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Review

Intestinal colonization resistance in the context of environmental, host, and microbial determinants

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SUMMARY

Microbial communities that colonize the human gastrointestinal (GI) tract defend against pathogens through a mechanism known as colonization resistance (CR). Advances in technologies such as next-generation sequencing, gnotobiotic mouse models, and bacterial cultivation have enhanced our understanding of the underlying mechanisms and the intricate microbial interactions involved in CR. Rather than being attributed to specific microbial clades, CR is now understood to arise from a dynamic interplay between microbes and the host and is shaped by metabolic, immune, and environmental factors. This evolving perspective underscores the significance of contextual factors, encompassing microbiome composition and host conditions, in determining CR. This review highlights recent research that has shifted its focus toward elucidating how these factors interact to either promote or impede enteric infections. It further discusses future research directions to unravel the complex relationship between host, microbiota, and environmental determinants in safeguarding against GI infections to promote human health.

INTRODUCTION

The gastrointestinal (GI) tract is the largest mucosal surface in the human body and is densely inhabited by microbial communities. It has long been recognized that a fundamental role of these resident microbiota is to protect their hosts against the colonization of bacterial pathogens targeting the gut.[1] This pivotal function, known as colonization resistance (CR), is universally conserved across the various kingdoms of life, extending from lower animals to humans. CR has been substantiated for a diverse array of human pathogens, including food- and water-borne ones such as *Salmonella enterica*,[2] enteropathogenic *Escherichia coli* (*E. coli*), *Shigella* spp., *Campylobacter* spp., *Vibrio cholerae* (*V. cholerae*), and *Listeria* spp.[3–8] Additionally, it extends to GI pathogens transmitted by other means, such as *Helicobacter* spp. and *Clostridiodes difficile* (*C. difficile*), as well as various antibiotic-resistant opportunistic pathogens, which may invade the gut and cause infections in immunocompromised hosts.[7,9] For all of these pathogens, severe disruption of the intestinal microbiota—whether through antibiotic use, reduction in diversity, or its complete absence, as seen in germ-free animals—fosters the growth of these gut pathogens. Furthermore, variations in microbial community composition, as observed in otherwise healthy hosts, lead to differing levels of CR against infections (Figure 1A).[10–13] This indicates that the microbiome could serve as a metric for CR, offering insights into an individual's susceptibility to infections. However, we are currently unable to make definitive statements or predictions on CR based on specific markers in microbial community composition. This is because CR is not solely dictated by the presence or absence of particular members of the microbiota but is rather shaped by intricate interactions among microbes and their host within the specific environment of the GI tract.

Over the past decade, research on the mechanisms of CR has significantly benefited from the proliferation of models and technologies in the microbiome research field. Next-generation sequencing technologies enabled microbial community profiling in large cohorts and contributed to the identification of candidate taxa for CR.[14–16] Major progress has been made by the development of gnotobiotic animal models[17,18] and bacterial cultivation, as well as protocols for human and animal fecal microbiota transplantation (FMT) to verify causally related microbes. Bacterial culture collections,[19] RNA sequencing, transposon-library screens,[20] as well as targeted and untargeted metabolomics analyses have played a crucial role to pinpoint mechanisms of protection.[21]

Overall, this recent work has changed our fundamental view on the nature and underlying mechanisms of CR. The once simplistic notion, which posited that universally protective microbial clades exist to provide CR through the stimulation of immune defenses, direct competition, or antagonism against pathogens, is giving way to a community-centered concept. In this evolving paradigm, CR emerges as a result of intricate microbial interaction networks that dynamically engage with the host and undergo functional changes in response to the metabolic, immune, and physicochemical environment. In the field of ecology, context dependence refers to "variation in the sign or magnitude of an ecological relationship depending on the conditions under which the relationship occurs or is observed; it is also known as 'contingency.'"[22] Bacteria exhibit a remarkable capacity to adapt their metabolism and behavior in response to environmental signals, a crucial attribute for survival in the dynamic environment of the mammalian gut ecosystem. The settings in which

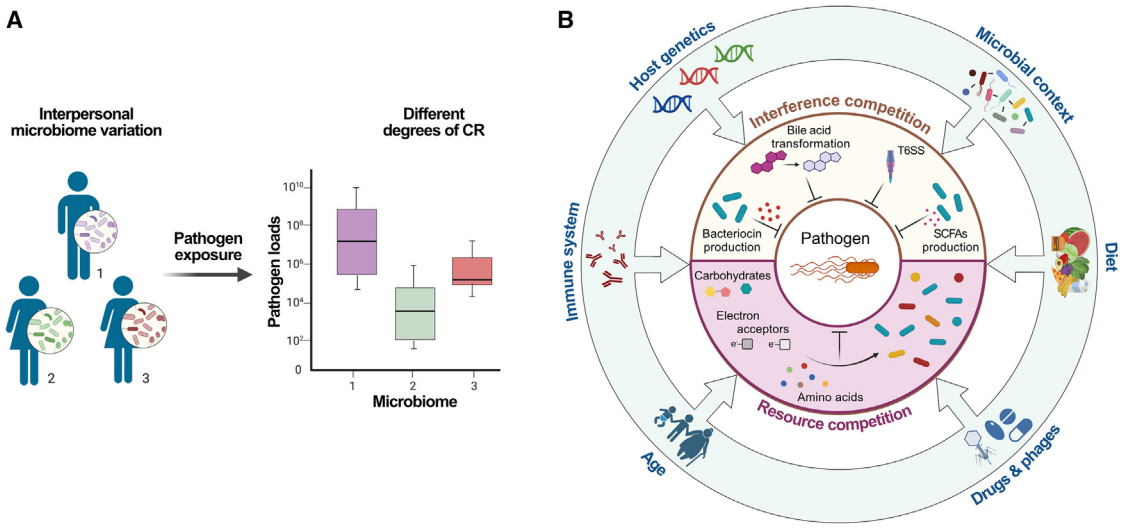

Figure 1. Contextual factors drive interindividual differences in colonization resistance by shaping microbiota-pathogen interactions

(A) The composition and ecology of the microbiota can vary significantly among individuals, leading to varying levels of colonization resistance (CR) against enteric pathogens upon exposure.

(B) Microbial mechanisms of CR can be grouped into two categories: resource competition and interference competition (inner circle). Interference competition includes the production of bacteriocins, T6SSs, bile acid species, and short-chain fatty acids. Resource competition refers to the depletion of carbohydrates, amino acids, and electron acceptors by commensal bacteria, which limits nutrient access to invading pathogens, ultimately preventing their colonization. Contextual factors, such as the overall microbial community composition, dietary habits, medication usage, and various host-related determinants such as developmental stage, immune function, and genetic background, can profoundly influence microbial CR mechanisms.

a particular phenomenon or behavior manifests depend on contextual factors. These include the overall composition of the microbial community, dietary habits, drug use, the metabolic and nutritional environment of the gut, and various host-related determinants, including genetic, developmental, physiological, and immune factors. This complexity presents a significant challenge in understanding bacterial phenotypes, their roles in microbial networks, and their relationships with hosts. Acknowledging and addressing the sources of context dependency for a specific microbial phenomenon is essential for advancing its mechanistic comprehension, predictive capabilities, and generalizability in microbiome research.

This review focuses on discussing the role of context in CR within the microbial, metabolic, and host-imposed environments (Figure 1B). Specifically, we focus on the initial stages of pathogen infection rather than later stages when inflammatory responses modify the environment and the delicate balance between pathogens and the microbiota.[23] We provide a comprehensive overview of the current knowledge regarding how microbial communities, their individual components, and interactions among them establish conditions that exclude pathogens from the GI tract. Additionally, we offer insights into potential avenues for future research directions and experimental approaches to be taken to unravel the interrelationship of the plethora of contributing determinants that act on host and microbiota to generate an environment permissive or resistant to GI pathogen infection.

MICROBIAL MECHANISMS OF CR

In most cases, only low quantities of ingested pathogens make their way into the gut, requiring them to proliferate significantly to cause an infection. The microbiota can directly interfere with the growth of incoming pathogens in two fundamental ways (Figure 1B): resource competition and interference competition. Pathogens primarily rely on resources such as carbohydrates and amino acids for growth. However, adequate quantities of iron, trace elements, and electron acceptors must also be available for their proliferation. Certainly, nutrient preferences vary among different pathogens owing to metabolic differences. Depending on the type of pathogen and potential resistance mechanisms, antimicrobials produced by members of the microbiota, ranging from narrow- to broad-spectrum, can further restrict growth or even lead to pathogen killing. These antimicrobials encompass bacteriocins and type VI secretion systems (T6SS), capable of inducing killing either independently of or depending on contact. Additionally, microbial metabolites such as short-chain fatty acids (SCFAs) or bile acids, originating from the host but modified by the microbiota, play a role in this process. The most specific way the microbiota blocks the infection is by interfering with the expression and function of the pathogen's virulence factors. Below, we will give a detailed overview of the latest discoveries in this field.

Resource competition

Over 4 decades ago, Rolf Freter introduced the nutrient niche concept, suggesting that the composition of gut bacterial communities is primarily influenced by the availability of key limiting nutrients. According to this concept, an invasive species can successfully colonize the gut only if it can more efficiently consume at least one limiting nutrient compared with the rest of the community.[24]

Commensal species have developed specializations in utilizing distinct resources, including carbohydrates, amino acids,

vitamins, and minerals.[25] Yet, they can adapt their nutrient spectrum in more diverse communities to allow for co-existence,[26] thereby collectively depleting all available nutrients. *Citrobacter rodentium* (*C. rodentium*), a mouse intestinal pathogen serving as a model for human enteropathogenic *E. coli*, for example, utilizes amino acids available in the gut of germ-free mice but switches to amino acid biosynthesis pathways in the presence of a complex microbiota. This illustrates that the microbiota competes for amino acids with the pathogen and the pathogen can adjust its metabolism in a microbiota-dependent manner.[27] Recent studies have provided strong support for the critical role of competitive exclusion of pathogens by commensals that share nutrient niches with the pathogen.[28–30] Eberl et al. demonstrated that *E. coli* enhances CR against its close relative *Salmonella enterica* serovar Typhimurium (*S*. Tm) by vying for a limiting carbon source galactitol.[31] This principle extends beyond enteric pathogens as potentially harmful commensals, such as multidrug-resistant *Enterobacteriaceae*, in general, follow a similar pattern. Osbelt and colleagues revealed that *Klebsiella oxytoca* (*K. oxytoca*), with a broader carbon utilization spectrum, overlaps with all carbon sources utilized by *Klebsiella pneumoniae* (*K. pneumoniae*), thereby thwarting its invasion.[32] Intriguingly, both studies highlighted that the microbial context, specifically the overall microbiota composition, governs the ability of these individual bacteria to confer CR (see below).

The degree of CR a diverse community can provide can be predicted by the "carbohydrate blocking principle:" the greater the overlap of nutrient sources with the pathogen, the more protective the community.[33] Communities harboring highly competitive species for carbohydrate utilization inhibit the colonization of invasive species by maximizing niche overlap with the invading bacteria.[34] Essentially, this collective work provides a mechanistic basis for the correlation of community diversity with host health in general and, in particular, with resistance to enteric pathogens.[10,35]

Exclusive nutrients that can only be used by pathogens, but not the microbiota, can promote infection by establishing a unique nutrient niche. This phenomenon is exemplified by the sugar alcohol galactitol, which enhances the growth of *K. pneumoniae* and *S*. Tm.[30,33] Another sugar alcohol, sorbitol, supports the growth and toxin production of *C. difficile*.[36] Of note, the commonly used food additive trehalose was implicated in facilitating the spread of hypervirulent *C. difficile* strains. Trehalose can serve as an exclusive nutrient and enables *C. difficile* to outcompete certain resident commensals by fostering its proliferation.[37] This points to the important contextual role of diet on CR (section dietary impact on CR: feeding the microbiome, the host, or the pathogen?).

Besides carbohydrates and amino acids, enteric pathogens compete for minerals (e.g., iron and zinc), vitamins, and electron acceptors with the microbiota. Although competition for iron and zinc is a major factor in colonizing the inflamed gut, it seems to play a rather minor role in the initial growth of pathogens in the homeostatic intestine.[38,39] Vitamins are synthesized by the microbiota, are shared between different commensals, and may even foster pathogen colonization.[40] The contribution of commensal vitamin competition to CR remains unclear and warrants further investigation.[41,42] Growth of facultative anaerobic enteric pathogens, including *S*. Tm and *E. coli*, is promoted in the presence of oxygen or the alternative electron acceptors nitrate, tetrathionate, and fumarate, which enable anaerobic respiration.[43] Thus, depletion of oxygen or competition for these electron acceptors enhances CR.[11,17,44] The recent discovery of a range of compounds that serve as alternative electron acceptors for commensal bacteria necessitates further exploration into their involvement in the competition between microbiota and pathogens.[45]

Interference competition

Production of antimicrobial weapons

Many commensal bacteria release small molecules with various biological activities, ranging from modulation of the immune system to inhibition of other bacteria.[46] Bacteriocins are the most researched and documented group of natural products generated by the microbiota.[47] They have an important role in shaping the gut community as bacteria can use them to target competitors occupying a similar niche or even different phyla within a distinct niche.[48,49] Bacteriocins also target and specifically eliminate intestinal pathogens without causing disturbance of the overall community composition. For example, *Blautia producta* produces a lantibiotic capable of reducing colonization by vancomycin-resistant *Enterococcus faecium* (*E. faecium*), which displays reduced activity against other commensal bacteria.[50] *Limosilactobacillus reuteri* (*L. reuteri*) releases a broad-spectrum antimicrobial substance, termed 3-hydroxypropionaldehyde, which is commonly known as reuterin. Reuterin inhibits vegetative *C. difficile* by inducing oxidative stress and membrane damage, ultimately leading to death.[51] Interestingly, *Enterococcus* spp. frequently carry a plasmid-encoded defense system that detoxifies reuterin and mediates a beneficial cross-feeding interaction between *L. reuteri* and *Enterococcus*.[52] On the other hand, enteropathogens produce bacteriocins that help to invade a preformed community.[53] Intriguingly, *Listeria monocytogenes* produces a bacteriocin that kills commensal *Prevotella spp.*, which otherwise exacerbates infection.[54]

Of note, some bacterial cytotoxins that target eukaryotic host cells can also cause DNA damage in bacteria: tilimycin produced by *K. oxytoca* acts as mutagen and increases mutations in opportunistic pathogens such as *K. pneumoniae* and *E. coli*.[55] In the same way, colibactin, a genotoxin produced by gut bacteria that encode a nonribosomal peptide, synthetase-polyketide synthase, induces DNA damage in enterohaemorrhagic *E. coli* (EHEC). The consecutive SOS response triggers Shiga-toxin production.[56]

Expression of antimicrobial compounds is generally very tightly regulated. Some bacteriocins are only produced in a bacterial subpopulation as their release is often accompanied by bacterial lysis.[57] Environmental cues that activate expression include nutrient limitation, cellular damage, and stress. Therefore, the environmental context plays a major role in bacteriocin-mediated competition. For example, bacteriocin-dependent competition of *E. coli* strains and *S. Tm* only takes place in the inflamed gut, where iron limitation and oxygen radicals stimulate colicin and microcin expression.[53,58]

Besides releasing antimicrobial compounds, bacteria can also kill in a contact-dependent manner by means of T6SSs. On the one side, pathogens including *S*. Tm and *V. cholerae* were shown to employ T6SS to facilitate infection.[59,60] On the other

side, commensals can use them to fight off enteric pathogens. Recent research revealed that *C. rodentium* utilizes a T6SS to colonize the gut by targeting commensal *Enterobacteriaceae*; yet concurrently, resident *E. coli* species employ T6SSs to counteract *C. rodentium* invasion.[61]

Production of inhibitory metabolites

Commensal bacteria also modify the local physicochemical environment of the gut by releasing metabolites, which mitigate the growth of pathogens. Specific commensal bacteria generate SCFAs, such as butyric acid, propionic acid, and acetic acid. These metabolites are products of microbial anaerobic fermentation in the gut, play a crucial role in determining gut pH, and inhibit the growth of certain microbe populations in the intestine.[62–64] Sorbara and colleagues showed that the generation of an acidic gut environment by the cecal and colonic microbiota, combined with increased production of SCFAs, were pivotal conditions for CR.[65] Nevertheless, the overall mechanisms of SCFA-mediated CR remain complex, as specifically excluding these metabolites without disrupting the native microbiota remains challenging.

Another class of metabolites relevant for CR are host-derived bile acids. Primary bile acids are synthesized in the liver and conjugated with glycine or taurine before they reach the proximal part of the small intestine via the biliary system. The microbiota deconjugate these conjugated bile acids in the intestinal tract, producing glycine, taurine, and deconjugated primary bile acids, which can subsequently be modified by certain commensal bacteria to generate secondary bile acids.[66] In humans, specific members of the microbiota were shown to influence the gut's chemical environment via bile salt hydrolase (BSH) enzyme activity. A specific BSH diminishes the colonization of *V. cholerae* by breaking down taurocholic acid, a conjugated primary bile acid that triggers the expression of virulence genes, into taurine and cholic acid.[12] Secondary bile-acid-producing commensals are also well known to mediate CR against *C. difficile*.[15] Although primary bile acids have been described to induce *C. difficile* spore germination, secondary bile acids inhibit *C. difficile* germination, growth, and toxin production.[67] An emerging topic in this area of research is the physiological role of microbially conjugated bile acids (MCBAs: deconjugated bile acids that become reconjugated by enzymatic activity of commensal bacteria).[68] MCBAs distinctly affect *C. difficile* growth and germination.[69] Of note, bile acid release into the GI tract after consumption of a high-fat diet can lead to transient disruption of the microbiota and alleviate CR against *S*. Tm.[70] Thus, the production of bile acids is controlled by complex regulatory pathways involving diet, metabolism, and liver functions. These factors collectively determine both the quantity and composition of bile acid pools, as well as the timing of their release into the gut, thereby affecting CR.

Interference with virulence factor expression

Besides influencing the growth or viability of pathogens, microorganisms can directly or indirectly interfere with the production of pathogen virulence factors, consequently diminishing their capacity to induce disease. For instance, toxin expression is tightly regulated and activated in response to environmental signals. *C. difficile* produces two toxins, TdcA and TdcB, which mediate cellular damage and disease. Expression of both toxins is globally controlled by carbohydrate and amino acid spectra.[40,71] Specifically, depletion of arginine by enterococci provides a metabolic cue for *C. difficile* to enhance toxin expression.[71] Arginine sensing is also involved in inducing expression of *C. rodentium* and EHEC locus of enterocyte effacement (LEE) pathogenicity islands, which encode a type III secretion system (T3SS).[72] Moreover, the T3SS is also controlled by the concentration of indole, a heterocyclic amine produced by the microbiota.[73] Expression of the *S*. Tm invasion genes was found to be downregulated in the presence of *Mucispirillum schaedleri* (*M. schaedleri*), a nitrate-respiring commensal bacterium, which inhabits the intestinal mucus layer. In the anaerobic milieu, nitrate serves as a trigger for *S*. Tm to induce the expression of virulence genes. Nitrate depletion by *M. schaedleri* presumably counteracts this mechanism and prevents *S*. Tm-mediated inflammation.[74] Bile acid species also influence virulence factor expression of a variety of pathogens including *S*. Tm,[75] *C. difficile*,[69] and *V. cholerae*. For example, via the depletion of taurocholic acid in the murine small intestine, *Blautia obeum* can reduce expression of the virulence factor gene *tcpA* in *V. cholerae*.[12] Quorum sensing, a chemical communication process that operates within and between different bacterial populations, as well as with the mammalian host, also plays an important role in regulating the timing and extent of virulence factor expression. New advances in this field have been recently summarized.[76]

VARIOUS CONTEXTUAL FACTORS SHAPE THE MECHANISMS UNDERLYING CR

Microbial context

As mentioned earlier, contextual factors significantly impact microbial mechanisms related to resource and interference competition, consequently influencing the extent of CR. Among those are the overall diversity and composition of intestinal microbial communities, which are collectively referred to as microbial context. A major contributor determining overall microbiota composition and functional potential is human lifestyle—in particular, as determined by the level of industrialization. This connection is closely tied to social factors, changes in diet, standards of living, improved overall health, and drug use.[77] The process of industrialization is notably associated with the loss of evolutionarily conserved core microbiota and a general decline in biodiversity. Intriguingly, these shifts, involving genera such as *Akkermansia*, *Bacteroides*, and *Alistipes*, coincide with functional changes related to oxidative carbohydrate degradation. This suggests a potential adaptation to the sugar-rich diets prevalent in European countries.[78] Notably, a recent study by Porras demonstrated that geographic differences in microbiota are linked to CR against *C. rodentium*.[13] However, this study did not identify any association with alpha diversity or functions related to carbohydrate degradation. Further investigation is required to ascertain the potential role of industrialization as a determinant of CR.

Recent studies identified correlations of numerous bacterial species within complex communities with CR, albeit with conflicting results reported in many cases. Frequently, CR cannot be attributed to a single organism. Rather, it results from the interactions of multiple members of the microbiota in a context-dependent manner.[79] In the upcoming sections, we will discuss

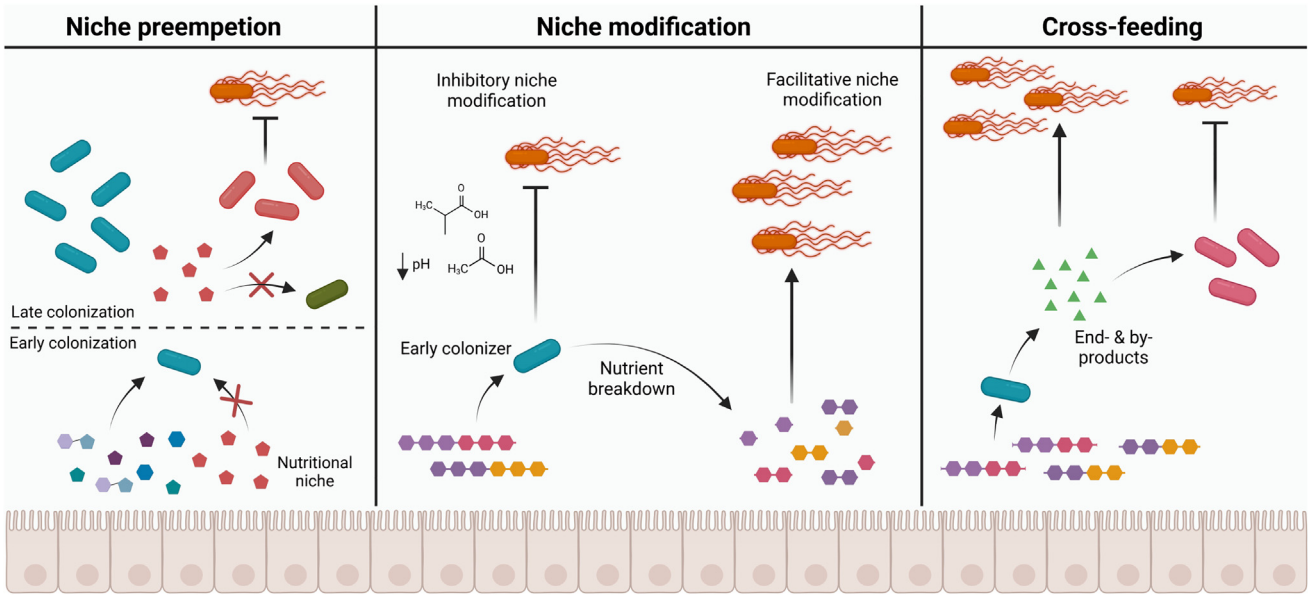

Figure 2. Microbial context dictates community structure and impacts pathogen susceptibility

The intestinal microbiome exhibits several ecological mechanisms underlying its ability to confer colonization resistance against pathogens. Left: niche pre-emption implies that early gut colonizers can selectively deplete nutrients and, therefore, limit nutritional niches available to late colonizers. Late colonizers utilize and deplete remaining nutrients, leaving no resources for invading pathogens. Middle: niche modification refers to a scenario in which early colonizers can alter the available niches, thereby either facilitating or impeding the invasion of pathogens. This may include the breakdown of complex carbohydrates into compounds that can be consumed by the pathogen or the generation of environmental conditions that are hostile to the invader, such as low pH. Right: the resident microbiota can additionally influence colonization resistance through cross-feeding of end- or by-products to other bacteria. This process may support the proliferation of protective commensals or serve as a nutrient source for pathogens.

potential mechanisms that may underlie the context-dependent nature of microbiota-mediated CR.

Priority effects influence the chance of bacterial invasion

Every additional member of a community has the potential to modify the environmental conditions that dictate whether a secondary species can successfully colonize or not. In the case of priority effects, the establishment of one species may either hinder or promote subsequent colonization by another.[80] These context-dependent feedbacks add an additional layer of complexity to microbial community assembly and may also pertain to the invasion of pathogens. Mechanisms of priority effects include niche pre-emption via nutrient depletion/competition, niche modification or facilitation through the cross-feeding of metabolites, or environmental modulation such as pH alteration (Figure 2).[81]

In an assembling microbial community, all available nutrient niches will be subsequently occupied, eventually leaving no nutrients for pathogens to consume and grow. Niche preemption occurs on a first-come, first-served basis: an early-arriving microbe depletes growth-limiting resources that inhibit the establishment of a late-arriving microbe with a similar niche. For example, in FMT, priority effects are deterministic for the successful engraftment of donor strains.[82] As a result, a stable microbiota already occupies most niches, and interactions between the resident and incoming species are predominantly inhibitory.[83] Two studies comparing the transcriptional pattern of *C. difficile* and *Salmonella* in mice with distinct microbiota composition revealed that the pathogens adapted their substrate range in response to different microbial environments.[31,71] Thus, priority effects can explain how an incoming pathogen's niche is shaped by the pre-existing microbial community.

In the case of niche modification, early colonizers can alter the available niches, thereby influencing which late-arriving species can successfully colonize the community. In such cases, priority effects may exhibit inhibitory or facilitative tendencies.[84,85] For instance, *Akkermansia*, *Bacteroides*, and *Parabacteroides* are recognized for their capacity to break down polysaccharides into more easily accessible carbohydrates, enriching the nutrient pool potentially used by pathogens.[86] By contrast, bifidobacteria and lactobacilli can strongly acidify the infant intestinal environment by producing high amounts of lactic and acetic acids and thereby exclude potential pathogens.[87]

Cross-feeding

In complex bacterial communities, the community structure and higher-level functions are determined by trophic interactions.[88] In these trophic networks, primary degraders ferment complex polysaccharides and release intermediate products (i.e., formate, lactate, succinate, acetate, and H_2), which can be converted by secondary fermenters to the end products acetate, propionate, and butyrate. Trophic interactions enhance the stability of synthetic bacterial consortia and can serve as a foundation for designing functional live biotherapeutics with potential applications in precision microbiome modulation.[89]

One specific type of cooperative metabolic interaction in these networks is cross-feeding, the exchange of metabolic end- or by-products between members of a bacterial community.[90] Among the experimentally confirmed examples is the exchange of vitamins, amino acids, and dicarboxylic acids.[91–93] Amino acids contribute to the energy reservoir as part of the

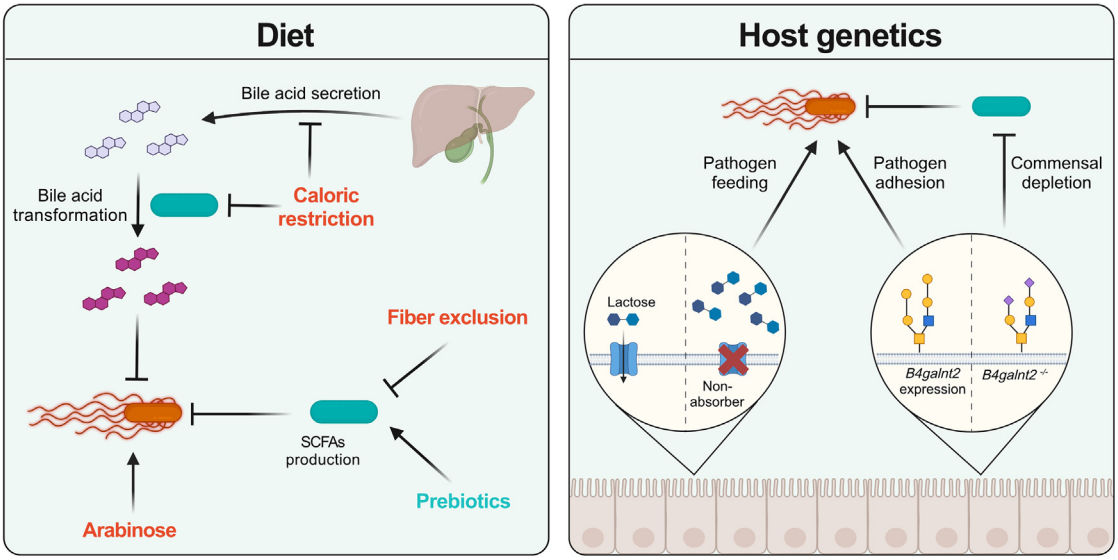

Figure 3. Environmental factors shape interference and resource competition between commensal and pathogenic gut bacteria

Left: dietary regimens control nutrient availability and bile acid pools. Inulin and other prebiotics increase the abundance of protective commensal bacteria, whereas fiber exclusion and arabinose may support pathogen blooming. Caloric restriction depletes secondary bile acids, which favors pathogen outgrowth. Right: host genetics may impact nutrient availability and pathogen physiology. Increased lactose availability in the intestine of lactose nonabsorbers can be exploited by *Enterococci* and fuel their growth. Variable expression or deficiency of blood-group-related glycosyltransferases alters the composition of glycan structures on intestinal epithelial cells. This may aid the adhesion of pathogens or deplete nutrients typically used by commensal bacteria.

central metabolism, function as a nitrogen source in transamination reactions, and serve as essential nutrients for amino acid auxotrophs. On the one hand, pathogens can benefit from microbial metabolites. For example, Stickland-fermentable amino acids, γ-glutamyl amino acids, polyamines, and ornithine provided by commensals increase *C. difficile* fitness during colonization.[40] Leucine and ornithine provided by enterococci, which also thrive in the gut of antibiotic-treated patients, additionally boost *C. difficile* growth in the gut.[71] On the other hand, cooperative interactions can also strengthen CR. Djukovic et al. described a CR mechanism against multi-drug-resistant *Enterobacteriaceae* that involves the cooperation between *Lactobacillus* spp. and Clostridiales. In this case, the *Lactobacillus*-powered expansion of Clostridiales results in a hostile environment for multi-drug-resistant *K. pneumoniae* by secretion of butyrate and depletion of nutrients such as serine, threonine, and glucose.[94] Other mechanisms beyond metabolite-based interactions have been reported and include xenosiderophore utilization between commensals and pathogens as a mechanism promoting resilience of the microbiota in response to inflammation.[95] Moreover, commensal *Paracoccus aminovorans* can facilitate multispecies biofilm formation, which enhances intestinal colonization of *V. cholerae*.[96] Collectively, these discoveries underscore the importance of investigating the individual behavior of and interactions between members of the intestinal ecosystem that shape the microbial context encountered by incoming pathogens.

Dietary impact on CR: Feeding the microbiome, the host, or the pathogen?

Diet significantly influences the nutritional landscape of the intestinal tract, and dietary interventions are a convenient approach to modify the gut microbiome toward improved human health (reviewed previously[97]). Numerous direct and indirect mechanisms involving the interplay of diet and CR against enteropathogens have been elucidated (reviewed previously[98]). Dietary compounds can disrupt the integrity of the resident gut microbiome and thereby alleviate CR. Besides, nutritional compounds that cannot be utilized by commensal bacteria or the host may be available as an exclusive nutrient source for enteric pathogens. Moreover, dietary compounds have the potential to alter the mucosal barrier, epithelial metabolism, and immune responses.

Dietary fibers, prebiotics, and mucosal barrier-derived glycans serve as nutrient sources for the microbiota

Bacterial degradation of dietary plant-derived carbohydrates relies on the presence of enzymes that can cleave oligosaccharide-specific glycosidic linkages. Utilization of such carbohydrates is exclusive to certain bacterial species containing the respective polysaccharide utilization loci. Some polysaccharides are also used as prebiotics, defined as food components that foster the growth of beneficial, health-promoting bacteria. Boosting the growth of such organisms can bolster CR against pathogens (Figure 3). Prominent examples are polysaccharides like inulin and pectin, as well as fructo- and gluco-oligosaccharides (FOS, GOS). Dietary inulin induces the outgrowth of *Parabacteroides*, *Lachnospiraceae*, and *Erysipelotrichaceae*, which protect against *C. difficile* infection by increasing the SCFAs acetate, butyrate, and propionate (Figure 3).[99] On the contrary, L-arabinose liberated from dietary plant fibers facilitates the outgrowth and persistence of *S.* Tm.[100] Excluding L-arabinose from the diet reduces *S.* Tm loads and persistence in mice. In mouse models, the application of FOS and GOS showed protective effects against *S.* Tm and *Listeria* spp. infections.[101,102] Another important prebiotic is lactulose, a monosaccharide that cannot be absorbed by the host, which is therefore easily accessible to the gut microbiota. In patients with chronic liver

disease, lactulose metabolization by bifidobacteria enhances the production of beneficial bacterial metabolites including SCFAs, and impairs the expansion of multi-drug-resistant *E. faecium* species.[103] Ultimately, these alterations prevent systemic infections and thereby reduce mortality in patients with chronic liver disease.

Mucus glycans contain glycosidic linkages that are distinct from plant carbohydrates and are inaccessible to many gut bacteria due to the presence of terminal sulfate groups. The lack of dietary fiber uptake promotes the proliferation of mucus-degrading bacteria, leading to reduced mucus thickness and increased susceptibility to *C. rodentium* infection.[104] Increased *C. rodentium*-induced inflammation in fiber-deprived mice is facilitated by the lack of barrier-promoting SCFAs, an impaired gut mucus barrier, and the reduction in protective bacterial taxa.[105] Nevertheless, the limitation of mucus-derived nutrients in fiber-deprived mice also leads to niche exclusion of the mucus-dwelling bacterium *M. schaedleri*, which has been implicated in interference with *S*. Tm virulence gene expression but also the development of Crohn's disease-like gut inflammation.[74,106,107] Collectively, these studies highlight that diet-driven gut environmental changes might have opposite effects on the susceptibility to and pathogenicity of different pathogens, underlining the importance of context dependency.

Dietary emulsifiers and non-nutritive sweeteners

Dietary emulsifiers are commonly used food additives that improve food consistency. A recent study found that carboxymethylcellulose (CMC) and polysorbate 80 (P80) can directly modify the density, composition, and gene expression of bacterial populations.[108] CMC- and P80-induced transcriptional changes enhance motility, adhesion, and virulence of adherent-invasive *E. coli*, which facilitates mucosal invasion and drives pathogen-induced inflammation in a gnotobiotic mouse model.[109] Similarly, microbiome-modulating effects were also observed for non-nutritive artificial sweeteners and are accompanied by alterations in diet-triggered glycemic responses.[110] Furthermore, artificial sweeteners can promote conjugative gene transfer between bacteria and facilitate the spread of antimicrobial resistance within the gut microbiome.[111,112] The dietary sweetener sucralose was additionally shown to dampen T cell-mediated immune responses to bacterial pathogens.[113] Overall, these studies provide intriguing insights on how food additives may modulate the susceptibility to enteric pathogens.

Caloric restriction and fasting

In humans, caloric restriction is generally associated with beneficial outcomes, such as weight loss and improved metabolic health. However, these phenotypes are partially driven by the reduction of overall bacterial abundance and can therefore affect resistance to pathogens. Caloric restriction can result in reduced bile acid production and enable the outgrowth of endogenous *C. difficile*.[114] Fasting is a common approach to restrict the daily intake of calories and is often intuitively applied upon onset of infection-mediated intestinal symptoms. Fasted mice display increased CR against enteric pathogens including *S*. Tm by interfering with virulence gene expression, which suppresses invasion of the epithelium and impedes subsequent inflammatory responses.[115]

Diet-immune system interactions

The dietary regime of an individual inevitably also shapes their immune response toward invading pathogens. Severe acute malnutrition weakens the immune system of children by reducing monocyte activation and secretion of proinflammatory cytokines upon exposure to the enteric bacterial pathogen *S*. Tm.[116] This may contribute to the high childhood mortality due to infectious diseases. On the contrary, it was shown that the restriction of caloric intake may also have beneficial effects to the immune system by modulating the gut microbiome to delay immunosenescence.[117] Furthermore, dietary undernutrition impairs the immunoglobulin A (IgA) response to commensal bacteria.[118] In undernourished mice, certain *Lactobacillus* species adapt to the nutrient-deprived intestinal tract, which disrupts the glycan-mediated binding of secretory IgA (sIgA) to glycan structures on the bacterial surface to prevent IgA coating. Although such studies exemplify how diet can interact with the immune system to shape the environmental context in the intestine, additional research is needed to grasp how the described interactions and resulting alterations in gut microbial ecology affect susceptibility to enteric pathogen colonization.

Host immune system

The gut microbiome is substantially shaped by the innate and adaptive branches of the mucosal immune system, which interact with bacteria at intestinal sites. Beneficial immune responses preserve intestinal balance by discerning commensal microbes while also safeguarding against disease-causing bacteria. The resident microbiota is involved in maintaining an anaerobic milieu in the gut, termed microbiota-nourishing immunity.[119] Proinflammatory mucosal immune responses can suppress commensal bacteria and create conditions in the gut that promote the proliferation of facultative anaerobic bacteria and enteric pathogens. Specifically, alterations in host cell-energy metabolism resulting from a decrease in SCFA-producing bacteria contribute to an elevated presence of oxygen. Additionally, heightened levels of nitrate and tetrathionate, coupled with nutrients generated in response to inflammation by both the host and the microbiota, foster the proliferation of facultative anaerobic pathogens. Conversely, there is a range of antimicrobial mechanisms, where pathogens exhibit enhanced resistance compared with the microbiota. These mechanisms involve iron and zinc availability constraints by the host-derived antimicrobial molecules lipocalin-2 and calprotectin, alongside the secretion of antimicrobial molecules such as bactericidal lectin RegIIIß. Comprehensive review articles on this topic have been published recently.[23,120]

The intestinal IgA response—To coat or not to coat

Many critical immune effector functions in the gut are mediated by the humoral branch of the adaptive immune system. Natural IgA is formed at low frequencies in naive B cell populations and is enriched via selection in Peyer's patches, independently of exposure to microbiota- or diet-derived antigens.[121] Importantly, natural IgA is polyreactive to a diverse set of gut bacteria but shows distinct binding patterns that favor the targeting of Proteobacteria while sparing most Bacteroidota and Bacillota. Additionally, antigen-specific sIgA is produced by microbiota-reactive B cells residing in the lamina propria, which differentiate

into antibody-producing plasma cells upon antigen sampling and presentation by M cells and dendritic cells, respectively. Secreted IgA directly interacts with bacteria at mucosal sites and can influence the ecology of commensals and pathogens by multifaceted mechanisms (reviewed previously[122]).

Coating of pathogenic bacteria by sIgA can mediate bacterial agglutination, which retains pathogenic bacteria in the gut lumen and prevents bacterial interactions with the mucosal tissue—a process referred to as immune exclusion.[123] This prevents the activation of the mucosal immune system by bacterial surface antigens and may restrict access of the pathogen to mucosa-derived nutrients, which leads to niche exclusion. IgA coating may also block the attachment of bacterial surface antigens to epithelial host receptors, ultimately facilitating pathogen clearance via peristalsis. Oral vaccination with inactivated *S*. Tm induces pathogen-reactive mucosal sIgA and restricts pathogen growth by enchaining daughter cells during bacterial cell division.[124] Interestingly, plasmid transfer between enchained bacterial cells is aggravated, highlighting another level of IgA-mediated modulation of bacterial ecology. Humans with IgA deficiency display reduced gut bacterial diversity and increased abundance of *E. coli* species with pathogenic traits.[125] However, the lack of pathogen IgA coating as a protective mechanism can be partially compensated for by pathogen coating with IgG and IgM antibodies, limiting infection-mediated complications in these patients.[126]

Besides direct interactions with enteric pathogens, the mucosal immune system shapes the intestinal microbial context by modifying the colonization ability of several commensal species (reviewed previously[122]). SIgA targets bacterial surface and nonsurface membrane antigens, including lipopolysaccharide, type 1 fimbriae, and outer membrane porins.[127] Since these structures play a pivotal role in bacterial physiology in the intestinal tract, IgA binding might impair the fitness of antigen-harboring bacterial populations and select for subpopulations with reduced expression of these antigens and potentially altered ecology. Because the targeted membrane antigens often serve as entry-receptors for bacteriophages, IgA-mediated transcriptional changes have immediate consequences for bacteriophage susceptibility of commensal bacteria.[127] Collectively, via the described mechanisms, IgA can modify the composition and ecology of the intestinal microbiome and thereby alter the susceptibility to enteric pathogens. Besides the intricate regulatory mechanisms provided by the enteric humoral immune system, the environmental context in the gut is further shaped by innate and cellular immune system components, such as antimicrobial peptides, toll-like receptors, and microbiota-reactive T cells (reviewed previously[128]).

The role of host genetics in shaping the intestinal environment

How the genetic background of an individual impacts the gut microbiome and susceptibility to pathogen colonization remains an understudied area of research. This is in part because of other environmental factors such as diet, drugs, and anthropometric measurements, which outweigh their effect on microbiome composition and associated phenotypes.[129] This may explain insufficient reproducibility of microbiome-associated genome-wide association studies.[130] Nevertheless, abundant evidence suggests that host genetics consistently influence the composition and ecology of the gut microbiome, with implications for susceptibility to pathogens.[131]

The apical surface of enterocytes is usually covered in oligosaccharide-containing antigens, which are accessible to the gut microbiota. These antigens are synthesized by glycosyltransferases and contain terminal glycan structures that differ depending on host genotype and glycosyltransferase expression patterns. Glycosylated surfaces can serve as potential nutrient sources or molecular attachment sites for commensal and pathogenic bacteria.[132] Thus, changes in glycosylation patterns can lead to the selection of microorganisms with the ability to attach to or to degrade these compounds.

In humans, the *AB0* blood group and fucosyltransferase 2 (*FUT2*) loci encode for glycosyltransferases, which determine the erythrocyte *AB0* antigens and their secretor status, respectively. Since their expression in enterocytes may also alter glycan availability in the intestine, certain variant alleles of these loci are linked to gut microbiome alterations and susceptibility to infectious disease.[133] Recently, the presence of a structural variant in the genome of the health-associated commensal *Faecalibacterium prausnitzii*, which enables N-acetylgalactosamine utilization was strongly associated with the *AB0* locus, highlighting the tight connection of the *AB0* locus with microbial ecology.[134] N-acetylgalactosaminyltransferase 2 (*B4galnt2*) is involved in blood group antigen synthesis in rodents and is variably expressed in the intestinal tract of wild mice. *B4galnt2* intestinal expression is associated with susceptibility to *S*. Tm-induced gut inflammation, due to the depletion of protective strains from the resident gut microbiota (Figure 3).[135] On the contrary, loss of *B4galnt2* expression renders mice susceptible to *C. rodentium*.[136] *B4galnt2*-deficient mice show an increase in mannosylated glycans on intestinal epithelial cells, which facilitates adhesion of *C. rodentium* via type I fimbriae.

Another common mechanism of gene-microbiome interactions is mediated by modifying the uptake and metabolization of diet-derived nutrients. A specific polymorphism that prevents intestinal absorption of dietary lactose was associated with increased incidence of *Enterococcus*-mediated graft-versus-host disease and mortality in patients undergoing allogeneic hematopoietic cell transplantation.[137] In these individuals, the nonabsorbed lactose can be utilized by *Enterococcus* species, fuels their expansion, and exacerbates intestinal and systemic inflammation (Figure 3).

Age-specific characteristics of infection susceptibility

Different human life stages exhibit unique physiological traits that influence microbiome composition and infection susceptibility. During the early years of life, the intestinal microbiome undergoes unique alterations that can be clustered into a developmental phase, a transitional phase, and a stable phase.[138] Collectively, these phases of microbiome maturation are marked by changes in specific phyla in developmental and transitional phases and a steady increase in bacterial diversity. A study in mice revealed that the intestinal microbiome of neonates lacks bacteria from the order Clostridiales, which renders them more susceptible to *S*. Tm and *C. rodentium* infections.[139]

Delivery mode—Starting off the "right" way

Critical determinants of microbiome structure during the early years of life are the mode of feeding and the route of birth. One

characteristic feature of infants delivered via cesarean section (C-section) is a reduction in microbiome stability and the loss of Bacteroidota at the age of 2 weeks, which potentially stems from reduced colonization with rectal *Bacteroides* strains.[140] Although these alterations may directly impact infection susceptibility, clinical evidence is scarce. The most comprehensive analysis so far only reported a slightly increased infection rate in infants delivered via C-section at the age between one and two.[141] Another study concluded that infants delivered via C-section are not preferentially colonized by hospital-associated pathogens, compared with vaginally delivered infants.[142]

Ecological cues of the infant microbiome and their role in pathogen control

Despite the reduced bacterial diversity and the lack of certain phyla in the developing microbiome of neonates, intra- and interspecies competition between potentially pathogenic bacteria is high, and ecological principles of the adult microbiome, such as priority effects, remain important for this ecosystem, for example, for *E. coli* colonization.[142] Bifidobacteria are among the first colonizers of the infant gut and convey strong priority effects for subsequent microbiome development.[143] How strong bifidobacteria shape community assembly is dependent on the utilization of human milk oligosaccharides, which are provided by the breast milk.[144] These ecological principles foster the development of a balanced microbiome, which is competent to block the invasion of pathogens.

Immune-system-driven CR in the developing gut

Regular microbiome maturation during the early stages of life is not only critical for microbiome-mediated CR but also aids in the development of the immune system to control enteric infections. Arresting microbiome progression during weaning in mice leads to stunting of microbiota-driven immune system maturation, and increases the susceptibility to *S*. Tm in a gnotobiotic model of early-life microbiota.[145] Protective maternal antibodies can be transferred from the mother to the child *in utero* across the placenta or *ex utero* via the breast milk. It has been shown that IgA and IgG induced by *M. schaedleri* are transferred to the offspring via the breast milk and protect from inflammation in a genetic model of *M. schaedleri*-induced colitis.[146] Interestingly, in pathogen-naive mothers, some of these antibodies are induced by the maternal gut-resident microbiota and cross-react with surface antigens of enteric pathogens.[128] Such microbiota-elicited maternal IgG was shown to be protective from enterotoxigenic *E. coli* and *C. rodentium* infection in pups, partially by interfering with pathogen attachment at mucosal sites.[128,147] Besides maternally derived humoral immune boostering, breast milk can also modify the microbiota composition of babies by selective depletion of certain Gram-positive microbes via the complement system. Specifically, it was shown that complement deficiency of the mother renders pups susceptible to lethal *C. rodentium* infection in an antibody-independent manner.[148]

Old-age-associated factors

Elderly individuals have an increased risk of numerous morbidities and often display features of immunosenescence, which makes them vulnerable to lifetime-shortening ailments, including infectious diseases (reviewed previously[149]). Importantly, they also experience a wide range of lifestyle changes that may impact gut microbiota composition and infection susceptibility directly or indirectly. Among the most influential factors are the increased use of medication, generational differences in eating and workout routines, and the reduction of social contacts through self-isolation. As a result of these alterations, the microbiome of the elderly is characterized by the absence of the *Prevotella*-rich enterotype signature[150] and the loss of *Clostridiales* and *Bifidobacterium* (reviewed previously[149]), both bacterial clusters that are involved in the prevention of numerous enteric infections (Table 1). The disentanglement of how old-age-associated lifestyle, microbiome, and immune system alterations affect the susceptibility to enteric pathogens requires further investigation.

Drugs and phages

Antibiotics are routinely applied orally to clear local or systemic infections with bacterial pathogens. However, due to their broad target spectrum, the effects of antibiotics are not limited to harmful bacteria but can also modulate growth rate and ecology of the intestinal microbiota—a process referred to as collateral damage.[165] Therefore, antibiotic therapy is a predisposing factor of enteric infections via the disruption of the resident microbiota and associated manipulation of the metabolic environment. Collateral damage by antibacterial drugs can be partially compensated for by FMT, which includes the repopulation of the bacteria-depleted intestine with the stool microbiome of healthy donors. FMT is a highly effective therapeutic approach to cure first and recurrent *C. difficile* infection, showing superior performance to standard-of-care vancomycin treatment.[166,167]

By depletion of host sugar-utilizing commensals, antibiotic treatment reduces carbohydrate competition in the colon and increases the availability of sialic acid, which aids colonization and expansion of *S*. Tm and *C. difficile*.[86] Similarly, antibiotics can decrease the abundance of protective *Bifidobacteriaceae* and Bacteroidales, which increases the availability of carbon and nitrogen sources and reduces bacterial metabolites that inhibit the growth of carbapenem-resistant Enterobacteriaceae.[168] Interestingly, collateral damage of the gut microbiota is not only induced by antimicrobial but also by numerous human-targeted drugs.[20] Several of such therapeutics were shown to break CR of a synthetic bacterial community against *S*. Tm *in vitro* and in specific pathogen-free mice.[169]

Overcoming antibiotics-induced collateral damage

To overcome the detrimental side effects of antibiotics and fine-tune targeted microbiome modulations, the development of narrow-spectrum antimicrobials is warranted. In this regard, a recent study demonstrated that the natural product chlorotonil A antagonizes established *C. difficile* infection in mice while causing limited alterations in the composition of rodent and porcine microbiomes.[170] As a result, chlorotonil A treatment does not increase the risk of infection relapses as is commonly observed for treatment with broad-spectrum antibiotics. Another approach based on a similar principle is the development of pathogen-specific antagonists, so-called pathoblockers or antivirulence agents. These are small molecular compounds that specifically target virulence factors but do, in general, not kill or reduce fitness of the pathogen. A recent study identified several compounds that inhibit motility and impair stomach colonization of the gastric pathogen *Helicobacter pylori*, without altering the diversity of the intestinal microbiota.[171] Furthermore, a synthetic molecule targeting a key pathogenicity regulator of *Salmonella* is currently

Table 1. Intestinal bacteria and underlying mechanisms that influence intestinal colonization resistance to pathogens

Taxon	Mechanism of action	Effect on pathogen infection	Reference
Bacillota			
Enterocloster clostridioformis	triggers antimicrobial mechanisms in gut epithelium	*Salmonella* ↓	Beresford-Jones et al.[151]
Enterococcus faecalis	carbohydrate competition	*Salmonella* ↓	Eberl et al.[31]
Enterococcus faecalis	cross-feeding, regulation of toxin production	*Clostridioides difficile* ↑/↓	Smith et al.[152]
Enterococcus faecalis	bacteriocin	vancomycin-resistant enterococci ↓	Kommineni et al.[48]
Blautia obeum	bile acid metabolism	*Vibrio cholerae* ↓	Alavi et al.[12]
Blautia producta	lantibiotic	vancomycin-resistant enterococci ↓	Kim et al.[50] and Caballero et al.[153]
Lacticaseibacillus rhamnosus (previously *Lactobacillus rhamnosus*)	amino acid and carbohydrate competition	multidrug-resistant *Enterobacteriaceae* ↓	Djukovic et al.[94]
Ligilactobacillus murinus (previously *Lactobacillus murinus*)	amino acid and carbohydrate competition	multidrug-resistant *Enterobacteriaceae* ↓	Djukovic et al.[94]
Paracoccus aminovorans	biofilm enhancement	*Vibrio cholerae* ↑	Barrasso et al.[96]
Clostridiales	butyrate production	multidrug-resistant *Enterobacteriaceae* ↓ *Escherichia coli* ↓ Salmonella ↓	Djukovic et al.[94], Rivera-Chávez et al.[154], and Byndloss et al.[155]
Bacteroidota			
Bacteroidetes	immune signaling	*Klebsiella pneumoniae* ↓	Sequeira et al.[156]
Bacteroides thetaiotaomicron	propionate production/ degradation	*Salmonella* ↓/↑	Jacobson et al.[157] and Shelton et al.[158]
Bacteroides thetaiotaomicron	succinate production	*Citrobacter rodentium* ↑	Curtis et al.[159] and Ferreyra et al.[160]
Bacteroides thetaiotaomicron	fucosidase activity	*EHEC* ↑	Pacheco et al.[161]
Prevotella copri	immune signaling	*Listeria* ↑	Rolhion et al.[54]
Pseuodomonadota			
Escherichia coli	carbohydrate competition	Enterohemorrhagic *E. coli* ↓ *Salmonella* ↓ multidrug-resistant *Enterobacteriaceae* ↓	Eberl et al.[31], Maltby et al.[162],and Connor et al.[163]
Klebsiella michiganensis	carbohydrate competition	*Escherichia coli* ↓ *Salmonella* ↓	Oliveira et al.[30]
Klebsiella oxytoca	carbohydrate competition	*Klebsiella pneumoniae* ↓	Osbelt et al.[32]
Verrucomicrobiota			
Akkermansia muciniphila	mucin degradation	*Salmonella* Typhimurium ↑	Ganesh et al.[164]
Actionbacteriota			
Bifidobacterium	acetate production	Enterohemorrhagic *E. coli* ↓	Fukuda et al.[6]
Deferribacteriota			
Mucispirillum schaedleri	interference with virulence factor expression	*Salmonella* ↓	Herp et al.[74]

under development as a potential treatment for *Salmonella* infections.[172] An alternative approach to pathoblockers is the use of strain-specific bacteriophages, which can be safe and effective strategies to treat and prevent GI infections.[173] Previous research suggests that reducing the load of protective bacteria from the gut microbiome can open niches for competing pathogens and increase infection susceptibility in a gnotobiotic mouse model of *S.* Tm infection.[174] Future research should focus on identifying strategies to eliminate pathogenic bacteria using bacteriophages and replacing them with nonpathogenic competitors.

CONCLUDING PERSPECTIVE

Given the complex multidirectional interactions between microbial and environmental contributors outlined in this review, studying one aspect of CR without considering other

contextual factors appears unrealistic. Therefore, we advocate for future research to adopt holistic approaches controlling for environmental factors when focusing on microbial interactions and vice versa to maintain real-world relevance. Holistic approaches should involve integrating various techniques to capture the complexity of microbial communities and their interactions within their natural environment. Time-series metaomics analyses could reveal how metabolite profiles, which provide a snapshot of the enteric nutrient landscape encountered by pathogens, correlate with shifts in microbial community composition, dietary changes, alterations of the disease status, or drug usage. Multiomics data can be integrated with computational modeling techniques to predict and simulate microbial community behavior under different environmental conditions. These approaches would enable researchers to generate testable hypotheses on causally relevant microbes and their functions and gain insights into the emerging properties of complex microbial systems.[175] Following the identification of candidate protective determinants from large-scale human microbiome datasets, underlying mechanisms could be elucidated using synthetic microbial consortia and gnotobiotic mouse models.[175] Human personalized gut microbiome biobanks and personalized synthetic communities could help to systematically analyze protective mechanisms and CR phenotypes in different natural microbial community contexts.[176] Complementary *in silico* development and application of microbial community-scale metabolic models could reduce the need for extensive animal research and allow for the rapid estimation of an individual's infection risk.[177] In order to guarantee prediction accuracy, such models should be established using high-throughput clinical or experimental data combined with computer-assisted modeling approaches and wet lab as well as real-world validation. Specific biomarkers could be benchmarked to predict an individual's infection risk and pave the way for personalized interventions to protect vulnerable patients.[175] In conclusion, recent scientific advances and our updated perspective on CR will aid the development of efficient strategies to prevent and combat bacterial infections, keeping in mind that context matters.

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AUTHOR CONTRIBUTIONS

S.W., M.S.S., and B.S. together created the outline of the review. S.W. and M.S.S. designed all the figures and wrote the original draft manuscript. B.S. reviewed and edited the draft manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

ChatGPT, v. 3.5, a language model developed by OpenAI in San Francisco, CA, USA, helped in language editing and proofreading.

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