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Commensal inter-bacterial interactions shaping the microbiota

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The gut microbiota, a complex ecosystem of microorganisms of different kingdoms, impacts host physiology and disease. Within this ecosystem, inter-bacterial interactions and their impacts on microbiota community structure and the eukaryotic host remain insufficiently explored. Microbiota-related inter-bacterial interactions range from symbiotic interactions, involving exchange of nutrients, enzymes, and genetic material; competition for nutrients and space, mediated by biophysical alterations and secretion of toxins and anti-microbials; to predation of overpopulating bacteria. Collectively, these understudied interactions hold important clues as to forces shaping microbiota diversity, niche formation, and responses to signals perceived from the host, incoming pathogens and the environment. In this review, we highlight the roles and mechanisms of selected inter-bacterial interactions in the microbiota, and their potential impacts on the host and pathogenic infection. We discuss challenges in mechanistically decoding these complex interactions, and prospects of harnessing them as future targets for rational microbiota modification in a variety of diseases.

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Introduction

Bacteria are social organisms that occupy multiple ecosystems and exhibit different inter-species and intra-species interactions, ranging from symbiosis to competition and predation [1,2]. Moreover, bacteria can acquire genetic material from their environment through horizontal gene transfer, which may alter their fitness and capacity to adapt to emerging conditions [3]. Bacterial communities can organize themselves in protective multi-cellular biofilms, using quorum sensing and other evolved communication mechanisms [4]. Collectively, these communication networks may involve secreted molecules, biophysical interactions, and indirect impacts by the host, which may be energetically costly to the individual microbe, while promoting indirect benefits to the community [5,6]. Conversely, bacteria also antagonize other bacteria, either by outcompeting their neighboring microbes, through improved adaption towards harvest of common resources, or by releasing toxins that directly harm competing cells. Through these important community functions, bacteria may prevent other microbes from colonizing their niche, a process termed colonization resistance [7]. In some cases, bacterial predators consume other bacteria, thereby contributing to the balance and biodiversity in prokaryotic communities [8].

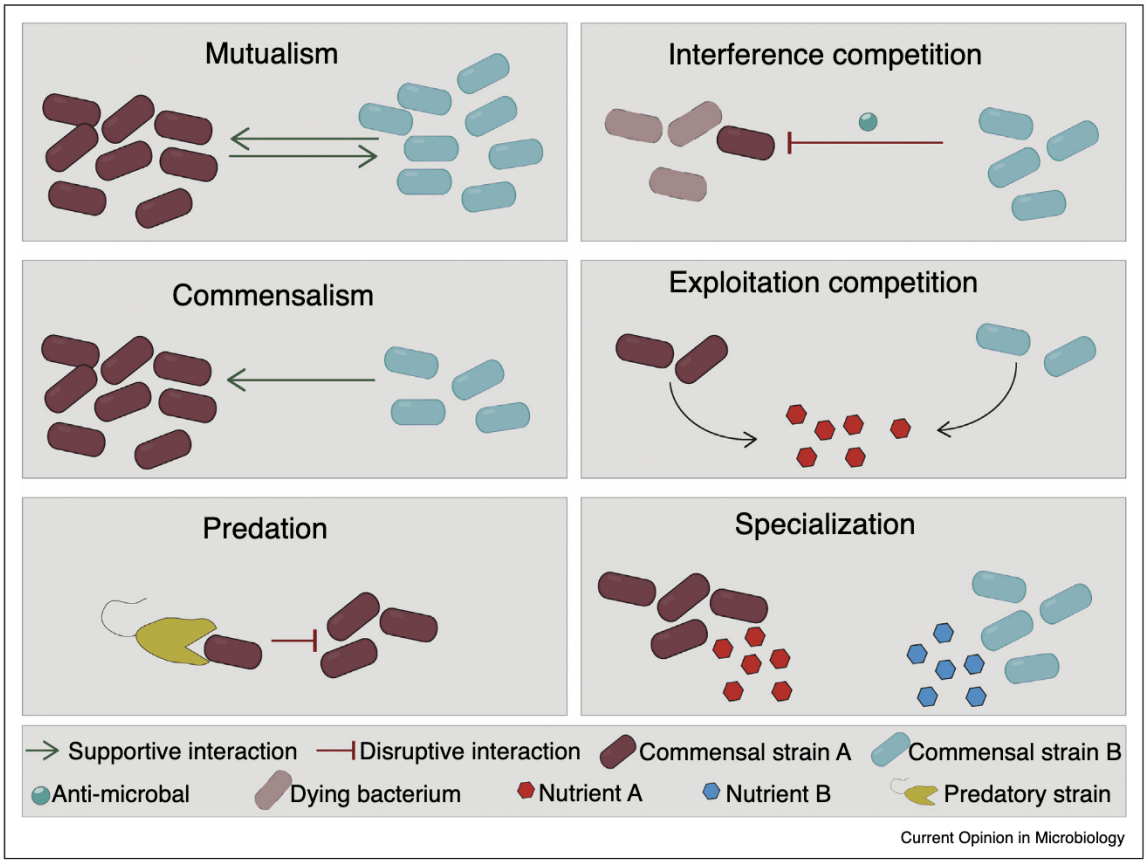
Commensal bacterial communities evolve within the context of their environment. This is exemplified by the complex microbiota community in the human gut, which constitutes a versatile ecosystem that is shaped by diet, medication, age, and lifestyle and encompasses diverse inter-bacterial interactions. Alteration in the bacterial gut microbiota community structure, or dysbiosis, may potentially impact its host's health, by contributing to the pathogenesis of a range of illnesses such as obesity, diabetes, cardiovascular disease, and even cancer and neurodegeneration [9]. As such, understanding the impact of inter-bacterial interactions on microbiota composition and function [10] may enable to modulate downstream host physiology. Despite advances in describing inter-bacterial microbiota interactions, many aspects related to their molecular nature remain poorly understood [11]. In this review, we exemplify different modes of intra-microbiota bacterial interactions and their impacts on the most well studied commensal kingdom, the bacterial gut microbiota. Other microbial interactions, such as bacterial–fungal interactions [12], bacterial–parasite interactions [13], and bacterial–phage interactions [14], and their roles in shaping the microbiota community are reviewed elsewhere.

Commensal metabolic cooperation and competition

Inter-bacterial interactions (collectively summarized in Figure 1) may involve mutual exploitation of metabolic circuits. These interactions may promote survival and growth in some cases, and nutrient deprivation in others. Among these is mutualism, a process, in which two organisms benefit from interacting with each other [15], and commensalism, a relationship in which one species gains benefits from another, whereas the other is not affected by this relationship [16]. In contrast to these 'positive' interactions, a range of 'negative' interactions involve competing metabolic interactions, and are in many cases dominant to positive interactions [17]. One such negative interaction, named exploitation competition, includes competition for shared resources, such as space and nutrients, *without direct* bacteria–bacteria interactions. Competition over nutrients can be avoided through specialization, in which divergence in bacterial exploitation of food sources reflects the different genetic characteristics of neighboring species, and results in metabolic diversification [18–20].

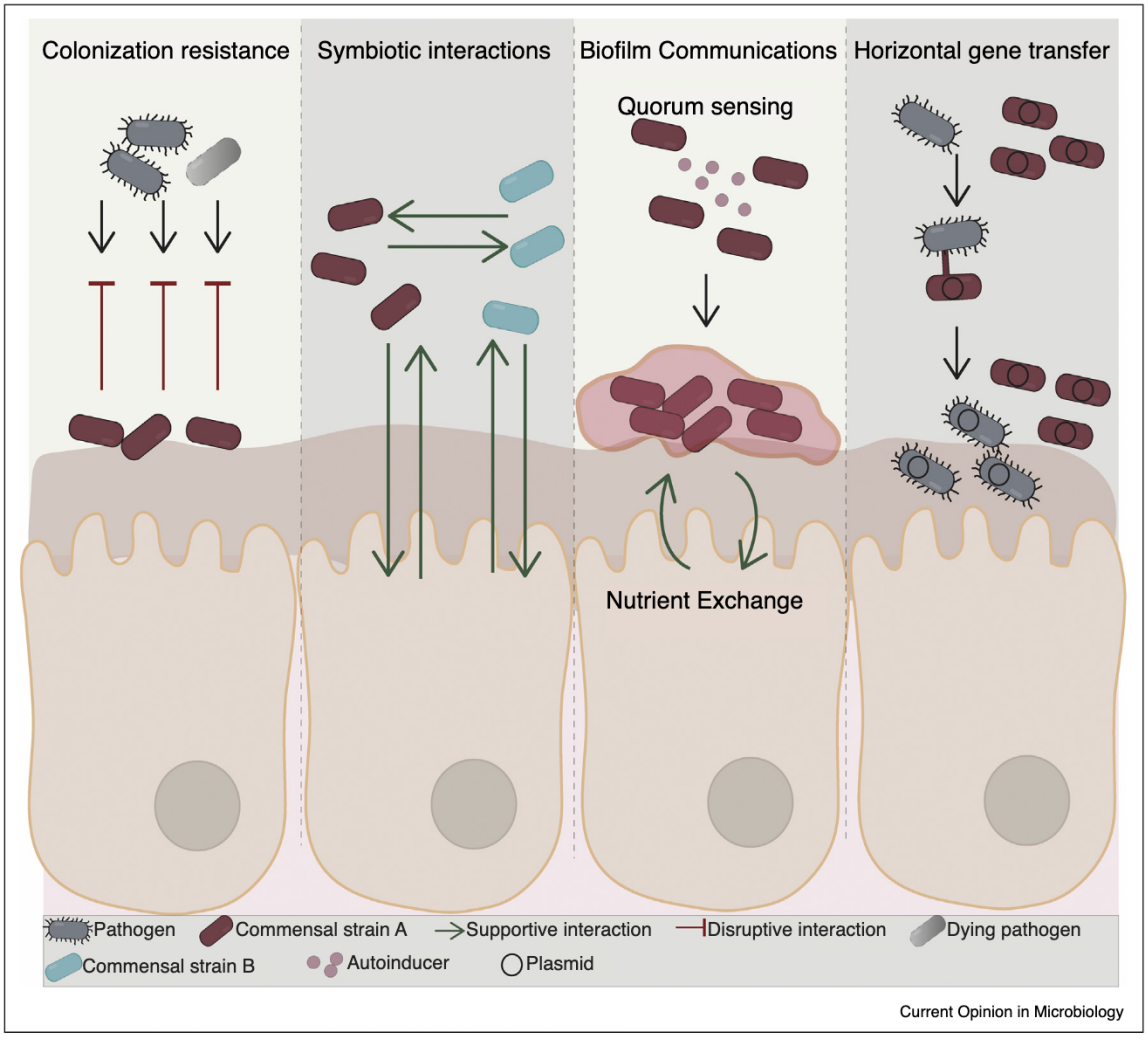
The gut microbiota is composed of multiple metabolically inter-connected commensal members featuring the full range of the above interactions (exemplified in Figure 2). *In* vitro cultures of isolated commensal strains often lack the abilities to synthesize survival-essential metabolites, which are normally produced by neighboring bacteria in the natural habitat [21–23]. For example in a bio-reactor co-culturing experiment, the absence of Bacteroides dorei negatively impacted the abundance of other 10 cultured gut microbes [24]. The underlying metabolic interactions driving these inter-commensal dependencies are mainly mediated by the ability of gut microbes to constitutively secrete primary and secondary metabolites to their environment [21], while other commensals in the niche derive these metabolites and utilize

Figure 1



Examples of prokaryotic inter-bacterial interactions.
Bacteria engage in a variety of symbiotic and competitive relationships. An interaction in which two strains gain an advantage is called mutualism. Commensalism describes a symbiotic relationship, in which only one strain of the interacting strains gains an advantage in its fitness, while the other is not affected. Predation describes the interaction, where one bacteria strain feeds on another. Interference competition denotes bacteria competing for resources by altering their niche or directly harming neighboring microbial strains through the release of toxins or other modifying molecules. In exploitation competition, bacteria compete for shared resources, thereby limiting the resources of competing strains. Specialization is driven by bacterial genetic modification, enabling the prevention of competition between bacteria through diversification of resource utilization.

Figure 2



Examples of inter-bacterial interactions impacting the microbiota and host.
Colonization resistance involves inter-commensal communications coordinating niche protection, and commensal–pathogen interactions preventing invading pathogens from displacing commensals from their niche and infecting the host. Symbiotic relations between commensal microbes can increase the community's biodiversity and promote a richer communication network with the host, such as a bilateral nutrient exchange, thereby mutually benefitting both the host and its microbiota. Quorum sensing is a microbial communication interactome, in which individual bacteria coordinate their behavior within a community. In the microbiota, quorum sensing can contribute to the formation of biofilms, which are adherent to the host and enable optimized nutrient exchange with attached host cells. Horizontal gene transfer enables inter-microbial exchange of genetic material. In the microbiota, horizontal exchange of antibiotics/anti-microbial resistance genes from commensals to pathogens may confer advantages to invading pathogens, by extending their niche penetration and persistence capacity, thereby harming the host.

them [24]. For example, *Bacteroides fragilis* produces the neurotransmitter GABA (γ-aminobutyric acid), which constitutes a carbon and energy source for the survival of the isolate KLE1738 [23]. Similarly, some bacterial strains require — *Escherichia coli* derived menaquinone (vitamin K2) for their growth [25]. Of note, menaquinone also constitutes a nutrient for the mammalian host (Figure 2).

Some members of the gut microbiota have evolved syntrophic relationships, in which cooperative bidirectional cross-feeding allows both organisms to gain benefits. For example, *Bacteroides ovatus* digests polysaccharides extracellularly, supplying by-products that benefit other microorganisms such as *Bacteroides vulgatus* in the occupied niche [5,26]. *B. vulgatus*, in turn, increases the fitness of *B. ovatus* in their habitat. Inhibitory interactions in the microbiota are exemplified by commensals competing over iron, which is taken up by the bacteria via siderophores, microbial iron chelating compounds. Some prokaryotes evolved mechanisms to use heterologous siderophores, sequestering iron away from the actual siderophore producers [27]. Specialization in the microbiota, as means of avoiding competition over shared

nutrients, is exemplified by Bacteroidetes, which are able to degrade polysaccharides (pectin and starch–3), in contrast to Firmicutes, which can degrade monosaccharides and disaccharides [19]. By such metabolic diversification, competition over these nutrients by the two phyla is circumvented.

Commensal interference competition

In addition to metabolic interactions, bacteria affect each other through interference competition by secreting bactericidal compounds, in purpose to outcompete other species. The potency and specificity of these bacterial-produced anti-microbials, as well as defence mechanisms aimed at dismantling their effect, contribute to the stability and diversity and spatial segregation of microbial populations. Commensal interference competition can feature predator–prey dynamics, in which one community limits the growth of another, or paper–scissors–rock-like dynamics, in which multiple bacterial populations synergize in limiting and promoting the growth of the other [28–30]. Importantly, commensal antagonistic behaviour may result in colonisation resistance, preventing commensal microbial colonization of a common niche, or facilitate pathogen colonization (Figure 2) [31,32]. Interestingly, some species, such as *Bdellovibrio bacteriovorus*, engage in purely predatory behaviour in which they actively feed on other bacteria [33].

In recent decades, multiple molecules with bactericidal and bacteriostatic functions were identified to be secreted by bacteria and play key roles in driving antagonistic interactions between competing bacterial strains and species [34–36]. In contrast to antibiotics, which are small molecules featuring a relatively broad spectrum of activity by targeting key cellular microbial processes (such as translation and cell wall synthesis), bacteriocins are proteins or peptides which feature a narrow host and killing spectra, usually targeting close relatives that occupy similar niches [37–39]. For example, colicins, a well-studied family of bacteriocins, are exclusively produced by Enterobacteriaceae, and specifically target this group of bacteria [40,41], while Bacteroidales species secreted antimicrobial proteins (BSAP)-1 and BSAP-2 toxins are distinctly present in *B. fragilis* and *Bacteroides uniformis*, respectively. Bacteriocins are released to the extracellular space via secretion mechanisms or through cell lysis by a fraction of the microbial population. A unique class of toxins are R-type bacteriocins, which are soluble type VI secretion systems (T6SS)-like complexes that, upon penetration of the membrane of the targeted bacterium, do not deliver toxic molecules, but rather cause membrane destabilisation leading to cell death [42]. Mechanisms of action of bacteriocins are extremely diverse and also include nuclease activity, pore-formation, cell wall lysis, inhibition of cell wall, DNA or protein synthesis [43].

In addition to soluble factors, bacteria have evolved contact-dependent mechanisms to compete with other species, which include polymorphic toxins, that are anchored at the cell surface of the producer and secretion systems [44–46]. The most well studied of these systems, type VI secretion system (T6SS), allows gram negative bacteria to inject nucleases, peptidoglycan hydrolases and membrane pore-forming proteins into other bacteria [47]. Other systems, such as type IV secretion system (T4SS), contact dependent inhibition (CDI) and the Esx pathway also play a role in delivery of toxic loads [48–52]. Moreover, extracellular vesicles (EV) enable transfer of diverse molecules through a process called outer membrane transfer, in which receptor mediated interaction leads to an exchange of portions of cell surface membranes between bacteria. Through this process, lipoprotein toxins can be delivered to interacting bacteria [52–55].

Bacteria also engage in competition through modulation of their niche, for example by secretion of molecules that affect acidity or molecules, such as hydrogen peroxide, that cause oxidative stress. Moreover, they may induce responses in the host, such as inflammation, to indirectly affect population density and composition and thereby gain competitive advantage over other microbes [56,57]. To mitigate the high metabolic costs associated with antimicrobial manufacturing and secretion, bacteria developed regulatory mechanisms that relay signals from the environment (pH, exogeneous molecules, metabolites, and more) or signals generated by microbiota communities (debris from lysed bacteria, 'eavesdropping' on quorum sensing, sensing attack via T6SS) to generate bacteriocins only upon necessity [58–61].

Both soluble factors and contact-dependent antagonistic mechanisms do not provide self-discrimination, hence bacteria have to generate immunity mechanisms against their own effector toxin molecules [62]. These 'immune' strategies involve inhibitors, scavengers, and enzymes hydrolysing effectors, such as β-lactamases, alternative ortholog receptors that do not bind to toxins, and surfactin disrupting EVs [63–67]. The range of defence mechanisms against a particular insult can be wide. For example, *Bifidobacterium bifidum* converts bile salts to deoxycholate to inhibit T6SS of *Vibrio cholerae* [68], while, upon attack by T6SS *Pseudomonas aeruginosa* retaliates and uses its own T6SS to counter-attack, resulting in a behaviour called 'duelling' [69]. Biophysical community structure was also shown to feature protective functions. For example, bacteria within biofilms are protected from antibiotics-related damage [70–72].

Commensal quorum sensing and other communicative machineries

To gain higher efficiency in particular community functions, including antagonism of other competing communities, and support of kin selection, bacteria often behave

in a coordinated manner [73]. This mode of communication is mediated via coordinated secretion and sensing of soluble factors, named autoinducers, while the synchronised downstream response to these signals is termed quorum sensing (QS). QS is present in gram positive and negative bacteria and regulates an array of functions, ranging from production of toxins and virulence factors to formation of biofilms [4,74–76]. Gram positive bacteria secrete modified oligopeptides, so-called, autoinducing peptides (AIPs) as signaling molecules [77]. In contrast, gram negative bacteria utilize small molecules as autoinducers.

An example of a well-studied family of autoinducers, mainly produced by gram negative bacteria, are acylated homoserine lactones (AHL). They are produced by Lux-I type proteins and due to their hydrophobic tails are able to diffuse through inner and outer cell membranes [78]. They vary in length, structure and modifications of their acyl chain, which provides a basis for species specificity when recognised by proteins from the LuxR receptor family [79–81]. Interestingly, genomic studies revealed that several bacteria, such as *E. coli* or *Klebsiella pneumoniae*, can receive such signals, but not produce them as they harbour the AHL receptor homolog, but lack AHL synthetase homolog activity [82,83]. Similarly, furanosyl borate diester, also known as autoinducer 2 (AI-2), a by-product of *S*-adenosyl-L-methionine recycling, is produced by a wide array of genera, but sensed only by some of them, notably *V. cholerae*. Interestingly, its virulence gene expression is repressed by AI-2, secreted by gut commensals [84–86]. Although AI-2 has functions in regulating cellular phenotypes, the fact that it is a by-product of key metabolic pathways and that it is not sensed by most of its producers, leads to the prospect that in addition to functioning as a signalling cue, AI-2 may modulate a variety of other microbial functions [87,88].

Ribosomal-translated peptides, secreted mainly by gram positive bacteria into the extracellular space and sensed through histidine kinase receptors of two-component systems [77], may function as both autoinducers [89] and antimicrobials, as exemplified by the Nisin peptide of *Lactococcus lactis* which also acts as a lantibiotic [90,91]. Many potential autoinducers feature a yet unresolved function and structure. For example, the structure of autoinducer-3, which is sensed by catecholamine receptor QseC, was only recently identified [92,93]. Of note, massive autoinducer secretion is energy consuming, but may lead to production of public goods, that is, molecules that can be utilised by neighbouring bacteria, provided they feature the metabolic capacity to harvest them [94,95]. In mixed species communities, secretion of quorum sensing molecules, may be exploited by cheats, for example by degradation of peptides and feeding on the released amino acids [96]. Such degradation of QS molecules to harvest energy leads to quorum quenching, in which the concentration of an autoinducer ceases to reflect the bacterial concentration in the niche [97]. Other mechanisms of interference with quorum sensing include secretion of enzymes, such as lactonases or acylases that degrade AHLs, or secretion of QS antagonists, such as Bacillus-derived fengycins, that inhibit the Agr system of *Staphylococcus aureus* [98,99].

Besides autoinducers, inter-bacterial physical interactions, such as the ones mediated by nanotubes, have been suggested to mediate communication channels between prokaryotic organisms [100], in facilitating bacterial organization into complex biofilms. For example, channels within *E. coli* biofilms may transport particles and may contribute to nutrient distribution within the biofilm [101]. The diverse microbial members of biofilms feature different functions, such as the capacity of some members to secrete polysaccharides and protein polymers that form the framework of the biofilm. Biofilm formation and maintenance requires an adaption of different single organisms within the multicellular community. For example, as the nutrient contribution varies within the biofilm, prokaryotes at the bottom of the biofilm are exposed to more waste molecules and less nutrients, and adopt by featuring less metabolic activity than bacteria located at the surface of the biofilm. In *V. cholerae* biofilms, a structured and defined subset of cells anchors the biofilm to its environment, while another mediates the expansion of the biofilm in a RbmA-dependent manner [102•]. In the gut, biofilms are adherent to the epithelia, mucus or food particles and can exert a protective function against invading pathogens [103,104]. Moreover, biofilms enable prokaryotes to prolong their residence time within the gut, promote the exchange of nutrients with the host, and fortify the host intestinal barrier [105,106]. Gut biofilm alterations were described in association with inflammatory bowel disease, cancer and infection [107], and are contemplated to involve pathobionts such as *Helicobacter pylori* [108] and *Clostridium difficile* [109,110].

Commensal horizontal gene transfer

Horizontal gene transfer (HGT) involves the introduction of foreign DNA into a eukaryotic or prokaryotic organism [3]. Within the microbiota, HGT contributes to the dynamic evolution of symbiotic and pathogenic microbes, continuously providing bacteria with new genes and associated functions, which potentially carry advantages against selective pressures in the ecological niche of the gut [3]. There are three main well-described types of HGT in prokaryotes. Conjugation consists of a directly transfer DNA from one bacteria to another bacterial cell of the same or different species by building a conjugation pilus between the two cells [3]. In contrast, transformation describes the process in which naked DNA from the surrounding environment is introduced into a naturally competent bacterium [3,111]. Transduction describes the

transfer of foreign DNA into a prokaryotic cell using a virus or viral vector as a shuttle [112]. Besides these three mechanisms, gene transfer agents (GTA), which are phage-like elements that are encoded by genes that are located on the chromosome of some bacteria and archaea, offer another route of HGT [113,114]. Bacterial expression of these genes leads to the production of tailed GTA particles, similar to phage particles. However, in contrast to phages, GTA particles contain only random pieces of host DNA, which are not sufficient to encode for the GTA particles themselves, hence they do not possess replicative properties. The GTA particles are released upon lysis of the host cell, attach, through their receptor tail to neighboring cells, followed by infection of their DNA cargo into the cytoplasm. Transposons are genetic elements that are usually mobile within a bacterial cell and not between cells, and are integrated into the chromosomal DNA. Some transposons encode for a type IV secretion system and are called Integrative and Conjugative Elements (ICE). Upon unknown stimuli, these genetic elements are excised from the chromosomal DNA and can be injected into neighboring cells by the T4SS, hereby presenting another route of HGT [115]. Moreover, genes, but also RNAs, are transported through outer membrane vesicles (OMV) from gram negative bacteria into other organisms [116]. In addition, nanotubes are reported to deliver cargo from one bacterial cell to a bacterium of the same or different species to overcome nutrient deprivation or to spread non conjugative plasmids, carrying antibiotic resistance genes [117•]. However, it was recently suggested that gram positive and negative bacteria (*Bacillus megaterium*, *Bacillus subtilis*, *Deinococcus radiodurans* and *E. coli*), are most likely not able to exchange cargo via these tubular membranous structures and that nanotubes are rather formed as a stress response of dying bacterial cells. The transfer of non-conjugative plasmids was therefore suggested to be mediated only via transformation of naturally competent cells [117•].

Computational and mathematical methods are increasingly used to track HGT in the microbiota community. Historical methods based on the composition of the gene (genomic signature) enable to identify the transferred genes by host unspecific characteristics like GC content and codon usage [118,119]. Other tools, used to identify inter-bacterial transferred genes, are phylogenetic methods, which detect incongruence between the species tree of recipients and donors of genes [120]. Kleiner *et al.* have developed 'transductomics', a method based on DNA sequencing, which allows to track the ongoing transduction events in microbiota communities [121•], based on the comparison between sequencing data of virus-like particles and that of whole microbial communities.

HGT contributes to spread of antibiotic resistances within microbial communities, such as the gut microbiota, thereby leading to emergence of multi-resistant pathogens. It also contributes to inter-commensal transfer of virulence genes [122]. A deeper understanding of these processes may allow to interfere with or manipulate the transfer of these genes, thereby impacting microbiota community structure [123,124]. The inheritance of mobile genetic elements, often involved in inter-microbial communications, can be maintained by toxin-antitoxin genes to guarantee its persistence during host division. Within a defined toxin-antitoxin operon, expression of these two genes is closely linked to each other, which allows cells to survive the presence of the stable toxin due to permanent expression of its instable conjugate antitoxin. Upon passing of the toxin and antitoxin to the plasma of the dividing daughter cell, the antitoxin degrades quicker than its toxin, resulting in cessation of toxin neutralization and damage inflicted on the daughter cell, unless a plasmid encoding for new antitoxin expression is present [125].

In the gastrointestinal tract, HGT can lead to the introduction of novel genes into microbiota commensals through dietary exposure. Seaweed, for example, is a common dietary component in Japan and carries specific bacteria (which may be regarded as the 'seaweed microbiota') that express the carbohydrate-active enzymes porphyranases and agarases. Interestingly, these carbohydrate-active enzymes were detected more frequently in the metagenomes of Japanese people, while being absent in metagenomes of North American individuals, indicating a likely inter-community HGT of these genes from ingested seaweed-related microbes into the indigenous microbiota of individuals consuming a seaweed-based diet [126].

While HGT is commonly believed to induce genomic enrichment, by providing a source of genes from other bacteria, it may also support the loss of genes in some contexts. For example, the obligate bacterial strain *Burkholderia gladioli* (Lv-StB), which is part of the microbial community of the beetle *Lagria villosa*, produces the defensive molecule lagriamide targeting pathogenic fungi and bacteria. The ability to produce lagriamide was gained by horizontal acquisition of the putative lagriamide lga biosynthetic gene cluster. Interestingly, this gain of gene cluster and its associated essential and unique defensive functions has likely allowed the bacterium to reduce the size of the rest of its genome as it is provided by essential nutrients from other members of the microbiota community [127••].

HGT within microbiome communities can help bacteria to adapt to varying environmental stimuli [128]. These mechanisms are of major importance in context of antibiotic resistance gene spread, [129] which is even enhanced by the formation of biofilms [130]. In addition, when comparing microbiome communities in natural

biofilms of the macroalgae *Ecklonia radiata* to microbial communities in the surrounding sea water, HGT was shown to drive the gain of considerably beneficial metabolic abilities within the biofilm, indicating the advantage of bacterial communities and their ability to utilize HGT to adapt to the environmental challenges [131]. Moreover, the genetic characteristics of *Bacteroidales* strains of the human gut have been shown to be constantly changed via HGT, potentially improving their fitness, allowing them to individually adapt to the specific environment of their host [132].

Impact of commensal communication networks on the host

The above complex commensal microbiota interactions are increasingly suggested to influence host fitness [9,133,134]. For example, Gould *et al.* varied the composition of the microbiota in *Drosophila melanogaster* by creating different combinations of defined microbial communities [135••]. Five common bacterial strains of laboratory flies were combined in all possible variations (in total 32 combinations) and their impact on host fitness was assessed. Interestingly, the lifespan and fecundity of flies were heavily dependent on the microbial network structure and not only on the abundance of single species or the collective presence of a microbiota. Expectedly, an increasingly diverse and complex microbiota configuration was accompanied by enhanced competition between the different commensal species. Importantly, inter-bacterial interactions were suggested to adversely impact the host through induction of nutrient deprivation, while microbiota-depleting antibiotic treatment increased the lifespans of flies. However, it is important to note that a reduced fly lifespan is not necessarily indicative of a reduced fitness [136], and that microbiota-mediated reduced lifespan was accompanied with higher fertility, suggesting that microbial interactions may interchangeably impact a variety of host functions.

Quorum sensing of pathogens can increase their virulence for example, by optimizing the release of virulence factors and coordinate themselves into biofilms in accordance to their population size, thereby enhancing their success in establishing infection in the host [39,137–139]. The opportunistic pathogen *P. aeruginosa* organizes in biofilms to promote its virulence and is a major cause of infections in cystic fibrosis (CF) [140]. Inhibition or prevention of QS increases the clearance of the pathogen in mice and rats [141,142]. Interestingly, biofilms, which grew on plastic beads in a synthetic CF sputum media, evolved a reduction in quorum sensing after 10 days of growth, mediated by loss-of-function mutations in the lasR gene [143,144], which confers higher resistance to β-lactam antibiotics [143,145]. Some inter-bacterial interactions induce a competitive advantage by exploiting the host, as exemplified by the multi-host pathogen *Erwinia carotovora,* which uses *D. melanogaster* as a vector to quickly expand and efficiently infect plants, its final hosts. Quorum sensing was found to constitute an essential mechanism, by which *E. carotovora* occupies the niche in its intermediate fly host, by optimally regulating the release of its virulence factors [146••].

Commensal metabolism and metabolite secretion can also impact the virulence of pathogens, thereby protecting or harming the host [147]. For example, the human commensal *Bacteroides thetaiotaomicron* promotes the infection of *Salmonella typhimurium* and *C. difficile* through liberation of sialic acid [148]. Similarly, *B. thetaiotaomicron* provides succinate, which is sensed by the pathogen, *Enterohemorrhagic E. coli* (EHEC), leading to increased expression of the enzyme mucinase, contributing to the virulence of EHEC [149]. Similarly, *C. difficile* converts microbiota-produced succinate to butyrate, which enhances its expansion [150]. In contrast, the gut microbiota can prevent pathogen colonization through a variety of metabolic activities. For example, the gut commensal *Clostridium* scindens, which synthesizes secondary bile acids from host-derived bile acids, including deoxycholate and lithocholate, resists colonization of *C. difficile* in a secondary bile acid-dependent manner [7]. Similarly, mice can be primed by a prior infection with *Yersinia pseudotuberculosis* to release taurine, a constitute of bile, in response to a new infection with *K. pneumoniae*. Deltaproteobacteria, commensals of the microbiota, convert taurine to sulfide to mediate colonization resistance, whereby sulfide inhibits the pathogen's respiration [151••].

The host can benefit from commensal exclusion of invading pathogens by colonization resistance [152]. Antibiotic treatment depletes the protective microbiota and thereby disrupts this endogenous resistance against invading pathogens [153,154]. However, in mice, colonization of antibiotics-treated mice with *Klebsiella michiganensis* is able to exclude invading *E. coli* by competition for nutrients. Similarly, *K. michiganensis* prolongs survival of mice after infection with *S. typhimurium* by inhibiting the expansion of the pathogen [155•].

Challenges and prospects in studying inter-bacterial communication networks

Mechanistically studying inter-bacterial interactions in mammalian microbiotas remains a daunting task due to the high complexity and biodiversity of these communication networks. Moreover, current *in vivo* models (such as laboratory mice) do not fully reflect the real-life scope of commensal interactions, given variabilities in murine genetic backgrounds, inter-vivarium microbiota and dietary differences, and technical variability stemming from differences in experimental protocols. One elegant recently suggested solution to this challenge involves 'wildling mice', laboratory mice harboring a real-life wild

mouse microbiota, which have been recently demonstrated to better proxy human phenotypes [156].

In vitro-based coculturing experiments are similarly challenging, given variations in growth conditions and microbial behavior as compared to the *in vivo* setting. In addition, such systems inherently disregard the host's impact on the dynamicity and nature of inter-bacterial interactions [157]. Nevertheless, the improvement of advanced culture techniques increasingly allows for cultivation of hundreds of previously 'non-culturable' gut commensals, providing new possibilities to mechanistically examine inter-bacterial interactions in the highly controlled *in vitro* setting [158]. Additionally, the use of synthetic *in vitro* environments, which range from batch cultures, organoids, to continuous cultures combined with host epithelial cells (also termed gut on a chip or HuMix) constitutes a promising method potentially enabling a more physiological elucidation of commensal inter-bacterial interplay.

Determining causality of inter-bacterial interaction networks in impacting community structure and the host remains a major challenge in microbiota research. As such, differentiating between primary 'driver' impacts to secondary 'passenger' impacts that stem from, rather than cause, community structure variations, remains a formidable task. Genetic microbial manipulation, involving ablation of key components of the microbial interactome, constitutes a critical modality in obtaining such mechanistic and reproducible insight, but is complicated by multiple genomic and microbiological challenges, such as restricted competence of many bacterial cells and difficulties in culturing of many commensal microbes. One step towards meeting this challenge was recently introduced by Mimmee *et al.*, who utilized CRISPR-Cas technologies to manipulate a single abundant gut commensal strain, *B. thetaiotaomicron*, in generating defined perturbations impacting gut microbiota metabolic circuitry, thereby allowing a detailed assessment of their impacts on community structure and downstream host responses [159]. Another tool, named metagenomic alteration of gut microbiota by *in situ* conjugation (MAGIC), enables manipulation of whole microbial communities using bacterial conjugation that leads to defined commensal-restricted protein expression [160•]. Further expansion of the toolbox enabling to study defined checkpoints orchestrating inter-microbial communication may help to extend the possibilities of reaching mechanistic understanding of these important interactomes.

Developing interventions targeting key hubs of inter-microbial interactomes constitute another exciting challenge (as exemplified in Figure 3). For example, the alarming spread of antibiotic resistance through HGT risks in generating microbiota antibiotics-resistant reservoirs. One potential future solution to this threat may involve bacterial competition through commensal generation of anti-microbial molecules. Identification of such anti-microbials through computational identification of gene clusters may enable the characterization of new bioactive anti-microbial molecules [161–163]. Utilization of this approach enabled the recent identification of the novel antibiotic corbomycin featuring a distinct mechanism of action [164•]. Furthermore, the application of synthetic bacteriocins to precisely target selected bacterial species or genera instead or as complementation of broad-spectrum antibiotics, could help to overcome the development of resistances [165]. Hereby, 'precision probiotics' could be used as bacterial chassis to directly secrete the bacteriocins in the gut.

A different anti-microbial approach involving inter-microbial community interactions consists of predatory bacteria. *B. bacteriovorus* and *Micavibrio aeruginosavorus* are obligate predators of Gram-negative bacteria that may be utilizable, in some contexts, as an alternative for antibiotics in treating multi-resistant pathogen infection [166–168]. Likewise, bacterial predators can prevent the overpopulation of one dominating bacterial species in the microbiota, thereby restoring the diversity of the indigenous community [169]. However, some studies raise concerns as to safety of use of these predators, as their impacts on microbiota composition may be more complex and less predictable than originally contemplated. Likewise, the use enzymes such as specific proteases to break biofilm structures, may enable releasing bacteria while rendering them susceptible to antibiotics [170]. In addition, supplementation of quorum sensing and/or quorum quenching molecules could help to disrupt bacteria–bacteria communications while reducing their virulence or toxicity [171]. Collectively, these experimental treatment modalities constitute exciting avenues of research in coming years.

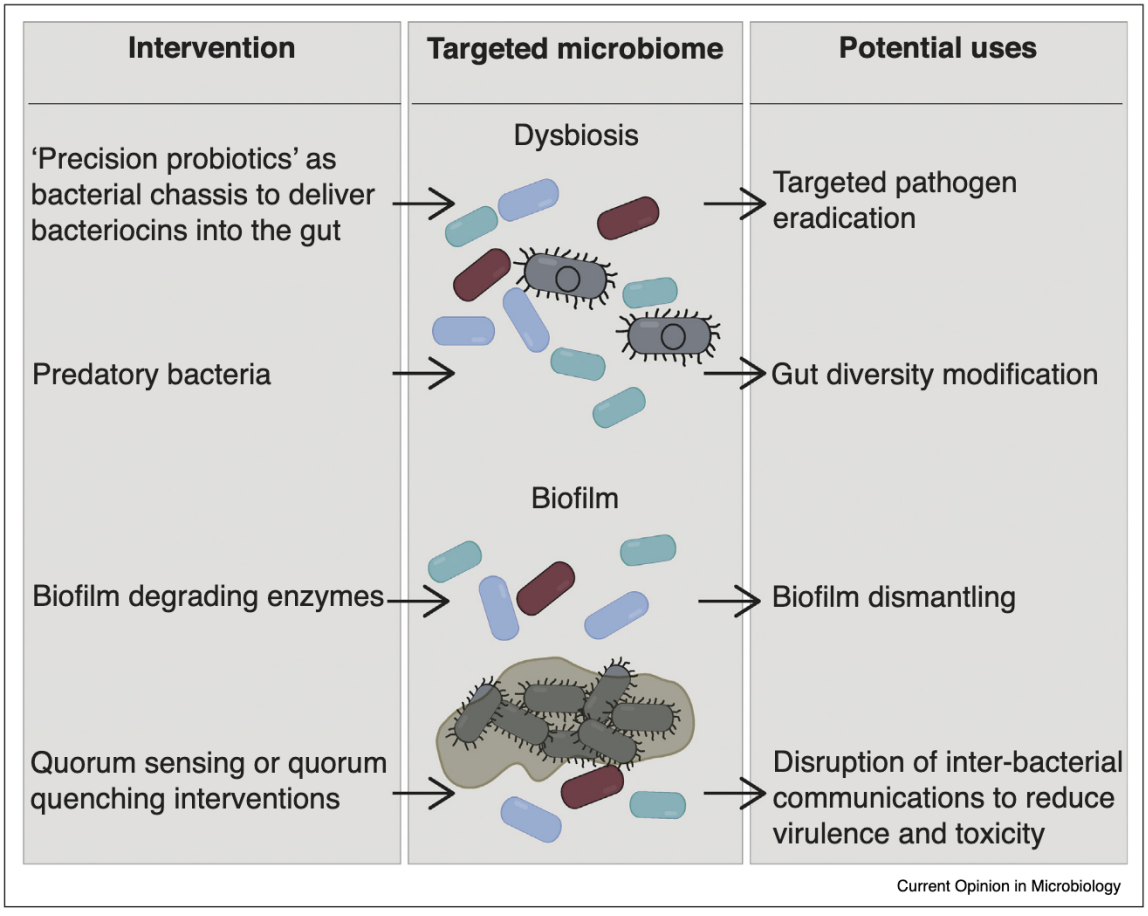
Concluding remarks

The gut microbiota constitutes a new *in vivo* frontier in the study of inter-microbial interactions and their potential impacts on commensal community structure in health and disease. Mechanistically investigating the molecular basis of such interactions may enable to identify intervention checkpoints for rational manipulation of the microbiota. Nevertheless, reaching such milestone is far from trivial, and must involve a deeper understanding of the diversity of inter-bacterial and host–bacterial interactions and their impacts on disease pathogenesis.

Author contribution

All authors performed an extensive literature research, contributed substantially to discussion of the content, wrote and edited the manuscript.

Figure 3



Interference with bacterial communications as putative future interventions.
Invading pathogens or resident pathobionts can harm the host. Modified bacteria could be used to introduce bacteriocins into the microbiota, to specifically target pathogens while replacing or complementing the use of broad-spectrum antibiotics. Predatory bacteria can feed on overpopulating commensals to restore species diversity and eliminate pathogens and pathobionts. Biofilms can promote the virulence and persistence of pathogens and consequently the spread of infection. Biofilm matrix degrading enzymes, like proteases, can disassemble biofilms, thereby releasing bacteria to make them susceptible to antibiotic treatment. Quorum sensing can promote the virulence of some pathogens by promoting the formation of biofilms or expression of virulence genes. Disrupting this communicative pathway by quorum sensing interference or quenching such as by administration of synthetic autoinducers, may repress the virulence of some pathogens, while preventing the formation of pathogen-protective biofilms.

Conflict of interest statement

EE is the scientific co-founder of DayTwo and BiomX, in topics unrelated to this work.

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