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VIEWPOINT

Commensal Host-Bacterial Relationships in the Gut

Lora V. Hooper and Jeffrey I. Gordon*

One potential outcome of the adaptive coevolution of humans and bacteria is the development of commensal relationships, where neither partner is harmed, or symbiotic relationships, where unique metabolic traits or other benefits are provided. Our gastrointestinal tract is colonized by a vast community of symbionts and commensals that have important effects on immune function, nutrient processing, and a broad range of other host activities. The current genomic revolution offers an unprecedented opportunity to identify the molecular foundations of these relationships so that we can understand how they contribute to our normal physiology and how they can be exploited to develop new therapeutic strategies.

The first draft of our complete DNA sequence represents a historic event in our quest for self-knowledge (*1, 2*). Knowing our genotype highlights the need to understand how environmental factors interact with our genetic traits to influence health and predispose us to illness. In the midst of the current revolution in comparative and functional genomics, it is therefore appropriate to consider another form of self-knowledge: the contributions of our microbial partners to our biology. From birth to death, we are colonized by a vast, complex, and dynamic consortium of microorganisms that may outnumber our somatic and germ cells (*3*). The Nobel laureate Joshua Lederberg has suggested using the term "microbiome" to describe the collective genome of our indigenous microbes (microflora), the idea being that a comprehensive genetic view of *Homo sapiens* as a life-form should include the genes in our microbiome (*4*).

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Bacteria have inhabited Earth for at least 2.5 billion years (*5*). As a result, our predecessors have had to adapt to a biosphere dominated by microbes. However, we have minimal knowledge of how coevolution with indigenous microorganisms has shaped our genome and microbiome, as well as our physiology and postnatal development. For example, the human genome encodes 223 proteins with significant homology to bacterial but not eukaryotic proteins, suggesting that they were acquired through horizontal transfer of bacterial genes (*1*). Unfortunately, the components of our microbiome remain poorly defined. Like most complex ecosystems, enumerating membership in the various microbial societies that reside on our body surfaces has been hindered by the fact that most societal members cannot be cultured ex vivo. Moreover, most microbial genome-sequencing projects have focused on pathogens. Those that have embraced nonpathogens have turned to Archaea to understand the evolutionary diversification of protocytes and eukaryotes or to extremophiles to examine their adaptations to harsh environments and their potential for performing commercially applicable chemistry (*6*).

Interactions between bacteria and their hosts can be viewed in terms of a continuum between symbiosis, commensalism, and pathogenicity, with symbiosis and commensalism grouped under the general heading of mutualism (Fig. 1). "Symbiosis" refers to a relationship between two different species where at least one partner benefits without harming the other and is typically centered on metabolic capabilities that allow either or both partners to exploit an otherwise unavailable or poorly utilizable nutrient foundation (*7, 8*). The term "commensal" comes from the medieval Latin "commensalis," meaning "at table together," and generally refers to partners that coexist without detriment but without obvious benefit. A pathogenic relationship results in damage to the host. Symbiosis and commensalism have been viewed as potential outcomes of a dynamic "arms race" (*9*) initiated when a pathogen encounters a vulnerable host. In this race, a change in one combatant is matched by an adaptive response in the other. In some settings, the arms race evolves toward attenuation of virulence and peaceful coexistence, with or without frank codependence (symbiosis). In other circumstances, the pathogenic relationship is sustained by the development of effective countermeasures that bypass the host's innate or adaptive defenses (Fig. 1). Ewald has coined the term "evolutionary epidemiology" to underscore how a comprehensive analysis of disease prevalence and spread must include the set of adaptive responses of host and pathogen to one another and their outside environment over time (*10*). He and others have emphasized that the concept of obligate evolution of parasites (pathogens) to benignness should be rejected on the

basis of empiric as well as theoretical considerations (*11*).

The Intestine as an Arena for Studying Mutualistic Relationships

Because most of our bacterial symbionts and commensals reside in our intestine (*3*), it should be an arena where their interplay with us should have great, if not the greatest, significance to our biology. The species composition of symbionts and commensals varies along the length of the gut, changes as we develop and age, and is influenced by our environment. Molecular approaches, such as broad-range sequencing of 16*S* ribosomal RNA (rRNA) genes (*12*), are just now being used to define shifts in the composition of the gut flora during an individual's life or to assess its biodiversity in geographically defined healthy populations and in different disease states (*13*). The benefits provided by most identified members of this microflora have yet to be deciphered. Therefore, pending further information, we will use commensal as a generic label as we discuss current information, hypotheses, and questions about the foundations of mutualism in the intestine.

Immune Tolerance to Gut Commensals

Although the mammalian gut must be sufficiently permeable to support efficient absorption of nutrients, it must avoid potentially damaging immune responses to dietary proteins and commensals. Innate defenses, such as epithelial production of α-defensins and mucins, help prevent bacteria from crossing the mucosal barrier (*14–16*). Additional protection is afforded by secretory immunoglobulin A (sIgA). sIgA against commensal antigens is specifically induced in the intestinal mucosa (*17*). In contrast to the sIgA response to pathogen-derived epitopes, which requires costimulation by antigen-specific T cells, induction of sIgA against commensal antigens is T cell independent in mice (*17*). Such independence presumably allows the host to respond to shifts in the commensal flora without eliciting a deleterious immune response. This pathway may be part of an evolutionarily primitive form of adaptive immunity (*17*).

Nonpathogenic bacteria may directly influence the intestinal epithelium to limit immune activation. Neish *et al.* (*18*) demonstrated that an avirulent *Salmonella* strain abrogates production of inflammatory cytokines in cultured human intestinal epithelial cells. The mechanism involves IκB, which blocks nuclear factor κB (NF-κB) nuclear localization. The *Salmonella* strain was able to inhibit ubiquitination and degradation of IκB, thus blocking NF-κB–directed transactivation of genes encoding inflammatory mediators (*18*). In addition, commensals can help fortify the epithelial barrier. *Bacteroides thetaiotaomicron* is a prominent, genetically manipulatable member of the normal mouse and human distal intestinal microflora (*19–21*). *B. thetaiotaomicron* colonization of germ-free mouse intestine induces expression of decay-accelerating factor, which inhibits cytotoxic damage from microbial activation of secreted complement components; complement-reactive protein (CRP)–ductin, a putative receptor for intestinal trefoil factors that facilitate repair of damaged epithelium; and Sprr2a, a member of the family of small proline-rich proteins known to participate in cutaneous barrier functions (*22*).

There is mounting evidence that commensals acquired during the early postnatal period are required for the development of tolerance not only to themselves but also to other luminal antigens (*23, 24*). For example, Sudo *et al*. reported that T helper 2–mediated immune responses to ovalbumin were not susceptible to oral tolerance induction in germ-free mice, but susceptibility was restored after the introduction of a single component of the preweaning microflora into neonates (*23*). The increasing prevalence of atopy (tendency to allergy) in Western industrialized societies has led to the hypothesis that an overly hygienic life-style has altered the normal pattern of intestinal colonization during infancy and produced a lack of tolerance to otherwise harmless food proteins and inhaled antigens (*25, 26*).

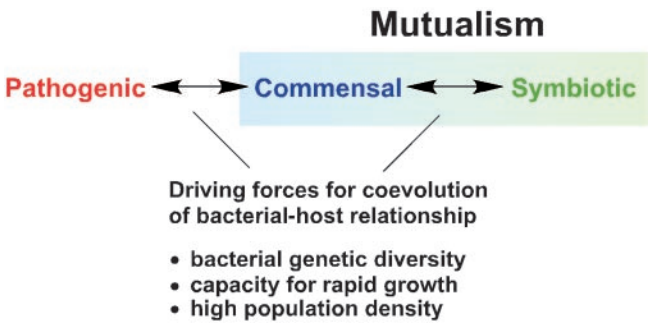

Fig. 1. Mutualism. Commensalism and symbiosis are presented as part of a continuum, distinguished by the identification of specific benefits derived by one or both members of a host-bacterial partnership. Commensalism or symbiosis is a potential but not inevitable outcome of the dynamic coevolution of host-bacterial relationships. Genetic diversity reflects the balance of factors that promote variation (point mutation, recombination, and gene transfer) versus factors that act to stabilize the genome (DNA repair enzymes, restriction modification systems, and barriers to horizontal transfer of genes) (6).

Contributions of the Commensal Flora to Pathologic States

The relationship between indigenous gut microbes and their hosts can shift from commensalism toward pathogenicity in certain diseases. Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, affects 0.1% of the population in Western societies. The pathogenesis of IBD appears to involve an "inappropriate" activation of the mucosal immune system. This activation has been linked to a loss of tolerance to gut commensals (*27, 28*). Several observations illustrate this point. Both Crohn's disease and ulcerative colitis respond to treatment with broad-spectrum antibiotics (*29, 30*). The spontaneous colitis that develops in human leukocyte antigen–B27/β2-microglobulin transgenic rats and in knockout mice that lack interleukin-2 or T cell receptors is abrogated when animals are raised under germ-free conditions (*31–33*). Conventionally raised mice deficient in interleukin-10 (IL-10) develop patchy chronic colitis similar to that encountered in humans with Crohn's disease, whereas germ-free mice do not (*34, 35*).

What is not clear is whether the inflammatory responses in IBD, both within the gut and at extraintestinal sites, are elicited in response to a specific subset of intestinal microbes or whether tolerance to commensals is affected generally. An interesting question is whether barrier function is first compromised by "intrinsic" defects in epithelial integrity, by infection with enteropathogens, or by loss of commensal-dependent signals necessary to maintain the physical integrity of the epithelium and hypo-responsiveness of the mucosal immune system. Part of this question may be answered when human IBD susceptibility genes, such as *IBD-1* (*36*), are identified. Other clues are coming from comparisons of conventionally raised and germ-free animals. For example, conventionally raised IL-10–deficient mice exhibit increased ileal and colonic permeability by 2 weeks of age, well before the appearance of histopathologic changes in the gut. This change in permeability, which is accompanied by increased production of interferon-γ and tumor necrosis factor–α, does not occur in germ-free IL-10$^{-/-}$ mice (*37*).

Assessing the Impact of Commensals on Other Aspects of Gut Physiology and Development

Because the intestinal ecosystem is characterized by dynamic and reciprocal interactions among its microflora, epithelium, and immune system, cultured cells may not accurately portray in vivo responses to commensals. An alternative approach is to use germ-free inbred strains of mice as genetically defined simplified in vivo assay systems for

studying the impact of colonization, with single or multiple members of the microflora, on intestinal gene expression. DNA microarrays provide a powerful tool for comprehensively profiling transcriptional responses to colonization in these gnotobiotic systems and thereby defining the breadth of potential functions modulated by commensals.

In addition to fortifying barrier functions, DNA microarray analyses have shown that colonization of germ-free mice with *B. thetaiotaomicron* affects expression of host genes that regulate postnatal maturation, nutrient uptake and metabolism, processing of xenobiotics, and angiogenesis (*22*). The increased expression of genes involved in absorption of carbohydrates, as well as breakdown and absorption of complex lipids (*19*), provides a potential molecular explanation for the observation that germ-free rodents must consume ~30% more calories to sustain their body weight than do conventionally raised animals (*38*). These findings suggest a testable hypothesis: namely, that compositional differences may exist in the microflora of lean and obese individuals and that such differences could affect their nutrient-processing capabilities.

Establishing Microbial Communities in Different Regions of the Gastrointestinal Tract

The host and microbial factors that direct establishment and maintenance of a spatially diversified gut microflora in mice and humans remain largely unknown. Community formation likely proceeds through a complex regulatory network of host-microbial and microbial-microbial interactions predicated on exploiting and developing suitable nutrient foundations and dependent on intra- and interspecies communications systems. Nutrient exchange in the constantly perfused gut could occur through biofilms (*39*), although biofilm formation in the intestine has not been reported to date. Given the importance of quorum sensing in regulating microbial-microbial communications and biofilm formation, it seems likely that it would be used by some or many components of an emerging bacterial community to establish residence in intestinal habitats.

Development of dental plaque provides the one well-studied example of community formation that employs some of these proposed mechanisms. The complex biofilm plaque community is assembled through an orderly process involving initial adhesion of early colonizers (e.g., *Streptococcus* spp.) to a host-derived structure (an acquired pellicle on the tooth surface), followed by secondary colonization through interbacterial adhesion and intergeneric communications. Ultimately, a structure is created that is predominated by Gram-negative anaerobes (*40*–*42*).

Studies with germ-free mice have revealed that positioning of *B. thetaiotaomicron* in the postnatal distal small intestine (ileum) may be achieved, at least in part, through an active collaboration between host and microbe centered on glycan synthesis and utilization. Production of a subset of epithelial fucosylated glycans is normally induced in the ileum at the suckling-weaning transition in conventionally raised but not in germ-free mice (*43*). This induction occurs at the same time that *B. thetaiotaomicron* and other commensal anaerobes are first gaining a foothold. Synthesis of these epithelial glycans is elicited by a *B. thetaiotaomicron* signal whose expression is regulated by a fucose-binding bacterial transcription factor. This factor senses environmental levels of fucose and coordinates the decision to generate a signal for production of host fucosylated glycans when environmental fucose is limited or to induce expression of the bacteria's fucose utilization operon when fucose is abundant (*44*).

These considerations suggest a potential explanation for the striking structural diversity of oligosaccharide outer chain segments in mammalian glycans. This diversity, which arises principally from the nontemplate combinatorial nature of carbohydrate synthesis and modification, has generally not been associated with clearly delineated functions. By matching host carbohydrate structures with the capacity of bacterial species to produce glycosidases and to use the resulting enzymatic products, these glycans may serve as a nutrient foundation that helps organize initial colonization of the developing intestine. An elaborate series of combinatorial bacterial-host and bacterial-bacterial interactions may subsequently shape the metabolic milieu in a manner permissive for establishing a more diversified collection of bacterial species (Fig. 2). Species diversification, in turn, could benefit the developing host by providing new metabolic capabilities at critical times during postnatal development, by supplying microbial factors that influence other aspects of host postnatal development (*22*), and/or by affording resistance to colonization by potential pathogens that cannot compete with entrenched residents of the microbial community for nutrients.

There are a number of carefully studied examples of symbionts influencing the development of host tissues, including *Vibrio fischeri*–induced development of a light organ in the squid *Euprymna scolopes* (*8*) or the formation of root or stem nodules in plants by various genera of soil bacteria (*7*). The idea that a bacterium such as *B. thetaiotaomicron* can collaborate with its host to regulate postnatal intestinal development is logical, considering their mutual reliance. The impact of commensals on postnatal developmental processes needs to be examined in other colonized mammalian tissues and in other eukaryotes that support a microflora.

Commensals as Therapeutic Agents

The adaptations of symbionts and commensals to life in nutritionally advantageous host niches provide a rationale for using these organisms as therapeutic agents. In its simplest expression, components of the normal flora are given as live biological supplements (probiotics) that confer some host benefit. For example, giving *Lactobacillus* spp. to IL-10–deficient mice attenuates their colitis (*45*). Probiotic preparations containing *Bifidobacterium*, *Lactobacillum*, and *Streptococcus* spp. are beneficial in treating chronic "pouchitis," a complication following surgical intervention for ulcerative colitis (*46*). In addition, nonpathogenic *Escherichia coli* provided effective probiotic therapy in a randomized double-blind trial of patients with active ulcerative colitis (*30*).

Unfortunately, molecular tools are not yet available to define the effects of such probiotic interventions on the composition of a host's microflora. The development of

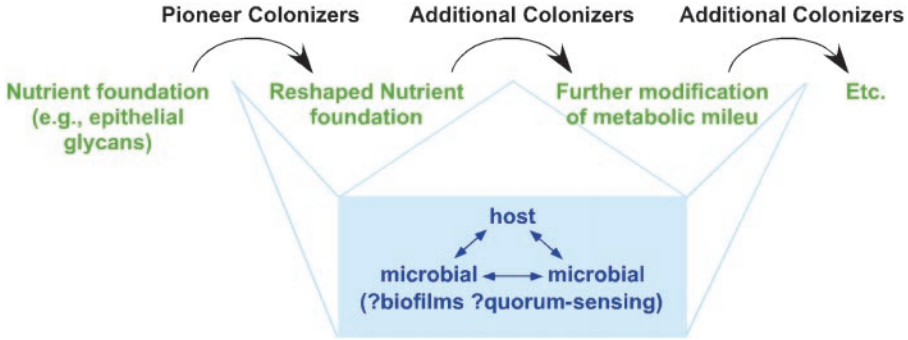

Fig. 2. Establishing a microbial community in the intestine. One postulated component of the nutrient foundation is the diverse collection of outer chain segments in epithelial glycans. Some microorganisms may function as "covert symbionts," whose contribution is to help to create a metabolic milieu that favors incorporation of other species into an emerging community that provides direct benefit to the host.

microarrays containing rRNA gene sequences from different members of the gut microflora represents a potential starting point for determining whether identifiable changes in species composition can be associated with particular disease states and, subsequently, for designing hypothesis-based therapeutic trials of probiotic supplements (Fig. 3).

Recent experiments have expanded the definition of probiotics by demonstrating that genetically engineered commensals can be used as platforms for delivering drugs, antimicrobial agents, and vaccines to defined host niches. For example, a strain of *Lactococcus lactis* programmed to produce IL-10 provided therapeutic benefit in two mouse models of IBD (*47*). The human commensal *Streptococcus gordonii*, engineered to produce an antibody fragment with antimicrobial properties, resolved vaginal *Candida albicans* infections in rats (*48*). Finally, oral inoculation of *Lactobacilli* expressing tetanus toxin fragment C induced local and systemic immune responses to the expressed antigen (*49*).

The ultimate therapeutic reduction of the symbiont-host or commensal-host relationship will be the identification of microbial products, produced in host niches, that affect processes disordered in a given disease state. For example, microbial signals that fortify the epithelial barrier or attenuate the activity of the mucosal immune system may be useful in treating IBD. Identifying such microbial signals will be challenging and may require simultaneous monitoring of microbial and host gene expression during the course of colonization of defined gnotobiotic models (Fig. 3).

Antibiotics

If probiotics offer benefit to the host, what are the dangers of drugs that significantly disrupt the microflora? Although the development of antibiotics has been one of the great triumphs of modern medicine, indiscriminate use predisposes humans to opportunistic infections and will certainly exacerbate the present crisis of antibiotic resistance (*50*). For example, the human colon, with a microbial density approaching 10^{12} organisms per gram, is well suited for horizontal gene transfer of antibiotic resistance genes via conjugal elements (plasmids or conjugative transposons) (*51*). Shoemaker *et al.* found such transfer between members of the genus *Bacteroides*, as well as between Gram-negative *Bacteroides* spp. and Gram-positive bacteria (*51*). Once transfer occurs, antibiotic resistance is maintained in the absence of antibiotic selection (*51*). Given the impact of commensals on immune and other physiologic functions, we also need to consider the possibility that disruption of our commensal relationships by indiscriminate use of antibiotics during or even after completion of postnatal development may be an environmental risk factor that contributes to disease predilection in certain hosts.

The Future

Future efforts to define the molecular foundations of mutualism in the human gut will be challenging and will require multidisciplinary approaches (Fig. 3). The rewards for attacking this complex problem in interspecies relationships should include new insights about the genetic and biochemical strategies that we and our microbial partners use to adapt to one another, new understanding of what constitutes a pathogen, and new approaches for preventing and treating infectious diseases.

Questions	Approaches
Defining membership in the intestine's microbial society as a function of host development, environment, and disease states	Enumeration based on rRNA genes
Defining genomes in the resident microflora	Microbiome genome anatomy project (μ-GAP) to complement human genome sequencing efforts
Identifying bacterial effects on host physiology and postnatal development	• Combining functional genomics and proteomics with gnotobiotic models • Development of methods to monitor host and bacterial biochemistry and physiology in gnotobiotic models

Fig. 3. Questions and suggested approaches for the future. The term "microbiome" (*3*) refers to the collective genomes of members of a microflora. The human intestinal microflora is estimated to contain 500 to 1000 species, at least 50% of which cannot be cultivated ex vivo. Assuming an average microbial genome size of 5 million base pairs (bp) and 4000 genes per genome, the 2.5-billion- to 5-billion-bp intestinal microbiome may contain 2 million to 4 million genes (i.e., ~50 to 100 times as many as our "own" genome). "Gnotobiotic" comes from the Greek "known life" and refers to animals with defined microbiological status [germ free (having no detectable microorganisms) or colonized with one or more known species].

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