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Diet–Host–Microbiota Interactions Shape Aryl Hydrocarbon Receptor Ligand Production to Modulate Intestinal Homeostasis

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Abstract

The aryl hydrocarbon receptor (AhR) is a ligand-activated basic-helix-loop-helix transcription factor that binds structurally diverse ligands and senses cues from environmental toxicants and physiologically relevant dietary/microbiota-derived ligands. The AhR is an ancient conserved protein and is widely expressed across different tissues in vertebrates and invertebrates. AhR signaling mediates a wide range of cellular functions in a ligand-, cell type–, species-, and context-specific manner. Dysregulation of AhR signaling is linked to many developmental defects and chronic diseases. In this review, we discuss the emerging role of AhR signaling in mediating bidirectional host–microbiome interactions. We also consider evidence showing the potential for the dietary/microbial enhancement of

health-promoting AhR ligands to improve clinical pathway management in the context of inflammatory bowel diseases and colon tumorigenesis.

Contents

INTRODUCTION

There is emerging and convincing evidence that the human microbiome and, in particular, intestinal microbial populations and their metabolites play critical roles in maintaining human health and preventing diseases such as immune disorders, bacterial infections, cancer, and obesity (135). It is estimated that nearly three million metabolites and compounds can be produced by the microbiota in the gastrointestinal (GI) tract (60). However, to date, only a small fraction has been identified, characterized, or translated into therapeutic or chemopreventive applications. One of the significant outcomes from ongoing studies is the identification of bacteria and their metabolites that are important in different diseases and their potential for development into novel microbial-based therapies (84). Tapping the vast reservoir of molecules produced by the microbiota is expected to have a significant impact on biotechnology and biopharmaceutical development.

Currently, the complex nutritional/dietary forces that guide the assembly and stability of the GI microbiota and their impact on host gene–microbiome interactions that mediate phenotypic traits (e.g., GI stem cells, metabolism, and the immune system) remain elusive. In addition, there is a dearth of mechanistic information that would be required to generate microbial and host biological signatures (predictive biomarkers) to diagnose and predictively screen disease risk. While it is clear that the GI microbiota has a significant impact on human health, cause-and-effect relationships between diet, the GI microbiota, and chronic diseases are not yet firmly established (57). Thus, understanding the cross talk between diet and microbes in the GI tract as a modifier of disease risk will create a new knowledge base for the development of novel approaches to treat and prevent a wide range of diseases and disorders observed in animals and humans. Here, we focus on evidence that diet and nutrients influence intestinal health and chronic disease, in part via their modulation of gut microbial metabolism and subsequent production of bioactive metabolites, which serve as ligands for the aryl hydrocarbon receptor (AhR), and on how AhR signaling in

the host shapes the community of gut microbiota. In addition, we describe the physiological functions of AhR signaling in the context of inflammatory bowel diseases and colon cancer.

THE ARYL HYDROCARBON RECEPTOR

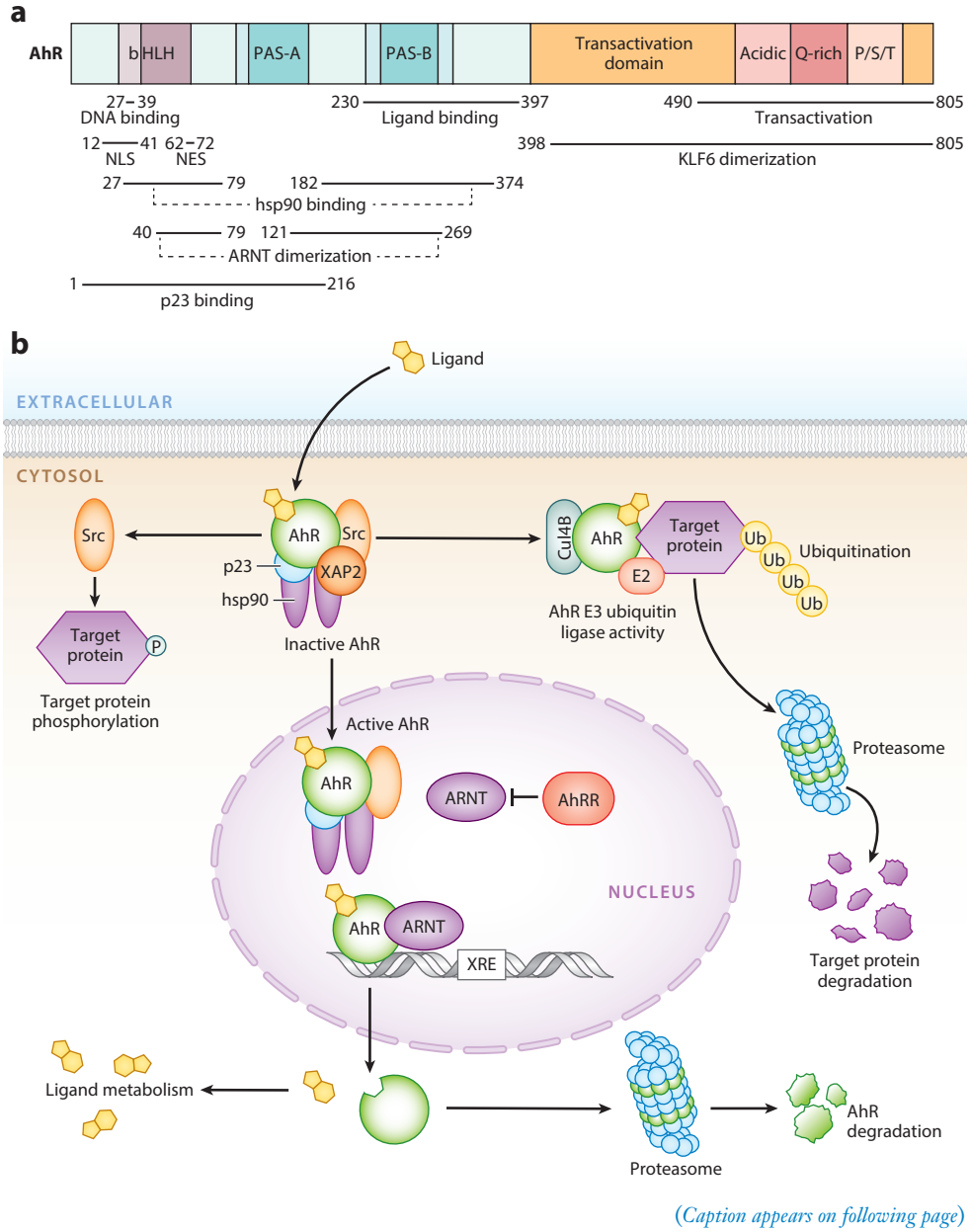
The AhR is an ancient and highly conserved protein that has evolved over 600 million years and is a member of the basic-helix-loop-helix-Per-ARNT-Sim (bHLH-PAS) transcription factor superfamily (**Figure 1*a***), which plays key roles in developmental biology, circadian rhythmicity, and environmental homeostasis (46, 56, 72). The bHLH domain of the AhR forms a homodimeric structure containing basic-rich amino acids and heterodimerizes with the AhR nuclear translocator (ARNT) to recognize an atypical E-box DNA sequence. The AhR has two PAS domains, PAS-A and PAS-B. Both bHLH and PAS-A domains contribute to the dimerization and stability of the AhR-ARNT complex, and the PAS-B domain contains a ligand-binding motif. Ligand binding induces conformational changes in the AhR that expose nuclear localization sequences, enhancing AhR-ARNT dimerization in the nucleus (121). In contrast to the relatively conserved bHLH-PAS domains, the transcription activation domain of the AhR is highly variable and uniquely confers transactivation potential by differentially recruiting LXXLL-containing coactivators, thus resulting in divergent expression of target genes (31, 32).

In the absence of ligands, the AhR is bound to several chaperone proteins in the cytoplasm, including heat shock protein 90 (hsp90), p23, and immunophilin-related protein XAP2 (**Figure 1*b***). Upon ligand binding, XAP2 dissociates from the cytosolic AhR complex (103), and the AhR-ligand complex is then translocated into the nucleus. Once in the nucleus, hsp90 and p23 are displaced by ARNT (27, 126) to form a heterodimeric AhR complex, which then interacts with *cis*-acting dioxin response elements (DREs) within the core sequence 5′-TNGCGTG-3′ or 5′-CACGCNA-3′ on promoters of AhR-responsive genes to affect their expression (76). An example of such an effect is inducing AhR-dependent expression of xenobiotic metabolizing genes, including several forms of cytochrome P450 (CYP1A1, CYP1A2, CYP1B1), glucuronosyltransferases (UGT1A1), and other phase II drug metabolizing enzymes (82, 104). The expression of cytochrome P450 enzymes can transform and metabolize AhR ligands, limiting their availability (8). In addition, the expression of the AhR repressor, a transcriptional AhR target, can compete with the AhR for dimerization with ARNT and suppress AhR signaling (89). Moreover, nuclear dissociation of the AhR from hsp90 results in exposure of a nuclear export sequence in the N-terminal region, which guides the export of the AhR into the cytoplasm for proteasomal degradation (25). Collectively, these routes provide a negative feedback loop to control the strength and duration of AhR signaling. The AhR can also regulate expression of genes that lack canonical DREs in their promoter regions, such as plasminogen activator inhibitor 1 (PAI-1) (49), independent of ARNT. The recognition of noncanonical DREs in the PAI-1 promoter requires the interaction between the AhR and the Kruppel-like factor (KLF) family member KLF6 (143). In addition, there is evidence that the AhR alone regulates nongenomic pathways (72), and this mechanism of action resembles similar effects observed in some steroid hormone receptors that activate both genomic and nongenomic pathways.

The AhR was initially identified as a hepatic cytosolic protein that bound a series of halogenated aromatic hydrocarbons including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is structurally similar to polychlorinated dibenzo-p-dioxins, biphenyls, dibenzofurans, and polycyclic aromatic hydrocarbons (PAHs), including 3-methylcholanthrene, β-naphthoflavone (BNF), and benzo[a]pyrene (**Figure 2*a***). This function was subsequently found to be evolutionarily acquired by vertebrate AhRs, since invertebrate AhRs are unable to bind to TCDD or BNF; this inability distinguishes invertebrate AhRs from their vertebrate homologs (20). The K_D value for

TCDD is on the order of 10^{-12} M, and the binding is almost irreversible even though there is no evidence for TCDD-AhR covalent binding (14). The reason for this tight binding is not well understood. With few exceptions, most other AhR ligands do not exhibit these tight interactions with the AhR, and computer modeling studies do not sufficiently resolve the issue of the ligand promiscuity of the AhR (8, 40, 127).

The toxicities of TCDD and related compounds are highly variable among different species, and this is also true among different strains of mice (8). For example, TCDD exhibits lower toxicity



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

AhR functional domains and signaling pathways. (*a*) Schematic representation of murine AhR functional domains and the location mapping of the amino acid sequences that interact with other proteins. (*b*) AhR signaling pathways. An inactive AhR is sequestrated within the AhR chaperone complex containing hsp90, immunophilin related protein XAP2, p23, and Src. Upon ligand binding, the AhR-ligand complex translocates to the nucleus, where hsp90 and p23 are displaced by the ARNT to form a heterodimer with the AhR. This heterodimer then binds to the DREs to regulate the expression of genes that are involved in various cellular functions, including xenobiotic metabolism, cell apoptosis and proliferation, self-renewal and differentiation of stem cells, immune regulation, and redox biology. Following transcription, the AhR is exported from the nucleus and degraded by the cytoplasmic proteasome. An activated AhR can function as an E3 ubiquitin ligase, inducing the ubiquitination and proteasomal degradation of target proteins. In addition, AhR ligand binding induces phosphorylation of Src kinase, initiating Src-driven phosphorylation cascades. Abbreviations: AhR, aryl hydrocarbon receptor; AhRR, aryl hydrocarbon receptor repressor; ARNT, AhR nuclear translocator; bHLH, basic-helix-loop-helix; DREs, dioxin response elements; hsp90, heat shock protein 90; NES, nuclear export sequence; NLS, nuclear localization sequence; PAS-A/B, Per-ARNT-Sim homology domain A/B; P/S/T, proline/serine/threonine; XRE, xenobiotic response element.

in DBA compared with C57BL/6 mice. This is attributed to the fact that C57BL/6 and DBA mice express AhR^b and AhR^d isoforms, which are high- and low-affinity forms of the AhR with respect to TCDD binding, respectively. Specifically, an A375V amino acid change in the AhR ligand–binding domain of the DBA receptor, in which the bulky side chain of valine hinders ligand binding, causes a tenfold decrease in ligand binding affinity. This is also observed in the human AhR ligand–binding domain (8).

The persistent and potent AhR ligand can cause multiple downstream biochemical and toxic responses (**Figure 2*b***). For example, the chlorinated aromatic compounds induce a common set of toxic responses including thymic atrophy, body weight loss, hepatic porphyria, cleft palate in mice, and acnegenic responses in humans, rabbits, and certain strains of mice (104, 114). In contrast, this pattern of toxic responses is not observed for BNF or PAHs, and the unique toxicities associated with TCDD and related compounds have been ascribed to persistent occupation of the receptor. Ongoing studies show that the AhR binds structurally diverse compounds including multiple classes of environmental aromatics and heteroaromatics, pharmaceuticals, dietary phytochemicals, and a host of endogenous compounds including microbiota-derived tryptophan metabolites, 1,4-dihydroxy-2-naphthoic acid, and serotonin (105, 115). Although endogenous ligands for the AhR have not been unequivocally assigned, two possibilities include the tryptophan-derived compounds 6-formylindolo[3,2-b]carbazole (FICZ) and 2-(1′H-indolo-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE). These structurally diverse AhR ligands with transient half-lives do not cause TCDD-like toxicities. In contrast, many of these compounds are classified as selective AhR modulators (SAhRMs), since they favorably modulate physiological responses, including immune cell proliferation/differentiation and redox homeostasis (**Figure 2*b***) (86, 115). Similarly, loss of the AhR results in reproductive tract and cardiovascular problems, and, in stem cell development, immune function deficits, altered portal duct fibrosis, ocular deficits, and uric acid stone formation in the bladder (8, 19, 22, 37).

In the past decade, the focus on AhR function has been bifurcated into (*a*) the AhR's initially recognized xenobiotic metabolizing role and (*b*) its other adaptive roles, such as organ development, cancer biology, and immune regulation.

DIET-DERIVED AHR LIGANDS

In addition to dioxin-like compounds and PAHs, many nonclassical, naturally occurring AhR ligands have been discovered in the past few decades. In general, these AhR ligands are nontoxic and exhibit modest-to-low binding affinities for the AhR with variable metabolic half-lives. The

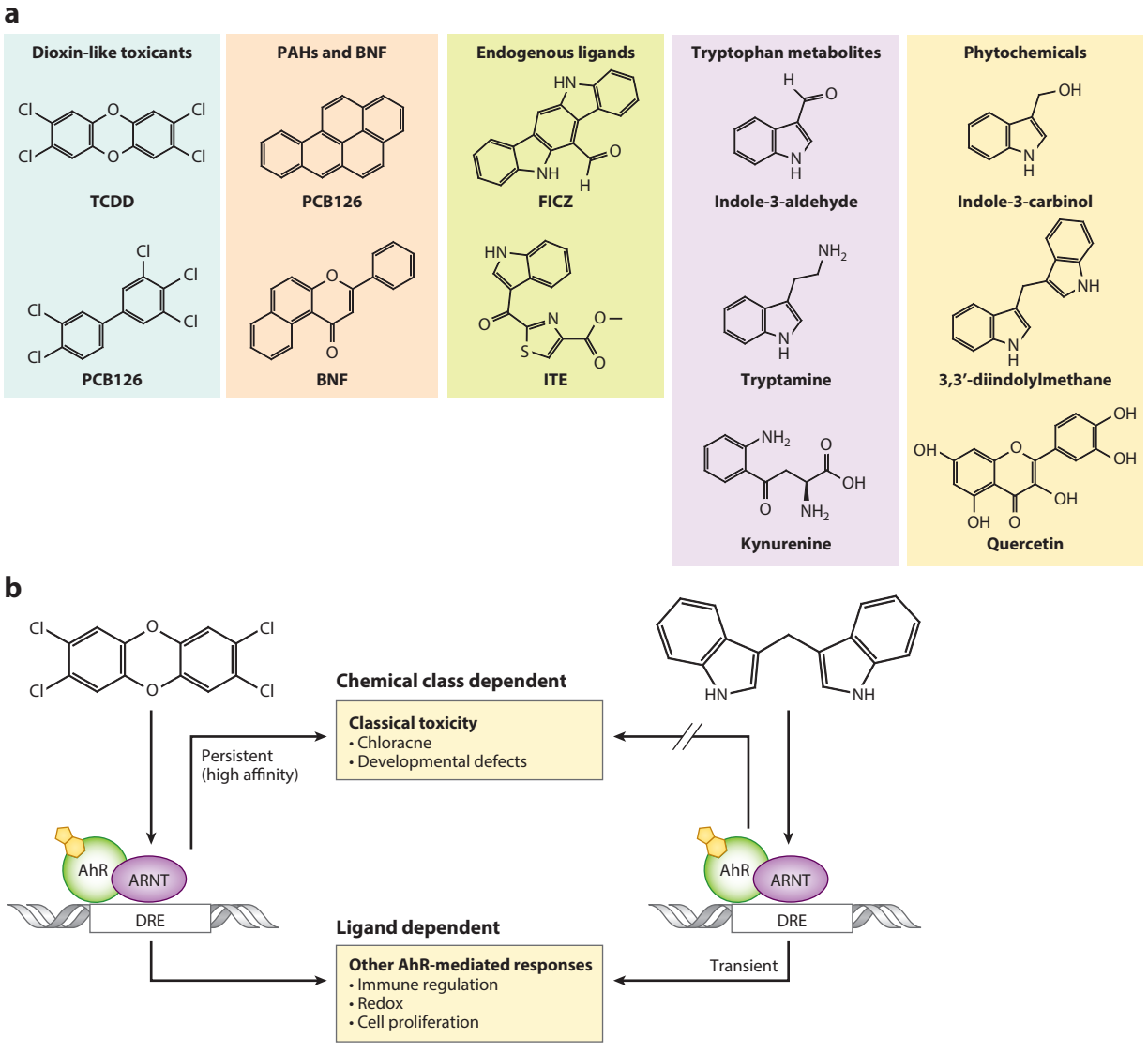


Figure 2

AhR ligands and associated functions. (*a*) Structures of different classes of AhR ligands. (*b*) The bifurcative effects of AhR activation by synthetic or natural AhR ligands. The persistent and potent AhR ligands, such as TCDD, induce classical toxicity, including chloracne and developmental defects in humans. However, natural AhR ligands derived from either diet or gut microbiota can bind to the AhR with various binding affinities and short half-lives. These AhR ligands (agonists and antagonists) do not elicit the classical toxicity but modulate many physiological functions, such as immune regulation, redox biology, and cell proliferation. Abbreviations: AhR, aryl hydrocarbon receptor; ARNT, AhR nuclear translocator; BNF, β-naphthoflavone; DRE, dioxin response element; FICZ, 6-formylindolo[3,2-b]carbazole; ITE, 2-(1′H-indolo-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester; PAH, polycyclic aromatic hydrocarbon.

major sources of naturally occurring AhR ligands are plant-derived dietary ingredients, gut microbiota metabolites of poorly digestible plant-derived dietary ingredients, and host metabolism of aromatic amino acids, such as tryptophan. Flavonoids and indole-containing glucobrassicin represent two main classes of dietary-derived AhR ligands (18, 52). Flavonoids are a large class of polyphenolic secondary metabolites that are widely distributed in fruits and vegetables. A subset of flavonoids, such as quercetin, taxifolin, and robinetin, can activate the AhR (59), whereas some flavonoids, such as luteolin, act as AhR antagonists (157). Typically, AhR ligands are assessed by DRE-driven cell-based reporter systems, downstream target gene (e.g., *CYP1A1* and *UTG1A1*) expression, and promoter binding assays. A major structural determinant of AhR activation is the number of hydroxyl groups with pentahydroxyflavonoids showing maximal potency (59). In addition, *Brassicaceae* family plants, such as Chinese cabbage, broccoli, brussels sprouts, and cauliflower, are rich sources of glucobrassicin, the glucosinolate precursor of indole-3-carbinol (I3C). Glucobrassicin can be enzymatically hydrolyzed and converted into I3C by myrosinase (β-thioglucosidase), which is present in intact plant cells and gut microbiota (12, 23). I3C itself is capable of activating the AhR but exhibits low binding affinity (~2 mM) (58). However, in acidic conditions found in the stomach, I3C undergoes acid condensation reaction to generate a variety of more potent AhR ligands, such as 3,3′-diindolylmethane (DIM), [2-(indol-3-ylmethyl)-indol-3-yl]indol-3-ylmethane, and indolo[3,2-b]carbazole (ICZ) (58, 139), of which ICZ exhibits the most potent AhR activation (~0.2–3.6 nM) (26). In addition, indigo and indirubin, present in traditional Chinese medicine and the dried leaves of the flowering plant *Isatis tinctoria*, which serve as dyes for textile coloring, robustly activate the AhR to induce Cyp1a1 expression in mammals (131).

HOST METABOLISM OF TRYPTOPHAN

Endogenous AhR ligands can also be produced by host cells. The most well-characterized ligand is kynurenine (Kyn). In the host, more than 95% of dietary tryptophan is degraded via the Kyn pathway, while less than 5% of tryptophan is metabolized into serotonin by tryptophan hydroxylase. The rate limiting reaction step in the Kyn pathway is catalyzed by the enzyme tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). TDO is constitutively expressed mainly in the liver and brain, while IDO is inducibly expressed in a number of tissues in response to proinflammatory cytokines, such as interferon-γ (IFN-γ) (136). Induction of the Kyn-IDO pathway plays an important role in immune tolerance/suppression and tumor pathogenesis (44, 98). The serum concentration of Kyn in healthy humans is ~1.8 ± 0.4 μM, which is within the dose range of AhR activation, even though Kyn binds to the mouse liver AhR with an apparent K_D of ~4 μM (98, 123). In patients with inflammatory bowel diseases (IBDs), the Kyn/tryptophan ratio in serum is increased, possibly due to increased IDO1 induction (96). Kyn can be further metabolized into kynurenic acid, xanthurenic acid, and cinnabarinic acid, which all serve as endogenous AhR ligands (81, 97). In addition, another potent AhR ligand, FICZ, can be produced in human keratinocytes from L-tryptophan under UV irradiation, and this compound activates the AhR at nanomolar concentrations, which are comparable with those observed for TCDD (33). In addition, gut microbiota–derived indole can be further processed in host liver tissue, where it is hydroxylated into 3-hydroxyindole by hepatic cytochrome P450 enzymes, including CYP2E1 (10), and subsequently sulfated by sulfotransferases into indole-3-sulfate (11), an important uremic toxin and potent endogenous AhR ligand (118).

GUT MICROBIOTA–DERIVED AHR LIGANDS

The human GI tract represents one of the largest interfaces (250–400 m^2) between the host and its external milieu in the human body. In the healthy adult, it has been estimated that ~4×10^{13}

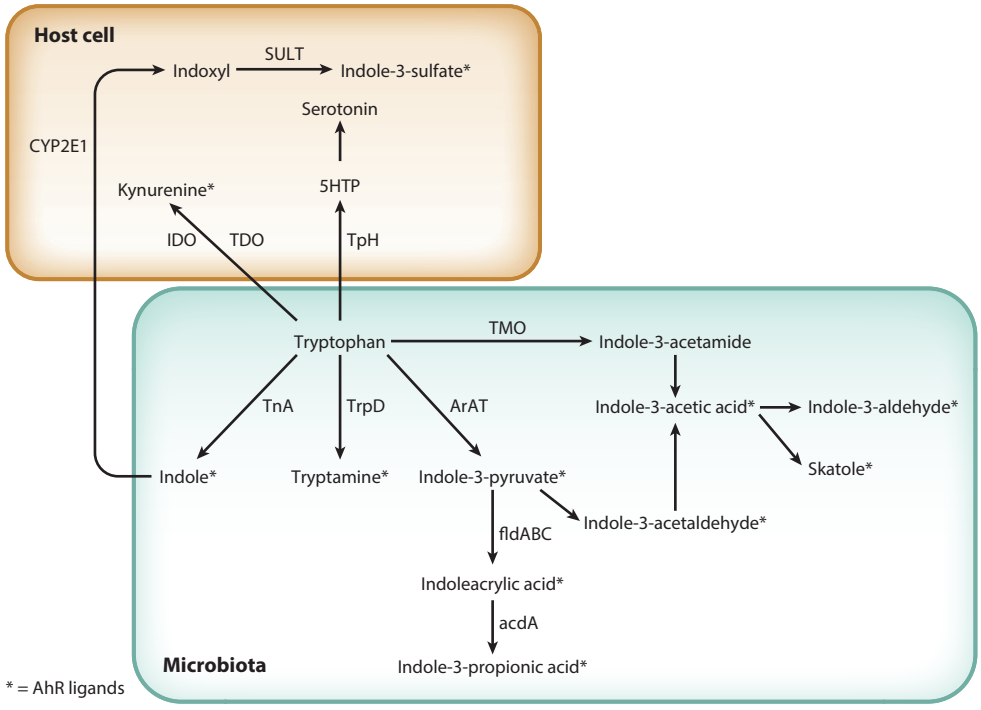


Figure 3

Pathways of tryptophan metabolism in human host cells and gut microbiota. Abbreviations: acdA, acyl-CoA dehydrogenase; ArAT, aromatic amino acid aminotransferase; fldABC, phenyllactate dehydratase gene cluster; IDO, indoleamine 2,3-dioxygenase; SULT, sulfotransferase; TDO, tryptophan 2,3-dioxygenase; TMO, tryptophan 2-monooxygenase; TnA, tryptophanase; TpH, tryptophan hydroxylase; TrpD, tryptophan decarboxylase.

microorganisms (microbiota), including bacteria, archaea, and eukarya, inhabit the large intestine (120). The gut microbiota consists of thousands of bacterial species dominated by four phyla: Firmicutes (~50–70%), Bacteroidetes (~10–30%), Proteobacteria (up to 10%), and Actinobacteria (up to 5%) (99). Notably, these microorganisms offer a range of beneficial properties to the host, including the fermentation of undigested carbohydrates, biosynthesis of vitamins, and generation of short-chain fatty acids and tryptophan metabolites. Since a number of recent reviews concerning the role of gut microbiota in health and disease can be found (1, 30), we focus our discussion on the role of microbiota with respect to the biosynthesis of tryptophan metabolites, which serve as endogenous AhR ligands.

Tryptophan is an essential and limiting amino acid in proteins and cells. Serum concentrations of tryptophan in healthy humans are in the range of 70 ± 10 μmol/L for males and 65 ± 10 μmol/L for females (39). Transformation of tryptophan by intestinal microbiota can produce several metabolites, including indole, indole-3-acetic acid (IAA), and tryptamine (TPM) (**Figure 3**). These tryptophan metabolites, found in the mammalian bloodstream, are primarily generated by gut microbiota, as evidenced by decreased or undetectable levels of tryptophan metabolites in germ-free mice compared with conventional mice (141). Numerous species capable of producing indole and other tryptophan metabolites have been identified and described in previous reviews (74, 110). Thus, we briefly discuss pathways for the formation of tryptophan catabolites. Although indole itself is capable of activating the human AhR at its physiological

concentration (250–1,100 μM) in human feces (62), it has minimal effects on the mouse AhR (51). In contrast, most of the indole derivatives, such as 3-methylindole (skatole), TPM, IAA, indole-3-aldehyde (IAld), indole-3-acetaldehyde (IAAld), indoleethanol, indole-3-pyruvate (IPyA), indole-3-propionic acid (IPA), and indoleacrylic acid (IA), are considered bioactive AhR ligands in the gut (**Figure 3**). Indole is exclusively synthesized from tryptophan by tryptophanase in ~85 gram-positive and gram-negative bacterial species, including *Bacteroides* spp., *Clostridium* spp., and *Escherichia coli* (73, 74). Alternatively, bacterial toluene *o*-monooxygenase activity can also convert indole to hydroxyindoles (113), although their prevalence in the intestinal community is unknown. The production of TPM from tryptophan by decarboxylation is mediated by members of the Firmicutes phylum (*Clostridium sporogenes* and *Ruminococcus gnavus*) in the human gut (142). IPyA is a major intermediate for the production of IAAld and IPA from tryptophan and is carried out by the catalytic activity of the aromatic amino acid aminotransferase (ArAT) enzyme in many bacterial species, including *Lactobacillus*. Lactobacilli can further convert IPyA into IAld by ArAT (154). Several species containing the phenyllactate dehydratase gene cluster (fldABC), such as *C. sporogenes*, *C. cadaveris*, and *Peptostreptococcus russellii*, can synthesize IA and IPA from IPyA (29, 144). In addition, tryptophan can be directly converted into indole-3-acetamide by the enzyme tryptophan 2-monooxygenase expressed in Actinobacteria (38, 128, 156). Indole-3-acetamide can be further catalyzed into IAA by indoleacetamide hydrolase (79).

REDUCED AHR LIGANDS IN INTESTINAL PATHOGENESIS

Mounting evidence indicates that reduced blood and fecal levels of gut microbiota–derived AhR ligands are associated with many human diseases, such as IBDs, obesity, type 2 diabetes, and high blood pressure (70, 92, 95). This is consistent with the fact that the diversity of gut microbiota is decreased in these patient populations, and the community of gut microbiota is altered compared with healthy individuals (21). Metagenomic analyses further reveal that the bacterial metabolism of tryptophan is reduced in IBD (117). Current studies provide some insights on species or strains of gut microbiota that are associated with reduced tryptophan metabolism in IBD. For example, the abundance of *Lactobacillus reuteri* and *Allobaculum stercoricanis* is decreased in Card9$^{-/-}$ mice, which are highly susceptible to dextran sodium sulphate (DSS)-induced colitis. Culture supernatants from the two bacteria strongly activate the AhR, possibly attributed to IAA or IAld (70, 154). Importantly, IBD-associated single-nucleotide polymorphism within CARD9 is correlated with reduced AhR activation by microbiota-derived metabolites (70). Supplementation of *Lactobacillus* strains, isolated from wild-type (WT) mice, can increase AhR ligand production and rescue susceptibility to DSS-induced colitis in mice with genetically associated dysbiosis (70). In addition, *Bacteroides fragilis*, which produces IAA or indole-3-lactate (110), is reduced among the top 10 species exhibiting the greatest changes in IBD individuals (80). As discussed above, *Clostridium* spp. can convert tryptophan into diverse AhR ligands, including TPM, IPA, IA, and indole-3-lactate. Interestingly, one study found a decrease in 17 human-derived *Clostridium* spp. strains in IBD individuals, and 5 out of the 17 strains were significantly reduced in individuals with ulcerative colitis (7). Colonization of the 17 strains or *Bacteroides fragilis* in germ-free mice induces Treg cells that produce interleukin-10 (IL-10) and suppresses experimental colitis (7, 112). Interestingly, AhR activation also induces IL-10–producing Treg cells (35). Monocolonization of germ-free mice with *C. sporogenes* results in production of IPA (141), and strains belonging to the *Clostridium* genus are more highly enriched in control mice compared with mice exhibiting 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis (16). Metagenomic analysis in IBD patients reveals a reduced presence and abundance of the fldABC, which is responsible for synthesizing IA and IPA from IPyA, as noted above. Oral gavage of *P. russellii*, containing the fldABC, enables the

production of IA, resulting in mitigation of DSS-induced colitis in specific-pathogen-free mice (144). These studies suggest that administration of AhR ligand–producing gut microbes can colonize the gut to produce AhR ligands in mice and provide protection against colitis. It will be interesting to determine if supplementation of tryptophan-catabolizing bacteria can colonize the human microbiome ecosystem, particularly in IBD patients, and generate AhR ligands that ameliorate gut inflammation and rescue the microbiome dysbiosis gradually.

REGULATION OF GUT MICROBES BY AHR SIGNALING

The gut microbial regulation of host AhR signaling is not unidirectional since modulation of AhR activation can also contribute to alterations in the gut microbial community. For instance, dietary exposure to 2,3,7,8-tetrachlorodibenzofuran can produce a shift from Firmicutes to Bacteroidetes in the gut microbiota, thereby altering host metabolism (155). Moreover, treatment with TCDD and 3,3′,4,4′,5-pentachlorobiphenyl has been linked to dysbiosis of gut microbiota and the deterioration of gut health in zebrafish and mice (102, 129, 133). In contrast, AhR activation by natural AhR ligands (e.g., I3C) has been shown to prevent pathogenic gut microbial dysbiosis by altering gut microbiome composition in mice with colitis (16, 17). This is consistent with reports that depletion of AhR ligands in the diet decreased α diversity of gut microbiota, while I3C supplementation restored microbiota composition (15). Similarly, in AhR null mice, significant alterations in phyla abundance of gut microbiota accompanied by functional shifts in bacterial metabolism have been observed, and these predispose the host to chronic inflammation and/or a metabolic stress state (68, 93). The regulation of AhR signaling on the composition of gut microbiota is likely mediated by affecting the maintenance of gut immune cells, including intraepithelial lymphocytes, innate lymphoid cells (ILCs), Th17 and Treg cells, and gut barrier functions. For instance, AhR activation by indole derivatives from gut microbiota skews the differentiation toward ILCs and Treg cells and inhibits ILC2 and Th17 cells (44, 75). Treg and ILC3 cells are required to maintain the tolerogenic immune response in homeostasis and prevent the excessive immune attack to symbionts (100). Interestingly, an aberrant expansion of segmented filamentous bacteria was observed in the feces of AhR null mice and contributed to the increased Th17 cell responses in the gut (107). In addition, the epithelial barrier separates host immune cells from gut lumen contents and reduces the invasion of commensal bacteria into the underlying mucosal layer to induce systemic inflammation, disrupting the balance of host and gut symbionts. AhR signaling plays a crucial role in regulating the intestinal barrier function, which is discussed in the following section. Therefore, the AhR acts at the bidirectional interface between the host and gut microbial communities and their AhR active metabolites. In the following section, we review how dysregulated AhR signaling contributes to IBDs and colon cancer.

THE AHR AND INFLAMMATORY BOWEL DISEASE

IBDs, including Crohn's disease and ulcerative colitis, are common chronic inflammatory disorders of the GI tract that usually involve severe diarrhea, abdominal pain, fatigue, and weight loss. Dysbiosis, impaired barrier integrity, and dysregulation of the immune system, such as excessive production of proinflammatory cytokines and massive immune cell infiltration, are commonly associated with IBDs (145). Interestingly, fecal extracts from individuals with either Crohn's disease or ulcerative colitis exhibit an impaired ability to activate the AhR due to decreased levels of IAA (70). This is consistent with the reduction in circulating microbiota-derived AhR ligands in individuals with IBD (92). Recently, AhR knockout (KO) mouse models and pharmacological modulators of the AhR have been used to probe the effects of the AhR on immune regulation and its role in IBD. For example, AhR null mice are more susceptible to lipopolysaccharide

(LPS)-induced, DSS-induced, or T cell–mediated colitis, while AhR activation by supplementation with AhR agonists can ameliorate immune responses and accelerate recovery from colitis (34, 65, 92).

The protective effects of AhR ligands in relation to intestinal barrier function appear to converge on the regulation of immune cell responses and the maintenance of gut barrier integrity. Emerging studies have demonstrated that the AhR participates in cell fate decisions involving many immune cell types, including ILCs and Th17, Treg, and Tr1 cells, and directly or indirectly affects the generation of key cytokines (44) that play an important role in shaping the interactions among immune cells, epithelial cells, and gut microbiota in the context of health and disease. A major focus of immune regulation by the AhR involves the modulation of IL-10 and IL-22 production and their signaling pathways (**Figure 4**). These cytokines are involved in the resolution of intestinal inflammation and promote wound healing in IBD (91, 160).

THE AHR AND IL-22

In the gut, many different types of immune cells, including ILCs, natural killer (NK) T cells, γδ T cells, Th17 cells, neutrophils, and $CD4^+$ T cells, are capable of producing IL-22 (101). Whole-body AhR-deficient mice exhibit reduced IL-22 expression and ROR γt^+ ILC3 cell development as well as increased intestinal Th17 cell numbers. Selective depletion of IL-22 producing ILCs in $Rag1^{-/-}$ mice after adoptive T cell transfer promotes Th17 cell response, suggesting a role for the AhR in balancing ILC and Th17 cell responses in the gut (107). This is consistent with the fact that AhR activation by FICZ treatment ameliorates TNBS-, DSS-, and T cell transfer–induced colitis in part by upregulating IL-22 and downregulating the expression of proinflammatory cytokines, such as IFN-γ, IL-17α, and tumor necrosis factor alpha (TNF-α) (92). Intestinal lamina propria mononuclear cells from patients with IBD treated with FICZ also exhibit decreased IFN-γ and increased IL-22 production (92). Interestingly, AhR activation by TCDD decreases methylation of the CpG island of FoxP3, a master regulator in the development of Treg cells, as well as demethylation of the IL-17 promoter in mesenteric lymph nodes and lamina propria cells during colitis, thereby inducing Treg cell differentiation and inhibiting Th17 cell production (124). Similarly, alpinetin, a plant-derived AhR agonist, has been shown to decrease the methylation level of FoxP3 in $CD4^+$ T cells by promoting the expression of miR-302, subsequently reducing DNA methyltransferase 1 expression (83). Thus, the AhR can control Treg cell differentiation by directly targeting the expression of FoxP3 (109), affecting IL-22 production. In addition, the AhR can directly control the expression of IL-22. Upon binding to DREs in the promoter of IL-22, the AhR cooperatively interacts with RAR-related orphan receptor gamma (RORγt) and signal transducer and activator of transcription 3 (STAT3) to promote IL-22 expression in mouse $CD4^+$ T cells and ROR γt^+ ILCs (108, 149). The regulation of AhR expression level can also modulate IL-22 production. For example, miR-15a/16-1 has been shown to regulate the expression of the AhR, and overexpression of miR-15a/16-1 decreases IL-22 production by inhibiting AhR expression in $CD4^+$ T cells (159).

Neutralizing IL-22 signaling by anti-IL-22 antibody exposure can suppress recovery from DSS-induced colitis, while IL-22 administration promotes crypt regeneration and recovery from DSS (24, 130, 132). These findings suggest that IL-22 treatment might be a possible therapeutic strategy for treating IBDs, a point that was recently challenged when IL-22 was shown under some conditions to initiate a pathological endoplasmic reticulum stress response in colonic epithelial cells (106). Interestingly, AhR activation by I3C or indigo naturalis (an AhR-active traditional Chinese medicine) decreases TNBS- or DSS-induced colitis and ameliorates microbial dysbiosis due to colitis in an IL-22-dependent manner (16, 63). Importantly, indigo naturalis or I3C treatment

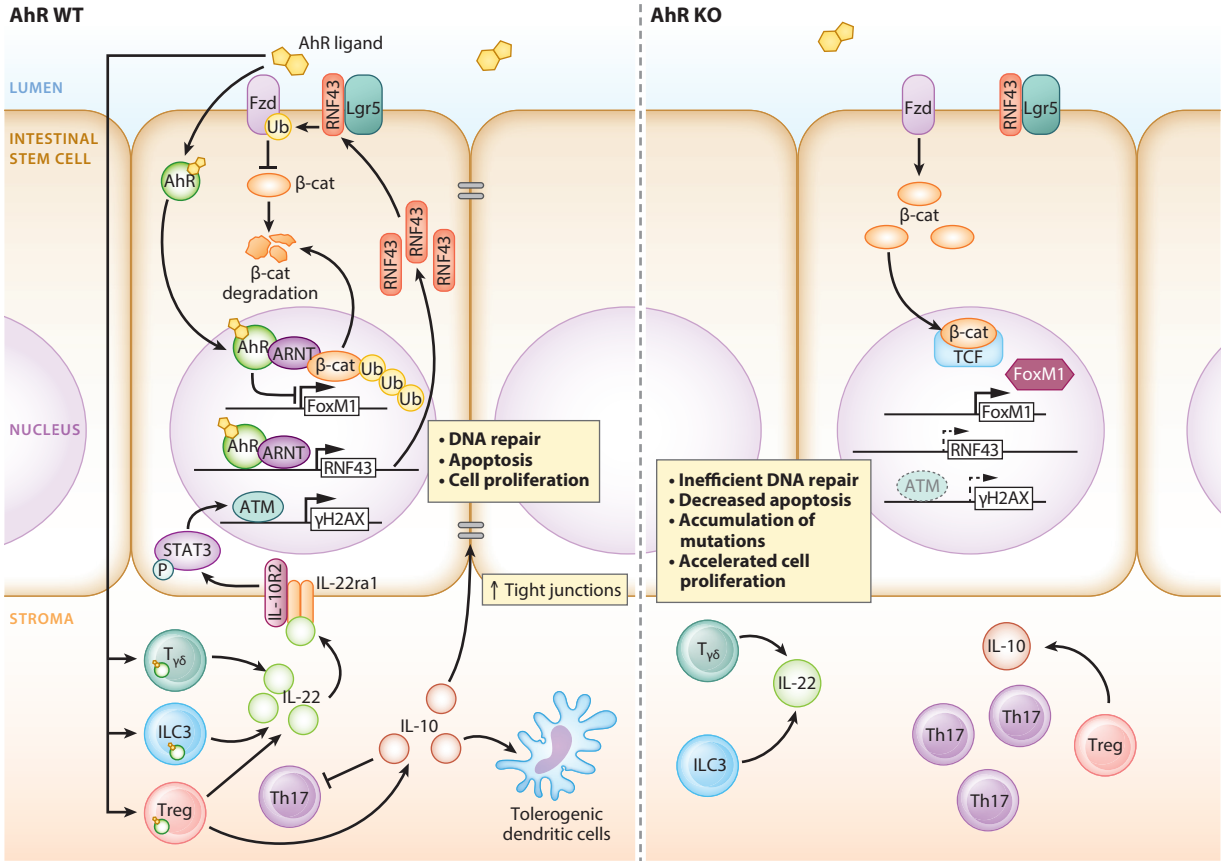


Figure 4

The AhR regulates colon tumorigenesis. Dietary/microbiota-derived AhR ligands can be directly sensed by colonic epithelial cells and resident immune cells in the gut lamina propria. In the intestinal mucosa, recent evidence suggests that an activated AhR is recruited to the promoter region of RNF43, a negative Wnt regulator, and potentiates RNF43 expression, in turn suppressing Wnt signaling and cell proliferation and self-renewal of intestinal stem cells. In addition, a ligand-bound AhR may act as an E3 ligase of β-catenin and induce its ubiquitination and proteasomal degradation, downregulating Wnt signaling, which is controversial among different groups of researchers and requires further investigation. Moreover, the AhR acts as a transcriptional suppressor of FoxM1 and regulates intestinal stem cell proliferation. In addition, cogent evidence indicates that upon ligand binding, the AhR can interact with DREs within the promoter regions of IL-10 or IL-22 and promote their production in gut ILCs, DCs, Treg cells, and γδ T cells. This is noteworthy, because elevated IL-10 can promote the generation of tolerogenic DCs and Treg cells and inhibit Th17 cell differentiation, leading to downregulation of proinflammatory cytokines, which mediate gut microbial composition and host homeostasis. In addition, IL-22 binding to the IL-22 receptor in ISCs induces phosphorylation of STAT3 and DDR following genotoxic insult, thereby promoting the integrity of ISCs. Loss of the AhR or limited AhR ligand availability renders ISCs defective to initiate DDR in response to genotoxins due to reduced IL-22 production, resulting in the accumulation of DNA mutations, and promotes ISC proliferation and the propagation and fixation of DNA mutations within intestinal epithelial cells. In combination with carcinogen exposure, loss of the AhR or limited AhR ligand availability promotes colon tumorigenesis. Abbreviations: AhR, aryl hydrocarbon receptor; ATM, ataxia telangiectasia mutated; β-cat, β-catenin; DCs, dendritic cells; DDR, DNA damage response; DREs, dioxin response elements; IL, interleukin; ILCs, innate lymphoid cells; ISCs, intestinal stem cells; KO, knockout; STAT3, signal transducer and activator of transcription 3; TCF, transcription factor; WT, wild type.

are effective for treating IBD patients (61, 94), partly by upregulating IL-22, implying that targeting the AhR could modulate the amplitude and duration of IL-22 signaling to treat IBD patients.

THE AHR AND IL-10

IL-10 is another potent anti-inflammatory cytokine affected by the AhR. Several immune cell types can produce IL-10, such as monocytes, macrophages, dendritic cells, NK cells, $CD4^+$ and $CD8^+$ T cells, and neutrophils (140) (**Figure 4**). The resulting IL-10 levels affected by the AhR could therefore be the consequence of IL-10 production or changes in the number of IL-10-producing cells. Therefore, AhR-dependent regulation of immune cell differentiation, including ILCs and Th17, Treg, and Tr1 cells (44), can affect the generation of IL-10. For example, AhR activation induces Tr1 and $FoxP3^+$ Treg cell differentiation and promotes IL-10 production (6, 35). NK cells from AhR null mice exhibit an impaired production of IL-10 (138). Similarly, reduced IL-10 expression has been observed in LPS-induced $AhR^{-/-}$ macrophages (159). Consistent with these observations, indigo naturalis can induce the expression of IL-10 and IL-22 in the colonic lamina propria lymphocytes by activating the AhR, thereby suppressing DSS-induced colitis (63). In addition, administration of the AhR agonist ITE induces IL-10-expressing Tregs and suppresses TNBS-induced colitis in humanized mice (41). As with IL-22, the AhR also directly regulates the expression of IL-10 both in mouse and human Tr1 cells in synergy with c-Maf (6, 35). AhR activation by Kyn and IPA robustly induces IL-10R1 expression in intestinal epithelial cells (3, 71).

Although the AhR and its ligands, such as tryptophan metabolites, protect against DSS-induced colitis and resistance to infection by *Candida albicans* (61), other AhR-active compounds are reported to be proinflammatory. For example, oxazalone has been identified as an AhR ligand that induces CD1d-dependent inflammation in mouse models of colitis (48, 55). Moreover, the toxicities induced by oxazolone in vivo are mitigated in mice where the AhR is silenced in epithelial cells, and in vivo and cell culture studies show that oxazolone decreases IL-10 (27). Thus, the AhR-dependent proinflammatory activity of oxazolone contrasts with the anti-inflammatory effects of most other AhR ligands, suggesting that oxazolone is a SAhRM with possible AhR antagonist activities for inflammatory pathways. The reasons for the AhR-ligand-dependent activity of oxazolone are unclear and suggest that the potential effects of structurally diverse AhR ligands in the intestine cannot necessarily be predicted or assumed.

THE AHR AND GUT INTEGRITY

Compromised mucosal barrier function, such as increased intestinal permeability, is observed in many IBD patients, and there is evidence that AhR signaling is involved in maintaining gut barrier function. For example, ligand-dependent AhR activation using FICZ attenuates TNBS- or DSS-induced colitis by enhancing gut barrier functions (71, 125, 152). AhR signaling can directly regulate the expression of the apical junctional complex, including occludin, ZO-1, claudin 4, and E-cadherin, in intestinal epithelial cells (119, 125, 152). Although the precise mechanisms have not been elucidated, recent data suggest that the AhR-Nrf2 axis or the inactivation of actin-regulatory protein ezrin/myosin IIA mediates apical junctional complex regulation (119, 125). In addition, AhR signaling participates in regulation of the gut immune responses, such as increasing the production of IL-10 to indirectly control the production of tight junction proteins (5) or decreasing the detrimental effects of proinflammatory cytokines on disruption of the tight junction proteins (125, 152). In addition to cytokine production, components involved in cytokine signaling contribute to gut barrier functions. AhR activation promotes epithelial wound healing by upregulating

expression of IL-10R1 in intestinal epithelial cells and decreases gut permeability caused by DSS (71). AhR signaling is also reported to affect the status of STAT1, STAT3, and STAT5, downstream mediators of cytokine signaling (44, 153). Little is known about how AhR signaling regulates the additional components mediating cytokine transduction and contributes to gut barrier functions. Cytokine signaling can impact the maintenance and differentiation of intestinal stem cells, possibly by affecting crypt regeneration (13, 77). Moreover, the self-renewal and differentiation of intestinal stem cells can be modulated by the AhR directly (47, 88). Intestinal-specific AhR KO inhibits the differentiation of goblet cells (88), which secrete MUC2 to form a physical barrier for preventing pathogen invasion. Interestingly, MUC2 KO mice exhibit clinical colitis symptoms and an impairment of the gut barrier lining (137). In an extension of this work, inoculation of IPA-producing *P. russellii* increases goblet cell number and mucin fucosylation (144), indicating that AhR activation by IPA promotes goblet cell differentiation. AhR signaling is also involved in intestinal epithelial repair programming after injury; for example, AhR activation increases the production of prostaglandin E_2 (134), which promotes the formation of wound-associated epithelial cells (90). Surprisingly, intestinal-specific AhR KO has no effect on gut permeability in colitis (47), which is in contrast to the increased gut permeability observed in AhR null mice (125), suggesting that nonepithelial AhR signaling is required for protection of gut permeability during colitis. Therefore, regulation of gut barrier integrity by the AhR represents the coordinated consequence of multiple mechanisms involving epithelial cells, immune cells, and other mesenchymal populations.

THE AHR AND COLON CANCER

Studies from animal models including rats, mice, and hamsters provide evidence that chronic activation of the AhR promotes tumor incidence in multiple tissue sites (66). Recent epidemiologic studies show that higher blood levels of TCDD are associated with increased risk of cancers in all sites combined and several specific cancers, including lymphoma and cancers of the small intestine and liver (147, 150). Thus, TCDD is now classified as a Group 1 human carcinogen on the basis of increased risk of all cancers combined (9). However, laboratory animal studies demonstrate that the AhR can function as a tumor-type dependent promoter or inhibitor of carcinogenesis, indicating that SAhRMs acting as agonists or antagonists have potential as cancer chemotherapeutic drugs (67, 116). Emerging studies using mouse models have suggested that AhR signaling plays an important role in regulating intestinal cancer (28, 47, 53, 64, 88).

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death in men and women combined in the United States. The lifetime risk of developing CRC is slightly lower in women than in men (4). The risk of developing CRC is affected by both environmental and genetic factors (45). Since the AhR acts as an environmental sensor, it is capable of integrating external environmental stimuli and host responses to modulate intestinal epithelial cells. Kawajiri et al. (64) were the first to report that global deletion of the AhR promotes spontaneous development of cecal tumors and expression of β-catenin and c-myc in epithelial cells of the ileum, colon, and cecum. In addition, administration of the natural AhR ligands I3C or DIM significantly reduced the number of tumors in the cecum and small intestine and dramatically downregulated β-catenin level in $Apc^{Min/+}$ mice, but not in $Apc^{Min/+}AhR^{-/-}$ compound mice (64). Consistent with these findings, global AhR KO enhances tumor incidence and multiplicity in colitis-associated colorectal tumorigenesis, and supplementation of I3C reduces the number of colorectal tumors in WT, but not in AhR null mice (28). Of note, no changes in β-catenin or c-myc were observed, and spontaneous tumor development was extremely low and did not reach statistical significance in AhR null mice (28). This is consistent with a recent study

using human colon cancer cell lines, where AhR activation failed to recruit CUL4B or β-catenin to form the complex for subsequent β-catenin degradation and the dampening of Wnt signaling (122).

Inflammation plays a crucial role in intestinal tumorigenesis, and AhR signaling substantially influences the development of immune cells (described in the section titled The AhR and Inflammatory Bowel Disease). IL-22, a potential therapeutic for chronic inflammatory diseases, is required for initiation of the DNA damage response (DDR) following chromosomal damage, and deletion of the IL-22 receptor in colonic stem cells impairs DDR-induced apoptosis, thus promoting the accumulation of mutations (42) (**Figure 4**). This is noteworthy, because global AhR KO mice produce less IL-22 and accumulate more DNA mutations after exposure to a carcinogen, e.g., azoxymethane (28). Interestingly, germ-free AhR null mice, or compound mice lacking the AhR and apoptosis-associated speck-like protein containing a CARD, exhibit decreased tumor development compared with specific-pathology-free AhR null mice (53). Therefore, the mechanism by which global AhR KO enhances intestinal tumorigenesis in AhR KO mice may be linked to a perturbation in immune function or dysregulated intestinal epithelial cells or both. Recent evidence indicates that intestinal-specific deletion of the AhR (Villin-Cre) promotes carcinogen-induced and colitis-associated colon tumorigenesis (36, 47, 88). Intestinal-specific AhR loss also enhances intestinal stem cell expansion, impairs intestinal stem cell differentiation (e.g., reduced goblet cells and absorptive enterocytes), and promotes cell proliferation in homeostasis and colitis (47, 88). Further analysis reveals that the AhR can interact with the promoter of the Wnt negative regulator, RNF43, and enhance its expression, consequently destabilizing Wnt signaling, as evidenced by decreased β-catenin levels and downstream target genes (88). Another study reported that intestinal-specific AhR KO promotes colitis-associated colon tumorigenesis by transcriptionally upregulating FoxM1, a master regulator of cell proliferation and cell cycle progression, and this response was independent of Wnt signaling. FoxM1 suppression recapitulates the effects of AhR activation and attenuates AhR KO–mediated phenotypes (47). It is noteworthy that DIM, an AhR agonist, effectively downregulates FoxM1 in various breast cancer cell lines and inhibits breast cancer cell growth (2). In addition, FoxM1 expression is transcriptionally suppressed by AhR activation in human colonic organoids (47), implying that dietary intervention targeting AhR signaling may be a promising therapeutic strategy for treating colon cancer.

With respect to colon cancer cell culture models, whether the AhR inhibits or promotes tumor growth remains controversial. For example, AhR activation by two piperidone analogs of curcumin, RL66 and RL118, promotes apoptosis in human DLD1, HCT116, LS513, and RKO colon cancer cell lines (87). AhR knockdown mediated by small interfering RNA promotes growth of HCT116 and HT29 cells (54). In addition, FICZ treatment decreases cell proliferation by inducing G1 cell cycle arrest but exhibits no effect on cell apoptosis in human LoVo colon cancer cells (151). Reduced cell proliferation and induction of p53, retinoblastoma, p21, and regucalcin are also observed in RKO cells treated with TCDD (148). However, in H508 and SNU-C4 human colon cancer cell lines, treatment with TCDD induces phosphorylation of Src, subsequently increasing phosphorylation of epidermal growth factor receptor and extracellular signal-regulated kinase 1/2, thereby promoting cell proliferation (146). The variable results from these studies suggest that phenotypic response is highly dependent on cell line sources, tumor types, and AhR ligands. Future studies are required to determine the different roles played by the AhR during colon tumor initiation and progression.

AhR deficiencies in humans are rare; however, there are reports of an association between AhR mutations and retinitis pigmentosa, autosomal foveal hypoplasia, and infantile nystagmus (85, 158). Currently, there is no clear association between somatic AhR mutations and CRC. The regulation of AhR signaling is mainly ascribed to AhR expression level and ligand

availability. Interestingly, there is preliminary evidence that AhR expression is altered in human CRC, compared with normal tissues (54, 64). For example, the expression of the AhR is upregulated in colonic tumors compared with normal tissue based on the Xena platform (**https://xenabrowser.net/**). Limiting AhR ligand availability promotes colitis-associated colorectal tumorigenesis in $R26^{LSL\text{-}Cyp1a1}$Villin-Cre compound mice, while supplementation with I3C suppressed colorectal tumorigenesis in those mice (88). Therefore, the results from animal models suggest that the AhR should be considered a chemoprevention target to reduce intestinal cancers.

PRECISION NUTRITION

AhR signaling plays a key role in shaping the interactions among intestinal immune cells, epithelial cells, and gut microbiota and regulating host response to IBDs and intestinal tumorigenesis. The modulation of AhR signaling is mainly linked to changes in AhR expression levels and ligand availability. For example, chronic reduction of cellular AhR activation has been linked to suppression of AhR ligand production in patients with numerous chronic diseases, including IBD, obesity, type 2 diabetes, and high blood pressure (70, 92, 95). The defect in AhR agonist production appears to be in part the result of an impaired capacity of gut microbiota to metabolize tryptophan into AhR agonists in mice and humans (70, 95). These findings suggest that the substantial interindividual variability in AhR-mediated response to dietary exposures can be ascribed to the heterogeneity of microbiome communities in humans. Moreover, polymorphisms of the human AhR may also contribute to individual sensitivity to AhR ligand exposure (69), and several AhR single-nucleotide polymorphisms have been significantly associated with many diseases, including IBDs (43, 50, 78). In addition, the AhR may be differentially expressed across different tissues, cell types, or cell contexts. For instance, AhR expression is slightly enriched in colonic stem cells, compared with progenitor cells (47), and reduced in the colonic mucosal tissues from patients with Crohn's disease, compared with healthy controls (92). Thus, it is possible that specific cell types or individuals with distinct comorbidities will respond differently to AhR ligand supplementation. Precision nutrition is an approach that aspires to offer individual tools to personalize dietary and lifestyle practices for optimal health (111), and future research should explore relationships between host AhR biology and microbiome changes in response to specific probiotics and dietary prebiotic intervention. In addition, it is important to develop (*a*) a biomarker to measure or predict individual response to AhR ligand dietary supplementation and (*b*) a gut microbiome regimen that produces AhR-active compounds.

Administration of AhR ligands or their enhanced microbial production not only can restore AhR signaling to regulate host physiology but also may affect the composition of the gut microbiome community. For example, I3C supplementation prevents pathogenic gut microbial dysbiosis and alters gut microbiome composition in mice with colitis (16, 17). It will be interesting to determine the longitudinal dynamic changes in microbiome composition, function, and microbial metabolites in response to diet or gut microbe intervention targeting the AhR in the context of health and disease. This will provide translational guidance and mechanistic insight into how targeting the AhR will ultimately improve the general well-being of the population, since dysbiosis is linked to many chronic diseases. Current studies from mouse models support our rationale that the AhR is a promising therapeutic or chemopreventive target for treating inflammatory diseases, including IBD, and intestinal tumorigenesis.

SUMMARY AND FUTURE DIRECTIONS

The AhR is an evolutionarily conserved ligand-activated transcription factor. In the past several decades, advances in studies on AhR biology have extended its initially identified function in

responding to toxic PAHs to its ancestral roles in the development of chemosensory neural systems, immunity regulation, and beyond. Gut microbiota and diet are major sources of AhR ligands that influence the whole body, including gut, liver, brain, and the immune system. Many human diseases are associated with decreased circulating levels of AhR ligands, partly due to dysbiosis. The cause-and-effect relationship between diseases and decreased AhR ligand availability or enriched AhR-producing microbiota that promote human health requires further elucidation. Interestingly, the ability of AhR signaling to regulate self-renewal and differentiation of intestinal stem cells intrinsically or extrinsically has recently been brought into the spotlight. Advances in studying AhR-mediated regulation of stem cells may provide additional insight on the role of the AhR as a target for chemoprevention. Since AhR function is cell type and context specific, the protective or deleterious roles of the AhR and its ligands require empirical assessment. Future research on the potential health impacts of dietary/microbiota-derived ligands is required in order to favorably modulate both the amplitude and duration of AhR signaling for treating chronic diseases.

The human AhR has different ligand binding affinities for select AhR ligands (**Figure 2**), including indole, compared with the mouse AhR (51). AhR-dependent biology is also complicated by the fact that promoter regions of potential AhR gene targets vary from species to species, leading to the possibility that studies in animal models do not fully mimic human responses. Thus, humanized models are needed to address some of the well-known discrepancies between the murine and human AhR. Importantly, a recent study using humanized mice demonstrates that nontoxic AhR ligand ITE supplementation provides protection against colitis by inducing Treg cells (41).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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