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The Intestinal Microbiota in the Pathogenesis of Inflammatory Bowel Diseases: New Insights into Complex Disease

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Abstract

Inflammatory Bowel Diseases (IBD) are a group of chronic diseases of increasing worldwide prevalence characterized by gastrointestinal (GI) inflammation leading to debilitating symptoms and complications. The contribution of the intestinal microbiota to the pathogenesis and etiology of these diseases is an area of active research interest. Here, we discuss key mechanisms underlying the chronic inflammation seen in IBD as well as evidence implicating the intestinal microbiota in the development and potentiation of that inflammation. We also discuss recently published work in areas of interest within the field of microbial involvement in IBD pathogenesis – the importance of proper microecology within the GI tract, the evidence that the intestinal microbiota transduces environmental and genetic risk factors for IBD, and the mechanisms by which microbial products contribute to communication between microbe and host. There is an extensive body of published research on the evidence for microbial involvement in IBD; the goal of this review is to highlight the growing edges of the field where exciting and innovative research is pushing the boundaries of the conceptual framework of the role of the intestinal microbiota in IBD pathogenesis.

Introduction.

Inflammatory Bowel Diseases (IBD) are a group of medical conditions characterized by the common pathology of chronic inflammation of the gastrointestinal (GI) tract. Multiple distinct diseases, with the potential for distinct etiologies, are gathered under the classification of IBD. The most common forms of IBD are Crohn's disease (CD), wherein inflammation can often be found in regional patches throughout the entire GI tract, including the small intestine, the cecum, the large intestine, and the rectum, and ulcerative colitis (UC), which is characterized by an evenly distributed inflammation usually involving the rectum, but not infrequently involving the entire colon (1).

As of 2015, 3.1 million adults in the United States, or 1.3% of the population, were estimated to be living with IBD (2), a relapsing, life-long illness. This stands as a marked increase over the 0.9% of the population living with IBD in 1999 (3). Indeed, since the mid-20th century, incidence rates of IBD have rapidly increased in the United States and in much of the industrialized world (4), a pattern that is now being repeated in newly

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industrialized and industrializing countries (5). The correlation between industrialization, along with its concomitant societal changes, and a rise in incidence and prevalence of IBD has been the impetus for much research into the causes and management of IBD.

Though genetic factors are implicated in the development of IBD (6), the alarming increase in the prevalence and incidence of IBD over such a short period of time makes genetic changes unlikely to be a major causative factor. Instead, the rapid increase in IBD has likely arisen from the convergence of genetic susceptibility with environmental and microbial factors. Microbes have been long been implicated in the pathogenesis of human disease. In the late 1800s, Robert Koch developed a series of foundational postulates (7) that would become the accepted criteria for determining microbial causation of a disease. These postulates stipulate that a disease-causing microbe would be found in all diseased but no healthy organisms, and that such a microbe should, once isolated from a diseased organism, be able to reproduce the disease in a healthy organism (7). There has been no such organism discovered in cases of IBD, and yet there is mounting evidence, which will be explored below, that microbes are playing a role in disease pathogenesis. The intestinal microbiota, the collective group of microorganisms residing in the human GI tract, has come under particular scrutiny for its potential involvement in IBD pathogenesis.

The intense scientific interest in the human intestinal microbiota, coupled with the unmet clinical need to understand the etiology of IBD, has resulted in a vast quantity of published research interrogating the connections between microbes and IBD. In this review, we aim to curate and contextualize this large body of research in order to provide a resource for the scientific and medical community. Specifically, we are highlighting recent research in several growing areas of interest (outlined in Figure 1) – (1) the role of distinct microbial communities occupying ecological niches within the GI tract, (2) the ways in which microbes serve to transduce other factors such as host genetics, xenobiotics, or diet, in the development of IBD, and (3) the ways in which microbial products are implicated in the development of IBD. Solving the complex problem of IBD etiology requires a team effort of individuals from many different fields, including microbiology, cell biology, physiology, bioinformatics, genetics, immunology, and clinical medicine. Our goal is that this review will facilitate entry by talented scientists from all these disciplines into the field of host-microbe interactions in IBD.

Part I. IBD Pathogenesis

In this section, we examine the current understanding of IBD pathogenesis to provide a foundation for recognizing the ways in which microbes are involved in the development of chronic inflammation of the GI tract.

The chronic inflammation observed in individuals with IBD is the main driver of the clinical manifestations of their disease. Indeed, part of the diagnostic criteria for these diseases is confirmation of inflammation via endoscopy or colonoscopy (8), and many treatments that are effective at inducing remission in IBD patients, such as corticosteroids (9, 10), or anti-TNF-α therapy (11), are anti-inflammatory. The precise mechanisms driving this inflammation are somewhat distinct across different types of IBD. However, generally,

elevated levels of lymphocytes such as T helper (T_H) 1 (12, 13) and T_H17 (14, 15) cells, as well as innate lymphoid cells (ILCs) (16) are observed in inflamed regions of the GI tract. Additionally, myeloid cells have been implicated in inflammation in IBD, with increased activation of dendritic cells (DCs) observed in IBD patients (17, 18).

In addition to the aberrations in cellular immunity observed in IBD, defects are also observed in the structural integrity and function of the intestinal epithelium. The intestinal epithelium of IBD patients is more permeable than that of healthy controls; this can be due both to defects in tight junction formation that increase paracellular permeability (19, 20) and altered transepithelial transport (21). Additionally, the mucus barrier that overlays the intestinal epithelium is defective in IBD, with patients exhibiting thinner mucus layers and reduced numbers of mucus producing goblet cells (22, 23). The evidence is unclear as to whether this defective mucus layer is a cause (22) or a consequence (23) of the inflammation seen in IBD. Fucosyltransferase is an enzyme, encoded by the *FUT2* gene, that contributes to the sugar structure of the mucins that make up with mucosal layer (24). A genome-wide association study (GWAS) identified an increased risk of CD in individuals carrying single-nucleotide polymorphisms (SNPs) in *FUT2* that render fucosyltransferase non-functional (25). Beyond defects in the integrity of mucosal and cellular barriers, the cells that make up those barriers in IBD patients are themselves often defective in several key cellular functions, such as ER stress pathways and autophagy (26).

A major function of the intestine is to form an effective, selective barrier that deters microbes and microbial factors from entering the bloodstream. The term ‘intestinal barrier’ is often used to describe the physical containment conferred by the gut epithelium, but also includes mucosal factors such as overlying mucus, luminal pH, antimicrobial peptides, and innate and adaptive immune cells, as well as deterrents that microbial communities provide such as bacteriocins. An effective intestinal barrier is therefore essential for health and, when compromised, can lead to IBD and other complex immune disorders. The precise role of the intestinal microbiota in the development or exacerbation of immunological and structural defects in the pathogenesis of IBD will be the central focus of this review.

Part II. The evidence for microbial involvement in IBD pathogenesis

There are several lines of evidence that support the hypothesis that microbes are involved in IBD pathogenesis. Increased risk of IBD is associated with events that effect change in the population structure of the intestinal microbiota or host genetic changes that impact microbial sensing, both of which can lead to altered host-microbe interactions. Many studies have found that antibiotic use, both in early childhood (27) and in adulthood (28), is associated with increased risk for the development of IBD (29). Additionally, an episode of acute infectious gastroenteritis also increases IBD risk (30, 31). Mutations in several genes whose products are required for the proper sensing of the intestinal microbiota by the host lead to an increased risk of IBD, including mutations that lead to defects in NOD2 (nucleotide-binding oligomerization domain-containing protein 2)-mediated bacterial sensing(32, 33) and CARD9 (caspase recruitment domain-containing protein 9)-mediated fungal sensing (34).

In addition to these microbe-associated risk factors for the development of IBD, IBD patients have altered intestinal microbial communities as compared to healthy individuals (35). In CD, these alterations are known to present before the onset of pharmacological treatment for IBD, eliminating the possibility that IBD therapies are solely responsible for microbial changes (36). Microbial changes are even present in uninflamed areas of the colon during UC, suggesting that inflammation is not necessarily the only driver of microbial dysbiosis (37), though intestinal inflammation certainly can change the intestinal microbial community (38). These reports establish the possibility that dysbiosis contributes to IBD pathogenesis and is not simply a result of an inflamed GI tract.

Though many studies have consistently shown alterations in the microbial communities in IBD patients, there is not one specific microbial community structure that has been consistently associated with IBD. Some observations in CD patients include reductions in *Faecalibacterium prausnitzii* (39), and *Erysipelotrichaceae* and *Bifidobacteriaceae* families (36), but increases in the *Fusobacterium* and *Escherichia* genera (40) and *Enterobacteriaceae, Pasteurellaceaea, Fusobacteriaceae, Neisseriaceaea, Veillonellaceae,* and *Gemellaceae* familes (36). In UC patients, a recent study reported an increase in 6 genera (including *Blautia* and *Veillonella*) and a decrease in 10 genera (including *Prevotella* and *Coprococcus*) (41). Other studies in UC patients have found increases in *Clostridium ramosum* and *Ruminococcus gnavus* (42) and decreases in *F. prausnitzii* and *Roseburia hominis* (43). This is a non-exhaustive summary of the reports that have been made regarding alterations in bacterial composition in the intestinal microbiome of IBD patients, many of which have been reviewed elsewhere (44). These results can be difficult to place in their proper context, as these studies often contain differences in methodology regarding patient inclusion criteria, sampling location, and method of determining community composition. Additionally, there may be many types of dysbiotic microbiota that are all contributing to similar disease states. In spite of the inability to identify one IBD-specific microbial community, there are certain consistent high-level observations across studies (summarized in Figure 2), which permits a conclusion to be drawn about overall trends in the intestinal microbiome of IBD patients. These observations include a decrease in microbial diversity (37, 41, 45), depletion of bacteria in the Firmicutes phylum (36, 41, 43), and an increase in bacteria from the phylum Proteobacteria (36, 41) in patients with IBD. A metagenomic analysis of microbiomes from IBD patients found an average of 25% fewer genes than microbiomes of healthy controls (46); this is consistent with the many observations of lower microbial diversity. There is also evidence that there may be certain microbial signatures that could be useful in discriminating CD from other types of IBD at the microbial level (40).

In this review, we will focus on the role of bacterial contributions to IBD pathogenesis, but there is growing interest in the role of other members of the microbiome, including fungi and bacteriophages, in IBD pathogenesis. Changes in the composition of the fungal community are particularly noted in CD patients (47). Data is more scarce regarding bacteriophage alterations in IBD patients, though one study reported increased bacteriophage numbers in both UC and CD patients, with *Caudovirales* being specifically enriched (48). This was supported by a recent report showing alterations in the enteric bacteriophage community in a murine model of colitis (49).

Further providing support for the hypothesis that the intestinal microbiota is involved in IBD pathogenesis, there is clinical evidence that several types of antibiotics are effective at reducing symptoms in IBD patients (50–53). These clinical observations, coupled with known IBD risk factors that alter the structure of the intestinal microbiota and observed changes in intestinal microbiota composition in IBD patients, suggest that microbes contribute to the aberrant immune response that characterizes IBD.

Layered onto this patient data, we must consider evidence from experimental animal models of colitis. The spontaneous colitis observed in IL-10 deficient mice (54) is dependent on microbes, as their colonic inflammation is attenuated by treatment with antibiotics prior to the onset of disease (55) or eliminated altogether in mice raised in germ-free conditions (56). A model of colitis that relies on spontaneous proliferation of adoptively transferred T-cells to promote pancolitis also fails to induce inflammation in germ-free mice (57). Additionally, intestinal inflammation is transferrable via the intestinal microbiota; germ-free IL-10 deficient mice colonized with human intestinal microbiota from IBD patients exhibit increased colitis as compared to those colonized with human intestinal microbiota from healthy controls (58). This implies the potential for a causative role of a dysbiotic microbiota in the development and relapses of IBD.

Animal models have also provided insight into the association between antibiotic use and risk of IBD in humans. Our group recently published a study examining the effect of antibiotic use in a genetically susceptible mouse model on risk of colitis. We observed that peripartum antibiotic exposure increased the risk of colitis development in IL-10 deficient mice, suggesting that alterations of the intestinal microbiota during development can have long lasting immune consequences (59). An independent study reported similar findings in the same mouse model, with transmission of an antibiotic-perturbed microbiota from dams to pups increasing the risk of colitis in those pups (60). Both these reports showed that acquisition of a dysbiotic microbiota very early in life increased risk of colitis. This is especially interesting in light of previous reports discussed above that have shown that antibiotic use in adult mice has the opposite effect, ameliorating colitis in IL-10 deficient mice (48). These studies provide meaningful insight into the risks associated with antibiotic use during the maturation of the intestinal microbiota and the host immune system.

Taken together, it is clear that intestinal microbes are related to the pathogenesis of IBD. One major question that remains is the degree of causation that can be ascribed to microbes in the case of IBD development. It is possible that alterations in the intestinal microbiota that are observed in IBD patients are primarily due to the development of disease, or are secondary to some other driver of disease, and are not themselves the cause of that disease development. However, there is sufficient evidence to determine that, to some extent, microbes are contributing to the disease pathogenesis of IBD.

Having established a basis for the importance of microbes in the pathogenesis of IBD, we now will focus on three particularly active areas of research in the field of microbial contributions to IBD pathogenesis - the microecology of the GI tract, the way in which microbes can transduce environmental and genetic factors, and the role of microbial products as a method of communication from microbe to host.

Part III. The microecology of the gastrointestinal tract

Initial DNA sequence-based studies on the composition of the human intestinal microbiota were done using fecal material (61–64), which was used as a convenient, but not necessarily correct, proxy for the resident microbes of the GI tract. Indeed, much of the current research investigating intestinal microbiota composition in IBD is still performed with fecal samples (40, 42, 65). Though many fascinating things continue to be learned using fecal samples, it is now appreciated that the microbial community found in feces does not tell the whole story of the intestinal microbiota. The first piece of evidence for this came from a study wherein distinct microbial communities were found in fecal samples and colonic mucosal biopsies from the same individual (66). From here, the research community developed the concept of distinct microecological niches within the GI tract. Intestinal microbes are organized by radial geography, with different populations of bacteria residing within the luminal contents as compared to those associated with the mucosal layer (67). In addition to this radial organization, intestinal microbes also exhibit a longitudinal geography, with distinct communities found in the small intestine versus the large intestine (68, 69). A recent study examined the spatial organization of the intestinal microbiota experimentally, by introducing a defined microbial community to germ-free mice followed by fluorescence in situ hybridization (FISH)-based imaging. They reported distinct organization patterns for different community members, with differences in microbial density and community composition throughout the GI tract (70). This agreed with the observations from human sampling-based studies that there is spatial organization of microbes within the GI tract. Thus, in addition to the overall microbial community membership, we need to consider how spatial organization may contribute to IBD.

The most established line of research into inappropriate spatial organization of microbes during IBD deals with examining the relationship between microbes and the mucus layer that overlays the intestinal epithelium. Many independent studies have shown that microbes are more likely to penetrate the mucus layer and are found closer to the intestinal epithelium in IBD patients than in healthy controls (22, 71, 72). This is due both to thinner mucus layers correlated with lower numbers of mucus-producing goblet cells (22) and defects in that thinner mucus that allows greater penetration of commensal bacteria resulting in closer bacterial proximity to the host epithelium (73). In addition to observations of greater numbers of attached and/or penetrative bacteria in the mucus layer of IBD patients, the membership of mucosally associated bacterial communities is distinct in IBD patients (41, 74). Some of this change in community membership is due to changes in mucolytic bacteria in IBD patients. Mucin-degrading bacteria that can utilize mucins as an energy source, such as the abundant commensal microbe *Akkermansia muciniphila* (75, 76), are part of the normal human gut microbiota. As a byproduct of their mucin utilization, these microbes liberate sugars from glycosylated mucins which then serve as a substrate for other bacteria (77), shaping the ecological niche and the corresponding community of mucosally associated bacteria. There is evidence that these mucosally resident mucin-degrading bacteria are altered in IBD patients, with a loss of *A. muciniphila* and an increase of Ruminococcus species (78). A separate study in a genetically susceptible mouse model of colitis observed that the composition of mucosally associated microbial communities

changed before there were any changes in fecal microbial communities or the onset of any symptoms; the mucosal community change was followed by an increase in bacterial penetration that correlated with increased intestinal inflammation (79). This suggests a model wherein the disordered spatial organization of microbes at the mucosal surface has the potential to be causal for subsequent colitis.

Additionally, there is evidence that normally benign commensal microbes that are improperly localized can contribute to disease in IBD, further supporting a role of microbial microgeography in pathogenesis. A recent study observed that fecal microbial communities of IBD patients were enriched for bacteria that are typically part of the oral commensal microbiota, and that the presence of these microbes in the GI tract of mice can induce T_H1 mediated inflammation similar to that observed in IBD patients (80). Similarly, microbes that are a normal part of the intestinal commensal microbiota can contribute to disease when they translocate across the mucosal barrier, a particular problem in patients with transmural CD. These patients exhibit specific enrichment of certain bacterial species in their submucosa at lesion sites and sites of surgical resection (81, 82), and commensal bacteria are known to drive inflammation after damage of the mucosal barrier (83).

Taken together, these studies point to a need for more research into the role of microecologically distinct microbial communities in the GI tract in the pathogenesis of IBD.

Part IV. Microbes as transducers of environmental and genetic factors.

A variety of genetic and environmental factors contribute to IBD pathogenesis; there is convincing evidence to suggest that some of these effects may be mediated through the intestinal microbiota. In this section, we will discuss ways in which these risk factors can result in microbial communities that are altered in IBD-relevant ways. In the next section, we will look at mechanisms by which these altered communities can affect their hosts.

Consumption of a typical Western diet, characterized by high amounts of fats and refined sugars and low amounts of high-fiber plant-based foods, is associated with the development of IBD (84). The mechanism by which this diet may contribute to IBD pathogenesis may be partially dependent on the microbiota. A recent study showed that the colonic mucus of mice fed a typical western diet exhibited decreased thickness and increased permeability after just one week, phenotypes known to be associated with IBD (22, 85). Importantly, these changes in colonic mucus were causally dependent on changes in the community of intestinal microbes (85). Typical Western diets are also characterized by the consumption of highly processed foods, many of which include dietary emulsifiers (86). In both a mouse model and an ex vivo model of the human intestinal microbiota community, these emulsifiers have been shown to alter intestinal microbial communities to increase their pro-inflammatory potential, resulting in increased colitis (87, 88). Mice fed a high fat and high sugar diet exhibited increased susceptibility to chemically induced colitis, a phenotype that was associated with changes in the composition of the intestinal microbiota and an increase of mucosa-associated *Escherichia coli* (89). Work from our group has established that in a genetically susceptible mouse model of colitis, a diet high in saturated milk fat increases colitis incidence. This diet drives an increase of taurine-conjugated bile acid production which

changes the intestinal environment, resulting in an outgrowth of the commensal microbe *Bilophila wadsworthia*. We show *B. wadsworthia* to be an immunogenic microbe that is able to drive colitis development in genetically susceptible mice (90). This study establishes a mechanistic connection between Western diet, the intestinal microbiota, and intestinal inflammation.

Smoking is another environmental risk factor for the development of IBD (91). The effect of smoking on IBD risk is complex. An early report showed that non-smokers had a higher incidence of UC than smokers (92). Further reports have shown that smoking cessation increases the risk of UC (93); this could indicate that non-smoking populations have higher incidence of UC due to previous smoking behavior. Some reports support this hypothesis, showing that former smoking behavior significantly increases the risk of UC but that current smoking behavior does not decrease that risk (93, 94). However, other reports have shown a decreased risk of UC development among current smokers as compared to those who have never smoked (95). The effect of smoking on CD risk is more straightforward, with consistent reports that current smoking behavior increases the risk of CD development (95) and worsens disease course (96). Smoking is known to alter the composition of the intestinal microbiota (97, 98) and these microbial alterations are likely to be one mechanism by which smoking behavior influences IBD risk. One study reported that both CD patients and healthy controls who smoked had an enrichment of members of the *Bacteroidaceae* and *Prevotellaceae* families in their feces as compared, respectively, to CD patients or healthy controls who didn't smoke. This enrichment was also observed in CD patients as compared to healthy controls, independent of smoking status (99). This result suggests that smoking may contribute to a dysbiosis involved in CD development. A separate study showed that smoking cessation also resulted in a reduction of *Bacteroidaceae* and *Prevotellaceae* families in the feces of healthy individuals over the course of 8 weeks (100). Of note, both of these studies used targeted fluorescence in situ hybridization (FISH) probes to quantify members of the microbiota. Another report has characterized the fecal microbiota of a small number of smoking and non-smoking CD patients using 16S sequencing and observed reduced richness and diversity in smokers with CD (101). Further studies are needed with more robust approaches to fully characterize the relationship between smoking and the microbiota in IBD patients. There is clear evidence that smoking influences risk of IBD development and that smoking alters the intestinal microbiota in a way that might contribute to disease, particularly in CD. More research is required to truly establish a causative role for the microbiota in mediating the effects of smoking on IBD risk, particularly around the role of smoking cessation and UC risk.

Other lifestyle factors such as circadian disruption and chronic stress have also been associated with IBD development (102, 103). Recent work has connected chronic stress in a mouse model to increased inflammation during experimental colitis, a phenotype which again was mediated by microbial changes upon the chronic stress (104). These studies suggest that one mechanism by which lifestyle factors may be mediating increased risk of IBD is through cultivation of an altered intestinal microbiota.

Microbes have also been implicated in the potentiation of inflammation, integrating signals from an inflammatory environment to propagate that inflammation. For example, recent

work has shown that intestinal inflammation drives an expansion of bacteria in the *Enterobacteriaceae* family. Blocking this expansion through inhibition of specific bacterial respiration pathways ameliorates colitis in mice (105). This evidence implicates these microbes in aggravating intestinal inflammation, a mechanism which is likely important in the development of IBD. This may be particularly important in IBD cases that are linked to acute infectious gastroenteritis; such episodes result in gastrointestinal inflammation which may then drive changes in the gastrointestinal microbiota that further drive chronic colitis.

Ongoing work also suggests that many of the genetic risk factors influencing IBD development do so through changes in the intestinal microbiota. For example, a recent study examined the intestinal microbiota of individuals at high-genetic risk for Crohn's disease but who had not been diagnosed with IBD. Increased genetic risk was correlated with decreases in certain bacterial species that were also decreased in IBD patients (106). Mutations in the *FUT2* gene are associated with increased IBD risk and alterations in the intestinal mucus layer; they are also associated with changes in the intestinal population of Bifidobacteria (107, 108). Bifidobacteria are able to use host mucus as a carbon source. Mutations in *NOD2* are perhaps the best characterized risk alleles for IBD; NOD2 is a signaling protein involved in bacterial sensing. Conflicting results have been published regarding the role of *NOD2* mutations in shaping the intestinal microbiota, with some studies finding associations between risk alleles and microbial community composition (109, 110) whereas others do not (65). Taken together, these correlational studies suggest that some genetic risk for IBD may be mediated through changes in the intestinal microbial community due to changes in nutritional availability (in the case of FUT2) or host feedback due to bacterial sensing (in the case of NOD2). As some of these microbial changes were observed in healthy individuals at genetic risk for IBD, it is obvious that they alone are not sufficient for causing disease in all cases (though it is not known whether the individuals in these studies might go on to develop IBD), but instead suggests a model whereby genetic risk that contributes to microbial dysbiosis may prime an individual for disease development upon further environmental triggers or perturbations of the microbiome.

In addition to transducing environmental signals to contribute to IBD pathogenesis, intestinal microbes are also involved in the host response to therapeutic intervention for IBD. For example, patients with IBD often require iron replacement therapy due to disease related anemia (111), however, there has been some evidence that oral delivery of iron to IBD patients aggravates the GI symptoms that characterize IBD (112). A recent study showed that oral iron supplementation in IBD patients impacted the intestinal microbiota; this shift in microbiota composition could potentially explain the symptom aggravation with oral, but not intravenous, delivery of iron (113). Microbes can also positively affect the activity of therapeutic interventions in IBD. Mesalamine is a bioactive small molecule used to treat UC. Recently published work has suggested that one mechanism of action by which mesalamine reduces symptoms is through direct modulation of the intestinal microbiota. Mesalamine inhibits a bacterial enzyme that catalyzes the synthesis of polyphosphates; in the absence of polyphosphates, the microbes are more sensitive to environmental stressors and unable to survive in an inflamed environment (114).

The recent publications highlighted here underline the role that microbes play in transducing signals from the environment to the host. In the next section, we will discuss the mechanisms by which microbes may be communicating with the host to effect changes in the host that lead to disease.

Part V. Microbial products

As microbiome researchers have ever more thoroughly categorized the microbes that make up the intestinal microbiota in states of health and disease, many in the field have begun to expand their thinking to include not only the identity of these microbes, but their function. Intestinal microbes mediate many of their effects on the host through microbial products, a broad category that includes everything from short chain fatty acids (SCFA) to metabolites of amino acids (115). Given the important role that these microbial products are known to play in communication from microbe to host, it is logical that investigators examining the role of microbes in IBD would seek to determine how microbial products may be contributing to disease pathogenesis.

Early efforts to determine the function of the intestinal microbiota utilized 16S rRNA gene sequencing of intestinal bacterial communities coupled with associated reference genomes for identified phylotypes to determine potential functional capacity as a proxy for microbiota function. One such study found that the intestinal microbiota of IBD patients contained less functional capacity for SCFA production and vitamin biosynthesis, suggesting the potential for alterations in microbiota function as well as composition in IBD (116). In an evolution of this approach, shotgun metagenomics was used to determine the actual as opposed to the inferred functional capacity of intestinal microbiota in healthy individuals as compared to those with IBD. Here again, differences were found in the functional capacity of the intestinal microbiota of IBD patients (117). Of note, the nature of the differences in functional capacity in IBD patients were not completely overlapping between these two studies (116, 117), a discrepancy that could be attributed to either differing methods in the determination of functional capacity or distinct groups of patients.

Metatranscriptomes of the intestinal microbiota from individuals with IBD have been examined, with level of gene transcription used as a proxy for function of that gene product. One recently published study compared metagenomes to metatranscriptomes from the intestinal microbiota of both healthy and IBD-patients. The results of this study underlined the need for examination of function and not just potential function, as abundant organisms in the GI tract were not always found to be transcriptionally active. Indeed, certain species were more transcriptionally active in IBD patients than healthy controls, implying that organisms that do not change in abundance in IBD patients could still contribute to IBD pathogenesis (118).

Recent studies have moved from examining functional capacity to actual function, using approaches that involve examining both the proteins that arise from transcripts (the proteome) and the small molecules that are generated by metabolic pathways consisting of those protein products (the metabolome). One study of the fecal proteome from IBD patients or healthy controls found a number of bacterial proteins that were enriched or depleted in

IBD patients as compared to controls (119). Interestingly, while many changes in protein levels positively correlated with changes in the abundance of the bacterial phylotype encoding that protein, certain proteins were enriched or depleted without a corresponding change in their encoding organism (119). For example, CD patients showed an increase in *Bacteroides* TonB proteins, which are required for the activity of outer membrane receptor proteins. However, there was not a proportional increase in the abundance of the organisms that would be predicted to be making these proteins (119). These results underline the importance of functional studies of the intestinal microbiome. Interesting results have also been derived from metabolome studies of patients with IBD. These studies consistently find altered metabolomes in the feces of individuals with IBD though there are disparate results as to which metabolites are altered, a finding that is likely due to differing methods of metabolite detection and determination coupled with differences in patient cohorts. Some findings of note in IBD patients from these studies include increases in amino acid levels, decreases in vitamin production, and decreases in SCFA levels (120–122).

These observational studies have provided the field with a wealth of data that will require many years of follow-up research in order to validate and place in its proper biological context. Studies examining the role of microbial metabolites in IBD pathogenesis are crucial for advancing the field.

Tryptophan metabolites are one example of microbial products with relevance for IBD pathogenesis. Tryptophan metabolites are ligands for a host protein, aryl hydrocarbon receptor (AHR), whose engagement results in IL-22 production. IL-22 contributes to mucosal homeostasis (123), a state which is disturbed in IBD. Indeed, in one genetically susceptible mouse model of colitis, the hypersusceptibility was associated with decreased microbiota-mediated metabolism of tryptophan, and sensitivity to colitis could be reduced through provision of an AHR agonist (124). Another recent study has shown that a commensal bacterium, *Peptostreptococcus russellii*, is protective in a mouse model of colitis. This was shown to be potentially due to the ability of *P. russellii* to metabolize tryptophan to indoleacrylic acid (IA), which then is capable of reducing inflammation by directly acting on mononuclear cells to downregulate inflammatory cytokine production. Indeed, the gene cluster responsible for the enzymatic ability of *P. russellii* to generate IA from tryptophan is underrepresented in metagenomes from the intestinal microbiota of IBD patients (125). Interestingly, there have been two clinical reports that suggest that increased tryptophan metabolism, not decreased, is associated with having IBD (126) and with more severe inflammation in UC (127). More work is needed to reconcile the apparent discrepancy between these clinical observations and the mechanistic understanding gained from animal models of the ability of tryptophan metabolism to reduce colitis.

Short chain fatty acid (SCFA) production by the intestinal microbiota also has relevance for IBD pathogenesis (Figure 3). Microbe-derived SCFAs are found both locally in the GI tract and systemically in the host (128); this property contributes to their utility as means of communication from microbe to host. SCFAs affect mammalian cells in a number of ways that could contribute to disease pathogenesis of a complex immune disorder such as IBD. SCFAs, particularly butyrate, which is produced during fermentation of dietary fiber by intestinal microbiota (129), can act as histone deacetylase (HDAC) inhibitors (130). In

animal models, HDAC inhibitors are protective against colitis (131); they have also been found to enhance T_{reg} populations in mice (132). Delivery of SCFAs also ameliorates colitis in animal models (133–135), with one recent study finding the mechanism of amelioration by butyrate to be dependent on driving differentiation of T_{reg} cells and decreasing T_H17 populations (133). SCFAs can also act on the host by binding to G-protein coupled receptors (GPCRs) (136); this activity is also relevant to IBD pathogenesis. For example, microbe-derived SCFAs can bind to the GPCR Gpr43 (also known as FFAR2) (137) and mice lacking Gpr43 are more sensitive to colitis (135, 138). This is partly due to the ability of microbe-derived SCFAs to signal through Gpr43 to activate the inflammasome in the intestinal epithelium (135), a pathway that is known to promote gut homeostasis (139). A second SCFA receptor, Gpr109a, may also be important in the context of IBD. Butyrate signaling through Gpr109a is protective during colitis (135, 140, 141). In this case, the mechanism may rely on Gpr109a signaling in colonic antigen presenting cells; in these cells, Gpr109a activation results in induction of T_{reg} cells (141). Taken together, these mechanistic studies point to a role for microbe-produced SCFAs in protection from colitis and suggest that microbial dysbiosis that results in reduced SCFA could contribute to IBD pathogenesis. Indeed, fecal SCFA levels are reduced in patients with IBD (43, 133, 142). In humans, a reduced potential functional capacity for butyrate production by the intestinal microbiota was associated both with having IBD and with reduced dietary fiber consumption (143).

In one recently published study, the authors monoassociated germ-free mice with a variety of commensal microbes known to be differentially abundant in IBD patients. They then analyzed microbial products in the gastrointestinal tract from each microbe, an approach that revealed distinct SCFA production profiles that correlated with changes in host intestinal physiology and gene expression that are relevant to IBD pathogenesis, such as immune system maturation and mucus layer development (144). Studies like this provide a starting point for further *in vivo* characterization of IBD-associated microbes and their microbial products, as there are likely many more microbial products that are influencing IBD pathogenesis than are currently known. Additional work must be completed in order to further understand the ways in which microbial dysbiosis is translated to the host in a way that promotes IBD pathogenesis.

Conclusion.

In recent years, new experimental tools and techniques have given scientists the ability to investigate the interplay between the intestinal microbiota and the host which houses it. Intestinal microbial communities have co-evolved with their hosts in a mutualistic relationship (145). However, aberrant intestinal microbes have been implicated in a number of human disease states, including cardiovascular (146), metabolic (147), and neurodegenerative diseases (148). In this review, we have outlined cutting-edge research into the role that these microbial communities play in the development of Inflammatory Bowel Diseases, a serious and growing health problem.

Patients with IBD often experience recurrent symptoms that reduce their quality of life. Understanding the pathogenesis of these diseases is crucial to the development of prophylactic and therapeutic measures for these patients. The complex association between

host genetics, the intestinal microbiota, and environmental influences make IBD pathogenesis a fascinating scientific puzzle that will require cooperative and interdisciplinary approaches to solve. Microbiologists have often been trained to study host-pathogen interactions within the intellectual framework provided by Koch's postulates, a framework which may need to become more flexible in the face of a complex immune disorder in which the intestinal microbiota is clearly implicated. Indeed, despite the foundational nature of Koch's postulates, developments in biomedical research have at various times prior to this put considerable pressure upon them (149, 150). Once again, it is time to re-examine traditional ways of thinking about microbe-associated diseases. IBD is a microbe-associated disease for which a single pathogen will likely never be identified. Perhaps it is not a single microbe that is causing disease, but instead an array of microbial functions that contributes to pathogenesis.

There are many publications investigating host-microbe interactions in the context of IBD. In this review, we have discussed the evidence that microbial communities are altered in IBD, and that some alteration can often be observed before disease onset. We have then focused three active areas of research contributing to the current understanding of how microbes are implicated in IBD. First, we discussed the research examining the microecology of the GI tract in the context of IBD. There are distinct communities of mucosal and luminal microbes as well as distinct communities longitudinally along the GI tract; evidence for improperly localized microbes in IBD patients underlines the importance of understanding these different populations. Future research that investigates the relationship between altered microbial communities and IBD pathogenesis should not disregard microecology when designing a study. Sampling location within the GI tract should be considered in both human studies, which will require close collaboration between clinicians and researchers, and animal studies. More research in this area would lead to a clearer understanding of how various microbial populations within the GI tract lead to health and would improve the resolution with which we can discuss the dysbioses that contribute to disease. Second, we examined recent studies regarding the ways in which microbes transduce environmental and genetic risk factors for disease. Observational studies have found that certain genetic backgrounds (e.g., mutations in *FUT2*) and environmental factors (e.g., consumption of a Western Diet) increase the risk of IBD development. Recent work suggests that microbes serve as a nexus for integrating these risk factors for IBD. That is to say, genetic and environmental risk factors lead to changes in the intestinal microbiota; these microbial changes then contribute to disease pathogenesis. More work is needed to determine whether the intestinal microbiota could serve as an intervention point where clinicians could work to reduce disease incidence in populations at higher risk. Third, we outlined attempts to determine how microbes are communicating with their hosts and contributing to disease through the production of small molecules. For example, tryptophan metabolites and SCFAs that are produced by intestinal microbes have profound effects on host physiology in ways that are relevant to IBD pathogenesis. The mechanisms of communication between an intestinal microbial community and its host are complex and just beginning to be understood. However, it is necessary that researchers consider not just microbial community membership in the context of disease pathogenesis, but function as

well. Understanding which functional changes in the microbial community contribute to IBD pathogenesis provides a potential intervention point in at-risk individuals.

The work discussed here further provides support for the idea that many microbes implicated in IBD are neither inherently good nor bad, but may simply contribute to disease only when in a certain location, when exposed to certain environmental triggers, or in certain genetic contexts. The published literature regarding the role of microbes in IBD is vast. Here, we have attempted to contextualize recently published work in three distinct areas that are reshaping the way that we think about microbes in IBD. Our aim is that this review will provide an accessible entry point to scientists and clinicians who have valuable skills and ideas to contribute to this important research topic.

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Abbreviations List:

CARD9	caspase recruitment domain-containing protein 9
CD	Crohn’s disease
FISH	fluorescence in situ hybridization
GI	gastrointestinal
GPCR	G-protein coupled receptor
GWAS	genome-wide association study
HDAC	histone deacetylase
IBD	Inflammatory Bowel Diseases
ILC	innate lymphoid cell
NOD2	nucleotide-binding oligomerization domain-containing protein 2
SCFA	short chain fatty acid
SNP	single-nucleotide polymorphism
Th	T helper
UC	ulcerative colitis

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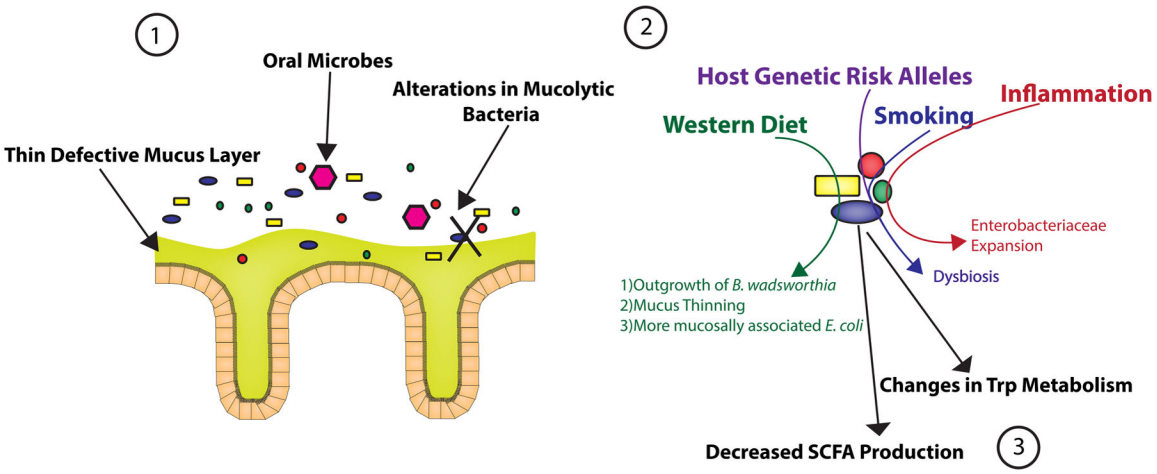

Figure 1. The Intestinal Microbiota in Inflammatory Bowel Disease Pathogenesis

This review outlines three areas of growing research focus in the field of microbial contributions to IBD pathogenesis. Many studies highlighted in the text are illustrated here. 1) The role of abnormal intestinal bacterial microgeography in patients with IBD. 2) The role of the intestinal microbiota in transducing genetic and environmental risk factors for IBD. 3) The role of the intestinal microbiota in producing microbial products that contribute to IBD.

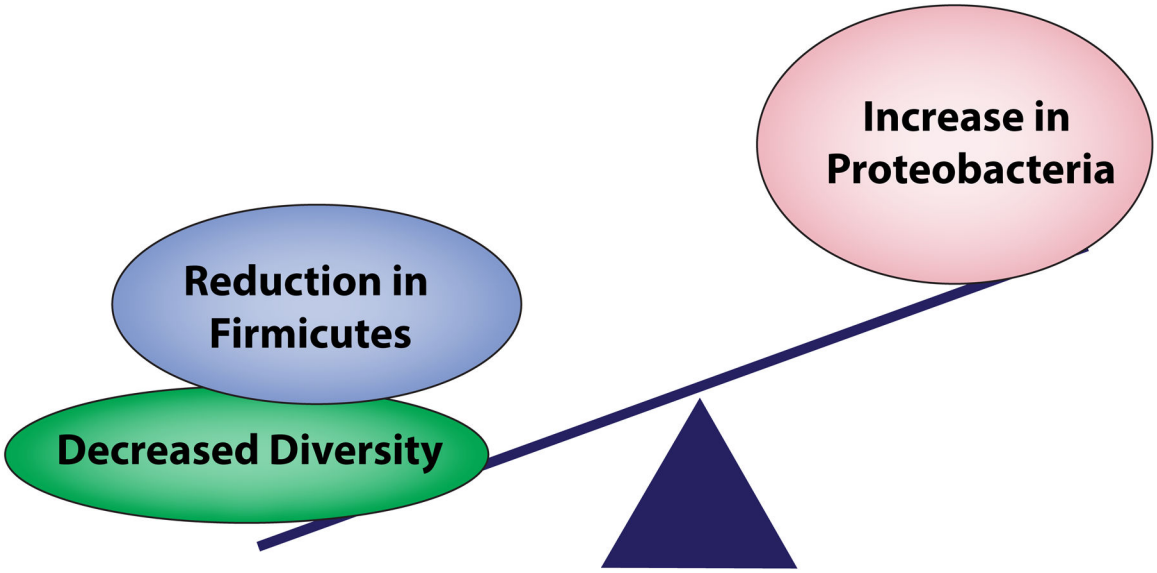

Figure 2. Dysbiosis in Inflammatory Bowel Disease

Observational studies have consistently observed several differences in the composition of the microbiome between healthy controls and IBD patients. The high-level microbial imbalance that is observed across many studies in IBD patients is summarized here.

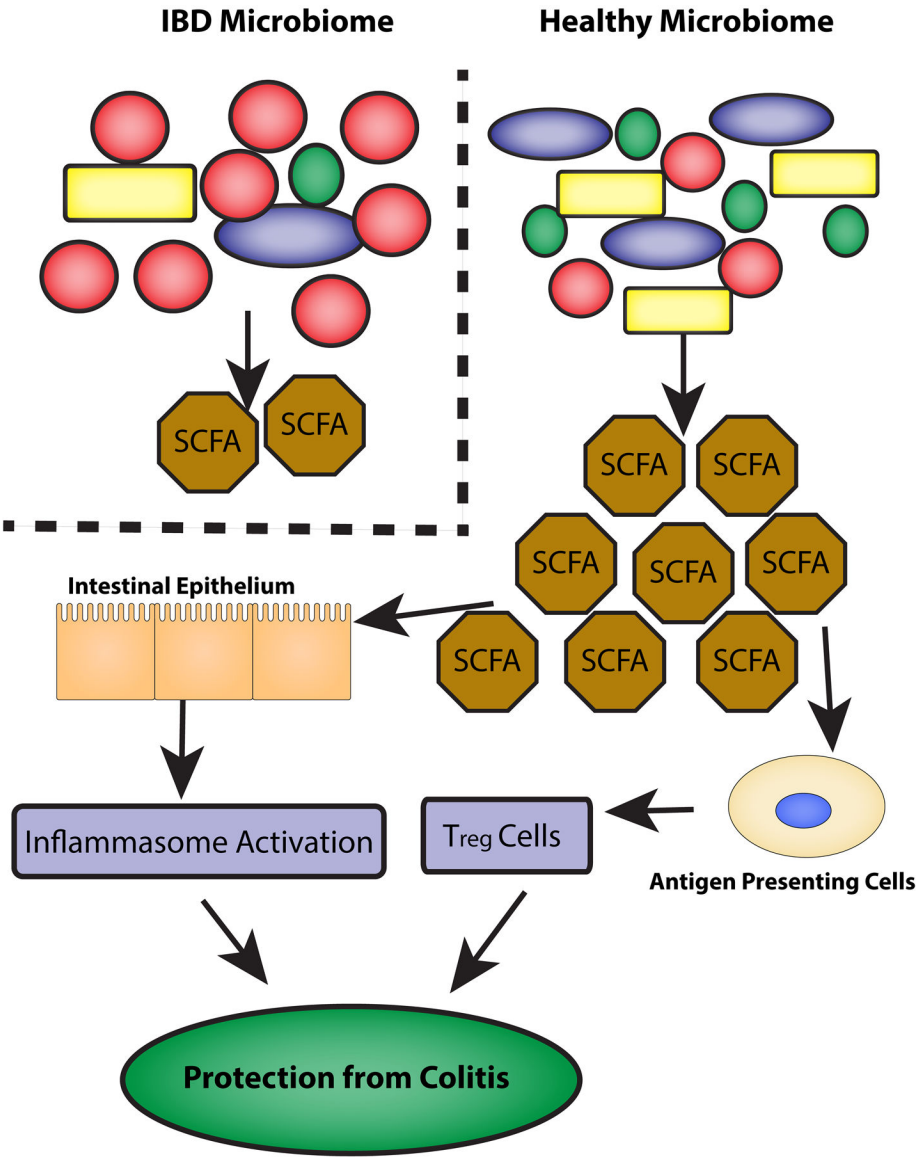

Figure 3. Loss of microbial functions in IBD microbiome leads to disease risk

SCFAs produced by a healthy intestinal microbiome are sensed by host epithelial and innate immune cells through GPCRs and through acting as HDAC inhibitors. This leads to inflammasome activation and the promotion of a healthy T_{reg} cell population. These contribute to intestinal homeostasis and provide protection against inflammation in the colon. Dysbiotic microbiomes observed in IBD patients often fail to produce normal levels of SCFAs. This is a non-exhaustive depiction of the ways that SCFAs contribute to protection from colitis.