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REVIEW

Intestinal inflammation and the diet: Is food friend or foe?

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Abstract

Inflammatory bowel disease (IBD) is a chronic intestinal illness of autoimmune origin affecting millions across the globe. The most common subtypes include ulcerative colitis (UC) and Crohn's disease. While many medical treatments for IBD exist, none come without the risk of significant immunosuppression and in general do not have benign side effect profiles. Surgical intervention exists only as radical resection for medically refractory UC. There exists a dire need for novel treatments that target the inherent pathophysiologic disturbances of IBD, rather than global immune suppression. One avenue of investigation that could provide such an agent is the interaction between certain dietary elements and the aryl hydrocarbon receptor (AHR). The AHR is a cytosolic transcription factor with a rich history in environmental toxicant handling, however, recently a role has emerged for the AHR as a modulator of the gastrointestinal immune system. Studies have come to elucidate these effects to include the enhancement of T_h cell subset differentiation, interactions between enteric flora and the luminal wall, and modulation of inflammatory interleukin and cytokine signaling. This review highlights advancements in our understanding of AHR activity in the digestive tract and how this stimulation may be wrought by certain dietary "micro-nutriceuticals", namely indole-3-carbinol (I3C) and its derivatives. Greater clarity surrounding these dynamics could lead to a novel diet-derived agonist of the AHR which is not only non-toxic, but also efficacious in the amelioration of clinical IBD.

Key words: Inflammatory bowel diseases; Aryl hydrocarbon receptor; Mucosal immunity; Dietary phytochemicals; Autoimmune diseases

Core tip: Inflammatory bowel disease (IBD) is a chronic illness with a paucity of safe and effective treatments, either medically or surgically. The aryl hydrocarbon receptor represents a novel target for future treatments of IBD using dietary ligands of the receptor. Many studies have examined the interplay between the aryl hydrocarbon receptor and gastrointestinal mucosal immunity, though there remains a gap in the understanding of how dietary ligands can modulate

this activity. Our objective was to highlight elements of current literature focusing on aryl hydrocarbon receptor biology, IBD, and how their interplay can be activated with dietary "micronutriceuticals".

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INTRODUCTION

The incidence of inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) has been increasing worldwide; it is now estimated that between 1 and 1.3 million Americans are currently diagnosed with IBD[1,2]. This increased incidence is possibly due to currently unidentified environmental factors, which interact with an inherent genetic predisposition[3]. IBD is a family of chronic inflammatory conditions primarily involving the digestive tract, and often having additional extra-intestinal manifestations. The unique chronic inflammatory milieu maintained by IBD predisposes patients to non-adenomatous colorectal cancer as well as small bowel adenocarcinoma[4]. To date there is no accepted etiology or preventive measures for these conditions. Even more, there exists no cure aside from radical surgery for refractory ulcerative colitis[5].

The medical management of IBD currently stands at topical intestinal anti-inflammatories, systemic immunosuppression/immunomodulation, and novel biologic agents. The response rates, or rather the percentage of IBD patients experiencing true and deep remission using currently available treatment, is notoriously low. Only just recently have gut-specific monoclonal antibody inhibitors such as vedolizumab, which targets the integrin $\alpha4\beta7$ receptor, been approved for the treatment of IBD, possibly ushering in an age of targeted therapies[6]. However, many if not all of the current treatment modalities for IBD have significant side effect profiles, exorbitant cost, or both[7,8]. A prospective avenue of treatment for IBD that avoids many of the pitfalls of current therapy involves modulating mucosal inflammation using bioactive phytochemicals delivered by the diet. In fact, it has been reported that diets rich in fruits and vegetables are protective of IBD, which may indicate a role for future diet-derived treatments[9,10]. The ideal treatment would have influences on gut barrier permeability, innate GI inflammation, and mucosal immunity, all pathophysiological hallmarks of IBD.

One potential mediator of anti-inflammatory dietary compounds is the aryl hydrocarbon receptor (AHR). The AHR is a chaperoned cytosolic protein that has been found to influence transcription after binding to an exogenous ligand[11]. It is a member of the basic helix-loop-helix transcription factor family as well as the Per-Arnt-Sim protein homology that regulates environmental adaptation to ligand exposure[12,13]. Once bound, the AHR can shed its cytosolic chaperones, heterodimerize with the aryl hydrocarbon receptor nuclear translocator, bind to specific xenobiotic response elements within the genome, and induce downstream genes *via* transcriptional activation (Figure 1)[14,15]. The canonical function of the AHR exists as an environmentally responsive "sensor" which acts to detoxify its own ligands *via* upregulation of phase Ⅰ and phase Ⅱ enzymes, most notably the cytochrome P450 superfamily[16]. Its biology has been most famously attributed to the metabolism of dioxin, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)[17]. In addition to its roles in toxin handling, recently the AHR has been implicated in inflammatory pathways, tumorigenesis, and immune regulation within the intestines[18-20]. These downstream effects of AHR activity have been linked to manipulations of T-cell response, interleukin (IL) production, as well as altered cytokine function[21]. All of these phenomena have been found to contribute in some way to regulation of intestinal immunity, mucosal integrity, and alterations to the microvasculature of the intestine, which are all pathological disturbances inherent to IBD[22]. While it is known that AHR biology is linked to the development and progression of IBD, it is yet to be determined if the AHR can be manipulated in such a way to exert a preventative, protective, or even therapeutic role in IBD *via* dietary ligands[23].

The well-studied dietary component indole-3-carbinol (I3C) has been recognized as a precursor to a host of AHR ligands that are active in the gut. The compound glucobrassicin (precursor to I3C) is found in high concentrations in the Brassica family of vegetables which includes broccoli, cabbage, and Brussels sprouts (Figure 2)[24]. Mastication-induced enzymatic hydrolysis of glucobrassicin produces I3C in the mouth. I3C then dimerizes to 3,3'-diindolylmethane (DIM) in the presence of gastric HCl as well as indole [3,2-b] carbazole (ICZ) among others further down in the GI tract[25]. It is known that DIM is the molecule which exerts more robust effects on the AHR, not its parent I3C[24]. AHR activation has been found to modulate activity of intraepithelial lymphocytes, preserve lymphoid organs in the gut, and maintain mucosal homeostasis[26,27]. Moreover, DIM-supplemented diets have been shown to attenuate colonic inflammation as well as suppress colitis-associated tumorigenesis in mice[28]. This effect may be due to the ability of DIM to modulate various inflammatory cell actions in the gut lining[29]. What is known for certain is that dietary AHR ligands are able to induce the receptor within the gut epithelium as well as globally[30]. These recent advances in the understanding of the effects of AHR stimulation *via* dietary ligands may lead to diet-derived novel anti-inflammatory agents which combat the inherent disturbances of IBD.

This review highlights current knowledge on AHR

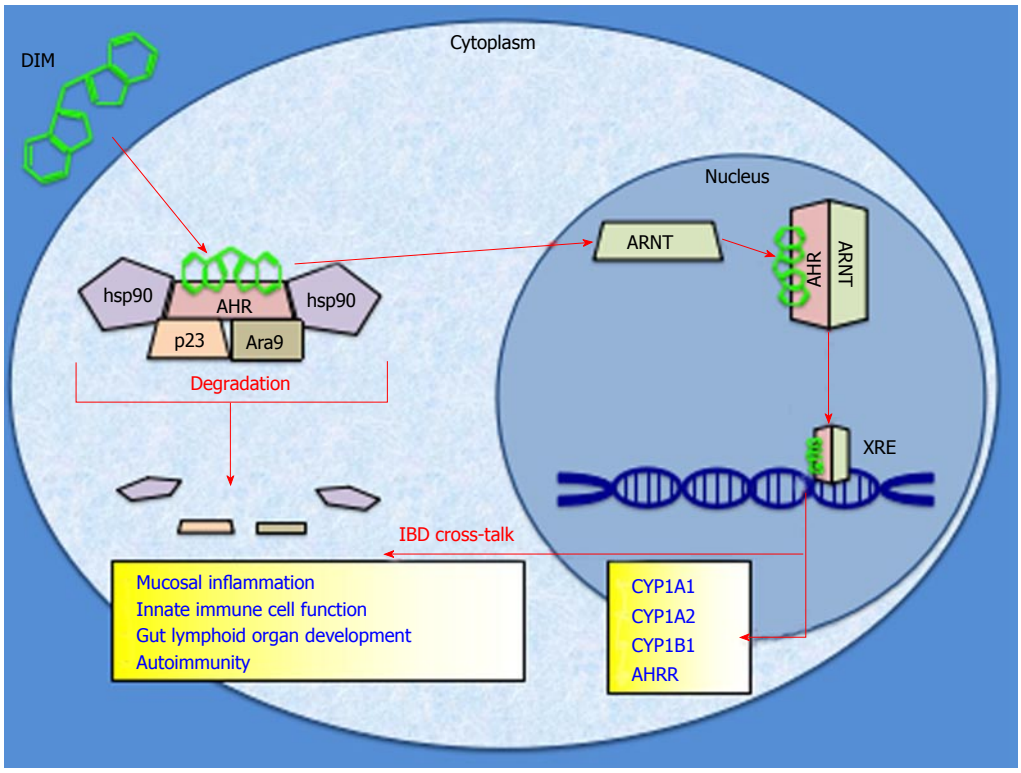

Figure 1 The aryl hydrocarbon receptor signaling pathway is depicted with 3,3'-diindolylmethane as a model agonist. Upon binding to a ligand, aryl hydrocarbon receptor (AHR) sheds its cytosolic chaperones and translocates to the nucleus to heterodimerize with aryl hydrocarbon receptor nuclear translocator (ARNT). This complex binds to the xenobiotic response element (XRE) within the genome and drives transcription of cytochrome P450 detoxifying enzymes. Proposed avenues of cross-talk with inflammatory bowel disease pathology are listed. IBD : Inflammatory bowel disease.

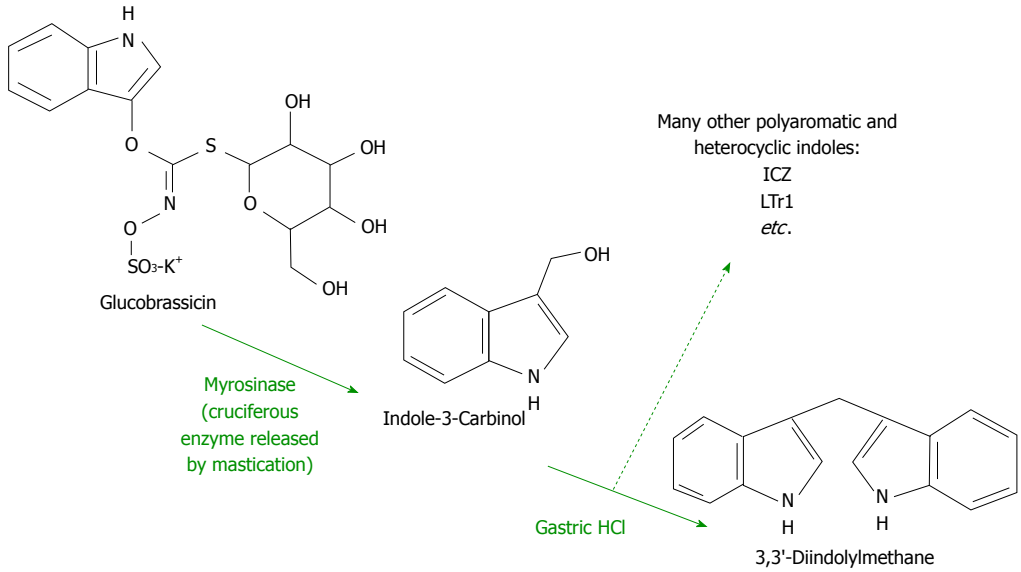

Figure 2 Presented is a simplified model for glucobrassicin digestion. I3C is freed from glucobrassicin by the mastication-released enzyme myrosinase. Gastric HCl drives dimerization of I3C to 3,3'-diindolylmethane, as well as other indole complexes that are released to the duodenum and distal digestive tract. I3C: Indole-3-Carbinol.

stimulation in the context of IBD, especially as it relates to dietary stimulation of the receptor. Continued study of the manipulation of the unique gastrointestinal inflammatory milieu associated with IBD could eventually lead to both novel therapeutics as well as diet-modifying strategies. Due to the apparent benign side effect profile of dietary AHR ligands, clinical application of this knowledge could reduce iatrogenic immunosuppressive morbidities associated with current IBD treatment as well as improve overall disease

control.

LITERATURE SEARCH

A systematic literature search was conducted using PubMed and Google Scholar for "aryl hydrocarbon receptor", "AHR", "IBD", "ulcerative colitis", "3,3'-diindolylmethane", "indole-3-carbinol", and "mucosal immunity". Searches containing relevant synonyms and combinations of the above terms were also utilized. Eighty-nine relevant references were identified and cited within this review. Included studies ranged from basic science investigations to clinical trials.

IN VITRO INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

The biology of the AHR is well studied in numerous *in vitro* models, however, recently the common understanding of the AHR solely acting as a toxicological sensor that upregulates detoxification enzymes has been challenged[31]. Interactions between the receptor and dioxin (TCDD) have always been the cornerstone of mechanistic and physiologic AHR studies, however it is now known that there is a wide compendium of exogenous chemicals that operate *via* the AHR[32-34]. In fact, it is micronutritional chemicals such as the indole family including I3C and DIM that have recently been identified as the bridge between AHR signaling and anti-inflammatory as well as chemoprotective effects in the gastrointestinal system[35]. These chemicals have been found to enhance mucosal integrity, maintain intraepithelial lymphocyte populations, as well as sensitize the GI tract to certain populations of enteric flora[36,37]. In contrast, TCDD treatment has been found to weaken mucosal immunity in the gut[38]. This would present a possible bifunctional role for the AHR and IBD. Further investigation of these actions is warranted to elucidate their role within the inherent disturbances of IBD. An important step in understanding the role of both the AHR and its dietary ligands is to examine their roles modulating inflammation *in vitro*.

Research surrounding the aryl hydrocarbon receptor and various aspects of immunity has recently exploded, especially concerning the effects of dietary ligands. First, it is important to note that not only has DIM been found to activate the AHR *in vitro*, but has also been found to elicit multiple chemoprotective responses in various intestinal cell lines[39-42]. In addition to its ability to upregulate the AHR in cells of the digestive tract, DIM treatment also modulates immune cell activity. For instance, DIM treatment suppresses the inflammatory response of murine macrophages *in vitro via* downregulation of TNF-α, IL-6, and IL-1β[43]. These effects and more were also found when murine dendritic cells were treated with I3C. This protocol prompted a downregulation of TNF-α, IL-6, and IL-1β as well as an upregulation of IL-10[44]. These are important findings as activated macrophages as well as these inflammatory cytokines, especially TNF-α, play key roles in the pathogenesis of IBD[45-49]. In fact, many of the most widely used biologic agents for the treatment of IBD are anti-TNF-α antibodies[50].

In addition to various cytokine and interleukin abnormalities, IBD has also been linked to various T-cell populations and their relative size and function in the GI tract[51]. Two distinct populations that have been linked to IBD disease activity are T-regulatory cells (T_{reg}) and T_h17 T-cells[52-54]. The action of T_{reg} cells has been found to be protective, while T_h17 cell activity has propagated inflammatory damage in IBD. It is well established that the aryl hydrocarbon receptor modulates various populations of immune cells, which has implications for the future treatment of IBD[55]. In fact, AHR stimulation *via* natural ligands has been linked specifically to upregulated T_{reg} cell activity and inhibition of T_h17 cell activity[27,55-57]. These effects have been further proven to be AHR-dependent[58]. Another immunomodulatory effect of *in vitro* AHR stimulation comes as a consequence of T_{reg} cell biology. AHR activity enhances T_{reg} differentiation and thus increases the population of immunoregulatory/anti-inflammatory cell populations that are responsive to IL-10[58]. This is not only important because, as mentioned earlier, DIM treatment of murine immune cells leads to the induction of IL-10 , but also because IL-10 has a firmly seated role in the pathophysiology of IBD. Mice null for IL-10 have been found to be deficient in various immunoregulatory functions in the GI tract[59]. Even more, in a small trial, patients with CD responded favorably to treatment with recombinant IL-10 producing microbes[60]. Further study of the interaction between dietary AHR ligands and immune cell function could lead to a better and more targeted understanding of their interplay.

There exists a large battery of cellular cascades and signaling pathways enhanced, inhibited, or modulated by the actions of dietary indoles such as I3C and DIM, though there remains a gap concerning a full understanding of their anti-inflammatory effects[61]. Further *in vitro* protocols focusing solely on the interaction between the AHR and certain "micronutriceuticals" like I3C and DIM could one day lead to a better understanding of their cellular effects in the context of IBD.

IN VIVO INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

The AHR has been extensively studied *in vivo*, mainly through the use of murine models null for the AHR to better understand its unique role in toxicology. Previous research has suggested the need to better understand the potential immunological function of AHR across various disciplines[62]. The AHR has been previously implicated as an important autoimmune target *in vivo* as it alters expression of the T_h17 cell subset and

associated cytokines in response to environmental toxins in the intestine[56,63]. Perhaps one of the most interesting avenues of research linking environmental exposures to altered immune response *via* the AHR can be found in the pathogenesis of IBD[21]. To best study the complex interaction of environmental factors and AHR expression in the context of immune function in the gut, many *in vivo* models have been developed to pick apart this inflammatory environment.

Due to the historical classification of AHR as the dioxin receptor, many models have been developed using TCDD treatment after induction of IBD. Dextran sulfate sodium (DSS) is a commonly employed agent to induce colitis in murine models, and multiple studies have shown that pre-treatment with low dose TCDD can prevent inflammation associated with colitis and/or reduce inflammation when administered after the onset of colitis in mice[57,64]. A similar study using trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice as a model for CD, showed that animals treated with TCDD recover quicker and experience less colonic damage than those that are untreated[43]. While these studies show promise for the role of AHR in IBD, dioxin is a carcinogen that is highly persistent in tissue, leading to efforts to identify novel AHR ligands with low toxicity for use *in vivo*.

As a non-toxic agonist of the AHR, β-naphthoflavone (βNF) has shown great potential in attenuating colitis through reducing the histological score in both wild-type and AHR null mice with varying severities of DSS-induced colitis[65]. Perhaps even more interesting is the use of an endogenous mammalian AHR ligand such as the non-toxic tryptophan byproduct 6-formylindolo(3,2-b)carbazole (FICZ), which has been shown to protect mice from DSS-, TNBS-, and T-cell transfer-induced colitis through reduced inflammatory cytokine levels and lack of IL-22 induction[18]. While these compounds attenuate colitis without the potential toxic side effects of TCDD, research into the use of dietary phytochemicals as AHR ligands is of even greater interest for the treatment of IBD[66]. One study showed that the AHR is induced by phytochemicals derived from plants of the Brassicaceae family, which includes broccoli, cabbage, kale, and others. It was found that this AHR activation is required for development of RORγt^{+}-expressing innate lymphoid cells (ILCs), as shown by increasing pools of these cells when mice are fed a diet supplemented with I3C, a product of glucobrassicin breakdown[26]. Another study established a role for I3C in controlling bacterial colonization of the gut, sustaining immune function, and protecting epithelial barrier organization as it pertains to colitis severity[27]. I3C remains a compound of great interest for the treatment of IBD, but the activity of I3C in the diet is most likely dependent on the activity of DIM, the dimer product of I3C hydrolysis by gastric acid. DIM would make up the majority of the indole load that reaches portions of the intestinal tract distal to the duodenum.

DIM has previously been shown to alleviate hepatic inflammation through shifting of diet-induced T_h17 dominance to T_{reg} dominance[67]. These data were further supported in studies where DIM was shown to attenuate experimental colitis as determined by pathological findings in mouse models, including evidence that DIM works through the AHR to decrease the T_h17 cell population while increasing the number of T_{reg} cells[29,68]. In DSS-induced colitis experiments, DIM has been shown to attenuate the disease by reducing the clinical severity of colitis, including prevention of colonic shortening and weight loss in addition to dramatically decreasing the number of tumors in AOM/DSS treated mice, which provide a common model of colitis-associated colorectal cancer[28].

In vivo models to study the AHR and IBD remain warranted, as there are numerous unidentified factors that affect progression of the disease. In particular, the interaction between immune cells and the gut microbiome is of growing interest to the research community. For example, AHR null mice succumb to infection by Citrobacter Rodentium because the absence of AHR signaling leads to a lack of RORγt+ ILCs that consequently do not produce enough IL-22[69]. Furthermore, the balance between ILCs and T_h17 cells regulated by AHR has been shown to control the composition of commensal flora[69]. In fact, the menaquinone precursor 1,4-dihydroxy-2-naphthoic acid, an AHR ligand produced by *Propionibacterium freudenreichii* has been shown to inhibit DSS-induced colitis in mice and is even commercially available in Japan as a dietary supplement that holds promise as an IBD treatment agent[70]. These findings are critical to the continued study of IBD, as interactions between dietary factors and various states of colonic dysbiosis have been shown to contribute to disease progression[71,72].

HUMAN AND CLINICAL INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

While there is a wealth of data and analysis surrounding the aryl hydrocarbon receptor and DIM in both tissue culture and murine models, there are few studies in humans related to IBD, clinical or otherwise. Some correlations have been made however, and these have prepared the way for many potential future studies. Arsenescu *et al*[23] found that AHR activity is upregulated in colonic biopsy tissue in IBD patients when compared to healthy controls. Even more, this increased activity mirrored that of IL-8, a neutrophil chemotactic that is elevated in IBD patient tissues[23,73]. Conversely, it has also been reported that biopsies from patients with CD exhibit downregulated levels of AHR, which is thought to be due to T_h17 cell infiltration of inflamed tissue in CD[18]. This underscores the inherent bifunctionality of the AHR. Even though there are few studies which investigate human tissue, they do provide some exciting

evidence to a role for the AHR in human IBD.

There are not currently any clinical trials using DIM for any form of IBD. However, there are multiple chemopreventive and chemotherapeutic trials using both DIM and its parent I3C in the context of a variety of neoplasms. These trials aimed to treat, prevent, or modulate hormone response in breast cancer, vulvar epithelial neoplasia, cervical intraepithelial neoplasia, and recurrent respiratory papillomatosis[74-77]. Again, while these examples are outside the realm of IBD, they do serve to prove that a clinical trial using I3C and/or DIM is biologically feasible in humans. In addition, there have been multiple studies which have analyzed the pharmacodynamics of these compounds in humans, which provide groundwork to one day optimize dosing protocols for trials aimed at IBD[78-80]. One pharmacokinetic and safety investigation established that not only are I3C and DIM non-toxic at doses ranging from 200-800 mg daily, but also that in most of the participants tissue concentrations over 1 mmol/L were observed[81].

What all of this work has done is prove that both I3C and DIM have some form of biologic and therapeutic activity in humans. Whether or not this activity is the result of AHR stimulation remains to be seen. Moving forward, a clinical trial utilizing these phytochemicals to combat IBD is warranted. The concept of using natural chemicals to treat intestinal inflammation is not new. Curcumin, the biologically active derivative of the spice turmeric, has been found to modulate numerous inflammatory, oxidative, and tumorigenic pathways in various tissues, including the colorectum[82-85]. Numerous *in vitro* and *in vivo* studies have propelled curcumin into multiple IBD-related clinical trials. The first of these investigations was a very small pilot study which discovered that in IBD patients curcumin treatment lowered both erythrocyte sedimentation rates and CD Activity Index scores *vs* placebo[86]. More recently, Hanai *et al*[87] found in their RCT that curcumin performed well *vs* placebo for maintenance therapy of mild-moderate ulcerative colitis. While oral delivery proved to have therapeutic activity, curcumin enemas have also been employed in the treatment of distal colitis with similarly efficacious results[88]. In relevance to the paradigm of I3C/DIM acting *via* the aryl hydrocarbon receptor, curcumin as well as other dietary phytochemicals have been found to modulate AHR activity[89]. These trials of curcumin provide relevance to investigating the therapeutic potential of natural dietary chemicals such as I3C and DIM in the context of IBD.

CONCLUSION AND FUTURE DIRECTIONS

The complex and often dangerous treatment of IBD is a dilemma faced by gastroenterologists and colorectal surgeons alike. The intricate inflammatory milieu of IBD presents many avenues for potential targets to attenuate the inherent autoimmunity of the condition. In order to better understand the role that dietary ligands of the AHR play in attenuating IBD, potential avenues of study should focus on the aryl hydrocarbon receptor as it pertains to intestinal barrier function, immune regulation, and inflammation. To achieve this, portions of the IBD phenotype would be isolated and measured under AHR stimulation by a dietary agonist such as I3C or DIM. Also, the binding affinities of these compounds to the AHR in an array of gastrointestinal tissues must be established in order to localize the cell and tissue types where these agents will achieve the most robust response. Another important line of inquiry is to delineate the molecular cross-talk between AHR stimulation and the numerous other pathways previously identified as those that drive IBD. More globally, tissue-specific AHR activity should be investigated in order to ascertain off-target effects of treatment with a dietary AHR agonist. Finally, the most rigorous examination of these agents would be a randomized controlled trial of I3C or DIM for the treatment of IBD within the Phases set by the FDA. However, incorporation of dietary AHR ligands into human clinical studies demands a crystal clear picture put forth by exhaustive *in vitro* and *in vivo* murine models as to how these compounds exert their effects. Throughout these various investigations, it would remain important to delineate additional molecular pathways engaged by these dietary ligands in addition to the AHR in order to better understand their complete mechanisms of action.

Further investigation of how IBD-related cascades can be manipulated exogenously, perhaps *via* the AHR, could one day lead to diet-derived and well-tolerated regimens for those with ulcerative colitis and CD. That being said, it must be appreciated that the AHR is only one of many potential signaling cascades that may influence the IBD phenotype in humans. The characterization of a diet-derived agent, AHR agonist or not, that targets the hallmark imbalances in IBD without compromising host immune function would revolutionize current medical treatment modalities and save many from radical surgical intervention.

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