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Modulation of the gut microbiota to improve innate resistance

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One major benefit from the association of hosts with the complex microbial communities that establish at body surfaces is the resistance to pathogen infection. This protective role of symbiotic microbes is becoming ever more relevant, given the alarming rise of multidrug-resistant pathogens and severe infections in patients following extensive antibiotic treatment. Herein, we highlight some recent mechanistic studies that have provided insights into how the highly dynamic dialogue amongst intestinal bacteria and between intestinal bacteria and their host can contribute to protect the host against pathogens in and outside the gut. We then discuss how delineating the rules of this dialogue can help design strategies to modulate the microbiota and improve host resistance to infections.

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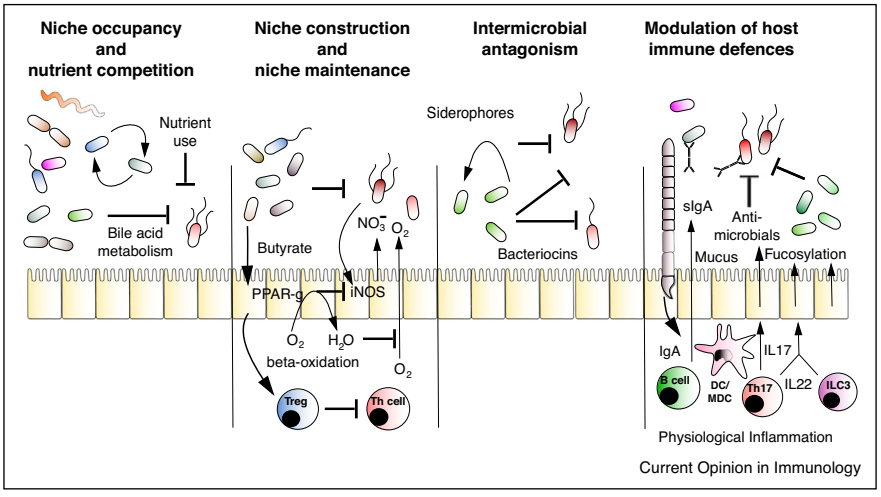
Introduction

Microbes, by far the most prominent form of cellular life on Earth, colonize all possible environments [1]. Bacteria notably gather into more or less complex communities at body surfaces, where their composition is shaped by ecological constraints and co-evolution with the host [2,3]. One major benefit derived from host-association with symbiotic bacteria, and particularly with the extensive bacterial community in the intestine, is an increased resistance to pathogen colonization. This benefit is evident in humans and animals orally treated with antibiotics or in animals raised in germ-free conditions as, under these conditions, the host becomes dramatically more sensitive to infections by a large range of pathogens [4,5]. Resistance to pathogens in the intestine, but also at extra-intestinal sites, is influenced by the composition of the gut microbiota. Moreover, there is increasing evidence that recent changes in lifestyle and diet, which strongly impact the gut microbiota composition, may compromise this protective effect. Overall, the human adult gut microbiome contains approximately 10^{13} resident bacteria [6], with the vast majority residing in the colon. As in mice, it is mainly composed of two major phyla, *Bacteroidetes* and *Firmicute*, but exhibits extensive diversity at the species level (~150–400 bacterial species per individual) (reviewed in [7]). Among the minor phyla, Proteobacteria have a major importance. Although they represent less than 1% of intestinal bacteria in the adult intestine, this group encompasses most enteropathogens and flourishes in the inflamed gut [8,9]. Much work has been devoted to understand how resident gut bacteria can, together with their host, form a complex living ecosystem that, at steady state, efficiently opposes colonization by outside invaders while also preventing the outgrowth of preexisting minor subsets of bacteria with pathogenic traits (pathobionts). Herein, we summarize four complementary mechanisms (recapitulated in Figure 1) by which the intestinal microbiota is thought to confer innate protection in and outside the gut and discuss ways to preserve or reinforce this effect.

Niche occupancy and competition for nutrients

Metagenomic studies suggest that resident gut bacteria share a common core of genes [10] that are necessary to forage local nutrient resources and to cope with the very strong ecological constraints met along the gastrointestinal tract. There is also evidence of extensive interspecies transcriptional interactions [11] and of cooperative interactions enabling cross-feeding between distinct *Bacteroides* species [12•]. Resident bacteria may thus not only compete for metabolic niches but also adapt and build cooperative metabolic networks to establish a highly diverse microbial community [13]. The importance of having a highly diverse microbiota to efficiently resist pathogen invasion is illustrated by the increased risk of severe infections of enteric origin in neonates [14] (when intestinal niches are not yet fully colonized), as well by the threat of severe nosocomial intestinal or invasive infections after antibiotic treatments that cause prolonged

Figure 1



Mechanisms involved in gut microbiota-mediated resistance against enteropathogen infection. The microbiota occupies and actively modulates nutritional niches, limiting niche availability to pathogens through nutrient competition and the construction of unfavorable environments. Pathogens are also restricted through direct inter-bacterial antagonism and the activation of the host immune system by the microbiota. Host immune activation feeds back to niche construction by making available specific carbon sources such as fucose. DC: dendritic cell; MDC: monocyte-derived cell; ILC3: Type 3 innate lymphoid cell.

disruption of the colonic microbiota (reviewed in [4]). Accordingly, fecal transplantation, which replenishes intestinal niches, has proven to be a very efficient method to treat the severe post-antibiotic therapy colitis resulting from the outgrowth of *Clostridium difficile* (reviewed in [15]). Strikingly, the presence of specific resident *Clostridium* species able to enzymatically convert primary bile acids, which derive from host cholesterol metabolism, into secondary bile acids was shown to be mandatory to inhibit the sporulation of *C. difficile* [16], providing an interesting example of how the host and the microbiota can work together to contribute to their common protection against the outgrowth of pathogenic bacteria. This example is also an illustration of how intermicrobial antagonism can result in host protection against pathogens.

Intermicrobial antagonism

Resident bacteria generally use antimicrobial peptides to increase their competitiveness within the intestinal niches that they share with closely related species. They can thereby also limit pathogen outgrowth. For example, nisin produced by *Lactococcus lactis* exerts a potent microbicidal activity against a broad spectrum of Gram-positive bacteria, including *Staphyloccus aureus* and *Listeria* (reviewed in [17]), while microcins produced by several commensal strains of *Escherichia coli*, including *the* probiotic Nissle strain, can inhibit the growth of enteropathogens such as *Salmonella enterica* or of pathobionts such as adherent-invasive B2 *E. coli* strains [18•]. *E. coli Nissle* microcin acts by binding siderophore receptors that are induced in pathogenic Enterobacteriaceae upon iron starvation [19]. Accordingly, this microcin exerts its protective anti-bacterial activity only in the inflamed gut, when resident bacteria and Enterobacteriaceae compete for iron [18•]. Commensal strains of *E. coli* may thus protect their niche and, as a consequence, their host against invasion by enteropathogens. A hundred years after isolation by Alfred Nissle of the eponym *E. coli* strain from the stools of a German soldier resistant to dysentery, these data sustain Nissle's hypothesis that *E. coli Nissle* may be useful to therapeutically displace enteric pathogens [20]. Observations with the siderophore-microcin produced by *E. coli Nissle* also suggest that coupling antibiotics with siderophores may be a strategy to target and enhance drug efficacy against specific pathogens [18•]. Along the same line, Salzman and colleagues recently proposed to use a strain of *Enterococcus faecalis* engineered to express a bacteriocin to outcompete and eliminate multidrug-resistant strains of *Enterococcus*, which are a leading cause of severe hospital-acquired infections [21].

Niche construction and maintenance of a healthy ecosystem refractory to pathogen colonization

A third mechanism that limits intestinal pathogens is niche construction, whereby gut microbes not only adapt to their environment but also contribute to its modification for their own advantage. For example, recent work has unraveled how butyrate-producing resident *Clostridia* maintain the anaerobic environment of the colon that favors their growth at the expense of *Enterobacteriaceae*, which are facultative anaerobes that thrive in more