Published in final edited form as:

Mol Nutr Food Res. 2017 January ; 61(1): . doi:10.1002/mnfr.201600129.

Diet, gut microbes, and the pathogenesis of inflammatory bowel diseases

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Abstract

The rising incidence of inflammatory bowel diseases in recent decades has notably paralleled changing lifestyle habits in Western nations, which are now making their way into more traditional societies. Diet plays a key role in IBD pathogenesis, and there is a growing appreciation that the interaction between diet and microbes in a susceptible person contributes significantly to the onset of disease. In this review, we examine what is known about dietary and microbial factors that promote IBD. We summarize recent findings regarding the effects of diet in IBD epidemiology from prospective population cohort studies, as well as new insights into IBD-associated dysbiosis. Microbial metabolism of dietary components can influence the epithelial barrier and the mucosal immune system, and understanding how these interactions generate or suppress inflammation will be a significant focus of IBD research. Our knowledge of dietary and microbial risk factors for IBD provides important considerations for developing therapeutic approaches through dietary modification or re-shaping the microbiota. We conclude by calling for increased sophistication in designing studies on the role of diet and microbes in IBD pathogenesis and disease resolution in order to accelerate progress in response to the growing challenge posed by these complex disorders.

Keywords

Diet; IBD; microbiota; pathogenesis; microbial metabolism

1 Introduction

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), present a significant global health challenge. The worldwide incidence rates for CD and UC have risen in recent decades [1]. As with many other complex diseases of immunity, epidemiological trends in the occurrence of IBD suggest a link to Western culture and lifestyles. The highest incidence and prevalence of IBD is found in the United States and Europe [1]. IBD are expanding rapidly in Asia, particularly in Japan, India, and the Middle East, where Westernization has progressed significantly [2]. Migrants who come into contact

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Conflict of interest statement: K.T.D. and E.B.C. have no conflicts to declare.

with Western societies appear to be at high risk of developing IBD, even after they return to their home countries [3].

Genetic and environmental factors play a critical role in IBD pathogenesis. Genetic analyses of IBD have identified over 200 loci associated with UC or CD risk [4–6]. Meanwhile, a variety of environmental and behavioral factors are linked to IBD pathogenesis, including diet, smoking, stress, sleep patterns, hygiene, and antibiotic use [7]. The intestinal microbiota represents another major contributor to disease risk [8]. Unraveling the complex network of interactions underlying IBD pathogenesis is essential for making advances in the diagnosis and treatment of these disorders that could curtail their global expansion.

There is a great deal of interest in the link between diet, the intestinal microbiota, and IBD [9–11]. Diet plays important roles in intestinal function and immune activity. It also shapes the intestinal microbiota community structure [12] and influences community function by acting as a source of material for microbial metabolism [13]. Both diet and the microbiota are seen as potential targets for therapeutic intervention in IBD. In this Review, we will summarize recent advances in our knowledge of how diet and the microbiota, acting independently or in concert, contribute to IBD risk. We will also discuss these findings in the context of efforts to develop IBD treatment focused on manipulating diet or the microbiota.

2 Diet as a risk factor in IBD

The ability of specific foods or dietary patterns to influence the risk of CD and UC has been extensively studied. Early investigations relied on retrospective case-control studies; while these studies assessed a broad range of dietary factors, a number of reports produced conflicting results on the benefit or detriment of certain foods, and many were unable to produce statistically significant results due to small sample size [9, 14]. In recent years, prospective studies of large population cohorts in North America and Europe (Table 1) have attempted to resolve previous discrepancies and controversies regarding dietary effects of macronutrient composition on IBD risk, but with varying success.

Several lines of evidence point to aspects of the typical Western diet that may promote the development of IBD. The contemporary diet of many Westerners contains high quantities of animal protein and fat, sugar, and processed foods, and low amounts of plant-based foods [12, 15, 16]. Increased meat consumption has been associated with increased risk of both CD and UC [16, 17]. The connection between fat intake and IBD is more tenuous: a systematic review of 19 diet studies claimed that high total fat intake was associated with elevated risk of CD and UC [16], but this claim has been challenged elsewhere [18], and recent prospective studies of dietary patterns in two large cohorts found no association between total fat consumption and risk of CD or UC [19, 20]. Likewise, total sugar intake, also typically elevated in Western diets, appeared to have no effect on IBD risk in a prospective cohort [21]. However, a more recent prospective analysis of dietary patterns demonstrated that a diet marked by high sugar and soft drink consumption plus low vegetable intake was associated with increased UC risk for patients diagnosed more than 2 years after dietary assessment was completed [20].

Intake of polyunsaturated fatty acids (PUFA) was positively associated with increased risk of CD in case-control studies of adult and pediatric IBD patients [16, 22–24]. However, more recent data from prospective cohort studies has suggested that omega-3 PUFA may lower risk of CD [25] or have no effect on CD risk [19]. Omega-3 PUFA may also have a minor protective effect in the context of UC risk [19, 26]. Conversely, omega-6 intake has been positively associated with CD [16, 22, 23] and UC [27], although data from a recent prospective study does not support this connection [19]. Interestingly, a prospective analysis of a multinational European cohort concluded that IBD risk was not altered by consumption of a Mediterranean diet, which is high in omega-3 PUFA [20]. The effects of omega-3:omega-6 PUFA ratios on disease susceptibility may be modulated by genetic variants in fatty acid metabolism genes such as *CYP4F3* and *FADS2* [28]. This finding points to the need for further studies of how diet-gene interactions contribute to IBD risk.

Fruit and vegetable intake has been associated with decreased risk of CD [16, 23, 29, 30]. There is some evidence that vegetable intake also protects from UC [16], although recent prospective cohort studies disagree on this point [20, 30]. Interpreting low fruit and vegetable intake as causative for IBD may be confounded by the fact that patients may avoid these foods when intestinal symptoms arise [18].

Animal studies have generally supported the notion that fat intake plays a crucial role in the etiology of intestinal inflammation. Mice fed a diet with 40% of energy from fat, meant to represent the typical fat content of a Western diet, developed colitis more rapidly after dextran sodium sulfate (DSS) treatment than chow-fed mice that consumed 20% of calories from fat [31]. In the *Il-10*$^{-/-}$ mouse, which is genetically susceptible to intestinal inflammation, long-term consumption of a diet high in milk fat increased the penetrance of the colitis phenotype from 30% to 60% [32]. However, it is difficult to establish a direct link between this observation and human IBD risk, since dairy intake is not associated with IBD risk in analyses of patient dietary habits [16, 20]. Data concerning the effects of PUFA intake on intestinal inflammation in rodent models have been more difficult to interpret. A diet supplemented with omega-3 fatty acids protected against colitis in a CD45RBhi adoptive transfer model of colitis [33]. After induction of colitis by 2,4,6-trinitrobenzene sulfonic acid (TNBS), rats consuming an omega-3-rich diet responded better to 5-aminosalicylic acid therapy than those receiving a control diet [34]. However, omega-3 fatty acids, but not omega-6 fatty acids or saturated fats, were found to aggravate DSS colitis in another study [35]. The lack of agreement among these findings may reflect genetic variation of fatty acid metabolism among different mouse strains, differential mechanisms of rodent colitis, or the timing of receiving the diet (prior to inflammation vs. during inflammation).

Artificial food additives prevalent in Western diets may promote intestinal inflammation by interfering with barrier function in the gut. Emulsifiers are detergent-like molecules used in processed foods, particularly those with high fat content, such as ice cream. Treatment of intestinal epithelial monolayers and isolated Peyer's patches *in vitro* with low concentrations of the emulsifying agent polysorbate-80 (P80) enhanced the ability of bacteria to translocate across the barrier [36]. Diets with P80 or another emulsifier, carboxymethylcellulose (CMC), compromised mucosal integrity in mice, resulting in greater proximity of luminal

microbes to the epithelium and chronic low-grade intestinal inflammation. In *Il-10−/−* or *Tlr5−/−* mice, emulsifier intake increased the incidence of colitis. These agents also changed the microbial profile of the mouse intestine, creating blooms of mucus-degrading bacteria such as *Ruminococcus gnavus* and *Akkermansia muciniphila*, and expansions of pro-inflammatory Proteobacteria [37]. While a direct role for emulsifier action on host physiology or microbes has not been investigated in human IBD, these results support the idea that contemporary changes in the constitution of our diets can predispose individuals to intestinal inflammation [38]. Currently there are no controlled epidemiological studies that have investigated a potential association between emulsifier consumption and IBD risk in patient populations. However, there is a rough correlation between emulsifier consumption in a given country and that country's rate of CD incidence [38]. Because processed foods containing emulsifiers may also contain high quantities of fats and sugars, dietary assessment studies of IBD patient populations may not be adequately suited to build a strong case for the effect of emulsifiers on IBD risk. A possible approach may involve randomized controlled trials of IBD patients to see if limiting exposure to emulsifiers affects induction or maintenance of remission. One such proposal involves testing the effect of introducing emulsifiers into enteral nutrition therapy for CD patients and observing their remission rate in comparison to unexposed controls [38].

3 The gut microbiota and IBD

The microbial community assemblage (microbiota) of the gastrointestinal tract plays numerous critical roles in human physiology and metabolism, leading to the suggestion that the microbiota comprise a virtual super-organ [39]. Among its functions include: extracting indigestible nutrients from food that are otherwise inaccessible to humans; vitamin synthesis; promoting intestinal homeostasis by regulating secretions and motility; and educating the immune system to develop mucosal tolerance. Host-microbe interactions are central to the pathogenesis of IBD. Many of the genes associated with IBD risk, such as *NOD2* [40, 41], involve innate immunity and sensing of microbial components. Variants in these genes may create dysfunctional immune responses to the normally tolerated microbes in the intestine.

Intestinal dysbiosis, or a deviation from optimal homeostasis and metabolism of the gut microbiota, is a hallmark of IBD. IBD patients have lower diversity in their gut microbiota [42, 43]. There is often a significant loss of bacteria that produce short-chain fatty acids (SCFA), such as *Roseburia* and *Phascolarctobacterium* [44, 45]. The butyrate producer *Faecalibacterium prausnitzii* is dramatically less abundant in CD patients, illustrating a loss of microbial metabolic capacity [44–46]. The loss of anti-inflammatory SCFA produced by these bacteria may also contribute to the pathophysiology of intestinal inflammation. Pathogenic bacteria that attach to the mucosa, such as adherent-invasive *Escherichia coli* [47] and *Fusobacterium* species [48], are found in greater quantities in IBD microbiomes. Attachment of these bacteria could stimulate immune responses that exacerbate IBD.

For much of the past century, investigating microbes has depended upon culture-based methods, limiting the study of many heretofore-uncultivable microbial strains from the intestine. With the advent of deep sequencing technologies, it has become possible to catalog

the full complement of microbial genes in the intestine [49, 50]. Metagenomic analysis of IBD microbiomes demonstrates that, while only 2% of bacterial genera show significant changes in abundance relative to healthy controls, 12% of genetic networks comprising unique metabolic pathways were significantly increased or decreased [44]. These included basic metabolic modules such as amino acid biosynthesis and carbohydrate metabolism. Some pathways underwent disease-specific changes. For instance, glutathione metabolism genes were more abundant in UC, which could be a bacterial protection mechanism against reactive oxygen species produced in the inflamed gut. In ileal CD, SCFA metabolism genes were underrepresented, while type II secretion systems, such as those used by pathogenic *E. coli*, became more abundant. It remains unclear if these changes are causal in IBD etiology, or simply microbes reacting to the development of a hostile, inflamed gut environment.

Emerging studies suggest that microbes are not just passive actors in IBD pathogenesis. A wealth of evidence supports the notion that changes in the activity of the gut microbiota can push a susceptible host toward disease. In recent years, the concept of “pathobionts” has emerged in the IBD field. Pathobionts are commensal organisms that can become harmful to the host in the proper environmental milieu [51]. Devkota *et al.* [32] showed how diet can trigger pathobiont expansion in the context of intestinal inflammation. Mice fed milk fat-enriched diets released a large quantity of taurocholic acid, a bile acid, into the intestine. This promoted a bloom of the sulfite-reducing bacterium, *Bilophila wadsworthia*, which was associated with increased incidence of colitis in *Il10*$^{-/-}$ animals. Interestingly, oral gavage of taurocholic acid alone was sufficient to recapitulate both the increased incidence of colitis and the *B. wadsworthia* outgrowth in these animals. Although the precise mechanism of how *Bilophila* could promote inflammation was unclear, Devkota and colleagues noted that taurocholic acid provides a source of sulfur that *B. wadsworthia* can convert into hydrogen sulfide, a genotoxic agent that is elevated in human IBD.

The causes of IBD-associated dysbiosis are unclear, but numerous environmental and lifestyle factors may contribute to it. Early life events play key roles in the acquisition of the gut microbiota, and improper microbiota development in the first years of life is associated with later risk for numerous inflammatory conditions [52]. Childhood proximity to pets [53] or livestock [54] is associated with reduced IBD risk, suggesting the importance of exposure to microbes at a young age. Breastfeeding helps the development of the intestinal microbiota in infants, as breast milk contains oligosaccharides that are consumed by intestinal bacteria, as well as secretory IgA, an immune mediator of gut homeostasis [55, 56]. While some population studies have implicated breastfeeding as a protective factor against IBD [53, 57], other studies have found no evidence to this effect [58, 59]. Dysbiosis is also more pronounced following antibiotic use [45].

Diet controls gut microbiota assembly and may play a key role in establishing dysbiosis related to IBD. Numerous studies of the relationship between diet and microbiota in human populations have delineated specific patterns of microbes that correlate with high intake of plant or animal foods. Compared with European children eating a typical Western diet, children in a rural African village subsisting on a primarily vegetarian, fiber-rich diet have a gut microbiota characterized by a higher ratio of phylum Bacteroidetes to phylum Firmicutes, more abundant *Prevotella* and *Xylanibacter* species capable of metabolizing

plant polysaccharides, and decreased *Shigella* and *Escherichia* [60]. Gut microbial communities are thought to form two major “enterotypes” that are linked with long-term dietary patterns: a *Bacteroides* enterotype is linked with high intake of animal fat and protein, while a *Prevotella* enterotype is linked with intake of carbohydrates and fiber [15]. Short-term dietary change can have a rapid impact on reshaping the gut microbiota. An animal-based dietary regimen leads to microbial community changes within 24 hours, marked by increases of bile-tolerant *Alistipes, Bilophila*, and *Bacteroides* species [61]. Although diet can induce rapid changes in the microbial population, it may not affect enterotypes shaped by long-term dietary preferences [15]. Microbes that are responsive to dietary change have been implicated in IBD. Notably, animal-based diets rich in protein and fat promote the growth of *Bilophila* and reduce the abundance of SCFA-generating *Roseburia* [61]. Animal-based diets are also associated with increases in Enterobacteriaceae including *Escherichia* [60]; pathogenic variants of *E. coli* are often found near areas of inflammation in CD patients with ileal disease [44, 45, 47, 62].

4 Microbial metabolism: effects on intestinal inflammation and IBD

Apart from the outgrowth of harmful bacteria, IBD-associated dysbiosis is also characterized by a loss of beneficial microbes that metabolize dietary components into pro-homeostatic molecules. Fermentative bacteria in the intestine convert dietary fiber to short-chain fatty acids (SCFA) including acetate, propionate, and butyrate [63]. SCFA play a critical role in immune homeostasis in the intestine by promoting the differentiation of regulatory T cells via upregulation of the FoxP3 transcription factor (Treg) [64, 65]. A possible mechanism for this transcriptional response involves epigenetic activation of the *FoxP3* locus in conjunction with the inhibition of histone deacetylase enzymes by butyrate [64]. Activation of the G-protein-coupled receptor GPR43 (or Ffar2) may also mediate the ability of SCFA to modulate immune responses [65, 66]. SCFA production is impaired in IBD, as demonstrated by measurements of decreased fecal SCFA in patients [67], and from bacterial community analyses demonstrating lower abundances of SCFA-producing bacteria such as *Faecalibacterium prausnitzii* and *Roseburia* in active IBD [44]. In rodent models of colitis, administration of SCFA [64, 65] or SCFA-producing commensal microbes [46, 68–70] reduced disease severity. It is worth noting that studies involving the effect of SCFA in animal models of IBD typically involving exposure of the test group to SCFA or commensal bacteria before the initiation of disease. Mice fed a high-fiber diet prior to DSS treatment were protected against colitis; however, the same diet had no beneficial effect if consumed after establishment of DSS colitis [71]. Likewise, dietary fiber has not been convincingly shown to improve active IBD in numerous randomized controlled studies [72].

Bile acid signaling is another point of convergence between the host, gut microbes, and dietary factors which can influence health [73]. Bile acids assist in digestion by emulsifying fats so that they can be absorbed in the intestine. They are made from cholesterol in the liver, and prior to their release in the digestive tract they undergo conjugation to glycine or taurine. Deconjugation of bile acids in the intestine occurs via bile salt hydrolase (BSH) enzymes expressed exclusively by bacteria. Bacteria can further modify bile acids through dehydroxylation. The balance of bile acid composition in the intestine is a determinant of microbiota composition [74]. The products of bacterial bile acid metabolism act as ligands

for bile acid receptors FXR and TGR5. FXR activation in the intestine promotes anti-inflammatory signaling and barrier function [75]. IBD patients have higher concentrations of sulfated and conjugated bile acids in their stool than healthy controls [76]. Furthermore, IBD-associated dysbiosis affects the abundance of BSH genes in the intestinal microbiome; in particular, there is a significant decrease of Firmicutes-associated BSH genes in CD patients [77]. Increased levels of conjugated bile acids can support the growth of pathobionts such as *Bilophila wadsworthia* [32]; concomitantly, the increased ratio of conjugated to unconjugated bile acids would result in a loss of the latter's anti-inflammatory properties through reductions in FXR signaling and increased expression of pro-inflammatory cytokines [75, 76].

Hydrogen sulfide (H2S) is a gaseous molecule whose involvement in IBD pathology is controversial [78, 79]. Higher quantities of H2S can be measured in the feces of UC patients than healthy subjects [80, 81]. H2S inhibits beta-oxidation of SCFAs by colonocytes, depriving them of energy and compromising barrier function [82]. H2S also enhances T cell activation [83](Miller et al. 2012) and acute exposure to H2S causes genomic damage [84]. On the other hand, H2S has been demonstrated to suppress inflammation and promote mucosal healing in animal models of colitis [85–87].

Microbes are an important source of hydrogen sulfide in the gut [78]. *Bilophia wadsworthia* generates hydrogen sulfide via reduction of taurine [88]. High intake of milk fat promotes delivery of taurine-conjugated bile acid to the intestine, thus providing *Bilophila* with a taurine source for H2S metabolism. The bloom of *Bilophila* may induce a T-cell response that drives colitis in a genetically susceptible host [32]. *Fusobacterium nucleatum* can produce H2S via cysteine degradation [89]. Pathogenic *F. nucleatum* has been isolated as a component of the dysbiotic IBD gut [44, 90] and may serve as a predictor of disease severity [45].

A further connection between diet, microbial metabolism, and control of inflammation recently emerged from studies of the intestinal function of aryl hydrocarbon receptor (AhR). AhR is a ubiquitously expressed nuclear receptor that activates xenobiotic metabolism genes in the presence of compounds such as dioxin. Unexpectedly, AhR also plays a key role in adaptive immunity by participating in the differentiation and activity of T cells, including Th1, Th2, and Th17. In IBD patients, AhR expression in the intestine is dampened [91], potentially via upregulation of miRNA-124 [92]. This may create conditions of pro-inflammatory immune activation, as well as local sequelae such as the development of fibrosis [93]. An important dietary source of AhR ligands is indole-3-carbinol, a compound found in cruciferous vegetables [94]. It has been speculated that indole-3-carbinol's effects on AhR may contribute to the protective effect of vegetable consumption in modulating IBD risk [30, 95]. Furthermore, gut microbes can also produce AhR agonists. Feeding mice a tryptophan-rich diet leads to an expansion of *Lactobacillus reuterii*, which can metabolize tryptophan into indole-3-aldehyde [96]. This compound stimulates AhR-dependent expression of *Il-22*, which can ameliorate symptoms of DSS colitis. More recently, Lamas *et al.* [97] demonstrated that the ability of the gut microbiota to produce AhR ligands from tryptophan is linked with host genetic variation in *CARD9*, an IBD risk gene. Fecal samples from IBD patients carrying copies of the *CARD9* risk allele or *CARD9*$^{-/-}$ mice contain

lower levels of tryptophan-derived indole compounds that may function as AhR ligands, and these samples were impaired in their ability to activate AhR [97]. This work reinforces the concept of AhR as a focal point for maintenance of a positive host-microbe relationship in the gut. Moreover, it further underscores the importance of considering gene-diet or gene-microbe interactions when investigating environmental factors contributing to IBD risk.

5 Dietary and microbial approaches to IBD therapy: advances and challenges

Therapeutic manipulation of diet [10, 11] or the microbiome [9, 98, 99] is highly sought after as an adjunctive or replacement treatment strategy. Although much is known about dietary and microbial factors associated with IBD risk, strategies that aim to correct these factors by supplying a particular dietary element or restoring the microbial community are not always effective. This has been seen with studies of omega-3 supplementation in CD, which demonstrated no benefit in maintenance of remission [100, 101]. Certain dietary interventions, then, may be better if used preventatively, rather than therapeutically or in maintenance of remission. However, without effective means for determining who is at risk of developing IBD, designing dietary strategies aimed at IBD prevention will be difficult.

The goal of IBD treatment, which used to focus primarily on symptom management, has advanced in recent years to include long-term remission with evidence of tissue and systemic recovery from inflammation, preferably without relying on the use of corticosteroids or immunosuppressants which pose health risks when used for a prolonged period [102]. Mucosal healing, or endoscopic remission, is a prognosticator of extended remission in both UC and CD [103, 104]. Clinical biomarkers that correlate well with increased remission include low fecal calprotectin [105] and low serum C-reactive protein (CRP) [106, 107].

Several dietary intervention strategies have been shown to promote clinical remission and mucosal healing. Exclusive enteral nutrition (EEN) is a dietary replacement therapy used in the treatment of pediatric CD [108]. In prospective, open-label studies of children with CD, EEN has shown the ability to induce mucosal healing and normalize clinical and biochemical markers [109, 110]. However, EEN is less effective than corticosteroids at inducing remission in adult CD patients [108]. Sigall-Boneh *et al.* [111] investigated the ability of partial enteral nutrition in combination with a CD exclusion diet to induce remission in 47 children and young adults with active CD. After six weeks, remission was achieved in 70% of the cohort, as measured by disease indices and C-reactive protein measures. Chiba *et al.* [112] examined the effectiveness of a semi-vegetarian diet (SVD) to help maintain remission in a cohort of Japanese CD patients. After 2 years, patients consuming SVD had a lower relapse rate than omnivorous patients, concomitant with reduced CRP levels [112].

Evaluations of dietary interventions have not consistently applied these criteria to define their efficacy. For example, recent studies on the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet have relied on patient questionnaires regarding disease symptoms, such as stool frequency [113, 114]. While there

were significant improvements in symptomatic indices reported by these patients, the conclusion that these treatments are effective ways to achieve long-term health goals requires more thorough investigation into the impact of the low FODMAP diet on clinical and endoscopic disease markers.

Microbiota-targeted approaches have demonstrated some promise for treating IBD [98, 99]. In fecal microbiota transplantation (FMT), microbes from the stool of healthy donors are applied via enema or endoscopic delivery into the diseased intestine. FMT has been successfully used to treat recurrent *Clostridium difficile* infections [115]. Several early case studies of FMT applied to IBD patients suggested its potential use to treat active disease [116]. A randomized controlled trial published in 2013 that looked at FMT for inducing remission in UC found no significant benefit [117]. However, a more recent RCT concluded that FMT significantly outperformed placebo in inducing remission in UC patients [118].

A number of randomized controlled trials have investigated the effectiveness of probiotics for treating IBD, with mixed results. A 2014 meta-analysis concluded that probiotics were effective as primary or adjunctive therapy in inducing and maintaining remission in UC, but not CD [119]. The probiotic mixture VSL#3 has shown especially promising results as a UC therapy [120–123]. Less consistent benefits have been observed in clinical trials of *E. coli* Nissle 1917 [124, 125]. A clinical benefit of probiotics in CD has not yet been demonstrated, although in one randomized clinical trial, it was shown that patients taking VSL#3 after bowel resection surgery had lower levels of mucosal pro-inflammatory cytokines than patients receiving a placebo [126]. Dietary approaches to reshaping the microbiota involve the consumption of prebiotics, which supply food substrates that could promote the growth of beneficial bacteria. Randomized controlled trials of prebiotic consumption have demonstrated potential benefits for treating active UC [127, 128], but not for CD [129]. A more promising approach to microbial manipulation for the treatment of CD may lie in the use of “synbiotics” which combine probiotic strains with prebiotic dietary components. Synbiotic therapy using *Bifidobacterium longum* and an inulin/oligofructosaccharide blend has been shown to improve clinical profiles and reduce inflammatory markers in active CD [130].

Finally, identification of anti-inflammatory metabolites synthesized by gut microbes has raised interest in their potential use as “postbiotic” therapies. Much of this research has yet to progress into human clinical studies, but it will be interesting to follow its development in the coming years. For example, Nakao and colleagues [131] performed a small-molecule screen for AhR agonists from a library of microbe-derived compounds. The top hit was 1,4-dihydroxy-2-naphthoic acid (DHNA), a vitamin K2 precursor made by *Propionibacterium freudenreichii*, a bacterium that grows on Swiss cheese. Introducing DHNA into the diet of mice for one week protected them from DSS colitis [131]. Because DHNA is available as a nutritional supplement in Japan, the authors proposed follow-up studies on the efficacy of DHNA for reducing IBD risk. While FMT, probiotics, prebiotics, synbiotics, and postbiotics hold promise as future treatment approaches for IBD, successfully establishing these as alternatives to current treatment regimens will require a deeper understanding of the ecological processes underlying IBD-associated dysbiosis. Strategies to introduce beneficial strains of bacteria into the diseased intestine, either singly or as communities, may be

hampered by the intrinsic resilience of the IBD microbiota to recolonization, just as microbial communities in healthy people help confer resistance to the establishment of pathogens [132, 133].

6 Prospects

IBD arises through a complex set of interactions between host genetics, gut microbes, the immune system, and environmental influences that include diet. The diseases are highly idiopathic, and the traditional classification of IBD into two phenotypes, CD and UC, likely does not reflect the true range of disease states that produce inflammation of the intestine. Each patient's variation of IBD reflects a unique combination of contributing factors, intrinsic and extrinsic, continuous and historical; no single factor is likely to be responsible in every case. Addressing the challenges of identifying causal factors in IBD requires systems-level approaches that capture the nature of interactions between the different players in disease pathogenesis. There is still much that can be learned from patient populations, both in cross-sectional case-control studies as well as prospective longitudinal studies, but careful stratification must be performed to identify signals of disease-associated variables. Attention should be paid to dietary patterns, use of antibiotics or other medications, disease location, and so forth.

Dietary strategies to successfully treat IBD and maintain disease remission are an attractive alternative to presently available medical and surgical therapies. In assessing the impact of these approaches, it will be important to compare dietary therapies to our current arsenal of IBD treatments with respect to clinical standards of care. Mucosal healing has been recognized as a key prognosticator of deep remission in IBD [103, 134, 135], and clinicians investigating nutritional treatment of active disease should adopt this assessment criterion, as was done for EEN [136]. As we progress in our understanding of the causes of IBD, we must also remain open to the prospect that dietary regimens may need to be personalized for individuals or subsets of patients based on genetics, immune status, personal history, and other factors. A tailored approach may be useful for treating disease, as well as for achieving the yet-elusive goal of prescribing diets to prevent the onset of IBD in high-risk patients.

Over the past decade, we have made important strides in understanding the role of the intestinal microbiota in IBD pathogenesis. However, we still lack much in terms of mechanistic insight into how microbes contribute to the onset of disease. We propose several approaches to study design that would remedy this deficit of knowledge. Longitudinal studies of patient populations at risk of developing IBD should include microbiome analyses in order to shed light on potential causative events related to microbial ecology. The interpretation of dysbiosis in IBD patients should be undertaken with sufficient appreciation for clinical metadata that helps identify important associations that take place in subsets of patients, which would more accurately reflect the idiopathic nature of IBD.

Future efforts to study IBD-associated dysbiosis should include a greater focus on the mucosa-associated microbiota. The intestinal mucosa and stool are inhabited by distinctive microbial communities [45, 137]. Intestinal microbes residing near the mucosal surface can regulate local immunity via direct contact with host tissues or by diffusible chemical signals

[138]. In new-onset CD, the degree of dysbiosis is greater in ileal or rectal mucosal biopsies than in stool; furthermore, mucosal communities from ileal or rectal biopsies outperform fecal communities in predictive models for CD diagnosis [45]. These findings suggest that communities recovered from biopsies may offer greater insight into dysbiotic processes and host-microbes interactions that drive the pathophysiology of IBD. Rectal biopsies, in particular, may offer easy access to high-value microbiome data.

Finally, advances in sequencing technology and computational approaches to analyzing genomic data on microbial communities should be harnessed to go beyond our present focus on taxonomic groups in order to learn more about specific strains of microbes that are likely to possess unique functions that play a role in the development of complex diseases [139].

Research into animal models of IBD still represents our best opportunities to discover the mechanisms of pathogenesis. The use of gnotobiotic mouse models to examine the functions of specific microbial communities in the context of genetics and diet is an area that holds much promise. As the microbiome field moves away from descriptive studies toward a deeper understanding of microbiota function, the importance of metabolomics studies, in tandem with other meta-'omics (genomes, transcriptomes, proteomes) will be paramount to discovering how host and microbes choreograph their interactions in health and disease. Similarly, metabolomics approaches to studying single microbes [140] or IBD patient populations [141] will contribute important knowledge of bioactive molecules that could translate into therapeutic innovations for inflammatory bowel diseases.

Acknowledgments

This work was supported by National Institutes of Health/NIDDK grants R01DK097268, R56DK102872, and T32DK007074 (to E.B.C.), and by an NIDDK center grant to the University of Chicago Digestive Diseases Research Core Center (P30DK42086). The authors thank Dr. Joseph Pierre for helpful discussions regarding the manuscript.

Abbreviations

AhR	aryl hydrocarbon receptor
BSH	bile salt hydrolase
CD	Crohn's disease
DHNA	1,4-dihydroxy-2-naphthoic acid
DSS	dextran sodium sulfate
EEN	exclusive enteral nutrition
FXR	farnesoid X receptor
GWAS	genome-wide association studies
IBD	inflammatory bowel diseases
PUFA	polyunsaturated fatty acids

SCFA	short-chain fatty acids
TNBS	2,4,6-trinitrobenzene sulfonic acid
UC	ulcerative colitis

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Table 1

Prospective cohort studies of dietary influence on IBD risk

Diet factor	Sample features	Findings	Reference
A. European Prospective Investigation into Cancer and Nutrition (EPIC) (nested case-control studies)			
Dietary pattern	Cohort size=366,351; UC: cases=256, controls=1022; CD: cases=117, controls=468	"Sugar and soft drinks" diet increased risk in UC cases diagnosed >2 years after diet survey (Highest vs lowest quintile: IRR 1.68, 95% CI 1.00–2.82, p=0.02). Low vegetable intake enhanced risk associated with high sugar and soft drink intake. No pattern associated with CD. Mediterranean diet not associated with reduced risk for UC or CD.	Racine et al. 2016 [20]
Carbohydrates	Cohort size=401,326; UC: cases=244, controls=976; CD: cases=110, controls=440	No associations between UC or CD risk and total carbohydrate, sugar, or starch intake	Chan et al. 2014 [21]
Fatty acids	Cohort size=229,702; CD: cases=73, controls=292	DHA intake inversely associated with CD risk (trend across quintiles: OR 0.54, 95% CI 0.30–0.99, p=0.04). No effect seen for intake of EPA, alpha-linolenic acid, linoleic acid, or oleic acid	Chan et al. 2014b [25]
Omega-3 PUFA	Cohort size=25,639; UC: cases=22, controls=91	Association between DHA intake and reduced UC risk (trend across tertiles: OR 0.43, 95% CI 0.22–0.86, p=0.02). Similar protective trends were observed for increasing intake of EPA (p=0.06) and total omega-3 PUFA (p=0.10).	John et al. 2010 [26]
Fatty acids	Cohort size=203,193; UC: cases=126, controls=504	Increased linoleic intake associated with UC risk (trend across quartiles: OR 1.32, 95% CI 1.04–1.66, p=0.02). DHA intake associated with decreased UC risk (trend: OR 0.59, 95% CI 0.37–0.94, p=0.03). No association between EPA, alpha-linolenic acid, or oleic acid and UC risk.	Tjonneland et al. 2009 [27]
Various macronutrients and micronutrients	Cohort size=260,686; UC: cases=139, controls=556	Trend suggestive of elevated risk from increased total PUFA intake (trend across quartiles: OR 1.19, 95% CI 0.99–1.43, p=0.07). No other macronutrient or micronutrient showed association with altered risk of UC.	Hart et al. 2008 [24]
B. Nurses' Health Study (cohort studies)			
Dietary fat	Cohort size=170,805 women followed over 26 years; cases: UC=338, CD=269	Higher intake ratio of omega-3/omega-6 PUFA associated with reduced incidence of UC (trend across quintiles: HR 0.69, 95% CI 0.49–0.98, p=0.03). Trend of inverse association between total omega-3 intake and UC risk (HR 0.72, 95% CI 0.51–1.02, p=0.13). Trend of positive correlation between trans-unsaturated fat intake and UC risk (HR 1.34, 95% CI 0.94–1.46, p=0.07). No associations between dietary fat intake and CD incidence observed.	Ananthakrishnan et al. 2014 [19]
Dietary fiber	Cohort size=170,776 women followed over 26 years; cases: UC=338, CD=269	Higher intake of dietary fiber associated with lower incidence of CD (Highest vs. lowest quintile: HR 0.59, 95% CI 0.39–0.90). A strong negative correlation to CD risk was ascribed to fruit intake, and a weaker negative correlation to vegetable intake. No effects of dietary fiber on UC risk were observed.	Ananthankrishnan et al. 2013 [30]
C. Other			
Animal protein	E3N (France): cohort size=67,581 women, mean follow-up time=10.4 years; cases: UC=44, CD=30	Intake of total protein, but not total carbohydrate or fat, associated with higher risk of both UC (p=0.06) and CD (p=0.04). Higher intake of animal protein, particularly meat and fish, were positively associated with IBD risk.	Jantchou et al. 2010 [17]