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The Aryl Hydrocarbon Receptor (AHR) as a Potential Target for the Control of Intestinal Inflammation: Insights from an Immune and Bacteria Sensor Receptor

Larissa Pernomian[1] · Murillo Duarte-Silva[2] · Cristina Ribeiro de Barros Cardoso[1]

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Abstract
The aryl hydrocarbon receptor (AHR) is widely expressed in immune and non-immune cells of the gut and its activation has been correlated to the outcome of inflammatory bowel diseases (IBD). In ulcerative colitis and Crohn's disease, there is an excessive chronic inflammation with massive accumulation of leukocytes in the gut, in an attempt to constrain the invasion of pathogenic microorganisms on the damaged organ. Accordingly, it is known that dietary components, xenobiotics, and some chemicals or metabolites can activate AHR and induce the modulation of inflammatory responses. In fact, the AHR triggering by specific ligands during inflammatory conditions results in decreased IFNγ, IL-6, IL-12, TNF, IL-7, and IL-17, along with reduced microbial translocation and fibrosis in the gut. Moreover, upon AHR activation, there are increased regulatory mechanisms such as IL-10, IL-22, prostaglandin E_2, and Foxp3, besides the production of anti-microbial peptides and epithelial repair. Most interestingly, commensal bacteria or their metabolites may also activate this receptor, thus contributing to the restoration of gut normobiosis and homeostasis. In line with that, *Lactobacillus reuteri*, *Lactobacillus bulgaricus*, or microbial products such as tryptophan metabolites, indole-3-pyruvic acid, urolithin A, short-chain fatty acids, dihydroxyquinoline, and others may regulate the inflammation by mechanisms dependent on AHR activation. Hence, here we discussed the potential modulatory role of AHR on intestinal inflammation, focused on the reestablishment of homeostasis through the receptor triggering by microbial metabolites. Finally, the development of AHR-based therapies derived from bacteria products could represent an important future alternative for controlling IBD.

Keywords AHR · Inflammation · Microbiota · Inflammatory bowel diseases · Gut

Introduction

The aryl hydrocarbon receptor (AHR) that belongs to the family of the basic helix-loop-helix/Per-Arnt-Sim proteins [1] is widely expressed on vertebrate cells [2]. It recognizes and metabolizes a wide range of molecules that include mainly xenobiotic compounds, some chemicals such as 6-formylindolo (3, 2-b) carbazole (FICZ), polycyclic aromatic hydrocarbons like 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) [3], and the environmental contaminant dioxin, present in cigarette smoking [4]. After ligand binding, the cytoplasmic AHR translocates to the nucleus, where it triggers the transcription of several genes related to the metabolism of the recognized compounds. There is an activation of the enzymes of cytochrome P450 family 1A1 (CYP1A1) which metabolizes the receptor ligands, permitting a feedback modulation of AHR-induced responses. Then, following receptor triggering, the cells express the P450 enzymes to reduce the ligands' availability, thus terminating the receptor activation [5].

AHR has been implicated in many immune or inflammatory processes, such as those presented in cardiovascular diseases [6], multiple sclerosis [7], rheumatoid arthritis [8], depression, obesity [9], and allergic responses, among others. Then, there have been some attempts to develop novel treatments for constraining inflammation, focused on AHR activation. For example, a new approach has been used based on a nonsteroidal topical anti-inflammatory drug able to modulate AHR. This drug, named Tapinarof, led to great improvement

✉ Cristina Ribeiro de Barros Cardoso
cristina@fcfrp.usp.br

[1] Department of Clinical Analysis, Toxicology and Food Sciences, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

[2] Department of Biochemistry and Immunology, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

in atopic dermatitis [10, 11]. In addition, gut bacteria or its metabolites may also trigger AHR responses. In line with that, a recent study demonstrated that the administration of AHR agonist or a *Lactobacillus* strain able to produce AHR ligands ameliorated alterations related to metabolic syndrome, which was shown to be associated with an impaired capacity of the gut microbiota to metabolize tryptophan into AHR agonists in mice and humans [12].

Despite the toxic effects triggered by its major ligands, it is clear that the receptor plays a relevant role in the modulation of inflammatory responses, especially on the intestinal mucosal surfaces. Indeed, many leukocytes such as macrophages [13], dendritic cells [14], T lymphocytes [15], and innate lymphoid cells [16] express AHR and therefore its activation may significantly influence the ongoing immune reactions, since many genes including those related to cytokine expression, have dioxin-response elements [17, 18]. Hence, studies have focused on the role of AHR ligands in the resolution of inflammatory diseases.

Inflammatory Bowel Diseases and AHR

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) or ulcerative colitis (UC) are disabling conditions of the gut, developed as a result of the interaction among loss of tolerance, genetic predisposition, and environmental triggers [19]. In this scenario, there is dysregulation of innate and T cell responses with impaired influx or function of regulatory cells [20], together with a significant local dysbiosis. In the intestine, a large number of microorganisms coexist and participate in the organ development, maturation, and modulation of host responses. This complex and dynamic microbial ecosystem may be modified by genetic factors of the host [21], infections, use of antibiotics, diet, and environmental stimuli [19].

The AHR expression influences the establishment of microbial community in the gut [22]. For example, the ingestion of 2,3,7,8-tetrachlorodibenzofuran (TCDF), which activates the receptor signaling, led to disrupted mice metabolism and altered the microbiota–host homeostasis, including the intestinal bacteria composition [23]. Hence, it is plausible to assume that the interaction between this receptor and intestinal microorganisms interferes in the mucosal immunity regulation. Indeed, AHR plays a protective role in gut inflammation, as described in most studies until now.

Since dysbiosis plays a central role in the development of Crohn's disease and ulcerative colitis, the manipulation of gut microbiota has been exploited for the development of new therapies for these diseases. Accordingly, we proposed that the downregulation of the gut inflammation could occur by the AHR activation with commensal bacteria or its metabolites, with subsequent recovery of the normobiosis and mucosal homeostasis. Indeed, many probiotics are derived from these microorganisms that inhabit the healthy human gut. Thus, species such as *Lactobacillus* and *Bifidobacterium* could represent an important adjuvant (but not substitutive) approach to the conventional therapies, especially for UC [24, 25], while the benefits for CD are still not clear [26, 27]. Therefore, here we raise the discussion on the benefits of activating AHR by bacteria derived from the commensal microbiota and on the modulation of human intestinal inflammation. However, while the effectiveness of these agents seems promising and a wide range of data for mouse intervention can be found, more clinical studies are needed to understand not only their mechanisms of action but also their effects on human gut immunity, especially regulatory responses activated by AHR pathways.

AHR in the Gut Barrier and the Initial Inflammatory Triggers

AHR may play different roles in the inflammatory responses, depending on the cells, tissues, or organs where the receptor is expressed, such as in the gut. The intestinal epithelial barrier is one of the first innate protections against pathogen invasion due to its essential role in gut anatomy. Together with the subjacent immune effectors, it permits the interaction with food antigens, besides the discrimination between invaders and commensal microorganisms that inhabit the gastrointestinal tract [28].

In intestinal epithelial cells (IECs), AHR pathway is required for the development of this population from local stem cells [29]. Also, the lack of this receptor compromises Goblet cells and the mucus production and increases the microbial translocation to other anatomical sites [30]. In experimental colitis, an AHR agonist, β-naphthoflavone, attenuated the disease and reduced the responses of human epithelial colonic cells induced by LPS treatment, indicating that the AHR activation in epithelia may, in fact, represent an important mechanism to regulate gut inflammation [31]. Moreover, in epithelial cells, the AHR ligand FICZ reduced the IL-7 production and ameliorated experimental colitis by decreasing the frequency of activated intraepithelial lymphocytes (IEL) associated with the gut barrier and inflammation development (Fig. 1) [32].

On the contrary, the lack of AHR or their ligands compromises the epithelial barrier, since this receptor controls the bacterial load, likewise the IEL frequency in the gut [33]. Interestingly, CD8αα^{+}TCRαβ^{+} IELs become resistant to apoptosis simultaneously to the upregulation of AHR and IL-15 receptor after FICZ treatment in an experimental colitis model. Upon AHR activation, these cells also produced higher amounts of IL-10 and lower IFN-γ [34], indicating a novel pathway to be explored in future development of IBD therapies.

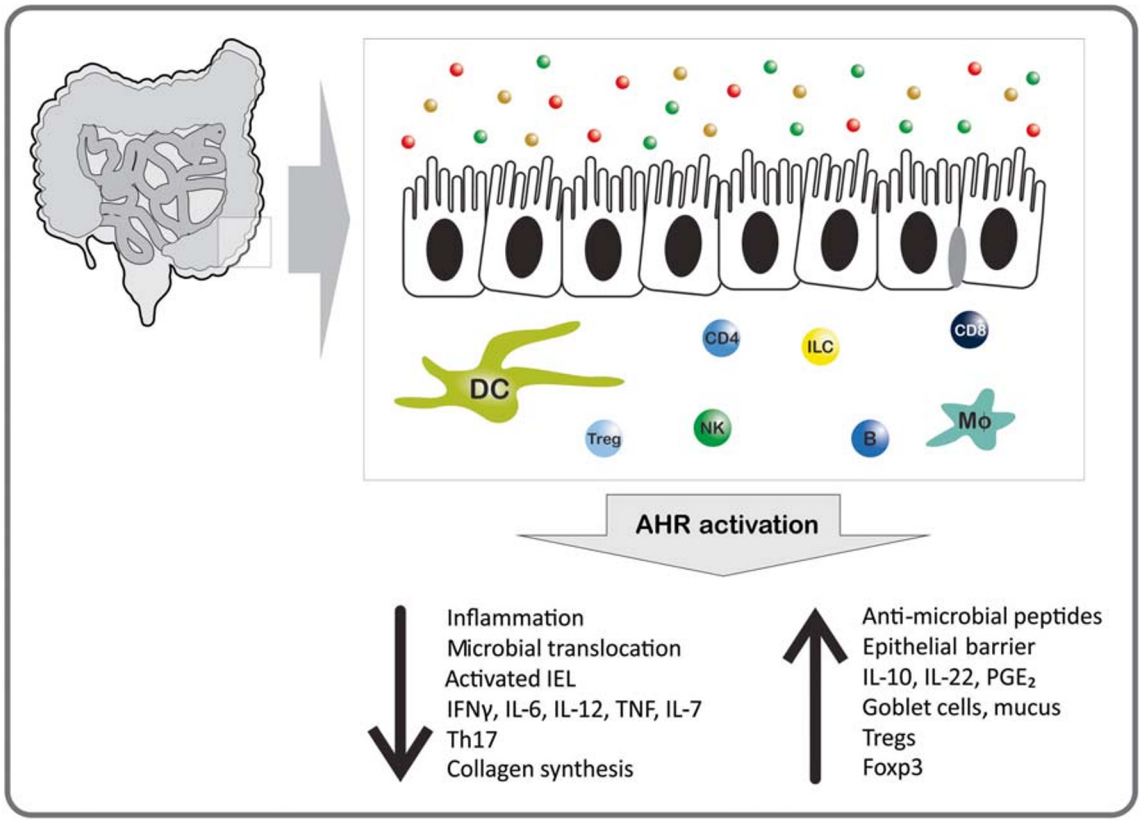

Fig. 1 The activation of aryl hydrocarbon receptor (AHR) controls intestinal inflammation. AHR is expressed by leukocytes and non-immune cells of the gut. Its activation by diverse ligands such as xenobiotics and dietary products results in the suppression of inflammatory responses, with reduction of cytokines such as IFNγ, IL-6, IL-12, TNF, IL-7, and Th17 reactions, along with a decrease in microbial translocation and collagen synthesis or fibrosis in the gut. On the contrary, upon AHR triggering, there is an augment in regulatory mechanisms mediated by IL-10, IL-22, prostaglandin E_2 (PGE_2), and Foxp3 (Tregs), besides anti-microbial peptides and restoration of the epithelial integrity. DC: dendritic cells; ILC: innate lymphoid cells; NK: natural killer; m : macrophages; CD4: CD4 T lymphocytes; CD8: CD8 T lymphocytes; Treg: regulatory T cell; B: B lymphocytes

AHR in the Balance of Adaptive Immunity: From Inflammation to Tolerogenic Responses

During experimental gut inflammation, AHR expression is increased in an attempt to constrain the detrimental consequences of colitis. Mice treated with dextran sulfate sodium (DSS) 3% showed augmented expression of AHR than those treated with DSS 2%, which in turn is higher than in healthy mice, like a dose-response expression of the receptor, dependent on the gut inflammation imbalance [31]. Moreover, upon the breakdown of mucosal tolerance, the exacerbated immune response that underlies gut damage is driven by complex interactions between components of the innate and adaptive immune responses including neutrophils, macrophages, T lymphocytes, and inflammatory mediators, such as cytokines and eicosanoids [35], whose production may be altered by AHR activation. Indeed, the mice pretreatment with TCDD was protective against the harmful DSS effects and controlled the intestinal inflammatory reactions by a mechanism dependent on prostaglandin E2 production in the gut [36]. Furthermore, besides lipid mediators, the balance between effector T helper and regulatory cells (Tregs), which usually constrains excessive inflammatory conditions, is essential to determine the homeostasis in the intestinal mucosa and IBD outcome in affected subjects [37].

In general, the AHR activation constrains T cell responses and contributes to the inflammation control [38]. For example, in mice exposed to the colitogenic DSS, the AHR triggering by the dioxin TCDD restored the Th17/Treg ratio by inhibiting Th17 proliferation and inducing Treg differentiation [39]. Similarly, the AHR ligand 3, 3′-diindolylmethane (DIM) alleviated experimental colitis induced by oxazolone through reducing the Th2/Th17 cells and increasing Tregs [3]. In the 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced gut inflammation, the administration of TCDD by gavage, prior to the enema with TNBS, inhibited the response mediated by IL-6, IL-12, IFN-γ, and TNF, besides inducing an increase in $Foxp3^+$ Tregs in the gut (Fig. 1) [18]. Moreover, the AHR agonist 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) was able to suppress effector cells and induce regulation by CD39 and granzyme B in an in vitro approach, along with the amelioration of experimental colitis

in a humanized mice model, through reestablishment of immune tolerance in the intestine with Tregs [40]. In accordance, induced Tregs express AHR and this receptor is important to the accumulation of this population as well as its function in the gut (Fig. 1). In fact, the activation of AHR in Tregs protected against experimental T cell-mediated colitis [41]. In line with that, one of the drugs widely used for IBD treatment, mesalamine, plays an anti-inflammatory role in colitis by activating the AHR pathway and inducing Tregs in the colon via activated TGF-β [42]. Thus, a large body of evidences indicates that the AHR activation by ligands could be an alternative approach to the intestinal inflammation control, through the generation of regulatory mechanisms.

The IL-22 cytokine, produced by $CD4^+$ T cells and innate lymphoid cells (ILCs), plays a protective role in gut inflammation as well, mainly by maintaining the integrity of the intestinal epithelium and inducing anti-microbial peptides, which control bacterial translocation in dysbiosis. Considering the relationship between AHR and IL-22, mice injected with the ligand FICZ showed regulation of the excessive inflammation in experimental colitis, by mechanisms dependent on goblet cell differentiation [30] and on protective responses mediated by this cytokine [38]. The AHR activation induced high amounts of IL-22 by $CD4^+$ T cells; meanwhile, the lack of IL-22 producing ILCs and CD4 T cells promoted a more severe colitis in mice exposed to DSS [43, 44]. In addition to the protective role for the epithelium, IL-22 controls Th17 accumulation in the gut, involving AHR activation and local microbiota [45]. Moreover, upon receptor activation with FICZ, there is augmented IL-22 and diminished IFN-γ production by lamina propria cells, thus confirming a counter-regulatory response in IBD, induced by AHR signaling (Fig. 1) [38].

Apart from the Th17-IL-22 axis, the intestinal inflammation in Crohn's disease develops because of the chronic pathogenic Th1 and IFN-γ responses that mediate excessive inflammation and local tissue injury [46]. This cytokine induces indoleamine 2,3-dioxygenase (IDO1), the enzyme responsible for tryptophan conversion to kynurenine which, in turn, is an endogenous AHR ligand. After the receptor activation by kynurenine, the IL-10R1 is upregulated on IEC. Thus, mice exposed to DSS and treated with exogenous kynurenine presented reduced mucosal inflammation due to an improvement in IL-10 action [47]. When it comes to IBD long-term complications, strictures are one of the main outcomes in some patients presenting fibrosis areas in the gut and requiring surgical intervention, especially in ileal chronic disease. Once AHR activation attenuated the collagen synthesis (Fig. 1), it could be an important target for this chronic inflammatory and fibrotic complication of CD [48]. In a mouse model of intestinal obstruction, AHR triggering by FICZ reduced the intestinal permeability and the epithelial damage, by inhibiting the myosin light chain kinase (MLCK) and the phosphorylated MLC (pMLC) pathway [49]. Likewise, AHR activation by FICZ reduced both the dysfunction of epithelial barrier and the claudin-2 expression, besides maintaining the tissue integrity in cell culture and in vivo studies [50, 51].

On the other hand, some toxins have been linked to the induction of autoimmune diseases, supposedly by DNA epigenetic modifications during developmental exposure (unlike in adult life), resulting in dysregulated immune responses [52]. The correlation between TCDD, an AHR ligand, and autoimmunity is a phenomenon observed mainly in neonatal mice, exposed during mild-gestation or afterbirth [53–57]. This is probably because TCDD induces a disruption in thymic function, which plays the most important activity in early life on T cells selection and on autoreactive clone elimination [53]. Furthermore, TCDD is used in mice experiments as an AHR agonist, for the investigation of the effects of this receptor on immunity. However, in humans, the aim would not be the administration of this dioxin, but the use of protective microbiota and its metabolites, which bind to AHR, for inflammation control.

Therefore, even considering the different roles in inflammation, it is clear that AHR is mainly protective in IBD. Mice deficient for AHR showed a more severe colitis, while those treated with AHR agonist had attenuated disease progression. Nevertheless, though the deficiency of AHR in epithelia usually results in excessive inflammation, the absence of this receptor in T cells may lead to the amelioration of DSS-induced colitis, probably because of the reduced infiltration of Th17 lymphocytes in gut lamina propria [58]. In addition, AHR is essential to the maintenance of the IEL numbers in the intestine, as well as the local bacterial load, which increases in the absence of this receptor, resulting in augmented epithelial damage [33]. Indeed, recent evidences pointed to the importance of AHR ligands and gut bacteria in the modulation of inflammatory responses [59].

AHR Modulation by Intestinal Microbiota

As cited above, some bacteria exert immunoregulatory effects in the intestine, dependent on the activation of the AHR pathway, which culminates in anti-inflammatory responses. Indeed, while the maintenance of gut normobiosis is essential to the regulation of mucosal immunity and homeostasis (Fig. 2) [21, 60, 61], the dysbiosis contributes, undoubtedly, to the dysregulated inflammation. It encompasses the prevalence of pathogenic species which predispose to host diseases frequently caused by effector responses against the altered microbiota, with microorganism translocation in the gut (Fig. 2). However, studies are still necessary to unravel the opposite scenario that involves the direct beneficial effects of bacteria or their metabolites in the regulation of the ongoing immune responses.

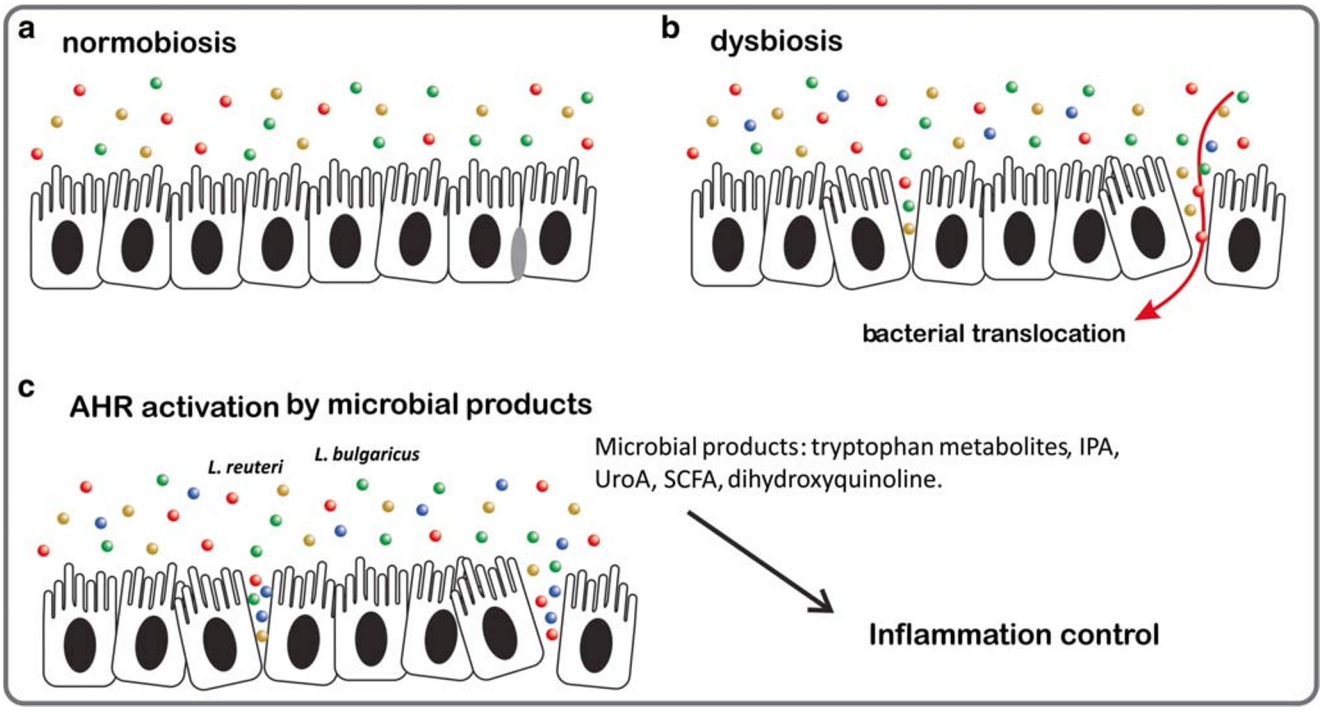

Fig. 2 Metabolites from gut microbiota may modulate local inflammatory responses and intestinal dysbiosis by AHR activation. In the absence of chronic inflammation, the gut homeostasis is maintained with an equilibrium between commensal and pathogenic microorganisms, in a normobiosis condition (A). Upon local dysbiosis and breakdown of epithelial barrier, there is microbial translocation and triggering of innate and adaptive reactions that amplify the local tissue damage and inflammation (B). Bacteria such as *Lactobacillus reuteri*, *Lactobacillus bulgaricus*, or microbial products (tryptophan metabolites, IPA, UroA, SCFA, dihydroxyquinoline and others) may regulate the excessive inflammatory reactions after AHR activation (C) and represent an alternative for future studies aimed at developing novel therapies for Crohn's disease or ulcerative colitis. IPA: indole-3-pyruvic acid; UroA: urolithin A; SCFA: short-chain fatty acids

The intestinal bacteria represent an important source of products able to trigger AHR [62]. However, the quality of the microbiota is essential to generate AHR ligands. For example, a high-fat diet alters the bacteria components and their capacity to produce some metabolites, such as tryptamine and indole-3-acetate (I3A), both AHR agonists [63]. Moreover, genetic polymorphisms also interfere in the microbial products. CARD9 (caspase recruitment domain family member 9) is necessary to the tryptophan metabolism and IL-22 induction, which protects the intestinal epithelium in colitis, associated with AHR activation. Yet the microbiota (and metabolites) of IBD patients presenting the risk allele of CARD9 does not trigger adequately the AHR molecule, indicating a relationship among intestinal inflammation, CARD9, and AHR activation or the production of its agonists by the host microbiota [64].

The tryptophan metabolites, which ameliorate intestinal inflammation [65], may also be derived from the microbiota and activate the AHR target genes on mouse colonocytes (Fig. 2). In this scenario, the modulation depends on specific agonist or antagonist activities of ligands such as indole-3-acetate, indole-3-aldehyde, indole, and tryptamine. These stimuli may induce different patterns of gene expression after receptor triggering, suggesting a selective AHR modulation by such microbial metabolites [66]. For instance, *Lactobacillus reuteri* originates indole derivatives from tryptophan metabolism and then activates AHR in $CD4^+$ T cells, which in turn downregulate the transcription factor ThPOK to the induction of $CD4^+CD8\alpha\alpha^+$ intraepithelial regulatory lymphocytes [67]. These data indicated that in the presence of tryptophan, a probiotic bacterium is able to mediate the induction of a regulatory profile to control intestinal inflammation through AHR (Fig. 2). In addition, the supplementation of pigs' diet with tryptophan resulted in increased diversity of the animals' microbiome, activation of AHR and CYP1A1 in the gut, with IL-8 reduction and improvement of epithelial barrier in the gut. These findings suggested once more an important relationship among tryptophan, microbial metabolism, and gut immunity regulation [68]. However, a novel mechanism of action of *Lactobacillus reuteri* was recently described in the R2lc and 2010 strains, involving novel identified polyketide synthase (PKS) clusters on the strains' genome, which are able to trigger AHR in a tryptophan-independent pathway [69]. Regarding other species, *Lactobacillus bulgaricus* strain OLL1181 ameliorated DSS-colitis by activating AHR signaling (Fig. 2) and inducing the gene expression of the AHR target cytochrome CYP1A1, not only in the gut of treated mice but also in samples of human colon cells [70].

The indole-3-pyruvic acid (IPA), which is a precursor of AHR agonists produced by gut microbiota, can itself activate

AHR and control experimental intestinal inflammation (Fig. 2). The oral administration of IPA to SCID mice in the T cell transfer colitis model reduced gut inflammation by inhibiting the expression of IL-12, IFN-γ, TNF, and IL-1β in the intestine, together with an increase in IL-10. Moreover, IPA induced the differentiation and augmented suppressive potential of Tr1 cells, as well as the accumulation of anti-inflammatory dendritic cells in the mesenteric lymph nodes, which was abolished by treatment with an AHR antagonist. These data indicated a relevant modulatory potential for this metabolite on colon inflammation through AHR activation [71]. Likewise, the oral treatment with 1,4-dihydroxy-2-naphthoic acid—DHNA, which is an AHR activator obtained from the cheese bacteria *Propionibacterium freudenreichii* ET-3, induced anti-microbial peptides such as RegIIIβ and γ in the intestine, and led to the control of inflammation in DSS-colitis [72].

In accordance, several studies have proposed the use of probiotics and prebiotics in the treatment of intestinal inflammation, to reestablish the equilibrium between microbial populations and their products in the gut. Besides a few older studies (ClinicalTrials.gov Identifier: NCT02093767), a recent clinical trial recruiting children and young adults with IBD is being conducted in order to evaluate the effects of the prebiotic inulin in gut bacteria and disease activity (ClinicalTrials.gov Identifier: NCT03653481). The ingestion of fibers is related to a reduced risk for Crohn's disease [73] and the short-chain fatty acids (SCFAs) butyrate, acetate or propionate, which are derived from bacteria metabolism of ingested fibers, play anti-inflammatory and immunomodulatory activities, by inducing regulatory T cells and constraining cytokines responses in the gut [74, 75]. Moreover, SCFAs act together with AHR ligands to increase the responsiveness and activation of this receptor in gut epithelial cells, a fact that could in theory, potentiate its anti-inflammatory role (Fig. 2) [76]. Importantly, butyrate triggers AHR in human intestinal epithelial cells, indicating once more that metabolites produced by gut microbiota may be an important source of immune-modulatory molecules able to control intestinal inflammation [62].

Apart from the ligands described above, the intestinal microbiota can also metabolize dietary compounds and generate other products that bind AHR, such as urolithin A (UroA). This metabolite has the capacity to reduce IL-6 and TNF production by macrophages and to bind AHR on IECs with further induction of tight junction proteins such as claudin 4, occludin, and zona occludens 1 (ZO1). In fact, mice with experimental colitis have an attenuated disease when treated with UroA (Fig. 2) and, considering that microbial translocation is a hallmark of IBD, the induction of tight junction proteins would be a great advantage on the control of patients' intestinal inflammation [77]. Furthermore, another microbial derivative such as 2,8 dihydroxyquinoline also plays a role in the AHR activation in human cells [78], thus pointing to an additional important bacteria product with the ability to regulate gut immunity (Fig. 2).

Beyond the potential of individual bacteria species and their metabolites to modulate AHR, the fecal microbiota transplantation (FMT) could also represent a novel interesting approach to achieve intestinal homeostasis, though not fully established yet. It consists of the transference of the intestinal content from a healthy donor to a receptor that is often inflamed, aiming at controlling the gut dysbiosis and restoring the local tolerance with beneficial microbiota. The FMT of normal mice donors to animals with experimental colitis ameliorated the intestinal inflammation, with augmented AHR expression as well as anti-inflammatory cytokines such as IL-10 and TGF-β. There was a later increase in *Lactobacillus* and *Bifidobacterium bacteria* in the receptors, together with elevated indole-3-acetic acid (IAA) levels, indicating a link between the AHR activation and microorganisms able to restore the gut normobiosis [79]. Otherwise, the gut microbiota depletion by wide range antibiotic-therapy resulted in the atrophy of intestinal mucosa and decreased production of antimicrobial molecules, which were restored after FMT. The reduction of AHR activation was associated with the diminished antimicrobial peptides, which was rescued by mice treatment with FICZ. These data pointed again to an interplay between gut microbiota and AHR pathway that seemed to be involved in the production of microbicidal molecules relevant to the maintenance of mucosal homeostasis [80].

Conclusions and Future Perspectives

In summary, AHR interacts with endogenous ligands produced by the host, besides a wide range of molecules. Since the signaling through this receptor is altered in IBD patients who usually present intestinal dysbiosis, the putative activation of this pathway could envisage a novel alternative treatment for such pathologies, particularly considering the beneficial effects of certain bacteria metabolites in the gut homeostasis (Fig. 2). Therefore, the future development of AHR-based therapies focused on prebiotics or metabolites derived from probiotic bacteria could represent a novel approach for achieving intestinal health in Crohn's disease or colitis patients. However, further clinical studies are still necessary to establish the safety and effectiveness of this proposed therapy.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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