The Aryl Hydrocarbon Receptor: Multitasking in the Immune System

Brigitta Stockinger, Paola Di Meglio,* Manolis Gialitakis,* and João H. Duarte*

Division of Molecular Immunology, MRC National Institute for Medical Research, Mill Hill, London NW7 1AA, United Kingdom; email: bstocki@nimr.mrc.ac.uk, pdimegl@nimr.mrc.ac.uk, egialit@nimr.mrc.ac.uk, jduarte@nimr.mrc.ac.uk

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*These authors contributed equally to this work.

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Abstract

The aryl hydrocarbon receptor (AhR), for many years almost exclusively studied by the pharmacology/toxicology field for its role in mediating the toxicity of xenobiotics such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), has more recently attracted the attention of immunologists. The evolutionary conservation of this transcription factor and its widespread expression in the immune system point to important physiological functions that are slowly being unraveled. In particular, the emphasis is now shifting from the role of AhR in the xenobiotic pathway toward its mode of action in response to physiological ligands. In this article, we review the current understanding of the molecular interactions and functions of AhR in the immune system in steady state and in the presence of infection and inflammation, with a focus on barrier organs such as the skin, the gut, and the lung.

INTRODUCTION

AhR: aryl hydrocarbon receptor

TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

bHLH: basic helix-loop-helix domain

PAS domain: PER (period circadian protein), ARNT (AhR nuclear translocator), SIM (single-minded protein) domain

The earliest studies focused on the aryl hydrocarbon receptor (AhR) were conducted to understand the mechanisms behind the toxicity mediated by its prototypic ligand 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (for reviews see 1, 2). Formed as a side product in industrial organic synthesis of herbicides, TCDD was found to be the chemical agent responsible for chloracne outbreaks in chemical workers following accidental exposure. In addition to this skin condition, characterized by the appearance of cysts, eruptions, pustules, and erythema, the clinical manifestations of TCDD exposure included life-threatening manifestations such as progressive liver failure, emphysema, renal failure, and myocardial degeneration, among other symptoms.

The medical description of symptoms after TCDD exposure and the studies in animal models that followed helped reveal the influence of this ligand-dependent transcription factor on the immune system. Studies in rodents described dose-dependent thymic involution, depletion of other lymphoid organs, and reduced circulating lymphocyte counts following exposure to TCDD, with a profound effect on the development of immune responses (3). Thus, many questions arose regarding the cellular and molecular mechanisms following AhR activation, but despite research over almost two decades, the molecular mechanisms through which AhR participates in immunological processes have remained largely unknown.

Interference with controlled AhR signaling may underlie many of the adverse effects of TCDD exposure on immune responses, but our knowledge of the mechanisms underlying most of the adverse effects caused by environmental pollutants is still limited. We require a thorough understanding of the basic physiological functions of AhR in the absence of xenobiotic interference before we can fully interpret the detrimental effects of xenobiotics on immune parameters. Thus, the focus of this review is on recent findings regarding the physiology of AhR signaling in the absence of xenobiotics.

THE AhR PATHWAY

AhR belongs to the family of bHLH PAS domain transcription factors, many of which are involved in sensing of environmental alterations such as circadian rhythm or oxygen gradients (4) (see **Figure 1**). It is widely expressed in the body (5) and evolutionarily conserved from invertebrates onwards (6), but its activity is tightly controlled. The first level of regulation occurs at the level of nucleocytoplasmic shuttling of the protein, during which AhR is retained in an inactive complex in the cytoplasm in the absence of a ligand (**Figure 2**).

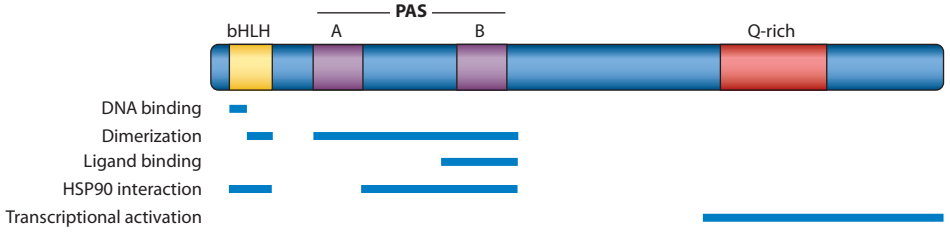

Figure 1

Functional domains of AhR. bHLH is the basic helix-loop-helix motif found in a family of transcription factors and is involved in DNA binding and protein-protein interactions. AhR contains two PAS domains (PER-ARNT-SIM), named after three proteins that contain it: period circadian protein, AhR nuclear translocator, and single-minded protein. PAS domains are required for protein-protein interactions and ligand binding. The proline-rich (Q-rich) domain is encompassed within the transcriptional activation domain.

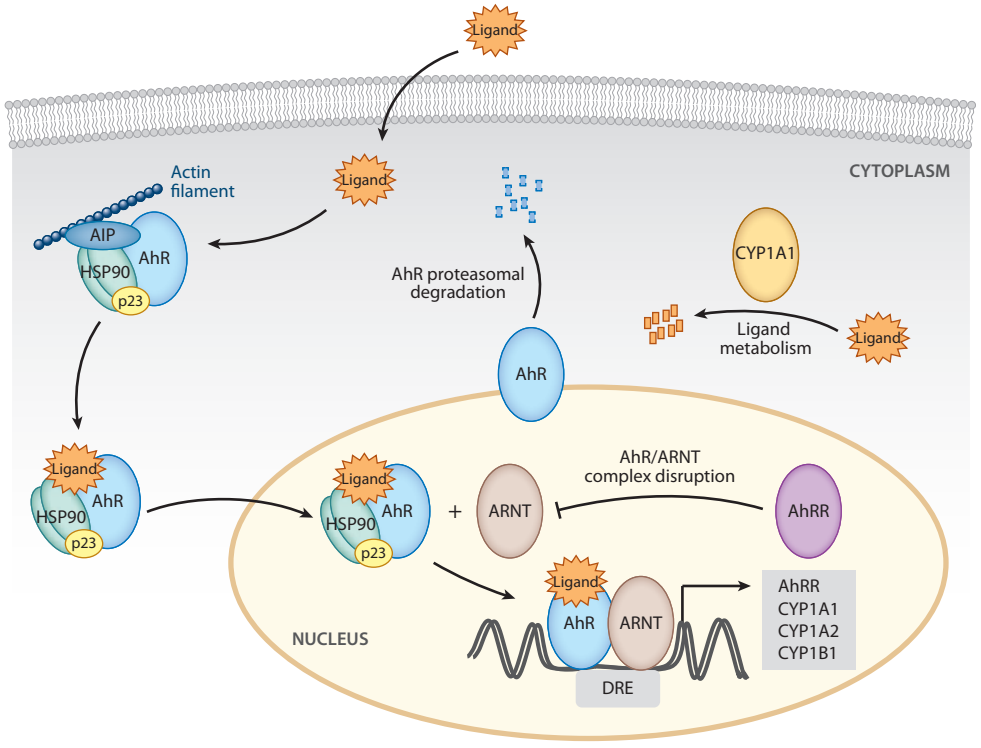

Figure 2

The canonical AhR pathway. In the absence of a ligand, AhR is present in the cytoplasm bound to actin filaments as an inactive complex with several chaperone proteins, including HSP90, AIP, and p23. Upon ligand binding, it translocates into the nucleus, where it is released from the complex, heterodimerizes with its protein partner ARNT, and finally binds genomic regions containing its binding motif [dioxin response element (DRE)], inducing transcription of target genes such as *CYP1A1*, *CYP1A2*, *CYP1B1*, and AhR repressor (*AhRR*). AhR signaling is regulated at three levels: proteasomal degradation of AhR, ligand metabolism by CYP1A1, and AhR/ARNT complex disruption by AhRR.

Several molecular chaperones are involved in the regulation of the AhR pathway. Association of heat shock protein 90 (HSP90) with AhR was documented simultaneously in two independent studies (7, 8), and the interaction was mapped to two different regions of AhR, the bHLH and the PAS domains, which are involved in DNA and ligand binding, respectively (9, 10). Three studies identified another member of the receptor complex, the AhR-interacting protein (AIP, XAP2, ARA9—they all refer to the same protein) (11, 12), which interacts with both the AhR (PAS domain) and HSP90 (13). More members of the HSP90 machinery were identified, such as the cochaperone p23, which interacts with both the HSP90 and AhR proteins (14, 15). The HSP90 machinery has various roles in AhR function that involve not only maintenance in an inactive form but also potentiation of ligand-induced activation. HSP90 is required to mask the constitutive DNA binding activity of AhR and to maintain the receptor in a conformation of high ligand-binding affinity (16). Ligand binding does not lead to HSP90 dissociation (17), but it may lead to a conformational change of the AhR that allows binding of its nuclear localization signal to importin β, thus controlling its nucleocytoplasmic shuttling.

Release of the chaperone complex from the AhR upon ligand binding requires ARNT (17). This is a constitutively nuclear protein and thus cannot disrupt the AhR-HSP90 complex interaction

DRE: dioxin response element

DC: dendritic cell

BMDC: bone marrow–derived dendritic cell

prior to ligand binding and nuclear translocation. Tight control of the cytoplasmic localization of AhR before ligand binding is ensured by the presence of p23 in the complex, which prevents translocation and nonspecific interaction with ARNT in the absence of a ligand (18, 19). Finally, association of AhR with the HSP90 chaperone complex seems to regulate the abundance of the receptor at the posttranslational level. The presence of AIP was required for the maintenance of high protein levels of AhR by inhibiting ubiquitination of AhR, possibly by the ubiquitin ligase carboxyl terminus of HSP70-interacting protein (20–22).

Numerous mechanisms potentially explain how AhR exerts transcriptional control of its target genes (**Figure 3**). The most studied role of AhR is in the direct regulation of its target genes, also termed the AhR gene battery. Upon activation, AhR functions as a bona fide transcription factor that binds genomic regions containing its binding motif [dioxin response element (DRE)] and regulates the expression of neighboring genes through its C-terminal region (23). This requires interaction with ARNT (**Figure 3*a***). It is not yet clear whether this heterodimerization is an absolute prerequisite for this function or whether AhR may interact with other transcription factors (**Figure 3*b***).

AhR directly controls transcriptional activity of its targets by interacting with subunits of the positive transcription elongation factor (P-TEFb complex) to regulate transcriptional elongation as well as subunits of the mediator complex (24–26). This interaction could be of particular importance for the communication of AhR-regulated transcriptional enhancers with their respective target promoters, as the mediator associates with cohesin complexes to regulate chromatin looping and cell type–specific gene expression patterns (27). Apart from direct interactions with the general transcription machinery, AhR can affect local chromatin architecture (28) by directly interacting with the Brahma/SWI2-related gene 1 (Brg1) subunit of the SWI/SNF chromatin-remodeling complex (29).

For remodeling, the respective chromatin sites need to be marked by the relevant histone posttranslational modifications. AhR can affect local histone hyperacetylation and methylation (30) either by directly interacting with coactivators such as the steroid receptor coactivator-1 (SRC-1) complex (31) or by displacing histone deacetylase (HDAC) complexes (30, 32). However, additional work on the genome-wide occupancy patterns of histone acetyltransferase (HAT) and HDAC enzymes in human T cells has revealed that these enzymes co-occupy active and poised genomic loci to maintain a certain abundance of histone acetylation, which prevents promiscuous transcription initiation or uncontrolled RNA polymerase II binding (33).

A recent high-throughput study of the occupancy of various transcription factors and their dynamics during the response to lipopolysaccharide (LPS) of in vitro differentiated bone marrow–derived dendritic cells (BMDCs) included the binding profile of AhR alongside many more transcription factors. A hierarchical transcription factor architecture was suggested in which AhR seems to be at the bottom, i.e., in the cluster of so-called dynamic transcription factors (34). These factors bind to fewer targets than pioneer or primer factors, and their recruitment correlates better with modulation of transcriptional activity of neighboring genes, i.e., having a direct role in transcriptional regulation (**Figure 3*c***). Thus, AhR seems to exploit a prespecified landscape of targets that is initially set by pioneer transcription factors and superimposed by an additional layer of primer factors. This is in line with the model of another nuclear receptor function, the glucocorticoid receptor (GR), which binds a predetermined set of targets marked by DNaseI hypersensitive chromatin (35). Specification of these sites for GR was carried out by activator protein 1 (AP-1), which in this case functioned as a pioneer factor (36). For AhR, PU.1 and Cebpb fulfill such roles during the response of BMDCs to LPS, although this may vary according to cell type and perhaps also the nature of the response that is elicited.

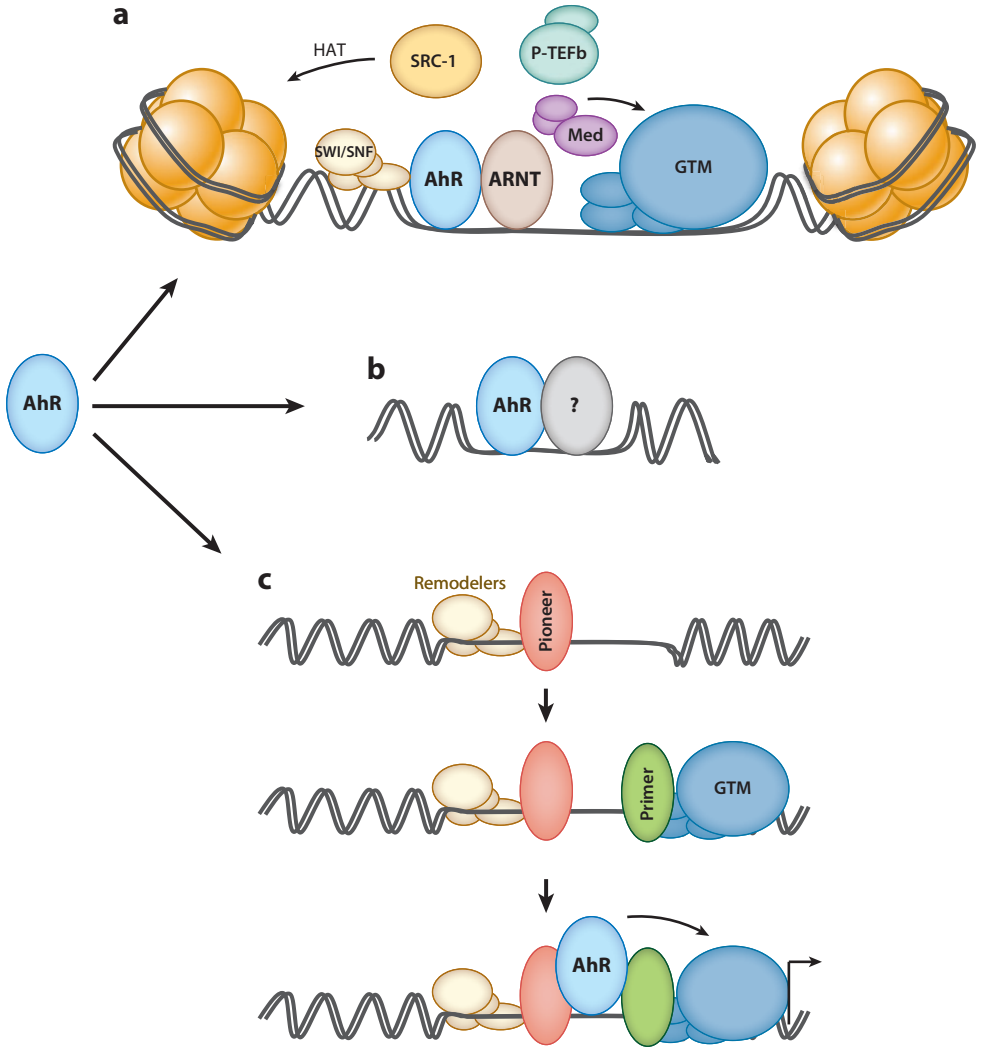

Figure 3

AhR interactions within the canonical pathway. (*a*) AhR/ARNT heterodimers recruit multiple protein partners to regulate transcriptional activation of their target genes. These include components of the SWI/SNF complex that remodel chromatin, coactivators such as the steroid receptor coactivator-1 (SRC-1) with histone acetyltransferase (HAT) activity, and components of the positive transcription elongation factor (P-TEFb) to control activity or the general transcription machinery (GTM). (*b*) AhR may heterodimerize with different protein partners to determine its set of target genes according to cell type and environment. (*c*) Another mechanism of target selection may involve the sequential recruitment of pioneer and primer transcription factors to poise specific loci for transcriptional activation. The activity of such loci may subsequently be controlled by AhR (dynamic factor) recruitment, possibly through interactions with the Mediator (Med) and P-TEFb complexes, as shown in (*a*).

IDO: indoleamine 2,3-dioxygenase

FICZ: 6-formylindolo[3,2-b]carbazole

Although the canonical pathway of AhR activation involving ligand binding and recruitment to DRE sites on chromatin has been studied extensively, reports suggest that some functions can be carried out independently of DNA binding. Investigation of AhR's role in cell cycle regulation has illuminated a DNA-independent mechanism of action. The cell cycle regulator $p27^{Kip1}$ may be directly regulated transcriptionally by TCDD-activated AhR to bring about cell cycle arrest (37). A study in human and mouse cancer cell lines showed that TCDD-mediated AhR activation led to its recruitment to the loci of E2F-regulated S phase–specific genes with subsequent repression through a mechanism implicating eviction of the HAT p300 from these loci (38). Another study in human breast cancer cells revealed that, in the absence of a ligand, AhR is part of a complex along with CDK4/CCND1 (cyclin D1) that regulates retinoblastoma protein phosphorylation. Upon activation with TCDD, AhR dissociates from this complex, allowing for reduced retinoblastoma protein phosphorylation and increased activity to bring about the G1/S arrest (39). However, whether AhR was directly involved in these events was not addressed, and these results were not confirmed in primary cells. AhR activation by means of TCDD as a ligand and the use of immortalized cell lines with a deregulated cell cycle contain hidden pitfalls and might not represent what happens in vivo.

Another function of AhR that diverges from the canonical pathway has been discovered through studies of its interactions with the estrogen receptor (ER). It had been shown previously that the two pathways of xenobiotic and estrogen response cross talk to yield estrogen-like action to AhR ligands in the absence of ER activation (40). Moreover, AhR can affect the estrogen response at the nongenomic level by regulating the ER protein levels via interaction with both the ER and the cullin 4B ubiquitin ligase complex (CUL4B). Therefore, investigators suggested that AhR acts as an E3-ubiquitin ligase, forming the $CUL4B^{AHR}$ complex and mediating the polyubiquitination of ER-α and subsequently its degradation, irrespective of the presence of ER ligand (41). Affinity purification of complexes associated with overexpressed AhR in HeLa cells allowed for detailed identification by mass spectrometry of the proteins participating in the complex. Separation of AhR-associated complexes on a glycerol density gradient yielded the ER-α in the same fraction as AhR, thus supporting that both nuclear receptors are part of the same complex with ubiquitinating activity. Nevertheless, further confirmation of the tripartite interaction would prove the E3 ubiquitin ligase activity of AhR beyond any doubt.

WHAT ARE THE ENDOGENOUS AhR LIGANDS?

Despite the predominant focus on AhR activation by xenobiotics over a period of more than 30 years, the driving force in the search for putative endogenous ligands was the developmental alterations observed in AhR-deficient mice, such as the consistent vascular defects resulting in patent ductus venosus (42). Two excellent comprehensive reviews have summarized the characteristics of a range of potential endogenous ligands (43, 44) and the caveats that apply, so we restrict discussion to those ligands shown to be physiologically relevant.

The most likely candidates are derived from metabolism of tryptophan (see **Figure 4**). Tryptophan is an essential amino acid and a precursor of many vital components in the body. Several degradation pathways generate metabolites with AhR-inducing activities. The major pathway of tryptophan metabolism in the body proceeds via the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), which generate the metabolite kynurenine. Investigators suggest that kynurenine is an AhR agonist, although the concentrations required [50 μM compared with 200 nM of the high-affinity ligand 6-formylindolo[3,2-b]carbazole (FICZ)] to elicit reporter activity in a hepatoma cell line (45) cast doubt on its relevance as an AhR activator under physiological conditions. However, a recent study indicated that kynurenine is generated in large

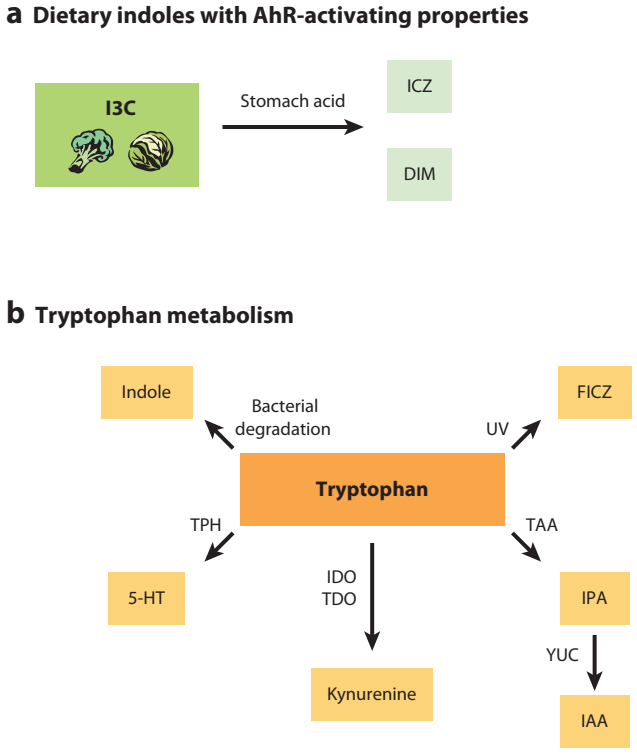

Figure 4

(*a*) I3C is produced from the breakdown of glucobrassicin in cruciferous vegetables such as broccoli and cabbage. The AhR ligands ICZ and DIM are generated under the influence of acidic pH in the stomach. (*b*) Several distinct pathways of tryptophan degradation result in distinct metabolites, some of which have strong AhR-activating properties (e.g., FICZ and IAA). (Abbreviations: 5-HT, 5-hydroxytryptamine; DIM, 3,3′-diindolylmethane; FICZ, 6-formylindolo[3,2-b]carbazole; I3C, indole-3-carbinol; IAA, indole-3-acetic acid; ICZ, indolo-[3,2-b]-carbazole; IDO, indoleamine 2,3-dioxygenase; IPA, indole-3-pyruvic acid; TAA, tryptophan aminotransferase of *Arabidopsis*; TDO; tryptophan 2,3-dioxygenase; TPH, tryptophan hydroxylase; UV, ultraviolet light; YUC, YUCCA.)

amounts by TDO in human brain tumor cells and is associated with AhR-mediated suppression of the antitumor response and malignant progression (46).

An important group of AhR ligands is indoles, which can be generated by bacterial metabolism of tryptophan and are also derived from metabolism of dietary intake. One of the dietary sources of AhR ligands are cruciferous vegetables, such as *Brassica*, which are rich in the glucosinolate glucobrassicin. This compound is enzymatically degraded to indole-3-carbinol (I3C), which is further converted to the high-affinity AhR ligands indolo-[3,2-b]-carbazole (ICZ) and 3,3′-diindolylmethane under acidic conditions in the presence of ascorbic acid in the stomach (47).

Another promising physiological ligand for AhR was discovered during exposure of L-tryptophan to UVB radiation, resulting in the formation of FICZ by photolysis, which can occur with both visible and UV light (48). FICZ can activate AhR at picomolar concentrations, has an affinity for AhR similar to that of TCDD, and is present in humans (49), particularly in the skin (50).

I3C: indole-3-carbinol

ICZ: indolo-[3,2-b]-carbazole

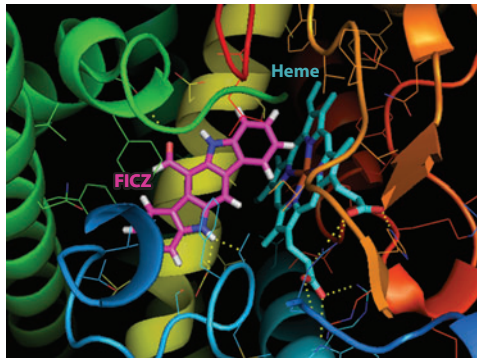

Figure 5

Model for binding of FICZ in CYP1A1. Colored ribbons represent the helical secondary structure of CYP1A1. Thin lines show side chains interacting with heme or FICZ (*pink*). Turquoise represents the heme prosthetic group with iron in a porphyrin ring (*red*). Yellow dots indicate hydrogen bonds. (FICZ was modeled into murine CYP1A1 by José Saldanha of the National Institute for Medical Research.)

REGULATION OF AhR SIGNALING

Physiological functions of AhR may require tightly controlled and transient signaling, and sustained AhR signaling may underlie pathological responses (51, 52). Central to the regulation of AhR signaling is autoregulatory feedback by the drug-metabolizing CYP enzymes. In contrast to TCDD, endogenous ligands such as FICZ or dietary phytochemicals are excellent substrates for the cytochrome P450 enzymes downstream of AhR, particularly CYP1A1, and are efficiently metabolized (49, 53, 54) (see also the model for FICZ in CYP1A1 in **Figure 5**). TCDD, in contrast, is resistant to such degradation and has an extended half-life (55). This likely causes prolonged AhR activation, which presumably can be counterbalanced only by additional control mechanisms such as the induction of the AhR repressor (AhRR) or proteasomal AhR protein degradation. The consequences of CYP enzyme–mediated degradation of AhR agonists are complex and may generate harmful end products, such as the prototypic example of the agonist benzo[*a*]pyrene, which is metabolized into a highly DNA-reactive procarcinogenic substance (56). Polymorphisms in AhR as well as the CYP enzymes that may affect activity likely shape biological processes and drug interactions, with complicated outcomes that are as yet difficult to integrate into effects on the immune system.

An interesting recent study suggests that a wide range of chemical compounds can inhibit the metabolism of FICZ by CYP1A1 and thereby indirectly cause AhR activation owing to elevated levels of FICZ as a consequence of impaired clearance (57). The assumption in the field is that AhR ligand recognition is highly promiscuous, inducing a response to a wide range of agonists. However, an alternative explanation is that most of the putative agonists are in fact inhibitors of CYP enzymes, thereby causing AhR activation indirectly via inhibition of metabolic degradation of endogenous agonists such as FICZ. Although this study was conducted largely in cell lines in vitro, it offers intriguing possibilities for how AhR signaling might be affected by environmental substances that are not themselves AhR agonists but rather cause alterations in AhR signaling via their effects on the AhR-dependent drug metabolizing enzymes.

AhRR: aryl hydrocarbon receptor repressor

AhR polymorphisms in different mouse strains result in distinct sensitivity to TCDD: (*a*) The low-responder allele d of DBA/2 and 129 is linked to a single amino acid change in alanine 375 to valine, (*b*) the C57Bl/6 strain carries the high-responder b1 allele, and (*c*) other strains such as BALB/c express AhR of intermediate affinity for TCDD (58). A mouse model expressing the

human AhR indicated that CYP1A1 induction by TCDD was reduced, suggesting that human AhR is of lower affinity at least in response to TCDD (59). Whether AhR affinity affects the physiological response to endogenous ligands other than CYP induction is currently unclear, but the effect of AhR ligands on Th17 induction does not differ substantially between mouse strains carrying high- versus low-affinity AhR (60).

Mutations in CYP1A1 have been described and studied in particular in relation to their association with cancer, although statistically verified results are lacking (61). No studies on the effects of CYP1A1 polymorphisms in the immune system exist yet. CYP1B1, the other enzyme induced in immune cell types, is not strictly dependent on AhR activation. Its high expression in tumor cells and its role in the metabolism of estradiol have been studied extensively in the context of carcinogenesis. This could also be relevant in immune reactions that are influenced by estrogen signaling (62), but no defined studies have been conducted to investigate particular roles of CYP1B1 metabolism in immune cells.

AhR activation is further regulated by activation of AhRR, which has a higher binding affinity for ARNT than does AhR and so can displace AhR from the interaction (63). Finally, it is thought that AhR is subject to proteosomal degradation following activation (64).

MOLECULAR INTERACTIONS OF AhR

Several genome-wide studies have addressed the question of the target specificity of activated AhR. Most were carried out on hepatocyte or breast cancer cell lines addressing programs elicited by different ligands using expression profiling or chromatin immunoprecipitation (ChIP)-chip approaches (65–68). A study more relevant to the immune system used a B cell line to study the role of AhR in LPS-induced B cell differentiation in the context of TCDD (69). This study identified several AhR targets that are also targets of key transcription factors involved in B cell maturation such as PAX5, BCL6, and PRDM1. AhR activation correlated with impairment in B cell maturation as implied by the expression profile. However, no functional assays were carried out in primary B cells to validate these findings on a physiological level.

Bioinformatic analysis of the identified AhR-binding sites from the aforementioned ChIP-chip data yielded a number of transcription factor binding motifs with enriched representation. It would be useful, though, to address whether the factors that bind to them are actually expressed in these cells and which of them bind simultaneously with (or prior to) AhR, or how the absence or presence of any of them would affect AhR binding. Moreover, inherent limitations of the in vitro system using a cell line preclude the study of various aspects of B cell biology such as the cell cycle and cell-cell interactions.

Many of the effects of AhR occur through cross talk with other cell signaling pathways. Interactions with inflammatory responses, cell cycle control, and hormone signaling have been documented and reviewed in detail (70). Here we refer selectively to a few examples of how AhR can affect immune responses.

NF-κB and STAT1 Pathways

A link between the NF-κB and AhR pathways was established quite early when the effects of IL-1β and TNF-α on TCDD signaling were studied in primary hepatocytes (71). It was found then that signaling through these cytokines suppressed the TCDD-mediated induction of the AhR target genes *Cyp1a1* and *Cyp1a2*. Subsequently, a direct interaction between AhR and the RelA subunit of NF-κB was shown to result in mutual suppression of transcriptional potential of both, as revealed by reporter assays (72). However, further characterization of the molecular mechanism

LXR: liver X receptor

of suppression of TCDD-elicited responses by NF-κB activation suggested that inhibition on the *Cyp1a1* promoter was probably indirect, given that AhR binding to the *Cyp1a1* enhancer was not affected (19). A possible mechanism of suppression is suggested by the fact that NF-κB has the potential in vitro to bind the κB sites upstream of the *Ahrr* gene and regulate its expression, as implied by EMSA (electrophoretic mobility shift assay) and reporter assays (73).

Further studies using peritoneal macrophages have revealed an interesting aspect of AhR and NF-κB pathway interaction (74). The inflammatory response of these cells to LPS was significantly augmented on an $Ahr^{-/-}$ background. Similarly, $Stat1^{-/-}$ macrophages also exhibited increased IL-6 production upon LPS stimulation, and a physical association between AhR and STAT1 proteins was confirmed. Both of these proteins interacted with the p50 subunit of NF-κB, thus implying a tripartite complex but not excluding the possibility of two separate complexes. Nevertheless, association of all three proteins with the *Il-6* promoter upon gene activation was confirmed by ChIP. While STAT1 recruitment depended on the presence of AhR, that of NF-κB did not, as suggested by analysis of $Ahr^{-/-}$ cells. It is therefore possible that activation of AhR and STAT1 in this system provides a block to the inflammatory response program initiated by NF-κB. However, this interaction did not occur in response to another TLR ligand, CpG-ODN for TLR9, although STAT1 was phosphorylated to similar levels. In neither case was the subcellular localization of AhR assessed during the LPS or CpG responses to see whether differences in AhR activation could explain this discrepancy. It seems likely that the mechanism suggested here is oversimplified and possibly involves more proteins or pathways that differ in the two responses.

Furthermore, AhR seems to have a different effect on STAT1 activation in various cell types: Induction of AhR in T cells under Th17-polarizing conditions inhibits STAT1 phosphorylation, thus reinforcing the Th17 transcriptional program by blocking the alternative pathway that leads toward Th1 effector differentiation (75). Consequently, it appears that AhR can acquire different functions according to the cellular context and nature of the stimuli, yielding divergent outcomes on the same targets.

Apart from the canonical NF-κB pathway, AhR can physically interact with RelB, a component of the alternative pathway, resulting in cooperative activation of human *IL8* gene transcription (76). However, results from $Ahr^{-/-}$ mice have shown that AhR limits inflammation, possibly by stabilizing the RelB protein (77, 78). The molecular details that determine which targets are affected in different cell types and how this is achieved still remain elusive and require further study.

Liver X Receptor Interactions

As with the ER, the liver X receptor (LXR) pathway also reportedly cross talks with the AhR. LXR regulates mainly cholesterol and fatty acid metabolism, but its expression in T cells motivated an investigation of its role in effector T cell differentiation. Activation of LXR by a synthetic agonist ameliorated the severity of experimental autoimmune encephalomyelitis (EAE), guiding subsequent research toward the development of the Th17 effector lineage (79). LXR agonists were found to inhibit production of IL-17 in vivo as well as in vitro under Th17 polarization conditions (80). The cross talk of the LXR with the AhR pathway is indirect and involves an LXR-induced gene, *Srebp-1*. SREBP-1 interacts directly with AhR, and it was suggested that the two proteins compete for an overlapping binding site. Hence, LXR signaling by means of SREBP-1 could displace AhR from a positive regulatory element and modulate IL-17 expression.

Despite the fact that AhR binding to the *Il-17* gene and its displacement by treatment with LXR agonists were shown by ChIP, investigators have not addressed whether this is a direct effect of SREBP-1 binding. In the same study (80), many genes involved in Th17 differentiation, such as *Rorc*

and *Ahr* itself, were shown to be downregulated by the action of LXR agonists, raising questions as to whether the results observed on *Il-17* transcription were due to competition, as suggested, or to diminished protein abundance of AhR or other proteins such as RORγt. Therefore, however tempting it is to speculate that direct competition for binding to particular chromatin locations could affect AhR activity on a subset of its targets, leaving the rest unaffected, the evidence to support such a notion is still incomplete.

NRF2: nuclear factor erythroid 2–related factor 2

Nqo1: NAD(P)H quinone oxidoreductase

AhR and RORγt Synergy

In addition to the above-mentioned role of AhR in promoting Th17 cell differentiation by inhibiting the IFN-γ pathway (75), AhR affects Th17 cell differentiation by enhancing production of IL-17 and enabling the cells to produce IL-22 (81). The precise molecular mechanism behind this phenotype remains elusive, but subsequent work revealed that RORγt facilitates recruitment of the AhR to the *IL-22* promoter in EL-4 thymoma cells infected with retroviruses expressing RORγt and AhR (82). Additionally, overexpression of both proteins in HEK293T cells revealed the potential of the two to interact physically, but the relevance of this interaction for the induction of IL-22 has not been shown. Although it is tempting to speculate that RORγt functions as the pioneer or primer factor to define AhR binding on the *IL-22* promoter, it is not yet clear whether it is the interaction of the two proteins or chromatin remodeling of the locus by RORγt that actually leads to the facilitated binding of AhR.

NRF2

The cross talk between the antioxidant response pathway controlled by nuclear factor erythroid 2–related factor 2 (NRF2) and the xenobiotic response pathway controlled by AhR has been studied extensively. Intraperitoneal administration of TCDD can induce liver expression of the known xenobiotic response genes as well as *Nqo1*, which is a component of the antioxidant response. In contrast, TCDD does not have a similar effect in an NRF2-deficient background (83)—antioxidant response genes are not upregulated, whereas the xenobiotic response gene *Cyp1a1* is induced to similar levels as in wild-type mice. However, in mouse embryonic fibroblasts, NRF2 deficiency partially inhibits the induction of *Cyp1a1* and *Cyp1b1* genes. AhR and NRF2 can regulate gene expression of each other at the transcriptional level, thus creating a link between the activities of the two pathways (84, 85). These pathways also converge at the protein level, as the two proteins also interact at the chromatin level (86). Antioxidant response elements (ARE) and DRE in the promoter region of *Nqo1* recruit the NRF2 and AhR proteins, respectively, with similar kinetics to regulate their activity.

A further study of cross talk between the two pathways in keratinocytes (KCs) revealed another interesting aspect of the functional synergy between AhR and NRF2. Using ketoconazole, an antifungal agent that can activate AhR, the authors observed nuclear translocation of NRF2 in the absence of any direct activation signal. This activation was AhR-dependent, as shown by siRNA-mediated knockdown. However, the authors did not assess whether this was a direct effect of the interaction of the two or whether NRF2 activation occurred indirectly, e.g., through the induction of some AhR target gene or through the metabolic activity of the CYP enzymes that could perhaps produce some NRF2 stimulus. Use of the DNA-binding mutants of AhR (87) could provide further insight into this mechanism.

Altogether, a picture emerges that suggests substantial multitasking of AhR in the immune system that is brought about by the various interaction partners and cross talk with other pathways (**Figure 6**).

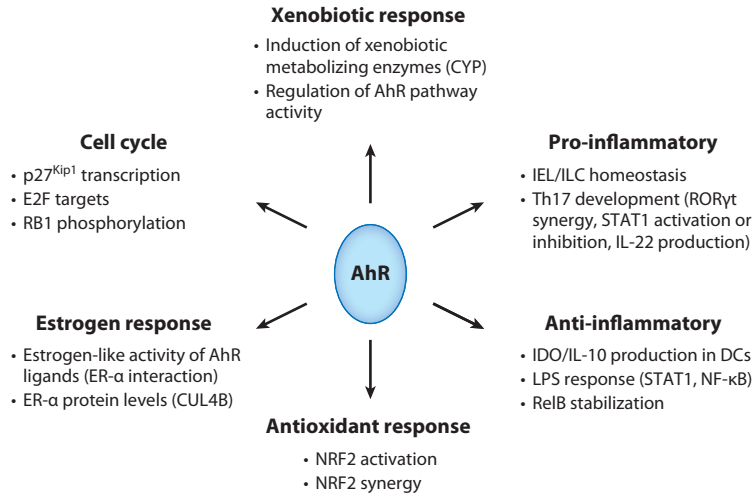

Figure 6

Multiple putative AhR functions in the immune system. AhR ligands affect several pathways and responses according to the cellular context. The exact molecular mechanisms through which many of these functions are achieved remain elusive, but several components have been described, pointing to synergy or antagonism at the protein-protein interaction or the chromatin level. (Abbreviations: DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; IEL, intraepithelial lymphocyte; ILC, innate lymphoid cell; LPS, lipopolysaccharide; NRF2, nuclear factor erythroid 2–related factor 2.)

WHERE IS AhR EXPRESSED?

AhR is widely expressed in the body and in particular in the immune system. The primary function of the immune system is to provide protection from pathogens. Apart from the peripheral immune organs such as spleen and lymph nodes, mature immune cells are located at the entry barriers of the skin, the lung, and the gut to confront pathogens at the these sites. AhR is highly represented in cell types at these barrier sites, in keeping with its primary function as an environmental sensor. Unfortunately, its expression has so far not been measured at the single-cell level owing to lack of suitable reagents. Thus, AhR expression has only been determined at the population level by methods such as microarray analysis, qPCR, or Western blotting. While this may be sufficient for cell types with consistent AhR expression such as myeloid cells or B cells, the substantial heterogeneity of T cells would make an assessment on the level of all T cells unreliable. Indeed, when T cells were purified on the basis of subset markers following in vitro differentiation or purified ex vivo, it became clear that AhR expression was restricted to a few subsets.

AhR is highly expressed in Th17 cells, not detectable in Th1 and Th2 cells, and marginally expressed in regulatory T cells (Tregs) (81). AhR is not expressed on naive T cells, and their activation per se does not induce AhR expression. It is important to note, however, that the amounts of tryptophan present in a culture medium can be converted to the endogenous high-affinity ligand FICZ and can increase the activity of cells cultured under Th17 conditions (88). In contrast, culture of T cells under conditions that induce Tregs does not lead to AhR activation either under baseline conditions (culture medium containing natural levels of tryptophan) or in the presence of AhR agonists such as TCDD or FICZ (60, 89). Furthermore, mice with a constitutively active AhR do not show any evidence of increased Treg differentiation or function (90). However, it remains to be tested whether Tregs present at sites of inflammation or in adipose tissue show higher levels of AhR expression than those found in lymphoid organs.

Table 1 The Garman and Tonegawa nomenclature for TCRγδ T cells

Garman (Reference 95)	Tonegawa (Reference 94)	Anatomical location	AhR	IL-17	IL-22
TCRVγ1.1	TCRVγ1	Systemic	+	–	–
TCRVγ2	TCRVγ4	Systemic	+	++	++ (induced)
TCRVγ3	TCRVγ5	Epidermis	+++	–	–
TCRVγ5	TCRVγ7	Intestine	+++	–	–
TCRVγ4	TCRVγ6	Reproductive tract, lung, oral mucosa	+++	++	++

The subset of type 1 regulatory T cells (Tr1) cells producing IL-10 that appears prominent in chronic infections and other particular manipulations [i.e., peptide immunization or activation via anti-CD3 (91)] was also reported to express AhR, which controls production of IL-10 and IL-21 via interaction with the transcription factor c-Maf (89, 92). It remains to be clarified if Tr1 cells really represent a subset or if they might be a reflection of the extensive plasticity T cells show under inflammatory conditions. IL-10 production is a feature of all T cell subsets, and it is conceivable that the IL-10-producing state is a late adaptation to chronic inflammatory conditions of an AhR-expressing T cell subset such as Th17 cells (93).

AhR is also important for innate TCRγδ T cells [**Table 1**, listed with reference to the two commonly used nomenclature systems (94, 95)]. A proportion of systemic Vγ2-expressing γδ T cells produces IL-22 in response to AhR ligation (96), whereas epidermal Vγ3 and intestinal Vγ5 γδ T cells appear to require AhR for survival, as AhR-deficient mice are profoundly lacking in these subsets (97). Interestingly, however, Vγ4-expressing γδ T cells, which are prominent in the lung, reproductive tract, and oral mucosa and have very high expression of AhR, are not diminished in AhR-deficient mice (B. Stockinger & M. Veldhoen, unpublished observations), suggesting different roles for AhR in distinct subsets. Furthermore, AhR expression is pronounced in intraepithelial CD8αα-expressing lymphocytes (97) and subsets of innate lymphoid cells (ILCs), notably those that are the main producers of intestinal IL-22 (82, 98, 99).

B cells isolated ex vivo all seem to express AhR, but again particular subsets, notably marginal zone B cells and the B1 B cell subset, have higher levels than the rest (B. Stockinger & M. Villa, unpublished data). Although B cells are targets for TCDD (100), our understanding of the physiological effects of AhR on regulation of B cell development and function is rudimentary at present. Microarray analysis of myeloid cells such as macrophages and DCs confirmed their expression of AhR (5), but we do not yet know whether specialized subsets in different parts of the body have differential expression of AhR.

Furthermore, AhR expression and functional responses to endogenous AhR ligands were shown in bone marrow–derived mast cells as well as in human mast cell lines and infiltrating mast cells of lung specimens from chronic obstructive pulmonary disease (COPD) patients (101). AhR expression on mast cells seems to be important for their growth and differentiation, as there were severe defects in the generation of bone marrow–derived mast cells from AhR-deficient mice associated with a lack of c-kit induction. Furthermore, tissue mast cells in AhR-deficient mice were substantially reduced and functionally deficient, suggesting an important role for AhR in this cell type (102).

COPD: chronic obstructive pulmonary disease

The widespread expression of AhR on many hematopoietic cell types, together with the occurrence of DREs in the promoters of a wide variety of genes (103), highlights the potential of AhR-mediated effects in the immune system. It should not be forgotten, however, that

nonhematopoietic cell types such as epithelial, endothelial, and stromal cells express AhR, as these are affected by immune stimulation and themselves influence inflammatory responses. Studies of the AhR pathway have mostly been conducted with liver, lung, and skin cell lines, but we lack a systematic assessment of AhR expression in primary nonhematopoietic cell types in different organs.

AhR is expressed in embryonic stem cells, and culture of such cells in the presence of AhR ligand FICZ induces AhR target genes such as *CYP1A1* (104). In hematopoietic stem cells, AhR is of functional importance, given that blockade of AhR signaling via an antagonist promotes the expansion of $CD34^+$ cells and prolongs their undifferentiated state (105). Still unknown are the outcomes of AhR signaling under physiological conditions and, in particular, the consequences of its disruption. Given that the AhR-deficient mouse strain has a broadly functioning immune system despite alterations and dysfunction in certain cell types, it appears unlikely that AhR signaling has a life-dependent impact on the function of stem cells under physiological conditions in the absence of xenobiotic perturbations.

CONSEQUENCES OF DYSREGULATED AhR SIGNALING IN THE IMMUNE SYSTEM

Investigations of the role of AhR in the immune system initially focused on analysis of the deleterious effects of TCDD. This is summarized in a recent review, which lists additional references (106), but is not further outlined here, as this review focuses on the physiological role of AhR.

The most obvious starting point for this is the analysis of AhR knockout mice, but surprisingly, until quite recently, few immunological phenotypes were identified in such mice. Three independent AhR-deficient strains were generated almost simultaneously (107–109), but only one appeared to have an obvious immune phenotype, such as reduced T and B cell numbers in the spleen or skin inflammation (110). Such defects were not detected in the two other strains, and given the substantial impact of the gut microflora on systemic immunity, it is conceivable that the observed differences may have been due to different microbial statuses in the animal facilities. The most widely used knockout strain to date is the one generated by Schmidt et al. (108), which is deposited at the Jackson labs (B6.129-AhR^{tm1Bra}/J Stock 002831). AhR-deficient mice of all three strains display vascular abnormalities such as patent ductus venosus and consequential liver phenotypes with reduced size, portal fibrosis, and steatosis and defects in reproduction (reviewed in 111). In a clean environment under strict specific pathogen–free conditions, AhR-deficient mice do not exhibit an overt immunological phenotype. However, it became clear in recent years that exposure to inflammatory stimuli reveals substantial defects at several sites of the body. We discuss these phenotypes in reference to the main barrier organs—the skin, the lung, and the gastrointestinal tract—in the following section. The mucosal surfaces of the mammalian intestine, skin, and airways are in direct contact with the external environment and thus exposed to physical or chemical damage as well as colonization and invasion by commensal and pathogenic microorganisms. Accumulating evidence points to a role for the AhR as keeper of the physical and immunological barriers present at these sites.

Furthermore, AhR may play a role in autoimmunity, and the high expression of AhR on Th17 cells—which are pathogenic drivers in a range of autoimmune conditions—may underlie the long-observed influence of environmental factors on susceptibility to infection and on development of autoimmune diseases.

Finally, AhR-expressing innate and adaptive T cells that produce IL-17 respond to AhR signals with production of IL-22 (81, 96), and a T cell subset depending on AhR and RORγt that produces IL-22, but not IL-17 or IFN-γ, has been identified in humans (112). The extent to which AhR controls IL-22 requires further investigation, and some of these issues are reviewed in Reference 113.

A current controversy in the field is the apparent ligand-specific influence on the outcome of experimental models of autoimmunity such as EAE. The current paradigm is that TCDD promotes immune suppression, whereas endogenous ligands such as FICZ promote Th17 cell responses and thereby pathology (114). However, in our view it seems more likely that the mode of application of a ligand rather than its nature defines the outcome. Thus, systemic administration of AhR ligands affects a multitude of tissues and cells types and appears to cause strong reduction of the concurrently induced immune response—even in the case of FICZ—without the involvement of numerical changes or induction of Tregs (60). In contrast, local injection of FICZ, which was incorporated into the antigen emulsion for induction of EAE, seemed to target and promote developing Th17 cells more directly, thereby exacerbating pathology in EAE (81).

AhR INFLUENCES ON IMMUNITY AT BARRIER SITES

Skin

The skin is one of the body's primary defense organs (**Figure 7**), able to confer protection against harmful agents, such as toxins and infection, while maintaining tolerance to commensal and self-antigens. To fulfill these tasks, the skin relies on a well-coordinated cellular network of epithelial, stromal, and immune cells, cooperatively ensuring immunosurveillance (115). Changes in both the

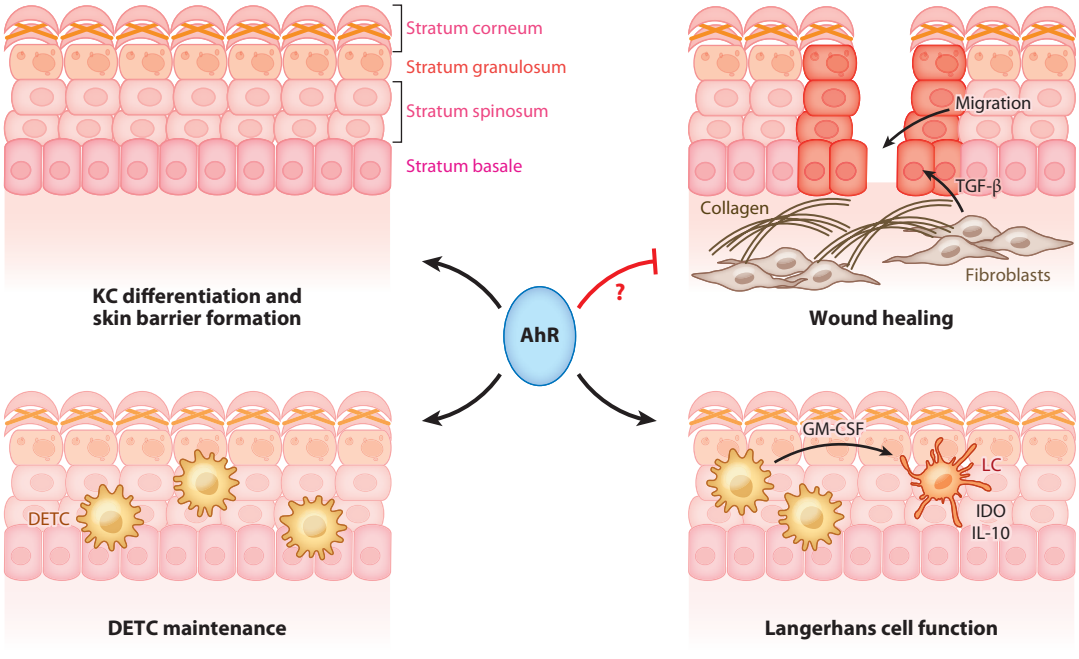

Figure 7

The role of AhR in the skin. AhR plays a critical role in skin homeostasis and barrier function by promoting keratinocyte (KC) differentiation, which gives rise to the multiple epidermal strata seen in the skin. Moreover, it contributes to skin immunosurveillance by maintaining the dendritic epidermal T cell subset in murine skin and tolerogenic functions of Langerhans cells, e.g., IDO and IL-10 production. AhR may also promote wound healing by favoring TGF-β production by fibroblasts, which in turn allows KC migration and accelerated healing. (Abbreviations: DETC, dendritic epidermal T cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; TGF-β, transforming growth factor β.)

physical structure and metabolic capacity of the differentiated layer of skin are largely responsible for its protective properties. During terminal differentiation, proliferating KCs are converted to squames that protect the underlying tissue from moisture loss and physical damage to prevent the invasion of pathogens. Given the constant exposure to the environment, it is not surprising that virtually all cell types present in the skin express the environmental sensor AhR. In the outermost skin layer, KCs as well as melanocytes, Langerhans cells (LCs) (116, 117), and murine DETCs (Vγ5 γδ T cells) (97, 118) express functional AhR. In the underlying dermis, fibroblasts and resident immune cells such as DCs, Th17 cells, and γδ T cells of the IL-17-producing subset Vγ2 express AhR.

One of the most prominent effects of systemic exposure to xenobiotics in humans is the development of chloracne, a noninflammatory alteration of keratinization of the polysebaceous unit, resulting in cysts, comedones, and noninfectious abscesses that may scar and take 2–3 years to resolve (119). Thus, early studies conducted in vitro in either primary or immortalized human KC cell lines used xenobiotics such as TCDD to activate the AhR pathway. Despite the caveat that exposure to TCDD represents an extreme AhR stimulus that does not resemble physiological exposure, some of the insights shown in these studies are nevertheless important to consider and collectively suggest a role for AhR in promoting skin barrier formation via enhanced KC terminal differentiation. AhR mRNA expression depends on the stage of KC differentiation, with increased expression in cells of the stratum spinosum that have withdrawn from the cell cycle and have entered their terminal differentiation pathway (120). In keeping with this expression pattern, CYP1A1 mRNA expression and activity is increased in primary KCs under differentiation-promoting culture conditions (50), and AhR mRNA is decreased in differentiation-deficient hyperproliferative psoriatic skin (120). AhR activation enhances terminal differentiation in human KCs cultured in monolayer (121, 122) and in three-dimensional epithelial organotypic culture systems (123), possibly antagonizing epidermal growth factor receptor signaling (122). TCDD-treated cells assume a typical flattened morphology and have earlier onset or altered expression patterns of differentiation genes such as those encoding filaggrin and involucrin (123). AhR activation also induces the expression of genes involved in cornified envelope and lipid matrix biosynthesis (122, 124), and this is thought to happen through an increase in cellular reactive oxygen species (ROS) formation (125). In utero exposure to TCDD accelerated the formation of the fetal epidermal barrier by one day (124). Finally, a recent study (126) showed that AhR activation underlies the beneficial therapeutic effects of coal tar in the treatment of atopic dermatitis, an inflammatory skin disease characterized by low levels of terminal differentiation proteins and poor barrier function. By using an organotypic culture system, the researchers found that coal tar, which contains a wide range of polycyclic aromatic hydrocarbons, activates AhR, thus promoting the induction of epidermal differentiation. *AHR* knockdown by siRNA completely abrogated this effect. Moreover, coal tar ameliorated several hallmarks of atopic dermatitis, including spongiosis and expression of proinflammatory chemokines, possibly via the activation of the antioxidative NRF2 pathway that has been linked to AhR (127). Thus, it is conceivable that AhR activation by endogenous ligands may support skin barrier formation, while constitutive, aberrant expression of AhR causes inflammatory skin lesions (128).

Several publications report a role for AhR in the regulation of the cell cycle (reviewed in 129), an issue that is still incompletely understood, given that sustained AhR activation via TCDD and lack of AhR activity in cells from AhR knockout mice have a similar outcome, resulting in inhibition of G1 cell cycle progression. Both growth-inhibitory and growth-promoting functions have been shown for AhR in various cell lines in the absence of exogenous activation (39, 130, 131). This has been ascribed to the different species and cell types analyzed, but technical and methodological issues are also likely to play a role in the discrepancies reported. For instance, the presence of different concentrations of tryptophan in various cell culture media can have a profound effect on the status of AhR activation due to the generation of FICZ (88, 132).

Nevertheless, a number of in vitro studies have shown that AhR-deficient cells proliferate significantly more slowly than do wild-type cells (39, 131, 133–135), whereas cells overexpressing AhR grow more quickly than their wild-type counterparts do (136). AhR knockdown in the immortalized human KC cell line HaCaT causes decreased proliferation compared to wild-type cells due to an accumulation of cells in the G0/G1 phase (131, 137). Knockdown of CYP1A1 had the same effect (131), suggesting that its enzymatic activity is involved in the regulation of the normal cell cycle, possibly by limiting AhR activation by degrading the endogenous ligands. However, treatment with TCDD induces inhibition of DNA synthesis through G1 cell cycle arrest (138).

Another scenario envisions that endogenous ligands may bind to AhR in the G1 phase of the cell cycle, transiently activating the receptor and inducing expression of target genes for whose promoter AhR has the highest affinity, such as *CYP1A1*. CYP1A1 would then metabolize ubiquitous endogenous agonists to minimize prolonged AhR activity. Thus, such transient activation would promote cell cycle progression, whereas sustained activation by dioxin or AhR absence would lead to growth arrest (131).

In a constantly renewing and self-regenerating tissue like the skin, proliferation is an essential task, most evident in the physiological process of wound healing. After physical trauma of the barrier, the skin mounts a robust inflammatory response, followed by new tissue formation and remodeling to contain the damage and prevent detrimental effects on deeper body organs (115). AhR is being recognized as a possible regulator of this cascade, possibly with distinct effects on the different cell types resulting in overall homeostasis. Although lack of AhR expression increases epithelial cell migration via overproduction of active TGF-β by dermal fibroblasts and results in accelerated wound healing (139), migration rates of primary endothelial cells and fibroblasts decrease in the absence of AhR, possibly via β1 integrin activation (140).

AhR signaling is also essential for hematopoietic skin-resident cells, namely epidermal γδ T cells and LCs. Vγ3 T cells (Garman nomenclature; see Reference 95), also named dendritic epidermal T cells (DETCs) for their morphology and location, migrate to the basal epidermis during fetal development, forming an interdigitating network with KCs and overlaying LCs. DETCs are involved in immunosurveillance and promote wound healing, aiding in KC proliferation via the production of growth factors such as insulin-like growth factor-1 (141).

DETCs express high levels of AhR and are strikingly absent in the skin of AhR-deficient mice (97, 118). Although DETC precursors are generated in the thymus and migrate to the epidermis, their proliferation is compromised in the epidermis, leading to their progressive loss after birth. Reduced levels of the tyrosine kinase and growth factor c-Kit in the residual DETCs remaining in AhR-deficient mice (118) suggest a possible mechanism by which AhR regulates DETC homeostasis. However, the functional consequences of the absent DETCs in AhR-deficient mice are still unclear, especially considering that AhR-deficient mice seem to have a faster wound healing response rather than a compromised one (139). The unique existence of DETCs in mice but not in humans also raises further questions about their physiological role in skin homeostasis. Nevertheless, mouse skin is fundamentally different from human skin and, despite having further protection conferred by hair, is perhaps even more exposed to pathogens and environmental triggers, requiring an additional layer of homeostatic control.

LCs are also compromised in AhR-deficient mice, as they have been reported to have impaired maturation in vitro, with smaller size, failure in upregulation of costimulatory molecules, increased phagocytic ability, and decreased mRNA levels of the tolerogenic enzyme IDO and of IL-10 (116). Researchers have suggested that these defects are due to the reduced level of GM-CSF in the epidermis of AhR knockout mice caused by the absence of DETCs (118). Interestingly, wild-type LCs do not express CYP1A1 or CYP1B1 upon AhR activation but instead express high levels of the AhRR. This may be a general feature of DCs, as it is also found in DCs generated

by culture of bone marrow cells in the presence of GM-CSF as well as in splenic DCs, all of which present with high levels of constitutive AhRR expression (B. Stockinger & M. Gialitakis, unpublished data). Generally, AhR activation seems to have anti-inflammatory consequences in DCs by inducing production of IDO and IL-10. However, a systematic comparison of all the different DC populations in different organs has not been done yet.

Our recent data in the mouse model of psoriasiform skin inflammation (J. Duarte, P. Di Meglio, H. Ahlfors, N. Owens, Y. Li, H. Müller, F. Villanova, I. Tosi, K. Hirota, F. Nestle, U. Mrowietz, M. Gilchrist & B. Stockinger, manuscript under review) indicate that absence of AhR results in exaggerated inflammatory responses and an exacerbation of the psoriasis-like symptoms. Although deficiency in AhR causes alterations in innate and adaptive immune cells as well, we found that AhR deficiency restricted to nonhematopoietic cells, in particular KCs, was sufficient to replicate the hyperinflammatory phenotype seen in AhR-deficient mice. Thus, cross talk between inflammatory mediators released by innate and adaptive immune cells and AhR-expressing nonhematopoietic cells seemed critical for maintaining equilibrium in the inflammatory response. Treatment of mice with FICZ during induction of psoriasiform inflammation dampened the inflammatory response.

Furthermore, we determined that short-term culture of skin biopsies from psoriasis patients in the presence of the AhR agonist FICZ or an AhR antagonist (142) modulated the gene-expression profile of psoriasis-associated genes. Thus, exposure of lesional skin biopsies to AhR agonist caused downmodulation of psoriasis-associated genes, whereas exposure to antagonist further increased their expression and also upregulated the expression of such genes in unaffected nonlesional skin from psoriasis patients. Thus, physiological AhR activation might be considered an immunological brake that prevents dysregulation of the inflammatory response.

Gut

The intestinal tract is the largest mucosal surface of the human body and a critical interface between the host and the external environment represented by food and gut-associated microorganisms (**Figure 8**). The intestinal lumen is home to several trillion bacteria, many of which are beneficial and live in a symbiotic or mutually beneficial relationship with their mammalian hosts. Dietary intake shapes this host-microbiota interaction, and the mucosal-associated immune system has the challenging task of concurrently providing protection from pathogenic agents and maintaining tolerance to commensal and harmless antigens.

The intestinal surface is lined by a single layer of columnar intestinal epithelial cells that forms a barrier between the intestinal lumen and the host's connective tissue or lamina propria (LP). Specialized intraepithelial lymphocytes (IELs), i.e., TCR$\gamma\delta$ and TCR$\alpha\beta$ CD8$\alpha\alpha$ T cells, are located between the basolateral surfaces of the epithelial cells and are a critical first line of defense against pathogens. In the LP, a variety of immune cells are present (B cells, macrophages, DCs, T cells, and ILCs) and participate in maintaining intestinal homeostasis.

The AhR has recently been established as a critical molecule for maintaining both IEL and ILC populations in the gut (82, 97–99, 143). Although dispensable during embryonic development or for homing to the target tissue of both cell types, AhR signaling is absolutely necessary for their survival after birth. Either AhR deficiency or a diet devoid of phytochemicals (derived from cruciferous vegetables) results in loss of TCR Vγ5 [intestinal $\gamma\delta$ T cells, using the Garman nomenclature (95)] and TCR$\alpha\beta$ CD8$\alpha\alpha$ IELs in a cell-intrinsic manner, via a mechanism that does not involve reduced proliferation but likely does involve reduced survival (97).

Deleterious consequences of AhR deficiency include exacerbated epithelial immunopathology, with more severe dextran sodium sulfate–induced colitis and increased bacterial load of potentially harmful strains. Moreover, the proliferation of colonic crypt stem cells is strongly reduced in the absence of AhR signaling.

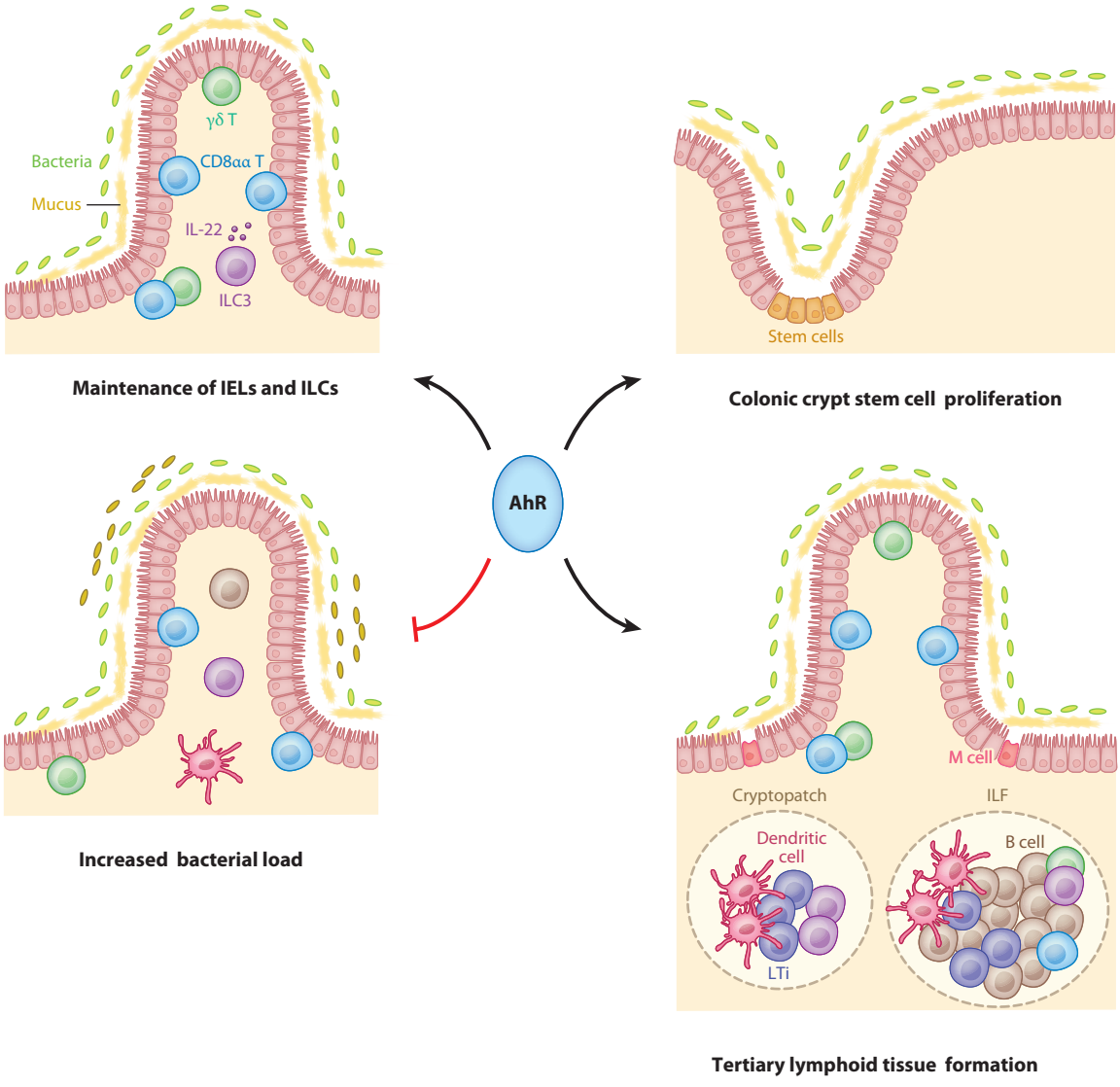

Figure 8

The role of AhR in the gut. AhR exerts multiple functions in the gut, acting as an essential keeper of the gut barrier. Dietary-derived AhR ligands ensure maintenance of intraepithelial lymphocytes (IELs) (e.g., γδ T cells and CD8αα T cells) as well as innate lymphoid cells (ILCs) (e.g., ILC3) and proliferation of colonic crypt stem cells. Moreover, AhR signaling is critically involved in the formation of tertiary lymphoid tissues such as cryptopatches and intestinal lymphoid follicles (ILFs). AhR deficiency leads to loss of ILC3 and IELs, loss of IL-22, disruption of colonic crypt stem cell proliferation, and dysregulation of intestinal bacteria.

ILCs are innate lymphoid cells lacking lineage markers for conventional innate and adaptive immune cells and are revealing themselves to be important effectors in tissue homeostasis and immunity. The recent identification of distinct subsets, very much mirroring subsets of T helper cells, necessitated a unifying classification based on their cytokine production profile and expression of transcription factors. This resulted in organization of ILCs into group 1, 2, and 3 ILCs (144). Group 1 consists of ILCs that produce IFN-γ; group 2 consists of ILCs that produce type 2

cytokines and are dependent on GATA-3 and retinoic acid receptor–related orphan receptor-α (RORα); and group 3 includes lymphoid tissue inducer (LTi), natural cytotoxicity triggering receptor (NCR)$^+$ ILC3, and NCR$^-$ ILC3, all producing IL-17 and/or IL-22 and dependent on the transcription factor RORγt for their development and function. Among group 3 ILCs, LTi and NCR$^+$ ILC3 express AhR, and this has been linked to their capacity to produce IL-22 (145). More recently, AhR expression has been shown by three independent groups to affect the homeostasis of these subsets (82, 98, 99). AhR deficiency in the hematopoietic compartment leads to profound loss of RORγt$^+$ LTi and NCR$^+$ ILC3 in the intestinal LP; the absence of postnatally developed cryptopatches and isolated lymphoid follicles; reduced IL-22 production; and inadequate protection against intestinal infection with the attaching and effacing bacterium *Citrobacter rodentium*. One of these studies (99) also showed a requirement for dietary-derived AhR ligands to support the maintenance of ILCs, similar to what was shown for IELs, whereas the other study (98) did not observe this phenomenon. This issue requires further clarification but might be dependent on the specific housing conditions of experimental animals.

Different molecular mechanisms underlie the beneficial effects of AhR signaling in the regulation of intestinal homeostasis, although there are some discrepancies among different studies. Intestinal RORγt$^+$ ILCs lacking AhR are more prone to apoptosis as a result of decreased expression of the antiapoptotic protein BCL2 and attenuated IL-7/IL-7R expression (82). Another study has shown reduced proliferative activity in the absence of AhR in a subset of CD4$^-$ RORγt$^+$ ILCs associated with reduced expression of the receptor tyrosine kinase Kit (99). AhR also modulates Notch signaling via transcriptional induction of Notch1 and Notch2 (98). However, mice deficient in RBP-Jk, a factor that associates with Notch receptors to drive transcription of target genes, have reduced numbers of ILCs but do not fully create a phenocopy of AhR-deficient mice, suggesting that both Notch-dependent and -independent mechanisms are in place to maintain ILC3. A recent study suggested that AhR-controlled IL-22 production by ILC3 is responsible for suppressing inflammatory Th17 cell responses, as AhR-deficient mice exhibited increased levels of segmented filamentous bacteria and expanded intestinal Th17 cell populations (146).

Further studies are required to provide solid mechanistic explanations and solve current discrepancies. Nevertheless, these studies have collectively established an essential physiological role for AhR activated via dietary components in preserving the homeostasis of intestinal barrier functions. It will be interesting to investigate whether perturbation of AhR signaling occurs in individuals with inflammatory gut disorders such as inflammatory bowel disease or Crohn's disease and if beneficial effects via physiological AhR ligands could be exploited in gut immunopathology.

Lung

AhR abundance in the lung (**Figure 9**) is comparable to what is found in organs known to constitutively express AhR, such as the liver (147). The lung is constantly exposed to the atmosphere and to airborne environmental pollutants that originate from human activity: vehicle exhaust, industrial processes, and cigarette smoke are only a few examples of the multiple sources of polycyclic aromatic hydrocarbons that are released into the atmosphere every day (148), and many of these compounds are readily recognized by AhR (149). The high expression level of AhR observed in the lung coincides with significant baseline expression of several members of the cytochrome P450 enzymes that are AhR target genes, with *Cyp1a1* and *Cyp1b1* being the most prominent (150). This indicates that the AhR pathway is activated and functional even during homeostasis. Whether this results from exposure to environmental ligands or to naturally occurring endogenous ligands is not known. A putative endogenous AhR ligand, 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), was isolated from porcine lung (151), although there are some concerns

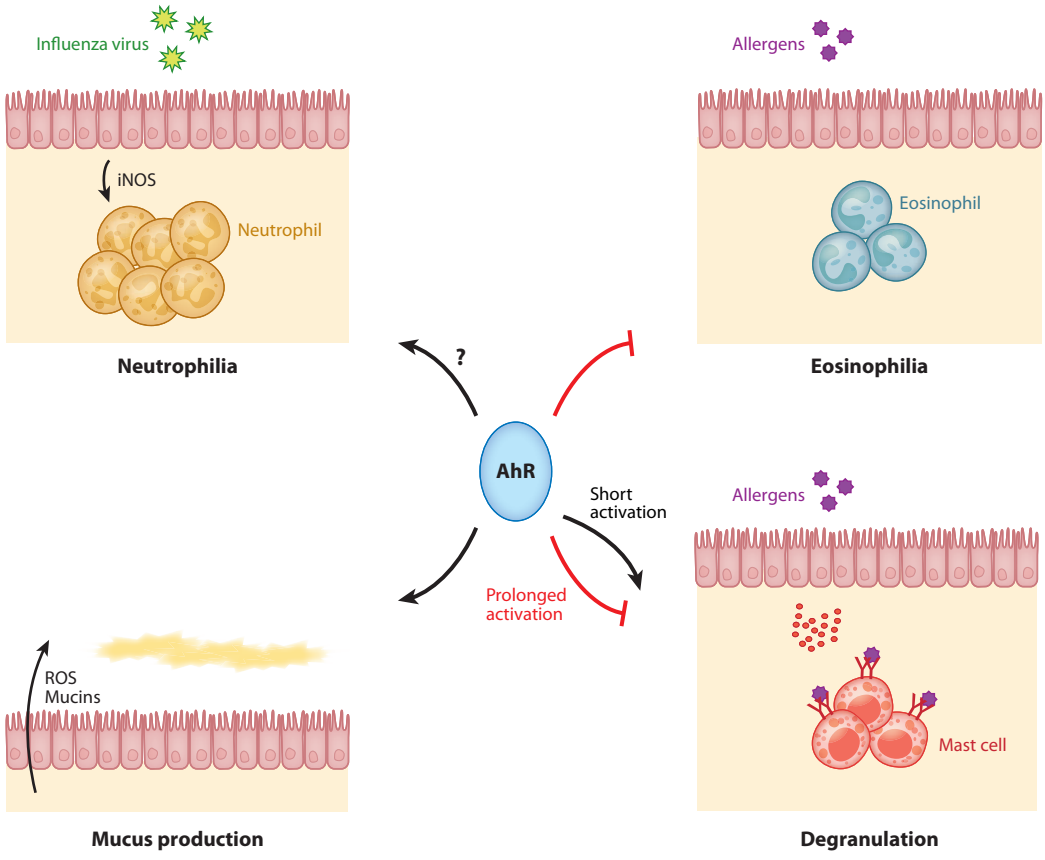

Figure 9

The role of AhR in the lung. AhR exerts distinct functions in the lung tissue, acting on different cell types.. In influenza infections, sustained AhR triggering by TCDD (similar to AhR deficiency) may promote neutrophilia via epithelial-derived iNOS expression. In the presence of allergens, AhR signaling dampens eosinophilia, whereas it either inhibits or promotes mast cell degranulation, depending on the duration of signaling. By acting on lung epithelia, AhR ensures adequate production of mucus via ROS and mucins. (Abbreviations: iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.)

that the harsh isolation conditions may have contributed to its formation during the process. The description of AhR-deficient mouse strains revealed no defects in lung development and function (108, 109), but the functional significance of AhR expression in this organ may become apparent only upon insult, infection, or aging.

AhR expression in the lung encompasses several cell types, both hematopoietic and structural in nature. Lung epithelial cells significantly shape the inflammatory response in this organ, as does the population of immune cells infiltrating the lung by producing chemokines, ROS, and mucins (reviewed in 152). In particular, the production of mucins and ROS by lung epithelial cells is modulated by AhR, given that the administration of an AhR ligand induces expression of MUC5B and MUC5AC (153), a process dependent on ROS production and AhR activity (154). The ability of lung epithelial cells to detect toxic airborne chemicals and to respond through mucin production, effectively reinforcing the physical barrier present in lung alveoli, might constitute an important defense mechanism against toxicity; equally important is the possibility that AhR participates in the formation of the mucin barrier in the lung during steady state, or even during

infection, through the influence of endogenous ligands. These questions are highly relevant and could have implications for a multitude of lung disorders such as allergy or COPD.

Several studies in lung infection models have shown that AhR can modulate the immune response, with particular emphasis given to influenza infection models (155). In concordance with the immunosuppressive aspect of AhR activation, exposure to dioxin prior to influenza virus infection in mice reduces the expansion and activation of $CD8^+$ T cells in mediastinal lymph nodes and in lung tissue, resulting in a dramatic reduction of IFN-γ production and cytolytic activity by these cells (156). The mechanism by which the observed T cell suppression is linked to AhR remains unclear, but a recent study suggests that the target of immunosuppression in this model is a population of lung-resident DCs (157). Lung-resident DCs not only participate in the local uptake of antigen to drive T cell differentiation in draining lymph nodes but also can produce cytokines that shape the inflammatory response locally. Additionally, AhR activation in DCs leads to expression of the immune-suppressive enzyme IDO (158, 159), a mechanism that might contribute to the reduced immunogenicity observed under systemic AhR activation.

Sustained AhR activation by TCDD causes increased mortality during influenza infection, accompanied by an increase in neutrophilia due to increased expression of iNOS by lung epithelial cells in dioxin-treated mice (160), which may account for the increased recruitment of neutrophils to the lung (161). However, neutrophilia is a prominent feature of infection/inflammation in AhR-deficient mice, which suggests that sustained AhR activation by TCDD may in some aspects mimic AhR deficiency.

A population of lung mast cells, a subset of immune cells that participates in allergic and anaphylactic responses, also expresses AhR, and its activation by FICZ can potentiate or inhibit degranulation in response to antigen-specific IgE crosslinking (101). Modulation of the degranulation mechanism appears to depend on the frequency and duration of AhR triggering, an idea that has been proposed previously as a general means of action of AhR (51). Importantly, and in contrast to what is observed with neutrophils (161), AhR modulation of mast cell function seems to be cell intrinsic, such that a single administration of FICZ results in increased degranulation, whereas repeated administrations of the ligand lead to inhibition of the process. Further supporting an important role for AhR in mast cells, a recent study reported that AhR-deficient mast cells respond poorly to stimulation owing to defective calcium signaling and mitochondrial function (102). These findings underscore the importance of the AhR pathway at barrier organs, as mast cells play important roles in the lung and skin immune systems. Notably, AhR activation can also modulate the lung immune response by eosinophils, another cell type associated with asthma and lung dysfunction. Here, FICZ administration reduced the pulmonary eosinophilia that normally follows OVA challenge in sensitized mice (162) and coincidentally reduced expression levels of the Th2 cytokines IL-4 and IL-5 in lung tissue.

It is worth noting that IL-17- and IL-22-producing Th17 cells, whose differentiation program is uniquely potentiated by AhR activation (81, 114), are thought to have a significant impact on lung disorders such as allergic asthma (163). The question of whether AhR can modulate lung immune responses through the IL-17 axis of inflammation has yet to be addressed, but published evidence supports this prediction: Bronchial fibroblasts are highly sensitive to IL-17, producing inflammatory mediators and chemoattractants such as IL-6, IL-8, and GRO-α in response to IL-17 stimulation (164), which means that any dysregulation of IL-17 levels in the lung can drastically affect the local inflammatory response.

CONCLUSIONS

The ability of AhR to act as an environmental sensor fulfills important roles in maintaining homeostasis at the barrier organs that are exposed to environmental signals in the form of dietary

components, UV-induced metabolites, and potentially other physiological ligands. The available evidence to date points to a role for AhR in controlling the extent of inflammatory reactions in response to the commensal microbiota as well as to tissue destruction. Progress is being made in defining the molecular mechanisms by which AhR exerts its influence in different cell types. It will be vital in the future to concentrate such efforts on primary cell types rather than cell lines and to investigate all cell types of barrier organs that express AhR.

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