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Review

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# When pathogenic bacteria meet the intestinal microbiota

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The intestinal microbiota is a large and diverse microbial community that inhabits the intestinal tract, containing about 100 trillion bacteria from 500–1000 distinct species that, collectively, provide multiple benefits to the host. The gut microbiota contributes to nutrient absorption and maturation of the immune system, and also plays a central role in protection of the host from enteric bacterial infection. On the other hand, many enteric pathogens have developed strategies in order to be able to outcompete the intestinal community, leading to infection and/or chronic diseases. This review will summarize findings describing the complex relationship occurring between the intestinal microbiota and enteric pathogens, as well as how future therapies can ultimately benefit from such discoveries.

This article is part of the themed issue 'The new bacteriology'.

## 1. Introduction

The intestinal microbiota is the collective term describing the large and diverse microbial community that inhabits our intestine. In humans, the microbiota contains about 100 trillion bacteria from 500–1000 distinct species that provide multiple benefits to the host. Among those beneficial functions, the intestinal microbiota plays a central role in (i) shaping the intestinal immune system [1] by contributing to immune system development and maturation, and (ii) nutrient acquisition, by greatly enhancing the metabolic capacity of the gut, thus providing a range of essential nutrients for the host [2]. Another important benefit conferred by the intestinal microbiota to the host intestine is the protection from colonization by exogenous pathogens—a phenomenon nowadays named colonization resistance—and from overgrowth of indigenous pathobionts (potential pathogenic symbionts of the microbiota) [3–5]. The colonization resistance, termed the 'microbial barrier' in the early 1980s [6], is the mechanism whereby the intestinal bacteria form a barrier to prevent incursion by new bacteria of other species or other strains of the same species. This notion is well exemplified by the range of infections resulting from the use of antibiotics, such as *Clostridium difficile* infection [7], as well as by the observation that many enteric pathogens induce stronger disease in mice under germ-free conditions (in the absence of an intestinal microbiota) or following antibiotic treatments [8–12] (figure 1). Mechanisms that regulate the ability of the microbiota to restrain pathogen growth are complex and include competitive metabolic interactions, localization to intestinal niches and induction of host immune responses [4]. Pathogens, in turn, have developed strategies in order to escape from colonization resistance conferred by the commensal community. Unexpectedly, the intestinal microbiota can also play a role in providing nutrients to some intestinal pathogens, or may play a direct role in activating virulence of pathogenic bacteria that will otherwise stay avirulent. In addition, in some particular conditions, the intestinal microbiota may actually drive disease, as is for example the case for inflammatory bowel diseases. This review will summarize these concepts and will describe the most recent findings elucidating the

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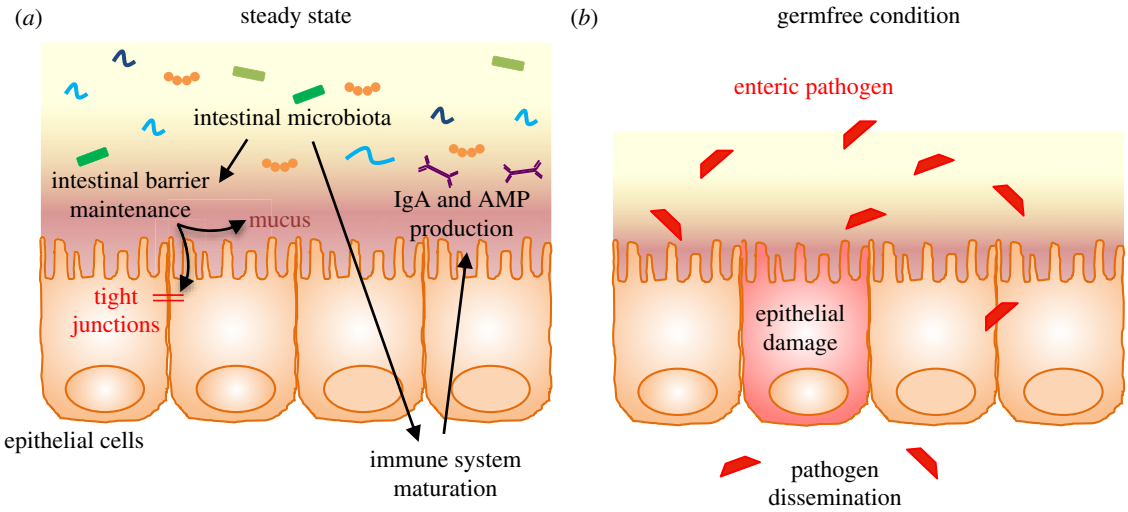


**Figure 1.** Microbiota/host homeostasis in the intestine. (*a*) The intestinal microbiota plays a central role in intestinal barrier maintenance (mucus production and intestinal tight junctions maintenance) and immune system maturation (lymphocytes development, production of IgA and antimicrobial peptides). (*b*) In the absence of an intestinal microbiota, enteric pathogens can induce epithelial damage and have the potential to disseminate. AMP, antimicrobial peptide; IgA, immunoglobulin A.

intriguing relationship between the intestinal microbiota and enteric pathogens. We will discuss how the understanding of microbiota–pathogen interactions may ultimately lead to new therapeutic approaches in order to treat infectious diseases.

## 2. Role of the intestinal microbiota in colonization resistance

The intestinal microbiota is playing a central role, through multiple mechanisms, in protecting the host intestine from pathogen colonization (figures 1 and 2).

### (a) Direct inhibition of colonization by enteric pathogens

The concept of protection of the host intestine from pathogens by commensal bacteria, also called colonization resistance, was first described to be the result of microorganism-mediated direct inhibition [13]. Indeed, many bacteria directly inhibit intestinal pathogens by competing for nutrients or by inducing the production of inhibitory substances. One example highlighting the former is the finding that the commensal *Bacteroidetes thetaiotaomicron* consumes carbohydrates used by the pathogen *Citrobacter rodentium*, thus leading to competitive exclusion of the pathogen from the intestine [14] (figure 2). By consuming common limited resources, the gut microbiota induces the starvation of competing pathogens [4]. Through the production of specific metabolites, the intestinal microbiota can also modify the host environmental conditions, then compromising pathogen growth and/or virulence. Butyrate, a short-chain fatty acid (SCFA) produced by the intestinal microbiota, can downregulate the expression of several virulence genes of *Salmonella enterica* serovar Enteritidis (*S.* Enteritidis) and Typhimurium (*S.* Typhimurium) [15] and has been shown to inhibit the growth of enterohaemorrhagic *Escherichia coli* (EHEC) [16]. Some *Bifidobacteria* strains can also protect from EHEC infection through the production of acetate [10].

The intestinal microbiota community is also able to produce a large number of broadly bioactive small molecules that act toward other members of the intestinal microbiota and/or toward enteric pathogens. Bacteriocins, for example, are antimicrobial peptides that can have narrow to broad activity spectrums and can selectively kill and/or inhibit the growth of competing bacteria [17]. As an example, *Bacteroides thuringiensis* is able to secrete a bacteriocin (thuricin CD) that directly targets spore-forming Bacilli and Clostridia, including *C. difficile* [18]. Similarly, some strains of *E. coli* are able to produce bacteriocin that can directly inhibit the growth of the EHEC enteric pathogen [19], and anti-*Listeria* bacteriocins were found to be expressed by *Enterococcus faecium* and *Pediococcus pentosaceus* [20,21]. Recently, a computational prediction of biosynthetic gene clusters that encode small molecules in the human gut microbiota identified almost 600 candidate clusters, including many newly annotated antimicrobial peptides, suggesting that these small molecules might mediate commensal–commensal and commensal–pathogen interactions [22]. Another *in silico* study identified 74 putative-encoding bacteriocin clusters in the gastrointestinal tract, based on the human microbiome project's reference genome database [23,24].

Another somewhat direct inhibitory effect of the intestinal microbiota toward pathogens is through a mechanism involving bile acids. Produced in the liver and delivered into the duodenum, bile acids are subsequently modified by the gut microbiota into a myriad of secondary bile acids that can act as anti-bacterial factors. Highlighting the role of the intestinal microbiota in secondary bile acid production is the observation of very low or undetectable levels in germ-free animals [25] and a dramatically reduced production following antibiotic treatment [26]. The best example of a protective mechanism conferred by microbiota-derived secondary bile acids is the observation that the depletion of microbial members involved in converting primary bile acids into secondary bile acids favours the colonization of the gastrointestinal tract by *C. difficile*, the most prominent pathogen exploiting antibiotic-mediated alteration of the microbiota [7,26–30]. Importantly, the administration of *Clostridium scindens* (a bile acid 7α-dehydroxylating bacterium) is sufficient to confer resistance to *C. difficile* infection in a secondary bile acid-dependent manner. Recent works have described that the intestinal microbiota can also indirectly control enteric pathogens by other mechanisms, such as by shaping the immune system and the inflammatory response (immune-mediated colonization resistance).

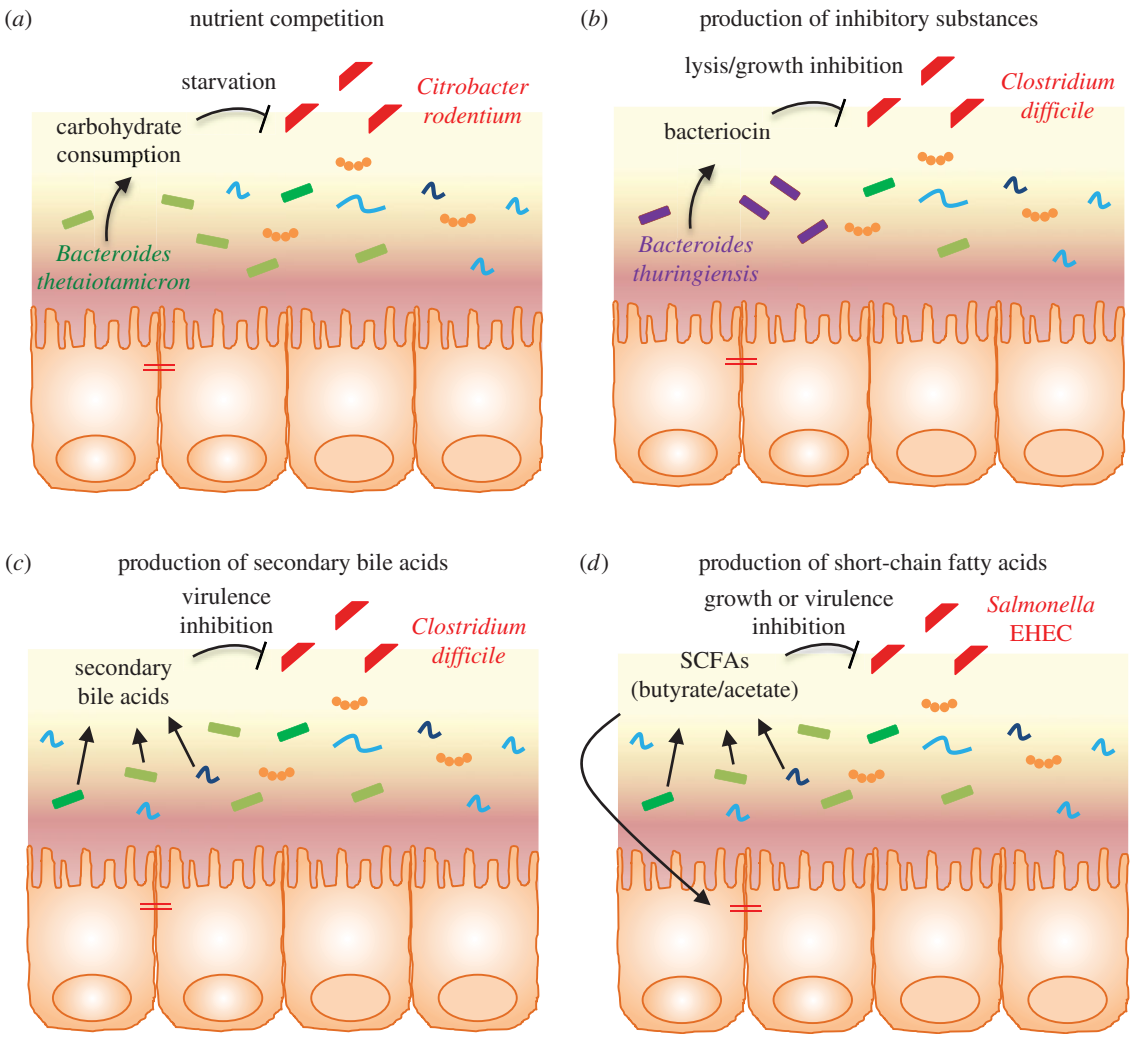


**Figure 2.** Intestinal microbiota-mediated colonization resistance. Examples of microbiota-mediated direct inhibition of intestinal colonization by enteric pathogens. Intestinal microbiota prevents colonization by enteric pathogens by competing for nutrients (*a*) or producing inhibitory substances such as bacteriocin (*b*), secondary bile acids (*c*) and short-chain fatty acids (*d*). EHEC, enterohaemorrhagic *Escherichia coli*; SCFAs, short-chain fatty acids.

## (b) Immune system maturation and inflammation process

The microbiota plays a primordial role in the maturation of the intestinal immune system, as demonstrated by the observation that germ-free mice are heavily immuno-depressed. Indeed, the intestine of germ-free animals lack Peyer's patches, and have a reduced expression of both antimicrobial peptides and immunoglobulin A (IgA), molecules implicated in intestinal immunity [31–36]. An example of a member of the microbiota that contributes to the immune system development is *Bacteroides fragilis*, with the demonstration that monocolonization of germ-free mice with this bacterium is sufficient to promote the development of CD4T lymphocytes [37]. Similarly, segmented filamentous bacteria have been described to be sufficient to drive the differentiation of CD4T cells into Th17 cells, important for protection against the intestinal pathogen *C. rodentium* [38–41].

The intestinal microbiota is also an inexhaustible source of ligands for the innate immune system. Antibiotic treatment is sufficient to increase susceptibility of mice to dextran sodium sulfate (DSS)-mediated colitis, a phenomenon that can be rescued by the administration of Toll-like receptor ligands [42]. Such a finding initiated the concept that pattern recognition receptor signalling originating from the intestinal microbiota is necessary for the steady-state protection of the intestine [42,43]. This has also been illustrated by the discovery that bacterial flagellin from the intestinal microbiota is able to prevent and cure rotavirus infection though a mechanism requiring flagellin receptors Toll-like receptor 5 (TLR5) and NOD-like receptor C4 (NLRC4) and involving interleukin-22 and interleukin-18 production [44]. Bacteria belonging to the *Clostridium* group cluster XIVa are able to induce the development of anti-inflammatory T regulatory cells [45], and SCFAs derived from the intestinal microbiota play a central role in maintaining the balance of inflammatory and anti-inflammatory T cell subsets [46–49]. Importantly, some TLR ligands, such as LPS, are modified by the host in order to be less bioactive, indicating the existence of mechanisms to detoxify such pro-inflammatory molecules, thus avoiding over-activation of the intestinal immune system in response to the commensal bacterial population [50–52]. All these reports are good examples of the roles played by the microbiota in the maturation of the intestinal immune system, where the intestinal bacterial population can generate pro-inflammatory or anti-inflammatory responses, both central for avoiding over-activation of the intestinal immune system but conferring protection against enteric pathogens.

## (c) Intestinal barrier maintenance

Another mechanism by which the intestinal microbiota protects the intestine against enteric pathogens infection is by acting on

the 'strength' of the intestinal barrier, such as the thickness and composition of the mucus layer, as well as the maintenance of the intestinal tight junctions. It is indeed primordial for the host to keep the intestinal microbiota at a safe distance from the intestinal epithelium, in order to minimize the appearance of tissue damage and inflammation [53]. The intestinal microbiota is restricted to the intestinal lumen by a mucus layer that overlays the epithelium. Treatment of mice with antibiotics reduces the mucus layer thickness and results in an increased contact of the bacteria with the intestinal epithelium monolayer that can be highly deleterious in the context of an enteric pathogen infection, as exemplified with *C. rodentium* [54]. In addition, the intestinal microbiota maintains the intestinal barrier though the production of SCFAs, which are a primary nutrient for the colonic epithelium and contribute to the control of mucin production [55,56]. Thus, a decrease in production of SCFAs may result in the reduction of mucus thickness/degradation of the mucus barrier.

## 3. When the intestinal microbiota leads to enteric pathogen virulence

While all the mechanisms described above are central to protect the intestine against bacterial infection and pathogens, the microbiota can also trigger bacterial virulence. For example, the intestinal microbiota can also produce metabolites that might unexpectedly enhance pathogen virulence expression and colonization in the gut [57–61] (figure 3*a*). *Bacteroidetes thetaiotaomicron*, found to lead to a competitive exclusion of *C. rodentium* through the consumption of similar carbohydrates [14], can also cleave sialic acid moieties from mucin and produce high levels of succinate that can lead to an enhanced colonization by *C. difficile* [58,59]. The production of fucose or succinate from the host mucin by commensal bacteria can also modulate the expression of the virulence factor ler, a master regulator of the locus of enterocyte effacement (LEE) genes in EHEC [60,62], thus contributing to EHEC virulence. Other examples of pathogens that utilize the intestinal microbiota to facilitate their own infection include *C. difficile* whose spores require by-products from the microbiota, such as bile salts, to germinate [63] and *S.* Typhimurium that utilizes di-hydrogen generated by the microbiota for its luminal growth [64]. Moreover, microbiota-produced ethanolamine is used as a nitrogen source and a regulator of virulence genes by EHEC, *S.* Typhimurium and *Listeria monocytogenes* [65–68]. *Akkermansia muciniphila*, a mucin degrading commensal bacterium that resides in the mucus layer and that can confer protection against obesity and metabolic disorders [69,70], is also able to exacerbate *S.* Typhimurium-induced intestinal inflammation by its ability to disturb host mucus homeostasis [71].

## 4. When intestinal microbiota alteration by a pathogen leads to chronic diseases

While previous examples illustrated how the intestinal microbiota can promote infection by enteric pathogens, some findings also revealed that intestinal microbiota alteration by a pathogen or a pathobiont can lead to chronic diseases. As an example, it was shown that colonization of adherent-invasive *E. coli* (AIEC, a pathovar of *E. coli* involved in Crohn's disease pathogenesis) during microbiota acquisition drove chronic colitis in mice lacking the flagellin receptor TLR5 [72]. The observation that such colitis persisted well beyond AIEC clearance leads to the conclusion that AIEC bacteria instigate chronic inflammation by altering the intestinal microbiota composition in a way that increases its pro-inflammatory potential [73]. These data suggest that AIEC, and perhaps other pathobionts, may instigate chronic inflammation in susceptible hosts by altering the gut microbiota composition so as to give it an inherently greater ability to activate innate immunity/pro-inflammatory gene expression [73], leading to the concept of pathobiome [74]. Similarly, *Yersinia enterolitica* infection of mice lacking the receptor TLR1 leads to an alteration of the microbiota composition and to the generation of anti-commensal immunity, that ultimately leads to the development of chronic intestinal inflammation [75]. Thus, these two findings describe that an acute infection can drive long-term immune and microbiota alterations, leading to chronic inflammatory disease in a genetically predisposed host.

## 5. How bacterial pathogens emancipate themselves from the intestinal microbiota

As discussed above, the intestinal microbiota is playing a central role, through multiple mechanisms, in pathogen colonization resistance. However, in turn, pathogens have evolved strategies to escape some of those mechanisms (figure 3*b–d*).

### (a) The use of alternative nutrients or niches

Even if the intestinal environment is qualitatively and quantitatively rich in nutrients, the large load of bacteria ultimately leads to competition. One mechanism by which an enteric pathogen can compete with the microbiota is by using a distinct metabolic repertoire. Ethanolamine, which is released into the intestine during epithelial cell turnover, is for example used by some pathogens [76], and genes involved in the use of ethanolamine are preferentially found in the genomes of enteric pathogens [77]. The foodborne illness pathogen EHEC is able to utilize galactose, hexuronate, mannose and ribose as carbon sources, while commensal *E. coli* cannot use such sugars [78,79]. In addition, some pathogens more efficiently utilize common resources, such as iron. Iron is essential for bacterial growth, and many bacteria produce siderophores in order to acquire ferric iron [80]. As a protective mechanism, host cells secrete lipocalin-2, which is able to block the siderophore enterobactin in *E. coli*, preventing iron acquisition and proliferation of commensal *E. coli* in the gut [81,82]. However, *Salmonella* and some pathogenic *E. coli* express modified enterobactins, named salmochelins, which are lipocalin-2 resistant, providing an important advantage of pathogens over commensals [4,81,82]. Pathogens can also reside in a distinct niche from the microbiota. Pathogenic *E. coli* can, for example, localize close to the intestinal epithelial surface, normally devoid of commensal microbiota, through the expression of molecules such as intimin, a LEE-encoded adhesion molecule [14].

Chemotaxis and mobility conferred by flagella enable *Salmonella* to identify and swim to nutritionally beneficial niches. Indeed, the methyl-accepting chemotaxis receptors Aer and Tsr were observed to respond *in vivo* to tetrathionate or nitrate, respectively, in order to confer a fitness advantage upon *S.* Typhimurium during inflammation by enabling

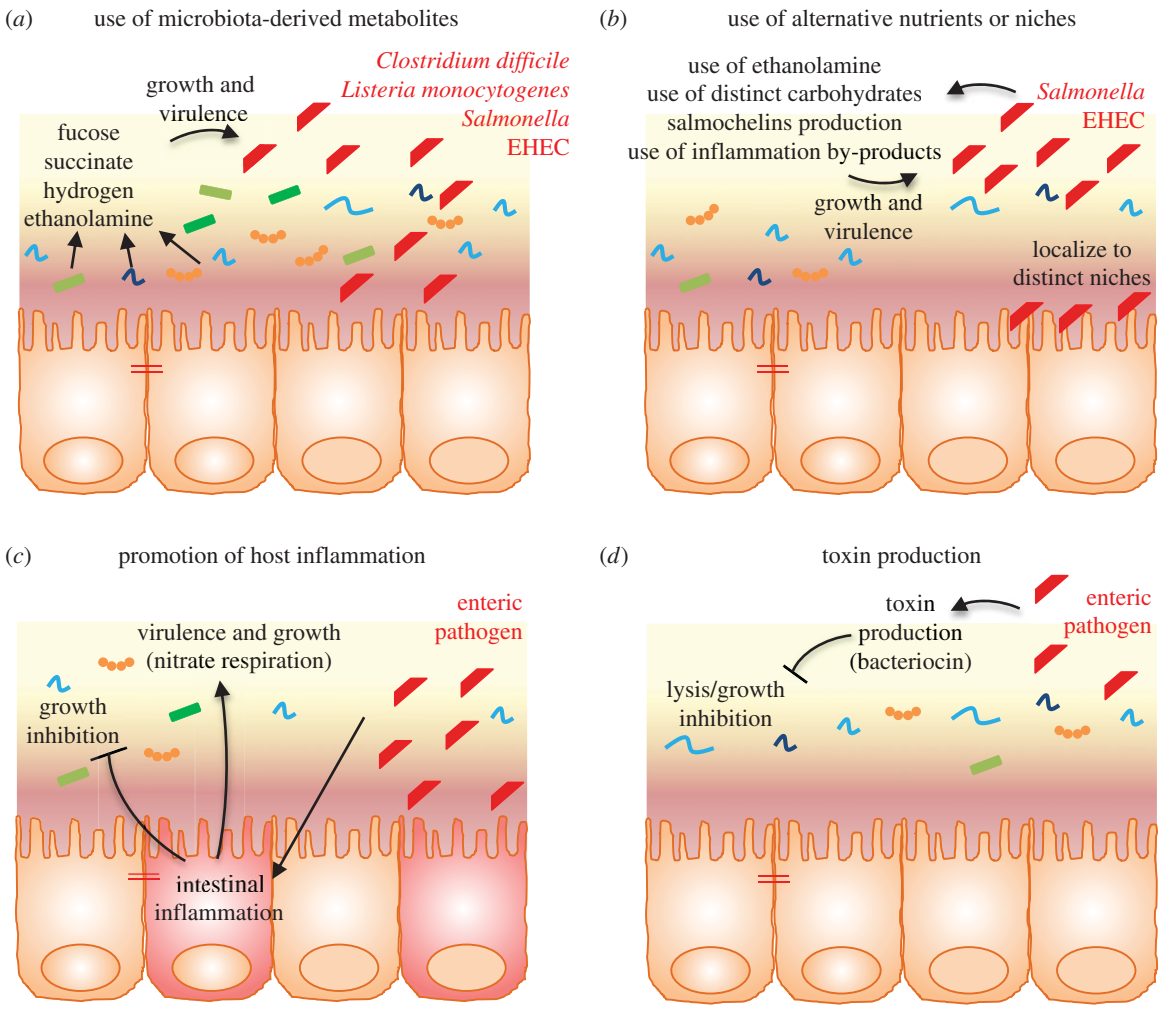


**Figure 3.** Pathogen strategies to overcome microbiota-mediated colonization resistance. (*a*) The production of metabolites by commensal bacteria can modulate the growth and expression of virulence genes by enteric pathogens. (*b*) Enteric pathogens can compete with the microbiota by using alternative nutrients and/or niches. (*c*) Promotion of intestinal inflammation by enteric pathogens inhibits commensal bacteria growth, conferring an advantage to enteric pathogens. (*d*) Enteric pathogens produce toxins that can directly and specifically target commensals. EHEC, enterohaemorrhagic *Escherichia coli*.

the bacteria to seek out favourable spatial niches containing host-derived electron acceptors that boost its luminal growth [83]. Pathogenic bacteria may also benefit from intestinal inflammation and/or by-products of the inflammatory response. For example, reactive oxygen species produced by neutrophils during inflammation react with luminal sulfur compounds (thiosulfate, $S_2O_3^-$) to form a new respiratory electron acceptor, tetrathionate ($S_4O_6^{2-}$). Unlike commensals, *Salmonella* contains the operon *ttrSR ttrBCA* that allows for the use of $S_4O_6^{2-}$, providing a growth advantage to *Salmonella* over commensal microbes in an inflamed environment [84]. Similarly, nitrate generated as a by-product of the inflammatory response conferred a growth advantage to the commensal bacterium *E. coli* over Firmicutes and Bacteroidetes in the large intestine of mice [85]. Although this mechanism of *E. coli* overgrowth in the inflamed gut involved commensal–commensal competition, pathogenic *E. coli* strains, which have nitrate reductase genes such as *NarZ* in their genome, may use a similar mechanism to acquire a growth advantage over the competitive commensal community.

## (b) Promotion of host inflammation

Another mechanism by which intestinal pathogens acquire a growth advantage compared to the commensal population is through the promotion of intestinal inflammation, that alters commensal survival. Indeed, the expression of virulence factors by pathogenic bacteria, such as toxins, leads to intestinal inflammation that, in turn, dramatically alters the gut microbiota composition and richness [86]. For example, during intestinal inflammation, neutrophils and macrophages expressing inducible nitric oxide synthetase (iNOS) are recruited, leading to an increased concentration of nitrate in the gut that confers an advantage to *Enterobacteriaceae* compared to obligate anaerobes, such as Bacteroidetes or Firmicutes [85]. Many *E. coli* pathovars are indeed able to utilize nitrate as an electron acceptor, such as AIEC associated with inflammatory bowel disease, and can profit from such growth advantage compared to the commensal population to more efficiently colonize the intestine [87–90].

In addition, the host inflammatory environment can enhance the expression of virulence factors, promoting the growth of pathogenic bacteria in host tissues. For example, interferon-? increased the expression of type I lectin by *Pseudomonas aeruginosa*, allowing adhesion of the bacteria to lung epithelial cells [91]. Hence, the gut inflammatory environment may also promote virulence factor expression by enteric bacteria.

## (c) Toxin production

Pathogens are able to produce inhibitory substances/toxins that can directly target the gut microbiota. Through its type VI secretion system, *Vibrio cholerae* is able to deliver toxic effectors directly to *E. coli* [92,93]. In addition, bacteriocin

production has been reported for *Salmonella* [94] and pathogenic *Shigella* strains [95–99], but its role in virulence or as a mechanism to outcompete microbiota are not yet known.

Taking into account that bacteriocins play an important role in bacterial relationships, it is very likely that they can contribute to the successful colonization of the intestine by pathogenic bacteria, by targeting specific commensals and therefore modifying the barrier maintenance, altering the immune surveillance and/or the gut metabolism to promote their colonization. Studying the role of bacteriocins produced by pathogenic strains on the microbiota and on virulence might reveal new mechanisms of pathogenicity and will help to decipher the complex relationship between the intestinal microbiota and some enteric pathogens.

## 6. Conclusion and perspectives

With the recent appreciation of the important roles played by the intestinal microbiota in health and diseases, a number of studies have highlighted its specific role in protection against enteric pathogen infection. It is important to note here that most mechanisms presented in this review have been discovered from animal models and/or *in vitro* works. Extrapolation to the human situation has to be considered with caution in a context of different dietary habits, intestinal architecture, microbiota composition, environment, immune system and genetic background. However, new therapeutic approaches may ultimately benefit from understanding the important inhibitory role of the intestinal microbiota against pathogen virulence [100], as exemplified by the recent use of fecal microbiota transplant for the treatment of recurrent *C. difficile* infection, which has more than 90% effectiveness compared with only 30% when using antibiotic treatment [101]. Targeted manipulation of the intestinal microbiota by bacteriocins and/or other antimicrobials has the potential to be a therapeutic tool for the prevention or treatment of dysbiosis-associated diseases [102]. Based on their very high specificity (at least for some of them), bacteriocins might represent ideal candidates with respect to the targeting of only undesirable populations. Importantly, there are already some proof of concept studies, such as the use of thuricin CD to specifically inhibit *C. difficile* in a distal colon model [103]. Similarly, bacteriocin production by the probiotic *Lactobacillus salivarius* UCC118 was shown to significantly protect mice against *L. monocytogenes* [104]. Moreover, it was recently shown that intestinal colonization with a bacteriocin-producing *Enteroccocus faecalis* results in the clearance of vancomycin-resistant enterococci, strengthening the concept that bacteriocins may be an effective therapeutic approach to specifically eliminate intestinal colonization by multiple-resistant bacteria without a profound disruption of the commensal population [104]. However, when identifying or choosing a bacteriocin as a therapeutic approach, the putative broad impact on the gut microbiota should be taken in account, even if less drastic than antibiotic use. For example, thuricin CD was also found to strongly inhibit *Lactobacillus fermentum* [18].

In addition, phage therapy can potentially have beneficial impact on human microbiota and associated host health [105]. Bacteriophages are virus particles that naturally infect bacteria with a high specificity and phage therapy consists of using these bacteriophages as antimicrobial agents [106,107]. Some groups are currently investigating their suitability as therapeutic strategy against some enteric pathogens, for example against AIEC associated with inflammatory bowel disease [108].

Finally, bacteria (both non-pathogenic and pathogenic) synthesize small diffuse signal molecules, called auto-inducers, in order for them to coordinately control the gene expression of the entire community in response to changes in cell density [109]. This process, termed quorum sensing, can be universal or highly specific, enabling bacteria to communicate within and between species. Hence, quorum sensing can have a major impact on the composition of microbial communities, and is also involved in the regulation of virulence gene expression by many pathogenic bacteria [110]. Therefore, the identification of chemical signals, receptors and targeted genes will be essential for our understanding of how bacteria–bacteria communication may be used in preventing colonization by pathogenic bacteria [100].

Additional studies are needed to decipher the complex relationship occurring between the intestinal microbiota and pathogenic bacteria that will ultimately help to define, and maybe engineer, a 'healthy' microbiome.

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