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New Horizons for the Infectious Diseases Specialist: How Gut Microflora Promote Health and Disease

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Abstract

The human intestine provides an expansive interface for interactions with the microflora. Increasing data support the hypothesis that host–microflora relationships are markedly dynamic, contributing to host health and disease pathogenesis. Despite outnumbering human cells 10-fold, the microflora most often assist the host through symbiotic relationships. The microflora are involved in maximizing host utilization of nutrients, induction of host immune responses, and promotion of intestinal cell and mucosal development. However, evolving data suggest that disturbances in this symbiotic relationship can lead the microflora to be pathogenic in diverse conditions such as inflammatory bowel disease, irritable bowel disease, obesity, graft-versus-host disease, HIV immunopathogenesis, and possibly cancer. Defining those microflora attributes that result in health and those that trigger disease is key to harnessing the microflora to promote human health.

Introduction

One of the largest interfaces for host–microbe interactions is the human intestinal mucosa. Among all organs, the human gut (especially the colon) harbors the largest and most diverse microflora, primarily bacteria. Pasteur postulated that host–microbe relationships are critical for human health and life [1]. Within days of birth, infants are colonized by a diverse collection of microorganisms that soon outnumber their somatic and germ cells [2•]. The microbiome (collective genome of indigenous microbes) eventually contains 100-fold more genes than the human genome and approximately 10-fold more cells than the total of all human cells [3]. In this summary, we present evidence indicating that the microbiome affects host homeostasis through host–microbe relationships that can be beneficial or pathogenic for the host. Accumulating evidence thus supports Pasteur's postulate that microorganisms are critical to human life.

The Basic Facts

As many as 80% of the 500 to 1000 bacterial species found in the human gut cannot be cultured [3,4]. The number of bacteria increases, moving distally in the gastrointestinal tract from less than 10^3 colony-forming units per gram of contents in the stomach and duodenum, to 10^4 in the jejunum, to 10^7 in the terminal ileum, and $10^{12–14}$ in the colon [5]. The assembly of the gut microbiome is poorly understood, but more light has been shed on this topic of late using molecular methods. Within 1 day of birth, infants are colonized with a

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relatively simple flora. The earliest colonizers are often seemingly opportunistic facultative aerobes including streptococci and *Escherichia colii* with later acquisition of anaerobes that will dominant for life [2•]. Throughout the first year of life, infants, like adults, have distinct and variable microbial communities that appear to be influenced by their environment. In infants, three bacterial phyla dominate (Proteobacteria, Firmicutes [comprising mostly *Clostridium* spp] and Bacteroidetes [comprising mostly *Bacteroides* spp]), whereas in adults, more than 99% of bacteria belong to only two bacterial divisions, the Firmicutes and the Bacteroidetes [2•,4]. By 1 year of age, the fecal microbial communities of infants, though still individually distinct, now resemble the profiles of the adult gastrointestinal tract, with anaerobes predominating and near universal acquisition of *Bacteroides* spp [2•]. *Bacteroides* spp are thought to comprise up to 30% of the total gut flora and consist of at least 10 species. The roles of distinct *Bacteroides* spp—or any other gut microbe for that matter—in health or disease are not understood, with most studies to date focusing on either *Bacteroides thetaiotaomicron* or *Bacteroides fragilis*. By contrast, the intestinal responses to specific *Clostridium* spp have received little attention. Given their preeminence in the microflora, Firmicutes and Bacteroidetes phyla appear to be the critical anaerobe groups involved in the host–microbe interactions relating to health and disease.

The host–microbe relationship can be divided into a continuum of symbiosis, commensalism, and pathogenicity [3]. Symbiosis and commensalism can further be considered to be types of mutualism. Specifically, symbiosis relates to the relationship between two organisms in which one or both benefit without harm to the other. A prime example is the utilization of indigestible food matter by human hosts, which requires the digestive capabilities of colonizing microflora; alone the host can not access these vital nutrient resources [6,7]. On the other hand, commensalism is derived from the Latin *commensalis*, which means “at the table together,” referring to coexistence without harm or obvious benefit to either organism. Pathogenicity must involve damage to the host. With adaptive responses by the host (eg, intestinal immunoglobulin [Ig] A secretion [8]), microbe–host relationships may lead to peaceful coexistence as seen in symbiosis or commensalism. However, pathogenicity can easily develop if the mutualistic balance is disrupted, perhaps, by changes in the microflora through acquisition of a new bacterial species or specific host factors such as immunodeficiency or host genetic polymorphisms.

Symbiosis

The microflora have seemingly important metabolic, trophic, and protective functions in the host gut (Table 1) [3,5]. An understanding of these functions of the microflora has largely been derived from studies in animal models, especially those bred in germ-free conditions, where a single bacterial species or communities of bacteria can be evaluated for their impact on host physiology, such as gut mucosal and immune development [1]. More recently, metagenomic analyses based on whole genome shotgun sequencing of the colonic microbiome has led to a theoretical framework for understanding the functional roles of the microflora in human health [9].

Metabolic functions

Colonic microflora ferment indigestible dietary residue and endogenous mucus using enzymes and biochemical pathways distinct to the colonizing bacteria [6,7,9-11]. The human host then benefits by energy recovery from these indigestible dietary substrates. These bacterial digestive processes release absorbable substrates for the host in the form of short-chain fatty acids and a fertile supply of substrates providing the energy and nutrition for bacterial proliferation. This mutually beneficial relationship is considered a classic example of host–microbial symbiosis. However, recent studies have provided more detailed insights into the mechanisms of this symbiotic relationship. Namely, germ-free mouse

experiments show that colonization with a single bacterial species, *B. thetaiotaomicron*, induces expression of sodium/glucose transporters in the intestinal epithelium, promoting absorption of glucose released by bacterial digestion of non-absorbed polysaccharides [6,10]. Whether this trait is specific for *B. thetaiotaomicron* or is replicated by other bacterial species within the microflora is unknown. Although bacterial digestion provides host and bacterial energy resources, these processes may also produce potentially toxic substances (eg, DNA-damaging molecules), though direct links between the release of these potentially toxic molecules and disease pathogenesis remain speculative [12,13]. Colonic microorganisms also play a critical role in vitamin synthesis, including vitamin K, B_{12}, biotin, folic acid, and pantothenate, as well as absorption of calcium, magnesium, and iron [5].

Trophic functions

Short-chain fatty acids released, in part, by bacterial digestion (as described above) have a trophic effect on the colonic intestinal epithelium, allowing gut microflora in part to regulate proliferation and differentiation of intestinal epithelial cells. Cell differentiation is highly influenced by the microbial community. For example, germ-free animals have reduced epithelial cell turnover in colonic crypts compared with controls [1]. As another example, colonization of germ-free mice with only *B. thetaiotaomicron* induces villous capillary formation in the intestinal mucosa, further promoting the host's absorptive capabilities [14]. Bacteria can also play a role in the development of a competent mucosal and possibly systemic immune system. In contrast to conventional mice that possess a native microflora, germ-free mice have lower densities of lymphoid cells in the gut mucosa, fewer IgA-secreting plasma cells, and reduced submucosal T-cell populations [15,16••]. Ongoing sampling of the gut microflora by the mucosal immune system drives production of mucosal IgA (secreted at the rate of 3–5 g/d). IgA secreted into the gut lumen binds microflora antigens, serving to maintain host–bacterial mutualism [8]. Recent data further suggest that a specific bacterial molecule (ie, polysaccharide A of the *B. fragilis* capsule) contributes to systemic T-cell development [17].

Protective functions

The commensal microflora are thought to provide a barrier effect in the gut and thus a crucial line of defense to inhibit colonization by pathogenic bacteria. Animals and humans that receive broad-spectrum antibiotics are often more susceptible to infection with, for example, *Salmonella* spp, *Klebsiella oxytoca*, or *Clostridium difficile*. Adherent nonpathogenic bacteria may prevent the attachment or entry of pathogenic species into epithelial cells by competing for attachment sites in the brush border of the intestinal cells. This concept is sometimes termed “colonization resistance” and is one mechanism by which probiotics may confer disease resistance. Other potential mechanisms by which commensal bacteria may impede pathogenic bacteria include competing for nutrient availability and thus limiting utilization by pathogenic bacteria; producing antimicrobial substances, termed bacteriocins or microcins, which inhibit the growth of pathogenic bacterial competitors; and inhibiting the activity of virulence factors [5,18].

Normal commensal flora appear essential to the maintenance of homeostasis in the gut and to the host's ability to limit gut injury [19]. Toll-like receptors (TLRs) are a family of pattern-recognition receptor proteins that recognize conserved molecules released by bacteria, and they are considered part of the innate immune (“first responder”) inflammatory host response to bacterial infection. However, murine experiments have shown that a colon with limited bacterial stimulation (through treatment with antibiotics) is more susceptible to TLR-regulated injury, and the gut bathed in its normal microflora is more resistant to injury [19]. These counterintuitive results suggest that the colonic microflora, through their

regulation of TLR function, are critical contributors to intestinal homeostasis. Additional experiments suggest that members of the microflora also induce the host to express bacteria-binding lectins and antimicrobial peptides that serve to foster and maintain symbiotic host–microbial relationships in the gut [20,21].

Pathogenicity of Gut Bacteria

Several disorders are proposed to result, in part, from changes in the composition or function of the microflora (Table 2). These conditions may result from indigenous gut microbes acquiring virulence factors that change them from commensals/symbiotes to pathogens. Examples include *C. difficile* or *B. fragilis* that do or do not produce secreted toxins and even *Salmonella* spp that may be pathogenic or nonpathogenic [22]. Alternatively, the pathogenicity of the microflora may result from environmental exposures shifting the host–microbe equilibrium and/or underlying host genetic polymorphisms that regulate inflammatory responses to the microflora.

Inflammatory bowel disease

Inflammatory bowel disease (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC), is proposed, in part, to be a disease precipitated by the host's microflora [23••,24]. IBD pathogenesis is complex, reflecting the interactions of host genetics and antigenic stimulation by intestinal flora and resulting in vigorous gut immune responses, although no specific pathogen has yet been implicated.

From the perspective of host genetics, the function of at least some of the specific host genes strongly associated with IBD (NOD2 [CD only], ATG16L1 [CD only], and the interleukin [IL]-23 receptor [CD and UC]) are linked to immune responses to microbial antigens [25]. NOD2, a member of the caspase recruitment domain family, binds muramyl dipeptide present in the cell wall of essentially all bacteria; ATG16L1 is an autophagy gene modifying the intracellular processing of bacteria; and the IL-23 receptor appears to be necessary for certain immune responses to intestinal bacteria [26]. Recently, in a murine model, loss of the transcription factor T-bet led to spontaneous colitis, suggesting that additional genes influencing the symbiote-host relationship remain to be identified [27]. Excess epithelial permeability reported in IBD family members—and thus likely to be genetically defined—is further thought to enhance direct contact between the colonic flora and the immune system, possibly permitting disease initiation [16••].

Numerous murine models have demonstrated the necessity of the intestinal flora for development of colitis, and they have suggested that in the immunodeficient murine host (such as IL-10 knockout mice), specific organisms differ in the site and speed of colitis induction [23••]. Consistent with these experimental results, patients with bowel inflammation have high concentrations of mucosal bacteria (exceeding 10^9/mL) and a dense, adherent mucosal biofilm mass composed predominantly of *B. fragilis* group organisms, but controls do not [28]. Patients with IBD also demonstrate increased mucosal secretion of IgG antibodies against commensal bacteria and active T lymphocytes against antigens of the bacteria such as flagellin [23••,29]. This finding suggests a breach in the local mucosal tolerance mechanisms. In smaller experiments, reinfusion of intestinal contents to previously excluded ileal segments reactivated mucosal lesions, supporting the link between active IBD and the microflora [5]. Lastly, CD is partially responsive to antibiotic treatment (eg, metronidazole, ciprofloxacin, and rifaximin), consistent with the concept that enteric bacteria are important in disease pathogenesis.

Obesity

The gut flora play an integral role in fat storage. Germ-free mice, which normally have smaller fat pads compared with conventional mice, will increase body fat by 60% within 14 days when colonized with normal gut flora. This increase in body fat occurs despite a 30% reduction in food intake associated with increased leptin levels, an adipocyte hormone that suppresses appetite [30]. Gut microflora seem to induce lipogenesis by suppressing the production of fasting-induced adipocyte factor, an inhibitor of lipoprotein lipase [30]. When fasting-induced adipocyte factor is inhibited, fat cells increase due to enhanced triglyceride deposition.

Through a series of experiments including transfer of flora from obese mice (genetically engineered to have leptin deficiency) to germ-free mice, recent intriguing data have linked a higher proportion of Firmicutes compared with Bacteroidetes in the gut flora to the phenotype of murine obesity [31,32••]. The microbiome of the obese mice, in which Firmicutes predominated, appeared to influence the efficiency in which energy was harvested. Most relevant was the determination that obese humans also exhibited Firmicutes dominance similar to that noted in the obese versus lean mice [33]. Upon weight loss occurring over a year of study, these individuals exhibited a shift in their microbiome to favor the Bacteroidetes. These results support the concepts from murine studies that energy utilization from food is regulated in part by our gut microflora and that modification of the flora may influence human physiology.

Translocation of bacteria and their molecular components

Bacterial translocation is defined as the passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa [5]. The dissemination of viable microorganisms, usually gram-negative such as in the genera *Escherichia*, *Proteus*, and *Klebsiella*, may produce sepsis, shock, multisystem organ failure, and death of the host. In animal models, translocation is dependent on an overgrowth of bacteria in the small intestine, a decline in the immune defenses of the host, and/or a breakdown in the intestinal mucosal barrier. Bacterial translocation can occur in various disease processes. Patients undergoing surgery have a significant risk of postoperative sepsis secondary to translocation. For example, healthy people undergoing laparotomy had culture-positive mesenteric lymph nodes up to 5% of the time [5]. Often, bacterial translocation occurs in patients with multisystem organ failure, severe acute pancreatitis, liver cirrhosis (especially with spontaneous bacterial peritonitis), intestinal obstruction, or IBD.

More recently, bacteria translocation, as assessed by the biomarker lipopolysaccharide (LPS), the gram-negative bacterial endotoxin, has been proposed to promote the development and severity of graft-versus-host disease following allogeneic bone marrow transplant [34]. Similarly, systemic LPS was elevated in individuals with HIV infection but not in uninfected controls, correlating with measures of innate and adaptive immune stimulation, the hallmarks of progressive HIV-associated immunodeficiency [35]. In these patients, successful treatment with antiretroviral therapy decreased plasma LPS levels. These results suggested that restoration of immune function, including likely mucosal immune function, repaired the breach in the gut mucosal barrier, thereby limiting microorganism translocation and detrimental systemic immune activation. These data collectively suggest an important and intricate relationship between systemic and mucosal immunity that is regulated in part by the microbiome. Additional studies will be critical to further examine these interrelationships in other chronic illnesses associated with systemic immune activation.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a highly variable disorder of unknown etiology that affects many people. Scant data exist regarding alterations in intestinal microflora in IBS, and sophisticated molecular microbiologic approaches have not yet been used to study IBS. A recent study has demonstrated decreased levels of coliforms, lactobacilli, and bifidobacteria in the feces of IBS patients and increased anaerobes, including *Bacteroides* spp, in the colonic mucosa [36]. Furthermore, some IBS patients appear to have abnormal lactulose breath tests, implicating bacterial overgrowth as contributing to the pathogenesis of IBS [37]. A link between IBS and bacterial overgrowth is further supported by an up to 75% improvement in gastrointestinal complaints after neomycin treatment [37]. Similar improvement has been noted after treatment with rifaximin.

Increasing studies suggest that IBS can also be precipitated by infectious acute gastroenteritis. In fact, various studies have shown that 7% to 31% of subjects with acute gastroenteritis had prolonged post-gastroenteritis symptoms consistent with IBS [37]. A large cohort study showed that 28% to 36% of patients who had been infected with either *E. coli* O157:H7 or *Campylobacter jejuni* met Rome I criteria for IBS, whereas IBS was noted in only 10% of the control population [38]. These clinical observations suggest the hypothesis that inflammation triggered by specific enteric bacteria can lead to breaches in the mucosal barrier and disruption of the symbiotic relationship between host and flora that serves to prolong mucosal inflammatory responses and gastrointestinal symptoms. However, what puts an individual at risk for postinfectious IBS is unknown. Recent data have shown an association between IL-8 polymorphisms and gastrointestinal symptoms with *C. difficile* or enteroaggregative *E. coli* infections, suggesting a clue to the regulation of the host responses and symptoms to enteric pathogens [39,40]. Further study of postinfectious IBS may lead to new diagnostic and therapeutic approaches to these difficult-to-manage illnesses.

Cancer

Colonic flora have long been proposed to be an environmental factor that modulates risk of colonic cancer in humans [12]. Compared with germ-free mice, conventionally raised mice have intestinal microflora that produce carcinogens such as alkylating agents and nitroso compounds [1]. Furthermore, germ-free mice with a mutation in the adenomatous polyposis coli gene (Apc^{Min}), who are prone to multiple intestinal adenomas, develop twofold fewer tumors in the small intestine compared with conventionally raised Apc^{Min} mice [1]. Three recent studies suggested specific mechanisms by which certain intestinal flora bacteria may contribute to the development of colorectal cancer. One study found that a significant portion of *E. coli* strains carry a genomic island encoding a cytotoxin that leads to megalocytosis by blocking mitosis through induction of DNA double-strand breaks [41]. A second study demonstrated that the commensal bacterium *Enterococcus faecalis* stimulates macrophage expression of cyclooxygenase (COX)-2 through production of extracellular superoxide [13]. COX-2 expression is associated with chromosomal instability in mammalian cells, a potential precursor of oncogenic transformation. The importance of the COX-2 pathway to oncogenesis is supported by clinical trials demonstrating the protective effect of COX-2 inhibitors in prevention of sporadic colorectal adenomas [42]. In a prospective cross-sectional epidemiologic report, fecal enterotoxigenic *B. fragilis* (ETBF) was isolated in 38% of 73 patients with colorectal cancer but in only 12% of 59 sex- and age-matched concurrent controls [43]. ETBF is a molecular subspecies of *B. fragilis* that secretes a zinc-dependent metalloprotease toxin termed the *B. fragilis* toxin (BFT). BFT has been shown to stimulate colonic epithelial cell proliferation and proinflammatory cytokine secretion in vitro, mechanisms that may contribute to the reported association of ETBF with colorectal cancer [44]. Additional studies are needed to assess whether select members of

the microflora and/or a specific “oncogenic microbiome” that are predictive of risk for colorectal tumor formation can be identified and thus provide potential avenues for development of new preventive approaches for these common tumors.

Treating with Bacteria

Probiotics are living, nonpathogenic microorganisms (usually bacteria or yeast) that have been used for centuries for their potential health benefits [45]. Probiotic organisms theoretically tilt the microflora toward a more symbiotic relationship with the host, although precise mechanisms remain unclear. Certain probiotics, VSL#3 (seven-strain combination of *Streptococcus*, *Bifidobacterium*, and *Lactobacillus* spp), *E. colii* Nissle 1917, and *Lactobacillus* GG, have been studied in multiple disorders. Although individual study results often have been inconclusive, meta-analyses of controlled clinical trials have suggested that probiotics can shorten the duration of acute diarrheal illnesses in children by 1 day, may prevent antibiotic-associated diarrhea in children and adults, and can diminish morbidity and mortality in necrotizing enterocolitis in infants [5,45,46]. In contrast, despite the proposed link between the gut microflora and IBD, there is a paucity of evidence to support the benefit of probiotics in the therapy of IBD. Probiotics have been tested for therapeutic efficacy in IBD, and with the exception of patients with pouchitis, the results have been disappointing [5,45].

Defining the mechanisms by which probiotics act is an area of active investigation. Multiple proposed mechanisms include improving gut barrier and/or epithelial function, enhancing mucosal immune responses, and/or interfering with the adherence of bacteria contributing to disease. For example, in a microbial-induced sepsis mouse model, VSL#3 administration was associated with a reduction in bacterial translocation, secretion of proinflammatory cytokines, and attenuated liver injury [47]. One current research goal is to define the molecules produced by the probiotic bacteria that are responsible for interfering with pathogenic mechanisms and/or that promote host cell or immune function [48].

Conclusions

Host-microflora interactions play a critical role in health and disease. The microfloral organisms, through a symbiotic relationship, assist in metabolic and trophic gut functions and promote protective mechanisms that serve to limit gut injury. Emerging data suggest these complex and as yet incompletely understood host-microbe relationships can go awry, resulting in microflora acting to induce or sustain quite diverse intestinal and systemic conditions, such as IBD, obesity, IBS, cancer, transplant rejection, and/or accelerated HIV pathogenesis. Hence, approaches that modulate the microflora may have potential therapeutic benefits for a variety of disorders, as recently suggested in human studies of obesity [33]. Our present understanding of the “normal flora,” gained by sensitive molecular approaches, is limited to only a few infants and adults, and similarly, our knowledge of the human flora in disease is rudimentary [2•,4]. Animal studies have been critical to achieving a better understanding of host-microbe interactions and refining hypotheses for potential evaluation in human studies. With the development of new, comprehensive analytical approaches to the microflora [2•,9,49], questions about gut ecology in health and disease in populations with differing genetic backgrounds, customs, and environmental exposures are now being addressed, with exciting opportunities for basic and translational investigations. The recently launched Human Microbiome Project (http://nihroadmap.nih.gov/hmp/) is designed to address these needs through carefully designed investigations and international collaborations that will define humanassociated microbial communities [50].

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Table 1

The role of microflora in host

Metabolic
Metabolize indigestible dietary residue into short-chain fatty acids
Induce expression of the sodium/glucose transporters in intestinal epithelium, promoting absorption of glucose
Enhance fat storage
Possibly produce DNA-damaging molecules
Synthesize vitamins
Trophic
Contribute to proliferation and differentiation of intestinal epithelium
Induce villous capillary formation in the intestinal mucosa
Assist in development of host immune system and oral tolerance
Drive production of mucosal immunoglobulin A
Develop systemic T cells via polysaccharide A
Protective
Provide microbe barrier
Competitively inhibit the binding of pathogenic bacteria in intestines
Produce antibacterial substances (bacteriocins or microcins)
Competitively consume nutrients that may be used by pathogenic bacteria
Regulate Toll-like receptors for intestinal homeostasis
Induce host bacteria-binding lectins and antimicrobial peptides

Table 2

Putative diseases related to microflora

Inflammatory bowel disease
Irritable bowel syndrome
Obesity
Cancer
Bacterial translocation illnesses
Graft-versus-host disease
HIV immunopathogenesis