre from plants that induces CYP1A expression by directly interacting with the AHR or enhancing AHR binding to XREs[266]. The impact of inulin on the gut microbiome, gut barrier function, bacterial metabolites and immune cells in individuals with chronic kidney diseases has been investigated (NCT05071131). Both preclinical and early clinical findings support the therapeutic potential of these compounds, but further clinical studies are needed before a definitive conclusion can be drawn about their clinical efficacy.

Increased interest in the AHR as a therapeutic target is evidenced by the rise in preclinical drug development programmes targeting the AHR (Table 3). DMVT-506, an AHR agonist with a similar pharmacological profile to tapinarof, is under development by Dermavant Sciences for other inflammatory diseases. In addition to topical formulations, DMVT-506 is being developed as an oral modified-release dosage form for IBD and as a dry powder inhalant for respiratory diseases including asthma and chronic obstructive pulmonary disease. Azora Therapeutics is developing both topical and oral formulations of the natural AHR agonist indirubin for allergic dermatitis[267] and Galileo Biosystems is developing therapeutic AHR modulating agents for the treatment of inflammatory and autoimmune diseases. Eli Lilly recently had two patents issued for AHR agonists, suggesting active interest in the area of inflammation[268,269].

Abandoned small molecule clinical programmes

Examining abandoned clinical programmes is important to identify common pitfalls, refine methodologies, improve future research design, optimize resource allocation and ensure ethical considerations and patient safety, ultimately contributing to more successful clinical research outcomes. For instance, laquinimod is a small molecule AHR agonist that has been in development for neuroinflammatory disease. In the EAE mouse model of MS it had beneficial effects on clinical score, inflammation and demyelination that were not observed in AHR knockout mice[270].

Laquinimod progressed to human clinical studies. In a double-blind randomized phase III clinical trial (ALLEGRO) in patients with relapsing–remitting MS, a 0.6 mg oral dose of laquinimod showed modest benefit compared with placebo in reducing the annualized relapse rate, the primary end-point of the study[271]. A subsequent clinical trial (BRAVO) assessed the safety and efficacy of 0.6 mg oral laquinimod compared with the standard of care (IFNβ$_{1a}$ once-weekly injection) and with placebo in patients with relapsing–remitting MS. Although secondary measures of clinical benefit were observed, the primary end-point of the annualized relapse rate was not significantly different after laquinimod treatment compared with placebo, in contrast to the benefit seen with IFN-β-1a treatment[272]. These results prompted the termination of laquinimod development by Teva Pharmaceuticals. Interestingly, in the BRAVO study there was a baseline imbalance between the active and placebo groups, with worse conditions in the active groups, which might have influenced the drug effect assessment. Therefore, further investigation of laquinimod mechanisms should provide a clearer understanding of its effects on progressive MS. An eye drop formulation of laquinimod is being developed for the treatment of the inflammatory disease non-infectious uveitis. A phase I clinical study (NCT05187403) established that this formulation is safe and well tolerated, and a phase II study in non-infectious uveitis is planned[273]. Although laquinimod did not demonstrate sufficient efficacy in MS clinical trials, its potential for treating other neuroinflammatory conditions remains under investigation. Indeed, its suppressive effects on astrocyte-intrinsic pathogenic responses[274] suggests potential applications for the therapeutic management of neurodegeneration.

Table 2 | Clinical trials

Compound	Function	ID	Status	Sponsor	Description
Kynurenine (Kyn)	Endogenous AHR agonists	NCT04646902	Active, not recruiting	Universidade Nova de Lisboa	Investigate role of endogenous AHR ligands in distinguishing patients with hypertension associated with obstructive sleep apnoea
BAY2416964	Small molecule AHR antagonist	NCT04999202	Active, not recruiting	Bayer	Evaluate in combination with pembrolizumab in patients with advanced solid tumours
L-Tryptophan	AHR agonist	NCT03059862	Completed	McMaster University	Assess impact of a high and low-tryptophan (Trp) diet on AHR activation in healthy patients
BAY2416964	Small molecule AHR antagonist	NCT04069026	Completed	Bayer	Evaluate safety and efficacy in participants with incurable solid tumours unresponsive to existing treatments
Polycyclic aromatic hydrocarbons (PAHs)	Exogenous AHR agonists	NCT05789407	Completed	Jagiellonian University	Investigate whether exposure to persistent AHR agonists from organic pollutants is associated with pelvic endometriosis
–	AHR agonist	NCT01075360	Completed	National Taiwan University Hospital	Assess the impact of AHR on neuroblastoma development and its association with MYCN expression
IK-175	Small molecule AHR antagonist	NCT04200963	Completed	Ikena Oncology	Investigated as a single agent and with nivolumab, a humanized anti-PD1 antibody, for patients with advanced or metastatic solid tumours
Pollutants	Exogenous AHR agonists	NCT03788187	Completed	European Georges Pompidou Hospital	Impact of persistent organic pollutants on the metastatic ability of malignant breast tumours
TCDD	Exogenous AHR agonist	NCT00340873	Completed	National Cancer Institute	Evaluate toxicity in patients exposed to TCDD after a chemical explosion in Milan
Tapinarof	Exogenous AHR agonist	NCT04053387	Completed	Dermavant Sciences	Evaluate safety and efficacy of topical 1% cream in adults with plaque psoriasis
Tapinarof	Exogenous AHR agonist	NCT05014568 NTC05032859	Completed	Dermavant Sciences	Evaluate safety and efficacy of topical 1% cream to moderate to severe atopic dermatitis in children and adults
Tapinarof	Exogenous AHR agonist	ZBA4-1/ZBA4-2	Completed	Japan Tobacco Inc.	Evaluate the safety and efficacy of topical 1% cream to plaque psoriasis on a Japanese subpopulation
Tapinarof	Exogenous AHR agonist	NCT05142774	Completed	Dermavant Sciences	Evaluate safety and efficacy of long-term topical 1% cream to moderate to severe atopic dermatitis in children and adults
Laquinimod	Small molecule AHR agonist	NCT05187403	Completed	Active Biotech	Asses eye drop formulation for the treatment of non-infectious uveitis
CurQD/HF2	Exogenous AHR agonist	NCT03720002	Completed	Sheba Medical Center	A herbal formulation (HF2) for treatment of active ulcerative colitis
Indigo naturalis	Exogenous AHR agonist	UMIN000019103	Completed	Jikei University Hospital	Evaluate efficacy of short administration in patients with ulcerative colitis
Pollutants	Exogenous AHR agonists	NCT06213688	Not yet recruiting	Assistance Publique Hopitaux de Marseille	Evaluate whether AHR activation by exogenous ligands contributes to atopic dermatitis and psoriasis
L-Tryptophan	AHR agonist	NCT05576038	Recruiting	McMaster University	Investigate the impact on coeliac-related symptoms
LION laquinimod	Small molecule AHR agonist	NCT06161415	Recruiting	Quan Dong Nguyen	Assess safety, tolerability and distribution as topical eye drops in patients undergoing vitrectomy
Inulin	Dietary AHR agonist	NCT05071131	Recruiting	Charite University	Impact on gut microbiota and gut barrier function in patients with advanced chronic kidney disease

AHR, aryl hydrocarbon receptor; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Probiotics targeting the AHR and related pathways

Probiotics are live microorganisms, primarily bacteria and yeast, found in fermented foods and dietary supplements. They are thought to promote digestive health and a balanced microbiota when consumed in adequate quantities[275]. Additionally, probiotics can be engineered to exert modulatory effects on the immune system[276,277]. Indeed, synthetic probiotics have been recently developed as immunotherapeutic approaches for cancer[278] and autoimmunity[279,280]. The commensal flora is a physiologic source of AHR agonists, hence probiotic-driven approaches for the modulation of AHR signalling constitute exciting new avenues for immunomodulation (Fig. 3).

In 2011, *Lactobacillus bulgaricus* OLL1181 was shown to induce AHR activation, increasing CYP1A1 and prostaglandin E_2 (PGE_2) levels and ameliorating DSS-induced colitis in mice[281]. Since then, several probiotics have been shown to promote intestinal barrier repair and suppress intestinal inflammation by modulating

Trp metabolism and AHR activation, including *Propionibacterium freudenreichii* (strain ET-3)[282], *Lactobacillus acidophilus*[283], *Akkermansia muciniphila*[284], *Bifidobacterium bifidum*[285,286] and *Ligilactobacillus salivarius* (Li01)[287].

The diet and the commensal flora participate in complex interactions that contribute to the regulation of inflammation via the AHR and other mechanisms[288,289]. For example, *L. reuteri* uses Trp as a source of energy. Interestingly, dietary Trp promotes the expansion of *L. reuteri*, with the subsequent production of Trp metabolites that activate AHR-driven IL-22 production and STAT3 phosphorylation[290]. By maintaining and expanding gut T_{reg} cells[291], these Trp metabolites promote intestinal epithelial cell proliferation and mucosa homeostasis[292]. In addition, AHR activation by Trp metabolites downregulates the ThPOK transcription factor in intra-epithelial $CD4^+$ T lymphocytes, generating $CD4^+CD8\alpha\alpha^+$ cells that exhibit tolerogenic functions in the small intestine[293] (Fig. 3).

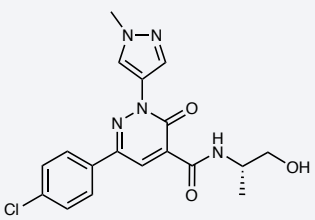
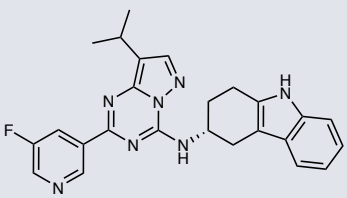
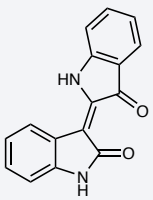
The gut–brain axis provides an avenue for the modulation of AHR signalling by the commensal flora. Indeed, some metabolites derived from dietary Trp cross the blood–brain barrier and act directly on CNS-resident microglia[216] and astrocytes[215] to activate AHR signalling, limiting the intrinsic pro-inflammatory activities of these cells as well as microglia–astrocyte communication (Fig. 3). A deeper understanding of the specific mechanisms involved in the modulation of AHR signalling by the commensal flora will pave the way for novel strategies in personalized medicine and immune-related disorders.

AHR-targeting nanoparticles for immunomodulation

Nanoparticles, typically ranging from 1 to 100 nm, offer unique opportunities for the therapeutic modulation of cells of interest in vivo. Nanoparticles can be prepared from multiple natural sources or synthesized from various materials, including metals and polymers, which endows them with specific functions that enable a myriad of medical applications[294,295]. Nanoparticles are being tested in preclinical studies on immunomodulation of the AHR pathway (Fig. 4a). For example, in mice, oral administration of nanoparticles loaded with the AHR agonist IAA was shown to normalize gut motility and serotonin secretion and to promote intestinal barrier integrity[296]. Moreover, oral administration of exosome-like nanoparticles derived from the plant *Portulaca oleracea* promoted the expansion of *L. reuteri*, increased the indole levels and induced AHR activation in conventional $CD4^+$ T cells, resulting in decreased pro-inflammatory cytokines and the amelioration of DSS-induced intestinal inflammation[297] (Fig. 4b).

The use of nanoparticles to co-deliver AHR modulators with antigens of interest has emerged as a promising approach to regulate pathogenic immune responses in an antigen-specific manner. For example, the AHR agonist ITE induces a tolerogenic phenotype in DCs and promotes the expansion of T_{reg} cells, ameliorating EAE[136]. Nanoparticles have therefore been developed to co-administer ITE with myelin or β-cell antigens to treat animal models of MS and type 1 diabetes (T1D),

Table 3 | Drugs under preclinical development

Compound	Structure	Formula	Company	Indication
BAY2416964		$C_{18}H_{18}ClN_5O_3$	Bayer	Solid tumours
IK-175		$C_{25}H_{27}CL_3FN_7$	Ikena	Several solid tumours
Indirubin		$C_{16}H_{10}N_2O_2$	Azora Therapeutics	–
TAMA	Not available	Several modulators — formulas are not available	Galileo Biosystems	Inflammatory and autoimmune diseases
HP163	Not available	Not available	Hercules Pharmaceuticals	Viral infections and cancer
DMVT-506	Not available	Not available	Dermavant	Inflammatory bowel disease (IBD)

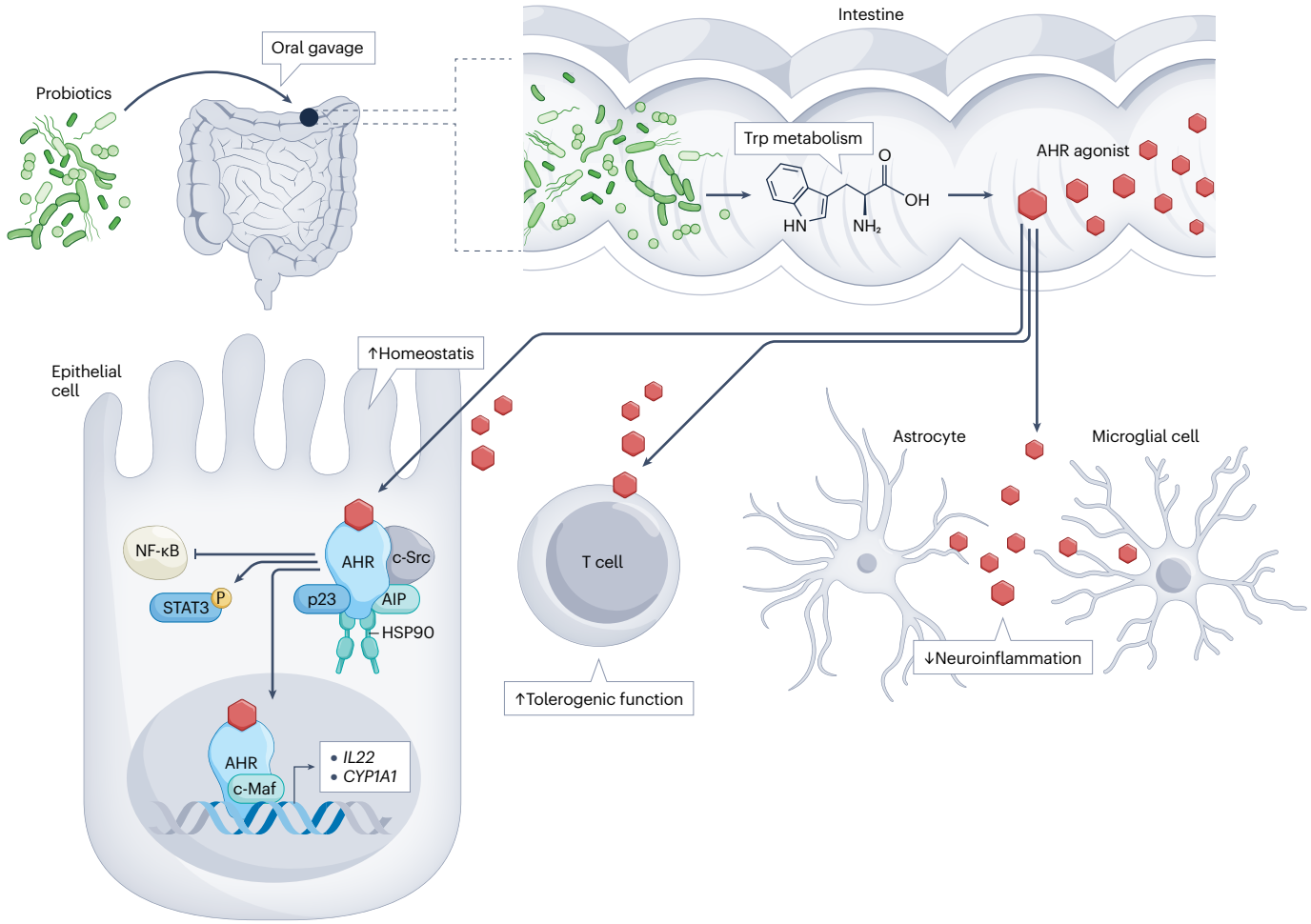


Fig. 3 | Probiotics impact AHR signalling. In mouse studies, oral delivery of engineered or natural probiotics induces tryptophan (Trp) metabolism and, consequently, generates aryl hydrocarbon receptor (AHR) ligands in the intestine. In intestinal epithelial cells, AHR activation promotes homeostasis by blocking nuclear factor-κB (NF-κB) activation, stimulating signal transducer and activator of transcription 3 (STAT3) phosphorylation and increasing expression of IL-22 and CYP1A1. In T cells, the activated AHR leads to generation of $CD4^+CD8\alpha\alpha^+$ double-positive cells and induces tolerogenic function. In central nervous system (CNS)-resident astrocytes and microglial cells, the AHR is activated by Trp metabolites to limit neuroinflammation. AIP, AHR-interacting protein; HSP90, heat shock protein 90; P, phosphorylation.

respectively. In both models, the administration of these nanoparticles induced tolerogenic DCs in vivo, and promoted the expansion of $Foxp3^+$ T_{reg} cells[298–300].

Given that AHR hyperactivation is a mechanism of immune evasion by viruses and tumours, nanoparticles loaded with the AHR inhibitor CH-223191 were found to decrease viral replication and ameliorate congenital Zika syndrome in ZIKV-infected pregnant SJL mice[116]. Similarly, nanoparticles loaded with 6′-bromoindirubin-3′-acetoxime, a synthetic compound that inhibits glycogen synthase kinase 3 (GSK3), reduced IDO1 expression and limited Kyn-driven AHR activation in tumour cells, augmenting the T cell-mediated killing of glioblastoma cells in vitro. In vivo, these nanoparticles improved survival in a preclinical model of glioblastoma[301].

For the successful implementation of nanoparticle-based AHR-targeting approaches, multiple questions need to be addressed, including the optimal nanoparticle design, as well as safety and biocompatibility issues. Designing optimal nanoparticles is challenging due to complex interacting factors including their stability, targeting specificity and variability in patients. However, the convergence of nanoparticle technology and AHR biology offers an innovative tool for antigen-specific immunomodulation[302].

Conclusions, challenges and future directions

Historically considered a liability target due to its initial identification as a receptor for man-made environmental toxins, the AHR has now emerged as a viable therapeutic target for inflammatory, infectious, cardiovascular and neoplastic diseases. The development, approval and commercialization of tapinarof has validated the AHR as a drug target, and additional AHR-targeting medicines are expected to be developed in the near future.

However, several challenges exist for the development of AHR-targeting drugs. A central goal is to design compounds that maximize

the therapeutic benefits of AHR signalling while minimizing potential detrimental effects. Avoiding toxicities linked to chlorinated ligands such as TCDD is critical. The terms SAHRMs and 'rapidly metabolized AHR ligands' (RMAHRLs) have been used as definitions to provide insights into the structure and physical chemical properties of AHR ligands, their differential binding properties and their biological effects[303]. SAHRMs preferentially regulate some, but not all, AHR target genes, whereas RMAHRLs are rapidly metabolized, and thus avoid toxicities linked to metabolically persistent agonists such as TCDD. This classification scheme facilitates grouping and mapping the chemical space of AHR ligands to identify useful structural and physical chemical properties for the design of new AHR-targeting molecules that have improved benefit to risk profiles.

The dissociation of the therapeutic and toxic effects of AHR signalling is also important to identify compounds that minimize potential drug–drug interactions. One approach is local delivery of a compound, which minimizes systemic exposure and effects on hepatic drug metabolism. Tapinarof and DMVT-506 demonstrate pharmacokinetic profiles that facilitate local delivery to epithelial tissues including the skin (Tapinarof and DMVT-506), gastrointestinal tract (DMVT-506) and lungs (DMVT-506). Nanoparticle-based approaches can also be used to target AHR modulators to specific tissues and/or cell types[302]. Alternatively, the use of probiotics engineered to produce rapidly metabolized AHR agonists can maximize mucosal delivery while limiting systemic exposure[304].

Regarding the potential use of soluble AHR inhibitors as anticancer drugs, several results suggest that additional strategies are required to improve efficacy. Deletion of the AHR in malignant murine oral squamous carcinoma cells blocks the ability of these cells to form tumours in vivo[257] by enhancing tumour-specific immunity. In contrast, although AHR inhibitors slow tumour growth, they do not completely prevent tumour formation[186]. This lower effectiveness reflects the fact that AHR inhibitors should have multiple effects in order to be efficacious tools for cancer therapy. In particular, AHR inhibitors should target the AHR in malignant cells, where it controls invasiveness, stemness and immunosuppressive genes[250,257,305,306], and also target the AHR in immune cells, where it promotes immunosuppressive phenotypes[255,307,308]. Anecdotally, increasing the dose of an AHR inhibitor does not improve cancer outcomes in preclinical models (reviewed elsewhere[187,309]), probably reflecting that a balance between beneficial and detrimental AHR signalling is reached at a certain dose. AHR inhibitors would be expected to limit the production of IDO1-driven immunosuppressive AHR agonists, and decrease levels of suppressive Foxp3$^+$T$_{reg}$/Tr1 cells[84,85] and CD39$^+$ macrophages[96]. However, in certain contexts AHR inhibitors might also reduce the expression of CD86 (refs. 132,143,144) and MHC molecules[310], the maturation of antigen-presenting cells[132,311,312] and levels of granzyme-B$^+$ tissue-resident memory T cells[178]. Therefore, additional strategies appear to be required to enhance beneficial effects on the immune system without the deleterious effects, including select AHR modulators, dose optimization and target delivery systems.

The AHR also plays a critical role in autoimmune diseases by modulating immune responses. Its activation can stimulate regulatory and anti-inflammatory pathways, whereas its dysregulation can contribute to immune system imbalance and autoimmunity[313]. Although the role of the AHR has been well characterized in inflammatory conditions such as dermatosis, MS/EAE, SLE and IBD, its involvement in many other inflammatory disorders remains underexplored and warrants further investigation. For example, AHR activation by TCDD increases the number of T$_{reg}$ cells in pancreatic lymph nodes, preventing diabetes in the non-obese diabetes mouse model of T1D (ref. 62). Moreover, T1D is associated with higher levels of IL-10, decreased AHR gene expression and increased Tr1 cell frequency[314], highlighting the potential for AHR-targeted immunomodulatory therapies.

In summary, once avoided as a liability target, the AHR has now emerged as a druggable target for therapeutic immunomodulation. The identification of important roles for the AHR in the physiological regulation of the immune response has encouraged and guided the development of AHR-targeting drugs. The commercialization of tapinarof has provided validation to the biopharmaceutical industry to pursue additional drugs focused on modulating AHR biology.

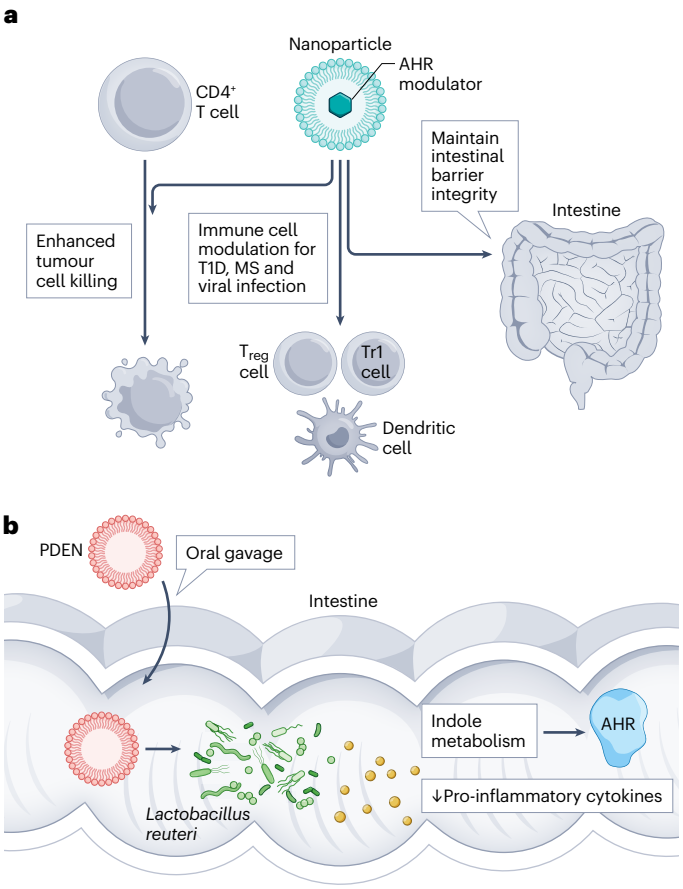


Fig. 4 | Nanoparticle-loaded agents for AHR modulation. a, Nanoparticles can be loaded with aryl hydrocarbon receptor (AHR) ligands or antigens to modulate antigen-specific immune responses in preclinical models. For example, nanoparticles loaded with 6′-bromoindirubin-3′-acetoxime, a synthetic compound that inhibits the kinase glycogen synthase kinase 3 (GSK3), reduced indoleamine 2,3-dioxygenase (IDO1) expression and limited kynurenine (Kyn)-driven AHR activation to enhance tumour cell killing by CD4$^+$ T cells; nanoparticles that co-deliver AHR ligands and antigens influenced dendritic cell (DC) and T cell polarization to boost regulatory responses; and nanoparticles loaded with the AHR agonist indole acetic acid (IAA) promoted intestinal barrier integrity. **b**, Plant-derived exosome-like nanoparticles (PDENs) from *Portulaca oleracea* enhanced growth of the *Lactobacillus reuteri* microbiota, inducing indole metabolism and activating the AHR, which led to decreased pro-inflammatory cytokines during colitis. MS, multiple sclerosis; T1D, type 1 diabetes; T$_{reg}$ cell, regulatory T cell; Tr1 cell, type 1 regulatory T cell.

An improved understanding of structure–activity relationships should lead to more efficient development of safe and efficacious AHR-targeted immunotherapies.

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All authors contributed to the writing and editing of the manuscript.

Competing interests
K.A.M. and D.R. are employees of Dermavant Sciences, for which they receive financial compensation in the form of salary and stock options. D.H.S. holds equity in and is a co-founder of Hercules Pharmaceuticals. F.J.Q is the Scientific Founder of AnTolRx and Violet Therapeutics, companies developing novel therapies for inflammatory and neurologic disorders; and is a consultant for Dermavant Sciences. C.M.P. declares no competing interests.

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