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The Role of the Aryl Hydrocarbon Receptor (AhR) in the Immune Response against Microbial Infections

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Abstract

Aryl hydrocarbon receptor (AhR), an important nuclear receptor, regulates the cellular response to environmental stressors. It is well known for its critical functions in toxicology, but is currently considered an essential regulator of diseases, with specific modulatory effects on immune, antimicrobial and inflammatory responses. The present chapter discusses AhR's function and mechanism in the immune response against microbial infections.

Keywords: aryl hydrocarbon receptor (AhR), functional mechanism, antimicrobial, immunity, gut immunity

1. Introduction

The ligand-activated transcription factor aryl hydrocarbon receptor (AhR) is structurally similar to other members of Per-Arnt-Sim (PAS) superfamily [1, 2], which consists of a conserved signaling network that regulates signal exchange between host and environment [3, 4]. It was originally found to play a role in regulating the reactions of exogenous chemicals such as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). However, AhR has been recently recognized as an essential regulator of host-pathogen interactions [5–9], especially affecting immunity, inflammatory response and antibacterial activity [5, 9–15]. The current chapter focuses on AhR's function in regulating immunity, inflammatory response and antibacterial activity.

2. Mechanism of AhR action

As a highly conserved nuclear receptor [10], AhR can regulate gene expression after binding to a ligand. AhR binds to its co-chaperones and maintains cytoplasmic localization [16, 17]. Ligand binding by AhR results in its release by co-chaperones and translocation into the nucleus, where it forms a heterodimer with the aryl hydrocarbon receptor nuclear translocator (ARNT) [18, 19]. Via binding to the genomic DNA—usually interacting with AhR response elements (AhREs, 5'-GCGTG-3') [20, 21], also referred to as dioxin (DREs) or xenobiotic (XREs) response elements [9, 10],

the AhR-ARNT heterodimer regulates multiple target genes such as Cytochrome P450 Family 1 Subfamily A Member 1 (CYP1A1), CYP1A2, CYP1B1, TCDD Inducible Poly (ADP-Ribose) Polymerase (TIP ARP), and aryl hydrocarbon receptor repressor (AhRR), which can inhibit AhR via a negative feedback circuit [22]. Target gene regulation is considered to be ligand dependent [21].

As a highly heterogeneous nuclear receptor, AhR binds to many ligands, including exogenous synthetic aromatic hydrocarbons [10, 23], exogenous natural chemicals [5, 6, 10, 14, 24] and endogenous ligands [25–29]. Tryptophan, an essential amino acid in humans, constitutes the precursor of many important components in the human body. Interestingly, the tryptophan (TRP) pathway has a critical function in immune and inflammatory responses through providing many ligands for AhR. In addition, AhR controls the expression and activation of tryptophan 2,3-dioxygenase (TDO2), indoleamine 2,3-dioxygenase (IDO), kynureninase (KYNU) and kynurenine 3-monooxygenase (KMO). The aforementioned enzymes catalyze the synthesis of kynurenine (KYN), which is a product of TRP metabolism, thus enabling feedback inhibition because KYN and AhR are agonists [30, 31].

3. AhR expression modulation

The interactions of AhR and its ligands, including polycyclic aromatic hydrocarbons (PAHs), can be used as a cytoplasmic signal sensor. The conformation of AhR changes, and it is transferred from the cytoplasm to the nucleus. The high-affinity ligand TCDD can exert toxic effects by binding with and activating AhR [32, 33]. Structural analysis of AhR revealed three domains: 1) The amino-terminal DNA binding domain (DBD) comprises the basic helix–loop–helix (bHLH) region and the nuclear localization signal (NLS); 2) The central PAS region encompasses two degenerate repeats; 3) The carboxy-terminal region features the transactivation domain (TAD) [34]. In addition, phylogenetic data showed that AhR constitutes an ancient protein whose functional orthologues are found in reptiles, amphibians, birds and mammals. However, there are many structural differences between human and murine AhR genes. Sequence analysis revealed approximately 85% structural similarity in the amino-terminal sequence, while the C-terminal region shows a low homology. The TAD or N-terminal domain is the least conservative [34]. The C-terminal domain is a highly unstructured sequence containing a transcriptionally active region and contributes to receptor transformation [35, 36].

AhR, heat shock protein 90 and X-associated protein 2 form multiple protein complexes in the cytoplasm. In the presence of ligands or agonists, AhR complexes undergo nuclear translocation and form heterodimers with ARNT. With a core sequence of 5'-GCGTG-3', the AhR/ARNT complex interacts with DREs in the proximal site of promoters of target genes. Both AhR and ARNT recruit additional transcription co-activators for gene regulation, e.g., CYP and AhRR. Once transferred into the nucleus, AhR undergoes proteasome-induced degradation [37]. AhR function is modulated and weakened by AhRR, another member of the PAS family. After AhR activation, the level of AhRR increases rapidly [38]. Meanwhile, AhRR has a transcriptional repressor domain and can dimerize with ARNT even without an agonist, to fulfill its function [39].

4. AhR response to bacterial pathogens

It is known that AhR has a critical function in controlling responses to a variety of microbial pathogens. For example, it is required to effectively clear the

Gram-positive pathogenic bacteria *Listeria monocytogenes* (LM). In mice, AhR inhibits LM by inducing ROS production via upregulation of the anti-inflammatory cytokine IL-10 and macrophage apoptosis inhibitor, resulting in suppressed macrophage apoptosis, reduced amounts of pro-inflammatory cytokines (e.g., Interleukin 6 (IL-6) and Tumor Necrosis Factor alpha (TNF- α)), and decreased the nuclear factor kappaB (NF- κ B) activation. In addition, AhR ligands can enhance the response of AhR WT mice to LM, but not of AhR^{-/-} mice [27].

When inoculated with log-phase LM intravenously, AhR deficient C57BL/6 J mice (AhR^{-/-}) showed higher susceptibility compared with AhR heterozygous (AhR^{+/-}) littermates. In comparison with AhR^{+/-} animals, AhR^{-/-} counterparts showed more colony forming units (CFUs) of LM in the spleen and liver, and more pronounced alterations in liver histopathology. Serum monocyte chemotactic protein 1 (MCP-1), IL-6, TNF- α and Interferon γ (IFN- γ) amounts were similar in AhR^{-/-} and AhR^{+/-} mice infected with LM. Elevated IL-12 and IL-10 amounts were detected in AhR^{-/-} mice infected with LM. In terms of capacity of uptake and inhibition of intracellular growth of LM, AhR^{+/-} and AhR^{-/-} macrophages were comparable *in vitro*. In addition, T cell-dependent response was similar in AhR^{-/-} and AhR^{+/-} mice, as determined by intracellularly labelling cluster of differentiation 4 and 8 (CD4⁺ and CD8⁺) splenocytes for IFN- γ and TNF- α . AhR^{-/-} and AhR^{+/-} mice with prior infection showed increased resistance to re-infection by LM. The above evidence suggests that AhR is necessary to build an effective resistance, but not required for adaptive immune reactions following LM infection [40].

Streptococcus pneumoniae, a common respiratory pathogen, represents a major cause of morbidity and death in humans, especially the elderly and children. The immune response after *S. pneumoniae* infection begins quickly in the lung, and the innate immune response can contain bacterial colonization in the ideal situation. Death, and bacterial load, cytokine/chemokine amounts, and immune cell infiltration in the lung have been assessed at different times in TCDD treated mice after *S. pneumoniae* infection. The survival rate of mice administered TCDD was significantly increased, while bacterial load in the lung was reduced. However, intriguingly, no evidence suggested that the protective effect was caused by increased inflammatory response. In fact, neutrophil amounts and inflammatory chemokine/cytokine levels in TCDD treated mice were lower than those of control animals. These findings suggest that AhR induction does not protect the animals by immune modulation, but likely by directly affecting lung cells upon infection [41].

Pseudomonas plecoglossicida represents the bacterial pathogen of fish visceral white spot disease with temperature dependent virulence [42]. AhR is also required for resistance to *P. plecoglossicida*. It was shown that *ahr1a*, *ahr1b*, *ahr2* and *cyp1a* amounts in various organs of *Danio rerio* and *Epinephelus coioides* infected with *P. plecoglossicida* have similar trends. It should be noted that the intestine, liver, heart and spleen are the most affected organs, while *ahr2* specifically shows a sharp increase in the spleen. After *P. plecoglossicida* infection, *ahr1a* amounts in macrophages are markedly reduced, while *ahr1b*, *ahr2* and *cyp1a* are overtly upregulated. The cell viability and immune escape rates of *P. plecoglossicida* were significantly increased in macrophages with *ahr1b* and *ahr2* knockdown. In conclusion, *ahr1a*, *ahr1b*, *ahr2* and *cyp1a* are involved in immune reactions to *P. plecoglossicida* in various fish organs, while *ahr1b* and *ahr2* might play a key role in splenic and macrophage immune reactions [43].

Huang et al. described the first pathogenic *Aeromonas salmonicida* (SRW-OG1) obtained from the warm water fish *E. coioides*, and studied AhR's role in the immune response to SRW-OG1 infection [44]. They found that AhR is induced by unknown ligands in the intestine, spleen and macrophages. At the same time, *ahr1a* and *ahr1b* amounts were markedly elevated in the intestine, spleen and macrophages,

while *ahr2* only showed an increase in the intestine, suggesting *ahr2* may contribute less to immune reactions compared with *ahr1a* and *ahr1b*. In SRW-OG1 infected *E. colioides*, major genes contributing to bacterial recognition, macrophage inflammatory response and gut immunity were overtly upregulated. However, decreased ROS amounts and the downregulation of other associated genes were equally detected, which indicated that SRW-OG1 could prevent ROS production by macrophages through its virulence mechanism. In addition, repression of AhR with an inhibitor or by gene silencing rescued the increases of *IL-1 β* and *IL-8* associated with SRW-OG1 infection, clearly demonstrating that induction of *E. colioides* macrophages by *IL-1 β* and *IL-8* is controlled by AhR. Nevertheless, AhR exerted no effects on bactericidal permeability-increasing protein/lipopolysaccharide-binding protein (BPI/LBP), reactive oxygen species (ROS) biosynthesis and associated genes. Compared with wild-type macrophages, survival and immune escape rates after SRW-OG1 infection were significantly increased in *ahr1a/ahr1b*-knockdown and 3', 4'-DMF treated macrophages. Taken together, *ahr1a* and *ahr1b* are necessary for the immune response to SRW-OG1 [44].

Lipopolysaccharide (LPS) stimulation is often utilized to model Gram-negative bacteria-induced sepsis for assessing AhR's functions in infection resistance and septic shock regulation. AhR and TDO2 are required for survival after the initial exposure to LPS [14, 20], while subsequent exposures are dependent on AhR and IDO1/2. LPS up-regulates TDO2 and IDO1/2, the rate-limiting enzymes of TRP transformation into KYN, and further induces AhR, thus downregulating pro-inflammatory cytokines and regulating long-term systemic inflammation [20]. In addition, compared with AhR wild type mice or immune cells, LPS challenged AhR^{-/-} mice or immune cells produce higher concentrations of pro-inflammatory cytokines, including *IL-1 β* , *IL-6*, *IL-18*, *IL-12*, *TNF- α* and *IFN- γ* , as well as NLR Family Pyrin Domain Containing 3 (NLRP3) that regulates multiple pro-inflammatory cytokines. The AhR agonists 3-methylcholine (3-Mc), 6-Formylindolo[3,2-b] carbazole (FICZ), KYN and TCDD could protect AhR WT mice, but conferred no protection to AhR^{-/-} animals, from extremely high amounts of pro-inflammatory cytokines and septic shock [45]. Thus, the immune response to bacterial pathogens requires AhR, and the underlying mechanisms are vital in identifying novel therapeutic agents to combat bacterial pathogens.

5. AhR response to viral pathogens

AhR is also associated with response to viral pathogens. For example, herpes simplex virus (HSV)-associated eye infection can lead to chronic immune-inflammatory response, causing blindness. However, in a mouse model, a single dose of TCDD could alleviate herpetic keratitis lesions, reduce viral load and decrease pro-inflammatory cytokine levels. However, similar effects were not obtained with FICZ, thus indicating a difference between both AhR ligands [46]. Therefore, response to viral pathogens requires AhR, and nontoxic AhR agonists could be used in the treatment of HSV-induced eye infections.

In influenza virus infection, activation of AhR doubles the number of neutrophils in the airway and interstitium of the lung, which reduces the survival rate from an otherwise sub-lethal infection [47, 48]. Interestingly, no increase in neutrophil inflammation or decreased survival was observed in AhR deficient mice treated with TCDD and influenza virus [37]. Innate immune reactions, including excessive pulmonary neutrophilia, can lead to severer pathological conditions and poor clinical outcomes after influenza virus infection [49–51]. Meanwhile, epidemiological reports have shown that exposure to environmental AhR ligands is associated with

elevated respiratory tract infection, pulmonary congestion and exacerbation of inflammatory lung disease [52–54]. Therefore, there is parallel evidence in rodent animal models and humans that AhR regulates neutrophil inflow during infection. Overall, these data suggest that AhR regulates a new pathway to regulate neutrophil migration during influenza virus infection. A possible new target gene of AhR is inducible nitric oxide synthase (iNOS). Meanwhile, activation of AhR can increase the expression of iNOS in the mouse lung upon infection with influenza virus [55].

6. AhR response to parasitic pathogens

The immune response to parasites also requires AhR. For example, immune response to *Toxoplasma gondii*, a pathogenic parasite causing toxoplasmosis, requires increased AhR-dependent production of IL-10. Indeed, AhR^{-/-} mice have reduced response to *T. gondii* and a less pronounced IL-10 increase [56].

After intraperitoneal infection with *T. gondii*, the death rate of AhR^{-/-} mice was significantly higher than that of WT mice. Moreover, AhR^{-/-} mice showed greater liver injury, and higher levels of NO, IgE and TNF- α , but lower IL-10 secretion in the serum. Interestingly, fewer cysts were found in the brain. The increased mortality was related to reduced IL-10, 5-LOX and GATA-3 expression levels, but increased IFN- γ expression in the spleen. In addition, AhR^{-/-} mice had increased IL-12 and IFN- γ amounts, but decreased TLR2 levels compared with wild-type mice in peritoneal exudate cells. These findings suggest that AhR is vital for limiting inflammation during toxoplasmosis [57].

Therefore, AhR is necessary for parasitic pathogen response. This provides information on a response pathway and can be used to design new treatments.

7. AhR and the intestinal microbiota

AhR is found at high levels in the epithelial barrier [58], and the intestinal barrier of AhR^{-/-} mice is inadequate, suggesting AhR might be important in maintaining or generating a healthy intestinal barrier [19]. In addition, low levels of AhR and AhR's target genes are found in sterile mice [9], and AhR is needed for maintaining the ROR γ ⁺ innate lymphoblastoid cell (ILC) balance in the intestine [18]. In addition, the TRP metabolizing indole biosynthesized by select bacterial components of the intestinal microbiota is an AhR ligand [59, 60]. Diet without indole or antibiotic treatment can lead to the differentiation of mononuclear phagocytes, dependent on AhR, into dendritic cells (DCs) [48], which are more susceptible to gut pathogens in mice [17]. Overall, the above findings suggest AhR might be important in host gut-microbiota interactions.

AhR also plays a role in the reciprocal relationship among intestinal bacteria, bacterial metabolites and the intestinal immune system. AhR-deficient ROR γ ⁺ ILCs (the main producers of gut IL-22) with lower IL-22 amounts make mice easily die upon *Citrobacter rodentium* infection. It was pointed out that treatment with FICZ markedly enhances ROR γ ⁺ ILC accumulation in AhR^{+/-} and AhR^{+/+} mice, but not in AhR^{-/-} animals [61]. Lactobacillus species (nonpathogenic intestinal bacteria) are capable of producing AhR ligands, including indole-3-aldehydes, from tryptophan in the gut, thus enhancing the production of AhR dependent IL-22 [62]. Indole-3-aldehydes induces AhR-associated transcription, but exclusively at elevated concentrations, indicating its low affinity. However, indole-3-acetaldehyde (a product of indole-3-aldehydes) produces the high-affinity ligand FICZ [63], which may be related to the effect reported by Zelante et al. IL-22 affects epithelial cells and

causes them to produce antimicrobial peptides, such as type III Reg (regenerating gene product) gamma (RegIIIg), and to stimulate tissue regeneration. Meanwhile, symbiotic bacteria may outperform bacterial pathogens and inhibit *Candida albicans* colonization [51]. Similar to keratinocyte and skin immune cell levels, AhR amounts are high in IECs and intestinal immune system cells [64].

In AhR-null mice, the number of intraepithelial lymphocytes (IELs) in the small intestine is significantly reduced [6, 64, 65], which is related to lower IL-22 amounts, and therefore to downregulated ileal antimicrobial peptides, including RegIIIb and RegIIIg. The microbial loads of the small and large intestines are also elevated. Loss of IELs is cell-intrinsic since AhR-deficient bone marrow cells do not reconstruct the gut in Rag^{-/-} mice [51]. Over time after birth, intestinal Group 3 Innate Lymphoid Cells (ILC3s) [66], ILC22 and CD32NKp46⁺ lymphoid tissue inducer cells are lost in AhR-deficient mice. Similarly, ILC3's inability to multiply in AhR-deficient mice constitutes an intrinsic function since AhR is required for the transcription of the cell-specific proliferator c-kit [67, 68]. As a result, secondary lymphoid structures, including cryptopatches and innate lymphoid follicles, are absent from the gut of AhR-deficient mice, which show susceptibility to *C. rodentium*. ILC3s feature the secretion of IL-17 and IL-22 [69]. AhR-deficient mice have elevated susceptibility to infection by *C. rodentium*, as well as dextran sulfate sodium (DSS)-associated colitis. DSS can damage the intestinal epithelium and induce inflammatory reactions and microbial dissemination. AhR-deficient mice containing wild-type IELs are resistant to DSS colitis, indicating IEL role in injury reduction.

AhR-deficient mice have lower amounts of skin and intestinal IELs and intestinal ILCs, thereby increasing susceptibility to *C. rodentium* infection. These cell types, and the generation of normal gut lymphoid follicles, are regulated by AhR ligands in the diet. In addition, activation of AhR by microbial products equally regulates the production of DP IELs, which constitute another critical group that controls intestinal immunity [70]. It may also be due to the lack of IL-22 that affects the commensal flora [71]. In fact, ID2, a transcription factor, regulates the expression of IL-22 in ILCs via AhR- and IL-23-dependent mechanisms, thereby modulating the intestinal colonization of *C. rodentium* [72]. In addition, AhR also controls the production of IL-22 by Th22 cells, which protect against intestinal pathogens [73, 74]. All these data suggest AhR has a critical function in controlling the interaction at environmental interfaces with microorganisms by regulating IL-22 and other cellular factors. Interestingly, *cyp1a1* overexpression leads to the exhaustion of physiological AhR ligands and also increases susceptibility to intestinal bacterial infections [75], highlighting that AhR ligand availability and metabolism are important in controlling AhR-dependent immune effects.

8. AhR and T cells

AhR plays an important role in controlling adaptive immunity, and regulating T cell differentiation and direct or indirect functions by affecting antigen presenting cells. It was found that TCDD-activated AhR could inhibit the immune response [76], which is subsequently associated with CD4⁺ T cell induction [77–79]. In addition, the role of AhR in Th17 function and T cell-induced IL-22 biosynthesis have also been determined [74, 80–83].

8.1 AhR and regulatory T cells (Tregs)

AhR shows high expression in Th17 cells, undetectable amounts in Th1 and Th2 cells, and low expression in Tregs. Tregs constitute a T cell subgroup, which helps

maintain tolerance to autoantigens, preventing autoimmune pathologies. FoxP3⁺ Tregs [84, 85] and IL-10-producing type 1 regulatory T cells (Tr1 cells) [86] are the most typical Treg entities. Foxp3⁺ Tregs and Tr1 cells are associated with AhR.

TCDD, ITE, KYN and laquinimod derivatives activate AhR, thus increasing FoxP3⁺ Treg amounts via various mechanisms, e.g., by directly activating epigenetic modifications that regulate Foxp3 transcriptionally and via DC regulation [80, 87–92]. In the presence of TGF- β 1, activating AhR with TCDD can also upregulate SMAD1 in human Tregs, resulting in stable expression of FoxP3 [93]. It was shown in mice with AhR-deficient T cells that AhR could also inhibit the activation of STAT1, which in turn inhibits FoxP3⁺ Treg differentiation [94]. In addition, AhR regulates the epigenetic modifier Aiolos, which downregulates genes associated with T cell's effector function, such as IL-2 [87]. However, the effect of AhR on FoxP3⁺ Tregs may be affected by the applied experimental model, which may reflect the different effects of tissue-specific action and/or AhR agonist provided by the symbiotic flora [95].

Tr1 cells participate in controlling tissue inflammation via IL-10 secretion. IL-27 promotes the differentiation of Tr1 cells [96–98], while IL-21 plays an autocrine role in their stabilization [98, 99]. IL-27 upregulates AhR in Tr1 cells via STAT3. Then, AhR amounts are maintained by transactivation of the AhR promoter by AhR itself [100–102]. The important role of AhR in Tr1 cells *in vivo* is reflected by insufficient Tr1 cell differentiation induced by long-term anti-CD3 treatment of AhR-mutant mice.

AhR triggered CD39 equally affects Tr1 cell differentiation. After induction, T cells secrete eATP [103], which then interferes with the differentiation of Tr1 cells through hypoxia inducible factor-1 α (HIF1- α). HIF1- α binding is superior to the interaction between AhR and ARNT, and promotes the degradation of AhR through the immune proteasome, thus inhibiting the differentiation of AhR dependent Tr1 cells [101]. The expression of CD39 driven by AhR can deplete eATP and promote the differentiation of Tr1 cells. Therefore, AhR regulates central genes in the Tr1 cell transcription program, while limiting the inhibitory effect of eATP-dependent HIF1- α induction on Tr1 cell differentiation. Overall, the above findings confirm AhR as a potential therapeutic target for immunomodulation.

8.2 AhR and T helper 17 (Th17) cells

Th17 cells, forming a unique CD4⁺ T cell subgroup, can biosynthesize Th17 cytokines and play key roles in the pathogenetic mechanisms of multiple inflammatory ailments. Their differentiation is triggered by IL-6 and transforming growth factor-beta (TGF- β). AhR can modulate Th17 cells by binding to the DRE site in the IL-17 promoter. In addition, AhR and STAT3 can synergistically upregulate Aiolos (IKZF3), an Ikaros family member, which can decrease the expression of IL-2, thus increasing Th17 cell amounts [64].

Th17 cells, producing IL-17A and expressing ROR- γ t, are involved in immune responses to extracellular bacterial and fungal pathogens, and participate in the pathological mechanisms of multiple autoimmune diseases [104, 105]. Their differentiation involves joint effects of TGF- β and IL-6 or IL-21 [106–108]. AhR shows high expression in Th17 cells and is activated by FICZ, which can enhance Th17 cell differentiation and promote IL-22 expression. On the contrary, AhR deficiency can cause Th17 cells to produce IL-22, which may reflect AhR's function in promoting ROR γ t recruitment to the IL-22 promoter.

8.3 AhR and other T cells

Th22 cells are a CD4⁺ T cell subpopulation. They produce IL-22 without IL-17's intervention and their differentiation is induced by IL-6, IL-21 or IL-23. AhR

controls the production of IL-22 in Th22 cells, and other cellular factors are essential for their mucosal immune functions [73, 109–111].

The AhR pathway also significantly affects CD8⁺ T cells. Activation of AhR by TCDD indirectly inhibits the primary response of CD8⁺ T cells to influenza virus through the regulatory mechanism of DC function [112]. In addition, CD8⁺ T cells of mouse models administered the AhR agonist TCDD in the developmental stage show a weak response to influenza virus infection later in life [113]. The above data indicate epigenetic alterations that can lead to prolonged functional defects in CD8⁺ T cells detectable after viral attack. Compared with other CD8⁺ T cell subsets, AhR expression is much higher in tissue resident CD8⁺ memory cells (TRMs). Taken together, these findings indicate that, similar to previously reported CD4⁺ T cell data, the AhR pathway plays a major role in regulating specific CD8⁺ T cell subgroups, such as TRMs and DP IELs.

AhR equally regulates $\gamma\delta$ T cells, which are tissue resident lymphocytes. It regulates first-line immune response at epithelial sites and controls tissue homeostasis [114]. Despite AhR expression in the totality of $\gamma\delta$ T-cell subgroups, AhR-deficiency significantly reduces the amounts of skin intraepithelial lymphocytes, mostly composed of V γ 3 and V γ 5 $\gamma\delta$ T cells in the intestine and CD8 $\alpha\alpha$ $\alpha\beta$ T cells [115]. AhR also regulates IL-22 expression by $\gamma\delta$ T cells that produce IL-17 [116, 117]. The above data indicate that AhR has a significant effect on T cells residing in tissues, which supports further investigation of AhR's function in non-CD4⁺ T cells.

In conclusion, AhR controls T cell responses at many levels and regulates transcription factors, enzymes, epigenetic modifiers and effector molecules that modulate T cell stability and metabolism. Lineage-specific responses to AhR induction may lead to ligand-specific effects, which are combined with cytokine-driven activities on the genome, thereby regulating AhR-interacting chaperones and controlling the accessibility of AhR's direct and indirect transcription targets [118]. Comprehensive studies of these interactions should provide insights into the design of immune-modulators against AhR.

9. AhR and B cells

The B lymphocyte is an important part of humoral immunity, which has high specificity against a variety of pathogens. After stimulation via an antigen receptor, activation of immature B cells leads to clonal expansion, antibody isotype conversion and differentiation into antibody-secreting plasma cells, thus producing strong immune reactions [119]. In the process of infection, mature B cells in the lymph nodes and secondary lymphoid organs undergo somatic hypermutation and produce plasma cells featuring elevated antigen affinity and unique effector function [120].

It seems that all B cells produce AhR, but specific subsets, e.g., marginal B cell and B1 B cell subsets, have higher levels than the others. Li and collaborators demonstrated that AhR contributes to the development of B lymphocytes, based on cord blood CD34 and feeder cells, which promote B cell development. Meanwhile, AhR induction inhibits the formation of early B cells and pro-B cells. AhR controls B cell differentiation by transcriptionally suppressing the early B cell genes EBF1 and PAX5 [121].

AhR, overtly induced after activation of B cells, has a critical function in regulating the fate of activated cells. Vaidyanathan and colleagues revealed AhR suppresses switch-like recombination by changing the amounts of activated cytidine deaminase. These authors showed that AhR suppresses B cell transformation into plasmablasts and plasma cells that secrete antibodies [122]. In addition, Villa et al.

provided evidence of a role for AhR in B cells, revealing that AhR expression is increased after administration of IL-4 as well as B cell receptor engagement. Nevertheless, the proliferation of AhR-deficient B cells is decreased, and cells could not progress to the S-phase. Furthermore, AhR-deficient B cells could not compete with the decreased AhR^{+/+} B cell capability of reconstructing the empty host, and could not induce antigen-dependent proliferation in mice. Gene expression profile analysis showed that AhR excision downregulates cyclin O, an important gene controlling the cell cycle [123].

10. AhR and dendritic cells (DCs)

DCs are essential in controlling T cell response and regulating immune tolerance [124]. AhR regulates DC differentiation and function, thereby profoundly affecting T cell-dependent immune reactions. AhR also affects antigen presentation by DCs. Bone marrow derived DCs (BMDCs) exposed to TCDD show decreased CD11c amounts, but increased production of MHC-II, CD86, IL6 and TNF α [125]. Similar findings were reported in TCDD treated splenic DCs [126]. However, different results were observed by using the AhR agonist ITE. The expression of MHC-II and co-stimulatory molecules and the production of Th1 and Th17 polarization cytokines in splenic DCs were decreased by ITE stimulation of AhR.

Recent experiments in ovalbumin-induced asthma models provide additional evidence for the physiological regulation of AhR in DCs, with AhR-deficient mice exhibiting enhanced inflammatory reactions, elevated Th2 differentiation and higher DC MHC-II and CD86 amounts [127]. In addition, AhR signaling has been reported to regulate the activity of CD103⁺/CD11b⁺ DCs during influenza virus infection, thereby reducing induction in protective CD8⁺ T cells [128]. Overall, this evidence confirms that AhR is a potential therapeutic target for regulating T cell responses in DC.

Multiple mechanisms are involved in AhR-associated regulation of DC function. AhR upregulates IDO 1 and 2 [129, 130], which catalyze the production of KYN, thus promoting the differentiation of FoxP3⁺ Tregs [131]. Indeed, AhR-deficient DCs could not induce Treg differentiation and Th17 cell proliferation in culture. It is consistent with the immunosuppressive effect of AhR in DCs. Recently, it was reported that IDO expression is maintained by an autocrine loop involving AhR and KYN in tumor infiltrating tolerogenic DCs [132]. Additionally, AhR induction in DCs induces a retinoic acid-dependent enzymatic mechanism, thus promoting FoxP3⁺ Treg differentiation and inhibiting effector T cells [133–137].

11. Conclusions

Studies evaluating AhR's functions in immune cell development, immune response modulation and immune tolerance have aroused great interest. Originally, AhR was considered a protein sensing environmental substances and regulating drug metabolism. Recently, the role of AhR in regulating normal physiological processes has attracted increasing attention. The organism must perceive and mount substantial responses to environmental changes. Indeed, AhR senses biochemical, chemical and physical environments. Combined with a small amount of high-affinity physiological ligands, including FICZ and ICZ, AhR plays a role in cell proliferation, differentiation and function.

Current evidence indicates that AhR has a critical function in host response to bacterial pathogens. It also overtly influences resistance to infections by

extracellular and intracellular bacteria. AhR is considered the best resistance factor for LM. It may have a new function in the innate immunity of LM infection, and AhR-deficient mice have increased sensitivity to LM. Activation of AhR can protect mice from the deadly attack of *S. pneumoniae*, inhibit bacterial growth and fight infection. AhR can also react with viral pathogens and parasitic infections. After infection by viruses and parasites, lack of AhR aggravates the host's inflammatory response. AhR regulates host's immune cells, confirming that AhR is a regulatory molecule with essential functions in the activation and induction of immune cells, e.g., T cells and inflammatory factors. Barrier organs are critical in immunity; specifically, large amounts of *ahr* are expressed in the intestine, which has a high potential for preventive and treatment interventions. AhR has a critical function in controlling the degree of inflammation in response to symbiotic microbiota and tissue destruction. Progress is being made in determining the molecular mechanisms by which AhR affects different cell types. To understand the complex process of AhR in immunity and antibacterial, to mitigate risks, and to develop novel treatment and prevention tools, more research is needed.

Abbreviations

AhR	aryl hydrocarbon receptor
PAS	pern-arnt-sim
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
ARNT	aryl hydrocarbon receptor nuclear Translocator
AhREs	AhR response elements
DREs	dioxin
XREs	xenobiotic
CYP1A1	cytochrome P450 family 1 subfamily A member 1
AhRR	aryl hydrocarbon receptor repressor
TDO2	2,3-dioxygenase
IDO	2,3-dioxygenase
KYNU	kynureninase
KMO	kynurenine 3-monooxygenase
KYN	kynurenine
DBD	the amino-terminal DNA binding domain
Bhlh	basic helix-loop-helix
NLS	the nuclear localization signal
TAD	the transactivation domain
LM	<i>Listeria monocytogenes</i>
IL-6	interleukin 6
TNF- α	tumor necrosis factor alpha
NF- κ B	the nuclear factor kappaB
CFUs	colony forming units
MCP-1	monocyte chemotactic protein 1
IFN- γ	interferon γ
ROS	reactive oxygen species
<i>BPI/LBP</i>	bactericidal/permeability-increasing protein / lipopolysaccharide-binding protein
LPS	lipopolysaccharide
NLRP3	NLR family pyrin domain containing 3
3-Mc	3-methylcholine
FICZ	6-formylindolo[3,2-b]carbazole
HSV	herpes simplex virus

iNOS	inducible nitric oxide synthase
DCs	dendritic cells
ILC	lymphoblastoid cell
RegIIIg	Type III Reg gamma
IELs	intraepithelial lymphocytes
ILC3s	group 3 Innate lymphoid cells
DSS	dextran sulfate sodium
Tr1 cells	type 1 regulatory T cells
HIF1- α	hypoxia inducible factor-1 α
Th17	T helper 17
TGF- β	transforming growth factor-beta
TRMs	tissue resident CD8 ⁺ memory cells
DCs	dendritic cells
BMDCs	bone marrow derived DCs

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