AMERICAN SOCIETY FOR MICROBIOLOGY | Infection and Immunity

Food Microbiology | Minireview

# Bacterial interactions on nutrient-rich surfaces in the gut lumen

**Bo Huey Chiang,**[1,2] **Giovanni Vega,**[1,2] **Sarah C. Dunwoody,**[1] **Michael L. Patnode**[1]

**AUTHOR AFFILIATIONS** See affiliation list on p. 9.

**ABSTRACT** The intestinal lumen is a turbulent, semi-fluid landscape where microbial cells and nutrient-rich particles are distributed with high heterogeneity. Major questions regarding the basic physical structure of this dynamic microbial ecosystem remain unanswered. Most gut microbes are non-motile, and it is unclear how they achieve optimum localization relative to concentrated aggregations of dietary glycans that serve as their primary source of energy. In addition, a random spatial arrangement of cells in this environment is predicted to limit sustained interactions that drive co-evolution of microbial genomes. The ecological consequences of random versus organized microbial localization have the potential to control both the metabolic outputs of the microbiota and the propensity for enteric pathogens to participate in proximity-dependent microbial interactions. Here, we review evidence suggesting that several bacterial species adopt organized spatial arrangements in the gut via adhesion. We highlight examples where localization could contribute to antagonism or metabolic interdependency in nutrient degradation, and we discuss imaging- and sequencing-based technologies that have been used to assess the spatial positions of cells within complex microbial communities.

**KEYWORDS** cell adhesion, polysaccharides, gut microbiota, food particle, toxin secretion systems, syntrophy

Resource harvesting by resident gut bacteria occurs in an environment with unique features. The density and diversity of bacterial species is high, leading to a large number of prospective positive and negative microbe–microbe interactions. In addition, the continuous motion of luminal contents has the potential to disrupt juxtapositions of microbial cells on timescales much faster than microbial doubling time. These features pose a significant challenge for the pairwise coevolution of microbial genomes in the gut and may restrict strong coevolution to the species that possess adhesion and migration systems, affording them frequent and sustained physical proximity to one another. For species that are stochastically dispersed, there may be therapeutic opportunities to intentionally direct them into spatial arrangements that enhance microbe–microbe interactions and promote functions that benefit human hosts. Gut biogeography across scales including organ compartments (10–100 cm) and distance from the mucosal epithelium (along the radial axis) act as major habitat subdivisions for microbes (1). These habitats support distinct collections of species that may evolve together based on their shared accumulation as a result of proliferation. However, there are large numbers of distinct species and strains in each of these habitats, raising the question of whether or not these organisms are stochastically distributed at the micron scale (1). Here, we review the existing evidence for micron-scale spatial organization of gut microbes with a particular focus on whether accumulations of dietary nutrients in the lumen could enable reproducible microbial interspecies interactions that lead to co-evolution of gut bacterial species.

**Editor** Anthony R. Richardson, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Address correspondence to Michael L. Patnode, mpatnode@ucsc.edu.

The authors declare no conflict of interest.

**Published** 20 March 2024

## DIETARY FIBER IS A HETEROGENEOUSLY DISTRIBUTED CARBOHYDRATE RESOURCE IN THE GUT

The chemical structures of dietary plant polysaccharides impact both their physical distribution in the intestinal lumen and their ability to serve as a carbon source for gut bacteria (2, 3). These complex carbohydrates are often derived from cell walls or energy storage structures (such as starch granules) and are resistant to hydrolysis in the upper gastrointestinal tract (4). Many of the biochemical pathways by which gut bacteria degrade dietary fiber have been described in detail (5–9). The spatial distributions of common fiber types and the impact of heterogeneous accumulations of these nutrients on the localization of the bacterial species that consume them are less well-understood.

Classes of fibers that are fully soluble are likely to be homogeneously distributed in the fluid phase of the intestinal lumen at the sub-micron scale. These include some inulins, pectic fragments, mannan, and some gums and mucilages that are naturally present in human foods and can also be added as partially purified components during food processing (10). These fiber types often have short polysaccharide chain lengths, charges, or other chemical features that limit interactions between chains (11–15). Such fibers are subject to degradation as bacteria encounter them stochastically after ingestion and, considering host intestinal mixing, are not likely to support reproducible physical associations between bacteria, as has been modeled using simplified systems (16). However, these fiber types may exist in a particulate or aggregated form when they are associated with the insoluble fibers discussed below.

Gel-forming fiber types concentrate carbohydrates into discrete regions within the gut lumen due to their semi-solid phase. For example, pectin is a widely consumed gelling agent and a major component of the primary cell wall in plants, particularly edible fruits (17). Pectic polysaccharides exist in three main structural forms: homogalacturonan (HG), rhamnogalacturonan I (RG1), and rhamnogalacturonan II (RG2). All three forms have a backbone of charged α-1,4-linked D-galacturonic acid units (alternating with L-rhamnose in the case of RG1), with sidechains of arabinan, galactan, or arabinogalactan common in RG1 and RG2 (18, 19). The negatively charged galacturonic acid in pectins triggers gel formation under acidic conditions when bound with positively charged ions like calcium (20). Pectin gels remain undigested and stable in simulated gastric conditions (21) and are actively under investigation as encapsulating agents for gastric digestion susceptible food ingredients, drugs, and bioactive compounds (22–25).

Gels can also be formed by resistant starch, an alpha-glucan that resists breakdown by mammalian amylases in the upper digestive tract (26, 27). Resistant starch 4 (RS4) is a subtype of resistant starch that is chemically modified by phosphorylation, acetylation, or etherification. While acetylated and phosphorylated RS4 is soluble (28) and etherification produces insoluble compounds (29), all three modifications lower gelatinization temperature, making them more susceptible to gel formation than their unmodified counterparts (28, 30). Like alpha-glucans, purified beta-glucans (with variably alternating 1,3 and 1,4 bonds) also form dense gels in conditions that simulate the small intestine (31). The stability of the colloidal gels formed by these fibers allows them to transit the intestine as dietary particles available for bacterial catabolism (32, 33).

Fiber types classified as insoluble are highly likely to form particles in the gut and serve as a source of polysaccharides that provide an advantage to bacteria that can colonize their surfaces. Fibers typically defined as insoluble include cellulose, hemicellulose, and several types of resistant starch (RS1, RS2, and RS3). Cellulose is the primary component of the cell wall of terrestrial plants (34) and consists of linear chains of glucose subunits connected by beta-1,4 bonds. When these chains self-associate, they form rigid crystalline fibrils that reduce their solubility in water (35). Although gut bacterial taxa capable of degrading cellulose have been detected in humans, including those in the *Clostridium*, *Eubacterium*, *Butyrivibrio*, *and Ruminococcus* genera (36), the degradation process is inefficient compared to that in microbial communities from other mammals such as ruminants (37). Hemicellulose is found in the primary and secondary cell walls of plants and typically contains xylans (often beta-1,4-linked xylose with diverse

side chains) and mixed-linkage glucans formed from interspersed beta-1,4 and beta-1,3 glucose (38). These polysaccharides are abundant in dietary plant cell wall fragments, though high degrees of sidechain substitution can increase their solubility in water (38, 39). Despite being chemically resistant and tightly associated with cellulose, hemicellulose is known to be degraded in the large intestine by several bacterial taxa, including *Bacteroides* species (40, 41). Lignin, a class of highly insoluble polyphenolic compounds that are physically associated with hemicellulose and cellulose, can also be broken down by some specialized gut bacteria (42). Resistant starch 1 and 2 are not integral to the plant cell wall but nonetheless have very limited solubility and are likely to introduce heterogeneity into the gut nutrient landscape (26). RS1 is sequestered in intact plant cells, while RS2 is present in compact starch granules most abundant in plants such as potatoes and bananas. RS3, also known as retrograde starch, is made up of granules that gelatinize after heating and recrystallize after cooling, resulting in material that is partially insoluble in water (26). All three types of resistant starch are fermentable by the microbiota (9, 43–45) and likely provide selective pressure to access and exploit these resources.

## SPATIAL DISTRIBUTION OF DIETARY AND HOST-DERIVED NITROGEN

Due to the abundance of carbon sources in the mammalian gut, nitrogen often serves as a limiting nutrient for microbes (46). Nitrogen is an essential element for the growth of bacteria and contributes to the synthesis of proteins, nucleic acids, and peptidoglycan. Soluble nitrogen sources, including dietary nitrate and excreted urea, are harvested by bacteria in the intestine. Isotype tracing studies demonstrated that Firmicutes obtain nitrogen from host urea while Bacteroidota (formerly Bacteroidetes) rely more on host mucin in a simplified diet context (47). Although the delineation of nitrogen sources that support gut microbes in a typical, complex human diet context is not easily determined, the importance of nitrogen is made clear by the expression of nitrogen acquisition genes induced by fiber supplementation (48).

Dietary proteins from plants, including protein-rich cereals and pulses (49), can form insoluble (and thus highly concentrated) aggregates. Cereal proteins (from wheat, rye, barley, maize, oats, and rice) and pulse proteins (from peas, beans, lentils, and chickpeas) are generally categorized as either albumins, globulins, glutelins, or prolamins based on their solubility (via Osborne fractionation) at standardized salinity, pH, and ethanol concentrations (50). The human gastrointestinal tract provides the conditions required to solubilize many plant proteins, especially when food processing techniques are employed, including cooking and soaking (51). However, certain classes of proteins have low scores for digestibility (52, 53) and form aggregates that escape digestion in the stomach and small intestine (54). Additionally, proteins that do not typically survive transit to the large intestine can be rendered stable in the gut by trypsin and chymotrypsin inhibitors present in plant tissues (51) and alterations to the digestive tract such as increases in gastric pH (55). These variables influence whether or not plant protein aggregates are available to bacteria in the colon.

Animal-derived foods typically contain higher total protein content than plant foods, and as such, the majority of protein in most adult human diets comes from consuming mammals, fish, poultry, and dairy (56). While host proteases are capable of breaking down a majority of the protein from animal-derived foods, collagen is not highly soluble in water (57), and has been shown to survive digestion processes (58). Bacteria from the *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Bacillus* genera have been shown to encode proteins that bind to human collagen for tissue colonization and host infection (59), demonstrating that collagen can act as a substratum for adhesion. In addition, mice fed a high-fat diet supplemented with collagen from fish skin exhibited an increase in the abundance of *Bacteroides*, *Streptococcus*, *Faecalibaculum*, and *Clostridium* in the intestine (60), raising the possibility of potential competitive interactions that are centered around collagen metabolism.

Bacteria can also obtain nitrogen from sources originating from the epithelium. The epithelial mucus layer undergoes constant renewal as mucin glycoproteins are secreted and form a gel in the gut lumen (61). Some human gut microbes are known to utilize mucin as a nitrogen source, including *Akkermansia muciniphila* and members of the *Bacteroides* genus (62, 63). *Akkermansia* and *B. thetaiotamicron* compete with one another *in vitro* and *in vivo*, and genes involved in carbohydrate metabolism, glycan biosynthesis, and antimicrobial activity were associated with their interactions (64). In addition to secreted proteins, epithelial cells themselves that are sloughed into the lumen (65) contain abundant protein, nucleic acids, glycosaminoglycans, and membrane-derived phospholipids, such as phosphatidylethanolamine, that can form concentrated regions rich in nitrogen-containing compounds (66, 67). Phosphatidylethanolamine in the membranes of these cells can be broken down by phosphodiesterases into ethanolamine and glycerol, which provide nutrient sources for certain gut microbes, including species in the Pseudomonadota (formerly Proteobacteria) phylum (66–68). Nonpathogenic *E. coli* strains were observed to outcompete pathogenic *E. coli* (EHEC) when cultivated in minimal media containing ethanolamine plus glucose or glycerol (68), raising the prospect that epithelial cell-derived lipids in the gut could contribute to microbial competition.

## MEASURING BACTERIAL CELL LOCALIZATION IN THE INTESTINE AT THE MICRON SCALE

The development of a working model for the physical organization of the gut microbiota has been hindered by several factors: (i) the large number of individual species that must be tracked; (ii) the difficulty in tagging the highly heterogeneous dietary substrata that serve as nutrient landmarks; (iii) the necessity to study spatial organization in the host, as opposed to in cell culture systems; and (iv) the dynamic nature of the highly mixed intestinal contents. The transit of luminal contents through the large intestine is facilitated by smooth muscle contractions that create backflow, redistributing dietary compounds and bacteria at up to 1,000-fold the rate of simple diffusion (69, 70). Such extensive mixing introduces highly stochastic distributions of different bacterial species and food particles relative to one another in the large intestine, making histological characterization difficult. Several recently developed experimental approaches seek to address these challenges.

Fluorescence *in situ* hybridization (FISH) microscopy has revealed that bacteria in many turbulent environments, such as in the oral microbiota, can adopt spatial patterns (71, 72), raising the prospect that certain species in the intestine are found in reproducible arrangements. Recent work has revealed heterogeneously distributed bacterial clusters in the gut environment using gnotobiotic mice colonized with human gut microbiota (73). In the context of a standard diet containing plant polysaccharides, distinct clusters of bacteria from the broad phylogenetic groups Bacteroidales and Bacillota (formerly Firmicutes) were observed spatially excluded from one another. However, a diet lacking plant polysaccharides induced more homogeneously distributed taxa, possibly due to the increased reliance on mucin, resulting in the thinning of the mucin layer and decreased bacteria–epithelial cell distance. Combinatorial Labeling and Spectral Imaging (CLASI)-FISH detects probes with a unique fluorophore combination, significantly increasing the number of species that can be imaged simultaneously (74). CLASI-FISH applied to gnotobiotic mice colonized with a model human gut microbiota consisting of 15 type-strains demonstrated substantial mixing of bacteria in the colon with enrichment of subsets of strains in the lumen versus at the epithelium (75). HiPR-FISH, high-phylogenetic-resolution microbiome mapping by fluorescence *in situ* hybridization, is an advanced form of CLASI-FISH that relies on sequential labeling and multiplexing to identify over 1,000 unique fluorescence signals. When applied to mouse colon tissue sections, small multicellular clusters of the same strain were observed (76).

Recent sequencing technologies have also provided insights into bacterial spatial organization in the intestine. MaP-Seq, metagenomic plot sampling by sequencing,

captures spatial information by embedding a microbial community in gel and fragmenting the sample into particles of defined size. By sequencing the barcoded 16S rRNA amplicons from individual particles, data describing the identity and physical proximity of microbial cells are obtained. MaP-Seq using mouse intestinal segments with and without dietary fiber intervention identified the formation of distinct clusters of different bacterial groups that are heterogeneously distributed as well as co-associations between groups on the scale of tens of microns (77). Importantly, the technologies described above assess only a single temporal snapshot of this densely populated and actively mixed system and are unable to distinguish transient juxtaposition from sustained proximity. Supplementing these approaches to identify long-lived spatial structural features in the gut requires time-lapse imaging modalities (78) or physical isolation of the units of structure such as aggregations of bacterial cells and nutrients.

## ADHESION AS A MEANS TO ACCESS DENSELY CONCENTRATED NUTRIENTS

The majority of commensal gut bacterial taxa in healthy adult humans are non-motile. *Bacteroides*, *Bifidobacteria, Ruminococcus, Lactobacillus, Faecalibacterium*, and *Akkermansia* are typically not capable of directed migration in the classical sense (79–83). *Bacteroides,* which are prominent degraders of many of the heterogeneously distributed nutrients discussed above, lack flagella or type IV pili (84). It is posited that innate and adaptive immunity has suppressed the evolution of flagella in commensal gut microbes (85, 86) and that invading pathogens employ directed migration to outcompete commensal bacteria (87). Given the dynamic and heterogeneous distribution of nutrients and bacteria in the human intestine, adhesion may be especially valuable for efficient nutrient harvesting.

Biofilms are collections of cells embedded in an extracellular matrix, typically adhering to a biotic or abiotic surface (88). Biofilms have been observed in the human intestine, though the species responsible for generating the biofilm matrices has been difficult to establish (89–92). Saccharolytic bacteria, such as those in the genus *Bacteroides* and *Bifidobacteria,* were detected on undefined food residues in human fecal samples (93). By measuring short-chain acid production in strains isolated from these particles, it was observed that arabinogalactan degradation rates were higher in biofilm-forming communities, while the degradation rate for starch and mucin and the fermentation rate of soluble oligosaccharides was higher in planktonic populations (93). *Bacteroides* use an adhesive appendage designated as the type V pilus to generate biofilms on non-specific surfaces, such as plastic and glass (94). Type V pili are similar to type I pili in Enterobacteriaceae but require lipoprotein precursors and outer membrane proteinases (95). These pili include stalk proteins that may accommodate multiple tip adhesins that could mediate attachment to nutrient-rich surfaces. In the case of *B. thetaiotaomicron,* biofilm formation is also regulated by capsular polysaccharide expression (96).

Carbohydrate-specific adhesion is well-documented in members of *Bifidobacteria* (97) and *Ruminococcus* (98). *Bifidobacteria* has been extensively characterized for the ability to adhere to and catabolize granular starch from maize, potato, and barley under *in vitro* conditions simulating the upper GI tract (99). Starch adhesion exhibited strain-specific variation, with all highly adhesive strains also exhibiting starch degradation. Moreover, *Bifidobacteria* adhesion is inhibited by soluble starch breakdown products, low pH, or proteinase K pretreatment, suggesting the involvement of cell surface proteins, potentially the highly conserved type IVb Tad (tight adherence) pilus (99, 100). *Bifidobacteria* were observed to adhere and colonize the surface and crevices of the starch granules in the mouse intestine using FISH (101). *Ruminococcus bromii* also adheres to starch via a starch binding and degradation system known as the amylosome, which is highly specific for helical glucans in amylose (102, 103). Adhesion to cellulose is a well-known feature of cellulosome-expressing rumen microbes (104, 105), but it has also been indirectly observed in *Ruminococcus champanellensis*, a cellulolytic species isolated from human fecal samples. Single-molecule force spectroscopy revealed that

the formation of two distinct binding complexes variable in binding strength allows catch-bond behavior of the bacteria to cellulose under high shear force (106).

*Bacteroides* also demonstrate adhesion to specific carbohydrate surfaces. The genus *Bacteroides* is highly abundant in adult humans and has adapted to degrade a diverse array of carbohydrates in the gut. Strain-specific carbohydrate adhesion was observed in roughly one-third of the 160 *Bacteroides* and *Parabacteroides* screened for their binding to 60 different dietary polysaccharide-rich surfaces (107). Adhesion to galactan, mucin, and oat hull fiber was particularly robust, and galactan adhesion was recapitulated in the intestines of gnotobiotic mice. However, the genes involved in specific adhesion have not yet been identified.

## MICROBIAL ANTAGONISM ENHANCED BY PROXIMITY

Bacterial cells that adhere to insoluble nutrient sources are poised to participate in competitive interactions with co-adherent strains. Many Gram-negative bacteria express a contact-dependent type VI secretion system (T6SS), a membrane-embedded protein complex that facilitates interbacterial competition through the injection of toxins into adjacent target cells. This molecular delivery apparatus consists of variable gene clusters encoding core proteins and additional accessory subunits that vary between bacterial taxa (108–110). The mechanism of attack involves the contraction of the needle-like tube–sheath complex (TTC), which propels the polymeric tube and spike complex (111) to penetrate the membrane of adjacent prey cells, delivering toxic effector proteins in a proximity-dependent manner (112, 113).

Contact with an adjacent cell triggers the assembly and firing of the T6SS at the contact site. The assembly, contraction, and disassembly of T6SSs occurs on the order of tens of seconds (114), which is consistent with the robust killing observed in cells cultured on solid media. Furthermore, while T6SS assembly can be localized randomly on the cell periphery (115), localization is disproportionately high at cell–cell contact sites when bacterial cells are allowed to establish sustained contact. Contact-dependent T6SS assembly has been observed in *Pseudomonas aeruginosa* (116), *Acinetobacter* species, and *Burkholderia thailandensis* (117) and can occur between heterologous bacterial species. In a process known as "tit-for-tat," T6SS attacks from a *V. cholera* cell are detected by *P. aeruginosa*, which triggers T6SS assembly and firing for a counterattack at the contact site (118). *P. aeruginosa* must fire several times in response to an attacking cell in order for this defense to be effective, further emphasizing the need for sustained contact (119). The outer membrane protein OmpA, periplasmic protein TslA, and bacterial surface capsule production modulate contact-dependent T6SS assembly at the contact site (117). Thus, the juxtaposition of the outer membranes of bacterial cells adhering to the same molecular surfaces in the intestine may provide an enhancement of T6SS killing.

The T6SS has been extensively characterized in the intestinal pathogen *Vibrio cholerae* (120) and commensal gut *Bacteroides*. Three genetic architectures (GAs) of the T6SS have been identified in gut Bacteroidales, two of which are horizontally transferred between strains to influence interbacterial antagonism (121, 122). GA3, which is exclusive to *Bacteroides fragilis* species, is the most well-described and is known to be utilized for potent bacterial killing. The susceptibility of potential prey to T6SS attacks is highly dependent on its repertoire of immunity proteins (123). Many *B. fragilis* strains, including those that do not encode a T6SS themselves, contain immunity proteins that provide protection from effector proteins associated with other *B. fragilis* strains (124). *In vitro*, *B. fragilis* NTCC 9343 targets *B. thetaiotaomicron* (122), and further, *B. fragilis* NTCC 9343 and *B. fragilis* 638R target numerous gut Bacteroidales strains, including other *B. fragilis* strains that do not contain the same T6SS locus (125). The expression of the T6SS gene cluster in the enteroaggregative *E. coli sci1* is activated in iron-limited conditions (126), suggesting that nutrient availability in the intestine may modulate T6SS-dependent competitive dynamics. However, effects of dietary plant polysaccharides on T6SS expression have not been thoroughly investigated. Interestingly, *B. fragilis* binds to mucin

*in vitro* (127) and also exhibits nonspecific adhesion (107), either of which could place *B. fragilis* in proximity with target cells in the intestine.

*In vivo* evidence for T6SS-mediated killing in the gut has largely come from studies using mono- and bi-colonized gnotobiotic mice. Several bacterial species have been shown to gain a competitive advantage from the T6SS with respect to their colonization of the mouse intestine, including *B. fragilis* 638R (125) and *Salmonella typhimurium* (128). *V. cholerae* was shown to antagonize commensal *E. coli* using its T6SS in the mouse intestine (129). In the infant rabbit model, the T6SS in *V. cholerae* provides a competitive advantage, dependent upon the utilization of T6SS by other bacteria present (130). Direct T6SS-mediated competition between *Citrobacter rodentium* and commensal *E. coli* Mt1B1 was shown in the mouse intestine (128). Interestingly, *Bacteroides* strains that are susceptible to T6SS predation *in vitro* may avoid being targeted *in vivo*, suggested by the differential susceptibility of *B. thetaiotaomicron* to *B. fragilis* killing *in vitro* versus *in vivo* (124). In these *in vivo* studies, it is not clear whether the participating strains exhibit a high degree of sustained colocalization. It is likely that T6SS-expressing cells and susceptible prey cells would encounter one another less often in a well-mixed community of hundreds of species, and in such cases, co-adhesion to the same surface could enhance their interactions.

Intestinal bacteria also engage in contact-independent killing via antimicrobial peptides known as bacteriocins secreted by Gram-positive and Gram-negative bacteria (131, 132). The activity of many bacteriocins in the intestinal environment has been confirmed using mouse models (133, 134). Bacteriocins can be bacteriostatic or bactericidal, and the majority have a narrow set of species targets that are often closely related to the producing strain (135). Gram-positive *Ruminococcus* and *Lactobacillus* secrete bacteriocins (136, 137), and Gram-negative *Bacteroides,* including *B. ovatus* and *B. thetaiotaomicron*, and *Phocaeicola vulgatus* produce bacteroidetocins that are related to class IIa bacteriocins (138–140). The bacteroidetocins have shown no effect on members of the other major phyla in the gut (*E. coli*, *Lactobacillus*, *Enterococcus*, and *Bifidobacterium*) but are highly effective against Bacteroidota (formerly Bacteroidetes), including *Prevotella*, *Parabacteroides*, and other *Bacteroides* (140). The effectiveness of bacteriocins is dependent on the concentration that reaches the target cell, and in the case of bacteroidetocin binding to its molecular target BamA, it is likely reversible, necessitating higher concentrations than that of an enzymatic toxin (141). In the densely populated gut environment, the deployment of bacteriocins may provide the strongest effect against co-adherent cells in proximity, especially since many gut bacteria (for example, *E. faecalis*) secrete extracellular proteases and peptidases that likely destroy bacteriocins before they diffuse or circulate over long distances to reach target cells (142–145).

## EFFECT OF PROXIMITY ON EXCHANGES OF METABOLIC PRODUCTS AND GENETIC INFORMATION

Bacteria participate in commensal and mutualistic interactions via nutrient sharing, which can also be enhanced by proximity. Nutritional cross-feeding of metabolic products, known as syntrophy, has been observed in fiber degraders, such as *Bacteroides* species, which can sustain the growth of non-saccharolytic members in the gut microbiota (146). The archeon *Methanobrevibacter smithii* consumes the acetate and hydrogen produced by *B. thetaiotaomicron,* relieving the growth suppression of these metabolites on *B. thetaiotaomicron* in co-cultures (147). Notably, the interaction between *B. thetaiotaomicron* and *M. smithii* was accompanied by the formation of multi-species microbial clusters of variable sizes when these bacteria were co-cultured. *Bacteroides* can also provide polysaccharide breakdown products to neighboring strains. For example, *B. ovatus* ATCC8483 was observed to secrete inulin hydrolase (incurring a fitness cost) to support the growth of *P. vulgatus* (148), despite the dispensability of this hydrolase for inulin degradation by *B. ovatus*. *Ruminococcus bromii*, a primary starch-degrading species in the gut microbiota, was increased in humans consuming a resistant potato starch-supplemented diet, which was associated with an increase in butyrate (149). In

the same subjects, a major butyrate producer, *Eubacterium rectale*, was correlated with the increase in *R. bromii,* raising the possibility of a cross-feeding relationship whereby *R. bromii* degrades the resistant starch and releases breakdown products for *E. rectale*. Inter-phylum cross-feeding has been observed between *R. bromii* and *B. thetaiotaomicron,* whereby the degradation of potato amylopectin by *R. bromii* produces glucose that can be utilized by *B. thetaiotaomicron* (150). *In vitro* co-culturing experiments also demonstrated that the degradation of the plant cell wall polysaccharide xylan by *B. longum* and *B. pseudocatenulatum* leads to the production of lactate, which is then utilized by *Megasphaera indica* for growth (151). These examples highlight the ability of strains with known particle-binding phenotypes to participate in cooperative microbe–microbe interactions.

The exchange of genetic information between bacteria via horizontal gene transfer (HGT) is prevalent in the gut microbiota and can also be proximity-dependent. HGT can provide beneficial functions via the transfer of genes involved in antibiotic resistance (152), immunity against the antibacterial effectors (123), and nutrient utilization (153). HGT by conjugation is thought to be a major mechanism of information exchange in the gut (154, 155) and depends on the conjugative type IV pilus or the F-pilus, a multi-protein complex on the donor cell. Extension and contraction of the F-pilus draws the recipient close for mating bridge formation, and DNA transfer requires direct cell-cell contact (156). The conjugative pilus is encoded on plasmids that replicate autonomously or mobile genetic elements that require integration into the chromosome (157). *Bacteroides* species are known to serve as both donors and recipients of conjugative transposons that code for a fully functional conjugative apparatus that is excised from the donor chromosome and integrated into the recipient chromosome during mating (158). In *E. coli,* the average length of the F-pilus is 1.7 µm, and when deployed, the F-pilus requires 4–5 min to reach its full length (159). These characteristics of the F-pilus emphasize the importance of distance between the donor and recipients and the requirement for both cells to maintain persistent contact. *In vitro* assays of *E. coli* plasmid transfer reveal higher rates of transfer in isolated intestinal mucus (160), and accompanying biofilm assays confirmed that conjugation is favored in positionally fixed immediately neighboring bacteria.

## CONCLUSIONS

Both antagonistic and mutualistic microbial interactions are enhanced by proximity, and there is evidence for the evolution of adhesion as a localization strategy for bacteria in the gut (Fig. 1). Understanding the microbial interactions that occur in the intestine and identifying which have resulted from bacterial co-evolution may require knowledge of their underlying mechanisms at the micron scale (161). Although many

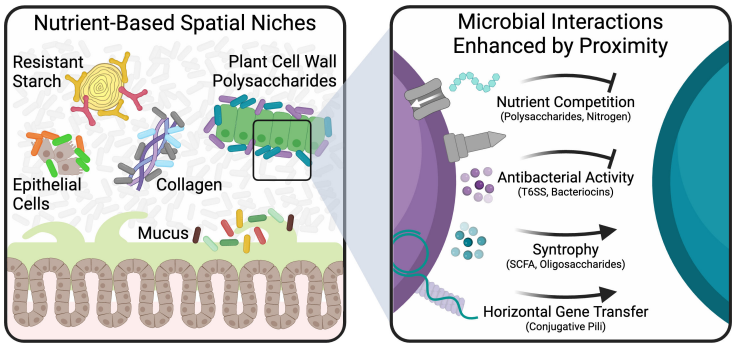


**FIG 1** Nutrient-rich particles in the gut lumen and microbe–microbe interactions that are enhanced by cell proximity. (Left) Diet-derived and host epithelium-derived particles presenting surfaces that can support gut bacterial adhesion. (Right) Competitive (blunted lines) and cooperative (arrows) interactions between gut microbes that are mediated by the listed molecular systems. T6SS, type-VI secretion system; SCFA, short chain fatty acids.

forms of interspecies cooperation and competition do not require cell-to-cell contact, the redistribution of the bacteria and small molecules generated by intestinal mixing limits the effectiveness of interactions over long distances. Future model communities designed to reveal novel types of microbial interactions could be selected by isolating particle-associated bacteria from the gut. Insights will also come from analogous systems, such as marine particle-attached bacterial communities (162). The discovery of genes and dietary substrates that control microbial localization and potentiate interactions may provide tools for manipulating the spatial proximity of both commensal and pathogenic species to optimize the health of the host.

## ACKNOWLEDGMENTS

We thank J. Bando for critical reading of the manuscript. Due to space limitations we are unable to cite many additional studies relevant to the topics discussed.

Funding for the authors was provided by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (award id DK124445) and National Institute of General Medical Sciences (NIGMS) (award ID GM150732 and GM135742).

## AUTHOR AFFILIATIONS

[1]Department of Microbiology and Environmental Toxicology, University of California, Santa Cruz, California, USA
[2]Graduate Program in Biological Sciences and Engineering, University of California, Santa Cruz, California, USA

## AUTHOR ORCIDs

Bo Huey Chiang http://orcid.org/0009-0004-0411-8310
Giovanni Vega http://orcid.org/0000-0003-3202-5408
Sarah C. Dunwoody http://orcid.org/0009-0006-9861-0588
Michael L. Patnode http://orcid.org/0000-0003-1981-5261

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## AUTHOR BIOS

**Bo Huey Chiang** received his M.S. from the University of California, San Diego. His previous research focused on the phylogenetic relationships among Nearctic shield-back katydids, as well as California Channel Island and Isla Guadalupe endemic ant species. He is currently exploring the mechanisms controlling adhesion of Bacteroides thetaiotaomicron to dietary fiber and the ecological interactions between co-adhering strains.

**Giovanni Vega** received his B.S. in Molecular, Cellular, and Developmental Biology from the University of California, Santa Cruz. His previous research focused on Wolbachia and its manipulation of the host, Drosophila simulans, to promote bacterial spread through cytoplasmic incompatibility. His current work deals with the interactions between gut bacteria, dietary fiber, and the host immune system.

**Sarah C. Dunwoody** is an undergraduate student at the University of California, Santa Cruz. Her research focuses on the role of microbial cell adhesion to dietary glycan particles in the establishment of contact-dependent bacterial interactions in the human intestine. She is also developing high-throughput screening assays for bacterial interactions.

**Michael L. Patnode** completed his undergraduate degree in Biochemistry at the University of Washington, and his PhD at the University of California, San Francisco in the lab of Dr. Steven Rosen where he focused on immunology and glycobiology. He carried out post-doctoral work with Dr. Jeffrey Gordon at Washington University in St. Louis, investigating how host diet shapes gut microbial communities, before joining the Microbiology and Environmental Toxicology Department at UC Santa Cruz in 2020.