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Interrelated Roles for the Aryl Hydrocarbon Receptor and Hypoxia Inducible Factor-1α in the Immune Response to Infection

Sagie Wagage and Christopher A. Hunter*

Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract: Cells of the immune system utilize multiple mechanisms to respond to environmental signals and recent studies have demonstrated roles for two closely related proteins, the aryl hydrocarbon receptor (AHR) and hypoxia inducible factor-1α (HIF1α), in these processes. The AHR is a transcription factor that is activated by diverse ligands found in the diet and environmental pollution as well as by microbial and host-derived products. In contrast, HIF1α is a transcription factor that is active under low oxygen conditions and mediates cellular responses to hypoxia. These evolutionarily conserved proteins have roles in the interrelated processes of metabolism, tumorigenesis, and vascular development. Additionally, the AHR and HIF1α have multiple effects on innate and adaptive immunity. This article provides an overview of the biology of these transcription factors and reviews the effects of AHR and HIF1α signaling on immunity to infection. There are many parallels between these two pathways and their functions highlight the importance of AHR and HIF1α activity particularly at barrier surfaces in coordinating responses to pathogens.

Keywords: Adaptive immunity, aryl hydrocarbon receptor, hypoxia inducible factor-1α, infection, innate immunity, transcription factor.

INTRODUCTION

One of the major challenges faced by the immune system involves the generation of an appropriate inflammatory response to control pathogen growth while limiting immune-mediated damage to the host. In order to achieve this balance, immune cells need to sense and interpret environmental signals properly in order to promote or attenuate inflammation. The immune system employs an array of sensors to detect environmental cues, including nuclear hormone receptors, cytokine receptors, and Toll-like receptors. The transcription factors the aryl hydrocarbon receptor (AHR) and hypoxia inducible factor-1α (HIF1α) are members of the same superfamily and provide the immune system with additional means of reacting to external signals. The AHR is activated by numerous structurally diverse ligands including dietary and microbial agonists, endogenous host-derived molecules, and xenobiotic compounds that are byproducts of industrial processes [1]. In contrast, HIF1α activity is regulated by oxygen concentration and allows cells to respond to hypoxia [2].

The AHR and HIF1α are expressed in numerous immune cells, including hematopoietic stem cells, macrophages, natural killer cells, and different T cell subsets [3-13], and signaling through these transcription factors affects multiple aspects of the immune response. Consequently, the presence of AHR ligands in environmental pollution implies that the effects of AHR signaling on the immune system may have epidemiological consequences. Indeed, previous studies have linked AHR activity to elevated susceptibility to autoimmunity and led to the suggestion that this pathway contributes to the increasing rates of autoimmune diseases seen in highly industrialized countries [10]. The AHR also has a number of effects on the immune response to infection and children exposed to elevated levels of pollutants that activate this transcription factor exhibit an increased incidence of ear infections, chicken pox, and respiratory infections [14-16].

In addition to their effects on the immune system, signals through the AHR and HIF1α influence a number of related physiological processes. For example, AHR activation promotes the metabolism of xenobiotic compounds by inducing the expression of cytochrome p450 monooxygenases as well as other enzymes [17], whereas HIF1α induces the expression of genes involved in glycolysis, which allows cells to switch from oxidative to glycolytic metabolism and adapt to hypoxic conditions [18]. The AHR and HIF1α have perhaps been most extensively studied because of their roles in cancer biology. The involvement of the AHR in xenobiotic metabolism can lead to the production of carcinogens [19], while HIF1α promotes numerous aspects of carcinogenesis through its effects on cell proliferation, changes in metabolism, and angiogenesis [19, 20]. Although the expression of HIF1α is associated with poor prognosis in many human cancers, both HIF1α and the AHR have been reported to have context-dependent tumor suppressor effects [19, 20].

The AHR and HIF1α also influence development in invertebrates and mammals. The *Drosophila* AHR homolog Spineless contributes to leg and antennae development, and the establishment of the retinal mosaic that enables color vision [21, 22]. In mice, the ductus venosus, which connects the umbilical and portal veins to the inferior vena cava typically closes after birth, but adult AHR deficient ($Ahr^{-/-}$) mice retain a patent ductus venosus [23, 24]. AHR deficient

*Address correspondence to this author at the Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; Tel: 215-573-7772; Fax: 215-746-2295;
E-mail: chunter@vet.upenn.edu

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embryos also exhibit defects in liver perfusion, and the livers of *Ahr*$^{-/-}$ mice are characterized by decreased hepatocyte size, fatty metamorphosis, and portal fibrosis [23, 25-27]. *Ahr*$^{-/-}$ mice also maintain fetal vascular structures in the eye and exhibit altered kidney vasculature, cardiac hypertrophy, and increased blood pressure [23, 28-30]. Analogously, HIF1α deficiency leads to disorganized vascularization of the yolk sac, decreased cephalic vascularization, and embryonic lethality [31, 32]. This function of HIF1α mirrors the effects of the *Drosophila* homolog Sima, which promotes the branching of tracheal tubes that distribute oxygen to the tissues [33]. Together, these findings indicate that the AHR and HIF1α have opposing roles in vascular development; the AHR contributes to the pruning of vascular structures, which involves the removal of vessels as the vasculature matures, while HIF1α promotes the sprouting of new vessels [23]. Interestingly, the developmental roles for Spineless and Sima are reminiscent of the functions of *Drosophila* Toll, which was initially characterized for its effects on development but was subsequently shown to function in innate recognition [34]. Similarly, the AHR and HIF1α influence developmental processes as well as innate and adaptive immunity. This review discusses the impact of these transcription factors on immune responses to infection and highlights the interrelated roles of these two pathways.

STRUCTURE AND EVOLUTION OF THE AHR AND HIF1α

The AHR and HIF1α function as heterodimers and are members of the basic helix-loop-helix-PER-ARNT-SIM (bHLH-PAS) superfamily of proteins. Both transcription factors are structurally similar, with an N-terminal bHLH domain that contributes to dimerization and DNA binding, a central PAS domain that also mediates dimerization, and a C-terminal transactivation domain that mediates transcription [24, 35]. The PAS sequence is an evolutionarily conserved motif present in *Archaea*, *Bacteria*, and *Eucarya* that is associated with proteins that mediate cellular responses to environmental cues and developmental signals, including photoreceptors, circadian clock proteins, chemoreceptors, voltage-gated ion channels, and regulators of embryonic development [36]. In contrast to the expression of the PAS motif in all three domains of life, bHLH-PAS family members are found primarily in metazoans [37]. Phylogenetic studies indicate that the AHR and HIF1α arose from the duplication of an ancestral gene following the divergence of sponges but before the ancestor to Placozoa, Cnidarians, and Bilaterians [38, 39]. Accordingly, AHR and HIF1α homologs have not been identified in sponges, but are present in some of the simplest metazoans, including placozoans, corals, sea anemones and nematodes [38-43]. The conservation of HIF1α in a broad range of animals that occupy diverse habitats reflects the importance of oxygen sensing in the evolution of metazoans, as the maintenance of oxygen homeostasis is essential for multicellular organisms that rely on oxygen for the process of energy generation [42, 44]. Although the AHR is also evolutionarily conserved, invertebrate AHR homologs do not bind to canonical xenobiotic AHR ligands, suggesting that this AHR function evolved in chordates [38, 45]. It is unclear whether the AHR affects immunity in invertebrates, but *Caenorhabditis elegans* mutants with increased HIF-1 activity are more susceptible to infection with *Staphylococcus aureus* [46].

SIGNALING THROUGH THE AHR AND HIF1α

While the AHR has E3 ubiquitin ligase activity that allows it to modulate protein degradation [47], it is the transcriptional activity of this protein that has been most extensively studied. As illustrated in Fig. (**1**), in the absence of an agonist, the AHR is present in the cytosol in a complex with its chaperone proteins [24]. Upon ligand binding, this complex translocates into the nucleus where the AHR interacts with the AHR nuclear translocator (ARNT) to form a competent transcription factor that binds to dioxin responsive elements and mediates gene transcription. Classical xenobiotic AHR agonists consist of halogenated aromatic hydrocarbons and polycyclic aromatic hydrocarbons, but structurally diverse synthetic and physiologic molecules can activate this pathway [1]. These compounds include byproducts of industrial processes such as benzo[a]pyrene and 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), which is the prototypical AHR agonist and a potent toxin whose effects include wasting, thymic involution, liver toxicity, porphyria and carcinogenesis [48]. AHR ligands are also present in cigarette smoke and vehicle exhaust, which could impact the lungs and skin [49, 50], while plant-derived AHR agonists present in the diet make the intestine a major site of exposure to these compounds [1].

AHR ligands can also be produced by microorganisms that include gut resident commensal bacteria [51], and it has been proposed that the AHR functions as a pattern recognition receptor [52]. Indeed, the production of AHR agonists by *Malassezia* yeasts is associated with the presence of these compounds in the skin of patients with diseases linked to these organisms [53-55]. More recent studies have shown that the AHR is activated by pigmented virulence factors expressed by *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*, and *Ahr*$^{-/-}$ mice exhibit increased mortality following challenge with these pathogens, indicating that these bacterial pigments serve as a class of pathogen-associated molecular patterns [52]. Additionally, extracts from the parasite *Toxoplasma gondii* contain peptides that resemble plant lipoxygenases that allow this protozoan to catalyze the production of lipoxin A_4 [56], an AHR ligand that can also be produced by the host [1]. Thus, by acting through the AHR, certain metabolites produced by pathogens may act as viability-associated pathogen-associated molecular patterns, which allow the immune system to distinguish between live and dead microorganisms [57]. While there are numerous exogenous sources of AHR ligands, the developmental roles for this transcription factor imply the presence of endogenous pathways that engage the AHR. For example, ultraviolet light promotes the formation of the high affinity AHR ligand 6-formylindolo [2,3-b] carbazole (FICZ) from tryptophan in the skin [58-60]. L-kynurenine, a product of tryptophan degradation that can be formed during the host response to infection, can also activate the AHR [1, 61]. Given the multiple sources of AHR agonists, this transcription factor

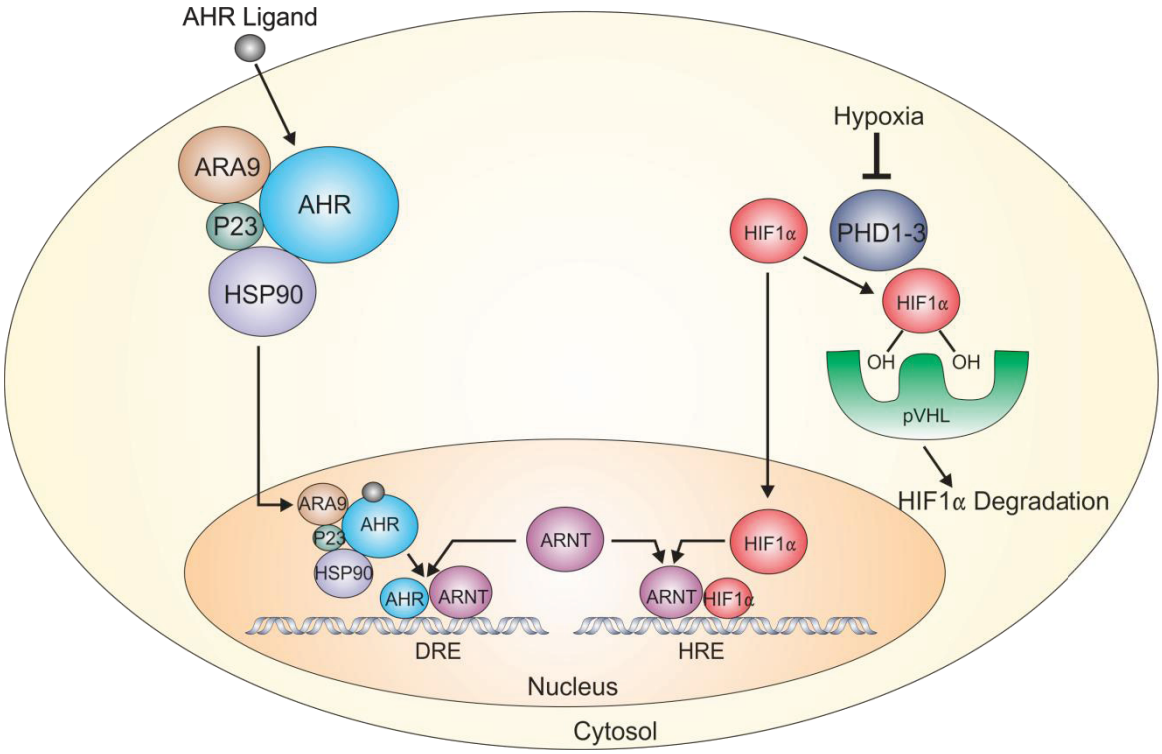

Fig. (1). AHR and HIF1α mediated signaling. In its inactive form, the AHR is localized to the cytosol in a complex with the chaperone proteins ARA9, p23, and HSP90. Upon ligand binding, this complex translocates to the nucleus where the AHR heterodimerizes with ARNT, forming a competent transcription factor that binds to dioxin response elements (DREs). Under normoxic conditions, HIF1α is hydroxylated by the PHDs, which are oxygen sensitive prolylhydroxylases. HIF1α hydroxylation leads to its recognition by the E3 ubiquitin ligase pVHL, which targets HIF1α for proteasomal degradation. Hypoxia inhibits the activity of the PHDs, leading to the stabilization of HIF1α and its translocation into the nucleus. HIF1α then heterodimerizes with ARNT, forming a transcription factor that binds to hypoxia response elements (HREs).

may provide the host with the ability to sense environmental and dietary molecules as well as ligands produced by pathogens or as part of the immune response to infection.

In contrast to the AHR, HIF1α is activated in environments with low oxygen (Fig. **1**) [2]. Under normoxic conditions, oxygen and iron sensitive prolylhydroxylases (PHD1-3) hydroxylate HIF1α, which leads to its recognition by an E3 ubiquitin ligase, a complex that includes von-Hippel-Lindau protein (pVHL), targeting HIF1α for proteasomal degradation. Although this review focuses on the effects of HIF1α, higher metazoans express two other HIFα proteins, termed HIF2α and HIF3α. While these proteins are less well-studied, HIF3α is thought to influence the activity of other HIF complexes, and HIF2α has been shown to have effects on immunity and is also regulated by the activity of PHDs and pVHL [20].

Under hypoxic conditions, the PHDs, which serve as oxygen sensors, are less active, leading to the accumulation of HIF1α protein, its nuclear translocation, and binding to ARNT to form a competent transcription factor. Many of the processes modulated by the transcriptional activity of HIF1α, such as erythropoiesis, glycolysis, and angiogenesis, are associated with adaptation to hypoxia [2]. The epidermis and intestine are relatively hypoxic, implying that the effects of HIF1α activity may be particularly significant at these barrier sites [62, 63]. Additionally, inflammation is associated with the metabolic demands of inflammatory cells and pathogens at sites of infection as well as disruptions in blood flow, which can lead to the generation of local hypoxic conditions [64, 65]. The formation of hypoxic regions is accordingly characteristic of many infected tissues [66-70] and HIF1α may allow immune cells to adapt to these conditions. In addition to being activated under low oxygen conditions, HIF1α activity can also be induced by cytokines, growth factors, or microbial products [13, 71, 72], which might prime immune cells to adapt to low oxygen conditions or provide a hypoxia-independent means of eliciting HIF1α-driven responses.

ROLES FOR THE AHR AND HIF1α IN INNATE IMMUNITY

The previous sections highlight roles for the AHR and HIF1α in environmental sensing and metabolism, which are processes that impact immune function. Accordingly, these transcription factors influence multiple aspects of innate immunity, which is exemplified by the effects of HIF1α on the biology of macrophages and neutrophils (extensively reviewed in [64]). These cells rely heavily on glycolysis to generate ATP and HIF1α deficient macrophages and neutrophils contain decreased levels of ATP even in normoxic conditions [73]. In mice with a myeloid cell deletion of HIF1α, this altered metabolism is associated with impaired macrophage migration and decreased inflammatory responses [73]. HIF1α also promotes neutrophil survival

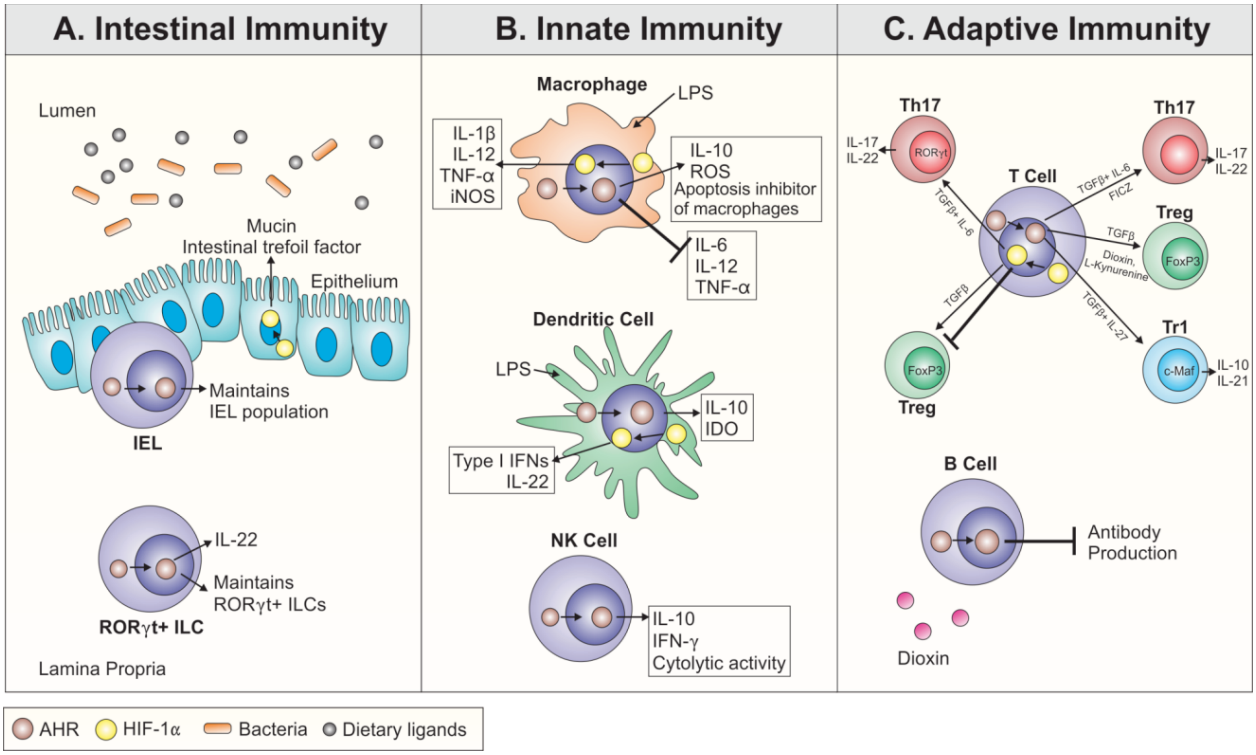

Fig. (2). Impact of the AHR and HIF1α on immune function. (**A**) In the intestine, the AHR promotes the maintenance of IELs and the maintenance and function (IL-22 production) of RORγt$^+$ ILCs. At this site, epithelial cell expression of HIF1α induces the expression of mucin and intestinal trefoil factor, which contribute to local barrier function. (**B**) In the innate immune system, the AHR enhances macrophage expression of IL-10, reactive oxygen species (ROS), and the apoptosis inhibitor of macrophages while inhibiting the production of IL-6, IL-12, and TNF-α. HIF1α promotes macrophage expression of IL-12, IL-1β, TNF-α, and iNOS. AHR signaling also promotes dendritic cell IL-10 and IDO expression, while HIF1α promotes the production of IL-22 and type I interferons. The AHR also enhances NK cell IL-10 secretion, IFN-γ production, and cytolytic activity. (**C**) In T cells, the AHR promotes Th17 development and IL-22 production and can promote Treg differentiation under certain conditions. AHR signaling also enhances the ability of Tr1 cells to produce IL-10 and IL-21. HIF1α also promotes Th17 development and has been shown to have effects that enhance or limit Treg differentiation. Activation of the AHR by dioxin inhibits B cell antibody production.

under hypoxia and neutrophils from patients with a VHL deficiency, which is associated with reduced degradation of HIF, exhibit decreased apoptosis under normoxia [74, 75].

There has been a growing appreciation that the AHR and HIF1α are both able to modulate cytokine production in a variety of innate cell populations (Fig. **2**). In macrophages stimulated with LPS, the AHR promotes IL-10 expression but limits the production of IL-6, IL-12, and TNF-α [6]. Similarly, AHR deficient dendritic cells stimulated with LPS exhibit defects in IL-10 production [76]. *Ahr*$^{-/-}$ mice that have been given LPS are more susceptible to LPS-induced sepsis, and the liver enzyme tryptophan 2,3, dioxygenase, which catalyzes tryptophan degradation, promotes the generation of AHR ligands in this context [6, 77]. Signaling through the AHR also contributes to LPS tolerance, a state in which exposure to a low dose of LPS elicits refractoriness to subsequent LPS treatment [77]. In contrast to the increased susceptibility of *Ahr*$^{-/-}$ mice to LPS, mice with a targeted deletion of HIF1α in macrophages have impaired production of IL-12 and TNF-α in response to LPS and are more resistant to this model of sepsis [13]. HIF1α also promotes macrophage IL-1β expression following LPS stimulation [78], and HIF1α deficient dendritic cells exhibit defects in their ability to express type I interferons and IL-22 [79, 80]. Interestingly, HIF1α also promotes the expression of multiple genes in macrophages associated with an alternatively activated M2 state [81], and LPS stimulation increases macrophage expression of both the AHR and HIF1α [6, 13]. How signals from these two transcription factors are integrated to influence macrophage polarization or to determine the balance between pro- and anti-inflammatory cytokine production remains unclear.

A more nuanced perspective on the impact of the AHR on dendritic cell function is provided by studies in which some AHR agonists promote the production of IL-6, IL-12, and TNF-α, while other ligands inhibit the expression of these proteins [54, 82-87]. Different AHR agonists also act to enhance or inhibit dendritic cell expression of CD80 and CD86 [54, 82, 83, 85, 88-93], and HIF1α promotes the expression of these costimulatory molecules [94, 95]. Concordantly, following influenza virus challenge, dioxin treatment impairs the ability of dendritic cells to activate antigen specific CD8$^+$ T cells [96, 97]. These effects of the AHR and HIF1α on macrophages and dendritic cells are consistent with a role for these transcription factors in innate sensing that influences the generation of adaptive immunity.

While the AHR and HIF1α impact the regulatory functions of macrophages and dendritic cells, they can also promote antimicrobial effector mechanisms in these cells. Signaling

through the AHR enhances dendritic cell expression of indoleamine 2,3, dioxygenase (IDO), which catalyzes tryptophan degradation [76, 91]. While this pathway enhances the ability of dendritic cells to promote Treg differentiation [76, 91], tryptophan depletion also limits the growth of pathogens such as *T. gondii*, *Chlamydia* sp. and *Leishmania* sp. that are auxotrophic for this amino acid [98, 99], implying that this role for the AHR may be relevant to the control of these organisms. In addition, AHR activity promotes macrophage production of reactive oxygen species and induces expression of the apoptosis inhibitor of macrophages [100], a secreted protein that promotes resistance to cell death [101] and enhances macrophage survival following infection with *Listeria monocytogenes* [100]. As a result, AHR deficient macrophages are impaired in their ability to control *L. monocytogenes* [100] and *Ahr*$^{-/-}$ mice challenged with this microbe develop elevated bacterial burdens [100, 102]. Similarly, during challenge with group A *Streptococcus*, HIF1α enhances neutrophil production of antimicrobial peptides and induces optimal macrophage iNOS expression and NO_2^- production [70]. Mice with a myeloid cell specific deletion of HIF1α consequently have a reduced ability to control group A *Streptococcus* [70]. HIF1α signaling also increases macrophage phagocytic activity under hypoxic conditions [103] and promotes macrophage expression of Slc11a1/Nramp1 [104], a metal ion transporter that localizes to phagosomes and promotes resistance to a variety of intracellular pathogens [105]. Thus, HIF1α deficient macrophages are impaired in their ability to upregulate Slc11a1/Nramp1 in response to *Salmonella typhimurium* [104]. HIF1α in monocytes has also been implicated in "trained immunity," a process in which epigenetic reprogramming leads to behavior that resembles memory in innate populations [106]. In a model of trained immunity, wild type mice pretreated with β-glucan, a cell wall component of *Candida alibcans,* are less susceptible to subsequent infection with *S. aureus*, but mice with a myeloid cell specific deletion of HIF1α that are primed with β-glucan remain susceptible to *S. aureus* [106]. Thus the AHR and HIF1α influence many aspects of cell intrinsic pathways involved in the control of microbial growth, but questions remain regarding the sources of ligands that promote these AHR functions, as relevant agonists may be derived from the host or from pathogens.

Recent studies have shown that the AHR also impacts the function of natural killer cells, which are lymphocytes involved in tumor surveillance and innate immunity to many intracellular infections. AHR deficient NK cells have defects in IFN-γ expression and cytolytic activity and are impaired in their ability to control tumor growth [7]. Although AHR signaling is less important for NK cell IFN-γ production in the context of toxoplasmosis, NK cells from *Ahr*$^{-/-}$ mice infected with *T. gondii* are impaired in their ability to express IL-10, which is associated with improved parasite control [107]. Although NK cells also express HIF1α under hypoxic conditions [12], additional studies are needed to determine the effects of HIF1α on the function of these innate lymphocytes.

EFFECTS OF AHR AND HIF1α SIGNALING ON ADAPTIVE IMMUNITY

T and B cells also need to function in diverse environments such as secondary lymphoid structures, peripheral tissues, and barrier surfaces to effectively respond to infection. The AHR and HIF1α may have a role in allowing cells of the adaptive immune system to sense and adapt to these diverse settings. While there are multiple T cell subsets that mediate resistance to distinct classes of pathogens, the effects of the AHR and HIF1α are perhaps best studied in the Th17 subset of $CD4^+$ T cells, which is associated with wound-healing, autoimmunity, and anti-fungal responses. Both transcription factors are highly expressed in Th17 cells and promote the production of IL-17 and IL-22 by these cells [8-11, 108]. HIF1α promotes the glycolytic pathways that contribute to Th17 development and transcription of RORγt [8], the canonical transcription factor associated with these cells [9]. In contrast, AHR activity does not increase RORγt expression [10, 109], but the AHR indirectly represses the expression of IL-2 [110], a cytokine that inhibits Th17 differentiation [111]. This transcription factor also induces expression of the microRNA-132/212 cluster, which is required for enhanced Th17 differentiation in response to AHR activation [112]. The significance of AHR and HIF1α mediated effects on Th17 cells has been studied most extensively in the context of autoimmunity. Thus, *Ahr*$^{-/-}$ mice or those with a T cell specific deletion of HIF1α are less susceptible to experimental autoimmune encephalomyelitis, which is associated with decreased Th17 activity [8-10].

The AHR and HIF1α also impact $FoxP3^+$ regulatory T cell responses, but this literature appears contradictory. AHR activation by dioxin or kynurenine promotes Treg development [108, 113], whereas different ligands, such as FICZ, induce Th17 cells [108]. However, others have reported that FICZ and dioxin enhance the development of both Th17 cells and Tregs [11]. Regardless of the varying effects of different AHR ligands, both the AHR and HIF1α can increase FoxP3 expression, the induction of Tregs, and their suppressive function [108, 114, 115]. However, other studies indicate that HIF1α can also inhibit Treg generation, possibly by physically interacting with FoxP3 and targeting it for degradation [8, 9]. These apparently contradictory reports likely indicate that the observed effects of the AHR and HIF1α are context-dependent. The AHR also affects the function of another subset of T cells involved in immunoregulation, termed type 1 regulatory T cells (Tr1), which develop in response to stimulation with TGF-β and IL-27. AHR activity in Tr1 cells promotes expression of the transcription factor c-Maf as well as IL-21 and IL-10 [116], highlighting a critical role for this transcription factor in inducing IL-10 production by multiple innate and adaptive cell types. These studies collectively indicate that the AHR and HIF1α can influence the differentiation of Th17, Treg, or Tr1 subsets, three processes in which TGF-β has a central role (Fig. **2**). Accordingly, TGF-β promotes the stabilization of HIF1α protein and affects AHR expression in a cell type-specific manner [117-119]. Additional studies are needed to understand how signals through the AHR and HIF1α are integrated with TGF-β-mediated pathways in T cells.

In the setting of infectious disease there are several studies that illustrate the impact of the AHR and HIF1α on other T cell subsets. For example, AHR activation with dioxin limits the inflammatory damage caused by ocular herpes simplex virus infection [120]. This protection is associated with decreased cellular infiltration into the cornea and an elevated ratio of Tregs to effector T cells due to the increased apoptosis of effector T cells [120], but it is unclear

whether this is caused by the direct effects of AHR signaling on T cells. In a model of cecal ligation and puncture, T cell specific deletion of HIF1α leads to increased production of IFN-γ by $CD8^+$ T cells, elevated expression of TNF-α and IL-6, decreased bacterial burdens, and improved survival [121, 122]. Similarly, during chronic infection with LMCV clone 13, a T cell specific VHL deletion leads to enhanced HIF activity and increased $CD8^+$ T cell induced immunopathology associated with higher levels of IFN-γ and TNF-α production by these cells [123]. In another model of chronic infection, *Ahr*$^{-/-}$ mice infected with *T. gondii* have decreased parasite burdens but succumb to this challenge, which is associated with increased levels of serum TNF-α [124]. Although the role of T cells in this phenotype is unclear, these effects are consistent with a role for the AHR in limiting T cell-mediated pathology.

The AHR and HIF1α also have effects on B cells, which express increased levels of the AHR following activation [125, 126]. Studies with chimeric mice have indicated that AHR deficiency in the hematopoietic and nonhematopoietic compartments affects B cell development [127]. Conversely, treatment with dioxin also alters B cell lymphopoiesis [127] and in mice infected with *Plasmodium yoelli,* dioxin directly suppresses antibody production, which is associated with increased parasitemia [128]. Similarly, following challenge with influenza, mice treated with dioxin express decreased levels of virus-specific IgG but elevated amounts of IgA [129]. There is evidence that some of these dioxin-mediated alterations in antibody production are due to effects on immunoglobulin gene transcription [130] and that AHR activation affects the expression of genes involved in B cell differentiation [131]. However, whether the generation of endogenous AHR ligands also impacts these processes is not clear. Evidence of a role for HIF1α in B cell development is provided by studies in which chimeric mice with a HIF1α deficient adaptive immune system display abnormalities in B cell populations and increased production of autoantibodies [132]. These observations raise the questions of whether HIF1α also affects B cell differentiation and antibody production and whether the AHR and HIF1α influence the development of plasma cells and memory B cells required for long-term protective immunity in response to infection or immunization.

ROLES FOR THE AHR AND HIF1α AT BARRIER SURFACES

The sections above highlight the influence of the AHR and HIF1α on cells of the innate and adaptive immune system and suggest that these transcription factors may be important at barrier surfaces, which are rich in immune cell populations as well as sources of AHR agonists. The observation that aged *Ahr*$^{-/-}$ mice develop colonic inflammation and rectal prolapses associated with *Helicobacter hepaticus* established a role for the AHR in intestinal immunity [28]. Subsequent work has shown that *Ahr*$^{-/-}$mice have reduced numbers of intestinal intraepithelial lymphocytes [133] and although *Ahr*$^{-/-}$ mice have normal populations of RORγt$^+$ innate lymphoid cells (ILCs) in the Peyer's patches, these cells are dramatically decreased in the lamina propria [134-136]. The RORγt$^+$ ILCs that remain in the absence of the AHR exhibit defects in the production of IL-22, a cytokine that elicits the production of antimicrobial peptides, and *Ahr*$^{-/-}$ mice have reduced expression of these peptides in the small intestine [136]. As a result of their defect in RORγt$^+$ ILCs and IL-22 production, *Ahr*$^{-/-}$ mice are highly susceptible to infection with *Citrobacter rodentium* [134-136]. The AHR also impacts the intestinal microbiome and *Ahr*$^{-/-}$ mice have elevated bacterial loads in the small intestine [133] although the relative composition of the microbiota in *Ahr*$^{-/-}$ mice is similar to wild type controls when evaluated at the phylum level [136]. *Ahr*$^{-/-}$ animals also have increased levels of Th17 promoting segmented filamentous bacteria in the intestine as a result of their defects in IL-22 expression [137]. This dysbiosis is associated with the increased susceptibility of *Ahr*$^{-/-}$mice to experimental colitis [133] and contributes to an increased frequency of cecal tumors in *Ahr*$^{-/-}$animals [138].

The studies described above highlight the complex interplay between the microbiota and the AHR, and raise the question of whether the altered commensal populations in *Ahr*$^{-/-}$ animals affect responses to intestinal infection. The composition of the intestinal microflora is also influenced by the diet [139] and mice fed a diet low in AHR agonists have reduced populations of intestinal intraepithelial lymphocytes and RORγt$^+$ ILCs, indicating that the steady state maintenance of these populations depends on dietary AHR agonists [133, 135]. Further studies are needed to assess the importance of dietary AHR ligands during infection, when compounds that activate this transcription factor may be produced as part of the host immune response or by pathogens. Interestingly, another compound obtained through the diet, the vitamin A metabolite retinoic acid, affects multiple aspects of immunity that are also influenced by the AHR, including Treg and Th17 differentiation and the size of the RORγt$^+$ ILC population in the gut [140, 141]. The finding that *Ahr*$^{-/-}$ mice and wild type animals treated with dioxin exhibit perturbations in vitamin A metabolism [142], suggests that AHR mediated effects on this pathway could also impact immune responses. Thus, altered vitamin A metabolism represents an underexplored pathway through which AHR signaling may influence immunity in the intestine.

Like the AHR, HIF1α has a number of effects on intestinal immunity. Consistent with its role in the generation of Th17 cells, mice with a T cell specific deletion of HIF1α have a reduced population of Th17 cells in the colonic lamina propria and an increased frequency of Tregs [8]. These mice develop more severe intestinal inflammation following treatment with dextran sodium sulfate [143]. However, in agreement with studies indicating that HIF1α promotes Treg suppressive function, this transcription factor is required for the ability of Tregs to provide protection in a transfer model of colitis [114]. In the intestinal epithelium, local neutrophil respiratory burst activity can generate hypoxic microenviroments, which in turn promote HIF1α activity that can protect against experimental colitis [144]. Signaling through HIF1α in intestinal epithelial cells promotes the expression of factors that enhance barrier function such as intestinal trefoil factor, ectonucleotidases, and mucin [145-147]. Thus, HIF1α deficiency in these cells is associated with impaired intestinal barrier function and increased susceptibility to chemically induced colitis, whereas the deletion of VHL in epithelial cells leads to

increased HIF activity and protects against colitis [62]. In contrast, studies using a different model of chemically induced colitis found that epithelial VHL deficiency in the intestine increases inflammation [148]. This apparent discrepancy is reminiscent of studies that showed that IL-17 can be protective or pathological in different models of colitis [149]. In the context of infection, stimulation with intestinal bacteria can also induce the expression of epithelial HIF1α [150-152], and HIF1α activity in the intestinal epithelium promotes resistance to oral challenge with *Yersinia enterocolitica* [152]. Following exposure to *Clostridium difficile* toxin, the absence of HIF1α in intestinal epithelial cells results in increased inflammation and tissue damage [153]. Conversely, treatment with a PHD inhibitor, which leads to increased HIF levels, protects against this challenge [153].

In addition to its role in intestinal barrier function, HIF1α also has effects in the skin. Thus, mice with a keratinocyte specific deletion of HIF1α challenged with Group A *Streptococcus* develop elevated bacterial burdens and more severe skin lesions, which are associated with decreased expression of the antimicrobial peptide cathelicidin by keratinocytes with a knockdown of HIF1α [154]. Complementary work has shown that treatment with a HIF1α agonist or a pharmacological compound that stabilizes HIF1α leads to increased resistance to skin infection with *S. aureus* [155, 156]. Although it remains unclear whether the AHR has a similar role during skin infection, the AHR is operational at this barrier site and *Ahr*$^{-/-}$mice have a reduced population of skin intraepithelial lymphocytes [133]. These mice also develop skin lesions as they age [28], and exhibit increased susceptibility to the psoriasiform disease model of imiquimod-induced skin inflammation, while the treatment of wild type mice with FICZ is protective during this challenge [157]. In a different model of AHR hyperactivation, mice that express a constitutively active form of the AHR in keratinocytes develop inflammatory skin lesions and express increased levels of antimicrobial peptides [158]. The clinical relevance of AHR activation in the skin is illustrated by reports that human exposure to dioxin is characterized by chloracne, a skin condition involving the development of pustules [159]. These studies highlight the impact of the AHR and HIF1α on multiple aspects of immunity in the intestines and the skin, which is consistent with the notion that these are relatively hypoxic tissues that are also major sites of exposure to AHR ligands.

EXPLOITATION OF THE AHR AND HIF1α BY PATHOGENS

Although the AHR and HIF1α enable the immune system to respond to environmental conditions, these pathways can also be targeted by pathogens to promote their survival and replication. This phenomenon is illustrated by the ability of *Chlamydia pneumonia* to actively degrade HIF1α during the later phases of infection, which is associated with the resistance of infected cells to apoptosis [160]. In contrast, other pathogens exploit the AHR and HIF1α. Treatment with AHR ligands promotes the reactivation of HIV-1 and other viruses in cell culture, suggesting that AHR activity can promote viral replication [161-164]. Similarly, HIF1α associates with the HIV-1 long terminal repeat and promotes viral gene transcription [165], and hypoxia enhances LCMV replication in a HIF1α dependent manner [166]. Macrophages infected with the parasite *Leishmania donovani* have increased HIF1α activity and HIF1α knockdown leads to decreased parasite growth [167]. Similarly, optimal replication of the intracellular parasite *T. gondii* is dependent on HIF1α [168] and this parasite stabilizes the expression of HIF1α by decreasing the abundance of PHD2 [169]. The effect of this transcription factor on *T. gondii* growth is less apparent at high oxygen concentrations, a finding that highlights the importance of considering oxygen concentration as an experimental variable when studying the effects of HIF1α. An additional role for HIF1α during infection is demonstrated by studies with *Bartonella henselae*, which activates this transcription factor in infected cells and thereby promotes the expression of infection-induced vascular endothelial growth factor (VEGF), which may contribute to the vasculoproliferative disorder elicited by this organism [170]. Similarly, cervical cancer cells transfected with oncoproteins from human papilloma virus type 16 (HPV-16), an etiologic agent of cervical neoplasia, exhibit increased levels of HIF1α, which promotes the expression of VEGF and *in vitro* capillary formation [171]. Furthermore, transgenic mice that express both HPV-16 oncogenes and a constitutively active form of HIF1α develop larger cervical cancers than mice expressing HPV-16 oncogenes alone [172]. This exploitation of the AHR and HIF1α by numerous pathogens may reflect a microbial strategy to manipulate the host cell metabolic state in order to facilitate pathogen growth. Alternatively, given the multiple immunological roles for the AHR and HIF1α, the ability to target these pathways may provide microorganisms with a means to alter the host immune response.

CONCLUSION/FUTURE PERSPECTIVES

Increasing attention is being paid to the widespread and context dependent effects of the AHR and HIF1α in multiple aspects of innate and adaptive immunity. The parallel roles of these transcription factors in antimicrobial effector mechanisms and the development of Th17 and Treg cells suggest that understanding the functions of one pathway should inform experiments to evaluate the contributions of the other. For example, the effects of AHR signaling on group 3 innate lymphoid cells and the composition of the intestinal microbiota raise the question of whether HIF1α might also influence these populations. Similarly, the observations that HIF1α has multiple effects in intestinal epithelial cells that promote barrier function suggest that the AHR may play a comparable role. Although many studies have investigated these pathways in isolation, work that examines the effects of the AHR and HIF1α in parallel could provide valuable insight into how these transcription factors coordinate resistance to infection. The striking parallels in the effects of the AHR and HIF1α on immune responses raise the possibility that low oxygen and the presence of AHR ligands are interpreted by the immune system as being indicators of similar challenges that warrant similar responses. What might account for these parallels? One possibility is that AHR and HIF1α signaling are especially

important in barrier surfaces such as the skin and intestines, which are major sites of exposure to AHR ligands and are considered to be relatively hypoxic. Indeed, the AHR and HIF1α promote responses such as the production of antimicrobial peptides and the generation of Th17 cells, which are critical at barrier surfaces.

The possible effects of other bHLH-PAS family members on immune responses are an important additional consideration. It is unclear whether ARNT contributes to all of the immunological effects of the AHR and HIF1α, and both transcription factors can also form heterodimers with ARNT2, a protein that is thought to be expressed primarily in neurons [19]. An additional potentially relevant family member is the AHR repressor (AHRR), an AHR target gene that can compete with the AHR for binding to ARNT and act as an inhibitor of AHR activity [24]. Additionally, BMAL1, a bHLH-PAS protein involved in circadian rhythm that pairs with CLOCK or NPAS2 to form a competent transcription factor, also impacts immune responses [19, 173]. Thus, in addition to the AHR and HIF1α, other members of the bHLH-PAS family have immunological effects and it is unclear how these pathways are integrated to shape the immune response.

One theme common to many of the previous sections is the question of what the relevant sources of AHR ligands are during homeostasis or inflammation. This consideration is important, as different AHR agonists have disparate immunological effects, raising the question of how various AHR agonists mediate distinct responses. The rate at which AHR ligands are metabolized could explain some of their unique effects; for example FICZ is metabolized rapidly but dioxin persists, which may contribute to its toxicity [174, 175]. Thus, certain AHR agonists likely promote transient AHR activation while others induce prolonged AHR activity, which may explain some of the differential effects of these compounds.

Finally, the recognition that HIF1α and the AHR have multiple effects on the immune system has led to interest in targeting this pathway therapeutically. Although transcription factors are generally regarded as poor drug targets, the ligand dependent nuclear hormone receptors, which include immunologically relevant proteins such as retinoic acid receptors and peroxisome proliferator-activated receptors, are considered "druggable" [176, 177]. The AHR and HIF1α are structurally distinct from nuclear hormone receptors, but signaling through the AHR is analogous to nuclear hormone receptor function in that ligand binding induces transcriptional activity. The availability of various compounds that modulate AHR and HIF1α activity suggests that it may be possible to manipulate these pathways for therapeutic gain [1, 178-180]. However, the development of therapies based on altering AHR and HIF1α signaling requires a more complete understanding of the context-dependent effects of these transcription factors.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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