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The aryl hydrocarbon receptor in immune regulation and autoimmune pathogenesis

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ABSTRACT

As a ligand-activated transcription factor, the aryl hydrocarbon receptor (AhR) is activated by structurally diverse ligands derived from the environment, diet, microorganisms, and metabolic activity. Recent studies have demonstrated that AhR plays a key role in modulating both innate and adaptive immune responses. Moreover, AhR regulates innate immune and lymphoid cell differentiation and function, which is involved in autoimmune pathogenesis. In this review, we discuss recent advances in understanding the mechanism of activation of AhR and its mediated functional regulation in various innate immune and lymphoid cell populations, as well as the immune-regulatory effect of AhR in the development of autoimmune diseases. In addition, we highlight the identification of AhR agonists and antagonists that may serve as potential therapeutic targets for the treatment of autoimmune disorders.

1. Introduction

The aryl hydrocarbon receptor (AhR) is a member of the periodic circadian protein (PER)-AhR nuclear translocator (ARNT)-single-minded protein (SIM) superfamily of transcription factors, in which the PER-ARNT-SIM (PAS) domain senses both endogenous factors (such as oxygen tension or redox potential) and exogenous factors (such as poly-aromatic hydrocarbons and environmental toxins) [1]. Early studies on AhR were conducted to understand the mechanistic basis for the toxicity mediated by the prototypic ligand 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) [2,3]. Since the last decade, growing attention has been paid to the role of environmental pollutants (e.g. TCDD) in the development of immunological diseases including autoimmune disorders [4]. With the stimulation of exogenous AhR ligand (TCDD) in immunocompetent cell populations, AhR was found to regulate various biological processes, including development and homeostasis. For example, AhR plays a role in differentiating Th17 cells and regulatory T cells (Tregs) [5,6], maintaining innate lymphoid cells (ILCs) [7], mobilizing myeloid-derived suppressor cells (MDSCs) [8,9], and B-cell maturation [10,11].

Although AhR was originally thought only to mediate the toxic effects of dioxins, a variety of physiological ligands such as those derived from diet, symbiotic flora, and host metabolism also interact with AhR [1]. Many studies have shown that AhR directly or indirectly regulates numerous genes for various biological functions, including cell differentiation, malignant transformation, immune response regulation, circadian rhythm control, cell metabolism, adaptive and innate immunity [12,13]. The identification of natural ligands and analysis of AhR-deficient mice have demonstrated the important physiological role of AhR [14]. Recent studies suggest that the AhR signaling pathway may be implicated with autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), multiple sclerosis (MS), autoimmune hepatitis (AIH), and inflammatory

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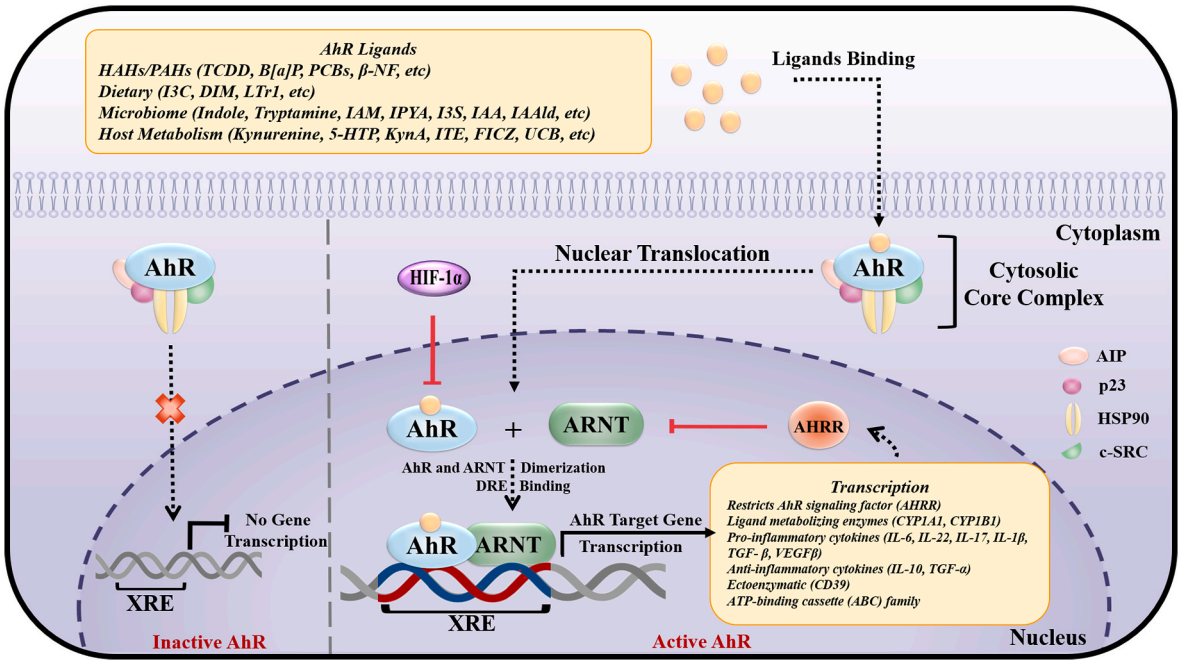

Fig. 1. Mechanisms of AhR activation.

bowel disease (IBD). The AhR agonists or antagonists has been applicated in various autoimmune disease models. For example, phagocytosis of apoptotic cell fragments by macrophages triggers AhR signaling, and AhR activation induces the immunomodulatory cytokine IL-10, which suppresses the downstream inflammatory response to regulate immune tolerance in SLE [15]. Different AhR agonists such as TCDD and 6-formylindolo [3,2-b] carbazole (FICZ) play contrasting roles in experimental autoimmune encephalomyelitis (EAE), with the former inducing differentiation of Treg cells and inhibiting EAE, while the latter interfering with differentiation of Treg cells and promoting differentiation of Th17 cells and exacerbating EAE [5]. Moreover, increased availability of AhR ligand 5-Hydroxyindole-3-acetic acid (5-HIAA) promotes the regulation of Breg suppressor function and inhibits the differentiation of germinal center (GC) B cells and plasma cells, thereby ameliorating arthritic symptoms [16]. In contrast, the dysfunction of AhR signaling may be associated with impaired immunosuppressive function in some autoimmune diseases, for example, the defective response of Th17 cells of Crohn's disease to AhR signaling is manifested by impaired upregulation of extracellular enzymes-CD39 [17], which plays an immunosuppressive role, and similarly in Th17 and Treg cells of autoimmune hepatitis patients [18]. On the other hand, a recent study has shown that the dietary supplementation with the natural AhR ligand indole-3-propionic acid (IPA) improves salivary gland pathology and restores polymorphonuclear MDSCs (PMN-MDSCs) immunosuppressive function in ESS mice [19]. Many questions arose regarding the cellular and molecular consequences of AhR activation, but despite many investigations for almost two decades, the molecular basis by which AhR participates in immunological processes remains largely unknown [2].

In this review, we discuss the roles of AhR in regulating multiple immune cells and immune responses within the context of autoimmunity. Further understanding AhR regulation of immune cell and the effect of AhR agonists and antagonists will facilitate the development of new targeted therapies for the treatment of human disease.

2. AhR ligands and activation

2.1. Mechanisms of AhR activation

AhR is a transcription factor of the PAS (Pern-ARNT-Sim) family. The PAS protein domain is a basic spiral ring helix structure that mediates broad responses to numerous environmental pollutants and cellular metabolites [20]. Inactive AhR is located in the cytoplasm complexed with several chaperones that stabilize it. The cytoplasmic AhR complex contains the following: (1) a heat shock protein (HSP) 90 (HSP90) dimer maintaining AhR in a conformation that maximizes its affinity for ligands [21]; (2) an AhR-interacting protein (AIP; also known as XAP2) that enhances the stability of the AhR-HSP90 complex [22,23]; (3) a co-chaperone, 23-kDa glycoprotein (p23), that protects AhR from ubiquitin mediated degradation, which is similar to AIP and ensures cytoplasmic localization of AhR [24,25]; and (4) c-Src, which is involved in the initial steps of AhR activation upon ligand binding and participates in non-genomic mechanisms of AhR signaling [26]. When a ligand binds to the AhR complex within the cytoplasm, it induces a conformational change in AhR that results in complex separation and nuclear translocation. After AhR enters the nucleus, its binding partner ARNT (also known as hypoxia-inducible factor 1β, HIF-1β) induces the transcription of various target genes via dioxin response elements (DREs) at AhR-ARNT binding sites [27–29]. In a negative feedback loop that limits AhR activation, AhR ligand degradation is facilitated by the cytochrome p450 (CYP1) enzymes, CYP1A1 and CYP1A2, which are directly activated by AhR. In addition, Aryl hydrocarbon receptor repressor (AHRR) competes with the AhR ligand complex to form a heterodimer with ARNT, represses the activation of AhR-dependent transcription [30]. Similarly, HIF-1α has been shown to compete with AhR for its interaction with ARNT. AhR is involved in regulating the half-life of HIF-1α and mediated the differentiation of type 1 regulatory T (Tr1) cells by regulating the degradation of HIF-1α [31]. Inhibition of HIF-1α in Th17 cells reestablishes the normal response of unconjugated bilirubin (UCB) to cellular AhR signal activation, thereby enhancing the immunosuppressive effect of UCB on Th17 cells [17].

AhR controls a variety of biological reactions through endogenous and exogenous ligands, which leads to increased transcription of heterogeneous metabolic enzymes, namely CYP1A1 and CYP1B1. At the same time, AhR is involved in regulating the transcription of a variety of genes, such as cytokines (such as IL-10, IL-17, IL-22), CD39 and ATP-binding cassette (ABC) family of drug transporters [17]. AhR is expressed in Th17 cells and is able to promote the production of IL-17A, IL-17F and IL-22 [5,6]. AhR plays an important role in maintaining the

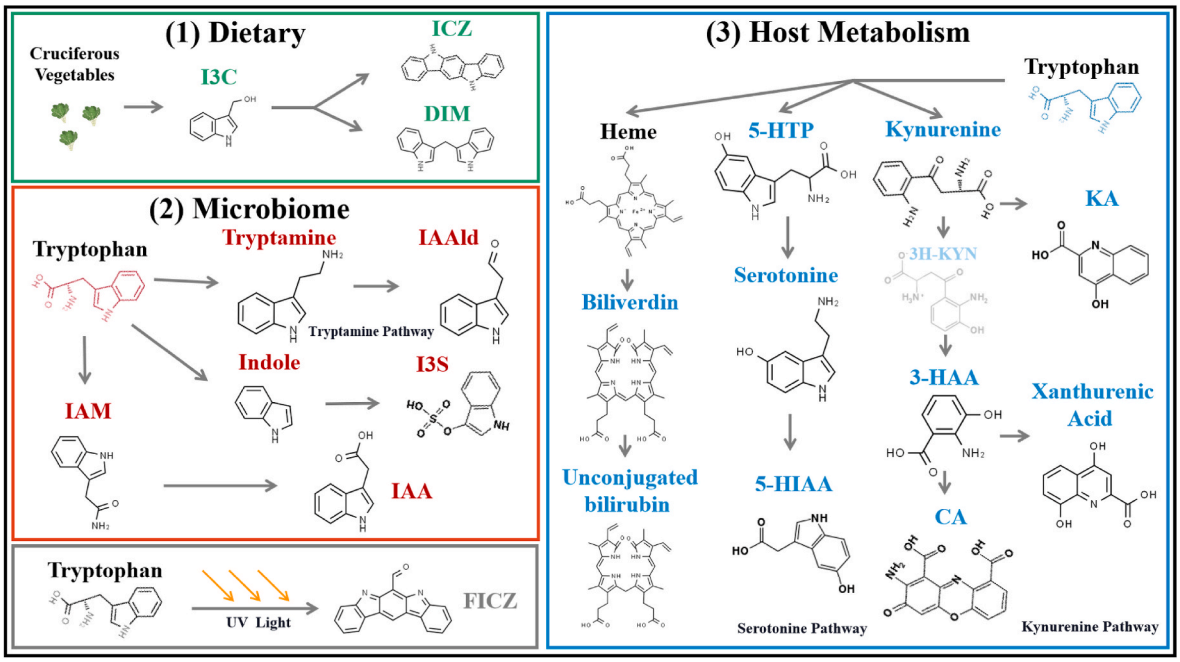

Fig. 2. AhR endogenous ligands.

1. Indole-derived AhR agonists derived from diet: cruciferous vegetables of the family *Brassicaceae* are a rich source of glucosinolate, which after hydrolysis, generates I3C and its downstream condensation derivatives, DIM and ICZ, AhR dietary agonists.
2. Tryptophan-derived AhR agonists: the direct transformation of Trp into several molecules produced by the kynurenine pathway (KP), the Trp hydroxylase 1 (Tph1) pathway, heme catabolite, and tryptophan photometabolites.

dynamic balance of Bregs function and directly regulates the expression of IL-10 in Bregs [16]. In addition, the dynamic balance of ILC3 and the generation of IL-22 need the participation of AhR, and the absence of AhR leads to the reduction of ILC3 that produces IL-22 [32]. CD39 is an ectoenzyme that catalyzes the conversion of extracellular ATP and ADP to AMP, which is subsequently converted into immunosuppressive adenosine. Expression of CD39 correlates with immunosuppressive properties of cells and promotes cell transition to a less pathogenic phenotype. Activation of AhR induced CD39 inhibition of Foxp3^{+}iTreg cells in responder T cells in the presence of transforming growth factor-β1 (TGF-β1) [33]. Recent studies have shown that binding of AhR to endogenous ligand UCB upregulates CD39 expression in Th17 cells, while ligation of AhR in Crohn's patient-derived Th17 cells leads to low CD39 expression and ineffective immunosuppressant effect on UCB [17,34]. Similar impaired CD39 upregulation was observed in Treg and Th17 cells from patients with autoimmune hepatitis. This immunosuppressive dysfunction is associated with dysregulation of AhR signaling, and interference with the dysregulation signaling pathway restores the upregulation of CD39 in Treg and Th17 cells [18].

In summary, AhR, a ligand-activated transcription factor, enters the nucleus of a cell where it interacts with ARNT, forming a heterodimer complex that binds to specific xenobiotic responsive element (XRE) sequences, regulating multiple biochemical pathways [35]. To date, a large number of chemicals, with significantly different structures, have been found to interact with and activate AhR. In addition to a large number of exogenous ligands, there are a variety of naturally occurring dietary compounds, endogenous molecules, and gut microbial components that can bind to AhR [36] (Fig. 1).

In the absence of ligand, AhR is sequestered in the cytoplasm with chaperones and immunophilin-like proteins such as HSP90, AIP, p23, and c-Src. Upon interaction with an agonist, conformational changes result in translocation of AhR to the nucleus where it interacts with ARNT. The heterodimer binds to a specific XRE found in the promoter of target genes, thereby regulating the transcription of those genes (AhR signature). AhR drives the expression of CYP enzymes, which degrade AhR ligands. AhR also induces the expression of its repressor, AHRR, which inhibits the formation of the AhR/ARNT complex required for AhR signaling.

ARNT, AhR nuclear translocator; XRE, Xenobiotic responsive elements; HSP90, Heat shock protein (HSP) 90; AIP, AhR-interacting protein; p23, Co-chaperone 23-kDa glycoprotein; AHRR, Aryl hydrocarbon receptor repressor.

2.2. Exogenous ligands

AhR, originally identified as a receptor for environmental pollutants, has been extensively studied in the fields of toxicology, pharmacology, and clinical medicine. Potent exogenous ligands for AhR, such as halogenated aromatic hydrocarbons (HAHs) and poly-aromatic hydrocarbons (PAHs), have been well characterized. HAHs and PAHs, TCDD, Benzo [a] Pyrene (B[a]P), polychlorinated biphenyls (PCBs), and β-naphthoflavone (β-NF) are the most common exogenous ligands of AhR. Many studies have identified multiple TCDD mechanisms and pathways for AhR activation and thereby regulating the immune response [37–39].

2.3. Endogenous ligands

In the past decade, a large number of non-toxic nutrients and endogenous ligands have been shown to interact with AhR. These include a variety of endogenous signals from diet, host metabolism, gut microbiota, and plant/mammalian enzymes [1,14,40]. Upon ligand binding, AhR affects gene expression in mouse and human cells through promoter binding, recruitment of coactivators and corepressors at specific DNA regions, and interaction with signal transduction machinery [1]. Here, we focus on discussing endogenous and physiological AhR ligands generated by cells and microbiota, and from dietary sources that have been shown to modulate innate immune and lymphocyte cell proliferation, apoptosis, differentiation, and migration [41,42].

An abundant source of AhR agonists is the diet, including vegetables,

Table 1
AhR agonists and antagonists.

Activity	Source	Examples	Ref
AhR Agonists	Halogenated aromatic hydrocarbons (HAHs)/ Polyaromatic hydrocarbons (PAHs)	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	[59]
		Polychlorinated biphenyls (PCBs)	[59]
		Benzo [a] pyrene (B[a]P)	[60]
	Dietary	Dietary compounds 3, 3′-diindolylmethane (DIM)	[61]
		Indole-3-Carbinol (I3C)	[62]
		Indolo [3,2-b] carbazole (ICZ)	[63]
	Microbiome	Tryptophan	[64]
		Indole	[64]
		Indole Acetic Acid	[64]
		Tryptamine	[64]
		Indole-3-Pyruvic Acid (IPA)	[65]
		5Hydroxyindole-3-acetic acid (5-HIAA)	[16]
	Host metabolism	Kynurenine (Kyn)	[66]
		Kynurenic Acid (KynA)	[67]
		6-Formylindolo [3,2-b] carbazole (FICZ)	[68]
		2-(19H-Indole-39-carbonyl)-thiazole-4-carboxylicacid methyl ester (ITE)	[69]
		5-Hydroxy-tryptophan (5-HTP)	[70]
		5-Hydroxytryptamine (5-HT)	[71]
		3-Hydroxyanthranilic Acid (3-HAA)	[72]
		Biliverdin	[54,55]
		Unconjugated bilirubin (UCB)	
	Synthetic	VAG539	[73]
		APT102	[74]
AhR Antagonist	CH22319		[75]
	Stem Regenin 1 (SR1)		[76]
	3′,4′-Dimethoxyflavone (DMF)		[70]
	GNF35		[77]

fruits, and tropical plants. In particular, cruciferous vegetables from the family *Brassicaceae* are a rich source of glucoseinolate conjugates capable of activating AhR in mice and humans. After consumption, glucosinolates undergo hydrolysis, generating indole-3-carbinol (I3C) and its downstream condensation derivative, 3,3′-diindolylmethane (DIM), which is an AhR agonist [43,44]. Flavonoids are another major source of AhR ligands in the diet, including a large class of polyphenolic secondary metabolites that are widely distributed in fruits and vegetables. A subset of flavonoids including quercetin, taxifolin, and robinetin can activate AhR [45].

The metabolism of tryptophan (Trp) is also a physiological source of AhR agonists. Trp metabolism follows three major pathways in the gastrointestinal tract [46]: (1) The direct transformation of Trp, by gut microbiota, results in ligands for AhR. These include tryptamine, indole, indole-3-acetamide, indole-3-acetic acid, indole acrylic acid, indole-3-aldehyde, indole-3-lactic acid, indole-3-propionic acid, and indole-3-pyruvate. Moreover, indole can be further metabolized into other biologically active metabolites such as indoxyl-3-sulfate, indole-3-propionic acid, and dioxindole [14,47,48]. Thus, synthesis of putative AhR ligands by the intestinal commensal microflora provides a constant source of ligands for AhR stimulation. AhR acts as a sensor of the microbiota community and maintains host-microbe homeostasis by means of its established role as a modulator of immune function [49]. (2) The kynurenine pathway (KP) of both immune and epithelial cells generates kynurenine (Kyn) via indoleamine 2,3-dioxygenase (IDO) 1 [50,51]. Kyn can be metabolized into potent AhR ligands such as kynurenic acid, xanthirenic acid, and cinnabarinic acid, with these KP end products involved in the regulation of a number of host biological processes including neurotransmission, inflammation, and the immune response [46,52]. (3) The serotonin 5-hydroxytryptamine (5-HT) production pathway produces AhR ligands in enterochromaffin cells via Trp hydroxylase 1 (Tph1) [53]. Butyrate supplements can improve arthritis by altering the composition of the microbiota and increasing the production of the serotonin-derived metabolite, 5-HIAA, which regulates the function of Bregs that reduce arthritis severity in a mouse model [16]. Several endogenous soluble metabolites of tryptophan, namely tryptamine and indole acetic acid, as well as bilirubin (BR), the breakdown product of heme. Heme oxygenase-1 catalyzes the degradation of heme into ferrous iron, carbon monoxide, and biliverdin, the latter is converted to UCB by biliverdin reductase [54]. UCB is a tetrapyrrole compound that is catabolic from heme. It can activate AhR and induce AhR-dependent gene expression at higher concentrations, and biliverdin can also activate AhR [55,56]. Recently, bilirubin has been reported to activate AhR in Th17 cells to produce CD39, thereby exerting an immunosuppressive function to suppress experimental colitis, suggesting that bilirubin contributes to an AhR dependent anti-inflammatory effect *in vivo* [17,34].

A photo-oxidation ligand for AhR results from exposure of L-tryptophan to ultraviolet B (UVB) radiation and visible light, which produce FICZ by photolysis [57]. FICZ activates AhR at pico molar concentrations. It has an affinity for AhR similar to that of TCDD and is present in humans, particularly in the skin [58] (Fig. 2, Table 1).

I3C, indole-3-carbinol; DIM, 3,3′-diindolylmethane; ICZ, indolo [3,4-b] carbazole; IAM, Indole-3-Acetamide; IAA, Indole Acetic Acid; I3S, indoxyl-3-sulfate; IAAld, Indole-3-Acetaldehyde; KA, Kynurenic Acid; 3H-KYN, 3-Hydroxy Kynurenine; 3-HAA, 3-Hydroxyanthranilic Acid; CA, Cinnabarinic Acid; 5-HTP, 5-Hydroxytryptophan; 5-HIAA, 5-Hydrox-yindole-3-Acetic Acid; FICZ, 6-formylindolo [3,2-b] carbazole.

3. AhR activation and signal pathways

3.1. HIF-1α

Hypoxia-inducible factor (HIF) is a key transcriptional regulator of vascular oxygen supply, metabolic demand, and angiogenesis [78]. Under hypoxic conditions, hypoxia-inducible-factor-1-alpha (HIF-1α) binds to ARNT heterodimers to regulate a series of genetic programs [79]. Further, AhR binding to ARNT is required for an AhR induced immune response, such that interference with AhR/ARNT transcriptional activity is regulated by HIF-1α.

Tr1 cells are Foxp3^{-} regulatory CD4^{+}T cells that produce IL-10. Control of Tr1 cell differentiation and metabolism is poorly understood. However, studies have shown that aerobic glycolysis enhances the differentiation of Tr1 cells through HIF-1α and AhR-controlled metabolic programs. Early metabolic reprogramming of Tr1 cells is controlled by HIF-1α. At a later time, AhR promotes HIF-1α degradation

and controls Tr1 cellular metabolism. Thus, AhR and HIF-1α cooperate to support Tr1 cellular metabolism, which is involved in modulating the immune response of Tr1 cells [31]. Tc22 are IL-22-producing CD8 cells, which have been shown to activate the metabolic intermediates, HIF-1α and AhR, in the presence of coenzyme A (CoA), thus driving the production of IL-22 [80].

Norisoboldine (NOR) is a newly discovered endogenous ligand of AhR. Studies have shown that it can attenuate osteoclast (OC) differentiation and bone erosion by activating AhR and subsequently inhibiting HIF-1α signaling pathways. NOR can stably bind AhR, up-regulate AhR nuclear translocation, enhance AhR-ARNT complex accumulation and inhibit ARNT–HIF–1α complex accumulation in RAW 264.7 cells [81]. In addition, NOR can also promote the differentiation of Treg cells in colitis model under hypoxia condition, thus alleviating the disease development of colitis [82]. Th17 cells from AIH patients have a defective response to AhR ligation, resulting in an impaired up-regulation of CYP1A1, the downstream target gene of AhR. AhR dysfunction in AIH patients may be due to increased HIF-1α, an AhR repressor. In AIH patients, hypoxia exerts an inhibitory effect on AhR signaling that is at least partially reversed upon exposure to HIF-1α molecular silencing. Based on these experimental results, a new immunotherapy approach has been proposed in which HIF-1α antagonist/silencer can regulate the normal activation of the AhR signaling pathway, improving effector cell function as a means by which to treat disease-related immune regulation deficiency [18]. Th17 cells obtained from peripheral blood of patients with Crohn's disease expressed low levels of CD39 and failed to recover their immunosuppressive function after UCB treatment. This may be due to the hypoxia induced by chronic inflammation promotes the increase of ABC transporters, the former hypoxia-induced HIF-1α significantly affects AhR/ARNT signal transduction by reducing the availability of AhR ligand, the latter increased transporter leads to the effluence of AhR ligand such as UCB from Th17 cells and reduces the availability of substrates. Therefore, hypoxia reduces the sensitivity of Th17 cells to UCB-stimulated AhR, and this deficiency in Th17 cell response to AhR activation is reversed when HIF-1α or transporter is blocked [17].

In conclusion, the cross-talk between AhR and HIF-1α is involved in different metabolic programs related to the differentiation of immune cells and the pathogenesis of autoimmune diseases.

3.2. NF-κB

Nuclear factor-κB (NF-κB) protein is an important regulator of the immune response and is involved in a variety of signaling pathways. The complex cross-talk between these signaling pathways is important to the biological functions of NF-κB and AhR during the immune response of different cell types during different disease states. However, the cross-talk between AhR and NF-κB signaling is still not fully established [83,84].

Recent studies have shown that DIM, an active metabolite of cruciferous I3C, regulates a series of cellular immune responses primarily through AhR. DIM reverses the epithelial-mesenchymal transition (EMT) process and inhibits cancer cell metastasis by regulation of the AhR signaling pathway and by inhibition of the NF-κB pathway [85]. Further, kynurenine induced AhR signaling in gliomas can modulate the phenotype of macrophages, with AhR depletion increasing NF-κB activation of macrophages *in vitro*. Mechanistically, macrophage up-regulation of SOCS2 expression and Krüppel-like factor 4 (KLF4) degradation in AhR-null mice relieved NF-κB signaling, indicating that AhR controls macrophage polarization by regulation of NF-κB [86]. Interestingly, NF-κB regulates the expression of kynurenine pathway genes and AhR in triple-negative breast cancer (TNBC) cells. Down-regulation of Iκκ-epsilon, a positive regulator of NF-κB activity, reduces the expression of tryptophan 2,3-dioxygenase (TDO2) and kynureninase (KYNU). That study demonstrated that increased transcription of TDO2, KYNU, and AhR in TNBC was specifically induced by and dependent upon NF-κB [87].

In summary, NF-κB and AhR signaling pathways are mutually regulated, resulting in cell type and stimulus specific responses.

3.3. Nrf2

AhR was originally identified as a regulator of biological and toxicological responses to environmentally toxic planar aryl hydrocarbons such as HAHs and PAHs with high affinity for AhR. Due to the role of AhR in xenometabolism, there have been extensive toxicology, pharmacology, and medical studies of AhR. Kelch-like ECH-associated protein 1 (KEAP1)-nuclear factor erythroid 2-related factor 2 (Nrf2) is another important system that protects the human body from environmental pollutants. KEAP1 is a sensor protein that detects environmental contaminants that activate the transcription factor, Nrf2. Nrf2 protects the body from immune toxicity by inducing the expression of genes involved in detoxification, antioxidation, and anti-inflammatory activities [4].

Activation of keratinocyte growth factor (KGF)-2 protects the skin from UV damage. The activation of Nrf2 by KGF-2 is significantly inhibited by the AhR antagonist GNF351. These observations suggest that KGF-2 activates Nrf2 to play an antioxidant role by activation of AhR after UVB irradiation. The research demonstrated, for the first time, that KGF-2 stimulates Nrf2 activation via the AhR pathway, thereby protecting keratinocytes from UV-induced cellular damage [88]. The activity of a major microbial metabolite, urolithin A (UroA) and its potent synthetic analogue (UAS03), requires the activation of AhR. Nrf2 is a target of the AhR signaling cascade. UroA/UAS03 enhances intestinal barrier function by activation of an AhR-Nrf2-dependent pathway that induces tight junction (TJ) proteins [89]. CDDO-Im, an activator of Nrf2, promotes IL-17A and IL-22 responses by mouse Th17 cells. Further, IL-22 production induced by Nrf2 in $CD4^{+}$T cells is dependent on AhR. In $CD4^{+}$T cells, Nrf2 protein directly binds to the antioxidant response element (ARE) motif of AhR, then Nrf2 induces IL-22 production by promotion of AhR transcription [90]. These results demonstrate the antioxidant and anti-inflammatory effects of AhR through direct regulation of Nrf2 transcription and suggest the potential use of agonists and inhibitors as therapeutic targets for treatment of immune-based disease.

3.4. MAPK

Interference with the mitogen activated protein kinase (MAPK) pathway leads to alterations in cellular processes such as differentiation, proliferation, and apoptosis, which are also altered by the AhR pathway. Cross-talk exists between MAPK and AhR pathways, but the specific interactions are not well understood. A new report has identified cross-talk between the AhR pathway and the MAPK pathway in the nervous system. TCDD was shown to enhance NGF-induced neurofilament light (NFL) expression and the phosphorylation of ERK1/2 and p38 in PC12 cells. MAPK inhibition blocks NFL expression, while an AhR inhibitor not only inhibited the up-regulation of NFL expression, but also reversed the phosphorylation of ERK1/2 and p38 [91]. B[a]P promotes the phosphorylation of Src and ERK1/2, with inhibition of Src and ERK1/2 phosphorylation reducing CYP1A1 induction and AhR nuclear translocation. These observations suggest cross-talk between AhR and MAPK pathway members [92]. Indoxyl sulfate (IS) interferes with osteoblast formation by inhibition of ERK and p38 MAPK pathways downstream of AhR, while resveratrol (RSV) ameliorates the anti-osteogenic effect of IS by inhibition of AhR and downstream signal transduction [93]. In contrast, macrophages of chronic kidney disease (CKD) patients exposed to a typical uremic toxin, exhibited IS induced inflammation by acceleration of the AhR/NF–κB/MAPK cascade, which did not activate NLRP3 inflammatory bodies but did limit mature IL-1β production [94].

4. Role of AhR in regulating immune cell functions

4.1. Innate immune cells

4.1.1. Macrophages

Macrophages play an important role in development, internal environment stability, tissue repair, and immunity [95]. When tissue injury occurs, macrophages are activated and recruited to the site of injury, where they promote inflammation, wound healing, fibrosis, anti-inflammatory effects, anti-fibrosis effects, decomposition, and tissue regeneration [96]. Macrophages are divided into two subclasses, proinflammatory M1 and anti-inflammatory M2 cells, based on their production of nitric oxide and arginine [97]. AhR has been shown to be involved in the regulation of macrophage conversion into pro-inflammatory or anti-inflammatory phenotypes, mediated by macrophage-dependent cellular pathways [98]. Further, AhR activation indirectly regulates interaction between other immune cells and macrophages and the conversion of monocytes to macrophages [99].

Several studies have shown that AhR expression in LPS-stimulated macrophages significantly increases the expression of IL-10, while loss of AhR reverses this effect [100,101]. Further, there is a functional 5-HT/5-HT_{2B}/AhR axis in human macrophages. 5-HT enhances the activity of AhR and up-regulates the macrophage expression of anti-inflammatory target in a 5-HT_{2B} dependent manner, affecting the macrophage gene profile [71].

Activation of AhR by difference agonist classes (e.g. FICZ, B[a]P and PCB126) promotes the transformation into a pro-inflammatory macrophage phenotype that exacerbates an inflammatory response [99,102]. AhR can also indirectly regulate the polarization of macrophages, in that, FICZ induces the activation of AhR to promote the transcriptional regulation of miR-142a, which indirectly inhibits the expression of HIF-1α, thereby reducing the polarization of M1 macrophages [103].

These findings demonstrate that AhR mediates immune regulation as a transcription factor or by non-genomic signaling, each of which promotes the conversion of macrophages to anti-inflammatory or pro-inflammatory phenotypes that influence disease outcomes.

4.1.2. Dendritic cells

Dendritic cells (DCs) are bone marrow-derived cells of the lymphoid myeloid hematopoietic lineage that plays an important role in both the innate and acquired immune response [104]. A recent study reported that AhR may influence innate immunity by controlling DC differentiation from monocyte precursors. Increased expression of Blimp1 induced by AhR activation promotes DC differentiation by monocytes in mice and humans [105]. Both FICZ and I3C enhance AhR activity, which increases a mononuclear cell-derived DC transcription signature [105]. Thus, AhR sensing may be a key driver of macrophages/DC balance in inflammatory tissue [27].

AhR signals are involved in the regulation of DC function by reducing polarization of pro-inflammatory T cells and by promoting the differentiation of anti-inflammatory Treg cells. In fact, the AhR agonist, 2-(1′H-in-dole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), not only regulates DCs in EAE, but also induces DCs to produce retinoic acid that promotes the generation of Treg cells [106]. TCDD-activated AhR induces increased expression of IDO1 and indoleamine 2,3-dioxygenase-like protein (IDO2) in DCs, which catalyze Kyn production, promoting $Foxp3^+$ Treg differentiation [107]. Similarly, AhR deficient DCs fail to promote Treg differentiation and Th17 cell generation *in vitro* [108]. Indole-3-propionic acid (IPA) can effectively treat chronic inflammation of the colon by activation of AhR, which reduces DC induced IFN-γ production and increases IL-10 cell differentiation in inflammatory bowel disease (IBD) in mice. Increased numbers of anti-inflammatory $CD103^+$ $CD11b^-$ DCs in mesenteric lymph nodes (MLNs) significantly reduces the severity of colitis [65]. Overall, these studies support the anti-inflammatory effect of AhR in DCs.

AhR can also affect DC function in that particulate matter (PM) enhances DCs activation, co-stimulation, and antigen presentation in an AhR dependent manner, which is absent in AhR deficient DCs [109]. However, different results were obtained when ITE, an AhR agonist, was used. ITE stimulation of AhR decreased the expression of MHC class II and co-stimulatory molecules on splenic DCs [106]. Further, AhR deficiency increased DC functional activation as well as higher levels of cell surface MHC class II and CD86 molecules [110].

Collectively, these results suggest that activation of AhR in DCs promotes immune-regulatory effects whereas loss of AhR affects DC function.

4.1.3. Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a population of myeloid cells generated during pathologic conditions. These cells represent a pathologic state of activation for monocytes and relatively immature neutrophils [111].

Recent studies have shown that TCDD induced activation of AhR, within the peritoneal cavity, mobilizes MDSCs with immunosuppressive function. Treatment with an AhR antagonist significantly decreased TCDD-induced MDSCs, indicating that immunosuppression by TCDD is by an AhR-dependent mechanism [8]. TCDD induced AhR-mediated MDSC mobilization is dependent on CXCR2 expression in that CXCR2 blockade reduced TCDD-mediated MDSC induction [9]. Recent studies have shown that defective AhR activation results in impaired PMN-MDSCs regulation in an experimental Sjögren's syndrome (ESS) mouse model. IPA, a dietary tryptophan metabolite that activates AhR, promotes the differentiation of PMN-MDSCs that have the capacity to inhibit $CD4^+$T cell function. That is, IPA restores the function of PMN-MDSCs in ESS mice by activation of AhR [19].

4.1.4. Natural killer cells

The molecular basis for the effects of AhR on NK cells is largely unclear. Peripheral blood mature NK cells are known to lack AhR, but inhibition of AhR expression is induced by STAT3 during IL-21-driven NK activation and proliferation, with increased CD56 expression. In NK cells, AhR regulates gene sets that are highly associated with multiple signaling and metabolic pathways as well as the oxidative stress response [112]. In particular, human peripheral NK cell populations are differentially susceptibility to AhR modulation. Peripheral $CD56^{bright}$ NK cells express high levels of AhR mRNA and are highly sensitive to AhR ligands. However, AhR mRNA expression gradually decreases as NK cells display a more mature phenotype, $CD56^{dim}$. Finally, AhR ligands modulate $CD56^{bright}$ NK cell surface receptors and cytokine secretion [113].

AhR is a significant factor in the regulation of NK cell migration. In the absence of AhR, NK cells have a reduced capacity to migrate *in vivo*. Further, AhR binds the promoter region of the ASB2 gene, such that AhR interaction with the agonist, FICZ, induces ASB2-dependent filamin A degradation in NK cells, which increases the migration of primary NK cells [114].

4.1.5. Innate lymphoid cells

Innate Lymphoid cells (ILCs) are abundant in the mucosa of the intestine and lung and are considered to be innate of adaptive immune system $CD4^+$ helper T cells [115]. ILCs have been categorized into three distinct groups by transcriptional circuitry and effector function [116]: (1) Group 1 ILCs (ILC1 cells) are similar to Th1 cells [117]. (2) Group 2 ILCs (ILC2 cells) express the transcription factor GATA-3, a master regulator of the Th2 subset of helper T cells, which regulates IL-5 and IL-13 production [118,119]. (3) Group 3 ILCs (ILC3 cells) correspond to Th17 cells, expressing the transcription factor, RORγt, and producing IL-17 and IL-22 [120–122].

AhR signaling inhibits the expression of the IL-33 receptor (ST2), IL-5, IL-13, and the GFI1 transcription factor. AhR activation inhibits the function of ILC2 but enhances the maintenance of ILC3. The AhR pathway regulates intestinal ILC2-ILC3 balance, producing an immune

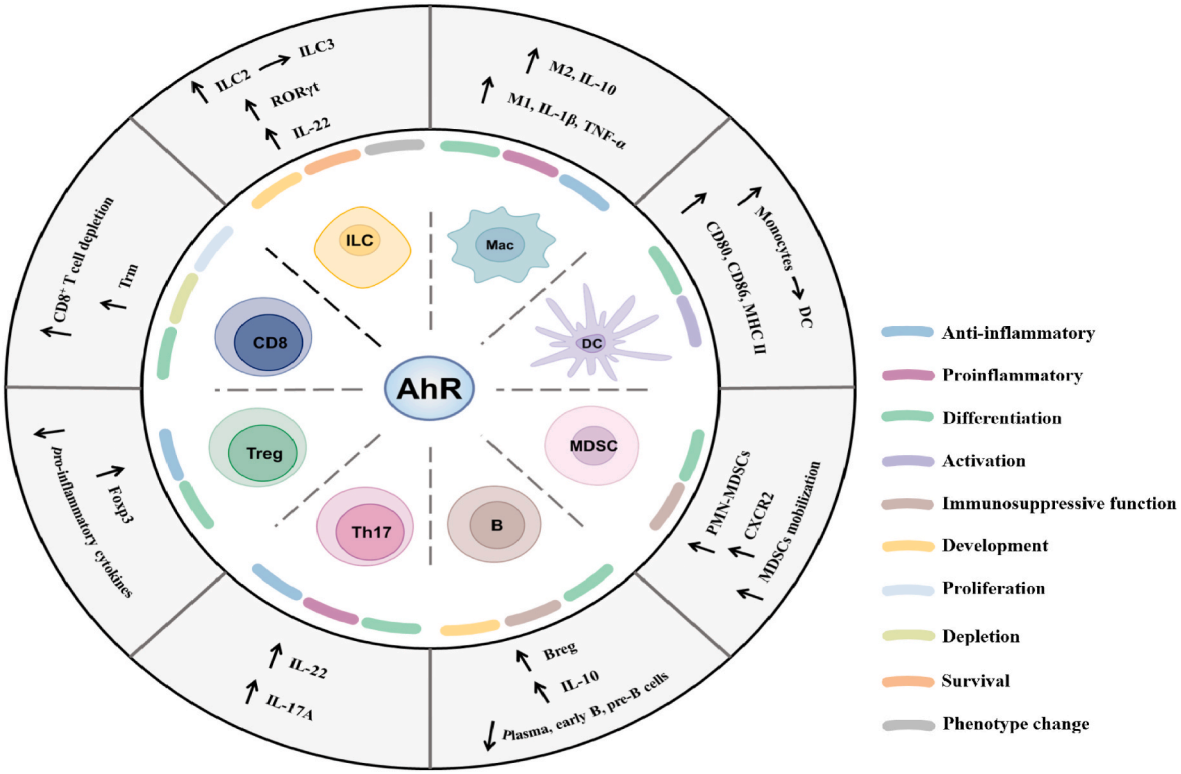

Fig. 3. The role of AhR in regulating immune cell functions.

protective response to various pathogens [123]. The AhR pathway is involved in the ILC phenotypic change in the inflammatory terminal ileum of patients with celiac disease, as shown by the transformation of ILC3 to ILC1 accompanied by down-regulation of AhR expression [124]. These results suggest that the AhR pathway is important in the regulation of the intestinal ILC phenotype.

AhR has been well studied in intestinal ILC3 and several important observations have been made. First, AhR is essential for their survival [41]. AhR increases the survival rate of ILC3s through the expression of the IL-7/IL-7R pathway and anti-apoptotic genes, thus promoting the maintenance of ILC3s [7]. AhR deficient ILC3s have reduced Ki67 expression, suggesting that decreased proliferation may lead to ILC3 deficiency [125]. Second, AhR is an important central node in the development of ILC3s [125,126]. Runx3 and its downstream target, RORγt, promote the development of ILC3s through AhR induction [127], while Ikaros inhibits the development of ILC3s by inhibition AhR expression [128]. AhR works by promoting transcription of Notch 1 and Notch 2, and by stabilizing c-Kit expression [129,130]. Finally, AhR regulates the production of IL-22 by ILC3s. In AhR deficient mice, ILC3 levels are very low, with cryptic cap dysplasia, isolated lymphatic follicles, and insufficient intestinal IL-22 production [129]. Further, tryptophan metabolites, produced by the gut microbiome, have been shown to activate AhR, which maintains intestinal balance by increasing IL-22 expression by ILC3s [131,132]. Microbiome derived short chain fatty acids (SCFA) can promote the expression of AhR and up-regulate the production of IL-22. Dietary supplement of SCFAs enhances the production of IL-22, which protects the intestines from inflammation [133]. Patients with alcoholic hepatitis have low fecal levels of indole-3-acetic acid (IAA). Patient use of IAA supplements activates AhR to increase ILC3 levels and IL-22 production in the gut, which has been shown to protect mice from alcohol-induced steatohepatitis [48].

4.2. *Lymphocytes*

4.2.1. *T cells*

Recent research has demonstrated AhR to be a key regulator of adaptive immune response, especially the differentiation of Tregs and Th17 cells induced by a variety of endogenous, microbial, dietary, and environmental ligands [134]. Treg cells express the transcription factor Foxp3, which play a pivotal role in the maintenance of immunological homeostasis and the prevention of peripheral self-tolerance breakdown [135]. TCDD, ITE, FIZC, Kyn, and PB502 are common ligands of AhR, which increase Foxp3^{+} Treg production through activation of AhR. Other AhR ligands such as NOR, Alpine, Baicalein, and Laquimod metabolites directly promote Treg differentiation with the capacity to alleviate colitis via activation of the AhR pathway [5,6,82,106,136–139]. These findings highlight an interesting aspect of AhR biology, i.e., individual AhR agonists can have opposing effects on Treg functional maturation [27]. Previous studies have shown that AhR directly promotes Foxp3 transcriptional regulation by binding to the Foxp3 promoter or indirectly by regulation of downstream signaling molecules such as TGF-β [5]. Further, AhR has been shown to directly regulate Tregs via G protein-coupled receptor 15 (GPR15), a gut-homing receptor that epigenetically promotes CD4^{+}T cell intestinal homing during steady-state and inflammatory conditions, through induction and control of Foxp3 transcription [140]. Studies have shown AhR to play an important role in intestinal homing and function of Tregs. AhR can inhibit pro-inflammatory cytokine production by Tregs, and that Tregs expressing AhR have stronger inhibitory activity *in vivo* [141].

AhR is highly expressed in Th17 cells but it is largely unclear how AhR activation regulates Th17 differentiation and function. Th17 cell differentiation is initiated by TGF-β in combination with IL-6 or IL-21, while TGF-β via AhR induction promotes IL-22 production by Th17 cells [142,143]. Recent studies have demonstrated that vinblastine, a broad immune-modulator, promotes phosphorylation of Smad2/3 and STAT3 in an AhR-dependent manner. With TGF-β1, vinblastine significantly inhibited IL-2 and T-bet, promoting phenotypic differentiation of

Table 2
Role of AhR in immune cell populations.

Cell type	AhR activation and ligands	Function	Ref
Macrophages	5-HT, FICZ, B [a]P, I3C	Induced IL-10 production	[160]
		Shifts the LPS-treated macrophages toward the anti-inflammatory side	[99,71,103]
DCs	IPA	Reduces mo-DC differentiation	[105]
	3-HAA	Enhanced DC activation, co-stimulation, and antigen presentation	[65,109,72, 161]
MDSCs	TCDD	Increased immunosuppressive function	[8,9]
NK cells	FICZ	Regulating NK cell migration	[114]
		Relevant to development and function	[112,113]
		Inhibiting NK cell maturation and function	[162]
ILCs	FICZ	Mediated ILCs phenotype conversion	[123,124]
		Produced IL-22	[133,163]
T Cells	5-HTP	Modulated Treg transcription	[82,134,137,
	Kyn	factors Foxp3 and promoted Treg differentiation	138,140, 141,164]
		Elevated IL-22 or IL-17A levels promote Th17 differentiation	[142–144]
		Induced depletion of $CD8^+$T cells and upregulated PD-1 expression	[70,148]
B Cells	Kyn	Impaired the production of early	[10,11,156]
	TCDD	B cells and pre-B cells	
	5-HIAA	Regulate the differentiation and function of IL-10-producing $CD19^+CD21^{hi}CD24^{hi}$Bregs	[16,159, 165]

T cells toward a Th17 rather than Th1 phenotype [144]. The AhR signaling pathway is not only involved in the production of IL-22 by Th17 cells, but also promotes the expression of IL-17 A. Germinal center kinase–like kinase (GLK) induces AhR nuclear transfer and RORγt interaction, with the AhR-RORγt complex activating T cells and IL-17 gene transcription [145]. Likewise, I3C increases the percentage of $CD4^+ROR\gamma t^+Foxp3^-$ Th17 cells in the lamina propria, intraepithelial layer, and Peyer's patches of the small intestine, regulating progression of Type 1 Diabetes (T1D) in non-obese diabetic (NOD) mice [146].

AhR signaling also seems to have significant effect on $CD8^+$T cells. TCDD was shown to inhibit the differentiation and proliferation of $CD8^+$T cells during influenza infection, affecting $CD8^+$T proliferation and immunomodulation [147]. The molecular basis for these effects on $CD8^+$T cells is unknown. However, it is known that a sustained high level of IL-2 leads to continuous activation of STAT5 in $CD8^+$T cells, increasing 5-HTP, which participates in the metabolism of tryptophan, thereby activating AhR. Activated AhR synergistically up-regulates $CD8^+$T cell inhibitory receptors and down-regulates cytokine and effector molecule production, suggesting that IL-2 is a novel inducer of T cell exhaustion [70]. The AhR agonist, Kyn, is transferred to adjacent $CD8^+$T cells through the transporter SLC7A8 (a common neutral amino acid transporters) and PAT4, which activate AhR and up-regulate $CD8^+$T cells and PD-1 expression [148–150]. Analysis of skin tissue-resident memory T cells (T_{RM}) formed after cutaneous herpes simplex virus type 1 infection showed high expression of AhR. Moreover, $AhR^{-/-}$ T_{RM} disappeared from tissues at a faster rate over time than wild-type $CD8^+$T cells, suggesting that AhR is essential to the maintenance of mouse T_{RM} populations [151].

4.2.2. B cells

B cells are a key player in adaptive immune response through secretion of immunoglobulin (Ig) [152]. It is largely unclear how AhR regulates the response of B cells. Previous studies have shown that the activation of AhR inhibits the differentiation and maturation of B cells in mice [153]. Ligand-activated AhR regulates B cell differentiation and lineage related gene transcription, with activation of AhR preventing differentiation of mature B cells into plasma cells [154,155]. TCDD activation of AhR inhibits the production of early B cells and pre-B cells. Gene expression analysis has shown activation of AhR to be directly involved in the transcriptional regulation of early B cell factor 1 (EBF1), a key transcription factor within the B cell lineage, with decreased expression of EBF1 and paired box gene 5 (PAX5) impairing the generation of B lymphocytes [10,156]. Similarly, TCDD affects B cell

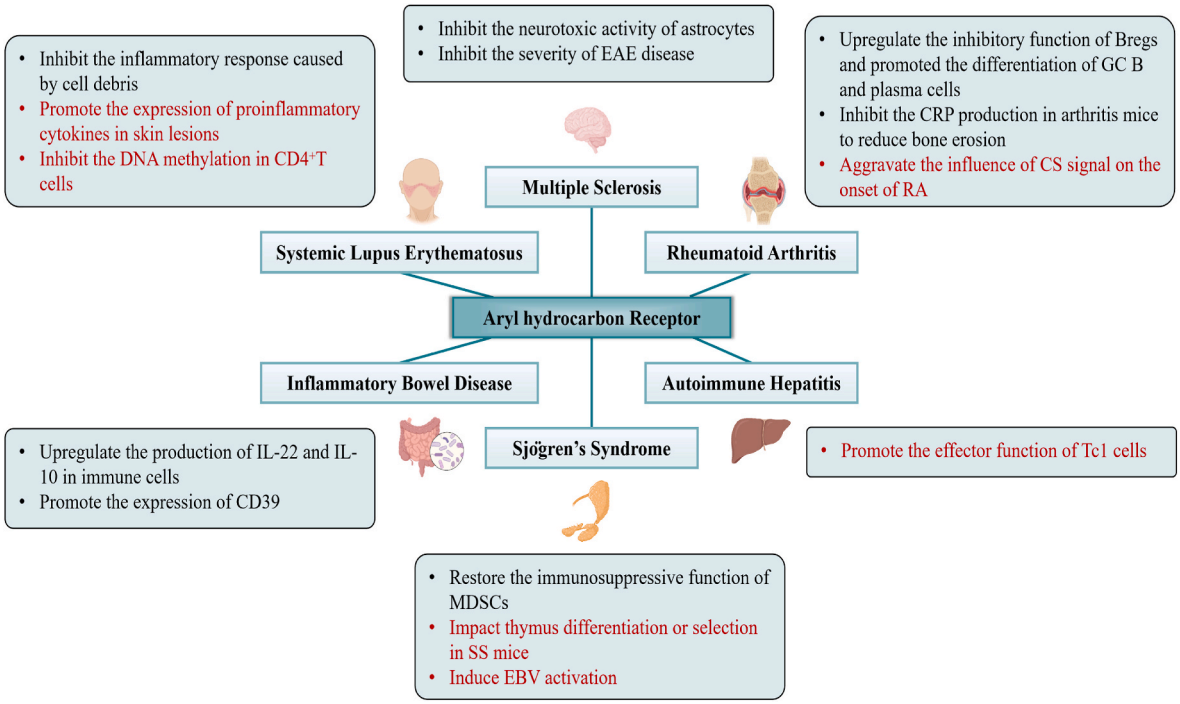

Fig. 4. AhR activity in autoimmune disease.

Table 3
AhR agonists or antagonists in autoimmunity immunotherapy therapeutics.

Name	Type	Disease	Function	Ref
Verteporfin (C1)	AhR antagonists	SLE patient	Verteporfin (C1) inhibited GLK kinase activity and AhR–ROR-γt interaction, that suppressed the disease severity in autoimmune mouse models and IL-17A production in T cells from patients with SLE.	[145]
ITE	AhR agonists	EAE model	Nanoliposomes (NLP) deliver tolerant AhR ligand ITE and disease-specific polypeptide antigens by reducing myelin-specific Th1 and Th17 effector cells, increasing antigen-specific Treg cells, and inhibiting pathogenic inflammatory modules resident in astrocytes and microglia in the central nervous system. Preclinical mouse model to induce antigen-specific tolerance and inhibit MS.	[175]
Laquinimod	AhR agonists	EAE model	The AhR pathway is activated in Laquinimod-treated EAE mice. The AhR pathway regulates the differentiation and function of several cell populations that play important roles in neuroinflammation and inhibits disease progression.	[179]
Urolithin A (URA)	AhR agonists	EAE model	In the EAE model, URA acts as a partial agonist of AhR, inhibiting the infiltration of dendritic cell and pathogenic T cells into the central nervous system, inhibiting the inflammatory cytokines IL-17 and IFN-γ, and increasing the number of Tregs, effective mitigation of the disease process.	[174]
5-Hydroxyindole-3-acetic acid (5-HIAA)	AhR agonists	CIA model	SCFA butyrate supplements inhibit arthritis by increasing the activation of AhR by increasing the activation of 5-HIAA and regulating the function of Breg.	[16]
Indigo naturalis (IN)	AhR agonists	IBD model	IN treatment induces colonic Tregs localization in the colon and increased the number of Tregs, that suppresses experimental colitis.	[192]
Norisoboldine (NOR)	AhR agonists	IBD model	Attenuating ulcerative colitis by activating AhR to induce Treg cell production.	[82]
Alpinetin	AhR agonists	IBD model	Attenuating ulcerative colitis by activating AhR to induce Treg cell production.	[137]

development via effects on hematopoietic stem cells and hematopoietic progenitors that results in a decreased number of B-cell hematopoietic progenitors [157]. Further, TCDD affects the function of established mature B cells, which are highly sensitive target cells for TCDD-mediated AhR activation, with the activation of B cells inhibited and the ability to secrete immunoglobulin M (IgM) and immunoglobulin G (IgG) reduced [158].

Recent studies have shown that AhR is highly expressed in IL-10-producing $CD19^{+}CD21^{hi}CD24^{hi}$Bregs, and that AhR promotes and maintains the immunosuppressive state of Bregs by silencing pro-inflammatory transcriptional programs [159]. Dietary butyrate promotes the growth of bacteria that affect the metabolism of tryptophan, thus increasing the production of AhR endogenous 5-HIAA. 5-HIAA activates AhR-dependent gene transcription in B cells, promotes Breg function, and inhibits GC B cell as well as plasma cell differentiation, which has been shown to improve experimental arthritis [16] (Fig. 3, Table 2).

The effect of AhR activation on immune cells is shown in the Figure. AhR mediates its proinflammatory and anti-inflammatory effects by activating macrophage-dependent cellular pathways, while also promoting the transformation of macrophages into either an anti-inflammatory or proinflammatory phenotype. In DC cells, activation of AhR increases the DC transcription signature and drives the differentiation of monocytes into DCs. DC activation, co-stimulation, and antigen presentation are increased depending upon activation by different ligands of AhR. AhR mediates the mobilization of MDSCs in a CXCR2-dependent manner with those MDSCs exhibiting significant immunosuppressive activities. AhR also promotes differentiation and immunosuppression by PMN-MDSC. In B cells, the activation of AhR inhibits the differentiation and development of mouse B cells in the form of an impaired B-cell lineage, which prevents differentiation of mature B cells into plasma cells and the production of early B cells and pro-B cells. AhR is highly expressed in Bregs and is involved in the regulation and the immunosuppressive function of Bregs. In $CD4^{+}$T cells, ligands from various sources increase the differentiation of Tregs and Th17 cells by different AhR activating mechanisms, which directly regulate Foxp3 transcription and the homing of Treg cells to the gut. The AhR signaling pathway is not only involved in IL-22 production by Th17 cells, but also promotes the expression of IL-17A. In $CD8^{+}$T cells, AhR acts as a promoter of T cell depletion and is also important for the maintenance of T_{RM}. Finally, in ILCs, the AhR signaling pathway regulates the phenotypic transformation of ILCs. AhR is important to the survival of ILC3s and promotes the production of IL-22.

An up arrow (↑) indicates an increase, a down arrow (↓) indicates a decrease. Mac, macrophage; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; PMN-MDSCs, polymorphonuclear MDSCs; Bregs, regulatory B cells; Th17, IL-17^{+} helper T cell; Treg, regulatory T cell; Trm, tissue-resident memory cytotoxic T cell; ILC, innate lymphoid cell.

5. AhR in the autoimmune disease

Recent studies have indicated a critical role of AhR in autoimmune disease as revealed by the findings that abnormal AhR signaling may affect the development and function of innate and adaptive immune cells. Moreover, modulation of AhR signaling has been shown to effectively alleviate disease progression in patients with autoimmune disorders and experimental models [14,27].

5.1. Systemic lupus erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with abnormal immune system activity, characterized by chronic inflammation and immune complex deposition [166]. Defective clearance of biological wastes, such as apoptotic cells, is a key factor in tolerance loss and tissue damage with SLE. An improved understanding of the pathogenesis of SLE has provided new insight and is driving new interest in

targeted therapies for SLE [167]. Studies of AhR in phagocytosis and immune tolerance have identified an immunomodulatory phenotype for phagocytes exposed to apoptotic cell debris. Exocytosis triggers the activation of macrophage AhR, which induces the immunomodulatory cytokine, IL-10, resulting in downstream immune suppression. This result suggests that AhR plays a role in the regulation of immune tolerance by inhibition of the inflammatory response to cell debris. Blocking AhR in SLE mice increases serum proinflammatory cytokine and autoantibody levels, whereas AhR agonist treatment decreases autoantibody levels and disease. In conclusion, an AhR-dependent mechanism of autoimmune tolerance not only provides new insights into the molecular control of peripheral tolerance, but also reveals new "druggable" targets for therapeutic intervention of systemic autoimmune diseases [15].

Ultraviolet (UV) light exposure is a classic environmental trigger for the development of autoimmune disease, with photosensitivity of lupus erythematosus (LE) defined as an abnormal skin response to sunlight. This response is a major feature of most forms of LE and constitutes one of the 11 criteria used by the American College of Rheumatology to classify SLE [168]. When propranolol, a drug that can sometimes induce or aggravate lupus, is exposed to UV light, its downstream photoproducts induce a proinflammatory AhR signaling pathway, which significantly increases the secretion of proinflammatory cytokines. LE patients often show signs of cutaneous AhR activation, which is related to the expression of proinflammatory cytokines in skin lesions [169]. Previous studies have reported exacerbation of SLE by UVB exposure induced DNA hypomethylation [170]. Recently, UVB has been shown to inhibit the DNA methylase, DNMT1, in $CD4^{+}$T cells of SLE patients by activation of AhR. In this manner, the expression of silent mating type information regulation 2 homolog 1 (SIRT1) is inhibited, which is a deacetylase that inhibits the activity of DNMT1 protein in $CD4^{+}$T cells [171]. In addition, clinical and laboratory data from SLE patients have shown AhR expression to be significantly increased in PBMCs and Th17 cells of SLE patients, with the AhR ratio positively related to SLE activity. Further, the AhR ratio was significantly increased in SLE patients with skin lesions and ultraviolet allergy, which was confirmed to be an independent predictor of skin lesions in SLE patients [172].

Taken together, these results indicate that AhR may be a double-edged sword that can drive inflammatory and immunosuppressive phenotypes in T cells and macrophages, depending on the site of AhR activation and the ligands driving the response [27].

5.2. Multiple sclerosis

Multiple Sclerosis (MS) is a neurodegenerative disease in which abnormally activated immune cells attack the central nervous system (CNS). EAE is the most widely used MS animal model because of its similarity to the pathological features and disease progression of human MS [173].

Individual agonists of AhR can have separate and distinct biological effects. TCDD activates AhR and induces differentiation of Treg cells, which inhibit EAE, while AhR activated by FICZ interferes with the differentiation of Treg cells, which promotes differentiation of Th17 cells and aggravates EAE [5]. Similarly, urolithin A (URA), an intestinal microbial metabolite, blocks DC antigen uptake and presentation by directly targeting AhR, inhibiting Th17 polarization and mitigating EAE [174]. However, regardless of oral administration or nano-liposomes (NLPs) delivery, the endogenous AhR ligand, ITE, activates AhR and induces tolerant DCs that promote $Foxp3^{+}$Treg differentiation, inhibiting EAE [106,175].

Studies have shown astrocytes to be involved in the regulation of CNS inflammation [176]. Interferon-β, a therapeutic agent for MS, has been shown to up-regulate the expression of AhR in mouse astrocytes in an IFNAR1-dependent manner. AhR signaling in astrocytes controls recruitment of inflammatory monocytes to the CNS and the neurotoxic activity of astrocytes in EAE, thereby reducing inflammation and EAE disease scores [177]. Dietary Trp metabolites control microglial activation and the production of transforming growth factor α (TGF-α) and vascular endothelial growth factor-B (VEGF-B) through a mechanism mediated by AhR, regulating the pathogenic activity of astrocytes and disease progression of EAE. AhR activation promotes TGF-α expression and inhibits VEGF-B expression. TGF-α and VEGF-B inhibit and promote, respectively, the transcription of primary human astrocytes and central nervous system inflammation [178]. The MS treatment, Laquinimod, expands regulatory T cells and restricts T effector cells in an AhR-dependent manner in EAE, significantly affecting clinical scores, CNS inflammation, and demyelination. It is therefore likely that Laquinimod inhibits EAE through an AhR pathway [179].

Evaluating the effects of various AhR ligands on MS has helped to clarify the physiology of the CNS and the pathogenesis of the disease, while promoting the development of more effective therapeutic strategies for MS treatment [2,178,180].

5.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by cellular infiltration, synovial lining hyperplasia, pannus formation, with cartilage and bone destruction. Susceptibility to autoimmune diseases is influenced by environmental factors. Smoking is thought to be a key environmental factor affecting the incidence and severity of RA. Recent evidence indicates that cigarette smoking (CS) activates AhR in Th17 cells, leading to up-regulation of microRNA-132. miR-132 is packaged into extracellular vesicles by Th17 cells, acting as a proinflammatory mediator that inhibits cyclooxygenase-2 (COX2) expression and promotes osteoclast genesis [181–184]. I Increased cigarette smoke in RA patients enhances the risk for the shared epitope (SE) genetic risk factor, which synergistically interacts with AhR pathways, resulting in significantly enhanced osteoclast differentiation and Th17 polarization *in vitro*. Administration of AhR pathway agonists to transgenic mice carrying the human SE coding allele significantly increased arthritis severity, bone destruction, osteoclast, and IL-17-expressing cells in the inflammatory joints and draining lymph nodes of arthritic mice [185]. CS-induced AhR activation is closely related to RA. Therefore, understanding the regulation of AhR signaling will provide for new ideas for therapeutic targets that alleviate inflammation and bone injury associated with RA.

GNF351, a potent AhR antagonist, effectively attenuates IL-1β-mediated inflammatory signaling in primary HFLS-RA cells. The effect is attributed to inhibition of proinflammatory cytokine, chemokine, and prostaglandin production by AhR replacement within the promoter sequence. As a AhR antagonist, GNF351, represents a viable adjuvant therapeutic strategy for ameliorating the inflammation associated with RA [77]. Further, studies have shown reduced levels of pro-inflammatory cytokines in an arthritis model of $AhR^{-/-}$ mice immunized with collagen. Moreover, a deficiency of AhR in T cells inhibited the generation of Th17 cells and the occurrence of collagen induced arthritis (CIA) [186]. Leflunomide has been shown to inhibit inflammation and reduces bone erosion through its metabolite A77 1726. Mechanistically, Leflunomide can induce AhR-ARNT interaction, inhibiting the production of C-reactive protein (CRP) in the liver of lower CRP (CRP^{Lower}, CRP^{L}) arthritis rats and reducing bone erosion in arthritis rats. However, high CRP (CRP^{Higher}, CRP^{H}) rats up-regulate HIF1α-ARNT, which binds to AHRR and interferes with Leflunomide-AhR-CRP signaling. That study found the CRP-HIF1α-AhR signaling axis to be related to the limited efficacy of Leflunomide for treatment of RA, with a precision medicine-based treatment strategy for RA under development [187]. A new study has shown that supplementation with a microbe-derived metabolite, SCFAs, reduced the severity of arthritis by increasing the availability of the AhR ligand, 5-HIAA, by supporting the growth of tryptophan producing bacteria. Activation of AhR modulates Breg inhibitory function, reducing the differentiation of GC B cells and plasmablasts and thus improving

arthritis symptoms. These data suggest that supplementing diet with certain microbial-derived molecules may be a promising approach to treating arthritis [16].

In sum, the AhR signaling pathway regulates the response of immune cells, affecting the development of arthritis. As such, AhR agonists and antagonists may represent new approaches for the treatment and/or prevention of autoimmune arthritis [188].

5.4. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a disease characterized by chronic recurrent inflammation of the gastrointestinal tract due to a dysregulation of the immune response to intestinal flora. There are two major forms of IBD, Crohn's disease (CD) and ulcerative colitis (UC). Dietary components, exogenous substances, and certain chemicals or metabolites are known to activate AhR and induce an inflammatory response [1]. Rational design of AhR agonists can be used for IBD treatment. Oral compounds can increase AhR-mediated IL-22 production and accelerate mucosal healing by regulation of mucosal adaptive and innate lymphoid cells in dextran sodium sulfate (DSS) treated mice [189]. Similarly, APT102 has been shown to enhance levels of CD39 in the presence of AhR activation [74]. Additional studies have shown that the immunosuppressive effect of UCB in experimental colitis is mediated by activation of CD39 expression by AhR in Th17 cells. However, UCB confers specific immunosuppressive functions to Th17 cells by upregulating CD39, and these properties are severely compromised in the context of IBD [17]. Studies have shown that Th17 cells from the peripheral blood and lamina propria of Crohn's disease have impaired levels of the extracellular enzyme CD39 and are ineffective in immunosuppression of UCB. For the presence of AhR ligation in Th17 cells of Crohn's patient, there are two explanations: 1) Chronic inflammation induced hypoxemia causes high levels of HIF-1α production, which directly inhibits the response to AhR activation in Th17 cells and partly induces an increase in protein transporters promoting the efflux of the AhR ligand UCB in Th17 cells, and thus UCB fails to upregulate CD39 for immunomodulatory functions [34]. 2) Another study showed that glycolysis may be another important factor affecting the ability of Th17 cells to respond to AhR, and the high rate of glycolysis may be a consequence of defective control of metabolism by AhR. UCB controls glycolysis by inhibiting the levels of phosphoglycerate kinase 1 (PGK1) and aldolase-A (ALDOA) glycolytic genes in Th17 differentiated lymphocytes, which facilitates the acquisition of regulatory properties by Th17 cells [190]. Recently, complementary and alternative medicines, especially herbal medicines, have been increasingly used to treat patients with IBD [82,137]. Indigo Naturalis (IN), a compound derived from the Indigo plant, has been shown to ameliorate DSS-induced colitis in mice [191]. The up-regulation of IL-10 and IL-22 through AhR activation may play a key role in colitis improvement. Further, the accumulation of Helios^{+} Tregs induced by AhR signaling and activation of MHC II^{+} epithelial cells (ECs) has clarified a role for AhR in the induction of anti-inflammatory cytokines and the inhibition of intestinal inflammation. These results highlight the potential use of nontoxic AhR agonists for the treatment of IBD [192,193].

Interestingly, the intestinal bio dysregulation of IBD is caused by microbial metabolites that induce inflammation through a mechanism dependent on AhR activation [194]. Caspase recruitment domain family member 9 (CARD9) is known to be a susceptibility gene for IBD, and the microbiota of CARD9$^{-/-}$ mice has reduced levels of bacteria with tryptophan catabolic function. Indoles and tryptophan catabolites produced by the microbiota are endogenous activators of AhR and can regulate local IL-22 production, with any alterations in AhR ligand production affecting IL-22 levels. CARD9 is hypothesized to affect the composition and function of gut microbiota, altering microbial metabolite production and intestinal inflammation. Therefore, tryptophan catabolites derived from gut microbiota can be used as biomarkers of dysfunctional metabolism and may be targets for the development of new drugs for IBD patients [195].

Overall, understanding the effects of these metabolites on AhR activation within different immune cells may provide potential targets for the development of preventive and therapeutic measures that will improve the prognosis for patients with IBD [196].

5.5. Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic, multi-organ autoimmune disease characterized by a triad of symptoms (dryness, pain, and fatigue) [197]. In SS, T cells are dominant in mild and B cells are dominant in advanced lesions, with Th1, Th2, Th17, T follicular helper (Tfh) cells, and regulatory cells (Treg/Bregs) all involved in the pathogenesis of SS [198].

Low dose TCDD exposure affects thymus cell differentiation and selection in a mouse model of human SS. TCDD activation of AhR increases expression of CYP1A1 and affects the proliferation, differentiation, or apoptosis of thymus cells. TCDD interferes with negative selection, with apoptosis of double negative 3 (DN3) cells and selection of autoreactive T cells that react to autoantigens, resulting in autoimmune disease [199]. Further, the lytic replication of Epstein-Barr virus (EBV), a ubiquitous herpes virus, leads to new viral infections that may be a risk factor for the development of autoimmune diseases such as SS [200]. TCDD mediates the transition of EBV infection from latent to a lysis phase in B cell lines and salivary gland epithelial cell lines, with enhanced transcription of BZLF1 (BZLF1 is the first gene to be transcribed during EBV virus replication), suggesting that TCDD ligand-activated AhR may reactivate EBV. Further, AhR ligands in the saliva of SS patients activates AhR to mediate transcription of BZLF1, inducing reactivation of EBV in B cells and salivary epithelial cells [201].

We have recently found that AhR is highly expressed in PMN-MDSCs in patients with primary Sjögren's syndrome (pSS) and in experimental SS (ESS) in mice. Dietary supplement with the natural AhR ligand, IPA, improves salivary gland pathology in ESS mice and recovers PMN-MDSC immunosuppressant function [19,202,203]. These findings suggest that AhR is involved in the development of SS by regulating immune cell Functions.

5.6. Autoimmune hepatitis

Autoimmune hepatitis (AIH) is progressive liver inflammation of unknown cause, with several mechanisms thought to be involved in liver injury and disease progression [204,205]. Moreover, the frequency and function of peripheral blood effector CD4^{+}T and CD8^{+}T lymphocytes directly relates to AIH disease activity as well as biochemical and histologic markers [206–208]. The response of Treg and Th17 cells to AhR activation in AIH patients is impaired. This imbalance results, at least in part, from limited upregulation of CD39, an ectoenzyme key to immune tolerance, following AhR activation. Alterations of AhR signaling in Tregs and Th17 cells of AIH patients are linked to aberrant levels of estrogen receptor-α (Erα), an AhR non-canonical binding partner, and to increased expression of related regulatory factors, HIF-1a and AHRR. Consequently, transcription of genes regulated by the AhR/ARNT complex is impacted, suggesting that response to AhR is defective in both Tregs and Th17 cells derived from AIH patients. Interference with dysfunctional AhR signaling or enhanced down-stream CD39-driven pathways could re-establish immune homeostasis between regulatory and effector cells [18]. In a mouse model of AIH, dysregulation of the liver microbiome leads to expansion and translocation of *Lactobacillus* that produce the AhR agonist, indole-3-aldehyde (I3A), which plays a key role in mediating IFNγ-producing CD8^{+}T cell (Tc1 cell) cell effector function, triggering AIH disease. The development of AIH disease depends on AhR signaling, with blockade of this signal, reversing AIH pathology [209].

AhR signaling has a dual role in AIH pathology. Firstly, high levels of

AHRR and HIF-1α in AIH inhibit AhR signaling in Tregs and Th17 cells, leading to impaired cellular upregulation of CD39 [18]. On the other hand, *Lactobacillus* undergoes hepatic translocation secretes AhR ligand I3A which activates AhR signaling involved in regulating the induction of Tc1 cell differentiation and AIH-like pathology *in vivo* [209] (Fig. 4, Table 3).

AhR signaling affects the development and function of innate and adaptive immune cells, with abnormal AhR signaling associated with autoimmune diseases. AhR is a double-edged sword that can drive T cell and macrophage inflammatory and immunosuppressive phenotypes, depending on the site of AhR activity and the ligands driving the response.

6. Conclusions

Several AhR related ligands and antagonists have been studied in clinical trials, such as the effect of ingestion of the endogenous AhR ligand L-Tryptophan on celiac disease-related symptoms, and the evaluation of the combination of the AhR inhibitors IK-175/nivolumab and BAY2416964/Pembrolizumab in oncological diseases for safety and tolerability, etc. However, clinical trial studies on AhR related drugs in autoimmune diseases have not yet been addressed. In this review, we have presented the results of AhR studies in some autoimmune diseases in recent years, and it is believed that with continuous in-depth studies on the role of AhR signaling activation in immune regulation, drugs targeting the AhR signaling pathway may be used in the treatment of autoimmune diseases in the future (The information comes from clinicaltrials. gov.). Early studies have been focused on investigating AhR in the field of pharmacology/toxicology. Recently, the ligand activation specificity of this transcription factor and its wide expression in the immune system have attracted much attention as how AhR regulates the immune cell functions and maintains immune homeostasis. AhR not only regulates the differentiation and function of immune cells but also directly influences the severity of disease. AhR may act as a double-edged sword that drives innate immune and lymphoid inflammatory or immunosuppressive phenotypes, depending on AhR ligands and other unknown micro-environmental factors. Current studies have demonstrated a critical role of AhR in different immune cell populations. Moreover, the AhR-mediated signaling activation is involved in the development of AhR in autoimmune diseases. Thus, further investigations of AhR signaling in autoimmune pathogenesis will help identify the potential targets for the treatment of autoimmune diseases.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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