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The roles of aryl hydrocarbon receptor in immune responses

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Abstract

A number of recent studies have examined the functions of aryl hydrocarbon receptor (Ahr) in the immune system. Also known as dioxin receptor, Ahr is a ligand-activated transcription factor that serves as a receptor for various environmental toxins. The functions of Ahr in T cells depend on the specific ligand bound to the receptor. For instance, binding of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin to Ahr suppresses experimental autoimmune encephalomyelitis (EAE) by promoting the development of Foxp3$^+$ T_{reg} cells, whereas 6-formylindolo[3,2-b]carbazole enhances EAE by inducing the differentiation of IL-17-producing T cells. Furthermore, specifically deleting Ahr in T cells inhibits collagen-induced arthritis in mice. In macrophages and dendritic cells (DCs), Ahr is anti-inflammatory. In response to LPS, Ahr-deficient macrophages show increased production of pro-inflammatory cytokines, such as IL-6 and TNF-α, and Ahr-deficient DCs produce less of the anti-inflammatory cytokine IL-10. In this review, we discuss the roles of Ahr in macrophages and T cells. Moreover, studies examining Ahr activation in other cell types have revealed additional contributions to B cell and osteoblast/osteoclast differentiation. We also briefly summarize the current understanding of regulatory mechanisms underlying Ahr activation in various cells and discuss the potential clinical implications of cell-specific targeting of Ahr in pathologic conditions of the immune system.

Keywords: dioxin receptor, immune regulation

Introduction

Aryl hydrocarbon receptor (Ahr) is a ligand-activated transcription factor that mediates numerous cellular responses to toxins and plays critical modulatory roles in various immune cells during innate and adaptive immune responses. Ahr was originally investigated as a receptor for environmental contaminants, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). More recently, studies have examined Ahr in immune cells including T cells and antigen-presenting cells including dendritic cells (DCs) and macrophages. The balance between T_h17 cells and the other T-cell subsets is particularly critical to ensure that a specific T-cell subset does not predominate and—together with other transcriptional changes—cause disorders associated with aberrant cytokine production.

One approach has been to specifically delete Ahr in macrophages or T cells. Mice lacking Ahr in macrophages or T cells are used as models of inflammatory and autoimmune diseases, including LPS-induced shock and collagen-induced arthritis (CIA). In addition, Ahr has been investigated in experimental autoimmune encephalomyelitis (EAE) and dextran sulfate sodium (DSS)-induced colitis, among other disease models. In this review, we discuss the roles of Ahr in immune and non-immune cells, including contributions to various animal models of disease. Importantly, the signaling cascades and biochemical processes associated with Ahr are promising avenues to modulate immune responses in the clinic.

Ahr signaling pathways

Ahr is a ligand-activated member of the Per-Arnt-Sim family of basic helix–loop–helix transcription factors. Normally, Ahr forms cytoplasmic complexes with various proteins, such as heat shock protein 90, Ahr-interacting protein and p23 (1–3). Binding of Ahr to a xenobiotic ligand, such as TCDD, induces translocation of the Ahr complex into the nucleus, where it binds Ahr nuclear translocator (Arnt). In the nucleus, Ahr–Arnt heterodimers bind xenobiotic-responsive elements (XREs) in the promoters of responsive genes, including those encoding members of the cytochrome P450 family (4–7). Ahr repressor—a marker of Ahr activation—attenuates Ahr signaling (8).

REVIEW

Ahr is involved in cell proliferation, differentiation and cytokine secretion. Furthermore, several inflammatory response-related genes contain multiple potential XRE boxes in upstream sequences (9). It is likely that the different distributions of XREs contribute to the transcriptional regulation of various immune activities following Ahr activation. Yet, few studies have examined the precise roles of Ahr and XREs in these processes. Of note, the Ahr reportedly serves not only as a transcription factor but also as part of a ligand-dependent E3-type ubiquitin ligase complex to regulate selective protein degradation. Protein ubiquitination involves a ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin protein ligase (E3), which acts as a bridge between E2 and the substrate (10, 11). Ohtake *et al.* (10, 11) found that Ahr activation by such ligands as 3-methylcholanthrene (3MC) and β-naphthoflavone decreased protein levels of endogenous estrogen receptor (ER)α, ERβ and androgen receptor (AR). Ligand-bound Ahr assembles into the CUL4B-based atypical E3 ubiquitin ligase complex CUL4BAhr, which includes CUL4B, DNA-binding protein 1, Rbx1, subunits of the 19S regulatory particle of the 26S proteasome, Arnt and transducin β-like 3 (10, 11). Ahr has E3 ubiquitin ligase activity both *in vitro* and *in vivo* (11). For instance, reconstituted *in vitro* ubiquitination assays have shown that the E3 ubiquitin ligase activity of CUL4BAhr for ERα is dependent on 3MC and not on E2 (10, 11). On the other hand, degradation of ERα or AR in the uterus and prostate can be induced by Ahr activation but is not observed in Ahr-deficient ($Ahr^{-/-}$) mice (12, 13). In addition, following activation of TLRs, Ahr interacts with proteins involved in NF-κB signaling. Ahr activation also leads to proto-oncogene expression via 'cross-talk' with the p38 MAPK signaling pathway (14). For example, Ahr activates p38-MAPK signaling to regulate the expression of *c-jun*, which encodes an AP-1 subunit, by the Ahr ligand TCDD (14).

Ahr is activated in immune and/or cancer cells by many exogenous xenobiotic ligands, including TCDD, 3MC, bezo[a]pyrene (BaP), and such endogenous ligands as 6-formylindolo[3,2-b] carbazole (FICZ), Kynurenine (Kyn) and 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) (15–18). Receptor affinity and the degree of activation likely reflect the planarity, aromaticity and hydrophobicity of the ligand (15).

Ahr in T cells and autoimmune diseases

Three separate laboratories reported that Ahr regulates the differentiation of IL-17-producing T (T_h17) and T_{reg} cells (19–21). Using DNA microarrays, Kimura *et al.* (19) showed that Ahr is expressed under T_h17 cell-polarizing conditions characterized by IL-6 and TGF-β but not in response to either cytokine alone. IL-6 inhibits TGF-β-induced $Foxp3^+$ T_{reg} cell differentiation and initiates T_h17 cell development; these effects shift the balance between T_h17 and T_{reg} cells and contribute to the pathogenesis of several animal models of autoimmune diseases, including EAE and CIA (19–24). $Ahr^{-/-}$ naive T cells exposed to IL-6 and TGF-β *in vitro* fail to differentiate into T_h17 cells owing to a lack of inhibitory interactions between Ahr and negative regulators of T_h17 cell differentiation (e.g. Stat1 and Stat5) and/or binding of Ahr to the IL-17 promoter (19, 25, 26). An overview of Ahr in T_h17, T_{reg} and type 1 T regulatory (T_r1) cell development can be found in Figs 1 and 2.

Results from several studies on the role of Ahr in experimental autoimmune diseases have been summarized in Table 1. These results, however, do not entirely agree perhaps owing to differences in the examined ligands, cell types and/or regulatory signaling pathways. TCDD and FICZ promote T_{reg} and T_h17 cell differentiation *in vitro* (19). Veldhoen *et al.* (20) demonstrated that activating Ahr with FICZ enhances T_h17 cell development and promotes the development of EAE. On the other hand, Quintana *et al.* (21) reported that the effects of Ahr on T_{reg} and T_h17 cell differentiation are ligand specific; FICZ and TCDD

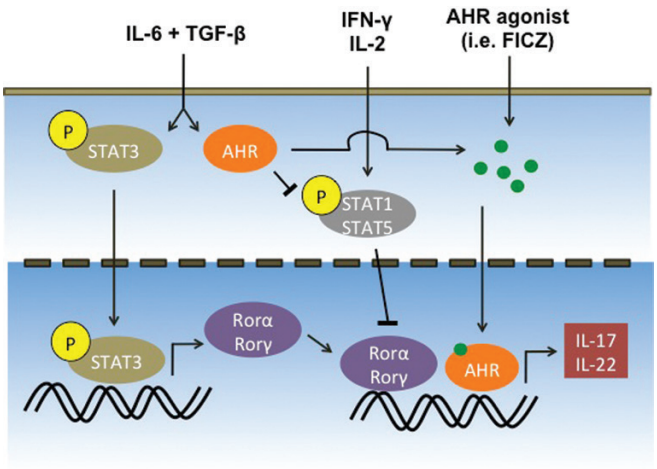

Fig. 1. Ahr and T_h17 cell development. T_h17 cell differentiation is induced by IL-6 and TGF-β. These cytokines trigger STAT3 phosphorylation, which in turns induces the expression of the T_h17 cell-specific transcription factors Rorα and Rorγ followed by IL-17 and IL-22 expression. Ahr is also expressed in response to IL-6 and TGF-β and participates in T_h17 cell differentiation. Ahr plays different roles in T_h17 cell generation including inhibiting STAT1 and STAT5 phosphorylation and directly binding the IL-17 promoter (19, 25, 26).

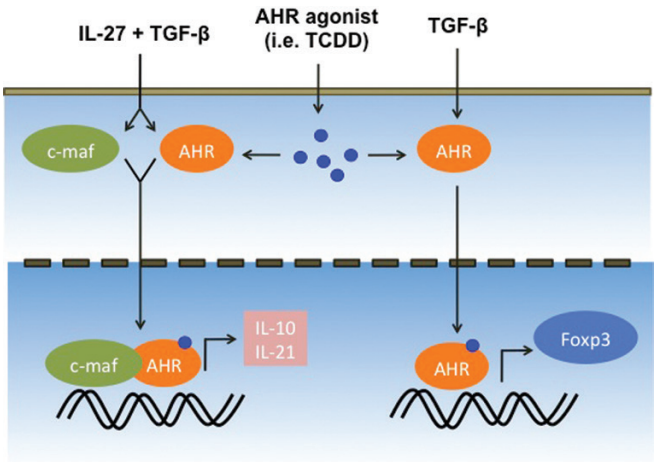

Fig. 2. Ahr and T_r1 and T_{reg} cell generation. Tr1 or T_{reg} cells develop in response to IL-27 and TGF-β, or TGF-β alone. T_r1 cell-polarizing conditions trigger the expression of transcription factors, including Ahr and c-maf, and Ahr–c-maf complexes bind to the IL-10 and IL-21 promoter regions. Ahr also directly interacts with the Foxp3 promoter under T_{reg} cell-polarizing conditions (21, 27).

Table 1. Effects of Ahr in experimental models of autoimmune disorders

Experimental model	Ahr status	Effects in immune cell populations	Effects on disease	References
EAE	Activated by TCDD	More T_{reg} cells Fewer T_h17 cells	Suppresses disease	21
	Activated by FICZ	Fewer T_{reg} cells Fewer T_h17 cells	Exacerbates disease	20, 21
	Activated by ITE	More tolerogenic DCs More T_{reg} cells	Suppresses disease	29
CIA	Deleted from T cells	Fewer T_h17 cells	Suppresses disease	30
Colitis	Activated by FICZ	Fewer IFN-γ^+ cells More IL-17^+ cells	Suppresses disease	38

promote and inhibit EAE development, respectively. Differences in the molecular stabilities of TCDD and FICZ may explain the disparate results associated with these Ahr ligands. The affinity of the rapidly metabolized FICZ for Ahr is higher than that of TCDD. On the other hand, TCDD also shows a high affinity for Ahr but is not metabolized. Ahr is less sensitive to Kyn than TCDD or FICZ, which may reflect the weakly basic aromatic amine in Kyn (Fig. 3). Thus, Kyn is used experimentally at millimolar concentrations compared with nanomolar for TCDD.

The different stabilities of these ligands may be caused by different enzymatic modifications during metabolism. For instance, Mezrich *et al.* (28) found that FICZ and Kyn differently affect T_{reg} cell differentiation and hypothesized that Kyn but not FICZ may be modified by Ahr-induced cytochrome P450 enzymes. To elucidate the intracellular mechanisms and effects of each Ahr ligand, the metabolism of each ligand should be examined in detail.

Contrary to findings from Veldhoen *et al.* (20) showing that $Ahr^{-/-}$ mice develop less severe EAE, Quintana *et al.* (21, 29) showed that Ahr^d mice, which express a low-affinity Ahr variant caused by a mutation in the ligand-binding site, developed more severe EAE and a reduced frequency of Foxp3$^+$ Treg cells in several tissues of Ahr^d mice. We recently reported that $Ahr^{-/-}$ mice are resistant to the development of CIA probably because of reduced T_h17 cell differentiation (30). These findings indicate that a lack of Ahr and a low-affinity variant of Ahr (Ahr^d) result in contrasting outcomes in various models of autoimmune diseases (20, 21, 29, 30). Ahr^d mice express a 104-kDa receptor with a ligand affinity that is 10- to 100-fold

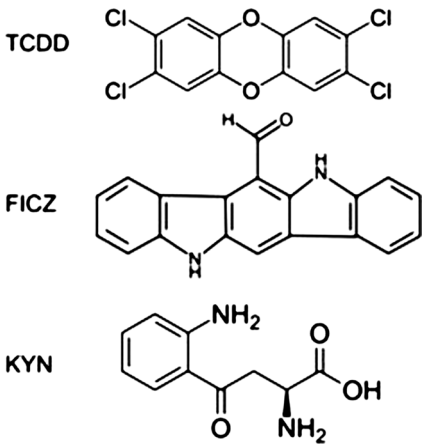

Fig. 3. Structure of selected Ahr agonists.

lower than that of the receptor produced by C57BL/6J mice. In a previous study, we found that the frequency of Foxp3$^+$ T_{reg} cells generated from naive T cells in the presence of TGF-β is mildly increased by Ahr ligands including TCDD and FICZ *in vitro* (19). On the other hand, the role of Ahr in T_{reg} cell development is still controversial (31–33). There is a possibility that Treg cells are proportionally overrepresented in the CD4 T-cell population induced by TCDD due to minimal receptor expression and they are likely to escape death by overstimulation (32). In this case, thus, whether the absolute number or percentage of T_{reg} cells is increased needs further consideration (32). Because the balance between T_h17 and T_{reg} cells is critical, understanding the conditions under which Ahr induces T_h17 or T_{reg} cell development during autoimmune disease development may shed light on the precise roles of Ahr. Veldhoen *et al.* (20) and Nakahama *et al.* (30) showed that Ahr deficiency in EAE and CIA disease models resulted in fewer T_h17 cells and no effects on Foxp3$^+$ Treg cells, respectively. Ahr, therefore, appears to be more critical to T_h17 cell development than T_{reg} cell generation. On the other hand, Quintana *et al.* (21) identified more T_h17 cells in EAE-treated Ahr^d mice compared with EAE-treated wild-type (WT) mice. The authors also observed fewer Foxp3$^+$ T_{reg} cells in thymus and mesenteric lymph node tissues isolated from naive Ahr^d mice compared with WT mice, suggesting that the smaller T_{reg} cell population in Ahr^d naive mice may facilitate the differentiation of T_h17 cells during disease development (29). The d allele was identified as having low affinity in the context of TCDD (34). Endogenous Ahr ligands possibly bind at low affinity to Ahr^d, which likely contributes to the differences observed between Ahr^d and $Ahr^{-/-}$ mice.

Recent studies have shown that Ahr is involved in IL-22 production from T_h17 cells and γδ T cells (20, 35). IL-22 is a member of the IL-10-related cytokine family and is highly expressed by T_h17 cells. IL-$22^{-/-}$ mice are less susceptible to CIA than WT mice, indicating that IL-22 is pro-inflammatory (36). Nakahama *et al.* (30) showed that $Ahr^{-/-}$ mice are resistant to CIA development owing to reduced T_h17 cell differentiation. Interestingly, Ahr deficiency specifically in T cells, but not in macrophages, suppresses the development of CIA. These results suggest that the pro-inflammatory effects of Ahr in mice with CIA are mediated via T_h17 cells and IL-22. IL-22 deficiency, however, enhances the development of inflammatory bowel disease in various models such as T-cell-mediated colitis and DSS-induced colitis (37). Treating mice with FICZ increases IL-22 levels and protects mice against colitis induced by trinitrobenzenesulfonic acid (TNBS), DSS or T-cell transfer, whereas

administering the Ahr antagonist 2-methyl-2H-pyrazole-3-carboxylic acid decreases IL-22 levels and causes severe colitis (38). In DSS- or TNBS-induced colitis, the epithelium of the gastrointestinal tract is destroyed, leading to further inflammation. Mucosal cell types—e.g. epithelial cells—are important for maintaining homeostasis during immune responses in the gut. Examining the functions of Ahr specifically in gut epithelial cells or intraepithelial lymphocytes (IELs) and innate lymphoid cells in the gut (see below) may help to elucidate the pathogenesis of inflammatory bowel disease.

Ahr in macrophages and inflammatory responses

Macrophages are important for innate immune responses, producing pro-inflammatory cytokines, and contribute to TLR-mediated tuning of adaptive immune responses. Kimura *et al.* (39) demonstrated that LPS-induced production of such pro-inflammatory cytokines as IL-6, TNF-α and IL-12 is augmented in $Ahr^{-/-}$ peritoneal macrophages compared with WT cells. Moreover, compared with WT mice, $Ahr^{-/-}$ mice are more sensitive to LPS (39, 40). Consistent with these findings, bone marrow-derived macrophages from $Ahr^{-/-}$ mice produce increased levels of IL-1β compared with WT cells (40). A recent study also demonstrated that overproduction of histamine in $Ahr^{-/-}$ peritoneal macrophages drives IL-6 expression (41). Of note, macrophages can be polarized into M1 or M2 cells in response to different stimuli (42). M1 macrophages produce high levels of pro-inflammatory cytokines, including IL-6, TNF-α and IL-12, to clear bacterial, viral and fungal infections, whereas M2 macrophages produce high levels of IL-10 in response to parasitic infections (42). Ahr is expressed in both GM-CSF-induced M1 and M-CSF-induced M2 macrophages, whereas Ahr expression is up-regulated by LPS in M1 but not M2 macrophages (our unpublished data). Altered expression of such pro-inflammatory cytokines as IL-6 in macrophages may underlie these Ahr-mediated effects.

Ahr is also involved in NF-κB-related signaling in stimulated macrophages. Ahr interacts with STAT1 on the IL-6 promoter, which suppresses LPS-induced activation of IL-6 expression by inhibiting the transcriptional activity of NF-κB (39). It is important to note that Ahr plays different roles in CpG–TLR9 and LPS–TLR4 signaling. Ahr is expressed in macrophages in response to CpG but does not regulate the production of pro-inflammatory or anti-inflammatory cytokines in these cells (39). Kimura *et al.* (39) demonstrated that LPS and CpG activate STAT1 in macrophages. Binding of Ahr and STAT1, however, has been observed in response to LPS stimulation but not CpG (39). These results suggest that Ahr does not contribute to CpG signaling in macrophages due to a lack of binding between Ahr and STAT1. LPS may induce the expression of currently unknown factors that are required for Ahr–STAT1 binding, whereas CpG does not. In addition, Gao *et al.* (43) revealed that, unlike CpG, LPS significantly induces plasminogen activator inhibitor-2 (Pai-2) expression in RAW 264.7 macrophages (22.7-fold increase in expression in response to LPS). Furthermore, Ahr cooperates with Pai-2 to regulate pro-inflammatory cytokine production in macrophages through an LPS-dependent mechanism that involves NF-κB but not Arnt (40). Therefore, Pai-2 expressed in response to LPS may be one of the undefined factors that are required for Ahr–STAT1 binding. The potential role of Pai-2 in the interaction between Ahr and STAT1 during inflammatory cytokine production should be further investigated.

In humans, macrophages are affected by Ahr activation and the resulting dysregulation of vitamin catabolism. The active form of vitamin D3 regulates immune responses, and vitamin D deficiency contributes to many diseases, including the deleterious effects of cigarette smoking. Matsunawa *et al.* (44) suggested that BaP-induced vitamin D3 deficiency and Ahr activation in macrophages mediate some of the effects of smoking. Ahr activated by BaP—a polycyclic aromatic hydrocarbon—stimulates vitamin D3 catabolism to modulate vitamin D signaling. Another study of human macrophages showed that Ahr cooperates with the transcription factor cellular viral musculoaponeurotic fibrosarcoma oncogene homolog (c-maf) to control β7-integrin expression in response to BaP (45). β7-Integrin is a newly identified molecular target of polycyclic aromatic hydrocarbons. Increased β7-integrin expression in response to these environmental contaminants most likely requires activation of cooperative pathways involving AhR and c-maf. β7-Integrin may be a homing receptor on memory and effector cells moving to lamina propria and on naive lymphocytes extravasating in the gut (46). Therefore, changes in β7-integrin expression in response to polycyclic aromatic hydrocarbons and the downstream Ahr–c-maf interaction may alter immune responses in the gut. In summary, Ahr regulates the inflammatory responses of macrophages by interacting with STAT1, Pai-2 or c-maf.

TLR activation in macrophages and T-cell responses in the CIA model appear to elicit contradictory Ahr activities (30, 39). Ahr may interact with other factors—e.g. interferon regulatory factor 4 (IRF4)—to affect the function and differentiation of T cells and macrophages. IRF4 plays crucial roles in T_h17 cell and macrophage differentiation. IRF4 is thought to positively regulate the development of several T-cell subsets, including T_h17 cells (47). In T_h17 cells, IRF4 deficiency reduces the expression of RORγt and RORα, both of which are important for T_h17 cell differentiation (48). IRF4-deficient mice do not develop EAE, and T_h cells from these mice fail to differentiate into T_h17 cells (48). On the other hand, in macrophages, IRF4 negatively regulates TLR signaling and the production of the pro-inflammatory cytokines TNF-α and IL-12 in response to LPS (49, 50). Additionally, IRF4 interacts with Jumonji domain-containing protein 3 to control M2 macrophage polarization (51). IRF4 has at least two distinct functions in T cells and macrophages, either promoting pro-inflammatory effects via enhanced T_h17 cell development or increasing anti-inflammatory effects by inhibition of pro-inflammatory cytokine production in macrophages or polarizing M2 macrophages. The promoter of IRF4 contains two AhR binding sites. Therefore, Ahr may bind to IRF4 in T cells or macrophages and regulate the function of these cells by affecting T_h17 cell differentiation or macrophage polarization, respectively. An interaction between Ahr and IRF4 may underlie the different regulatory roles of Ahr in T cells and macrophages and in experimental models of inflammatory diseases, such as CIA or endotoxin shock.

Ahr in DCs and anti-inflammatory effects

DCs play key roles in antigen presentation and the initiation of T-cell responses. These antigen-presenting cells can be divided into various subsets based on the expression profiles of phenotypic markers (52). Naive T-cell activation, proliferation and differentiation are induced by DCs and associated inflammatory cytokines. TCDD can induce Ahr expression and activation in DCs to enhance DC differentiation (53). In addition to TCDD, the TLR ligands LPS and CpG induce Ahr expression in bone marrow-derived DCs (BMDCs) (54). In response to LPS or CpG, WT and $Ahr^{-/-}$ BMDCs show similar IL-6 and TNF-α production, whereas IL-10 levels are significantly reduced in $Ahr^{-/-}$ BMDCs (54). In $Ahr^{-/-}$ mice, RelB, a regulator of NF-κB signaling, is rapidly degraded, which may reduce IL-10 production in $Ahr^{-/-}$ BMDCs (55, 56).

In addition, as yet unidentified factors likely underlie the discrepant results related to Ahr, such as cellular responses to TCDD, FICZ, ITE and tryptophan metabolites. Depending on the ligand, Ahr regulates $Foxp3^{+}$ Treg and T_h17 cells, resulting in different effects in various experimental disease models. In BMDCs, TCDD and FICZ induce the same phenotypic changes (57). Recently, Wu *et al.* (58) showed that a lack of Ahr reduces the expression of LPS-induced inflammatory genes, including *CYP1A1*, *COX-2*, *CEBPβ* and *IDO* in BMDCs. *IDO* encodes indoleamine 2,3-dioxygenase, an enzyme that degrades tryptophan into other metabolites (59). The alternative NF-κB pathway is also linked to the induction of IDO expression in DCs. Kyn—a first-round product of IDO-mediated tryptophan degradation—enhances T_{reg} cell development and inhibits IL-17 production from T_h17 cells (28, 60). Consistent with these results, Vogel *et al.* (53) demonstrated that the spleens of TCDD-treated mice show increased and decreased levels of the T_{reg} cell marker Foxp3 in response to induction and inhibition of IDO activity, respectively.

Taken together, these data suggest that Ahr deletion or activation alters the functions of BMDCs in response to various stimuli. Ahr plays important roles in DCs and regulates immune responses to promote or suppress the development of certain experimental and inflammatory diseases, whereas the profiles and effects of Ahr expression and activation in various DC subsets, including myeloid DCs and plasmacytoid DCs, are currently unclear. The regulatory roles of Ahr in the range of DC subsets should be further investigated.

Ahr activation and immunosuppression in B cells

B cells—key components of humoral immunity—are sensitive to such toxic compounds as TCDD. Ahr is an important mediator of the effects of TCDD on B cells (61). TCDD induces Ahr expression and results in LPS-induced inhibition of IgM secretion in the CH12.LX B-cell line (62). Changes in B-cell differentiation and antibody production may depend on BTB and CNC homology 2 (Bach2), a direct target of Ahr (63).

TCDD-mediated suppression of B-cell differentiation into plasma cells involves several transcription factors, including PR domain zinc finger protein 1 (Prdm1), B-cell lymphoma 6 (Bcl6) and paired box protein 5 (Pax5) (64). Bach2 expression in response to TCDD–Ahr binding or antigen activation inhibits Prdm1 and regulates the suppressive effects of Bcl6 and Pax5 (63). In addition, Tanaka *et al.* (65) found that IL-4 causes Ahr expression and activation in B cells. Ahr, however, is not involved in IgE synthesis by B cells (65), and the regulation of immunoglobulin synthesis requires further investigation. Suppressor of cytokine signaling 2 is dose dependently expressed in response to TCDD in murine B cells (66).

A lack of Ahr also affects the maturation of B cells from bone marrow. Thurmond *et al.* (67) demonstrated that $Ahr^{-/-}$ mice have more pro-/pre-B cells than $Ahr^{+/+}$ mice and TCDD reduces the number of pro-/pre-B cells in $Ahr^{+/+}$ mice. Interestingly, Ahr affects B cells only during early developmental stages. The precise mechanism by which the Ahr regulates the number of early pro-/pre-B and immature B cells is unclear (67). TCDD also impairs the effector functions of primary human B cells and suppresses IgM responses in most donors (68). TCDD activates the Ahr in B cells and impairs B-cell differentiation and IgM production.

We have summarized studies of interactions between Ahr and other downstream molecules in different cell types in Table 2.

Ahr in other cell types

Skin cells

Ahr is expressed in Langerhans cells, a DC subset that serves as antigen-presenting cells in the epidermis. $Ahr^{-/-}$ Langerhans cells do not mature or function properly, which may contribute to skin allergies (69). The lack of Ahr prevents the development of invariant epidermal GM-CSF-producing γδ T cells in the skin of mice, which may affect Langerhans cell maturation owing to reduced GM-CSF levels (70). Furthermore, Ikuta *et al.* (71) demonstrated that Ahr co-localizes with the transcriptional repressor B lymphocyte maturation protein 1, which is expressed from an Ahr target gene in epidermal keratinocytes and sebocytes. In normal human epidermal keratinocytes, the antifungal agent ketoconazole activates NF erythroid 2-related factor-2 (Nrf2) via AhR signaling (72). The AhR–Nrf2 pathway may provide a foundation for therapies for inflammatory skin diseases.

Neuroinflammatory and brain tumor cells

Platten *et al.* (73) suggested treating autoimmune neuroinflammation with the synthetic tryptophan metabolite *N*-(3,4-dimethoxycinnamoyl) anthranilic acid (3,4-DAA). Although many Ahr ligands are toxic and cannot be used therapeutically, 3,4-DAA is an orally active compound with favorable pharmacokinetics in humans. Established EAE in mice is ameliorated by 3,4-DAA (73). Recently, Opitz *et al.* (74) demonstrated that Kyn is also an endogenous Ahr ligand in humans. Generated by human brain tumor cells via tryptophan-2,3-dioxygenase (TDO), Kyn suppresses antitumor immune responses (74). Mechanistically, tumors can escape immune responses by expressing IDO or TDO and locally

Table 2. Molecules that interact/bind with Ahr and downstream effects

Molecules that interact/bind with Ahr	Cell type	Effects	References
Stat1, Stat5	T cells	Reverses suppression of T_h17 cell development	19, 20
IL-17 promoter	T cells	Promotes IL-17 production	25
Stat1/IL-6 promoter	Macrophages	Suppresses LPS-induced IL-6 production by inhibiting NF-κB signaling	39
Pai-2	Macrophages	Regulates LPS-induced pro-inflammatory cytokine production via NF-κB	40
Sp1/histidine decarboxylase promoter	Macrophages	Inhibits LPS-induced histamine production	41
BaP/c-maf	Macrophages	Increases β-integrin expression	45
Bach2	B cells	Inhibits B-cell differentiation	63

depleting tryptophan, which has led to studies of IDO and TDO inhibitors as antitumor therapies (75, 76).

Cells in the gut

Lee *et al.* (77) found that innate lymphoid cells secrete IL-22 to protect the intestinal mucosa from infection. Decreased levels of IL-22 in $Ahr^{-/-}$ mice are caused by markedly reduced numbers of innate lymphoid cells, including the $NKp46^+$ and LTi-like subsets (77, 78). These observations may relate to Notch signaling, an important downstream pathway of Ahr in the generation of $NKp46^+$ innate lymphoid cells (77, 78). Moreover, innate lymphoid cells expressing the nuclear receptor RORγt contribute to gut immunity, possibly because of the need for IL-22 (79). Ahr promotes gut immunity by regulating the function of $ROR\gamma t^+$ innate lymphoid cells (79). Additionally, IELs play important roles in intestinal immunity. Li *et al.* (80) reported that Ahr helps maintain the IEL population; Ahr deficiency reduced the number of IELs, increased the bacterial burden and promoted DSS-induced colitis (80). Each of these results supports a modulatory role for Ahr in immune responses in the gut.

Bone marrow and stem cells

Sakai *et al.* (81) found a defect in the long-term reconstitution activity of TCDD-treated hematopoietic stem cells (HSCs) but not in $Ahr^{-/-}$ HSCs. TCDD increased the number and damaged the stem cell functions of $CD34^-KSL$ ($CD34^-$, $c\text{-}kit^+$, $Sca\text{-}1^+$, lineage-negative) cells, whereas an absence of Ahr prevented effects on the stem cell activity of these cells (81). In this study, the authors hypothesized that TCDD affected the expression of several intrinsic factors that control HSC self-renewal and/or reconstitution activities (81). In particular, HOXB4 seems to play an important role because an upstream region of the *HOXB4* gene contains two XREs that may interact with TCDD-bound Ahr/Arnt (81). Therefore, Ahr/Arnt may inhibit HOXB4 expression in HSCs (81). Additionally, Boitano *et al.* (82) discovered the purine derivative StemRegenin 1 (SR1), which promotes *ex vivo* expansion of $CD34^+$ cells from primary human HSCs. Interestingly, SR1 is an Ahr antagonist and SR1-induced $CD34^+$ cell proliferation is mediated through direct binding to Ahr (82). Although the molecular mechanisms underlying the effects of Ahr in HSCs have not been detailed, using SR1 to antagonize the activity of Ahr may improve clinical approaches to HSC-based therapies (82). Recently, Korkalainen *et al.* (83) reported that activating Ahr with a low dose of TCDD (10 fM) affected osteoblast and osteoclast differentiation from bone marrow-derived stem cells. TCDD significantly reduces mRNA levels of various factors involved in osteoblast differentiation, including RUNX2, alkaline phosphatase and osteocalcin, and decreases the number of F-actin rings and $TRACP^+$ multinucleated cells, both of which are markers of osteoclast differentiation. These results suggest that Ahr contributes to bone quality in animals exposed to TCDD. Bone marrow stromal cells (BMSCs) regulate the growth and development of hematopoietic cell lineages. LPS-stimulated BMSCs produce cytokines, including IL-6 and GM-CSF. Interestingly, TCDD specifically suppresses LPS-induced IL-6 production in BMSCs, suggesting that Ahr agonists regulate BMSCs to trigger inflammatory responses to antigens (84). Ahr activation in hematopoietic stem/progenitor cells affects cellular trafficking and migration (85, 86). Tables 1 and 3 provide a summary of studies examining Ahr-mediated effects in various cells and tissues, and the potential functions of Ahr in several autoimmune disease models.

Conclusion

In summary, a number of studies have provided valuable insights into the roles of Ahr in immune responses, including regulating transcription factors, cellular proteins and responses to chemical compounds via the Ahr–Arnt, NF-κB and p38-MAPK signaling pathways. Immune cell-specific conditional knockout mice have been used to examine Ahr in various immune cell types, including macrophages and T cells. Ahr is an anti-inflammatory factor in macrophages, whereas it is likely pro-inflammatory in T cells. Studies of mice bearing specific deletions of Ahr in DCs, B cells or epithelial cells will likely provide additional insights. Furthermore, the ligands of Ahr activate multiple signal transduction pathways. Elucidating the mechanisms by which Ahr regulates immune responses will provide a foundation for therapeutically targeting this molecule in a range of autoimmune and inflammatory diseases.

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Table 3. Ahr-mediated effects in various cells and tissues

Cells/tissues	Ahr-mediated effects	References
T cells	IL-6 and TGF-β induce Ahr expression	19
	Ahr deficiency decreases the number of T_h17 cells	
	TCDD and FICZ promote the development of T_h17 and T_{reg} cells	
	Ahr and Kyn induce T_{reg} cell generation	28
	FICZ increases IL-22 production	38
Macrophages	Ahr deficiency enhances LPS-induced IL-1β production and LPS-induced IL-6, IL-12 and TNF-α expression	39, 40
	Ahr signaling decreases LPS-induced histamine production	41
	BaP increases vitamin D3 catabolism	44, 45
	BaP and c-maf increase β-integrin expression	
DCs	Ahr deficiency inhibits DC induction of T_{reg} cell differentiation and enhances T_h17 cell development	54
	Kyn decreases DC-mediated immunogenicity	
	Ahr deficiency does not affect LPS-induced IL-6 and TNF-α expression but inhibits IL-10 production	
	Ahr deficiency decreases LPS-induced inflammatory gene expression.	58
B cells	Ahr deficiency affects early B-cell development	67
	TCCD suppresses the differentiation of B-cell-derived plasma cells.	68
	TCCD enhances LPS-induced IgM secretion	
Skin	Ahr deficiency leads to functional defects in Langerhans cells and some γδ T cells	69, 70
Gut	Ahr deficiency reduces the numbers of innate lymphoid cells and intestinal epithelial lymphocytes	77–80
Bone	Ahr activation inhibits osteoblast and osteoclast differentiation	83
	TCDD suppresses LPS-induced IL-6 expression from stromal cells	84

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