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REVIEW

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Interbacterial warfare in the human gut: insights from Bacteroidales' perspective

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ABSTRACT

Competition and cooperation are fundamental to the stability and evolution of ecological communities. The human gut microbiota, a dense and complex microbial ecosystem, plays a critical role in the host's health and disease, with competitive interactions being particularly significant. As a dominant and extensively studied group in the human gut, Bacteroidales serves as a successful model system for understanding these intricate dynamic processes. This review summarizes recent advances in our understanding of the intricate antagonism mechanisms among gut Bacteroidales at the biochemical or molecular-genetic levels, focusing on interference and exploitation competition. We also discuss unresolved questions and suggest strategies for studying the competitive mechanisms of Bacteroidales. The review presented here offers valuable insights into the molecular basis of bacterial antagonism in the human gut and may inform strategies for manipulating the microbiome to benefit human health.

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1. Introduction

Humans, animals, plants, and microbes coexist within vast, interconnected ecosystems populated by closely interacting organisms. Within these systems, competition and cooperation play crucial roles in maintaining ecological balance.[1–9] Competition, in particular, plays a pivotal role in driving species diversity and evolution, shaping survival outcomes and social behaviors.[1–3,10–13] Microorganisms, with their simple structures, short lifecycles, high density, and genetic diversity, serve as ideal models for studying these complex interactions.[14,15]

The gut microbiota, a dense and diverse microbial community within the gastrointestinal tract, profoundly impacts human health,[15–21] earning its moniker as a "microbial organ". Among its members, competition is a crucial factor in microbial adaptation and survival.[10,11,22] Yet, how these interactions influence community structure and dynamics remain largely unknown.

As a dominant bacterial group in the human gut, Bacteroidales maintains a stable, long-term relationship with the host.[10,15,16] This group possesses diverse polysaccharide utilization systems, enabling the efficient utilization of dietary long-chain polysaccharides inaccessible to the host.[15–17] Certain Bacteroidales strains also produce short-chain fatty acids, critical for intestinal mucosal integrity and immune regulation.[16,17,20] However, under dysbiotic conditions or compromised intestinal barriers, Bacteroidales can become opportunistic pathogens.[16] Additionally, certain strains of Bacteroidales like Enterotoxigenic *Bacteroides fragilis* (ETBF) have been found to produce *Bacteroides fragilis* toxin, which has been closely associated with inflammatory bowel disease and colorectal cancer.[16,23,24]

Given their ease of cultivation and genetic manipulability, Bacteroidales serve as a valuable model for studying microbial interactions in the gut.[15,16] Residing predominantly in the densely populated colon, these bacteria rely on two primary strategies to compete:[10,11,20,25,26] interference competition, where they directly attack competitors through the production of harmful compounds, with the 'winner' acquiring the resource, and exploitative competition, where they indirectly compete by consuming resources needed by others (Figure 1). Despite recent advancements, the mechanisms underlying Bacteroidales antagonism remain poorly understood.

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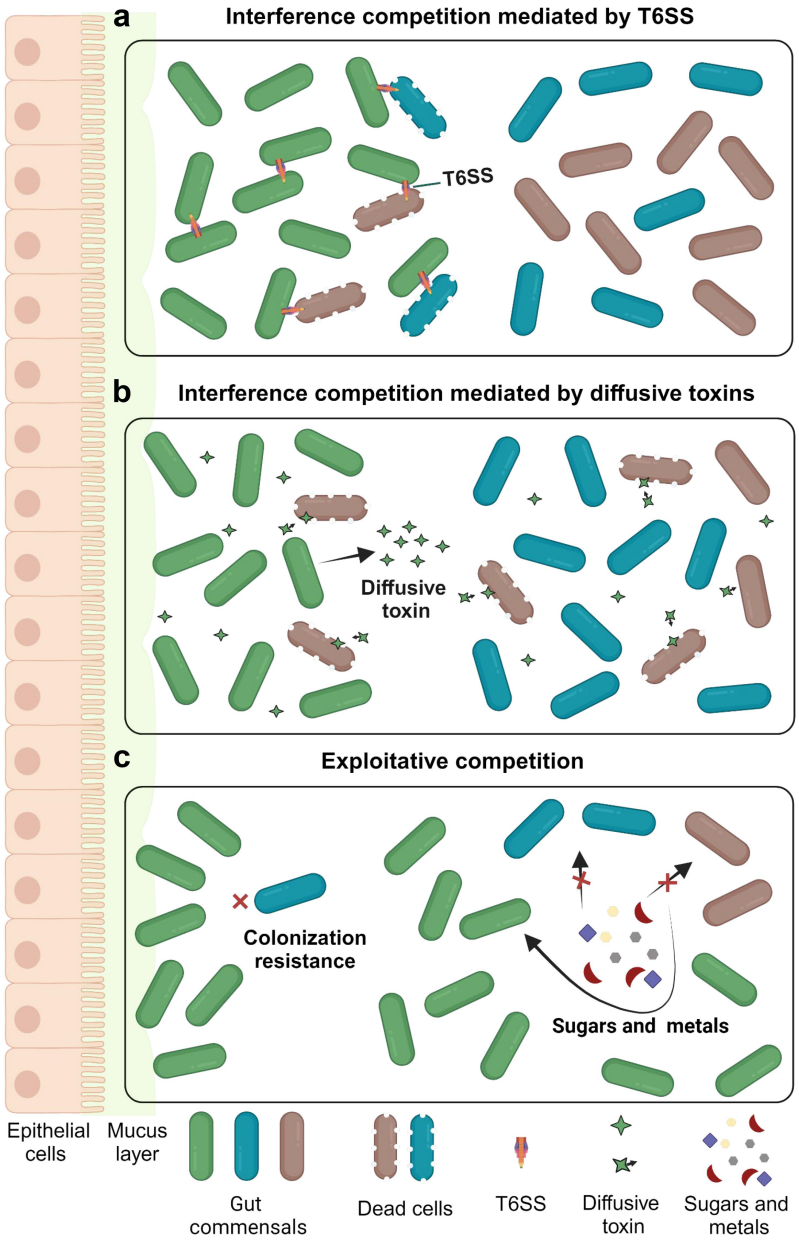

Figure 1. Competitive antagonism mechanisms within gut Bacteroidales. (a) Interference competition mediated by T6SS exhibits a relatively broad bactericidal range but operates within a short action distance. It primarily inclines to help establish the strain's own spatial niche, thereby restricting the invasion of other Bacteroidales members. (b) Interference competition mediated by diffusible toxins has a longer action range but a relatively narrower bactericidal spectrum and is inclined to target closely related species that tend to compete for similar ecological niches. (c) Bacteroidales have evolved specialized mechanisms to acquire and utilize nutrients efficiently, granting them a competitive advantage and allowing them to occupy distinct ecological niches.

This review explores the competitive interactions of gut Bacteroidales, with an emphasis on toxin-mediated interbacterial antagonism. By providing a comprehensive overview of these mechanisms, we aim to guide future research on microbial interactions and offer insights into the assembly and regulation of the gut microbiota.

2. Interference competition

Interference competition is a key strategy among bacteria, particularly in the densely populated environment of the gut. It involves direct antagonism, where bacteria inhibit or eliminate competitors to secure resources. Bacteroidales utilize sophisticated interference mechanisms to maintain

community stability and diversity.[10] These mechanisms fall into two main categories (Figure 1): contact-dependent antagonism mediated by the Type VI secretion system (T6SS)[27] and contact-independent antagonism mediated by the diffusible bacterial toxins.[28] T6SS systems mediate antagonism between spatially adjacent cells, providing a competitive advantage for resource acquisition at the same location and time. These systems do not confer advantages for resources that are distant or readily diffusible. In contrast, diffusible toxins exert antagonistic effects over broader spatiotemporal scales. As such, they confer a competitive advantage to resources that are specific competitive targets for both strains.

2.1. Contact-dependent antagonism mediated by T6SS

The T6SS is widely acknowledged as the prevalent and extensively investigated interbacterial antagonism molecular weapon, employed by many Gram-negative bacteria for contact-dependent interbacterial antagonism.[29] T6SS-positive strains deliver toxic effectors into target cells, specifically targeting essential bacterial components. These effectors can damage cellular envelopes,[30,31] disrupt enzymatic functions,[32] or modify essential molecules,[33,34] thereby effectively eliminating competitors. Effector-encoding strains neutralize the toxicity of effectors by expressing cognate immunity genes adjacent to the effectors to avoid self-killing. By outcompeting susceptible strains, T6SS-positive bacteria gain a competitive advantage, shaping microbial community composition and establishing dominance in specific ecological niches.

2.1.1. Overview of T6SS in Bacteroidales

The identification of T6SS in Bacteroidota was delayed until 2014 due to the absence of primary or profile sequence similarity between the 13 core T6SS proteins in Pseudomonodota and those in Bacteroidota. Unlike the general Pseudomonodota T6SS (T6SS^{i}) and Francisella T6SS (T6SS^{ii}), the Bacteroidota T6SS has distinct features and is classified as a separate subtype (T6SS^{iii}).[35]

The Bacteroidales T6SS is further divided into three subtypes based on their genetic architectures (GAs): GA1, GA2, and GA3 (Figure 2(a)).[36] While GA1 and GA2 T6SS loci are encoded on integrative conjugative elements (ICEs) and are commonly transferred among Bacteroidales species, the GA3 T6SS is uniquely found in *B. fragilis* .[37] Analysis of the predicted coding sequences (CDS) of the Bacteroidales T6SS loci reveals a conserved region and multiple variable regions. The conserved region encodes structural components required for the T6SS apparatus, including membrane, baseplate, spike, and tube complexes.[36] The variable regions encode diverse effector-immunity protein pairs and proteins with unknown functions (Figure 2(a)).

2.1.2. Distinct structure of Bacteroidales T6SS suggests unique effector delivery mechanisms

Bioinformatics analysis highlights that the Bacteroidales T6SS differs significantly from the Pseudomonodota T6SS in genetic architecture.[36] Specifically, it lacks several conserved core proteins (TssJ, TssM, and TssL) found in Pseudomonodota T6SS membrane complex (Figure 2(b)).[37] Recent findings have identified TssNOPQR as the unique membrane complex in Bacteroidales T6SS, suggesting a novel docking mechanism for the baseplate complex onto the membrane complex (Figure 2(b)).[38]

The inner tube complex of T6SS is composed of TssD proteins (Hcp), which facilitate the delivery of diverse low-molecular weight effectors.[39,40] While most Pseudomonodota typically encode a single Hcp in the individual T6SS locus, the Bacteroidales T6SS locus encodes up to six distinct Hcp variants.[36] Given the genetic linkage between Hcp and predicted effectors in the Bacteroidales T6SS loci, diverse Hcp may facilitate the delivery of various effectors (Figure 2(b)).

Further analysis of the variable regions within GA3 T6SS reveals distinct functional roles. Variable region 1 (V1) only encodes effector-immunity protein pairs, whereas variable region 2 (V2) also includes proteins of unknown function, potentially acting as adaptors for forming diverse spike complexes. We further conducted the analysis and quantification of various distribution patterns and abundances of the V2 region across all sequenced GA3 T6SS, revealing the potential presence of multiple representative T6SS delivery mechanisms (Figure 2(c)). Additionally, a recent

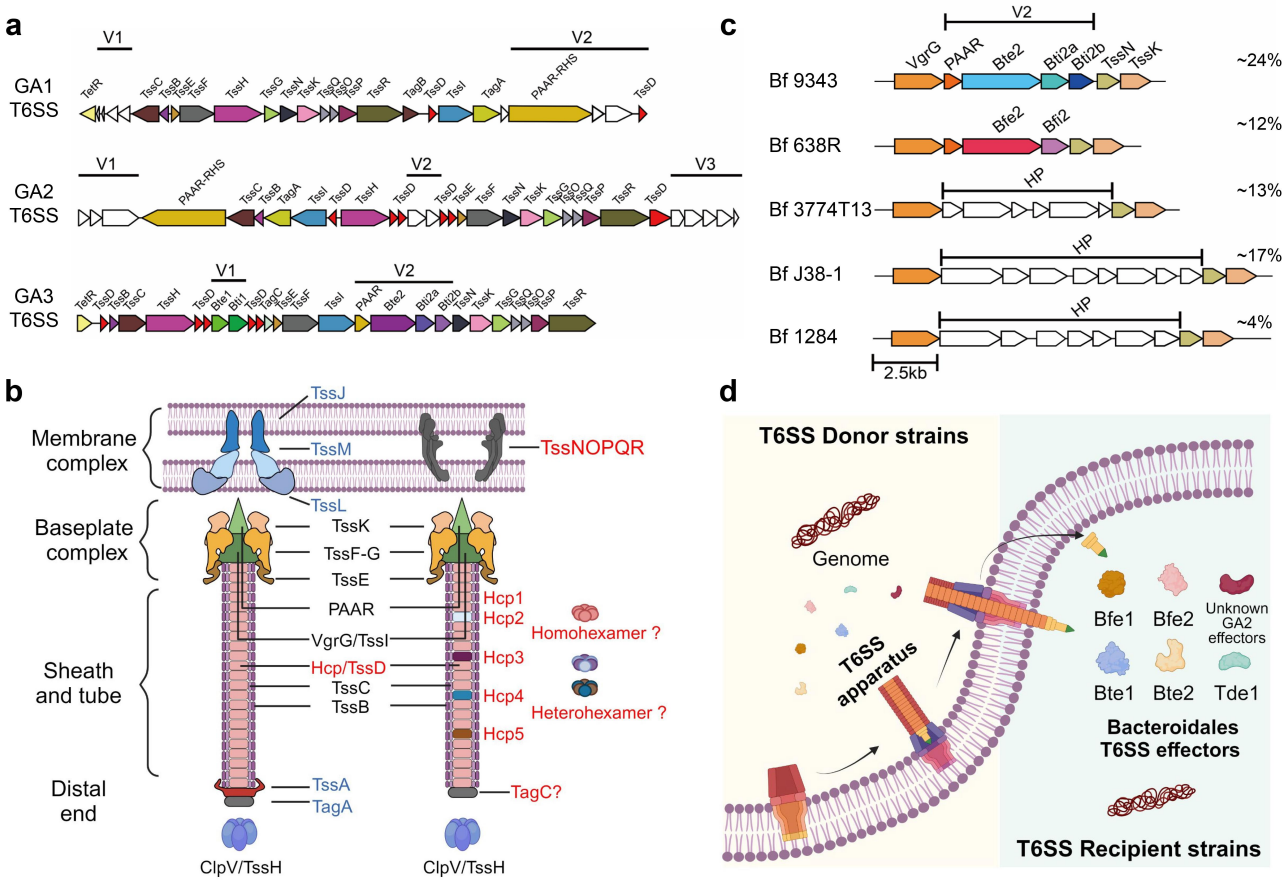

Figure 2. Interbacterial competition mediated by Bacteroidales T6SS. (a) Schematic representation of the three distinct genetic architectures (GA) of T6SS loci in gut Bacteroidales is illustrated. Predicted encoding products are shown above each gene region. (b) Structural components of Bacteroidales T6SS (right) are contrasted with Pseudomonodota T6SS (left). Both T6SS machineries share four key complexes – membrane complex, baseplate complex, sheath-tube, and distal end. Components unique to Bacteroidales T6SS are highlighted in red, while Pseudomonodota-specific elements are in blue. Notably, the Bacteroidales T6SS (GA3 T6SS) features a distinct membrane complex and a different Hcp inner tube. (c) GA3 T6SS V2 region of the five *B. fragilis* strains, representing five different V2 regions. The proportion of each V2 region within all publicly available *B. fragilis* genomes is indicated following the T6SS loci. Predicted encoding products are depicted above each gene region, with a scale bar representing 2.5 kb of T6SS loci. Hypothetical proteins (HP) of unknown function are identified in white. (d) Diverse effectors secreted by *Bacteroides* T6SS.

study revealed the structure of the *B. fragilis* cargo delivery complex (VgrG-PAAR-Hcp, without effectors), which represents a subset of the GA3 T6SS.[41] To fully elucidate the unique assembly and delivery mechanisms of the Bacteroidales T6SS, further biochemical experiments and high-resolution structural studies are required.

2.1.3. Mobile GA1 and GA2 T6SS loci in interbacterial competition

Genomic and metagenomic analysis has revealed the widespread presence of GA1 and GA2 T6SS (mobile T6SS) in Bacteroidales isolated from the human gut microbiota. Frequent horizontal gene transfer of these mobile T6SS loci suggests that they confer fitness advantages to the encoding strains.[42] Interestingly, the integration of GA1 T6SS into the genome of GA3 T6SS-encoding *B. fragilis* strains deactivates the antagonistic activity of the GA3 T6SS.[43] This finding implies that acquiring GA1 T6SS may alter the antimicrobial spectrum of GA3 T6SS encoding strains, reversing their roles as attackers and defenders and influencing gut microbiota composition.

Recent studies have identified multiple toxic effectors in the variable regions of certain GA2 T6SS loci, including predicted DNase, amidase, endotoxin, and bacteriocin domains.[44] While periplasmic toxicity of some effectors has been confirmed, no significant antagonism (1–3 log killing

was considered significant antagonism) of GA1 and GA2 T6SS was observed *in vitro* .[44] The physiological functions of these loci remain to be clarified (Figure 2(d)).

2.1.4. Ecological impact of GA3 T6SS-mediated interbacterial antagonism

GA3 T6SS demonstrates strong antagonistic activity *in vitro*. Effector proteins from GA3 T6SS, such as Bte1 and Bte2 in *B. fragilis* NCTC9343,[45] and Bfe1 and Bfe2 in *B. fragilis* 638 R,[46] exhibit specificity for targeting Bacteroidales but show limited activity against Pseudomonodota (Figure 2(d)). Multiple studies utilizing gnotobiotic mice have demonstrated the crucial role of GA3 T6SS in mediating competition between different *B. fragilis* strains in the mouse gut.[45,46] A compelling study on antibiotic cocktail-treated mice demonstrated that non-enterotoxigenic *B. fragilis* (NTBF) NCTC9343 effectively restricts enterotoxigenic *B. fragilis* (ETBF) ATCC43858 colonization through GA3 T6SS, potentially mitigating ETBF-associated disease in a murine host.[47] Unfortunately, the lack of homology with previously characterized proteins has posed significant challenges in characterizing the functional mechanisms of effectors from GA3 T6SS.

While the specific mechanisms of GA3 effector-mediated interbacterial antagonism remain unclear, studies have indicated that GA3 T6SS is associated with composition changes in human gut microbiota. An analysis of the human metagenomic datasets revealed a significant association between GA3 T6SS presence and the reduced abundances of *Bacteroides* and specific Firmicutes genera in the test samples. Frequent replacement of GA3 T6SS effectors was observed during early life, suggesting that at least one GA3 T6SS genotype enhances *B. fragilis* colonization in the infant gut. In stabilized adult gut microbiota, a reduced diversity of GA3 T6SS was observed, with a single GA3 T6SS genotype being dominated.[48] These findings indicate intense early-life competition among *B. fragilis* strains potentially shape long-term gut microbiota composition.

Given the diverse effectors used by GA3 T6SS to overcome Bacteroidales species, multiple mechanisms have been evolved to counteract T6SS effectors during intense interbacterial competition. Prevalent members of Bacteroidales in the human gut encode an acquired interbacterial defense (AID) gene cluster with multiple orphan immunity proteins for defending against T6SS-mediated interbacterial competition.[49] Acquisition of the AID system confers the ability of Bacteroidales to survive T6SS-mediated killing and maintain community diversity.

While GA3 T6SS exhibits robust antagonism *in vitro*, its activity *in vivo* may vary due to niche partitioning within the gut microbiota. Strong antagonism is expected among strains occupying overlapping spatial and nutritional niches but may be less apparent in species with limited direct contact. The fitness costs associated with maintaining functional T6SS have led to frequent inactivation or loss of these systems in closed gut communities.[50] Notably, despite the observed patterns of GA3 T6SS loss and the fitness costs of production in the mice gut, the majority of sequenced human gut isolated *B. fragilis* strains retained an intact T6SS. This suggests that lineages losing GA3 T6SS are not evolutionary successful over longer time scales. This is likely due to the strong selective pressures exerted by vertical transmission and early-life interbacterial competition, under which strains with an intact GA3 T6SS tend to outcompete others.[48,51]

2.2. Contact-independent antagonism mediated by diffusible toxins

In addition to the contact-dependent antagonism mediated by T6SS, gut Bacteroidales can also produce and secrete diffusible peptide or protein toxins capable of antagonizing a limited spectrum of targets over long distances, constituting a contact-independent antagonistic system. Currently, six types of contact-independent bactericidal toxins have been identified in gut Bacteroidales: Bacteroidales secreted antimicrobial protein (BSAP),[28,52–54] the Bacteroides fragilis ubiquitin (BfUbb),[55–57] the bacteroidetocins (Bd),[58,59] the Bacteroidales conjugally transferred plasmid-encoded toxin (BcpT),[60] the fragipain-activated bacteriocin 1 (Fab1),[61] and the cholesterol-dependent cytolysins like toxins (CDCL).[62] These molecules demonstrate unique bactericidal mechanisms and diverse distributions, reflecting

the intricate interactions within the gut microbiota (Figure 3; Table 1).

2.2.1. Bacteroidales secreted antimicrobial protein (BSAP)

BSAP represents the first identified class of secreted antimicrobial toxins in gut Bacteroidales, characterized by membrane attack complex/perforin (MACPF) domains with eukaryotic-like features.[28,52–54] These toxins likely exert their bactericidal effects through pore formation, similar to MACPF proteins in eukaryotes. Currently, four types of BSAP toxins (BSAP1-BSAP4) have been shown to possess clear antibactericidal toxicity.[28,52–54] They are produced by specific Bacteroidales species, with some species producing multiple BSAP toxins (for example, both BSAP1 and BSAP4 are produced by *B. fragilis*), capable of antagonizing strains of the same or closely related species, respectively.

BSAP1-BSAP4 target either the β-barrel outer membrane proteins (BSAP1 and BSAP4)[28,54] or O-antigen glycan of lipopolysaccharides (LPS) (BSAP2 and BSAP3)[52,53] on susceptible strains, respectively (Figure 3(a,b)). Notably, the gene location of the target gene for BSAP in BSAP-sensitive strains corresponds to the BSAP gene location in BSAP-production strains. Moreover, BSAP-producing strains overcome toxicity by synthesizing an orthologous nontargeted surface molecule near the BSAP's gene, indicating that they are acquired jointly. The target of BSAP1 (OMP) and the target of BSAP2 (LPS) were shown to be essential for the adaptive colonization of corresponding strains in mice, offering a physiological explanation for BSAP-sensitive strains to retain these genes and BSAP-production strains to encode orthologous surface molecules.[52]

Moreover, unlike the Bacteroidales species capable of producing either BSAP-1, −2, or −3, where strains typically either contain the BSAP gene and produce the corresponding BSAP toxin or lack the gene and are sensitive to the toxin, there are several *B. fragilis* strains that do not produce BSAP-4 yet display resistance to it due to harboring the resistant ortholog receptor.[54] Additionally, the sensitivity of certain strains to BSAP4 depends on the expression status of its target gene. Moreover, bacterial cocolonization investigations in mice or human gut metagenomes suggest that BSAP1 or BSAP2 can confer a certain fitness advantage to its producing strains compared to sensitive strains.[52] However, the specific mechanism of bactericidal action remains unclear after binding between BSAPs and their respective targets.

Despite conserved MACPF motifs, BSAP toxins have a low amino acid identity, indicating diversity in target specificity and mechanisms. Notably, over 320 MACPF domain-containing proteins have been identified in Bacteroidota. With a few exceptions, they are classified into clusters based on their species, producing 68 distinct clusters.[52] Currently, including BSAP1-BSAP4, bactericidal activity has been identified in these MACPF-containing proteins from seven clusters (clusters 1, 2, 10, 14, 15, 16, and 19).[28,52–54] A comprehensive exploration of their functions and targets remains a critical avenue for future research.

2.2.2. Bacteroides fragilis ubiquitin-BfUbb

BfUbb is the second diffusible antimicrobial molecule identified in intestinal *B. fragilis* and also exhibits eukaryotic-like features.[55] After cleavage of its signal peptide, the mature BfUbb protein consists of 76 amino acids, sharing approximately 84% similarity with human ubiquitin (HmUbb). A key distinction between BfUbb and HmUbb is the substitution of glycine at the C-terminus of HmUbb, crucial for covalent substrate binding, with cysteine in BfUbb. This cysteine enables the formation of a unique intramolecular disulfide bond, absent in HmUbb, which is essential for BfUbb's interaction with its substrate, peptidyl-prolyl isomerase (PPIase), and its antimicrobial activity.[56]

BfUbb was first discovered in 2011, when it was shown to covalently bind to the human E1-activated enzyme under non-reducing conditions, effectively inhibiting ubiquitination *in vitro* .[63] This, along with observed antigenic cross-reactivity between BfUbb and HmUbb, suggested a potential role for BfUbb in *B. fragilis*-host interactions,[63,64] although further validation is needed. In 2017, Comstock and her colleagues identified the bactericidal activity of BfUbb through transposon mutagenesis screening.[55] Subsequent studies elucidated BfUbb's mechanism of action against *B. fragilis* and how other *Bacteroides* species resist it.[56,57]

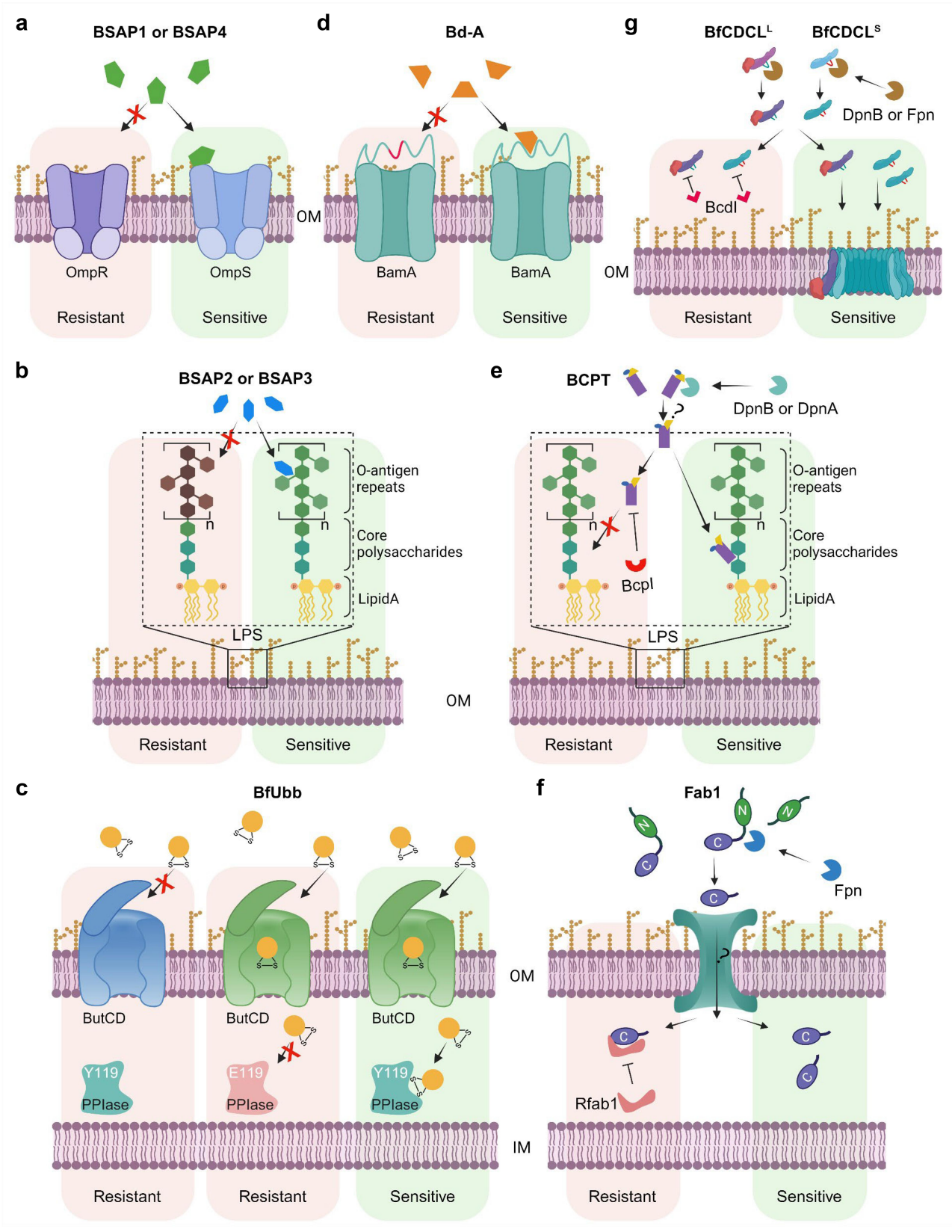

Figure 3. Schematic diagram illustrating the postulated functional mechanism of six diffusible toxins produced by Bacteroidales. (a,b) BSAP1-BSAP4 target the outer membrane protein (OMP) or lipopolysaccharides (LPS) of sensitive strains. Resistance arises from the expression of orthologous, non-targeted receptors. (c) BfUbb enters the periplasmic space of *B. fragilis* via ButCD and targets the PPIase that contains a tyrosine (Y) at position 119. (d) Bd-A toxin targets the BamA protein, which contains a conserved aspartic acid residue in extracellular loop 3, in sensitive strains. (e) BCPT targets the lipid A-core glycan of LPS in sensitive strains. Proteolytic

BfUbb gains access to the periplasmic space of *B. fragilis* via a specialized TonB-dependent transporter SusCD-like complex (designated as ButCD). Once inside, BfUbb targets an essential PPIase protein, disrupting its enzymatic and chaperone functions to exert potent bactericidal effects. Despite the universal presence of ButCD in *B. fragilis* strains (ButCD^{Bf}), some strains evade BfUbb's effects through a single-point mutation in PPIase, substituting tyrosine at position 119 with aspartate, which prevents BfUbb binding. Additionally, other *Bacteroides* species avoid BfUbb-mediated interspecies antagonism by encoding ButCD variants with limited sequence similarity to ButCD^{Bf}, thereby hindering BfUbb transport into their cells[56,57] (Figure 3(c)).

Co-culture assays, murine colonization studies, and human gut metagenome analyses demonstrate that BfUbb provides a significant competitive advantage in its producing strains over sensitive strains.[56] Notably, BfUbb exhibits exceptional efficacy in eliminating ETBF strains harboring BfUbb-sensitive PPIase in mice.[57] These findings highlight the potential of BfUbb as a therapeutic agent for preventing and treating ETBF-associated diseases.

2.2.3. Bacteroidetocins (Bd)

Bacteroidetocins (Bd) are a family of anti-Bacteroidales peptide toxins produced by various members of the Bacteroidota phylum.[58] Among these, Bd-A and Bd-B were primarily found in Bacteroidales and have been the most extensively studied, exhibiting properties similar to class IIa bacteriocins of Gram-positive bacteria.[58,65,66] These peptides are initially synthesized with a 15-amino-acid leader sequence, which is cleaved following a double glycine motif to yield mature peptides of 42 amino acids. Each mature peptide includes four cysteine residues involved in intramolecular disulfide bond formation. Additionally, the chemically synthesized mature Bd-A toxin exhibits effective bactericidal activity, indicating that it can correctly self-fold *in vitro* as well. Bd toxins specifically target members of the Bacteroidota phylum, including *Bacteroides*, *Parabacteroides*, and *Prevotella* species.[58,59]

Long-term evolutionary studies revealed that resistance to Bd-A in *Bacteroidales* strains is linked to mutations in the *bamA* gene, which encodes an essential β-barrel outer membrane protein (OMP) responsible for the assembly and insertion of β-barrel proteins into the outer membrane[59] (Figure 3(d)). A conserved aspartate residue at the N-terminus of extracellular loop 3 (el3) in BamA has been identified as critical for Bd-A sensitivity. While Bd-A-resistant BamA mutants exhibit no apparent growth defects *in vitro*, studies in mice demonstrated significant fitness attenuation, suggesting that these mutants are not competitive in the mammalian gut.[59] This highlights the potential of Bd toxins as therapeutic anti-Bacteroidales agents with a reduced likelihood of resistance evolution.

To date, 19 bacteroidetocin-like peptides have been identified from Bacteroidota through tblastn searches.[58] Among these, four Bd toxins – Bd-A, Bd-B, Bd-C, and Bd-D – have been validated for bactericidal activity. Bd-A, Bd-B, and Bd-D share a common feature of four cysteines and exhibit relatively broad-spectrum activity against Bacteroidales. In contrast, Bd-C, which contains only two cysteines, is less broadly toxic but targets specific strains resistant to the other three variants.[58] Differences in amino acid composition likely underlie the distinct activities of these toxins, suggesting that the remaining 15 Bd variants may possess unique bactericidal properties yet to be characterized.

Most *Bd* genes are located within a conserved gene locus that includes at least three additional genes: a protein with five transmembrane regions, a thiol oxidoreductase, and an ABC-like

activation by DpnA or DpnB is required for toxicity. Resistance arises through the immune protein BcpI. (f) Upon cleavage by Fpn, the proteolytically activated C-terminal fragment of Fab1 can be secreted into the supernatant and exert its toxicity on sensitive *B. fragilis* strains, whereas resistant strains possess resistance to Fab1 through encoding the immune protein Rfab1. (g) After being proteolytically activated by DpnB or Fpn, activated BfCDCL^{L}acts as a membrane-anchored platform to recruit activated BfCDCL^{S} and form the β-barrel pore, exerting bactericidal toxicity. Resistant strains possess resistance to BfCDCL by encoding the immune protein BcdI. The inner membrane (IM) and outer membrane (OM) of recipient bacteria are illustrated.

Table 1. The key information on the representative diffusion toxins of Bacteroidales.

	BSAP-1	BSAP-2	BSAP-3	BSAP-4	BfUbb	Bds	Fab1	BcpT	BfCDCL
Production strain	*B. fragilis*	*B. uniformis*	*p. vulgatus* and *p. dorei*	*B. fragilis*	*B. fragilis*	Diverse members of the Bacteroidota	*B. fragilis*	*P. vulgatus* and *P. dorei*	Six or more Bacteroides species including *B. fragilis*
Target specificity	*B. fragilis*	*B. uniformis*	*p. vulgatus* and *p. dorei*	*B. fragilis*	*B. fragilis*	Diverse members of the Bacteroidota	*B. fragilis*	*P. vulgatus*/*P. dorei* and some strains in Bacteroides, Phocaeicola and Parabacteroides	Some strains of *P. dorei*, *P. vulgatus*, and *B. uniformis*
Structure	UN	UN	UN	UN	Yes	UN	UN	UN	UN
Eukaryotic/ prokaryotic like features	MACPF	MACPF	MACPF	MACPF	Human ubiquitin	Class IIa bacteriocins of Gram-positive bacteria	No	No	Cholesterol-dependent cytolysins (CDC)
Proteolytic activation	UN	UN	UN	UN	No	No	Yes (Fpn)	Yes (DpnA and DpnB)	Yes (DpnB or Fpn)
Transporter	UN	UN	UN	UN	ButCD	UN	UN	UN	No
Receptor/Target	OMP	O-antigen glycan of LPS	O-antigen glycan of LPS	OMP	PPIase	BamA	UN	Lipid A-core glycan of the LPS	UN
Immunity protein	No	No	No	No	No	No	RFab1	BcpI	BcdI

UN, unknown; MACPF, membrane attack complex/perforin; OMP, outer membrane protein; LPS, Lipopolysaccharide; Fpn, fragipain; DpnA, doripain A; DpnB, doripain B; ButCD, BUbb transporter SusCD; PPIase, peptidyl-prolyl isomerase; RFab1, resistance to fragipain-activated bacteriocin 1; BcpI, BcpT immunity protein; BcdI, Bacteroidales CDCL immunity protein.

bacteriocin transporter. Deletion of any of these genes results in reduced Bd-B activity of its producing strains, and co-expression of all four genes in *Escherichia coli* is sufficient to confer upon it the ability to inhibit the growth of *Bacteroides thetaiotaomicron* VPI-5482, confirming their collective role in active Bd-B toxin production.[58]

Interestingly, strains producing Bd-A, Bd-B, or Bd-D were found to possess BamA variants sensitive to their own toxins and remain susceptible to self-intoxication *in vitro*.[59] Furthermore, Bd-B-producing strains and Bd-B-sensitive strains have been observed to coexist stably in the human gut while retaining sensitivity to Bd-B *in vitro*. These findings raise compelling questions about the mechanisms enabling Bd-producing strains to tolerate self-intoxication, their fitness for gut colonization, and the broader physiological roles of Bd toxins in the human intestine.

2.2.4. Bacteroidales conjugally transferred plasmid-encoded toxin (BcpT)

BcpT is another diffusible toxin identified in Bacteroidales, distinct from other known toxins in several aspects.[60] Encoded on a mobile plasmid, BcpT is named for its mode of transmission as the Bacteroidales conjugally transferred plasmid-encoded toxin. Genomic and metagenomic analyses indicate that this plasmid is primarily restricted to closely related species, *Phocaeicola vulgatus* and *Phocaeicola dorei*. However, the antibacterial specificity of BcpT is not only limited to *P. vulgatus* and *P. dorei*, as purified BcpT exhibits antibacterial activity against a broader range of species, including *Bacteroides*, *Phocaeicola*, and *Parabacteroides* .[60]

Unlike most proteolytically activated bacterial toxins,[24,58,61,65,67–70] BcpT requires cleavage at two distinct sites for activation. Cysteine proteases of the C11 family, doripain A (DpnA) or doripain B (DpnB), cleave BcpT at residues R65 and R199, resulting in a three-fragment active state.[60] Among these, DpnB is considered to play a dominant role in activating BcpT (Figure 3(e)). Although the exact mechanism following BcpT cleavage remains incompletely understood, the C-terminal fragment (residues 200–499) is thought to mediate receptor binding and antibacterial activity, while the N-terminal fragment (residues 20–199) may initially inhibit the function of C-terminal domain.[60]

Receptor blot studies identified the lipid A-core glycan of lipopolysaccharide (LPS) as the BcpT receptor, which could be bound by the proteolytically activated toxin[60] (Figure 3(e)). A small lipoprotein, BcpI, encoded by a 174-bp gene downstream of *bcpT*, provides an eightfold increase in resistance to BcpT, serving as its immunity protein. However, the precise antibacterial mechanism of BcpT and the protective role of BcpI remain areas for further research.

2.2.5. Fragipain-activated bacteriocin (Fab1)

Fab1 is a bacteriocin discovered in *B. fragilis* with activity exclusively targeting *B. fragilis* strains.[61] It was identified through transposon mutagenesis screening together with fragipain (Fpn), a C11 family cysteine protease responsible for its activation. Fab1 is produced as an approximately 50 kDa protoxin, which is cleaved by Fpn between residues R200 and A201 to generate a ~ 28 kDa C-terminal active fragment with bactericidal properties (Figure 3(f)). Additionally, without Fpn, Fab1 cannot be detected in the culture supernatant, indicating that Fpn is essential for both the secretion and activation of Fab1.[61]

The gene encoding Fab1 is accompanied by *rfab1*, an immunity gene located immediately downstream. RFab1 provides resistance to Fab1 in producing strains[61] (Figure 3(f)). While the *fpn* gene is nearly ubiquitous across *B. fragilis* genomes, *fab1* and *rfab1* are found in only ~ 20% of strains, reflecting the multifunctional roles of this protease family beyond toxin activation.[67] Some *B. fragilis* strains harbor *rfab1* but lack *fab1*, rendering them also insensitive to Fab1.[61] Despite these insights, the specific target and bactericidal mechanism of Fab1 remain unknown.

2.2.6. Cholesterol-dependent cytolysin-like toxins (CDCL)

Cholesterol-dependent cytolysin-like toxins (CDCL) represent a newly discovered class of diffusible toxins, named for their resemblance to

cholesterol-dependent cytolysins (CDC).[62,71] Initially identified in *Elizabethkingia anophelis* from the midgut of malarial mosquitoes,[72] CDCL have since been found widely distributed in Bacteroidota, including gut-inhabiting species.[62] In *B. fragilis*, CDCL (BfCDCL) are encoded by two adjacent CDC-like genes, producing a small component ($BfCDCL^S$) and a larger component ($BfCDCL^L$). Together, these components exhibit bactericidal activity against related *Bacteroides* species, though their receptor remains unidentified.[62]

BfCDCL activation also requires cleavage by C11-type proteases, including Fpn or DpnB, at residues R70 ($BfCDCL^L$) and R62 ($BfCDCL^S$), respectively (Figure 3(g)). The activated $BfCDCL^L$ likely serves as a membrane-anchored platform via its domain 4, recruiting activated $BfCDCL^S$ to form β-barrel pores that mediate bactericidal activity. A predicted outer surface localized lipoprotein, encoded upstream of the BfCDCL genes, functions as an immunity protein for BfCDCL (BcdI) (Figure 3(g)).[62]

Beyond the CDCL genomic pattern identified in *B. fragilis*, six additional CDCL toxin patterns have been identified in gut Bacteroidales genomes.[62] Among these, one pattern includes three adjacent CDCL genes confined to *P. vulgatus* and *P. dorei*. These patterns show varying sequence similarities, warranting further research to elucidate their bactericidal specificities, mechanisms, and physiological relevance.

3. Exploitative competition

Beyond interference competition, exploitative competition also plays an irreplaceable role in maintaining Bacteroidales' stable colonization of the mammalian gut (Figure 1). This form of competition involves limiting the growth of rivals by efficiently utilizing scarce resources. Unlike interference competition, where direct interactions between cells occur, exploitative competition operates indirectly, becoming especially significant under nutrient-limited conditions, such as in biofilm-like dense microbial communities.[73] Resources critical to microbial survival include nutrients (e.g., carbon, nitrogen, phosphorus, sulfur, hydrogen, calcium, iron, and trace metals) and spatial niches.[74–77] As microbes grow and accumulate biomass, they expand their spatial distribution and compete with other populations to colonize regions with higher nutrient availability.

3.1. Competition for nutrient resources

Competition for nutrients can occur through two main mechanisms: increased nutrient absorption or secreting factors that enhance nutrient acquisition. It is observed in *Saccharomyces cerevisiae* and *E. coli*, switching from fermentation to aerobic respiration under aerobic conditions, increasing their growth rate and absorbing nutrients more rapidly than their competitors.[78,79] The secretion of nutrient acquisition factors enhances competitive ability by producing digestive enzymes that hydrolyze complex nutrient molecules or synthesizing siderophores-like molecules to chelate and sequester essential metals. As commensal and mutualistic organisms, Bacteroidales have distinct advantages in resource acquisition, such as carbon, metals, and corrinoids.

3.1.1. Carbon

Bacteroidales exhibit a strong capacity for polysaccharide metabolism, supported by specialized genetic regions known as polysaccharide utilization loci (PULs), which enhance their ability to recognize and degrade complex carbohydrates.[80] Beyond benefiting themselves, Bacteroidales also establish cross-feeding networks that facilitate nutrient exchange within microbial communities.[81] However, when primary degraders restrict the release of free oligosaccharides or monosaccharides into the extracellular environment, they adopt a "selfish" mode of glycan catabolism.[82,83] This strategy promotes the dominance of these "selfish degraders" over other species (Figure 4(a)).

For example, *B. thetaiotaomicron* metabolizes yeast mannan by using surface endo-mannanases to produce large oligosaccharides, which are immediately captured and transported into the cell for further breakdown by periplasmic mannanases (Figure 4(a)).[82] This process ensures efficient utilization of the resource. In the co-culture experiments, the carbon is the only limiting nutrient, while other nutrients, such as nitrogen and trace metals, are provided in excess. Yeast mannan, as

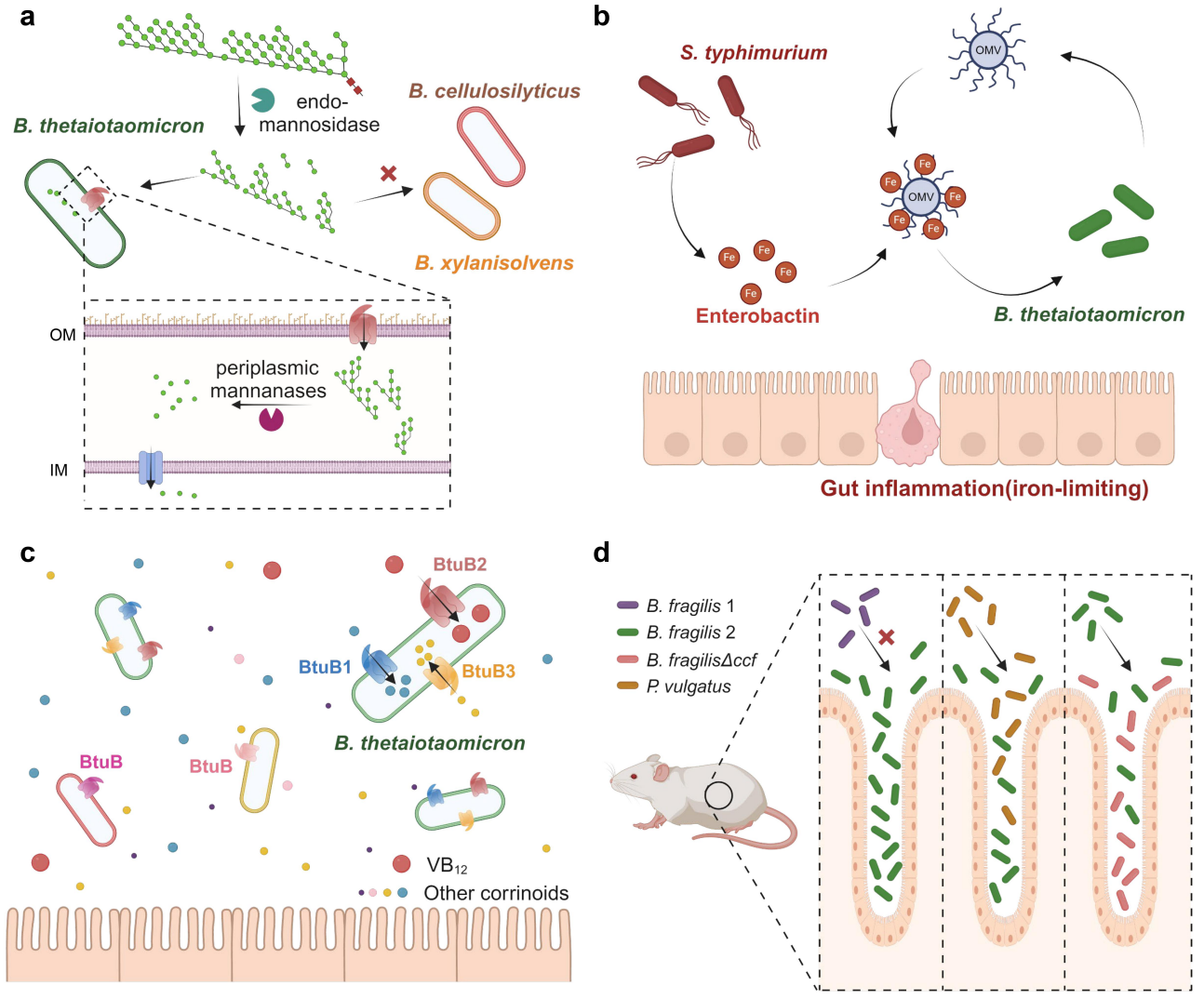

Figure 4. Examples of exploitative competition among *Bacteroidales* species. (a) *B. thetaiotaomicron* employs a specialized mannan degradation system that breaks down yeast mannan into large oligosaccharides on its cell surface. These oligosaccharides, inaccessible to *B. cellulosilyticus* and *B. xylanisolvens*, are subsequently depolymerized into mannose by periplasmic enzymes for exclusive utilization by *B. thetaiotaomicron*. (b) During inflammation, *Salmonella* scavenges iron using siderophores. *B. thetaiotaomicron* exploits *Salmonella* siderophores through its xenosiderophore utilization system, enhancing its fitness in iron-limited conditions during *Salmonella* infection. (c) Bacteroidales encode diverse transporters to acquire multiligand corrinoids, increasing their competitive advantage within the gut environment. (d) Germ-free mice colonized with wild-type (WT) *B. fragilis* exhibit colonization resistance to subsequent exposure to the same species. However, this resistance does not prevent colonization by other Bacteroidales species. In contrast, germ-free mice colonized with *B. fragilis* ccf mutants permit colonization by WT *B. fragilis*.

the sole carbon source, *B. thetaiotaomicron* outcompeted *B. cellulosilyticus* and *B. xylanisolvens* .[82] However, *B. thetaiotaomicron* may not have growth advantage under other carbon sources such as mannose, or other limiting nutrients. Under varying carbon source concentrations or different growth rates, the dominant strain may either further enhance or lose its growth advantage. Similarly, *B. ovatus* efficiently degrades various xylan polysaccharides, such as wheat arabinoxylan and glucuronoarabinoxylan. While the degradation products of wheat arabinoxylan, rather than glucuronoarabinoxylan, can support the growth of *Bifidobacterium adolescentis* (which cannot utilize the intact polysaccharide). This provides *B. ovatus* a competitive edge when using glucuronoarabinoxylan (e.g., corn bran xylan) as the sole carbon source.[83] However, in competition with *B. ovatus* and *Roseburia intestinalis* (both of which exhibited comparable growth on xylan as a carbon source), *R. intestinalis* eventually emerged as the dominant species, seemingly outcompeting *B. ovatus* after

propagation of the co-culture for two additional passages.[84] Nonetheless, these observations were made under controlled laboratory conditions with single-nutrient limitations. To more accurately reflect natural environments and achieve more realistic competition outcomes, it is imperative to introduce additional layers of complexity.

Bacteroidales enhance their adaptability by inducing specific outer membrane polysaccharide-binding proteins and glycoside hydrolases in response to dietary conditions.[85] In the absence of dietary polysaccharides, they switch to utilizing host mucus polysaccharides, thereby maintaining their stability in the intestinal environment.[86] An often-overlooked resource is genetic material, which can also serve as a nutrient. For example, *B. thetaiotaomicron* metabolizes ribose via its ribokinase-encoded ribose-utilization system, enhancing its colonization fitness in a diet-specific manner.[87] These effective glycan acquisition strategies provide Bacteroidales with a diet-specific competitive advantage *in vivo* .[87]

3.1.2. Iron

Iron is an essential element for most organisms, serving as a cofactor for metalloproteins involved in vital cellular processes such as DNA replication. A common strategy for acquiring iron is the secretion of siderophores, molecules that scavenge iron from the environment. Numerous studies have highlighted cross-species competition mediated by siderophores, with variations in siderophore-binding affinities and uptake capabilities influencing competitive dynamics.[88] For example, under iron-limited conditions, strains producing low-affinity siderophores may grow normally, but their growth is inhibited when high-affinity siderophores from other species are introduced.[89] Siderophores, as public goods, can also be utilized by non-producing strains with appropriate siderophore receptors, effectively transferring production costs to the siderophore producers.[90,91]

To date, there is no evidence that Bacteroides produce siderophores. However, Zhu *et al.* identified a xenosiderophore utilization system (xusABC) in *B. thetaiotaomicron* by analyzing its transcriptional response in the cecum of mice during *Salmonella* infection.[92] This system enables *B. thetaiotaomicron* to use siderophores produced by *Enterobacteriaceae* family members, enhancing its colonization resilience under nutritional immunity induced by *Salmonella* infection or noninfectious colitis (Figure 4(b)).[92,93] However, the xenosiderophore utilization system is not widespread in Bacteroidales, potentially giving *B. thetaiotaomicron* a unique competitive advantage during enteric *Salmonella* infection.

Heme, the host's largest iron reservoir, is typically bound to macromolecules like hemoglobin, and free heme is scarce.[94] *Bacteroides* and *Porphyromonas gingivalis*, as heme-deficient bacteria, cannot synthesize protoporphyrin IX de novo and must acquire heme from the environment. Previous studies have identified several hemophores in *Porphyromonas gingivalis*, such as HusA and HmuY, critical for competitive advantage *in vivo* .[95,96] While HmuY homologs have been identified in *Bacteroides*, deletion of these genes does not affect their *in vitro* growth.[97] The mechanisms underlying heme transport and competition in Bacteroidales remain largely unexplored.

3.1.3. Other metals

The acquisition of transition metals such as zinc and manganese is critical for microbial survival, alongside iron. Zinc is predicted to interact with 4–6% of bacterial proteins, playing key roles in gene regulation, cellular metabolism, and as a cofactor for various virulence factors.[98] Manganese, another essential cofactor, supports numerous bacterial enzymes involved in lipid, protein, and carbohydrate metabolism.[99] Under metal-limited conditions, microorganisms adapt by upregulating high-affinity transporters to import these nutrients. For instance, *E. coli* primarily uses the low-affinity ZupT transporter for zinc uptake under moderate availability but relies on the high-affinity ZnuACB system under extreme zinc scarcity. The deletion of ZnuA in *Campylobacter jejuni* significantly impairs intestinal colonization.[100] While homologs of ZupT and ZnuACB exist in Bacteroidales, their specific mechanisms and impact on competitive colonization under metal-limiting conditions remain unclear.

Additionally, the T6SS in pathogens like *Yersinia pseudotuberculosis* and *Burkholderia thailandensis*

has been shown to mediate exploitative competition by secreting protein-based carriers that facilitate manganese and zinc acquisition.[101,102] However, whether T6SS in Bacteroidales performs a similar role remains unexplored.

3.1.4. Corrinoids

Corrinoids, especially vitamin B12, are essential cofactors for methionine synthesis, propionate production, and other metabolic pathways. These compounds significantly influence the structure and function of the human gut microbiota.[103,104] Due to the incomplete or absent corrinoid synthesis pathways in Bacteroidales, these bacteria depend entirely on extracellular transporters for corrinoid acquisition.[105] Redundant corrinoid transporters are a common feature in gut microbiota. In *B. thetaiotaomicron*, three distinct vitamin B12 utilization systems have been identified (Figure 4(c)).[104] Among these, BtuB1 and BtuB3 have lower specificity or affinity for cobalamin compared to BtuB2, and each transporter exhibits distinct preferences for various corrinoids.[104] For example, strains encoding only BtuB1 outperform those with BtuB3 when provided with adeninylcobamide or benzimidazolylcobamide, but not with cobalamin, 2-methyladeninylcobamide, 5-methoxybenzimidazolylcobamide, or 5-methylbenzimidazolylcobamide.[104]

The diversity of vitamin B12 transporters in *B. thetaiotaomicron* is vital for its fitness *in vivo*, particularly in response to diet and community composition.[104] A dietary deficiency in vitamin B12 drastically increases the reliance on BtuB2 for microbial fitness. For instance, the relative abundance of BtuB2-deficient strains in mice on a vitamin B12-depleted diet is nearly two orders of magnitude lower compared to mice on a vitamin B12-enriched diet. Pre-colonization with a Bacteroidales community exacerbates this competitive disadvantage, whereas pre-colonization with Firmicutes and Actinobacteria, which can synthesize sufficient corrinoids, completely mitigates the defect.[104,106]

Corrinoid transport mirrors iron transport, as many gut microbes, including *B. thetaiotaomicron*, lack the ability to synthesize corrinoids but possess extensive machinery to capture these compounds from other species. Consequently, microbes capable of acquiring diverse corrinoids gain a significant competitive advantage over those with transporters specific to modified molecules.

3.2. Taking and holding the ecological niche

Space occupation is pivotal in microbial competition, encompassing both the colonization of new ecological niches and the prevention of competitor encroachment over the long term.[107] *B. fragilis* expresses specific mucosal colonization factors, such as the sulfatase BF3086 and glycosyl hydrolase BF3134, which are upregulated in both mucus and tissue environments.[108] These factors enable *B. fragilis* to penetrate the mucus layer and inhabit deeper crypt regions. When germ-free mice were colonized with either wild-type *B. fragilis* or the ΔBF3134 mutant individually, bacterial populations in feces and the colonic lumen remained comparable. However, in co-colonization experiments, the proportion of ΔBF3134 steadily declined, indicating the importance of mucosal colonization factors in occupying new niches.[108]

When a bacterial population occupies a favorable ecological niche, it must limit the invasion of competitors to ensure prolonged survival. Prior studies have demonstrated that germ-free mice mono-associated with a single Bacteroidales species are resistant to colonization by the same species but not different species (Figure 4(d)).[109] This colonization resistance is attained via species-specific nutrients or unique niches. *In vivo* genetic screening identified a conserved and unique class of PULs called commensal colonization factors (ccf), essential for *B. fragilis* robust mucosal colonization, preventing reinvasion by the same species (Figure 4(d)).[109] Additionally, the mucosal colonization-defective mutant ΔBF3134 and the capsular polysaccharide-deficient strain ΔPSB/C could not maintain colonization resistance by excluding competitors of the same species.[108,110]

4. Conclusion and future perspectives

The competitive interactions within the gut microbiota are as complex as the microbial communities themselves. Strong natural selection, driven by

exploitative competition among different genotypes, is often accompanied by interference competition. Both forms of competition are widespread in bacterial communities and play a significant role in shaping the outcomes of natural selection. This review has summarized recent advances in understanding the competitive interactions among dominant Bacteroidales strains in the gut, focusing primarily on interference and exploitative competition. We have aimed to distill and highlight the intricacies of these interactions to provide a foundation for future research on bacterial interplay within the gut. However, despite these advancements, numerous questions remain unresolved.

While the activities of certain toxins and molecules involved in Bacteroidales competition have been validated *in vitro* or through simplified *in vivo* models, much remained unknown about their mechanisms of action and specific roles within the host. This underscores the need for further exploration. Moreover, it is likely that many molecules and mechanisms mediating competition among Bacteroidales are yet to be discovered. Beyond traditional biochemical and genetic screening methods, emerging techniques such as bioinformatics-based mining and artificial intelligence-driven machine learning offer significant promise for the rapid, high-throughput identification of competitive molecular players from Bacteroidales genomes, proteomes, and metabolomes.

To fully understand both known and newly identified molecules, several critical questions need addressing: How are antimicrobial molecules secreted, delivered to target bacteria, and recognized by their receptors? What are their intrinsic properties, mechanisms of action, and regulation within the host environment? For nutrient-acquisition molecules, how are they secreted, how do they recognize and bind substrates, and how are these substrates recycled during passive competition? The lack of clarity in these areas hampers a complete understanding of the mechanisms and ecological roles of competitive antagonism mediated by these molecules.

In the intricate and densely populated microbial communities, various forms of competitive dynamics emerge, ultimately leading to

Table 2. The co-occurrence of T6SS genes or diffusible toxin genes in the selected Bacteroidales strains.

			T6SS	
Strain	Accession number	Diffusable Toxin	Effectors	The type of T6SS
Bacteroides cellulosilyticus CL02T12C19	GCF_000273015.1	BSAP-3	Putative GA1 effectors	GA1 T6SS
Bacteroides fragilis 3-1-12	GCF_000157015.1	BSAP-1	Putative GA1 effectors	GA1 T6SS
Bacteroides fragilis 638 R	GCF_000210835.1	BfUbb, BSAP-1, BSAP-4	Bfe1, Bfe2	GA3 T6SS
Bacteroides fragilis GS077	GCF_032190595.1	BSAP-1, BSAP-4, Fab1	Bte1 and other putative GA3 effectors	GA3 T6SS
Bacteroides fragilis CL05T00C42	GCF_000273765.1	ND	Putative GA2 effectors	GA2 T6SS
Bacteroides fragilis NCTC9343	GCF_000025985.1	BfUbb, Fab1	Bte1, Bte2	GA3 T6SS
Bacteroides fragilis YCH46	GCF_000009925.1	BSAP-1, BSAP-4, CDCL	Bfe1, Bfe2 and other putative GA1 effectors	GA1 T6SS, GA3 T6SS
Bacteroides fragilis US326	GCF_002811035.1	CDCL	Bfe2 and other putative GA3 effectors	GA3 T6SS
Bacteroides salyersiae BIOML-A1	GCF_008565595.1	CDCL	ND	ND
Bacteroides thetaiotaomicron CL15T12C11	GCF_019896115.1	BSAP-3, Bacteroidetocin B	Putative effectors	GA1 T6SS
Bacteroides thetaiotaomicron CMU108	GCF_015831785.1	BSAP-3, CDCL	ND	ND
Bacteroides uniformis BIOML-A5	GCF_009020755.1	ND	Putative GA1 and GA2 effectors	GA1 T6SS, GA2 T6SS
Bacteroides uniformis CL03T00C23	GCF_000273785.1	BSAP-2	Putative GA1 effectors	GA1 T6SS
Bacteroides uniformis CL03T12C37	GCF_018292165.1	BSAP-2	Putative GA1 and GA2 effectors	GA1 T6SS, GA2 T6SS
Parabacteroides distasonis ATCC 8503	GCF_000012845.1	BSAP-2, CDCL	ND	ND
Phocaeicola dorei CL02T00C15	GCF_000273035.1	BcpT	Putative GA1 effectors	GA1 T6SS
Phocaeicola dorei BIOML-A5	GCF_008572125.1	CDCL	ND	ND
Phocaeicola vulgatus BIOML-A11	GCA_009018855.1	ND	Putative effectors	GA1 T6SS, GA2 T6SS
Phocaeicola vulgatus CL01T12C17	GCF_007556405.1	BSAP-3, BcpT Bacteroidetocin A	ND	ND
Phocaeicola vulgatus CL09T03C04	GCF_000273295.1	BSAP-3	ND	ND
Phocaeicola vulgatus CL14T03C19	GCF_007556395.1	BSAP-3, BcpT Bacteroidetocin A	ND	ND
Phocaeicola vulgatus ATCC 8492	GCF_002959625.1	CDCL	ND	ND

ND, non-detected.

ecologically stable outcomes. Currently, research on the diverse competitive mechanisms among gut Bacteroidales is predominantly characterized by isolated and unilateral studies. However, gut bacteria, including Bacteroidales, coexist within a complex intestinal ecosystem. By integrating insights from previous studies, it has become evident that the concurrent presence of differing T6SS or diffusible toxin genes within Bacteroidales strains is prevalent (Table 2). Therefore, further exploration is essential to elucidate how these competitive interactions collectively function under different temporal, spatial, and environmental conditions.

Additionally, current studies on Bacteroidales competition often focus on interactions between two species or employ overly simplistic models. Most predictions derived from *in vitro* experiments have yet to be validated in more physiologically relevant environments, and varying culture conditions may also yield divergent outcomes. Consequently, the conclusions drawn from *in vitro* studies may not reliably reflect the competition dynamics and ultimate outcomes of Bacteroidales within complex microbial communities. Expanding research to include more complex, multispecies, or community-based models is essential for accurately reflecting the dynamics of these interactions within the intricate intestinal environment.

In conclusion, Bacteroidales form a highly dynamic and systematic competitive system that is central to maintaining stability and diversity within the gut microbiota. A deeper understanding of these competitive interactions will shed light on the complex processes underpinning gut microbiome assembly. Such insights could inform the development of therapeutic strategies aimed at sustaining or manipulating these intricate microbial communities.

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References

1. Palmer JD, Foster KR. Bacterial species rarely work together. Science. 2022;376(6593):581–582. doi:10.1126/science.abn5093.
2. Zhao Y, Liu Z, Zhang B, Cai J, Yao X, Zhang M, Deng Y, Hu B. Inter-bacterial mutualism promoted by public goods in a system characterized by deterministic temperature variation. Nat Commun. 2023;14(1):5394. doi:10.1038/s41467-023-41224-7.
3. Coyte KZ, Schluter J, Foster KR. The ecology of the microbiome: networks, competition, and stability. Science. 2015;350(6261):663–666. doi:10.1126/science.aad2602.
4. Foster KR, Bell T. Competition, not cooperation, dominates interactions among culturable microbial species. Curr Biol CB. 2012;22(19):1845–1850. doi:10.1016/j.cub.2012.08.005.
5. Giri S, Oña L, Waschina S, Shitut S, Yousif G, Kaleta C, Kost C. Metabolic dissimilarity determines the establishment of cross-feeding interactions in bacteria. Curr Biol CB. 2021;31(24):5547–57.e6. doi:10.1016/j.cub.2021.10.019.
6. D'Souza G, Shitut S, Preussger D, Yousif G, Waschina S, Kost C. Ecology and evolution of metabolic cross-feeding interactions in bacteria. Nat Prod Rep. 2018;35(5):455–488. doi:10.1039/c8np00009c.
7. Preussger D, Giri S, Muhsal LK, Oña L, Kost C. Reciprocal fitness feedbacks promote the evolution of mutualistic cooperation. Curr Biol CB. 2020;30(18):3580–90.e7. doi:10.1016/j.cub.2020.06.100.
8. D'Souza G, Kost C, Hughes D. Experimental evolution of metabolic dependency in bacteria. PlOS Genet. 2016;12(11):e1006364. doi:10.1371/journal.pgen.1006364.
9. Nadell CD, Drescher K, Foster KR. Spatial structure, cooperation and competition in biofilms. Nat Rev

Microbiol. 2016;14(9):589–600. doi:10.1038/nrmicro.2016.84.
10. García-Bayona L, Comstock LE. Bacterial antagonism in host-associated microbial communities. Science. 2018;361(6408):361. doi:10.1126/science.aat2456.
11. Wang S, Mu L, Yu C, He Y, Hu X, Jiao Y, Xu Z, You S, Liu S-L, Bao H. Microbial collaborations and conflicts: unraveling interactions in the gut ecosystem. Gut Microbes. 2024;16(1):2296603. doi:10.1080/19490976.2023.2296603.
12. Piccardi P, Vessman B, Mitri S. Toxicity drives facilitation between 4 bacterial species. Proceedings of the National Academy of Sciences of the United States of America; Vol. 116. 2019. p. 15979–15984. doi:10.1073/pnas.1906172116.
13. Yu Z, Gan Z, Tawfik A, Meng F. Exploring interspecific interaction variability in microbiota: a review. Eng Microbiol. 2024;4(4):100178. doi:10.1016/j.engmic.2024.100178.
14. Team TCe. A microbial future. Cell. 2024;187(19):5119–5120. doi:10.1016/j.cell.2024.08.042.
15. Wexler AG, Goodman AL. An insider's perspective: Bacteroides as a window into the microbiome. Nat Microbiol. 2017;2(5):17026. doi:10.1038/nmicrobiol.2017.26.
16. Zafar H, Saier MH Jr. Gut Bacteroides species in health and disease. Gut Microbes. 2021;13(1):1–20. doi:10.1080/19490976.2020.1848158.
17. Muramatsu MK, Winter SE. Nutrient acquisition strategies by gut microbes. Cell Host & Microbe. 2024;32(6):863–874. doi:10.1016/j.chom.2024.05.011.
18. Aparicio A, Liu Y-Y. Distinct dynamic phases observed in bacterial microcosms. Eng Microbiol. 2023;3(1):100063. doi:10.1016/j.engmic.2022.100063.
19. Wang Y, Dong Q, Hu S, Zou H, Wu T, Shi J, Zhang H, Sheng Y, Sun W, Kong X, et al. Decoding microbial genomes to understand their functional roles in human complex diseases. iMeta. 2022;1(2):e14. doi:10.1002/imt2.14.
20. Woelfel S, Silva MS, Stecher B. Intestinal colonization resistance in the context of environmental, host, and microbial determinants. Cell Host & Microbe. 2024;32(6):820–836. doi:10.1016/j.chom.2024.05.002.
21. Chen J, Xiao Y, Li D, Zhang S, Wu Y, Zhang Q, Bai W. New insights into the mechanisms of high-fat diet mediated gut microbiota in chronic diseases. iMeta. 2023;2(1):e69. doi:10.1002/imt2.69.
22. Kennedy NW, Comstock LE. Mechanisms of bacterial immunity, protection, and survival during interbacterial warfare. Cell Host & Microbe. 2024;32(6):794–803. doi:10.1016/j.chom.2024.05.006.
23. Scott N, Whittle E, Jeraldo P, Chia N. A systemic review of the role of enterotoxic Bacteroides fragilis in colorectal cancer. Neoplasia (New Y, NY). 2022;29:100797. doi:10.1016/j.neo.2022.100797.
24. Choi VM, Herrou J, Hecht AL, Teoh WP, Turner JR, Crosson S, Wardenburg JB. Activation of Bacteroides fragilis toxin by a novel bacterial protease contributes to anaerobic sepsis in mice. Nat Med. 2016;22(5):563–567. doi:10.1038/nm.4077.
25. Cornforth DM, Foster KR. Competition sensing: the social side of bacterial stress responses. Nat Rev Microbiol. 2013;11(4):285–293. doi:10.1038/nrmicro2977.
26. Hibbing ME, Fuqua C, Parsek MR, Peterson SB. Bacterial competition: surviving and thriving in the microbial jungle. Nat Rev Microbiol. 2010;8(1):15–25. doi:10.1038/nrmicro2259.
27. Basler M, Ho BT, Mekalanos JJ. Tit-for-tat: type VI secretion system counterattack during bacterial cell-cell interactions. Cell. 2013;152(4):884–894. doi:10.1016/j.cell.2013.01.042.
28. Chatzidaki-Livanis M, Coyne MJ, Comstock LE. An antimicrobial protein of the gut symbiont Bacteroides fragilis with a MACPF domain of host immune proteins. Mol Microbiol. 2014;94(6):1361–1374. doi:10.1111/mmi.12839.
29. Russell AB, Hood RD, Bui NK, LeRoux M, Vollmer W, Mougous JD. Type VI secretion delivers bacteriolytic effectors to target cells. Nature. 2011;475(7356):343–347. doi:10.1038/nature10244.
30. Sibinelli-Sousa S, Hespanhol JT, Nicastro GG, Matsuyama BY, Mesnage S, Patel A, de Souza RF, Guzzo CR, Bayer-Santos E. A family of T6SS antibacterial effectors related to l,d-transpeptidases targets the peptidoglycan. Cell Rep. 2020;31(12):107813. doi:10.1016/j.celrep.2020.107813.
31. Russell AB, LeRoux M, Hathazi K, Agnello DM, Ishikawa T, Wiggins PA, Wai SN, Mougous JD. Diverse type VI secretion phospholipases are functionally plastic antibacterial effectors. Nature. 2013;496(7446):508–512. doi:10.1038/nature12074.
32. Ting SY, Bosch DE, Mangiameli SM, Radey MC, Huang S, Park YJ, Kelly KA, Filip SK, Goo YA, Eng JK, et al. Bifunctional immunity proteins protect bacteria against FtsZ-targeting ADP-Ribosylating toxins. Cell. 2018;175(5):1380–92.e14. doi:10.1016/j.cell.2018.09.037.
33. Whitney JC, Quentin D, Sawai S, LeRoux M, Harding BN, Ledvina HE, Tran B, Robinson H, Goo Y, Goodlett D, et al. An interbacterial NAD(P)(+) glycohydrolase toxin requires elongation factor Tu for delivery to target cells. Cell. 2015;163(3):607–619. doi:10.1016/j.cell.2015.09.027.
34. Ahmad S, Wang B, Walker MD, Tran HR, Stogios PJ, Savchenko A, Grant RA, McArthur AG, Laub MT, Whitney JC. An interbacterial toxin inhibits target cell growth by synthesizing (p)ppapp. Nature. 2019;575(7784):674–678. doi:10.1038/s41586-019-1735-9.
35. Russell AB, Wexler AG, Harding BN, Whitney JC, Bohn AJ, Goo YA, Tran B, Barry N, Zheng H,

Peterson S, et al. A type VI secretion-related pathway in Bacteroidetes mediates interbacterial antagonism. Cell Host & Microbe. 2014;16(2):227–236. doi:10.1016/j.chom.2014.07.007.
36. Coyne MJ, Roelofs KG, Comstock LE. Type VI secretion systems of human gut Bacteroidales segregate into three genetic architectures, two of which are contained on mobile genetic elements. BMC Genomics. 2016;17(1):58. doi:10.1186/s12864-016-2377-z.
37. Coyne MJ, Comstock LE, Sandkvist M, Cascales E, Christie PJ. Type VI secretion systems and the gut microbiota. Microbiol Spectr. 2019;7(2). doi:10.1128/microbiolspec.PSIB-0009-2018.
38. Bongiovanni TR, Latario CJ, Le Cras Y, Trus E, Robitaille S, Swartz K, Schmidtke D, Vincent M, Kosta A, Orth J, et al. Assembly of a unique membrane complex in type VI secretion systems of Bacteroidota. Nat Commun. 2024;15(1):429. doi:10.1038/s41467-023-44426-1.
39. Howard SA, Furniss RCD, Bonini D, Amin H, Paracuellos P, Zlotkin D, Costa TRD, Levy A, Mavridou DAI, Filloux A, et al. The breadth and molecular basis of hcp-driven type VI secretion system effector delivery. mBio. 2021;12(3). doi:10.1128/mbio.00262-21.
40. Whitney JC, Beck CM, Goo YA, Russell AB, Harding BN, De Leon JA, Cunningham DA, Tran BQ, Low DA, Goodlett DR, et al. Genetically distinct pathways guide effector export through the type VI secretion system. Mol Microbiol. 2014;92(3):529–542. doi:10.1111/mmi.12571.
41. He W, Wu K, Ouyang Z, Bai Y, Luo W, Wu D, An H, Guo Y, Jiao M, Qin Q, et al. Structure and assembly of type VI secretion system cargo delivery vehicle. Cell Rep. 2023;42(7):112781. doi:10.1016/j.celrep.2023.112781.
42. García-Bayona L, Coyne MJ, Comstock LE, Blokesch M. Mobile type VI secretion system loci of the gut Bacteroidales display extensive intra-ecosystem transfer, multi-species spread and geographical clustering. PLOS Genet. 2021;17(4):e1009541. doi:10.1371/journal.pgen.1009541.
43. Sheahan ML, Flores K, Coyne MJ, García-Bayona L, Chatzidaki-Livanis M, Holst AQ, Smith RC, Sundararajan A, Barquera B, Comstock LE. A ubiquitous mobile genetic element changes the antagonistic weaponry of a human gut symbiont. Science. 2024;386(6720):414–420. doi:10.1126/science.adj9504.
44. Bao H, Coyne MJ, García-Bayona L, Comstock LE, O'Toole G. Analysis of effector and immunity proteins of the GA2 type VI secretion systems of Gut Bacteroidales. J Bacteriol. 2022;204(7):e0012222. doi:10.1128/jb.00122-22.
45. Wexler AG, Bao Y, Whitney JC, Bobay LM, Xavier JB, Schofield WB. Human symbionts inject and neutralize antibacterial toxins to persist in the gut. Proceedings of the National Academy of Sciences of the United States of America; Vol. 113. 2016. p. 3639–3644. doi:10.1073/pnas.1525637113.
46. Chatzidaki-Livanis M, Geva-Zatorsky N, Comstock LE. Bacteroides fragilis type VI secretion systems use novel effector and immunity proteins to antagonize human gut Bacteroidales species. Proc Natl Acad Sci USA. 2016;113(13):3627–3632. doi:10.1073/pnas.1522510113.
47. Hecht AL, Casterline BW, Earley ZM, Goo YA, Goodlett DR, Bubeck Wardenburg J. Strain competition restricts colonization of an enteric pathogen and prevents colitis. EMBO Rep. 2016;17(9):1281–1291. doi:10.15252/embr.201642282.
48. Verster AJ, Ross BD, Radey MC, Bao Y, Goodman AL, Mougous JD, Borenstein E. The landscape of type VI secretion across human gut microbiomes reveals its role in community composition. Cell Host & Microbe. 2017;22(3):411–9.e4. doi:10.1016/j.chom.2017.08.010.
49. Ross BD, Verster AJ, Radey MC, Schmidtke DT, Pope CE, Hoffman LR, Hajjar AM, Peterson SB, Borenstein E, Mougous JD. Human gut bacteria contain acquired interbacterial defence systems. Nature. 2019;575(7781):224–228. doi:10.1038/s41586-019-1708-z.
50. Robitaille S, Simmons EL, Verster AJ, McClure EA, Royce DB, Trus E, Swartz K, Schultz D, Nadell CD, Ross BD. Community composition and the environment modulate the population dynamics of type VI secretion in human gut bacteria. Nat Ecol Evol. 2023;7(12):2092–2107. doi:10.1038/s41559-023-02230-6.
51. Hill CA, Casterline BW, Valguarnera E, Hecht AL, Shepherd ES, Sonnenburg JL, Bubeck Wardenburg J. Bacteroides fragilis toxin expression enables lamina propria niche acquisition in the developing mouse gut. Nat Microbiol. 2024;9(1):85–94. doi:10.1038/s41564-023-01559-9.
52. Roelofs KG, Coyne MJ, Gentyala RR, Chatzidaki-Livanis M, Comstock LE, Huffnagle GB. Bacteroidales secreted antimicrobial proteins target surface molecules necessary for gut colonization and mediate competition in vivo. mBio. 2016;7(4). doi:10.1128/mBio.01055-16.
53. McEneany VL, Coyne MJ, Chatzidaki-Livanis M, Comstock LE. Acquisition of MACPF domain-encoding genes is the main contributor to LPS glycan diversity in gut Bacteroides species. The ISME J. 2018;12(12):2919–2928. doi:10.1038/s41396-018-0244-4.
54. Shumaker AM, Laclare McEneany V, Coyne MJ, Silver PA, Comstock LE, DiRita VJ. Identification of a fifth antibacterial toxin produced by a single Bacteroides fragilis strain. J Bacteriol. 2019;201(8):201. doi:10.1128/jb.00577-18.
55. Chatzidaki-Livanis M, Coyne MJ, Roelofs KG, Gentyala RR, Caldwell JM, Comstock LE, Mekalanos JJ. Gut symbiont Bacteroides fragilis secretes a eukaryotic-like ubiquitin protein that

mediates intraspecies antagonism. mBio. 2017;8(6). doi:10.1128/mBio.01902-17.
56. Jiang K, Li W, Tong M, Xu J, Chen Z, Yang Y, Zang Y, Jiao X, Liu C, Lim B, et al. Bacteroides fragilis ubiquitin homologue drives intraspecies bacterial competition in the gut microbiome. Nat Microbiol. 2024;9(1):70–84. doi:10.1038/s41564-023-01541-5.
57. Tong M, Xu J, Li W, Jiang K, Yang Y, Chen Z, Jiao X, Meng X, Wang M, Hong J, et al. A highly conserved SusCD transporter determines the import and species-specific antagonism of Bacteroides ubiquitin homologues. Nat Commun. 2024;15(1):8794. doi:10.1038/s41467-024-53149-w.
58. Coyne MJ, Béchon N, Matano LM, McEneany VL, Chatzidaki-Livanis M, Comstock LE. A family of anti-Bacteroidales peptide toxins wide-spread in the human gut microbiota. Nat Commun. 2019;10(1):3460. doi:10.1038/s41467-019-11494-1.
59. Matano LM, Coyne MJ, García-Bayona L, Comstock LE, Stephen Trent M. Bacteroidetocins target the essential outer membrane protein BamA of Bacteroidales symbionts and pathogens. mBio. 2021;12(5):e0228521. doi:10.1128/mBio.02285-21.
60. Evans JC, McEneany VL, Coyne MJ, Caldwell EP, Sheahan ML, Von SS, Coyne EM, Tweten RK, Comstock LE. A proteolytically activated antimicrobial toxin encoded on a mobile plasmid of Bacteroidales induces a protective response. Nat Commun. 2022;13(1):4258. doi:10.1038/s41467-022-31925-w.
61. Bao Y, Verdegaal AA, Anderson BW, Barry NA, He J, Gao X, Goodman AL. A common pathway for activation of host-targeting and bacteria-targeting toxins in human intestinal bacteria. mBio. 2021; 12(4):e0065621. doi:10.1128/mBio.00656-21.
62. Abrahamsen HL, Sanford TC, Collamore CE, Johnstone BA, Coyne MJ, García-Bayona L, Christie MP, Evans JC, Farrand AJ, Flores K, et al. Distant relatives of a eukaryotic cell-specific toxin family evolved a complement-like mechanism to kill bacteria. Nat Commun. 2024;15(1):5028. doi:10.1038/s41467-024-49103-5.
63. Patrick S, Jobling KL, O'Connor D, Thacker Z, Dryden DTF, Blakely GW. A unique homologue of the eukaryotic protein-modifier ubiquitin present in the bacterium Bacteroides fragilis, a predominant resident of the human gastrointestinal tract. Microbiol. 2011;157(11):3071–3078. doi:10.1099/mic.0.049940-0.
64. Stewart L, J DME, Blakely G, Patrick S. Antigenic mimicry of ubiquitin by the gut bacterium Bacteroides fragilis: a potential link with autoimmune disease. Clin Exp Immunol. 2018;194(2):153–165. doi:10.1111/cei.13195.
65. Drider D, Fimland G, Héchard Y, McMullen LM, Prévost H. The continuing story of class IIa bacteriocins. Microbiol Mol Biol Rev. 2006;70(2):564–582. doi:10.1128/mmbr.00016-05.
66. Kjos M, Nes IF, Diep DB. Class II one-peptide bacteriocins target a phylogenetically defined subgroup of mannose phosphotransferase systems on sensitive cells. Microbiology. 2009;155(9):2949–2961. doi:10.1099/mic.0.030015-0.
67. Pierce JV, Fellows JD, Anderson DE, Bernstein HD. A clostripain-like protease plays a major role in generating the secretome of enterotoxigenic Bacteroides fragilis. Mol Microbiol. 2021;115(2):290–304. doi:10.1111/mmi.14616.
68. Gordon VM, Leppla SH. Proteolytic activation of bacterial toxins: role of bacterial and host cell proteases. Infect Immun. 1994;62(2):333–340. doi:10.1128/iai.62.2.333-340.1994.
69. Liddington RC. Assembly and function of the anthrax toxin protein translocation complex. Sub-Cell Biochem. 2021;96:563–577. doi:10.1007/978-3-030-58971-4_18.
70. Jiang K, Chen Z, Zang Y, Shi Y, Shang C, Jiao X, Cai J, Gao X. Functional characterization of Vip3Aa from Bacillus thuringiensis reveals the contributions of specific domains to its insecticidal activity. J Biol Chem. 2023;299(3):103000. doi:10.1016/j.jbc.2023.103000.
71. Tweten RK, Hotze EM, Wade KR. The unique molecular choreography of giant pore formation by the cholesterol-dependent cytolysins of gram-positive bacteria. Annu Rev Microbiol. 2015;69(1):323–340. doi:10.1146/annurev-micro-091014-104233.
72. Evans JC, Johnstone BA, Lawrence SL, Morton CJ, Christie MP, Parker MW, Tweten RK. A key motif in the cholesterol-dependent cytolysins reveals a large family of related proteins. mBio. 2020;11(5):11. doi:10.1128/mBio.02351-20.
73. Nadell CD, Xavier JB, Foster KR. The sociobiology of biofilms. FEMS Microbiol Rev. 2009;33(1):206–224. doi:10.1111/j.1574-6976.2008.00150.x.
74. Barber MF, Fitzgerald JR. Mechanisms of host adaptation by bacterial pathogens. FEMS Microbiol Rev. 2024;48(4):48. doi:10.1093/femsre/fuae019.
75. Murdoch CC, Skaar EP. Nutritional immunity: the battle for nutrient metals at the host–pathogen interface. Nat Rev Microbiol. 2022;20(11):657–670. doi:10.1038/s41579-022-00745-6.
76. Lee JY, Tsolis RM, Baumler AJ. The microbiome and gut homeostasis. Science. 2022;377(6601):eabp9960. doi:10.1126/science.abp9960.
77. Zhang K, Delgado-Baquerizo M, Zhu YG, Chu H, Medema M. Space is more important than season when shaping soil microbial communities at a large spatial scale. Msystems. 2020;5(3):5. doi:10.1128/mSystems.00783-19.
78. MacLean RC, Gudelj I. Resource competition and social conflict in experimental populations of yeast. Nature. 2006;441(7092):498–501. doi:10.1038/nature04624.
79. Vulic M, Kolter R. Evolutionary cheating in Escherichia coli stationary phase cultures. Genetics. 2001;158(2):519–526. doi:10.1093/genetics/158.2.519.

80. Salyers AA, Vercellotti JR, West SE, Wilkins TD. Fermentation of mucin and plant polysaccharides by strains of Bacteroides from the human colon. Appl Environ Microbiol. 1977;33(2):319–322. doi:10.1128/aem.33.2.319-322.1977.
81. Koropatkin NM, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. Nat Rev Microbiol. 2012;10(5):323–335. doi:10.1038/nrmicro2746.
82. Cuskin F, Lowe EC, Temple MJ, Zhu Y, Cameron E, Pudlo NA, Porter NT, Urs K, Thompson AJ, Cartmell A, et al. Human gut Bacteroidetes can utilize yeast mannan through a selfish mechanism. Nature. 2015;517(7533):165–169. doi:10.1038/nature13995.
83. Rogowski A, Briggs JA, Mortimer JC, Tryfona T, Terrapon N, Lowe EC, Baslé A, Morland C, Day AM, Zheng H, et al. Glycan complexity dictates microbial resource allocation in the large intestine. Nat Commun. 2015;6(1):7481. doi:10.1038/ncomms8481.
84. Leth ML, Ejby M, Workman C, Ewald DA, Pedersen SS, Sternberg C, Bahl MI, Licht TR, Aachmann FL, Westereng B, et al. Differential bacterial capture and transport preferences facilitate co-growth on dietary xylan in the human gut. Nat Microbiol. 2018;3(5):570–580. doi:10.1038/s41564-018-0132-8.
85. Sonnenburg JL, Xu J, Leip DD, Chen CH, Westover BP, Weatherford J, Buhler JD, Gordon JI. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. Science. 2005;307(5717):1955–1959. doi:10.1126/science.1109051.
86. Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, Pudlo NA, Kitamoto S, Terrapon N, Muller A, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell. 2016;167(5):1339–1353.e21. doi:10.1016/j.cell.2016.10.043.
87. Glowacki RWP, Pudlo NA, Tuncil Y, Luis AS, Sajjakulnukit P, Terekhov AI, Lyssiotis CA, Hamaker BR, Martens EC. A ribose-scavenging system confers colonization fitness on the human gut symbiont bacteroides thetaiotaomicron in a diet-specific manner. Cell Host Microbe. 2020;27(1):79–92.e9. doi:10.1016/j.chom.2019.11.009.
88. Kramer J, Ozkaya O, Kummerli R. Bacterial siderophores in community and host interactions. Nat Rev Microbiol. 2020;18(3):152–163. doi:10.1038/s41579-019-0284-4.
89. Joshi F, Archana G, Desai A. Siderophore cross-utilization amongst rhizospheric bacteria and the role of their differential affinities for Fe3+ on growth stimulation under iron-limited conditions. Curr Microbiol. 2006;53(2):141–147. doi:10.1007/s00284-005-0400-8.
90. Harrison F, Paul J, Massey RC, Buckling A. Interspecific competition and siderophore-mediated cooperation in Pseudomonas aeruginosa. Isme J. 2008;2(1):49–55. doi:10.1038/ismej.2007.96.
91. Butaite E, Baumgartner M, Wyder S, Kummerli R. Siderophore cheating and cheating resistance shape competition for iron in soil and freshwater Pseudomonas communities. Nat Commun. 2017;8(1):414. doi:10.1038/s41467-017-00509-4.
92. Zhu W, Winter MG, Spiga L, Hughes ER, Chanin R, Mulgaonkar A, Pennington J, Maas M, Behrendt CL, Kim J, et al. Xenosiderophore utilization promotes bacteroides thetaiotaomicron resilience during colitis. Cell Host Microbe. 2020;27(3):376–388.e8. doi:10.1016/j.chom.2020.01.010.
93. Spiga L, Fansler RT, Perera YR, Shealy NG, Munneke MJ, David HE, Torres TP, Lemoff A, Ran X, Richardson KL, et al. Iron acquisition by a commensal bacterium modifies host nutritional immunity during Salmonella infection. Cell Host Microbe. 2023;31(10):1639–1654.e10. doi:10.1016/j.chom.2023.08.018.
94. Wandersman C, Delepelaire P. Bacterial iron sources: from siderophores to hemophores. Annu Rev Microbiol. 2004;58(1):611–647. doi:10.1146/annurev.micro.58.030603.123811.
95. Gao JL, Nguyen KA, Hunter N. Characterization of a hemophore-like protein from Porphyromonas gingivalis. J Biol Chem. 2010;285(51):40028–40038. doi:10.1074/jbc.M110.163535.
96. Butler CA, Dashper SG, Khan HSG, Zhang L, Reynolds EC. The interplay between iron, haem and manganese in Porphyromonas gingivalis. J Oral Biosci. 2015;57(2):91–101. doi:10.1016/j.job.2014.12.003.
97. Antonyuk SV, Sieminska K, Smiga M, Strange RW, Wagner M, Barnett KJ, Olczak T. Bacteroides fragilis expresses three proteins similar to Porphyromonas gingivalis HmuY: hemophore-like proteins differentially evolved to participate in heme acquisition in oral and gut microbiomes. FASEB J. 2023;37(7):e22981. doi:10.1096/fj.202300366R.
98. Kehl-Fie TE, Skaar EP. Nutritional immunity beyond iron: a role for manganese and zinc. Curr Opin Chem Biol. 2010;14(2):218–224. doi:10.1016/j.cbpa.2009.11.008.
99. Porcheron G, Garenaux A, Proulx J, Sabri M, Dozois CM. Iron, copper, zinc, and manganese transport and regulation in pathogenic Enterobacteria: correlations between strains, site of infection and the relative importance of the different metal transport systems for virulence. Front Cell Infect Microbiol. 2013;3:90. doi:10.3389/fcimb.2013.00090.
100. Hantke K. Bacterial zinc uptake and regulators. Curr Opin Microbiol. 2005;8(2):196–202. doi:10.1016/j.mib.2005.02.001.
101. Si M, Zhao C, Burkinshaw B, Zhang B, Wei D, Wang Y, Dong TG, Shen X. Manganese scavenging and oxidative stress response mediated by type VI secretion system in Burkholderia thailandensis. Proc Natl Acad Sci USA. 2017;114(11):E2233–E42. doi:10.1073/pnas.1614902114.
102. Wang T, Si M, Song Y, Zhu W, Gao F, Wang Y, Zhang L, Zhang W, Wei G, Luo Z-Q, et al. Type VI

secretion system transports Zn2+ to combat multiple stresses and host immunity. PLOS Pathog. 2015;11(7): e1005020. doi:10.1371/journal.ppat.1005020.
103. Degnan PH, Taga ME, Goodman AL. Vitamin B12 as a modulator of gut microbial ecology. Cell Metab. 2014;20(5):769–778. doi:10.1016/j.cmet.2014.10.002.
104. Degnan PH, Barry NA, Mok KC, Taga ME, Goodman AL. Human gut microbes use multiple transporters to distinguish vitamin B12 analogs and compete in the gut. Cell Host Microbe. 2014;15(1):47–57. doi:10.1016/j.chom.2013.12.007.
105. Goodman AL, McNulty NP, Zhao Y, Leip D, Mitra RD, Lozupone CA, Knight R, Gordon JI. Identifying genetic determinants needed to establish a human gut symbiont in its habitat. Cell Host Microbe. 2009;6 (3):279–289. doi:10.1016/j.chom.2009.08.003.
106. Wexler AG, Schofield WB, Degnan PH, Folta-Stogniew E, Barry NA, Goodman AL. Human gut Bacteroides capture vitamin B(12) via cell surface-exposed lipoproteins. Elife. 2018;7. doi:10.7554/eLife.37138.
107. Gude S, Pince E, Taute KM, Seinen AB, Shimizu TS, Tans SJ. Bacterial coexistence driven by motility and spatial competition. Nature. 2020;578(7796):588–592. doi:10.1038/s41586-020-2033-2.
108. Donaldson GP, Chou WC, Manson AL, Rogov P, Abeel T, Bochicchio J, Ciulla D, Melnikov A, Ernst PB, Chu H, et al. Spatially distinct physiology of Bacteroides fragilis within the proximal colon of gnotobiotic mice. Nat Microbiol. 2020;5(5):746–756. doi:10.1038/s41564-020-0683-3.
109. Lee SM, Donaldson GP, Mikulski Z, Boyajian S, Ley K, Mazmanian SK. Bacterial colonization factors control specificity and stability of the gut microbiota. Nature. 2013;501(7467):426–429. doi:10.1038/nature12447.
110. Donaldson GP, Ladinsky MS, Yu KB, Sanders JG, Yoo BB, Chou WC, Conner ME, Earl AM, Knight R, Bjorkman PJ, et al. Gut microbiota utilize immunoglobulin a for mucosal colonization. Science. 2018;360 (6390):795–800. doi:10.1126/science.aaq0926.