The Role of Diet in the Etiopathogenesis of Inflammatory Bowel Disease

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Abstract

Abstract | Crohn's disease and ulcerative colitis, collectively known as IBD, are chronic inflammatory disorders of the gastrointestinal tract. Although the aetiopathogenesis of IBD is largely unknown, it is widely thought that diet has a crucial role in the development and progression of IBD. Indeed, epidemiological and genetic association studies have identified a number of promising dietary and genetic risk factors for IBD. These preliminary studies have led to major interest in investigating the complex interaction between diet, host genetics, the gut microbiota and immune function in the pathogenesis of IBD. In this review, we discuss the recent epidemiological, gene–environment interaction, microbiome and animal studies that have explored the relationship between diet and the risk of IBD. In addition, we highlight the limitations of these prior studies, in part by explaining their contradictory findings, and review future directions.

Introduction

Crohn's disease and ulcerative colitis, collectively known as IBD, are chronic inflammatory disorders of the gastrointestinal tract that have an increasing incidence[1] and affect over one million individuals in the US and 2.5 million individuals in Europe[2,3], resulting in substantial morbidity4, health- care expenses and loss of productivity in the work environment[5,6]. Although the pathophysiology of IBD is largely unknown, it is thought to be related to an inappropriate immune response to commensal bacteria in genetically susceptible hosts (Fig. 1). A role for genetic risk factors in the development of IBD has been highlighted by the identification of >200 susceptibility loci in genome- wide association studies (GWAS)[7,8]. In addition to the genetic contribution to IBD pathophysiology, environmental factors also seem to substantially contribute to both the development and progression of IBD. For instance, twin studies have demonstrated a <50% concordance in the development of Crohn's disease and ulcerative colitis[9,10]. In addition, epidemiological studies have confirmed the rapid increase in the incidence of IBD in the US and developing countries that have witnessed a dramatic Westernization of lifestyle, with the worldwide prevalence of the disease having surpassed 0.3% at the turn of the twenty- first century[1,11]. Moreover, studies have shown that the incidence of IBD in immigrants to developed countries exceeds that of individuals from their country of origin[12–15].

Among environmental factors, diet is widely thought to have a pivotal role in the development of IBD. Although the exact pathophysiological mechanisms remain unknown, several plausible explanations have been proposed (Fig. 2). First, diet has a key role in defining the composition of the human gut microbiota and, consequently, that of microbial metabolites[16]. Second, food and nutrients associated with a Western diet — characterized by high intakes of red meat, sugary desserts, high- fat foods and refined grains — have been linked to increased mucosal inflammation as measured by stool calprotectin levels in human subjects[17]. Last, animal studies have demonstrated that dietary composition regulates mucosal barrier function, a crucial factor in the pathogenesis of IBD[18,19]. Despite these data, human observational studies investigating the role of diet in IBD have yielded contradictory and inconclusive results.

In this Review, we discuss the available data on the role of diet in the pathogenesis of IBD with a focus on epidemiological, gene–environment interaction, intervention, gut microbiome and animal studies. We also highlight the limitations of prior studies, particularly epidemiological and gene–environment studies, and review future directions that build upon these preliminary studies

Intervention studies

There has been a resurgence of interest in the potential of dietary intervention for the treatment of IBD. Although a comprehensive discussion of prior dietary intervention studies is beyond the scope of this review and has been previously published[20], the early success of these studies further supports a role for diet in the pathogenesis of IBD. For example, several studies have demonstrated that exclusive enteral nutrition (EEN), which involves the administration of a liquid diet formula for a defined period of time, improves both clinical symptoms and intestinal inflammation in patients with Crohn's disease; one randomized controlled trial demonstrated that a short- term EEN was superior to corticosteroids in promoting mucosal healing in paediatric patients with Crohn's disease[21,22]. Nevertheless, similar studies in adults, where compliance to such a restrictive diet might be challenging, have not been as promising[22]. Last, several uncontrolled human intervention studies have also reported promising results for other diets in the treatment of IBD, including the specific carbohydrate diet, the low- fermentable oligosaccharide, disaccharide, monosaccharide and polyol (FODMAP) diet and the Palaeolithic diet[23]. Although large, well- designed, randomized studies in humans are needed to fully examine the therapeutic effects of these diets in IBD, these early results suggest a role for diet in the pathogenesis of IBD and support the need for further investigation in this area.

Epidemiologic Studies

A limited number of prior studies have examined the association between specific dietary factors and risk of IBD[24–26]. Unfortunately, many of these studies have a number of drawbacks. Specifically, most prior studies were retrospective case–control analyses and are therefore subject to numerous limitations including recall and selection biases. Recall bias of diet before the onset of IBD symptoms is particularly problematic. For example, if individuals are recruited after an extended period following diagnosis, they might have considerably changed their diet or preferentially recall consumption of specific foods that exacerbate their symptoms. Similarly, recall of diet within a very brief interval after diagnosis is subject to concerns about reverse causation, whereby symptoms that immediately precede the formal diagnosis might alter dietary intake. In addition, the majority of previous studies collected dietary data at a single time point and were therefore unable to account for variations in dietary intake over time. There have also been very few studies that have rigorously validated dietary assessments within their study populations. Finally, because of the low absolute incidence of IBD in the general population, most prior cohort studies have been limited by sample size. Taken together, these limitations might contribute to the inconsistent associations between dietary factors and the risk of IBD that is generally seen in the scientific literature.

To address these limitations, several large prospective cohort studies over the past 10 years have attempted to better characterize the link between diet and risk of IBD by leveraging validated and updated dietary data collected during long- term follow- up (Table 1). The majority of these studies used the semi- quantitative food frequency questionnaire (SFFQ) to estimate long- term dietary intake. The SFFQ is a method of assessing food and nutrient intake over a specified period of time by obtaining data on the frequency — and in some cases portion sizes — of food and beverage consumption[27]. The SFFQ has several advantages over other forms of dietary assessment (such as 24-hour recall or dietary records) in that it focuses on patterns of dietary intake over longer periods of time and therefore avoids biases that could be introduced through the episodic or occasional consumption of specific foods and beverages. In addition, SFFQs are relatively easy to complete by participants, therefore providing an ideal method to conduct large- scale epidemiological studies of diet in chronic diseases. Last, the SFFQ has been extensively validated against diet records (Box 1), allowing for the use of statistical methods to account for measurement errors. By contrast, the SFFQ is limited by its use in

specific populations with well- characterized patterns of dietary consumption (for example, Western societies) and is subject to over- reporting of consumption of healthy foods as a consequence of social desirability bias.

Dietary studies in the Nurses' Health Study. The Nurses' Health Study (NHS) is a prospective cohort study that began in 1976 when 121,701 female registered nurses aged 30–55 years completed a mailed health questionnaire[28]. Similar baseline questionnaires were returned in 1989 from a parallel cohort of 116,686 female nurses aged 25–42 years that were enrolled in NHSII. Questionnaires have been mailed to members of both cohorts every 2 years, starting in 1976 for NHS and in 1989 for NHSII, to obtain updated information on diet, lifestyle and medical diagnoses, with a follow- up rate of >90% until 2012 for the NHS and until 2013 for the NHSII. Dietary data are collected every 4 years in these cohorts through a 161-item SFFQ.

Early work from the NHS and NHSII showed a low risk of Crohn's disease among individuals who consume high amounts of fibre, particularly fibre from vegetables and fruits29 (Table 1). By contrast, a high omega-3 (n-3) to n-6 polyunsaturated fatty acid (PUFA) ratio was associated with a low risk of ulcerative colitis, whereas a high intake of red meat was associated with an increased risk of ulcerative colitis[30,31] (Table 1). Owing to the increasingly recognized role of specific nutrients and electrolytes such as haem, potassium and zinc in regulating the intestinal barrier and immune function[32–39], studies from the past 5 years have focused on examining the relationship between quantity of nutrient consumption and risk of IBD. Preliminary data from these cohorts have shown an inverse association between dietary zinc and potassium intake and risk of Crohn's disease, whereas dietary sodium, haem and iron intake were not associated with IBD risk[31,40,41] (Table 1).

D***ietary studies in the European Prospective Investigation in Cancer study.*** The European Prospective Investigation in Cancer (EPIC) study, which investigated the link between dietary intake and the risk of common malignant diseases in the general population, comprised 519,978 men and women recruited from 23 centres in 10 European countries[42]. The EPIC–IBD study is a subcohort of the EPIC study that involved a total of 401,326 initially healthy men and women aged 20–80 years who did not have Crohn's disease or ulcerative colitis and who were recruited from 12 centres in 8 European countries between 1991 and 1998. EPIC–IBD participants provided information on age, gender and lifestyle factors (such as smoking, physical activity levels and dietary information) through the self- completion of questionnaires at baseline. The follow- up rate until 2010 in EPIC–IBD was >98%. Dietary assessment in EPIC–IBD was conducted at baseline when participants reported dietary intake using country- specific validated questionnaires42. In most centres, a self- administered SFFQ was used to assess dietary intake (with 88–266 food- related questions) over the previous 12 months. Interviewer- administered diet questionnaires were used in Greece and Spain and in Ragusa, Italy. In the EPIC study, almost 10% of the cohort (~37,000 individuals) was assessed using a single highly standardized, 24-hour recall of actual food consumption to account for any between- cohort differences that might exist in systematic exposure measurement error as well as for within-cohort attenuation biases in relative risk estimates. The energy-adjusted intakes were used to estimate correlations between SFFQ and 24-hour recall, and the mean intake levels estimated from 24-hour recall were used to account for within-cohort and between-cohort variations, respectively[43].

Before the establishment of the EPIC–IBD cohort, one study from EPIC that consisted of 260,686 participants from 10 centres across 5 countries investigated the associations between intake of a total of 18 nutrients, vitamins and minerals and the risk of ulcerative colitis[44]. No associations were detected, with the exception of a weak positive association between

increased total PUFA intake as a percentage of total energy intake and increased risk of developing ulcerative colitis. A similar broad analysis has yet to be published for Crohn's disease in this particular cohort. However, following these initial results, a subsequent study from the EPIC–IBD study further investigated the associations between intake of PUFAs and ulcerative colitis45. On the basis of findings by other groups that n-6 PUFAs are metabolized to pro- inflammatory lipid mediators[46,47], this study hypothesized that individuals with the highest dietary intakes of n-6 PUFAs would have an increased risk of developing ulcerative colitis. Indeed, the highest quintile for dietary intakes of the n-6 PUFA linoleic acid, as measured by the SFFQ, was associated with an increased risk of developing ulcerative colitis (OR 2.49, 95% CI 1.23–5.07)[45] (Table 1). Conversely, the same study found that participants with the highest quintile for dietary intakes of docosahexaenoic acid (DHA), an n-3 PUFA that is metabolized to anti- inflammatory lipid mediators, had a decreased risk of developing ulcerative colitis (OR 0.23, 95% CI 0.06–0.97). Although similar findings for DHA intake and risk of Crohn's disease have been reported in the EPIC–IBD study[48], no associations between n-6 PUFA intake and Crohn's disease have been found in EPIC–IBD to date[48] (Table 1).

By contrast, investigations into the role of monosaccharide, disaccharide and starch intake in developing ulcerative colitis or Crohn's disease in EPIC–IBD have not demonstrated any consistent associations[49] (Table 1). Interestingly, however, EPIC–IBD study participants in the highest quintile for diets rich in sugar and soft drinks had an increased risk of developing ulcerative colitis (incidence rate ratio (IRR) 1.68, 95% CI 1.00–2.82)50 (Table 1). This finding was mainly attributed to those individuals with a dietary pattern of high intake of sugar and soft drinks who had intakes of vegetables, legumes and fruit that were below that of the median population (OR 2.80, 95% CI 1.54–5.09)[50]. High consumption of milk has been shown to be associated with decreased risk of developing Crohn's disease but not ulcerative colitis, independent of dietary calcium intake[51]. However, the association did not show a dose–response relationship, and there was no association between total intake of dairy products, yogurt or cheese with either ulcerative colitis or Crohn's disease. Finally, investigations into alcohol intake and the risk of developing ulcerative colitis or Crohn's disease in EPIC–IBD have not reported any statistically significant associations[52], despite speculation that isoflavones in alcoholic beverages, which accumulate during the fermentation process[53], might have antioxidant and immune modulatory effects on the basis of findings from preclinical studies[54].

Limitations of prospective cohort studies and future directions. Despite offering unique opportunities to study dietary factors in relation to IBD incidence, both the EPIC and NHS studies are limited by the underrepresentation of individuals with an early onset of IBD (age <40 years). This drawback limits the generalizability of the findings of these studies, particularly regarding individuals who were diagnosed with IBD before the age of 40 years. Although dietary data derived from these cohorts have been extensively validated, the correlation between SFFQ and dietary records, considered to be the gold standard, is modest for many foods and nutrients, which in turn can be a source of considerable measurement errors. In addition, despite being the largest cohort studies to date that have examined the link between diet and risk of IBD, the number of incident cases of IBD in these studies is limited, precluding the identification of more modest associations.

Thus, there continues to be an unmet need for a comprehensive, prospective examination of the association between diet and risk of IBD. Such an effort could perhaps be achieved through the establishment of a large international consortium and could be used to achieve a number of important aims. First, such an effort could improve our understanding of the associations between dietary patterns and risk of IBD across cohort studies comprised of different populations with a wide distribution of participant characteristics. Second, it could be used to

examine the presence of dose–response relationships across a wide exposure range. Third, it could serve to generate summary estimates that have greater precision than the individual studies owing to the larger sample size, therefore allowing examination of the population-attributable risk of dietary factors in IBD. Finally, such a collaborative effort could allow for examinations of whether associations differ within specific population subgroups. These analyses are particularly important, as they might identify subgroups of the population that might benefit the most from specific lifestyle interventions. In addition, given that IBD is a heterogeneous disease, the evaluation of whether associations vary by disease subtype might lead to a better understanding of the aetiology of IBD.

Animal studies

Dietary factors are known to induce insulin resistance, influence the balance of fatty acids that elicit or reduce inflammation of the gut epithelium, modify intestinal permeability and contribute to sulfur production, all of which in turn alter the gut microbiota composition by promoting the growth of sulfate- reducing bacteria[55,56]. Animal studies have shown that a Western diet increases the susceptibility of mice to dextran sodium sulfate (DSS)-induced colitis and increases the infiltration of macrophages compared with a Mediterranean diet, which is characterized by a high intake of fruits, vegetables, whole- grain foods, poultry and fish57. In addition, a Western diet in mice alters host intestinal barrier function by increasing the colonization of adherent- invasive *Escherichia coli*[18]. Similarly, in mice, a high- fat diet was shown to disrupt gut barrier function by modifying the composition of luminal bile salts19. Although dietary fibre has been shown to exert its anti- inflammatory effect by modulating the composition of the gut microbiota, increasing colonic fermentation and promoting the production of short- chain fatty acids, studies in mouse models of colitis have also shown that fibre might have a direct immunomodulatory effect through inhibition of pro- inflammatory cytokine production in peripheral blood mononuclear cells[58]. Additionally, in a model of *Citrobacter rodentium* induced acute colitis, a fibre- rich diet reduced inflammation by modifying the host microbiota to increase production of short- chain fatty acids and by altering host immune mechanisms of bacterial recognition and response to promote host health. In contrast to fibre, dietary red meat exacerbates DSS-induced colitis in mice[59].

Although the exact mechanism underlying this observation is unclear, one potential explanation is that animal proteins increase luminal levels of sphingosine-1-phosphate, a sphingolipid involved in cell signalling that has been shown to increase inflammation in mice models of colitis[60–62]. Over the past 5 years, interest in the role of dietary sodium in regulating the immune response has been growing. Several animal studies have shown a role for dietary sodium intake in the development and progression of autoimmune disorders through IL-23–IL-23 receptor (IL-23R)-mediated activation of pathogenic pro- inflammatory T helper 17 (TH17) cells, which have a critical role in the development of IBD[34–36]. In addition to enhancing the induction of pro-inflammatory TH17 cells, sodium also seems to suppress immune tolerance by inhibiting the immunosuppressive functions of forkhead box protein P3 (FOXP3)+ regulatory T (Treg) cells[63]. Sodium might also lead to activation of proinflammatory macrophages64. In contrast to sodium, a study published in 2016 demonstrated the profound suppressive effect of potassium released into the extracellular fluid as a result of necrosis in human tumours on T cell effector function[33]. In turn, the study also demonstrated that augmentation of potassium efflux in tumour- specific T cells improved their effector function and promoted tumour clearance. Together, these findings demonstrate the critical role of sodium and potassium in regulating the TH17 cell:Treg cell balance (Fig. 2).

Gene-Environment Studies of Diet in IBD

Studies investigating the interaction between environmental components and genetic variants in functionally annotated genes have been increasingly used to help infer causal associations[65] and provide insight into potential biological pathways through which an environmental factor such as diet might contribute to the aetiopathogenesis of chronic diseases, including IBD. Genetic loci associated with IBD risk can be broadly categorized into those involving abnormalities in the innate and/or adaptive immune response and mucosal barrier function[66]. Experimental data also suggest that many of these pathways are influenced by dietary factors[67]. Thus, it is biologically plausible that specific dietary components have differential effects on the incidence of IBD according to the genetic background. Data on the influence of gene–environment interaction on IBD risk are sparse. This paucity is largely due to the limited availability of well- characterized cohorts with detailed, updated and validated data on dietary and lifestyle factors with simultaneous annotation of genetic variants. In addition, owing to the low incidence of IBD in the general population, many cohort studies have a limited number of participants, precluding the possibility of assessing gene–environment interactions. Nevertheless, the investigation of gene–environment interaction is an area of great unmet need, as results from such studies will not only shed light on the complex interaction between diet, genetic susceptibility and immune function but could also help to inform dietary recommendations for individuals at a high risk of IBD or those with established disease. Preliminary analyses of gene–environment interaction in studies incorporating dietary factors in IBD have been promising[40,68–70] (Table 2). An analysis from the NHS and NHSII, which included 169 individuals with Crohn's disease and 202 individuals with ulcerative colitis matched to 740 control participants, examined the interaction between total dietary intake of iron and haem iron and genetic variants associated with risk of IBD[31]. This study demonstrated an interaction between iron and haem iron intake and the ulcerative colitis susceptibility locus rs1801274, a coding variant in the FCGR2A (which encodes the low affinity immunoglobulin- γ Fc region receptor IIa) gene. Specifically, among women with the GG genotype, increasing haem iron intake was associated with a substantially lower risk of ulcerative colitis (OR 0.11, 95% CI 0.03–0.37 for each 1 g increase in haem iron intake) (Table 2). By contrast, among women with the TT genotype, increasing haem iron intake was associated with an almost threefold higher risk of ulcerative colitis (OR 2.76, 95% CI 1.02–7.48). Owing to the crucial role of FCGR2A in regulating humoral response to infection71 and the known importance of the rs1801274 variant in altering the binding capacity of the encoded protein product to C- reactive protein (CRP) and immunoglobulin G2 (IgG2)[72–74], these data provide evidence for an intriguing interaction between dietary haem intake and immune function in the development of ulcerative colitis. Similarly, in a nested case–control study of 202 individuals with ulcerative colitis and 169 individuals with Crohn's disease in the NHS and NHSII cohorts matched to 740 control participants on the basis of age, menopausal status, month of blood collection and fasting status, an interaction between dietary potassium intake and genetic variants in the IL-23 pathway that have been previously associated with risk of IBD in GWAS was identified[40,66]. Specifically, the rs7657746 variant of IL21 (which encodes IL-21) seemed to modify the association between potassium intake and risk of IBD (Table 2). Each 200 mg increase in dietary potassium intake was inversely associated with risk of ulcerative colitis (OR 0.90, 95% CI 0.82–0.98) among participants with the AA genotype, but not among those with the AG or GG genotypes. Similar findings were observed in patients with Crohn's disease in this study. As IL-21 has a key role in the development of TH17 cells through signal transducer and activator of transcription 3 (STAT3), a transcription factor required for the differentiation of TH17 cells in vivo, the findings from gene–environment interaction studies suggest a potential mechanism for the observed association[75]. IL-21 and IL-23 induce expression of the nuclear receptor RORγ

(also known as RORC), which, in synergy with STAT3, promotes IL-17 expression in CD4+ T cells, leading to the activation of TH17 cells[75].

In addition, IL-21 inhibits the transforming growth factor-β (TGFβ)-dependent generation of FOXP3+ Treg cells and induces TH17 cell activation[76]. Interestingly, in this study, the gene–environment interaction finding was further supported by in vitro studies demonstrating that potassium induces FOXP3 expression in naive and memory T cells and in pro-inflammatory TH 17 cells. This effect was present even in the presence of pro-inflammatory cytokine, suggesting that potassium suppresses inflammation in a pro- inflammatory milieu. Last, data from the NHS and NHSII have also demonstrated that two variants in CYP4F3, which encodes the cytochrome P450 4F3 enzyme (CYP4F3) involved in PUFA metabolism, might modify the association between n-3 and n-6 PUFA intake and risk of ulcerative colitis[69] (Table 2). Specifically, the association between n-3:n-6 PUFA intake ratio and ulcerative colitis was modified by the rs4646904 single nucleotide polymorphism (SNP) in CYP4F3 (Pinteraction = 0.049). A high (greater than or equal to the median) n-3:n-6 PUFA intake ratio was associated with a lower risk of ulcerative colitis among women with the GG or AG genotypes (OR 0.57, 95% CI 0.32–0.99), but not among those with the AA genotype (OR 0.95, 95% CI 0.47–1.93). Indeed, similar findings were previously reported in a case– control study of children with newly diagnosed Crohn's disease[70], suggesting that the interaction is robust.

Limitations of prior gene–environment studies and future directions. Despite the early promising results from gene–environment studies, it is important to acknowledge the limitations of these data. First, most of these studies had a limited sample size and were therefore not adequately powered to broadly assess (that is, on a genome- wide level) the presence of gene–environment interactions. Second, despite the presence of stringent *P* value thresholds in these preliminary studies, as demonstrated in previous validation studies, even robust findings might still represent spurious associations, further emphasizing the need for validation studies regarding gene–environment interactions[77,78]. Third, owing to the limited sample size and the adjustment of most of these studies for multiple variables, these preliminary studies might have been prone to type II error. Last, although gene–environment interaction analyses might elucidate potential biological mechanisms underpinning the link between diet and IBD, statistical interaction does not imply biological modification; thus, further mechanistic studies are needed to fully characterize the results of these studies. Despite these limitations, preliminary findings highlight the need for larger- scale analyses of the influence of the interaction between diet and genetics on risk of IBD, reinforcing the need for large international consortia composed of well-characterized cohort studies with simultaneous assessment of genetic and dietary data.

Gut microbiota studies

Diet is widely linked to the composition of the human gut microbiome and microbial metabolites[79]. Although much of the microbial diversity seen in the adult gut might be attained by the age of 4 years, the adult microbiome remains susceptible to the influence of diet[80]. Indeed, dietary patterns have been proposed to explain greater than half of the variation in the adult intestinal microbiome[80]. Accordingly, the gut microbiome has a crucial role in the pathogenesis of IBD, as evidenced by observations that infusion of intestinal luminal contents into excluded ileum triggers postoperative recurrence in patients with Crohn's disease[81]. Furthermore, in mouse models of colitis, microbial colonization is required for the development of active inflammation[82,83]. Thus, diet, through its modulatory effect on the gut microbiota, might modify the risk of developing IBD (Fig. 2).

Patients with established IBD have dysbiosis of the gut microbiome, which is characterized by reduced bacterial diversity, enrichment of bacteria of the family Enterobacteriaceae and reduced

abundance of bacteria of the phylum Firmicutes and the genus *Bacteroides*[80,84–86] (Fig. 2). Interestingly, similar patterns of bacterial enrichment have been reported in observational studies of healthy volunteers fed a high- fat, low- fibre diet, suggesting that prior epidemiological findings demonstrating an inverse association between fibre intake and risk of Crohn's disease are in part explained by diet-mediated alteration of the gut microbiota in genetically susceptible individuals[87,88].

The majority of prior studies investigating the interaction between diet, the microbiome and intestinal inflammation have been conducted in animal models of colitis. In mice, dietary haem iron was shown to directly injure the colonic surface epithelium through the generation of cytotoxic and oxidative stress[89,90]. Moreover, increased dietary haem iron intake has also been associated with marked changes in the composition of the gut microbiota, with an increased ratio of Gram- negative:Gram- positive bacteria in mice[91]. This effect was primarily driven by the increased abundance of Gram- negative species, including those belonging to the genera *Bacteroides* and *Akkermansia*, leading to a marked increase in lipopolysaccharide production[91]. In a 2017 study, *Akkermansia muciniphila* was shown in mice to be a pathobiont, promoting colitis in genetically susceptible hosts[92]. Interestingly, alteration in the function of the gut mucosal barrier related to dietary intake of haem iron seems to be dependent on the presence of sulfideproducing and mucin- degrading bacteria (for example, *Akkermansia* spp.)[89]. By contrast, in a mouse model of spontaneous ileitis, depletion of luminal iron altered gut microbial composition to promote inflammation[93]. Finally, a high- fat diet has been linked to changes in phospholipid profile and bacteria taxa in the gut, highlighting the complex interactions between the host and the gut microbiome in response to high fat intake[94,95]. More specifically, high intake of saturated fat altered the gut microbiome, characterized by an increase in the sulfite- reducing pathobiont *Bilophila wadsworthia*, and induced colonic inflammation in *Il10*-knockout mice[96]. This data provided a potential mechanism by which diets high in saturated fat might increase the risk of IBD in a susceptible host.

Human observational studies examining the interaction between diet, the microbiome and IBD are scarce. Among these studies is the ongoing multinational Genetics, Environment and Microbiome study that aims to identify factors that increase the risk of IBD[97,98]. This study is examining several environmental exposures, such as being breastfed and the composition of the microbiome, in a cohort of patients at high risk of IBD. Interestingly, preliminary data from this study have not shown a correlation between intestinal permeability — a key pathogenic pathway in IBD that is known to be influenced by diet[67] — and the gut microbiota[98]. Specific patterns of association have been reported in a large Dutch cohort, in which total carbohydrate intake and features of a Western diet, including high caloric intake and consumption of sugar-sweetened beverages, were negatively associated with gut microbiome diversity[99]. By contrast, features of a Mediterranean diet, such as consumption of fruits, vegetables and red wine, were associated with increased diversity of the gut microbiome. Red wine consumption was also associated with the increased abundance of *Faecalibacterium prausnitzii*, which has been proposed to have anti- inflammatory properties in patients with IBD[100].

Several studies have examined the correlation between host genetics and the gut microbiome in healthy individuals and patients with IBD[101–103]. Generally, these studies have established a potential association between several genetic variants, including IBD- specific risk variants, and the gut microbiome. However, perhaps the most intriguing finding has been the observation that gene–diet interaction could in part regulate the composition of the human gut microbiome. Using metagenomic data from >1,500 healthy individuals, it was found that the abundance of bacteria of the genus *Bifidobacterium* was regulated by a functional variant within the *LCT* gene, which encodes lactase, the enzyme responsible for the breakdown of lactose[104]. Interestingly, this

association was further modified by dairy intake. These studies further illustrate the interaction between diet, host genetics and the gut microbiome in human health and diseases of the gastrointestinal tract and highlight the complex relationship between these factors in studying IBD pathogenesis (Fig. 3).

Conclusions

There is a growing body of evidence suggesting a role for diet in the development of IBD, particularly among genetically susceptible individuals. In addition, data from animal studies suggest that dietary modification alters the risk of IBD. Nevertheless, there continues to be a substantial need for a comprehensive evaluation of the role of diet in the aetiopathogenesis of IBD. Such studies will be challenging because of the complex nature of the relationship between diet, genetics, the microbiome and disease activity (Fig. 3). Several large international collaborations are currently in the planning stages and hope to provide an in- depth prospective examination of the role of specific diets in IBD and overcome many of the shortcomings of prior studies. The successful execution of these studies will represent a critical first step in advancing our understanding of the role of diet in the pathogenesis of IBD.

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