

## Microbial collaborations and conflicts: unraveling interactions in the gut ecosystem

Shuang Wang<sup>\*a,b,c</sup>, Lingyi Mu<sup>\*a</sup>, Chong Yu<sup>\*a,c,d</sup>, Yuting He<sup>a,c,d</sup>, Xinliang Hu<sup>a,c,d</sup>, Yanlei Jiao<sup>a,c,d</sup>, Ziqiong Xu<sup>a,c,d</sup>, Shaohui You<sup>a,c,d</sup>, Shu-Lin Liu<sup>a,c,d</sup>, and Hongxia Bao<sup>id a,c,d</sup>

<sup>a</sup>Genomics Research Center, Key Laboratory of Gut Microbiota and Pharmacogenomics of Heilongjiang Province, State-Province Key Laboratory of Biomedicine-Pharmaceutics of China, College of Pharmacy, Harbin Medical University, Harbin, China; <sup>b</sup>Department of Biopharmaceutical Sciences (State-Province Key Laboratories of Biomedicine-Pharmaceutics of China), College of Pharmacy, Harbin Medical University, Harbin, China; <sup>c</sup>National Key Laboratory of Frigid Zone Cardiovascular Diseases (NKLFZCD) College of Pharmacy, Harbin Medical University, Harbin, China; <sup>d</sup>Harbin Medical University-University of Calgary Cumming School of Medicine Centre for Infection and Genomics, Harbin Medical University, Harbin, China

### ABSTRACT

The human gut microbiota constitutes a vast and complex community of microorganisms. The myriad of microorganisms present in the intestinal tract exhibits highly intricate interactions, which play a crucial role in maintaining the stability and balance of the gut microbial ecosystem. These interactions, in turn, influence the overall health of the host. The mammalian gut microbes have evolved a wide range of mechanisms to suppress or even eliminate their competitors for nutrients and space. Simultaneously, extensive cooperative interactions exist among different microbes to optimize resource utilization and enhance their own fitness. This review will focus on the competitive mechanisms among members of the gut microorganisms and discuss key modes of actions, including bacterial secretion systems, bacteriocins, membrane vesicles (MVs) *etc.* Additionally, we will summarize the current knowledge of the often-overlooked positive interactions within the gut microbiota, and showcase representative machineries. This information will serve as a reference for better understanding the complex interactions occurring within the mammalian gut environment. Understanding the interaction dynamics of competition and cooperation within the gut microbiota is crucial to unraveling the ecology of the mammalian gut microbial communities. Targeted interventions aimed at modulating these interactions may offer potential therapeutic strategies for disease conditions.

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## Introduction

The mammalian gastrointestinal tract (GI) is a complex ecosystem composed of a vast community of microbes known as the gut microbiota, which plays a pivotal role in host health.<sup>1</sup> The human gut microbiota comprises bacteria, archaea, eukaryotes and viruses. It has co-evolved with the host for millions of years.<sup>2–4</sup> Over 100 trillion microorganisms, representing more than 1000 different species, thrive within the human intestinal tract, and the composition can vary significantly between individuals according to different factors including diet, host genetics and age *etc.*<sup>5,6</sup> Imbalances in the composition of these intestinal microbes have been linked to an increasing number of host diseases and syndromes.<sup>1</sup>

It is generally recognized that the neonate's microbial colonization event first occurs at birth through the birth canal and subsequently from the immediate environment.<sup>7–9</sup> This colonization then continually matures and stabilizes during the first 3 years of life. In adults, the composition of the gut microbiota remains relatively stable, except in cases of extreme external stressors, such as antibiotics, diet, and infection.<sup>10</sup> The different species hosted within the human gut form a complex ecological interaction web, interacting with one another either positively or negatively to create and adapt to suitable living conditions.

**CONTACT** Hongxia Bao  [hbao@hrbmu.edu.cn](mailto:hbao@hrbmu.edu.cn); Shu-Lin Liu  [sliu@hrbmu.edu.cn](mailto:sliu@hrbmu.edu.cn)  Genomics Research Center, Key Laboratory of Gut Microbiota and Pharmacogenomics of Heilongjiang Province, State-Province Key Laboratory of Biomedicine-Pharmaceutics of China, College of Pharmacy, Harbin Medical University, Harbin, China

\*These authors contributed equally to this work.

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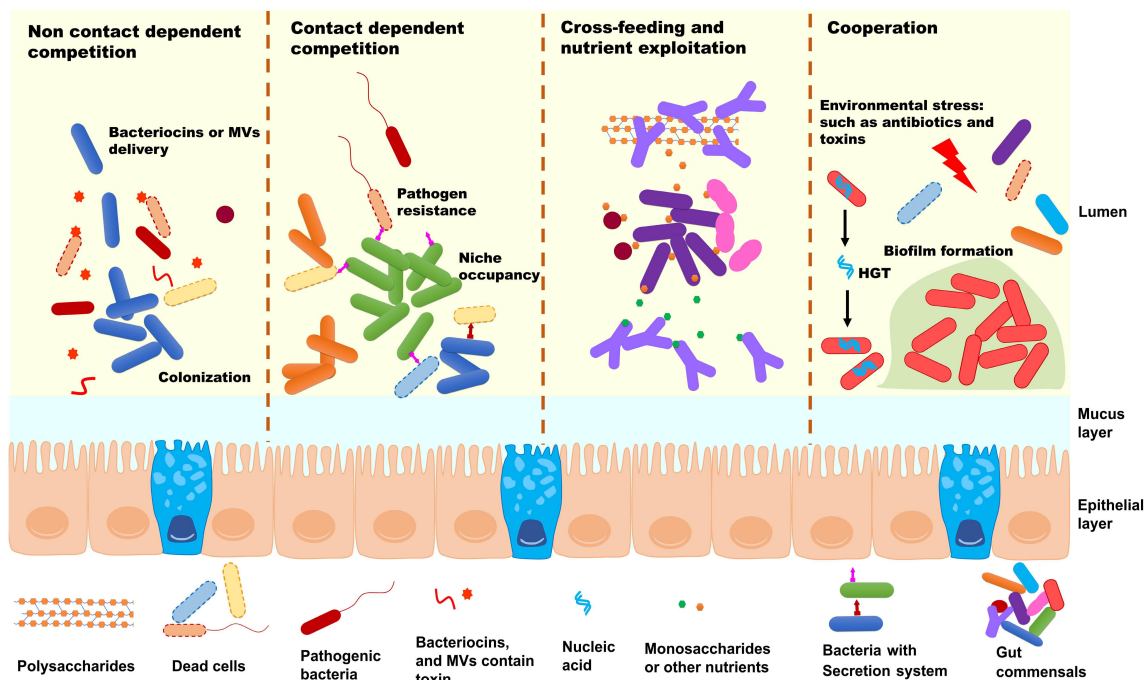
Competition and cooperation between microbes play a crucial role in shaping community composition and functioning in the gut.<sup>11</sup> Within these communities, bacteria compete with their neighbors for nutrients, including carbon, nitrogen, metals, phosphate, as well as for space where these nutrients are more abundant. Microbial communities also engage in cooperation to aid in resource digestion, combat antibiotics, or manage other environmental stresses.<sup>12</sup> Previous studies have indicated that there is often more pronounced competition between bacterial species than cooperation,<sup>13–15</sup> yet an increasing number of recent studies highlight the prevalence and ecological significance of cooperative phenotypes in the mammalian gut.<sup>16</sup>

There are trillions of microorganisms inhabiting the intestinal tract, and the microbiota members may engage in direct or indirect interactions. Understanding the interactions among these gut bacteria provides insight into the forces shaping the ecology of the human gut microbiota. This

review highlights the diverse competitive and cooperative interactions among the dominant gut flora, aiding in the comprehension of the dynamics of the gut ecosystem. Importantly, by embracing this dynamic perspective, we can better decipher the underlying mechanisms that shape community composition and function in both health and disease.

### Competitive interactions in the human gut

The microorganisms inhabiting the human GI tract live in close contact with each other in a complex and dynamic relationship (Figure 1). Exposure to various environmental factors can strongly influence microbial interactions, resulting in positive, negative, or neutral outcomes. A strain is considered to be competitive if it shows a phenotype that decreases the survival or reproduction of others.<sup>14</sup> It has long been recognized that there are two main types of competition: exploitative competition and interference



**Figure 1.** Scheme of gut microbial interaction in gut. Bacterial interactions, whether competitive or cooperative, involve a significant investment of energy and stringent regulatory control. Competitive interactions can take the form of exploitation, or interference, while positive interaction mostly related to nutrients cross-feeding and adaptation to environmental stress. Secretion of toxin by contact-dependent or independent manner will confers the bacterial colonization, facilitate niche occupancy, and also eliminate the pathogenic bacteria. Positive interactions among bacteria primarily revolve around optimizing resource utilization and adapting to environmental stresses such as antibiotics or toxins, which will enhance bacterial fitness to complex gut environment.

competition, both of which are categorized as real competition<sup>17</sup>. Interference competition is a direct form of competition in which one individual actively harms another or engages in chemical warfare, while exploitative competition occurs indirectly through competition for common resources<sup>17</sup>. Interference-based competition usually antagonizes competitors by releasing bacteriocins directly or in a secretion system-dependent manner.

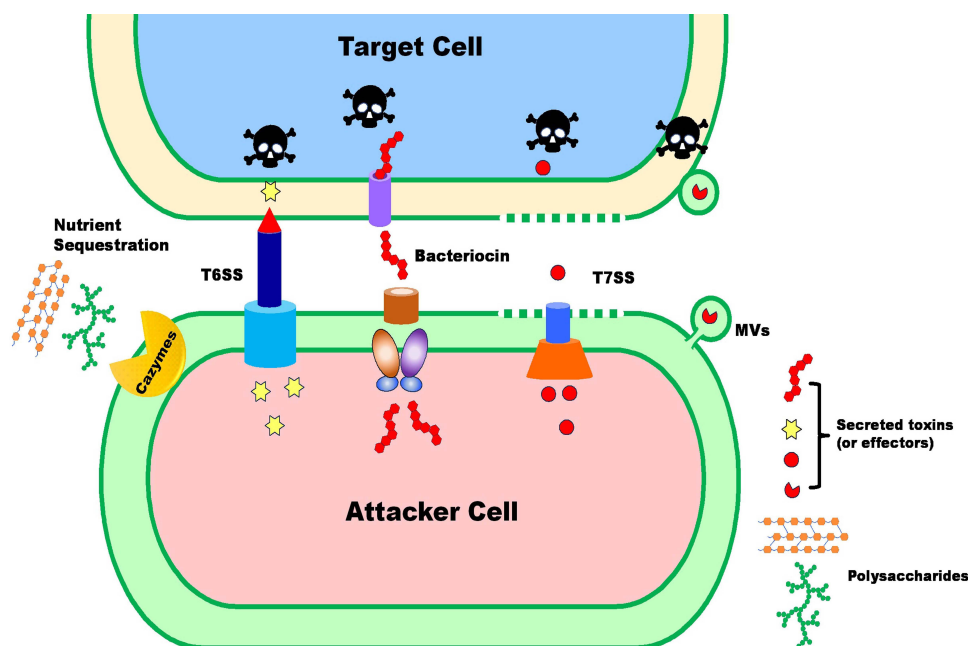
Bacterial secretion systems are a class of protein complexes that translocate cargos across the cytoplasmic membrane.<sup>18–21</sup> To date, there are 11 known bacterial protein secretion systems with considerable evolutionary and structural diversity. Most of the secretion systems are specific to Gram-negative bacteria, while only a few have been identified in Gram-positive bacteria. In certain cases, bacterial pathogens utilize these dedicated secretion systems to secrete effectors into the environment or directly into the cytoplasm of the target cells for pathogenicity or survival, or for promoting inter-bacterial competition.<sup>18,22,23</sup> Among the 11 identified bacterial secretion systems, the Type I secretion system (T1SS), Type IV secretion

system (T4SS), Type V secretion system subtype b (T5SS b), Type VI secretion system (T6SS), and Type VII secretion system (T7SS) have been proven to deliver antibacterial toxins.<sup>18,24,25</sup> Among these, T6SS and T7SS are prevalent in gut symbionts. In the following sections, we will provide an overview of the primary types of interference interactions mediated by secretion systems and bacteriocins that are commonly observed in the human gut ecosystem.

## Interference competition

### Type VI secretion system

Over the past years, T6SS has received considerable attention due to its contact-dependent cell-cell interactions with both bacteria and eukaryotic hosts.<sup>26</sup> T6SS is widely distributed in Gram-negative bacteria.<sup>27</sup> In human microbial ecosystems, T6SS loci have been found both in *Bacteroidetes* and *Proteobacteria*. The T6SS is a contractile nanomachine that injects effector proteins directly from the bacterial cytoplasm into target cells to exert their action<sup>28</sup> (Figure 2). Scientists, through mathematical



**Figure 2.** Main competition machineries in gut microbes. Bacterial competition in the gut can be mediated by contact-dependent secretion systems such as T6SS or T7SS, which lyse neighboring cells by injecting toxic effectors into host cells or the environment. Additionally, bacteria can harm distant cells by releasing bacteriocins directly into the environment or by carrying them via MVs. Moreover, exploiting nutrients in the environment through the direct acquisition or release of enzymes is also an important mode of competition among intestinal bacteria.

modeling, predicted that there are over one billion T6SS effector transmission events per minute per gram of colonic contents of gnotobiotic mice, indicating a critical potential of T6SS in shaping the gut ecosystem<sup>29</sup>. Over the past decade, significant progress has been made in elucidating the structure of the T6SS and understanding how it confers a competitive advantage to bacterial communities. In silico analysis revealed that T6SS clusters are prevalent in human gut *Bacteroidales* species with three distinct genetic architectures, GA1, GA2, and GA3.<sup>30</sup> Of the three GAs, GA1 and GA2 T6SS gene clusters are encoded on integrative conjugative elements and transferred extensively among numerous species of *Bacteroidales*, whereas GA3 T6SSs are only found in *B. fragilis*.<sup>30–32</sup>

A systematic gut microbiota metagenomic analysis revealed that GA3 T6SS contributes to early life competition and colonization, and may finally influence the gut microbiota composition in the human gut.<sup>33</sup> *In vitro* work demonstrates that, GA3 T6SS antagonizes almost all species of gut *Bacteroidales*, exhibiting a more strain-specific impact in a mouse gut model.<sup>29,34</sup> Furthermore, the GA3 T6SS mediated killing rate of gut commensals observed was much lower than the Lotka – Volterra model has predicted, suggesting complex and dynamic interactions of microbes in the gut ecosystem.<sup>29</sup> In the mouse gut, the abundance of T6SS producers will increase while competing with sensitive competitors and significantly decrease if co-existent with resistant or non-interactive strangers.<sup>35</sup> These findings suggest that GA3 T6SS-dependent competition mechanism within a microbial community is intricate and heavily relies on the surrounding microbial lineages inhabiting the same ecological niches, as well as their sensitivity to T6SS antagonistic actions (Figure 1). A genomic and metagenomic data based study indicated that GA2 and GA1 T6SS are widespread in *Bacteroidales* isolated from gut but absent in bacteria isolated from oral cavity or vagina, suggesting fitness advantage conferred by T6SS in gut environment<sup>36</sup>. In our recent work, we identified a variety of toxic effectors in GA2 variable regions and experimentally confirmed the periplasmic toxicity.<sup>37</sup> However, strong antagonistic effect

(1–3 log killing) has not been observed for either the GA1 or GA2 T6SSs. Currently, the main function of the GA1 and GA2 T6SS gene clusters remains to be determined. A very interesting study of Madeline *et al.* identified that the integration of the ICE encoding GA1 into GA3-containing *B. fragilis* genome will deactivate its GA3-dependent antagonism. Notably, instead, it will enhance the fitness of *B. fragilis* by GA1 T6SS dependent antagonism in the mouse gut.<sup>38</sup> Extensive intra-ecosystem transferring of GA1 ICE may equip the GA3-containing *B. fragilis* with additional weapon, which will prevent them from targeting *Bacteroidales* species containing the GA1 ICE, but outcompete their ancestral strain. This event will alter the T6SS sensitive target spectrum and even impact the spatial gut community structure. Besides that, prevalent members of *Bacteroidales* in human gut were identified to encode acquired interbacterial defense (AID) gene clusters with multiple immunity proteins for defense against T6S-delivered interbacterial competition.<sup>39</sup> The AID system acquisition will confer capacity for *Bacteroidale* to survive in T6SS mediated killing and may help sustain the diversity of community. In a healthy human gut, *Enterobacteriales* only account for less than 0.1% of microbiota<sup>40</sup>, but *E. coli* could be present in the gut microbiome of virtually all adult individuals.<sup>41</sup> The first T6SS-dependent antibacterial event of *E. coli* was identified in pathogenic *E. coli* strain EAEC 17–2 and APEC TW-XM. Researchers have proven the T6SS dependent antagonistic activity against neighboring nonpathogenic *E. coli*.<sup>42,43</sup> A recent study report that the mouse gut commensal *E. coli* Mt1B1 employs T6SS to outcompete pathogenic *Citrobacter rodentium* for niche defense, suggesting a T6SS-dependent competition potential for *Enterobacteriales* in the gut.<sup>44</sup>

Collectively, T6SS appears to be important for niche occupancy and sustaining gut microbiome diversity by promoting inter- or intra-species competition. The inherent antagonistic activity can be utilized as a tool to counteract target bacteria in human gut, particularly against certain potential pathogens (Figure 1). For example, introducing T6SS encoding non-toxicogenic

*B. fragilis* will eliminate the enterotoxigenic *B. fragilis* in mouse model.<sup>45</sup> Effective T6SS dependent antagonism of pathogenic *C. rodentium* by gut commensal *E. coli* may enhance its application value.

### The type VII secretion system

The Type VII secretion system (T7SS), also known as the Esx secretion system, is a secretion system specific to Gram-positive bacteria, first identified in pathogenic *Mycobacterium tuberculosis*.<sup>46</sup> *M. tuberculosis* and *M. marinum* both utilize the T7SS to deliver virulence factors into the extracellular milieu.<sup>47</sup> T7SSs are divided into two categories, Type VIIa system (T7SSa) and Type VIIb system (T7SSb), based on differences in core structural apparatus and exported substrates.<sup>48</sup> T7SSa is intensively studied in mycobacteria and is widely distributed in the *Actinobacteria* phylum, while T7SSb was initially characterized in *Staphylococcus aureus* and found in various *Firmicutes* including *Bacillus* and *Listeria* species in addition to *Staphylococcus*.<sup>49–52</sup> *Mycobacteria* can encode up to five homologous but functionally distinct T7SSa systems, designated as ESX-1 to ESX-5, which play various roles in bacterial physiology and virulence.<sup>53</sup> Meanwhile, T7SSb is involved in pathogenesis and interbacterial competition by exporting small toxins.<sup>54–56</sup>

T7SS is functionally similar to the T6SS of Gram-negative bacteria, utilizing effector-immunity (EI) repertoires to exert antagonistic effects through contact-dependent mechanisms (Figure 2). Mougous and colleagues demonstrate that *Streptococcus intermedius* export LXG toxins through Esx secretion pathway to compete with diverse *Firmicute* species.<sup>57</sup> Interestingly, *Firmicutes* metagenome screening showed that the LXG protein-encoding genes are widely distributed among many *Firmicutes* bacterial classes which are mainly adapted to the mammalian gut environment. *Bacillus subtilis*, a normal gut commensal, encodes six LGX proteins that induce growth inhibition when overexpressed in *E. coli*.<sup>58,59</sup> Moreover, recent research has confirmed that *B. subtilis* can outcompete its T7SS mutant sister cells in a T7SSb dependent manner.<sup>60</sup> Based on these findings, we speculate that Esx system-mediated interbacterial antagonism may contribute

to the corresponding *Firmicutes* species that become dominant in the gut microbial community by eliminating the sensitive target in the same ecological niches. However, in the few *Firmicutes* species that have been investigated, T7SS seems to be strictly regulated at the transcriptional or posttranslational level and may be activated under specific conditions.<sup>61,62</sup> For example, phage predation can induce the transcription of T7SS genes in *Enterococcus faecalis*, leading to bactericidal activity against gut commensals or pathogens, including *E. faecium*, *S. aureus*, and *L. monocytogenes*.<sup>63</sup> A study by Chatterjee and colleagues discovered that phage infection and sub-lethal antibiotic exposure can activate T7SS expression, subsequently triggering T7SS antibacterial activity in *E. faecium*.<sup>64</sup> Exposure to hemin enhances T7SS transcription and effector secretion in *S. aureus*.<sup>65</sup> These studies suggest that T7SS-mediated bacterial competition may play a significant role in preserving community stability under stressful conditions. Additionally, T7SSb is usually restricted to some *Firmicutes* species inhabiting in gut, suggesting a critical role of T7SS in shaping *Firmicutes*-rich bacterial communities by competing with other Gram-positive constituents in the gut.<sup>57,66</sup>

### Bacteriocins

Bacteriocins are a promising group of ribosomally synthesized antimicrobial proteins or peptides produced by certain microorganisms.<sup>67,68</sup> Many bacterial species have been demonstrated to produce bacteriocins for self-preservation and competition within their ecological niches. These molecules can be produced by both Gram-positive and Gram-negative bacteria, as well as many archaea. Bacteriocins employ distinct mechanisms to attack target bacteria, such as pore formation, inhibition of peptidoglycan synthesis, and interference with gene expression and protein synthesis (Figure 2).<sup>68,69</sup> Currently, several hundred bacteriocins have been identified. Some bacteriocins, including many enterobacterial toxins, typically exhibit narrow antimicrobial activity. In contrast, certain other bacteriocins, particularly small peptides derived from Gram-positive bacteria, have a broader spectrum of activity.<sup>67,70</sup>

The human gut microbiome serves as a rich source of bioactive bacteriocins.<sup>71</sup> Bacteriocin

production by gut commensals can either encourage or prevent the invasion of new bacterial strains into the community. Additionally, it can play a role in shaping the composition of microbiome members within their ecological niches.<sup>67</sup> A majority of human gut microbiome members have been observed to secrete one or more types of antagonistic bacteriocins. Examples include *Lactobacillus* spp., *E. coli*, *B. subtilis*, *Enterococcus* spp., and *Bacteroides* spp. As the most predominant bacterial phyla in the human gut, *Firmicutes* and *Bacteroidetes* produce the largest number of known bacteriocins, with *Actinobacteria* and *Proteobacteria* contributing to a major part of the remaining taxa.<sup>72,73</sup>

*Bacteroidetes* encode toxins containing the membrane attack complex/perforin (MACPF) domain. Currently, four *Bacteroidales*-secreted antimicrobial protein (BSAP) toxins (BSAP-1, BSAP-2, BSAP-3, and BSAP-4) have been identified as mediators of intraspecies competition.<sup>74–77</sup> Besides, *B. fragilis* is able to secrete an eukaryotic-like ubiquitin protein to compete with other *B. fragilis* strains.<sup>78</sup> Bacteroidetocins are another type of peptide toxins produced by diverse members of the *Bacteroidetes* phylum, which show a broader range of targets, including *Bacteroides*, *Parabacteroides*, and *Prevotella* species.<sup>79,80</sup> However, as of now, there is still a lack of *in vivo* experimental evidence to confirm their antagonistic effects.

Colicins, extensively studied bacteriocins produced by *Enterobacteriaceae*, are lethal for related bacterial species but not effective against the producing bacteria due to the presence of neutralizing immunity proteins<sup>81</sup>. These high-molecular-weight toxins attach to specific receptors in the outer membrane of susceptible cells and kill targets through pore formation and nuclease activity.<sup>82</sup> Over 26 different types of colicins have been described in *E. coli* strains to date.<sup>81–83–85</sup> Several studies have highlighted the significance of colicin production for the stable colonization of *E. coli* in the gastrointestinal tract and for survival during intestinal competition.<sup>86–88</sup> Colicin-producing strains cannot coexist with the sensitive strains and resistant strains in a liquid culture media, while all phenotypes could coexist in natural gut ecosystem.<sup>82,89</sup> That's possibly due to the spatial

isolation between producer strains and sensitive strains. Besides that, colicin synthesis is typically repressed under normal conditions and regulated by signals indicating DNA damage or nutrient limitation.<sup>17,90</sup> A study by Margaret A. Riley and colleagues confirmed that the coexistence of colicin-producing and sensitive strains is possible when producers are in a clumped spatial distribution<sup>82</sup>. Nutrient limitation or colicin induction through lethal toxins enables colicin-producing bacteria to compete and safeguard their niche against invaders. These findings further propose that competitively interacting populations, distributed spatially, can mutually exclude one another, maintaining steady-state coexistence in the ecosystem. This mechanism may foster microbial diversity in the environment.<sup>91</sup>

Microcins are low-molecular-weight compounds (less than 10 kD) classified as narrow-spectrum bacteriocins. They are mainly derived from *E. coli* and exhibit receptor-mediated antibacterial activity against Gram-negative bacteria. Although the antimicrobial activity of microcins has been well investigated *in vitro*, their role *in vivo* remains unclear<sup>92,93</sup>. A study by Manuela Raffatellu *et al.* provided evidence that *E. coli* Nissle 1917 microcins mediate competition against commensal *E. coli* in the inflamed gut. This competition could potentially reduce enterobacterial blooms and maintain diversity in the intestinal microbiota.<sup>94</sup>

*Firmicutes*, which include *Bacillus*, *Enterococcus*, *Streptococcus*, *Staphylococcus*, and many other prevalent gut commensals, are capable of producing various posttranslationally modified small peptide bacteriocins known as lantibiotics. Lantibiotics exert their bactericidal activity through pore formation or by preventing cell wall biosynthesis.<sup>95</sup> Nisin, the most extensively studied lantibiotic, demonstrates antimicrobial activity against a broad range of Gram-positive bacteria and is currently of interest for clinical applications. Oral administration of nisin can reshape the *Firmicutes* and *Proteobacteria* abundance of gut microbiota in animal models.<sup>96–98</sup> *Lactococcus lactis*, which produces nisin F, has been found to stabilize the bacterial population in the gastrointestinal tract of mice.<sup>99</sup> Gut-derived *Streptococcus*

*salivarius* exhibits a narrower spectrum of activity against *Fusobacterium nucleatum* through the secretion of nisin G.<sup>100</sup> Additionally, a novel probiotic bacterium, *Lactobacillus plantarum* P-8, produces plantaricin, which may contribute to a direct shift in the microbiota structure in the human gut.<sup>101</sup> In the gut environment, bacteriocin production will confer a colonization advantage for invading a bacteriocin sensitive ecosystem (Figure 1). Correspondingly, the bacteriocin producer dominant community will prevent sensitive strain colonization. In recent years, many studies have revealed the protective effect of bacteriocins against different intestinal pathogens including *Clostridium difficile*, *Staphylococcus aureus* and *Salmonella enteritidis* etc. Hence, the administration of bacteriocin-producing commensal may become a means for inhibiting potentially problematic bacteria in gut without disrupting the overall structure of the gut microbiota.<sup>102</sup> The antibacterial spectrum of bacteriocins secreted by different bacteria varies; some are broad-spectrum, such as nisin, while others are narrow-spectrum, like microcin. Targeted intake of bacteria that secrete bacteriocins with specific antibacterial spectrum, holds the potential to selectively adjust the structure of the intestinal microbiota. This modulation may promote conditions conducive to host health.

### Exploitation competition

In addition to engaging in direct competition using various tactics such as secretion systems or bacteriocins to harm each other, mammalian gut microbes also partake in indirect competition for shared resources. This type of competition is known as exploitation competition. In exploitative competition, organisms, particularly those with similar niche preferences, can limit their competitors by either consuming finite nutrients more effectively or by releasing molecules that consume nutrients<sup>14,103</sup> (Figure 2). Advances in metagenomics and metabolomics have enabled scientists to identify species compositions and potential interactions within microbiomes in the same ecosystem. A range of experimental assessments and mathematical

modeling have characterized these exploitative interactions among gut microbiome communities.<sup>104,105</sup> A metagenomics-based study indicated that pairs of species with the same nutritional profiles exhibit antagonistic behavior as they compete for a similar niche within the human gut.<sup>106</sup> For instance, *Clostridium* ASF356 and *Parabacteroides* ASF519 compete for glucose, with the former consuming a larger number of compounds in the community than the latter<sup>107</sup>. *Streptococcus oralis* and *Streptococcus gordonii*, sharing the same niche, display intense metabolic competition<sup>106</sup>. Interestingly, the metabolic competition index, determined by species' nutritional profiles, typically shows a positive correlation with the co-occurrence of species that compete for the same nutrients, suggesting that the intestinal microbiome is significantly influenced by habitat filtering.<sup>106</sup> *Bacteroides*, a dominant genus in the human microbiota, possesses a broad repertoire of carbohydrate-active enzymes (CAZymes) that help digest polysaccharides from the diet. This enzyme diversity can lead to competition between species.<sup>108</sup> For example, various *Bacteroides* species compete for resources like inulin and xylan in co-culture experiments.<sup>109</sup> In the mouse gut, *Bacteroides caccae* has been observed to out-compete *Bacteroides thetaiotaomicron* for inulin<sup>110</sup>. Another example involves the competition between a *Firmicutes* species, *Roseburia intestinalis*, and a *Bacteroides* species, both being efficient xylan degraders. However, *R. intestinalis* can outcompete *B. ovatus* during co-culturing in a medium supplemented with xylooligosaccharides.<sup>111</sup> Exploitative competition is common among organisms that share overlapping nutrient sources in the gut community, and it clearly affects population and community dynamics (Figure 1). In the gut environment, the competition phenotypes are not fixed. At low population densities, the competition within the community is primarily exploitative, as organisms compete for shared resources.<sup>112</sup> However, as the population density increases and resource levels decrease, this interaction shifts toward interference competition. In microbial communities, both exploitative and

interference competition can coexist, and the relative importance of each type of competition can vary depending on the specific ecological context and the characteristics of the competing species.

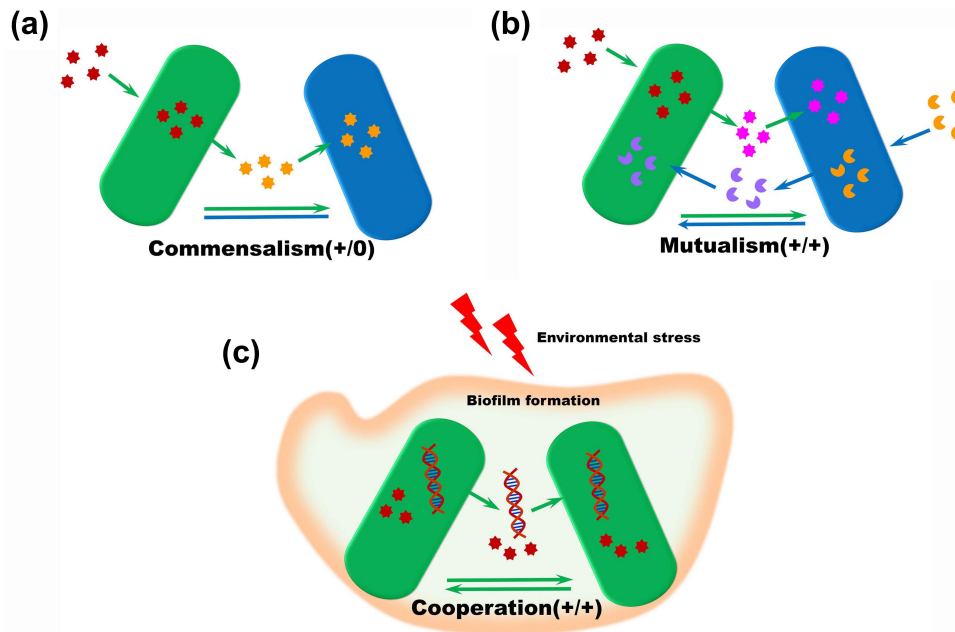
### Positive interactions in gut

Besides competing for nutrients, bacteria within the same ecosystem can also engage in positive interactions that mutually benefit each other. Some studies have suggested that competition dominates microbial species interactions, and positive interactions are much less common than competition in microbial ecosystems.<sup>113,114</sup> However, metabolic dissimilarity between co-occurring microorganisms could provide a survival advantage through complementary biosynthetic capabilities, suggesting a cooperation feature between microbes<sup>115</sup>. In recent years, both empirical and theoretical research has increasingly indicated that positive interactions among microbes are prevalent and could play significant roles in growth, composition, and the shaping of microbial communities.<sup>16–116–117,118</sup> Positive interactions are defined as instances where at least one partner involved in the interaction experiences

an improvement in fitness. Since interactions are often studied between pairs of microorganisms, we will also present them in pairs in the following sections. These interactions enhance the fitness of partners either unidirectionally or bidirectionally by generating beneficial metabolites, such as amino acids<sup>119,120</sup>, vitamins<sup>121</sup> or products from polymer degradation<sup>122</sup>. Generally, positive interactions between gut microbes fall into three main types: commensalism, mutualism, and cooperation<sup>105</sup>.

### Commensalism

Commensalism is a unidirectional positive interaction between two species, wherein one species experience increased benefits without causing any harm or providing benefit to the other species (Figure 3). Culture-based studies suggested that commensalisms were the most common positive interactions in bacterial community<sup>123</sup>. Dietary polysaccharides serve as a primary nutrient source for gut microbes, directly influencing the composition and metabolism of the microbiota<sup>124</sup>. The *Bacteroidetes* phylum is renowned for its ability to degrade a wide range of polysaccharides into monosaccharides, oligosaccharides, or other



**Figure 3.** Types of positive interactions within gut microbiome. positive interactions are common and important in a population. One species can utilize metabolites produced by another species (a), while different bacteria species can also cross-feed each other by exchanging metabolites(b). (c) bacteria sister cells could provide cross-protection by HGT, biofilm formation and cross feeding response to environmental stressors such as antibiotics or nutrient deficiencies.



fermentable end products, which can be utilized by other members of the microbial community.<sup>125</sup> This complex glycans utilization ability is typically facilitated by polysaccharide utilization loci (PULs), which encompass glycan-binding proteins, oligosaccharide transporter proteins, carbohydrate sensors, and CAZymes.<sup>126</sup> The strong polysaccharide utilization ability of *Bacteroides* enriches its own abundance and also provide various nutrients for other bacteria in the community (Figure 1). For example, *Bifidobacterium animalis* utilizes xylooligosaccharides, which are xylan hydrolysis products from *Bacteroides*, as a carbon source<sup>127</sup>. In a rat gut model, inulin fermentation by *B. uniformis* produces fructo-oligosaccharides and monosaccharides, which further support the growth of *Blautia glaucersea*, *Clostridium indolis*, and *Bifidobacterium animalis*.<sup>128</sup>

Among the first microbes to colonize the human gastrointestinal tract, *Bifidobacteria* are the most abundant bacteria in the infant gut and are believed to confer positive health benefits to their host. *Bifidobacterium* species also possess a diverse array of CAZymes that enable them to break down diet-derived glycans (e.g., starch and xylan) as well as host-derived carbohydrates like mucin and HMOs (Human Milk Oligosaccharides).<sup>129,130</sup> The resulting fermented products, such as sialic acid and glucose, are subsequently utilized by other members of the *Bifidobacterium* genus.<sup>131</sup> *In vitro* studies have also demonstrated that the 1,2-propanediol produced by *Bifidobacterium breve* can enhance the growth of *Lactobacillus reuteri*, and metabolites like acetate and lactate from *Bifidobacterium adolescentis* can be used by *Eubacterium hallii*.<sup>132,133</sup> The gut microbes, which has limited capacities for processing dietary and host-derived polysaccharides, typically relies on the fermentation products of other organisms capable of fermenting polysaccharides. Therefore, dietary glycans could increase the abundance of glycan-utilizing organisms and also influence the overall diversity and structure of the gut microbiome through positive microbe interactions.

### Mutualism

Mutualism involves a bidirectional positive interaction between two distinct species, and it is widely

observed in natural ecological communities<sup>134,135</sup> (Figure 3). In recent years, an increasing number of studies have been focusing on positive interactions among microbes and have defined similar interactions using various terms, such as syntropy, mutual/bidirectional cross-feeding, mutualism, and synergism, among others.<sup>136–139</sup> Mutualism refers to the exchange of metabolic products between individuals of different species for the benefit of both.<sup>138</sup>

Within the complex ecological community of the gut microbiota, numerous positive mutual interactions can be found. For example, *Bifidobacterium longum* and *Eubacterium rectale* are prevalent species in the human colon microbiota. When co-cultured on Arabinoxylan oligosaccharides (AXOS), *B. longum* NCC2705 consumes the arabinose substituents of AXOS and produces acetate, which serves as a substrate for *E. rectale* ATCC 33,656 to generate butyrate. Simultaneously, *E. rectale* releases xylose through extracellular AXOS degradation, further supporting the production of acetate by *B. longum*.<sup>137</sup> A study by Thi Phuong Nam Bui et al. reported that butyrate-producing bacterium *Anaerostipes rhamnosivorans* produces H<sub>2</sub>/CO<sub>2</sub>, which can be utilized by acetogenic *B. hydrogenotrophica* to form acetate. This acetate, in turn, is used by *A. rhamnosivorans* to initiate the conversion of lactate to butyrate.<sup>140</sup> In a gnotobiotic mouse model, the archaeal representative *Methanobrevibacter smithii* enhances *B. thetaiotaomicron* fermentation of fructans, resulting in acetate production. In reciprocation, *M. smithii* benefits from formate produced by *B. thetaiotaomicron*, which supports methanogenesis.<sup>141</sup> Beyond the mutual exchange of metabolites, mutualism can also involve the collaboration of different species to form a biofilm<sup>138,142</sup>. Gut commensals, including *B. bifidum*, *B. longum* subsp. *infantis*, *P. distasonis*, and *B. ovatus*, can create substantial biofilms when co-cultured in various combinations<sup>143</sup>, suggesting cooperative interactions in the formation of multi-species biofilms. However, the underlying molecular mechanisms and the specific roles of each strain in these cooperative effects still need to be determined. Mutual cross-feeding interactions can expand the metabolic niches of the interacting

individuals, promoting microbial diversity and preventing competitive exclusion.<sup>144,145</sup> Mutualistic trade-offs of essential metabolites, like amino acids, can reduce the biosynthetic burden for the utilization of metabolic pathways.<sup>146</sup>

### Cooperation

As discussed earlier, mutualism and commensalism involve interactions between distinct species, whereas cooperation described here implies an intraspecies interaction that enhances the fitness of neighboring cells sharing a specific genotype (Figure 3). Microbial cooperation within a single organism can bolster microbial tolerance to environmental and ecological stressors, such as antibiotics. A study by Yurtsev *et al.* demonstrated that co-culturing two resistant *E. coli* strains can lead to effective cross-protection, where they shield each other in a multidrug environment that inhibits the growth of either strain alone.<sup>147</sup> Similarly, a pair of amino acid auxotrophic *E. coli* strains can complement each other's deficiencies in a co-culture, demonstrating a cross-feeding cooperation effect.<sup>148</sup>

Within the human gut microbiome, horizontal gene transfer (HGT) events involving antibiotic-resistance genes (ARGs) are frequently observed among commensals and opportunistic pathogens (e.g., *E. coli* and *K. pneumoniae*, *E. faecalis* and *E. faecium*).<sup>149</sup> HGT of beneficial genes in the gut microbiome is also considered a form of cooperation.<sup>150</sup> It is common for microbes to gain or lost genes. Inter-bacterial HGT enables the acquisition of potentially adaptive genes to the recipient cells to help them survive in stressful environments (Figure 3). The formation of biofilms by prokaryotic organisms often necessitates significant cooperation to share extracellular polymeric substances among cells. Cells attached to a biofilm surface exhibit different phenotypes compared to their planktonic state, displaying stronger colonization abilities and greater tolerance to external stressors. Convincing evidence suggests that many gut bacterial species form biofilms on mucosal surfaces to enhance the efficiency of complex polysaccharide degradation and increase tolerance to

environmental stressors.<sup>151,152</sup> Gut molecules like bile have been shown to induce biofilm formation in gut bacteria, including *Bacteroides*, *Lactobacillus*, and *Bifidobacterium*, underscoring the potential importance of biofilm formation as a colonization-related factor for gut bacteria.<sup>153</sup> Cooperation events are more prominent when the microorganisms are confronted with various environmental pressures, including antibiotics and nutrient deficiencies. Such interactions may carry substantial ecological importance in upholding gut species stability when exposed to external stresses.

Understanding of the positive interaction networks based on nutrients utilization is crucial for developing a microbiota targeting diet to increase the abundance of beneficial gut microbes. Providing specific dietary fibers tailored toward enrichment of particular gut microbial member corresponding to their enzymatic profile could be an option to obtain predictable change in microbial composition. For example, administration of acetylated galactoglucomannan (AcGGM) fiber specifically aligned with enzymatic capabilities of butyrate-producing species *Roseburia* and *Faecalibacterium* increased the relative abundance of *Faecalibacterium* and specific phylotypes of *Roseburia* in porcine gut.<sup>154</sup> Meanwhile, abundance of a group of non-fiber-degrading taxa are also elevated, largely dependent on cross-feeding events. To leverage positive interactions among microbial communities and precisely regulate the gut microbiota, such as through exogenous dietary fibers, for optimizing host health, a deeper understanding of the complex interplay between gut microbial communities is required.

### Membrane vesicles: an interaction mechanism exhibiting dual functions

Within the gut microbial ecosystem, the balance between competition and cooperation among microorganisms is dynamic and greatly influenced by environmental factors. To navigate through complex and ever-changing environments, bacteria have evolved a dual functional mechanism, MVs, to interact bidirectionally with their community. This device enables the delivery of a wide array of cargoes, including nucleic acids, quorum sensing

signals, toxins, and valuable nutrients, facilitating both competitive interactions and the acquisition of beneficial effects. This adaptability allows bacteria to thrive in intricate environments.

MVs are bubble-like structures originating from the outer membranes of Gram-negative bacteria or cytoplasmic membrane vesicles formed by endolysin-triggered cell lysis in Gram-positive bacteria<sup>155</sup> (Figure 2). Proteomic and biochemical analyses have revealed that these small particles typically transport microbial substances, including nucleic acids, proteins, lipids, and metabolites, that impact diverse biological processes such as quorum sensing (QS), biofilm formation, and cell-to-cell communication<sup>156</sup>. Over the past decade, the majority of studies have focused on cytotoxic factors delivered by MVs in Gram-negative pathogens or commensals to manipulate the host immune response<sup>157</sup>. However, in this context, we will delve into the activity of gut bacterial MVs against different bacterial species within gut commensals.

Gut microbes could secrete active compounds contained within MVs into the intestinal lumen, influencing other commensals that are at a distance from their parent cells. Due to their cargo diversity, MVs exhibit various functions, from bacterial competition to nutrient utilization and even stress resistance.<sup>158</sup> Recent studies have indicated that the potential mechanism for delivering bacteriocins to target cells is through MVs. For instance, *B. fragilis* antimicrobial peptide BSAP-1 secretion is mediated by MVs.<sup>74</sup> Proteomic analyses of *Lactobacillus*-derived MVs showed that MVs could serve as vehicles for delivering antimicrobial peptides,<sup>159</sup> a finding further confirmed in a strain of *Lactobacillus acidophilus* by another study.<sup>160</sup> MVs originating from gut *Myxococcus xanthus* have demonstrated the ability to kill *E. coli* cells.<sup>161</sup> However, more evidence is needed to firmly establish the competitive role of microbiota-derived MVs in the gut.

Beyond facilitating competitive interactions among bacterial community members, gut microbiota MVs also promote positive interactions by releasing enzymes into the intestinal lumen. Proteomic analysis of outer membrane vesicles (OMVs) in *B. fragilis* and *B. thetaiotaomicron* has identified sugar hydrolases and proteases that are

preferentially packaged within the MVs.<sup>162</sup> Specific *Bacteroides* strains also deliver sulfatases through MVs to aid in the degradation of mucin glycans, thereby providing nutrients to other community members.<sup>163</sup> Hence, the enzymes enclosed within OMVs act as “public good” that provide benefits to the entire bacterial community. Additionally, besides delivering crucial enzymes for glycan degradation, MVs release enzymes that confer antibiotic resistance. MVs produced by *B. thetaiotaomicron* and several other species, which carry  $\beta$ -lactamases, can shield susceptible commensal bacteria from  $\beta$ -lactam antibiotics within the microbial community<sup>164</sup>. Furthermore, membrane vesicle-mediated HGT can facilitate the transfer of functional ARGs between bacterial species.<sup>165</sup>

## Conclusion and future perspective

Bacterial interactions play a pivotal role in shaping the diversity and stability of the gut microbiota. Nevertheless, this intricate and dynamic system is continually influenced by a broad range of factors, including diet, medication (especially antibiotics), infections, stress, and the overall health status of the host. Despite decades of research on microbial interactions, our comprehension of these interactions within natural communities remains limited. Through comprehensive and systematic investigations into the interplay of gut bacteria, both *in vivo* and *in vitro*, we can unveil the complex mechanisms that underlie gut microbiota stability and diversity. It is evident that we still have much to uncover about microbial interactions. The ongoing exploration of this area is imperative for advancing our understanding of the gut microbiota and for developing novel strategies to modulate it for therapeutic purposes.

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## ORCID

Hongxia Bao  <http://orcid.org/0000-0001-5026-5777>

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