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The Gut Microbiome and Inflammatory Bowel Diseases

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Abstract

Inflammatory bowel diseases (IBD) arise from a convergence of genetic risk, environmental factors, and gut microbiota, where each is necessary but not sufficient to cause disease. Emerging evidence supports a bidirectional relationship between disease progression and changes in microbiota membership and function. Thus, the study of the gut microbiome and host–microbe interactions should provide critical insights into disease pathogenesis as well as leads for developing microbiome-based diagnostics and interventions for IBD. In this article, we review the most recent advances in understanding the relationship between the gut microbiota and IBD and highlight the importance of going beyond establishing description and association to gain mechanistic insights into causes and consequences of IBD. The review aims to contextualize recent findings to form conceptional frameworks for understanding the etiopathogenesis of IBD and for the future development of microbiome-based diagnostics and interventions.

INTRODUCTION

Inflammatory bowel diseases (IBD) are a heterogeneous collection of chronic inflammatory disorders that generally include two separate conditions: ulcerative colitis (UC) and Crohn's disease (CD) (1, 2). The first IBD case which resembled what we call UC today was recorded in the late 1700s, and the term ulcerative colitis was coined in 1859 (3). Later, in 1932, CD was recognized as an entity separate from UC due to its transmural and often patchy pattern of inflammation that can affect any part of the gastrointestinal tract (4). In contrast, UC is restricted to the colon, typically starting from the rectum and spreading proximally to the cecum in many patients (5).

Despite many advances in technologies and experimental models, the etiology of IBD is still unknown. The greater incidence of IBD among identical versus fraternal twins and certain families supports a heritable component. Moreover, the identification of hundreds of genetic polymorphisms and mutations through genome-wide association studies (GWAS) of IBD provides further support for a genetic basis of IBD (6, 7). However, genetics alone is rarely sufficient to cause disease. The incidence and prevalence of IBD have been rising concomitantly with the industrialization, lifestyle changes, and urbanization of modern societies in a time frame too short to be explained by genetic drift or natural selection (8). In this regard, noninheritable factors, such as environmental factors, shifts from plant-based to animal-based processed diets, smoking, antibiotic administration, and so forth, must be considered in the etiopathogenesis of these diseases (9).

The idea that transmissible bacterial agents may be responsible for IBD was first proposed in the early 1900s (4). However, after decades of searching, no pathogens in the traditional sense were identified as the cause. In this regard, there has been an increased focus on the concept that indigenous gut microbes, when given the opportunity, can transform, trigger, and contribute to the etiopathogenesis of IBD. Major shifts in gut microbiota have been reported in association with active disease, for example, increases in the major phylotype Proteobacteria and decreases in Firmicutes (10, 11). In experimental IBD models, several genetically susceptible mouse strains develop colitis only in the presence of gut microbiota, and the frequency and severity of spontaneous colitis are determined largely by the composition of the microbiota (12).

IBD arise from a convergence of genetic risk, environmental factors, and microbial factors, each necessary but insufficient to cause disease (13, 14). We refer readers to a prior systematic review of the gut microbiome and IBD for a summary of past findings that support these relationships (15). Here, we highlight more recent advances that could shift the paradigms of IBD risk, etiopathogenesis, and eventual best practices relevant to prevention, management, and better clinical outcomes of IBD.

CHANGES IN GUT MICROBIOTA OF PATIENTS WITH INFLAMMATORY BOWEL DISEASES: CAUSE OR EFFECT?

Major shifts in the gut microbiota composition and function that promote potential disease states (dysbiosis) are commonly observed in IBD patients, but the significance of these changes is unclear. A key question remains: Is dysbiosis a cause or a consequence of immune activation and inflammation in IBD, or both? While the gut microbiota is fairly stable throughout life, it can be perturbed by dietary changes, environmental changes, infectious pathogens, lifestyle factors, medications, and so on. The development of IBD dysbiosis in turn has repercussions for host responses (e.g., immune and metabolic) that attempt to restore the balance in host–microbe relationships (**Figure 1**). Host response includes the release of antimicrobial peptides (AMPs), reactive oxygen species, immune mediators, mucus, and other factors to influence the composition and functions of the gut microbial community, the latter through modification of the regional ecosystems of

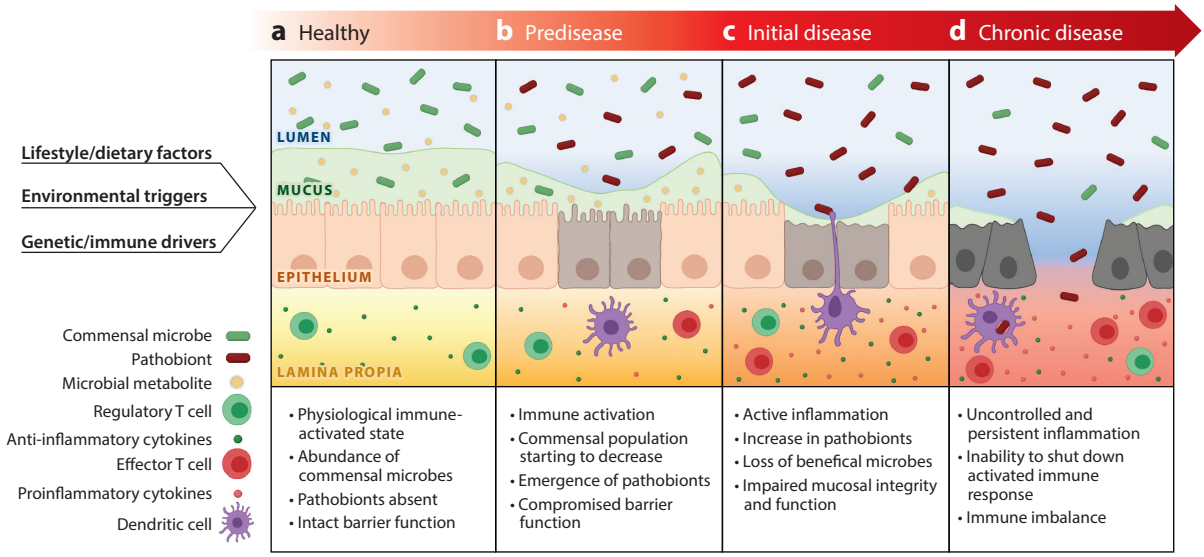

Figure 1

Hypothetical model for the development and progression of inflammatory bowel diseases (IBD). (*a*) Under healthy conditions, commensal microbes produce beneficial metabolites to help maintain an impermeable barrier composed of intact mucosal and epithelial layers. (*b*) In the predisease state of IBD, the disease is at a subclinical level. Genetic/immune drivers, environmental triggers, and lifestyle/dietary factors can all contribute to the occurrence of predisease. At this stage, certain commensal microbes transition to pathobionts that are more fit for an ecosystem where immune activation, the compromised barrier, mucus depletion, and other conditional factors come into play. (*c*) As the disease progress, patients enter the initial stage of the disease, where they display active inflammation and mucosal damage. The abundance of commensal bacteria significantly decreases as blooming pathobionts emerge and dominate. As a result, the microbiota produces fewer beneficial metabolites. (*d*) If the condition persists for a long time, patients will reach a chronic stage of disease with persistent inflammation. Persistent inflammation and long-term dysbiosis lead to immune imbalance and an inability to heal the mucus layer. As a result, the inflammatory and dysbiotic state is maintained, creating a chronic inflammatory cycle. Figure adapted from image created using BioRender.com.

the gut. Several studies have shown that the IBD-associated microbiota exhibits reduced diversity and enrichment of less abundant phyla such as Gammaproteobacteria (16, 17). However, few mechanistic insights have emerged from these associations because important clinical metadata to help contextualize the findings are usually lacking. In addition, studies have relied heavily on low-resolution 16S ribosomal RNA (rRNA) amplicon sequence analytics that provide compositional information limited to the family or genus level, which is insufficient to resolve interindividual variations among individuals with IBD. Moreover, 16S rRNA amplicon sequence variants provide no functional information, which is needed to better understand host–microbe interactions relevant to states of health and disease. Increasing numbers of studies now employ metagenomics, metatranscriptomics, and metabolomics, which, when viewed in the context of host metadata (e.g., clinical course, medications, mucosal gene expression, histology, immune indices), can be much more informative. The application of open-source, community-driven analysis and visualization as well as machine learning platforms can further facilitate the analysis and integration of these large and complex data sets (18–21). For example, Miyoshi et al. (22) accurately predicted which interleukin-10 (IL-10) gene knockout (*Il10* KO) mice would develop colitis on the basis of the metagenomic signatures of their antibiotic-induced dysbiosis.

Study designs have also improved to incorporate longitudinal observations, time-sequence sample collections, better controls, stratification of patients (e.g., CD versus UC), and associated

clinical metadata (e.g., medications, regional involvement, active versus inactive disease). For example, UC patients with ileal pouch–anal anastomosis were followed for up to 2 years with serial endoscopy and sampling of both host mucosa and pouch microbiomes. By performing both 16S rRNA and metagenomic analyses of luminal aspirates, mucosal brushings, and pinch biopsies, the authors of these studies were able to observe the emergence of potential pathobionts (i.e., commensal microbes that can transform into disease-promoting states) before the appearance of endoscopic changes or clinical symptoms (23, 24). The study by Huang et al. (24) also found that UC pouch but not familial adenomatous polyposis (FAP) pouch patients exhibited anomalous mucosal gene responses, potentially rendering them susceptible to developing pouchitis. The Integrative Human Microbiome Project prospectively examined the dynamic changes in the microbiomes of individual IBD patients over 1 year through combined metagenomic and metatranscriptomic analyses (19, 20). Certain microbial populations detected by metagenomic analysis appeared dormant, whereas others that were not detectable by metagenomics appeared functionally active on the basis of metatranscriptomic profiling. Jacobs et al. (25) reported shifts in microbial composition as well as in fecal metabolites (fecal bile acids, taurine, and tryptophan) that were associated with the development of IBD in pediatric patients compared with healthy siblings and parents. These observations have led us to propose the hypothetical sequence of events illustrated in **Figure 1**, where a variety of environmental, dietary, xenobiotic, immunological, and other factors create conditions that promote the transformation of certain commensal microbes to pathobionts that then trigger and/or contribute to the onset of disease in genetically susceptible individuals.

The majority of clinical studies of intestinal microbiomes have relied on fecal samples, which are an admixture of distal intestinal microbiota and are not representative of region-specific gut microbiota. Thus, more studies are turning to endoscopic approaches to acquire region-specific samples. Hirano et al. (26), for example, performed a paired analysis of mucosal biopsies of both inflamed and noninflamed sites of individual patients, finding increases in the relative abundances of *Cloacibacterium* and Tissierellaceae and decreases in the relative abundance of *Neisseria* in the inflamed sites. Libertucci et al. (27) analyzed mucosa-associated microbiota from site-matched colonic mucosal biopsies from CD patients with and without injury, finding altered microbial communities in the latter compared with the former or with non-IBD controls. Nishino et al. (28) collected mucosa-associated samples by brushing mucosal surfaces, finding significant differences in several genera between CD and UC mucosal surfaces. Collectively, these studies highlight the complex biogeography and diversity of mucosal microbiota that may underpin states of health and disease, but they still fall short in determining if these associations are cause or consequence.

Few studies have examined the role of other microbial kingdoms of the gut microbiome, such as fungi and viruses. Fungi have been implicated in some types of IBD, for instance, in patients with CD who are positive for the serum biomarker ASCA (anti–*Saccharomyces cerevisiae* antibody) (29). Three groups have reported an increase in *Candida albicans* in IBD patients, especially among those with CD (30–32). Another fungal species, *Malassezia restricta*, which is highly abundant in some CD patients, appears to elicit inflammatory responses through CARD9 (33), which is involved in antifungal defense and is downstream of Dectin-1, an innate fungal β-glucan receptor (34). Risk polymorphisms of both CARD9 and Dectin-1 have been associated with IBD (33). An animal study showed that Dectin-1, mannose receptors, and macrophage C-type lectin receptors are all involved in intestinal inflammation (35).

Changes in the viral community of the gut microbiota of IBD patients have also been described. Bacteriophages are viruses that parasitize and replicate within a bacterium, and their incorporation into bacterial genomes can affect bacterial gene expression and function. Increases in the levels of certain bacteriophage species in both luminal and mucosal samples of IBD patients have been

reported with deep metagenomic sequencing (36, 37). However, the functional significance of altered bacteriophage profiles in IBD remains unclear.

HOST FACTORS THAT SHAPE GUT MICROBIOTA COMPOSITION AND FUNCTION

IBD-associated immune dysfunction and mucosal inflammation can greatly alter regional ecosystems, affecting intestinal permeability; mucus content and composition; mucosal gene expression, function, and cellular content; and immune signals in the gut. These changes also affect gut microbial assemblage and function as well as the dynamics and connectivity among microbial members in ways that alter healthy host–microbe interactions to promote immune activation and inflammation in susceptible individuals. In this section, we review recent evidence that shows the impact of host factors on the gut microbiota.

Genetic Drivers and Intestinal Permeability

More than 200 risk variants have been identified by GWAS, and more are likely to be identified from studies of ethnic groups outside of Western countries or newly industrialized societies with rising incidence and prevalence of IBD (8). Not surprisingly, many IBD gene variants appear to be associated with microbial sensing and clearance, T cell differentiation and maintenance, and regulation of inflammatory mediators. Among these risk variants, mutations of the immunomodulatory IL-10 cytokine promote very early onset IBD in pediatric patients which may be dominant, as patients can present at birth with disease prior to the acquisition of gut microbiota (38). Similarly, the Samp1/Yit mouse line displays a CD-like disease of the terminal ileum that is driven largely by genetic factors, as offspring can exhibit this disease at birth. Furthermore, the severity increases in the presence of gut microbiota (39). In contrast, *Il10* KO mice develop frank colitis as adults, and as in most human IBD, the penetrance of disease is variable depending on institutional housing conditions, diet, and the presence of disease-promoting pathobionts (40).

A healthy mucus layer plays a crucial role in maintaining the symbiotic relationship between the host and gut microbiota for intestinal homeostasis. The mucus layer creates spatial separation between microbes and intestinal epithelium but also serves as a selective filter to allow critical host–microbe interactions. Intestinal microbes produce many important small molecules and food-derived nutrients for proper host immune, intestinal, and metabolic functions. Concomitantly, the host produces mucus, AMPs, and immunoglobulins that not only keep microbes at bay but also help select, nurture, and shape regional gut microbiomes. Both clinical and experimental studies have implicated impairment of intestinal mucosal barrier function as an important contributor to the risk and development of IBD. A thinner mucus layer leaves intestinal epithelium exposed to luminal microbes and induces immune activation to generate an inflammatory response. For example, mutations in mucin synthesis genes such as *MUC2* are associated with the development of colitis (41). *Mdr1a*-deficient mice lack the multidrug resistance gene for P-glycoprotein 170 normally expressed in intestinal epithelial cells and develop spontaneous colitis at approximately 12 weeks (42). In *Mdr1a*-deficient mice, intestinal mucosal dysbiosis associated with a significantly thinner mucus layer can be detected before the development of fecal dysbiosis and colitis (43).

Deficiency in host defense against microbes also leads to increased susceptibility to inflammation. Consistently, some gene variants associated with IBD (e.g., *NOD2*, *ATG16L1*, *CYBB*) are involved in autophagy and pathogen clearance (7). *NOD2*, for example, is an innate receptor for microbe-derived muramyl dipeptide and plays an essential role in microbial sensing. Combined deficiency of *NOD2* and *CYBB* leads to the accumulation of *Mucispirillum schaedleri*, a mucolytic anaerobe that, in turn, could trigger the onset of IBD (44).

Mucosal Immunoglobulins and Antimicrobial Peptides

Mucosal immunoglobulins have recently been linked to the development of IBD (45). Mucosal immunoglobulins are antibodies produced by B cell–rich mucosal inductive sites. Among the different classes of mucosal immunoglobulins, the role of immunoglobulin A (IgA) in IBD has been the most extensively studied (45). Selectively enriched IgA-binding fecal bacteria from IBD patients cause more severe colitis in an animal model (46). Another study showed that so-called natural, low-affinity, polyreactive antibodies that are T cell and antigen independent appear to help shape the gut microbiome, particularly in the small intestine (47). Other studies have reported that specific monoclonal IgAs activate the polysaccharide utilization loci of *Bacteroides thetaiotaomicron* and promote epithelial adherence of *Bacteroides fragilis* (48, 49).

In addition to IgA, mucosal immunoglobulins M, G, and D (IgM, IgG, and IgD) may contribute to intestinal homeostasis (45). Mucosal IgG, for example, exhibits selectivity in microbial binding (50). Furthermore, in UC patients, mucosal IgG appears to engage gut-resident macrophages and induce intestinal inflammation (51). The effects of immunoglobulin binding to gut microbes remain poorly understood.

AMPs secreted by specialized intestinal epithelial cells, including Paneth cells, have also been linked to intestinal homeostasis, regulation of gut microbiota, and IBD etiopathogenesis. Several CD-associated polymorphic genes, including *NOD2*, *ATG16L*, *IRGM*, *XBP-1*, *TCF7L2*, and *LRP6*, have been associated with Paneth cell dysfunction. For example, reduced α-defensin has been detected in ileal CD but not in UC or colonic CD (52). Recently, Pierre et al. (32) reported that peptide YY (PYY), previously known as an endocrine peptide involved in satiety control, is expressed in Paneth cells, suggesting an alternate role as an AMP. These authors showed that PYY has antifungal activity, selectively targeting the hyphae or virulent form of *C. albicans*. Intriguingly, an increased abundance of *C. albicans* has been observed in CD patients, possibly arising from Paneth cell dysfunction and compromised PYY production or secretion (30, 31).

Diet, Lifestyle, and Environmental Factors

Western diets high in saturated fats and simple carbohydrates and low in dietary fiber, along with other lifestyle changes, have been suspected of promoting the rapid rise in IBD cases among newly industrialized countries (9, 53). Diet is an important and dominant contributor to gut microbial assembly and function. One animal study showed that a low-fiber diet over multiple generations results in progressive and irreversible changes in gut microbiota, including decreased diversity and loss of polysaccharide-digesting microbes (54). A meta-analysis of observational studies of IBD (53) has implicated smoking, lack of breastfeeding, urban living, pollutants, and xenobiotic exposure as risk factors, in addition to diet. Several studies have suggested that circadian disruptions can increase intestinal inflammation and more aggressive CD (55). Furthermore, diurnal oscillation disruptions of certain members of the gut microbiota potentially promote imbalances in host–microbe interactions and contribute to IBD risk and progression (56).

The Early-Life Microbiome and Immune Development

The development of immune tolerance to the commensal microbiota happens early in life, during which the immune system develops antigen-specific tolerance to microbes and microbial products (57–59). The early-life microbiome plays a critical role in the proper development of immune tolerance by presenting a diverse repertoire of antigens and/or induction of regulatory T cells (Tregs) and natural killer T cells (NKTs) (60–63). *Il10* KO mice with antibiotic-induced dysbiosis

in early life are more prone to the development of spontaneous colitis if the immune system fails to develop tolerance to key members of the gut microbiota (61). In the early stage of life, goblet cell–associated antigen passages also form in the colon, facilitating the transportation of a variety of bacterial antigens from the lumen to lamina propria (58). Perturbations of the early-life microbiome with exposure to antibiotics, C-sections, formula feeding, diets, and so forth can limit its diversity and maturation, thereby compromising the development of immune tolerance to important commensal microbiota and increasing long-term risk for complex immune disorders like IBD (22, 61, 63). The implications of these findings are significant, as they suggest a rethinking of best practices for interventions aiming to restore the health of the early-life microbiome to promote long-term health as well as to reduce the risk for individuals genetically prone to certain disorders associated with gut dysbiosis.

In addition to immune development, maternal antibodies from placental transfer or breast milk may play a role in regulating immune homeostasis during early life. Nod2/Cybb-deficient mice develop spontaneous colitis after weaning, as maternal antibodies appear to mitigate inflammatory responses of offspring to microbiota before weaning; however, the mechanisms underlying this action remain poorly understood.

IMPACT OF GUT MICROBIOTA ON HOST HEALTH

The composition and functional impact of the gut microbiota, partially shaped by the host environment, can affect intestinal health and disease. In healthy individuals, the gut microbiota performs important functions including nutrient absorption, immune regulation, and barrier maintenance. Perturbations of the gut microbiota, particularly in genetically susceptible individuals, can contribute to the development of disease. This idea is supported by the observation that genetically susceptible animals rarely develop spontaneous colitis under germ-free conditions. One study showed reduced Tregs and B cell class switching in the colon during the transfer of IBD-associated microbiota to germ-free mice (16). Microbe-derived metabolites that directly interact with host immune signaling have been identified; key examples are highlighted in the sections below.

Pathobionts: From Commensal Microbes to Opportunistic Pathogens

For many years, classifying microbes as either commensal and health-promoting or disease-promoting was common practice. However, it has become more apparent that commensal microorganisms, given the opportunity, can cause an imbalance in host–microbiome interactions to promote disease. These microbes are referred to as pathobionts, as their fitness and functional properties can transition between states that differentially affect the host.

A longitudinal study of UC pouch patients found that certain strains of *B. fragilis*, normally found in low abundance in the commensal microbiota, bloom before and during pouchitis, suggesting that they may have triggered the onset of the disease (23). Another *Bacteroides* species was shown to increase the incidence of colitis in mice with antibiotic-altered microbiota (61). A time-series study detected a transient increase in *Ruminococcus gnavus* during active disease (64). The authors of this study identified a specific polysaccharide in *R. gnavus* that induced the production of tumor necrosis factor α (TNFα), a proinflammatory cytokine (65). *Bilophila wadsworthia*, a bile-tolerant, sulfite-reducing proteobacterium, increases in abundance with consumption of a diet high in saturated fat to promote colitis in *Il10* KO mice (40). *B. wadsworthia* has also been implicated in human IBD despite often being found in the gut microbiota of healthy individuals (66). Thus, the state of pathobionts and their role in promoting disease are highly context dependent.

Production of Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) are products of bacterial fermentation and play an important role in intestinal homeostasis (67). Propionate and acetate are produced mainly by Bacteroidetes, whereas butyrate is produced predominantly by Firmicutes. SCFAs can be utilized as a carbon source by intestinal epithelial cells, but they also bind to G protein–coupled receptors (GPCRs). Thus, SCFAs play an important role in mucosal healing, histone deacetylation, and gene expression. In addition, SCFAs exhibit immune-modulatory activity, including Treg development, cytokine production, and anti-inflammatory effects (68). SCFAs also regulate the rest of the microbial population by modifying the ecological milieu to select for specific microbial community members.

Among different SCFAs, butyrate function is the best understood. Microbe-derived butyrate promotes IL-10-independent epithelial barrier function through repression of Claudin-2, a channel forming tight junction proteins that normally disrupts gut barrier function (69). Butyrate was also shown to induce macrophage differentiation and AMP production (70). Due to its many beneficial functions, reduced butyrate production often signals dysbiosis; for instance, decreased butyrate-synthetic capacity of the gut microbiota has been reported in patients with active IBD (71).

Secondary Bile Acids

Bile acids are important components of bile that facilitate lipid digestion and absorption. Primary bile acids (PBAs) enter the intestinal tract from the duodenum and are converted to secondary bile acids (SBAs) in the colon by microbes (72). In IBD, many factors can perturb the bile acid pool and composition, including malabsorption and decreased conversion of PBAs to SBAs (73, 74). Inflammation-induced changes in intestinal epithelium can further impair the reabsorption of PBAs and SBAs. Such changes pose a higher risk of infection by *Clostridioides difficile*, as these conditions promote desporulation of *C. difficile* and activation of virulence properties (74).

Recent studies suggest that SBAs produced by microbes play an important role in T cell differentiation (75, 76). One study found that SBAs modulate a population of RORγ-expressing Tregs, and deletion of microbial bile acid metabolic pathways decreased this Treg population (76). Another study screened a library of bile acid metabolites and identified two bile acid derivatives with distinct functions: 3-oxo-LCA, which inhibits the differentiation of Th17 cells, and isoalloLCA, which promotes the differentiation of Tregs (75). This observation was confirmed in vivo (75). These findings suggest that microbial metabolites have an important role in modulating the homeostasis of host immune response.

A recent study of UC and FAP patients with ileal pouches reported a decreased abundance of microbial bile acid conversion genes and reduced levels of lithocholic and deoxycholic acids (77). Using an animal model, this study found that the administration of these bile acids mitigated dextran sulfate sodium–induced colitis via the activation of the TGR5 receptor (77).

Aromatic Amino Acid Catabolites

Microbe-derived aromatic amino acids may play an important role in immune activation, in intestinal epithelial barrier function, and in promoting anti-inflammatory or antioxidative conditions (78). These metabolites, often indole-derived compounds, are produced by different microbial species during the breakdown of tryptophan or other aromatic amino acids. The microbe-derived amino acid catabolites reach the systemic circulation to interact with host receptors.

Serum levels of tryptophan and tryptophan metabolites are reduced in IBD, especially in CD patients (79, 80), and IBD patients exhibit a diminished capacity to utilize tryptophan (81). Microbe-derived tryptophan catabolites serve as host signaling molecules through the activation of the aryl hydrocarbon receptor (AHR) or pregnane X receptor (78). AHR is highly expressed in intestinal epithelium and appears to promote the expression of genes involved in maintaining barrier integrity and immune cell differentiation (82). The activating ligands of AHR include a variety of tryptophan metabolites: indoleacrylic acid, indole-3-propionic acid, indole-3-ethanol, indole-3-pyruvate, and indole-3-aldehyde (81, 83–85). In an animal model, transplanting microbiota with impaired tryptophan catabolism increased susceptibility to colitis and inflammation in the recipient (86). Finally, administration of tryptophan and some of its metabolites appears to reduce colitis severity in a murine model (80), raising the possibility that they may have therapeutic potential in IBD (87).

Two recent studies found that metabolites derived from gut microbiota function as human GPCR ligands (88, 89). GPCRs are critical signaling molecules for immune and inflammatory responses and the maintenance of intestinal barrier function, and their dysfunction appears to be linked to the pathogenesis of IBD (90).

Sphingolipids

Sphingolipids, a class of molecules produced by both host and microbes, often differ between IBD and non-IBD subjects (91). Host-derived sphingolipids are important signaling molecules that regulate inflammation and immunity and have been implicated in IBD pathogenesis (92). However, sphingolipids can also be produced by gut microbes that can modulate host immune responses. For example, sphingolipids produced by *Bacteroides* inhibit the proliferation of invariant NKTs and protect against chemically induced colitis (93). IBD patients display diminished bacteria-derived sphingolipid production, which could be compensated for by an increase in host-derived sphingolipids (91). In a murine model, the lack of microbe-derived sphingolipids resulted in intestinal inflammation and altered host ceramide pools (94).

ADVANCES IN MICROBIOME-BASED THERAPEUTICS AND DIAGNOSTICS FOR INFLAMMATORY BOWEL DISEASES

Despite the rapid advances in enabling technologies, conceptual and mechanistic insights into the microbial basis of IBD lag behind, thus presenting a challenge to the development of novel microbiome-based biotherapeutics. Current pharmacological treatments for both UC and CD aim primarily at inhibiting host inflammation and include aminosalicylates; corticosteroids; Janus kinase inhibitors; and monoclonal antibodies to TNFα, IL-12/23, or integrins (95). Major limitations include a low response rate to the initial treatment and a further loss of response over time among the initial responders (95). Microbiome-based interventions are being actively explored for IBD, but so far their promise remains unrealized (96). Proposed microbial therapies for IBD include fecal microbiota transplantation (FMT), probiotics, synbiotics, prebiotics, and postbiotics. The underlying principle of these methods is to either introduce or promote potential beneficial microbes in IBD patients. FMT appears to have been effective for UC patients in several clinical trials; however, its long-term effect remains unknown (97, 98). So far, clinical trials have shown no evidence for the efficacy of commercial probiotics in the treatment of IBD (99). In addition, several clinical trials of dietary intervention for IBD were conducted but appear to be ineffective (100). Although microbe-derived therapeutics are still in the early stages, ongoing research and

clinical trials seem to suggest that following the microbial route may be the most fruitful way to develop an effective IBD therapeutic.

FUTURE ISSUES

Despite recent advances in our understanding of the role of microbiome in IBD, several obstacles to the development of effective microbiome-based therapies remain. Researchers must first determine whether engraftment of microbes is needed for sustained benefit and, if so, what microbes are best suited for this purpose. Given the significant interindividual differences in gut microbiota, it is likely that a highly personalized treatment will be required for microbiome-based interventions. The timing of the intervention is also important. On one hand, if disease-promoting gut microbiota emerge prior to the onset of IBD, it will be important to intervene at this early stage to rebalance the gut microbiome and reduce the risk for disease or to achieve sustained remission. On the other hand, experimental studies have shown that introducing keystone microbiota of the early-life microbiome after the immune developmental window cannot lower the risk for developing colitis. Thus, the timing and precision of microbiome-based interventions will be critical issues to resolve in developing next-generation biotherapeutics.

DISCLOSURE STATEMENT

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