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Enteric pathogen exploitation of the microbiota-generated nutrient environment of the gut

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Abstract

Residing within the intestine is a large community of commensal organisms collectively termed the microbiota. This community generates a complex nutrient environment by breaking down indigestible food products into metabolites that are used by both the host and the microbiota. Both the invading intestinal pathogen and the microbiota compete for these metabolites, which can shape both the composition of the flora, as well as susceptibility to infection. After infection is established, pathogen mediated inflammation alters the composition of the microbiota, which further shifts the makeup of metabolites in the gastrointestinal tract. A greater understanding of the interplay between the microbiota, the metabolites they generate, and susceptibility to enteric disease will enable the discovery of novel therapies against infectious disease.

Metabolic function of the host microbiota

The resident microbiota of the human gastrointestinal (GI) tract is incredibly dense and diverse, containing as many as 10^{12} organisms per gram [1]. While all three domains of life (bacteria, archaea and eukarya) have been identified in the adult human GI tract, only 8 out of 55 known bacterial divisions have been found within this environment [2]. The composition of this enormous community provides the host with a core set of microbial genes that encode the gut microbiome [3]. It is estimated that this microbial community has 70–140 times more total genes than the human host, which encode biochemical pathways that humans have not evolved, enabling the break-down of proteins and indigestible polysaccharides into essential amino acids, vitamins, and short chain fatty acids (SCFAs) (Figure 1) [4]. Shifts in the composition of the microbiota and microbiome that correlate with obesity are associated with an increased presence of organisms and genes that ultimately increase energy extraction, storage and usage of consumed nutrients [3,5]. As the microbiota between two individuals can deviate by hundreds of species and thousands of strain differences, the corresponding metabolite environment in the GI tract for each person is unique [2,6].

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Barrier function of the host microbiota

The microbiota can act as a barrier against incoming pathogens; this phenomenon has been described as colonization resistance [7]. There are several theories why the microbiota prevents pathogen colonization; some members of the microbiota can physically occupy pathogen attachment sites, some members can stimulate the mucosal immune system to alter tolerance of an invading pathogen, while others can consume nutrients the pathogen requires to proliferate.

One strategy to alter colonization resistance includes exogenously adding nutrients, also known as prebiotics, to promote the growth of individual microbiota species. An increased presence of *Bifidobacteria* and *Lactobacilli*, for example, has been shown to suppress bacterial infections caused by *Salmonella enterica* serovar Typhimurium (*S*. Typhimurium) [8,9]. However, prebiotic supplementation with nutrients thought to promote *in vivo* growth of *Bifidobacteria* and *Lactobacilli* did not inhibit *S*. Typhimurium colonization *in vivo*, but instead increased pathogen colonization when compared to mice fed a standard diet [10]. These studies indicate that identification of beneficial microbiota communities, and the nutrients that shape their composition, may be incomplete or not specific enough.

Host microbiota nutrient competition

Members of the GI microbiota have acquired specific mechanisms to exploit their environment and the nutrients available to them [11–13]. A recent global analysis of the microbiome encoded by 124 individuals revealed that there is a core set of genes that are likely required by any bacterium to thrive in the GI tract, including genes involved in the biodegradation of complex sugars and glycans present in the intestinal lining [14]. Evidence of the adaptability of the *Bacteroides* genus to host glycans was recently demonstrated when germ-free mice were co-colonized with *B. thetaiotaomicron* and a member of another common microbial community phyla, the Firmicutes' *Eubacterium rectale*. As a consequence of competition for dietary nutrients, *B. thetaiotaomicron* up-regulated glycoside hydrolases and signaled the host to produce mucosal glycans, presumably so that it could access a nutrient source its competitor *E. rectale* could not utilize [15].

Competition for nutrients is a strong force among the *Bacteroides* genus. During competition for dietary fructans, *B. thetaiotaomicron* uses a hybrid two-component signaling sensor to enable degradation and usage of fructans [16]. Additionally, genes that encode porphyranases and agarases, which enable some microbes commonly found in Japanese community members to digest seaweed, may have been transferred to the gut bacterium *Bacteroides plebeius* from the seaweed associated bacterium *Zobellia galactanivorans*, allowing *B. plebeius* to extract energy from otherwise indigestible food products [17]. A mutant library of *B. thetaiotaomicron* revealed that this microbe is highly adaptive to the microbiota composition and the availability of nutrients such as vitamin B12 [18].

Just what is the nutrient environment to which these commensal bacteria are adapting? During colonization of germ-free mice, commensal *Escherichia coli* were shown to utilize arginine, asparagine, aspartate, glucose/galactose, ribose, maltose, glucuronate, galacturonate and gluconate as substrates [19]. However, the nutrient environment of the GI tract is likely to be more complex with the addition of other microbiota members. For example, the levels of SCFAs found within germ-free animals are lower than in mice that had received a gut microbiota transplant from conventionally raised donors [20]. SCFA production has further been linked to the Firmicutes, as following antibiotic treatment of conventional mice, SCFAs decreased along with the diversity of the Firmicutes [21]. The production of some metabolites may even be a collaborative effort between distant

community members, as observations indicate that *E. rectale* uses *B. thetaiotaomicron* produced acetate to generate the SCFA butyrate [15].

Furthermore, in soil bacterial communities, physical fungal-bacterial interactions lead to the activation of fungal secondary metabolism genes that are normally silent under laboratory conditions [22].

The composition of the host microbiota alters the outcome of enteric pathogens

The composition of the host microbiota influences the susceptibility to enteric pathogen colonization, as microbiota communities with low complexity are increasingly prone to pathogenic colonization [23]. Evidence of this phenomenon was recently demonstrated when susceptibility to *S.* Typhimurium was increased after administration of clinically relevant doses of antibiotics that did not change the overall bacterial load of the microbiota, but did change the ratio of Firmicutes to Bacteroidetes [24,25]. The influence of the host microbiota upon an invading pathogen is not restricted to prokaryotes, as hatching of the parasitic nematode *Trichuris muris* in the large intestine of mice is dependent upon physical contact of the parasitic egg with microorganisms present in the gut microbiota [26]. The composition of the host microbiota has also recently been linked to eventual pathogen clearance [27]. Why the composition of the host microbiota is critical for initial colonization and eventual clearance by these pathogens is unclear. One theory, amongst many, is that the microbiota provides metabolites that can hinder or enhance virulence of enteric pathogens.

Enteric pathogens compete for carbon within the GI tract

Primary metabolites in the GI tract are in high demand, with many of them absorbed by the host, or consumed or converted into secondary metabolites by the microbiota [28]. The composition of one primary class of nutrients, carbohydrates, is controlled by members of the host microbiota. *B. thetaiotaomicron* alone contains over four times the number of genes involved in acquiring and metabolizing carbohydrates than the human host, and other *Bifidobacterium* strains secrete polysaccharide-hydrolyzing enzymes that ferment primary fructooligosaccharides into the secondary disaccharide lactate in the GI tract [2,29].

The ability of enterohemmorrhagic *E. coli* (EHEC) O157:H7 to catabolize the disaccharide maltose and other secondary carbon sources helps it compete with commensal strains of *E. coli* for colonization of the GI tract in a streptomycin-treated mouse model of infection [30]. The ability to exploit carbon sources to enhance virulence is not limited to EHEC. A recently constructed genome scale metabolic model for *S.* Typhimurium and *S.* Enteritidis revealed that these pathogens diverge from a commensal strain of *E. coli*, with the majority of the compounds that the pathogenic strains preferentially utilize over the commensal strain being carbon substrates [31]. Energy generation and colonization by the food-borne bacterial pathogen *Campylobacter jejuni*, which resides in the GI tract of its avian reservoir, depends upon scavenging of free amino and keto acids and chemotaxis towards the carbon sources asparagine, formate, lactate and chicken mucus [32–34]. In *Vibrio cholerae*, passage through the intestinal tract induces genes involved in succinate, glycine, and chitin utilization that enhance the ability of the pathogen to persist within aquatic environments, an important trait that enhances transmission and propagation of this water-borne pathogen [35]. These observations suggest that multiple enteric pathogens have the ability to respond to different carbon environments, and this response is beneficial for a pathogenic lifecycle. As the carbon environment is modulated by the host microbiota, understanding how the microbiota composition controls carbon sources that pathogens exploit will almost certainly lead to unique strategies to control colonization and virulence.

The microbiota can alter virulence properties of enteric pathogens

EHEC O157:H7 responds to metabolites secreted by the host microbiota to induce or repress virulence genes [36,37] (Figure 2). EHEC is transmitted to humans primarily through ingestion of foods contaminated by colonized cattle [38]. To colonize cattle, EHEC requires SdiA, a regulator that senses acyl-homoserine lactones (AHLs), which are produced by some members of the Bacteroidetes phyla [36] (Figure 2). Additionally, a virulence factor of EHEC, Shiga toxin 2 (Stx2), is produced and released into the environment by activated RecA, which induces the lytic cycle of the bacteriophage that encodes Stx2. Germ-free rats that are then colonized with human microbiota secrete molecules that both repress *stx2* mRNA expression, and inhibit the RecA mediated lytic cycle independent of known quorum-sensing pathways (involving SdiA, QseA, QseC or AI-3). *B. thetaiotaomicron* was shown to produce this inhibitory factor, implicating a member of the human microbiota in repressing a bacterial virulence factor [37] (Figure 2). Together, these two studies demonstrate that metabolites secreted by the host microbiota may modulate EHEC colonization and virulence gene expression in two distinct hosts, its cattle reservoir, as well as its human host.

Spatial nutrient differences could lead to pathogen tropism

Enteric pathogens preferentially colonize different regions of the GI tract, such as *S.* Typhimurium in the small intestine, and EHEC in the distal ileum and colon [39]. One potential reason for tissue tropism may be because metabolites that influence pathogen replication and virulence are differentially available in these regions. SCFAs are known to have significant influence upon enteric pathogenicity, and HIV is just one pathogen of many that have recently been demonstrated to respond to SCFAs, as they cue HIV activation in the gut [40]. SCFAs are also known to influence the inflammatory host immune response [41]. The composition of SCFAs in the GI tract is modulated by the microbiota. For example, the majority of the SCFA butyrate is produced by the resident microbiota [42], with butyrate amounts varying depending on the activity and composition of the microbiota [21,43]. Additionally, the levels of individual SCFAs vary in different regions of the GI tract, with formate and acetate predominating in the small intestine, while propionate and butyrate are higher in the colon [21,44,45] (Figure 3).

Interestingly, the SCFA formate acts as a diffusible signal to induce the expression of invasion genes in *S.* Typhimurium, while butyrate, a SCFA present at higher concentrations in lower regions of the GI tract, is known to repress invasion genes [46,47]. Conversely, exposure to butyrate enhances adherence of EHEC to Caco-2 cell monolayers during a tissue culture model of infection [48]. Furthermore, butyrate was also shown to influence activation of the locus of enterocyte effacement pathogenicity island of EHEC, which carries genes involved in the formation of attaching and effacing (A/E) lesions on intestinal epithelial cells [39,48]. In both *S.* Typhimurium and EHEC, the SCFA that enhances virulence, formate and butyrate, respectively, is highest in the region of the GI tract that these enteric pathogens preferentially colonize.

Pathogen mediated inflammation alters the microbiota and nutrient composition of the gut, further enhancing colonization

While the nutrient environment, which is modulated by the resident microbiota, influences initial colonization by an enteric pathogen, subsequent changes in the composition of the microbiota also lead to downstream changes in the nutrient environment and enteric colonization potential of the gut. Colonization by *Citrobacter rodentium*, a close relative of EPEC and EHEC, causes an inflammatory response in the GI tract, which corresponds to a

major alteration in the composition of the microbiota [24]. The inflammatory response and corresponding alterations to the host microbiota have been linked to further increases in pathogen growth, as well as an increased release of glycan and amino-acid rich mucins [24,49]. Additionally, acute gut inflammation caused by *S.* Typhimurium infection has recently been demonstrated to generate a respiratory electron acceptor, tetrathionate, that provides a competitive growth advantage to the pathogen over the competing microbiotia [50]. The release of nutrient rich compounds, such as mucins and glycans, as well as other novel growth factors, such as tetrathionate, likely foster pathogen growth, signifying that pathogen mediated inflammation and microbiota perturbations could be a mechanism employed by the pathogen to enhance its ability to replicate in the host after an initial infection has already been established.

Conclusions

One underexploited opportunity to prevent enteric infections is to target the mechanisms pathogenic bacteria undertake to respond to the unique nutritional environment found within the GI tract [51]. Because the rate of passage through the GI tract is rapid, the ability to respond and compete for nutrients is likely to be one of the most important factors controlling the success or failure of an invading pathogen [52]. As this nutrient environment is shared between pathogens and the host microbiota, novel avenues to control infection before and after the onset of disease can be discovered by carefully studying the mechanisms enteric pathogens and members of the host microbiota utilize to generate, compete, and exploit the nutrients within the GI tract.

Abbreviations used

(GI)	Gastrointestinal
(SCFAs)	short chain fatty acids
(*S.* Typhimurium)	*Salmonella enterica* serovar Typhimurium
(EHEC)	enterohemmorrhagic *E. coli*
(AHLs)	acyl-homoserine lactones
(Stx2)	Shiga toxin 2
(A/E)	attaching and effacing
(LEE)	locus of enterocyte effacement

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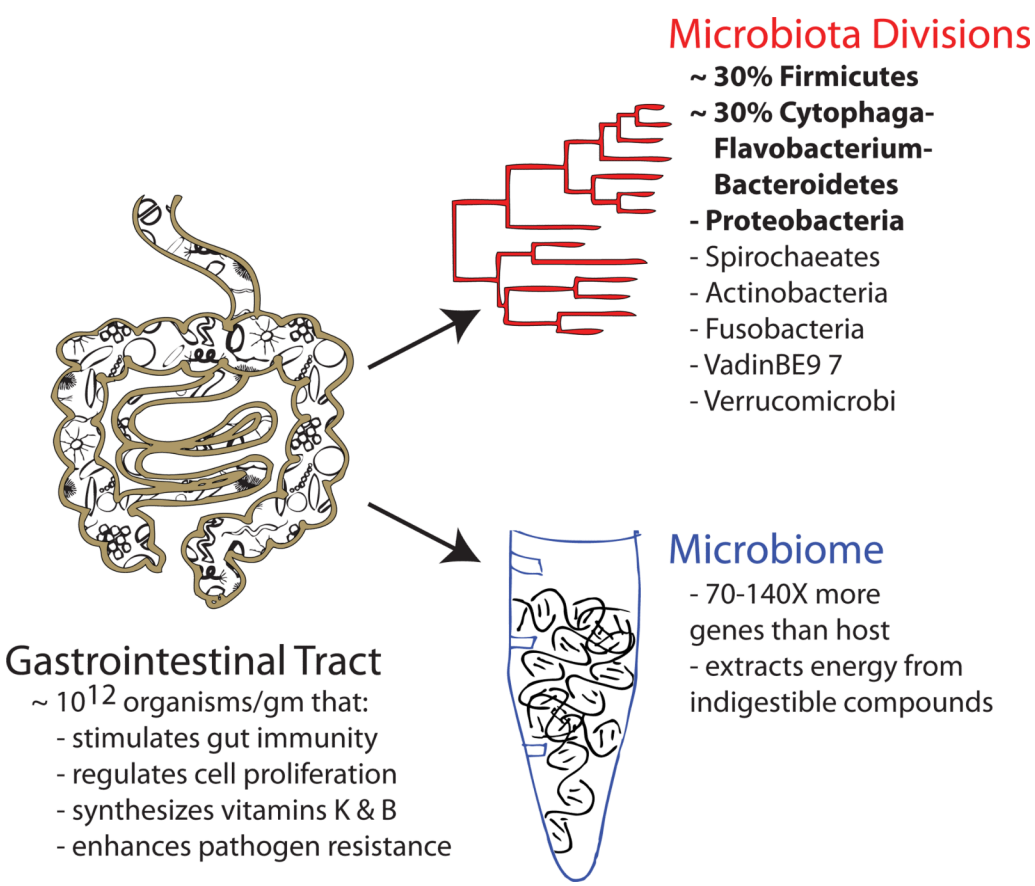

Figure 1. Functions of the host microbiota

Within the gastrointestinal (GI) tract is a community of commensal organisms, the microbiota, with an estimated density as high as 10^{12} organisms per gram of content [1]. Out of a total of 55 bacterial divisions identified thus far, only 8 have been identified within the human GI tract (dominant divisions are in bold) [2]. The genes encoded by this massive community are collectively termed the microbiome, which encodes an estimated 70–140 times more genes than encoded by its the human host [3,4]. Together, the organisms that reside in the GI tract and the genes they encode are necessary for the completion of essential tasks for the host, including stimulating gut immunity, regulating cell proliferation, vitamin synthesis, and mediating resistance to pathogen invasion and colonization.

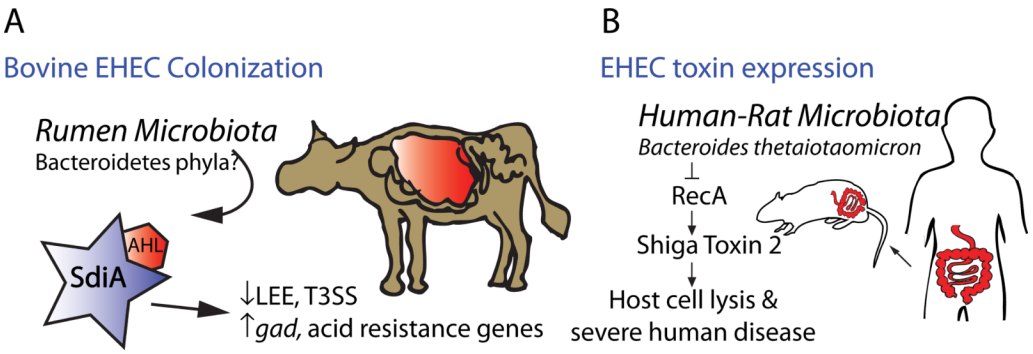

Figure 2. Chemical sensing between the microbiota and EHEC

(A) Members of the Bacteroidetes phyla produce acyl-homoserine lactones (AHLs). These signaling molecules are prominent within the rumen of the bovine gut, but not in other areas of the GI tract. AHLs isolated from the rumen stabilize folding of SdiA, an EHEC regulator that is necessary for colonization of cattle. Specifically, the rumen AHL-SdiA complex represses transcription and protein production by the locus of enterocyte effacement (LEE), a pathogenicity island that enables EHEC to colonize and promote disease in its human host, an undesirable phenotype for commensal colonization of cattle. Conversely, the AHL-SdiA complex activated the expression of gad acid-resistance genes and promoted survival in low pH, a phenotype necessary for EHEC survival within the acidic stomachs of the cow [36]. (B) Shiga Toxin 2 (Stx2) is a major virulence factor of EHEC O157:H7, which causes protein synthesis inhibition and ultimately cell death in the human host. Prokaryotes of conventionalized rats colonized with human microbiota produced molecules which repressed RecA mediated stx2 mRNA expression and Stx2 production. Subsequent analysis revealed that these inhibitory prokaryotic molecules are produced in part by *Bacteroides thetaiotaomicron*, a member of the normal human intestinal microbiota [37].

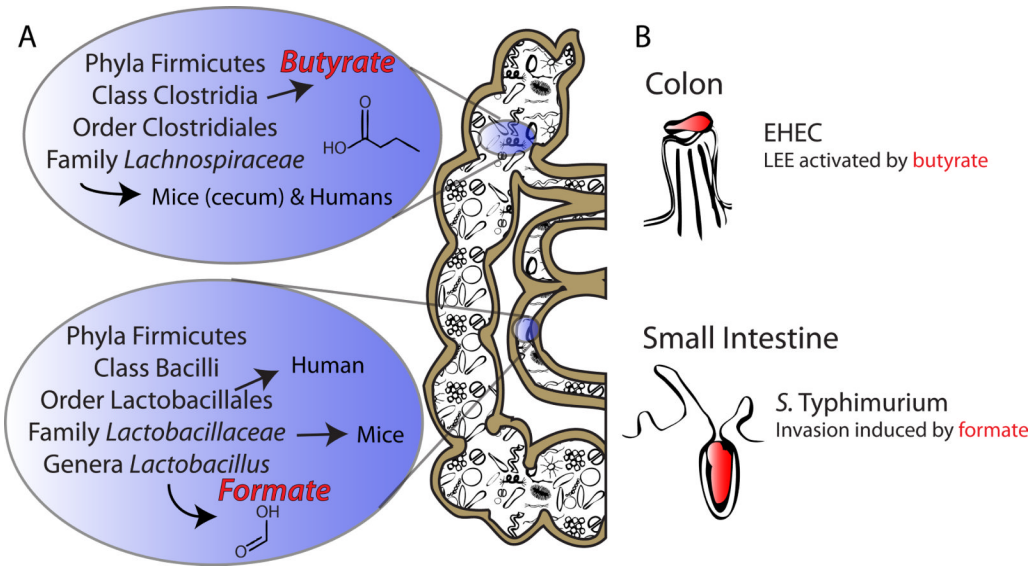

Figure 3. Short-chain fatty acid (SCFA) influence upon pathogen tropism

(A) The Firmicutes are a principal phyla in both the small intestine and the colon, with the family *Lachnospiraceae* dominating the colon [21,53]. The *Lachnospiraceae* are members of the Clostridia class, which are major producers of butyrate in the human colon [43,53]. The Lactobacillales order of the Bacillus class dominate the small intestine in humans, and upon further examination in mice, the family *Lactobacillaceae* within this order compose 24% of the total small intestine microbiota [21,53]. Genera belonging to this family include *Lactobacillus*, which heterofermentatively can produce formate as well as acetate and lactate. (B) EHEC primarily colonizes the colon of humans, where butyrate is a dominant SCFA [21,39,44,45]. In EHEC, butyrate activates the locus of enterocyte effacement (LEE) and enhances adherence of this pathogen in tissue culture [39,48]. *Salmonella enterica* serovar Typhimurium (*S*. Typhimurium) colonizes the small intestine, where formate is a dominant SCFA. The SCFA formate induces the expression of invasion genes in *S*. Typhimurium, while butyrate is known to repress these genes [46,47].