Advances in the Regulation of Intestinal Inflammation by the Aryl Hydrocarbon Receptor (Postprint)

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Abstract

Aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays a crucial role in environmental toxin responses, xenobiotic metabolism, and immune regulation. Recent studies have demonstrated that AhR is a key factor involved in immune regulation, and its modulation of inflammatory bowel disease (IBD) has emerged as a current research focus. This article reviews the structure of AhR, its ligands, signaling pathways, and recent advances in understanding AhR' s involvement in regulating intestinal inflammation, providing new insights for the treatment of IBD.

Full Text

Research Progress on Aryl Hydrocarbon Receptor Regulation of Intestinal Inflammation

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Abstract: The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays important roles in environmental toxin metabolism, xenobiotic metabolism, and immune regulation. Recent studies have revealed that AhR is a key factor in immune regulation, and its modulation of inflammatory bowel disease (IBD) has become a hot topic in current research. This article reviews the latest research progress on AhR structure, ligands, signaling pathways, and AhR involvement in regulating intestinal inflammation, providing new insights for IBD treatment.

Keywords: aryl hydrocarbon receptor; ligands; immunomodulation; inflammatory bowel disease

Polycyclic aromatic hydrocarbons (PAHs) are important environmental pollutants with strong carcinogenicity. Poland et al. [1] used radiolabeled ligand binding assays to demonstrate that a receptor could mediate the toxic effects of PAHs, which was named the aryl hydrocarbon receptor (AhR). Previous research focused primarily on AhR' s metabolic response to environmental aromatic hydrocarbons, but recent studies have found that AhR is a key factor in immune regulation. AhR is present in most immune cells and participates in regulating cell proliferation, differentiation, and cytokine secretion in adaptive and innate immune cell subsets [2]. AhR plays an important role in autoimmune regulation of regulatory T cells (Treg), T helper 17 cells (Th17), intestinal intraepithelial lymphocytes (IELs), and innate lymphoid cells (ILCs). Increasing evidence indicates that AhR plays an important role in regulating ulcerative colitis (UC), Crohn' s disease (CD), inhibiting intestinal infections, and maintaining intestinal health, making its regulation of intestinal inflammation a current research hotspot.

1 AhR Primary Structure

AhR is a large molecular weight protein, a transcription factor composed of 805 amino acids, belonging to the PAS (Period-Aryl hydrocarbon receptor nuclear translocator-Single-minded) subfamily of the ligand-dependent basic helix-loop-helix (bHLH) superfamily [1]. All mammalian bHLH-PAS proteins have similar molecular structures, indicating high conservation during AhR evolution. The AhR structure from N-terminus to C-terminus is mainly divided into three parts: bHLH, PAS, and C-terminal glutamine-rich region (Figure 1 [Figure 1: see original paper]).

The bHLH domain is highly conserved and essential for basic physiological activities. The PAS domain includes two repeat sequences, PAS-A and PAS-B [3]. The C-terminus shows species differences and polymorphism, with varying protein lengths [4]. The N-terminal bHLH domain facilitates DNA binding and protein dimerization. The C-terminal region of AhR receptor, comprising approximately 50% of the protein, is rich in glutamic acid and has transcriptional activation function, protecting binding sites for related co-factors such as E1A binding protein p300 (P300) and steroid receptor coactivator-1 (SRC1). The PAS-B region serves as the ligand-binding domain [5]. The PAS domain primarily functions in DNA recognition, ligand binding, and interaction with molecular chaperone proteins. The PAS-B structural domain overlaps with the AhR ligand-binding region, conferring protein-protein interactions, such as with heat shock protein 90 (HSP90) and retinoblastoma protein (pRb) [6-7].

Figure 1 Functional domains of AhR [3]. However, since the advanced structure of AhR has not been resolved, research on its ligand binding and transport

mechanisms has been limited. In recent years, researchers have used homology modeling to obtain the three-dimensional structure of the AhR ligand-binding region [8]. This structure consists of 5 -sheets and 1 -helix, and contains a hydrophobic ligand-binding pocket. It is currently believed that aromatic amino acid residues near the ligand-binding pocket, such as glutamine (Gln) 377, phenylalanine (Phe) 318, Phe 289, cysteine (Cys) 294, Gln 317, and threonine (Thr) 283, interact with the aromatic rings of ligands (all ligands have aromatic ring characteristics) through stacking forces between their aromatic side chains and the ligand' s aromatic ring, achieving ligand-receptor binding. Among these, Phe 318 plays a critical role in ligand binding [8-9].

2 AhR Ligands

AhR requires ligand activation to exert its functions. Its ligands must have at least aromatic compound structural features and hydrophobicity. Traditionally, AhR ligands mainly include two categories: halogenated aromatic hydrocarbons (HAHs) and polycyclic aromatic hydrocarbons (PAHs). However, increasing studies show that some synthetic and natural compounds with significantly different structures can also bind to AhR, indicating that AhR has high ligand diversity [10]. AhR ligands mainly include exogenous and endogenous ligands. Table 1 summarizes representative AhR ligands [10-15], which include tryptophan secondary metabolites (e.g., 6-formylindolo[3,2-b]carbazole [FICZ]), food-derived ligands (e.g., quercetin, genistein, daidzein [flavonoids], lipoxin A4/prostaglandin G [arachidonic acid metabolites]), and synthetic ligands (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD], 2,3,7,8-tetrachlorodibenzofuran, 3,3' ,4,4' ,5-pentachlorobiphenyl, 3-methylcholanthrene, benzo[a]pyrene, 2-(1' H-indole-3' -carbonyl)thiazole-4-carboxylic acid methyl ester [ITE], kynurenic acid, xanthurenic acid, 6,12-diformylindolo[3,2-b]carbazole [dFICZ], indolo[3,2-b]carbazole/3,3-diindolylmethane).

3 AhR Signal Transduction Process

In the absence of ligand, AhR forms a complex with co-chaperone protein 23 (p23), HSP90, and hepatitis B virus X-associated protein 2 (XAP2), existing in the cytoplasm. AhR ligands enter cells through passive transport, active transport, facilitated diffusion, and pinocytosis depending on their molecular weight [16]. When a ligand binds to AhR, the complex undergoes conformational changes and binds to nuclear importin , controlling nuclear-cytoplasmic shuttling of the complex [17]. In the nucleus, AhR forms a heterodimer with the aryl hydrocarbon receptor nuclear translocator (ARNT). The activated AhR-ligand-ARNT heterodimer specifically binds to dioxin-responsive elements (DRE), also called xenobiotic-responsive elements (XRE), on DNA fragments to exert transcriptional activity. The XRE of downstream regulated genes contains a common core sequence (N-GCGTG-C).

AhR activation induces cytochrome P-4501A1 (CYP1A1), which oxidizes AhR

ligands and leads to metabolic clearance and detoxification of ligands. When the AhR-ligand complex enters the nucleus and interacts with the XRE/DRE region, the ligand-AhR complex is removed from the nucleus after about 4 hours and degraded by related enzymes such as CYP1A1. However, when CYP1A1 expression is abnormal, it depletes intranuclear AhR ligands, creating a state similar to AhR deficiency, thereby affecting subsequent gene expression and causing pathological changes [18]. There are also two independent pathways that prevent excessive AhR activation: the ubiquitin/proteasome pathway degrades and transports activated AhR out of the nucleus, and the aryl hydrocarbon receptor repressor (AhRR) competes with AhR for ARNT binding. Activated AhR can induce AhRR expression, achieving negative feedback regulation of AhR pathway activity (Figure 1) [19].

Figure 1 AhR signaling process. Ligand enters cell → Receptor binds ligand → Increased cytochrome P4501A1. AhR: aryl hydrocarbon receptor; XAP2: hepatitis B virus X-associated protein 2; HSP90: heat shock protein 90; ARNT: AhR nuclear translocator; DREs: dioxin-responsive element; CYP1A1: cytochrome P-4501A1.

Figure 2 [Figure 2: see original paper] AhR signaling pathway [19].

4 AhR and Inflammatory Bowel Disease (IBD)

Multiple scholars have studied the relationship between AhR and intestinal inflammation. Qiu et al. [20] found that under germ-free conditions, 40% of AhR knockout mice (AhR-/-) developed colitis compared to wild-type mice (AhR+/+), with intestinal tissue showing thickening and fibrosis. The mouse intestines exhibited crypt damage and abscesses, reduced goblet cells, deformed glandular structures, and inflammation extending to the submucosa—typical IBD symptoms. Arsenescu et al. [21] used dextran sodium sulfate (DSS) to induce colitis in mice under germ-free conditions and found that all AhR-/- mice died within 7 days of DSS feeding. Monteleone et al. [22] found that compared to the control group (healthy human colon tissue), AhR mRNA expression abundance was significantly decreased in both UC and Crohn's disease patients, along with weight loss. Subsequent mouse experiments found that adding AhR antagonists exacerbated colitis. These studies demonstrate that AhR is an essential factor for maintaining intestinal health, and that AhR deficiency or blocked expression aggravates intestinal inflammation. AhR must be activated by various ligands to enter the nucleus and exert related functions. Many scholars have conducted extensive research on ligand-activated AhR-mediated intestinal inflammation signals in IBD models [23-26].

Li et al. [27] found that 6-formylindolo[3,2-b]carbazole (FICZ) could alleviate DSS-induced colitis while reducing expression of pro-inflammatory factors interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- (TNF-), and increasing expression of the anti-inflammatory factor interleukin-10 (IL-10). DSS-induced colitis caused decreased intestinal mucosal CYP1A1 expression,

which was significantly increased after FICZ addition. FICZ is a tryptophan photoproduct and an important endogenous AhR ligand that can not only alleviate DSS-induced colitis but also relieve colitis induced by trinitrobenzene sulfonic acid (TNBS) or T cell transfer [25-27]. Many studies have obtained similar results [28-29].

These studies indicate that AhR plays an important role in alleviating inflammatory bowel disease. Both endogenous and exogenous ligands can activate the AhR signaling pathway, and activated AhR can alleviate colitis induced by AhR deficiency, DSS, and TNBS, while non-AhR ligands (such as dimethyl sulfoxide) cannot activate the AhR pathway and cannot alleviate intestinal inflammation.

5.1 AhR Regulation of Intestinal Intraepithelial Lymphocytes and Related Factors

As a key component of the intestinal mucosal immune system, IELs are a unique cell population residing in the small intestinal mucosal epithelium. IELs have natural killer activity and can secrete various cytokines, thus playing an important role in immune surveillance and cell-mediated mucosal immunity. Li et al. [30] found that compared to other lymphocytes, IELs express high levels of AhR. Subsequent AhR gene knockout in mice resulted in 95% loss of small intestinal IELs, with no effect on lymph node or spleen cell proportions and numbers. Compared to wild-type mice, intestinal epithelial cell turnover was affected, thereby impacting mucosal barrier integrity. Along with reduced IEL numbers, AhR-/- mice showed significantly lower levels of granzymes A and B, matrix metalloproteinase-7 (MMP-7), and C-type lectins compared to control and indole-3-carbinol (I3C) supplementation groups. Girardi et al. [31] suggested that AhR knockout leads to strong host immunity, causing immune tolerance in IELs.

Li et al. [30] transplanted T cell receptor (TCR) -enriched intestinal T cells (an IEL subset) from the small intestine to reconstitute intestinal epithelial cells in AhR-/- mice. Bone marrow cells from control groups could reconstitute intestinal IELs in recombination-activating gene-1 (RAG1)-deficient mice, even those deficient in both RAG1 and AhR. However, AhR-/- mouse bone marrow cells could not reconstitute intestinal IELs, indicating that activated AhR is a cell-intrinsic requirement for IELs. AhR activity can directly affect the maintenance of the IEL cell pool.

The authors did not find evidence for AhR directly regulating target genes in IELs, but previous reports showed that mice with mutations in the receptor tyrosine kinase c-kit gene exhibited significantly decreased IEL cell pool capacity, a phenotype very similar to AhR-/- mice. This suggests that AhR may regulate IEL cell pool capacity through c-kit gene expression [32].

Li et al. [30] fed mice standard diet and purified diet for 3 weeks. The purified diet group showed significantly decreased ileal CYP1A1 (AhR target gene) and TCR + CD88 + IEL numbers, while adding 200 mg/kg I3C to the purified

diet restored IEL numbers and alleviated colitis. Granzymes A and B, MMP-7, and C-type lectin levels were significantly higher than in control and gene knockout groups. Studies have shown that IELs directly participate in immune surveillance by inducing apoptosis in infected cells through highly expressed granzymes [33]. MMP-7 mainly participates in intestinal damage repair and the bactericidal action of -defensins [34]. C-type lectins can be directly secreted into the intestinal lumen to eliminate Gram-positive bacteria [35].

In summary, ligand-activated AhR may maintain the IEL cell pool and preserve intestinal epithelial integrity by regulating c-kit gene expression, thereby increasing expression of granzymes A and B, MMP-7, and C-type lectins. These factors work together to enhance intestinal repair and bactericidal capacity, thus alleviating intestinal inflammation.

5.2 AhR Regulation of Intestinal ILCs and Maintenance of Intestinal Mucosal Homeostasis

ILCs are both effector cells of innate immunity and precursor cells of adaptive immunity [36-37]. ILCs are located in the intestinal mucosal lamina propria, intestinal cryptopatches (CP), isolated lymphoid follicles, and Peyer' s patches, mainly expressing the retinoid-related orphan nuclear receptor t-positive (ROR t+) ILC subset. Spits et al. [38] found that ILCs are an important signal for intestinal mucosal homeostasis.

Qiu et al. [20] found that adult AhR knockout mice showed increased programmed death and reduced numbers of ROR t+ ILCs. FICZ addition increased ROR t+ ILC numbers in wild-type and heterozygous mice but had no effect in control mice. Lee et al. [39] found that AhR deficiency significantly decreased ILC (CD4+ROR t+ ILC) numbers. Kiss et al. [40] found that AhR-/- mice showed suppressed ILC expansion and inhibited development of intestinal secondary lymphoid organs, cryptopatches, and isolated lymphoid follicles (ILF). These studies all indicate that AhR signaling participates in regulating ILC proliferation and survival.

Kiss et al. [40] found that AhR-/- mice expressed low levels of kit (mean fluorescence intensity 3500:1000). After feeding mice purified diet, purified diet plus 2 g/kg I3C, and control diet (grain-based diet containing polyphenol glucosinolates), both ligand-supplemented and control groups could activate AhR to upregulate kit gene expression (mean fluorescence intensity 500:2000:2000). This indicates that AhR directly regulates kit transcription. Studies have found that the kit promoter contains typical XRE [41-43]. Chromatin immunoprecipitation analysis revealed that activated AhR binds to the kit promoter, and adding AhR ligands to ROR t+ ILCs increased XRE occupancy in the kit promoter [40]. Kit is the stem cell factor (SCF) receptor, and SCF is crucial for maintaining the ILC cell pool at intestinal mucosal sites [44]. In vitro culture of ROR t+ ILCs containing SCF confirmed that c-kit plays an important role in postnatal ILC proliferation [40]. This demonstrates that the AhR pathway

directly regulates kit transcription, thereby controlling ILC proliferation and differentiation.

Lee et al. [39] found that feeding mice the AhR ligand dioxin (TCDD) increased colonic luminal Notch1 and Notch2 expression. Notch is considered a target gene of AhR [45-46], and ROR t+ ILCs can express Notch1 and Notch2 [46]. Possot et al. [47] cultured ROR t+ ILCs from adult bone marrow precursor cells and found that the Notch2 signaling pathway controls ROR t+ ILC generation. Mice lacking the Notch signaling pathway showed reduced ROR t+ ILC production. The Notch1 and Notch2 promoters contain XRE, and using AhR ligands can induce their promoters to bind with AhR for subsequent regulation [45]. This indicates that the AhR pathway also regulates the Notch signaling pathway, thereby controlling ILC proliferation.

ILCs mainly secrete cytokines such as interleukin-22 (IL-22), which can induce intestinal epithelial cells to produce mucins and antimicrobial peptides. IL-22 plays a key role in intestinal resistance to pathogens [48-51]. Lee et al. [39] found that IL-23 stimulation of ILCs from wild-type mouse intestinal mucosal lamina propria and Peyer' s patches produced large amounts of IL-22, while AhR knockout mice showed almost no IL-22 secretion. AhR knockout mice were quickly infected and all died within 2 weeks. Monteleone et al. [22] induced colitis in mice through TNBS, DSS, and T cell transfer, and found that adding the AhR ligand FICZ increased IL-22 secretion and alleviated colitis.

Zelante et al. [52] found that AhR knockout mice showed severely suppressed IL-22 secretion. Further experiments revealed that mouse intestinal antifungal capacity was related to IL-22 content and ILC numbers. Schiering et al. [53] found that abnormal expression of the CYP1A1 gene in mice depleted native AhR ligands, creating a state similar to AhR deficiency. Constitutive expression of CYP1A1, either systemically or restricted to intestinal epithelial cells, led to reduced numbers of intestinal AhR-dependent group 3 ILC subsets (ROR t+NKP46+, ROR t+NKP46-, ROR t+CD4+), decreased IL-22 secretion, and increased Citrobacter rodentium infection of the intestine. Increasing dietary AhR ligand intake could balance the effects of excessive AhR ligand degradation on intestinal immune function.

Islam et al. [29] found that tryptophan supplementation in wild-type mice increased AhR mRNA expression. Activated AhR promoted ILC proliferation and simultaneously increased IL-22 content. IL-22 induced secretion of regenerating protein 3 (Reg3) and mucins, improving intestinal antimicrobial capacity.

AhR can upregulate the kit and Notch pathways, which control ILC proliferation, differentiation, and turnover, maintaining stable ILC cell pools. When the intestine is threatened by bacteria, ILCs exert immune functions before T cells. ILCs secrete IL-22, thereby inducing secretion of antimicrobial proteins Reg3 and mucins for bactericidal activity and maintaining intestinal health. When AhR is absent or lacks ligand activation, the AhR activation pathway is suppressed, ILC proliferation and differentiation decrease, leading to reduced IL-22

secretion and increased intestinal infection. Therefore, AhR is an essential factor for maintaining intestinal mucosal homeostasis.

5.3 AhR Participates in Regulating Treg/Th17 Differentiation Balance to Modulate Intestinal Inflammation

Both Treg and Th17 cells originate from naïve CD4+ T cells, but their differentiation pathways and roles in intestinal inflammation are opposite. Treg cells have anti-inflammatory functions and maintain immune tolerance, while Th17 cells have opposite functions. Murine model studies have found a balance between these two cell types, where inhibiting Th17 promotes Treg generation.

The Treg transcription factor is forkhead box protein 3 (Foxp3) [20]. Treg cells mainly secrete interleukin-4 (IL-4), IL-10, and transforming growth factor- (TGF-). Treg cells are positively regulated by IL-10 and negatively regulated by IL-6, interleukin-21 (IL-21), and tumor necrosis factor- (TNF-) [54-55]. Studies have found that CD25+, CD4+ helper T cells can inhibit or even cure colitis [56-57]. The Th17 transcription factor is ROR t. Th17 cells produce the specific pro-inflammatory cytokine interleukin-17 (IL-17). Th17 generation is positively regulated by IL-1 , TNF- , and IL-23 [58], and negatively regulated by interferon- (IFN-), interleukin-27 (IL-27), and interleukin-2 (IL-2). Th17 cells also secrete IL-21, IL-6, TNF- , etc. [59]. These cytokines can collectively mobilize, recruit, and activate neutrophils. IL-17 can effectively mediate the excitation process of neutrophil mobilization, thereby effectively mediating tissue inflammatory responses. Zhang et al. [60] found that in UC model mice, Th17 differentiation and expression of related ROR t, IL-17, and IL-6 were increased, while Treg differentiation and expression of related Foxp3 and IL-10 were decreased. In DSS-induced colitis models, cytokine secretion from T helper 1 (Th1) and Th17 cells (IL-17, IL-6) was promoted [43].

Qiu et al. [20] found that AhR-/- mice promoted conversion of small intestinal naïve CD4+ T cells to Th17 cells, with increased expression of Th17 transcription factor ROR t and enhanced IL-17 production, while Foxp3 expression decreased. Singh et al. [24] used DSS (3%) to induce colitis in mice and found that compared to the DSS+vehicle group, the DSS+TCDD group showed significantly increased Treg percentages and numbers, while Treg percentages and numbers in the TCDD-only and vehicle-only groups showed only slight increases. RT-PCR detection revealed that compared to the vehicle-only group, the DSS+vehicle group significantly downregulated FoxP3 mRNA expression and significantly upregulated IL-17 mRNA expression. TCDD addition (DSS+TCDD) improved this situation. Meanwhile, in mice without DSS treatment, TCDD addition upregulated Foxp3 expression compared to the vehicle-only group without changing IL-17 expression.

To verify that TCDD regulates Treg differentiation through AhR, researchers conducted in vivo and in vitro experiments using wild-type C57BL/6 (AhR+/+) and AhR-/- mice. The results showed that TCDD promoted Foxp3 expression

in wild-type mice but had no effect on Foxp3 expression in AhR-/- mice. Concurrently, TCDD treatment of DSS-induced UC mice significantly upregulated Foxp3 expression in intestinal lymphoid tissue without significantly changing IL-17 expression, indicating that TCDD-activated AhR can induce Treg differentiation without inducing Th17 differentiation [24]. Islam et al. [29] found that tryptophan supplementation in wild-type mice significantly upregulated Foxp3 expression and downregulated IL-17 expression. Other studies found that kynurenine binding to AhR can promote T cell differentiation toward Treg and enhance Treg activity. Meanwhile, Treg can act on dendritic cells (DC) to promote differentiation of other regulatory T cells into Treg, forming a positive feedback process [61].

Studies have found that both Foxp3 and ROR t promoters contain XRE elements, so activated AhR can directly regulate these two transcription factors. AhR can promote Treg differentiation by inducing ROR t/C2 expression and initiating the ROR t/C2 signaling pathway. ROR t-deficient mice show reduced Treg tissue infiltration and alleviated autoimmune diseases [62]. Foxp3 is a specific transcription factor closely related to Treg regulatory function. Foxp3 transgenic mice with high expression show increased Treg numbers. Foxp3 is not a traditional transcriptional repressor that directly interacts with IL-2, IL-4, and IFN- gene promoters, but rather achieves suppression of corresponding cytokine expression by blocking activation of nuclear factor of activated T cells (NFAT) and nuclear factor-kappa B (NF- B), which are necessary for expression of various cytokines [63-64]. Kynurenine can proliferate Foxp3 and Treg through AhR-dependent mechanisms [65].

Some new studies indicate that the Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling pathway plays an important role in various Treg functions. For example, Chaudhry et al. [66] suggested that STAT activation in Treg can inhibit Th17 inflammatory responses by increasing expression of inhibitory cell molecules and chemokine receptors. Deletion of STAT3 in Treg can lead to colitis. Quintana et al. [67] found that activated AhR can promote Treg differentiation by regulating STAT1. In in vitro Treg/Th17 differentiation environments, STAT3 deletion severely impairs Th17 differentiation, shifting the Treg/Th17 balance toward Treg. After AhR binds to its ligand, it activates signaling pathways including STAT3 and NF- B to promote cell differentiation toward Th17 [68-69].

These studies indicate that AhR deficiency promotes Th17 differentiation, increases secretion of pro-inflammatory cytokines (IL-17, IL-21, and TNF-), reduces Treg cell differentiation, and aggravates intestinal inflammation. AhR ligand addition can promote Treg cell differentiation, increase secretion of anti-inflammatory cytokines (IL-10), inhibit Th17 differentiation, and reduce secretion of pro-inflammatory cytokines from these cells. Activated AhR regulates the balance between Treg and Th17 by controlling transcription factors Foxp3 and ROR t and through the JAK-STAT pathway. Some researchers believe that TCDD-activated AhR regulates Foxp3 and ROR t by inhibiting CpG is-

land methylation of Foxp3 and promoting methylation of the IL-17 promoter region, thereby promoting Treg differentiation, inhibiting Th17 differentiation, maintaining Treg/Th17 balance, and alleviating intestinal inflammation [24].

6 Summary

In recent years, numerous studies have investigated AhR involvement in immune regulation, particularly intestinal inflammation regulation. This article briefly reviews AhR participation in intestinal immune homeostasis and alleviation of intestinal inflammation. AhR inactivation aggravates colitis in IBD patients, while various ligands can activate AhR to help stimulate downstream regulatory gene expression. AhR alleviates intestinal inflammation by maintaining and exerting IELs and ILCs functions, protecting intestinal mucosal epithelial integrity, increasing anti-inflammatory factors, and inhibiting pro-inflammatory factors.

Food is the largest source of AhR ligands. Food-related nutrients such as tryptophan, soy isoflavones, arachidonic acid, quercetin, and baicalein are all AhR ligands. These ligands enter the intestine, bind to AhR, initiate related gene expression, and thereby regulate intestinal immunity. IBD patients consuming more vegetables helps alleviate colitis and benefits intestinal health. Microbial metabolites such as short-chain fatty acids can regulate AhR and its targets in the liver and intestine, while AhR signaling pathways can affect small intestinal microbiota composition, thereby regulating intestinal microbiota balance and maintaining intestinal health. Therefore, studying the relationship between related ligands regulating animal intestinal inflammation, receptors, ligands, and intestinal microorganisms can serve as a future research direction in animal nutrition regulation.

References:

[1] POLAND P,GLOVER E,KENDE S.Stereospecific,high affinity binding 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol:evidence that the binding species is receptor for induction of aryl hydrocarbon hydroxylase[J].Journal of Biological Chemistry,1976,25(16):4936-4946.

[2] POLAND A P,GLOVER E.Genetic expression of aryl hydrocarbon hydroxylase by 2,3,7,8 tetrachlorodibenzo-p-dioxin:evidence for a receptor mutation in genetically non-responsive mice[J].Molecular Pharmacology,1975,11(4):389-398.

[3] STOCKINGER B,DI MEGLIO P,GIALITAKIS M,et al.The aryl hydrocarbon receptor:multitasking in the immune system[J].Annual Review of Immunology,2014,32(1):403-432.

[4] HAHN M E.Aryl hydrocarbon receptors:diversity evolution[J].Chemico-Biological Interactions,2002,141(1/2):131-160.

[5] WALLER C L,MCKINNEY J D.Three-dimensional quantitative structure-

activity relationships of dioxins and dioxin-like compounds:model validation receptor characterization[J].Chemical Research Toxicology,1995,8(6):847-858.

[6] ANTONSSON C,WHITELAW M L,MCGUIRE J,et al.Distinct roles of the molecular chaperone hsp90 in modulating dioxin receptor function via the basic helix-loop-helix and PAS domains[J].Molecular and Cellular Biology,1995,15(2):756-765.

[7] ELFERINK C J,GE N L,LEVINE A.Maximal aryl hydrocarbon receptor activity depends on an interaction with the retinoblastoma protein[J].Molecular Pharmacology,2001,59(4):664-673.

[8] 蔺远, 张爱茜, 王连生. 芳烃受体与配体结合特定结构域的结构预测与分析 [C]//第四届全国环境化学学术大会论文汇编. 南京: 中国化学会,2008.

[9] 段毅涛, 赵辉, 黄鹤. 芳香烃受体内外源性配体研究进展 [J]. 环境与健康杂志,2013,30(5):456-459.

[10] KIMURA A,NAKA T,NOHARA K,et al.Aryl hydrocarbon receptor regulates Stat1 activation and participates in the development of Th17 cells[J].Proceedings of the National Academy of Sciences of the United States of America,2008,105(28):9721-9726.

[11] WANG H K,YEH C H,IWAMOTO T,et al.Dietary flavonoid naringenin induces regulatory T cells via an aryl hydrocarbon receptor mediated pathway[J].Journal of Agricultural and Food Chemistry,2012,60(9):2171-2178.

[12] DINATALE B C,MURRAY I A,SCHROEDER J C,et al.kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling[J].Toxicological Sciences,2010,115(1):89-97.

[13] HENRY E C,WELLE S L,GASIEWICZ T A.TCDD and a putative endogenous AhR ligand,ITE,elicit the immediate changes expression mouse fibroblasts[J].Toxicological Sciences,2010,114(1):90-100.

[14] LEHMANN G M,XI X,KULKARNI A A,et al.The aryl hydrocarbon receptor ligand ITE inhibits TGF 1-induced human myofibroblast differentiation[J].American Journal of Pathology,2011,178(4):1556-1557.

[15] WALL R J,HE G C,DENISON M S,et al.Novel 2-amino-isoflavones exhibit aryl hydrocarbon receptor agonist or antagonist activity in a species/cell-specific context[J].Toxicology,2012,297(1/2/3):26-33.

[16] GAD S C.Toxicology of the gastrointestinal tract[M].New York:CRC Press,2007:10.

[17] ESSER C,RANNUG A,STOCKINGER B.The aryl hydrocarbon receptor in immunity[J].Trends in Immunology,2009,30(9):447-454.

[18] PASTORKOV B,VRZALOV A,BACHLEDA P,et al.Hydroxystilbenes and methoxystilbenes activate human aryl hydrocarbon receptor and induce CYP1A

genes in human hepatoma cells and human hepatocytes[J].Food and Chemical Toxicology,2017,103:122-132.

[19] SCHMIDT J V,BRADFIELD C A.Ah receptor signaling pathways[J].Annual Review of Cell and Developmental Biology,1996,12(1):55-89.

[20] QIU J,GUO X H,CHEN Z M E,et al.Group 3 Innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through hydrocarbon receptor signaling regulation microflora[J].Immunity,2013,39(2):386-399.

[21] ARSENESCU R,ARSENESCU V,ZHONG J,et al.Role of the xenobiotic receptor in inflammatory bowel disease[J].Inflammatory Bowel Diseases,2011,17(5):1149-1162.

[22] MONTELEONE I,RIZZO A,SARRA M,et al.Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract[J].Gastroenterology,2011,141(1):237-248.e1.

[23] XUE J,NGUYEN D T,HABTEZION A.Aryl hydrocarbon receptor regulates pancreatic IL-22 production and protects mice from acute pancreatitis[J].Gastroenterology,2012,143(6):1670-1680.

[24] SINGH N P,SINGH U P,SINGH B,et al.Activation of aryl hydrocarbon receptor (AhR) leads to reciprocal epigenetic regulation of FoxP3 and IL-17 expression and amelioration of experimental colitis[J].PLoS One,2011,6(8):e23522.

[25] TAKAMURA T,HARAMA D,MATSUOKA S,et al.Activation of the aryl hydrocarbon receptor pathway may ameliorate dextran sodium sulfate-induced colitis in mice[J].Immunology & Cell Biology,2010,88(6):685-689.

[26] TAKAMURA T,HARAMA D,FUKUMOTO S,et al.Lactobacillus bulgaricus OLL1181 activates the aryl hydrocarbon receptor pathway and inhibits colitis[J].Immunology & Cell Biology,2011,89(7):817-822.

[27] 李良子, 刘中泽, 陈维刚, 等. 芳香烃受体对小鼠结肠炎的缓解作用及机制研究 [J]. 免疫学杂志,2017,33(1):13-17.

[28] SHIZUMA T,MORI H,FUKUYAMA N.Protective effect of tryptophan against dextran sulfate sodium- induced experimental colitis[J].Turkish Journal of Gastroenterology,2013,24(1):30-35.

[29] ISLAM J,SATO S,WATANABE K,et al.Dietary tryptophan alleviates dextran sodium sulfate-induced colitis through aryl hydrocarbon receptor in mice[J].The Journal of Nutritional Biochemistry,2017,42:43-50.

[30] LI Y,INNOCENTIN S,WITHERS D R,et al.Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation[J].Cell,2011,147(3):629-640.

[31] GIRARDI M,GLUSAC E,FILLER R B,et al.The distinct contributions of murine T cell receptor (TCR) + and TCR + T cells to different

stages of chemically induced skin cancer[J].The Journal of Experimental Medicine,2003,198(5):747-755.

[32] PUDDINGTON L,OLSON S,LEFRANÇOIS L.Interactions between stem cell factor and c-Kit are required for intestinal immune system homeostasis[J].Immunity,1994,1(9):733-739.

[33] FAHRER A M,KONIGSHOFER Y,KERR E M,et al.Attributes of intraepithelial lymphocytes as suggested by their transcriptional profile[J].Proceedings of the National Academy of Sciences of the United States of America,2001,98(18):10261-10266.

[34] WILSON C L,OUELLETTE A J,SATCHELL D P,et al.Regulation of intestinal -defensin activation by the metalloproteinase matrilysin in innate host defense[J].Science,1999,286(5437):113-117.

[35] ABREU M T.Toll-like receptor signalling in the intestinal epithelium:how bacterial recognition shapes intestinal function[J].Nature Reviews Immunology,2010,10(2):131-144.

[36] SPITS H,ARTIS D,COLONNA M,et al.Innate lymphoid cells-a proposal for uniform nomenclature[J].Nature Reviews Immunology,2013,13(2):145-149.

[37] HWANG Y Y,MCKENZIE A N.Innate lymphoid cells in immunity and disease[C]//KATSIKIS P,SCHOENBERGER S,PULENDRAN B.Crossroads Between Innate and Adaptive Immunity.New York:Springer,2013,785:9-26.

[38] SPITS H,DI SANTO J P.The expanding family of innate lymphoid cells:regulators and effectors of immunity and tissue remodeling[J].Nature Immunology,2011,12(1):21-27.

[39] LEE J,CELLA M,MCDONALD K G,et al.AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch[J].Nature Immunology,2011,13(2):144-151.

[40] KISS E A,VONARBOURG C,KOPFMANN S,et al.Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles[J].Science,2011,334(6062):1561-1565.

[41] SUN Y V,BOVERHOF D R,BURGOON L D,et al.Comparative analysis of dioxin response elements in human,mouse and rat genomic sequences[J].Nucleic Acids Research,2004,32(15):4512-4523.

[42] JUX B,KADOW S,LUECKE S,et al.The aryl hydrocarbon receptor mediates UVB radiation-induced skin tanning[J].Journal of Investigative Dermatology,2011,131(1):203-210.

[43] KADOW S,JUX B,ZAHNER S P,et al.Aryl hydrocarbon receptor is critical for homeostasis of invariant T cells in the murine epidermis[J].Journal of Immunology,2011,187(6):3104-3110.

[44] CHAPPAZ S,GÄRTNER C,RODEWALD H R,et al.Kit ligand and Il7 differentially regulate Peyer' s patch and lymph node development[J].The Journal of Immunology,2010,185(6):3514-3519.

[45] STEVENS E A,MEZRICH J D,BRADFIELD C A.The aryl hydrocarbon receptor:a perspective on potential roles in the immune system[J].Immunology,2009,127(3):299-311.

[46] LÜGERING A,ROSS M,SIEKER M,et al.CCR6 identifies lymphoid tissue inducer cells within cryptopatches[J].Clinical & Experimental Immunology,2010,160(3):440-449.

[47] POSSOT C,SCHMUTZ S,CHEA S,et al.Notch signaling is necessary for adult,but not fetal,development of ROR t+ innate lymphoid cells[J].Nature Immunology,2011,12(10):949-958.

[48] TRIFARI S,KAPLAN C D,TRAN E H,et al.Identification of a human helper T cell population that has abundant production interleukin distinct from Th-17,Th1 and Th2 cells[J].Nature Immunology,2009,10(8):864-871.

[49] ALAM M S,MAEKAWA Y,KITAMURA A,et al.Notch signaling drives IL-22 secretion in CD4+ T cells by stimulating the aryl hydrocarbon receptor[J].Proceedings of the National Academy of Sciences of the United States of America,2010,107(13):5943-5948.

[50] ZENEWICZ L A,FLAVELL R A.IL-22 and inflammation:leukin' through a glass onion[J].European Journal of Immunology,2008,38(12):3265-3268.

[51] ZHENG Y,VALDEZ P A,DANILENKO D M,et al.Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens[J].Nature Medicine,2008,14(3):282-289.

[52] ZELANTE T,IANNITTI R G,CUNHA C,et al.Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22[J].Immunity,2013,39(2):372-385.

[53] SCHIERING C,WINCENT E,METIDJI A,et al.Feedback control of AHR signalling regulates intestinal immunity[J].Nature,2017,542(7640):242-245.

[54] BI Y J,LIU G W,YANG R F.Reciprocal modulation between Th17 and other helper T cell lineages[J].Journal of Cellular Physiology,2011,226(1):8-13.

[55] COOMBES J L,ROBINSON N J,MALOY K J,et al.Regulatory T cells intestinal homeostasis[J].Immunological Reviews,2005,204(1):184-194.

[56] READ S,MALMSTRÖM V,POWRIE F.Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of Cd25+Cd4+ regulatory cells that control intestinal inflammation[J].Journal of Experimental Medicine,2000,192(2):295-302.

[57] MOTTET C,UHLIG H H,POWRIE F.Cutting edge:cure of colitis by CD4+CD25+ regulatory T cells[J].The Journal of Immunol-

ogy,2003,170(8):3939-3943.

[58] VELDHOEN M,HOCKING R J,ATKINS C J,et al.TGF in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-Producing T cells[J].Immunity,2006,24(2):179-189.

[59] KIMURA A,KISHIMOTO T.Th17 cells inflammation[J].International Immunopharmacology,2011,11(3):319-322.

[60] ZHANG L Y,ZHANG Y J,ZHONG W W,et al.Heme Oxygenase-1 ameliorates dextran sulfate sodium-induced acute murine colitis regulating Th17/Treg balance[J].Journal Biological Chemistry,2014,289(39):26847-26858.

[61] MEZRICH J D,FECHNER J H,ZHANG X J,et al.An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells[J].The Journal of Immunology,2010,185(6):3190-3198.

[62] CHEN Z J,LIN F,GAO Y Y,et al.FOXP3 and ROR t:transcriptional regulation of Treg and Th17[J].International Immunopharmacology,2011,11(5):536-542.

[63] PUNJ S,KOPPARAPU P,JANG H S,et al.Benzimidazoisoquinolines:a new class of rapidly metabolized aryl hydrocarbon receptor (AhR) ligands that induce AhR-Dependent Tregs and prevent murine graft-versus-host disease[J].PLoS One,2014,9(2):e88726.

[64] CHRISTIAANSEN A F,BOGGIATTO P M,VARGA S M.Limitations of Foxp3+ Treg depletion following viral infection in DEREG mice[J].Journal of Immunological Methods,2014,406:58-65.

[65] MIZUNO T,SUZUKI R,UMEKI S,et al.Crossreactivity of antibodies to canine CD25 and Foxp3 and identification of canine CD4+CD25 +Foxp3+ cells in canine peripheral blood[J].Journal of Veterinary Medical Science,2009,71(12):1561-1568.

[66] CHAUDHRY A,RUDRA D,TREUTING P,et al.CD4+ regulatory t cells control TH17 responses in a Stat3-dependent manner[J].Science,2009,326(5955):986-991.

[67] QUINTANA F J,WEINER H L.Environmental control of Th17 differentiation[J].European Journal of Immunology,2009,39(3):655-657.

[68] YANG E J,LEE J,LEE S Y,et al.EGCG attenuates autoimmune arthritis by inhibition of STAT3 and HIF-1 with Th17/Treg control[J].PLoS One,2014,9(2):e86062.

[69] ROSILLO M A,SÁNCHEZ-HIDALGO M,SÁNCHEZ-FIDALGO S,et al.Dietary extra-virgin olive oil prevents inflammatory response and cartilage matrix degradation in murine collagen-induced arthritis[J].European Journal of Nutrition,2016,55(1):315-325.

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