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Gut Microbiota Resilience Mechanisms Against Pathogen Infection and its Role in Inflammatory Bowel Disease

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Abstract

Purpose of Review Although extensive research has been conducted on microbial resilience, numerous unanswered questions persist. In this study, we highlight impactful research that elucidates the diverse mechanisms underlying the resilience of the gut microbiota against pathogen colonization and its implications on gut health and disease.

Recent Findings The increasing importance of gut microbiota resistance in the context of pathogenic infections has been extensively reported. The establishment of a homeostatic microbiome-host interaction, facilitated by intricate mechanisms originating from both the microbiota and the host, plays a crucial role in fostering resilience. However, pathogens have evolved several evasion strategies that can disrupt healthy microbiota composition, trigger environmental alterations, and induce inflammation, thereby potentially exacerbating inflammatory diseases in the gut.

Summary In this review, we aim to highlight the significance of different resilience mechanisms during intestinal infections and their potential for modulation to develop new interventions that can effectively ameliorate Inflammatory Bowel Disease (IBD).

Keywords Microbiota resilience · Intestinal infection · Pathogen evasion · IBD

Introduction

The discovery of the gut microbiota dates back to the pre-1900 era, when a plethora of microorganisms, which are abundantly present in the human body, were identified [1]. While microbiota and microbiome are terms that are often used interchangeably, they exhibit certain differences. Microbiota is comprised of living microorganisms that exist within a particular environment, such as the gut microbiota. On the other hand, the microbiome encompasses the collection of genomes in the environment, including microorganisms and metabolites. Consequently, the microbiome has a broader scope than the microbiota [2].

The microbiome is a complex ecosystem with diverse and variable compositions. The main phyla present in healthy humans are Firmicutes and Bacteroidetes, which represent 90% of the microbiota [3]. The extensive diversity observed in microbiomes complicates the task of defining a precise criterion for a natural or healthy microbiota. However, in the definitions, certain factors, such as increased diversity, symbiotic interactions with the host, stability, and resilience, which execute immune and metabolic functions, can be considered in the definitions [4]. The human microbiota is consistently influenced by the host and multiple external factors, including diet, exercise levels, medicine, antibiotics, genetics, immunity, and the intestinal barrier, which have the potential to perturb this ecosystem [5, 6]. Subsequently, the microbial ecosystem may or may not be able to revert to its original state; this phenomenon is referred to as resilience. The concept of resilience was recently proposed through a model that integrated tests and challenges to determine whether the microbiota comprises resilience, which was

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Topical Collection on *Microbe-Microbiome Interactions*

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assessed by its capability to resist and recover from stress [7].

The development of chronic diseases can plausibly initiate a decline in the capacity of the microbiota to effectively resist challenges or promptly and fully recover to a state of homeostasis. This can potentially lead to a new state of dysbiosis [7]. Dysbiosis occurs when there is a critical involvement of the microbiota in the development of diseases [8]. Under certain conditions, patients treated with antibiotics exhibit a diminished ability to restore the microbiota to its baseline levels, which can contribute to the development of diseases [9]. Nevertheless, a highly resilient microbiota possesses the capacity to regain a healthy state [10]. Hryckowian et al. described diet as an intervention that increases microbiota diversity and resilience [11]. Thus, the maintenance of the microbiota in a resilient state may substantially contribute to homeostasis and health. In this review, we focus on resident microbiomes and the importance of microbiota resilience in health and disease management.

Inherent Mechanisms of Microbial Resilience

The gut microbiota is a collection of bacteria present in the intestinal tract. They exhibit distinct spatial organization based on the location, including the lumen, mucus layer, and crypts, which determine their interaction levels with each other and with the host [12].

Spatial and Nutritional Competition

The disparity in location and microbial density are features that are influenced by oxygen levels, nutrient availability, pH, and immune factors, and these variables have the potential to affect the gut microbial composition and spatial location [13]. Bacterial distribution within the lumen is not uniform; in the small intestine, for instance, the transit is faster, and and the sugar availability favors Proteobacteria and Lactobacillales expansion, which are rapidly dividing facultative anaerobes [14]. Considering the spatial structure of the colon microbiota, the phyla Firmicutes and Proteobacteria are the most predominant in the crypts and mucosa, while Actinobacteria and Bacteroides occur at lower levels [15]. Additionally, the microbiota in the small and large intestines rely on different nutrients for their developmental functions. In the large intestine, bacteria utilize nutrients that have not been absorbed in the upper gastrointestinal tract [16]. Furthermore, several studies have shown the nutritional competition between commensal and pathogenic bacteria, for instance, indigenous *Escherichia coli* has been reported to compete for amino acids and other nutrients with enterohemorrhagic *E. coli,* which causes morbidity [17–19]. Studies exploring competition for nutrients exhibited by the gut microbiota, as a mechanism to combat pathogens, are still relatively recent; however, it is evident that this competition is related to groups of commensal bacteria that are directly related to these pathogens in terms of their metabolism. For instance, in the case of mice infected with *Citrobacter rodentium*, the infection can be controlled when the mice are colonized with *E. coli,* which engages in nutritional competition [20].

Inhibitory Metabolites

Compounds in the diet are metabolized by digestive enzymes in the upper gastrointestinal tract. However, some of these metabolites remain intact and are processed and metabolized by the gut microbiota [21]. The gut microbiota may interact either with the host directly, through metabolites provided by the bacteria, or by the transformation of diet-derived substrates, which are small molecules representing products of microbial metabolism [22]. These metabolites may affect the host (e.g., short-chain fatty acids (SCFA) and vitamins), other commensal bacteria (e.g., bacteriocins), and pathogens (e.g., lactic acid and hydrogen peroxide) [23]. These bacterial products can act as growth inhibitors for competitors. Additionally, the antibiotic effect exhibited by lactic acid-producing bacteria is attributed to the production of lactic acid through glucose fermentation. This process leads to alterations in the pH, which in turn acts as a protective mechanism against potential pathogen invasions, ultimately leading to oxidative stress and cell death [24]. The production of hydrogen peroxide (H_2O_2) by lactic acid bacteria, particularly within the Lactobacillus clade, is a commonly observed phenomenon, especially when exposed to aerobic conditions. This metabolic trait enables them to generate substantial amounts of H_2O_2 [25]. Additionally, the presence of both lactic acid and hydrogen peroxide not only influences the composition of microbial communities but also induces heightened elimination of *Salmonella typhimurium* by inducing DNA damage [26]. Similar to lactic acid, bacteriocins, which are proteins that induce cell death by altering membrane potential, exhibit a synergistic effect on the microbiome and cause its disruption [27]. These findings demonstrate the direct impact of microbiota metabolites on microbial resilience, acting as controllers and inhibitors of other pathogenic bacteria.

Host-Associated Mechanisms of Resilience

Besides the inherent colonization resistance displayed by microbiota components, there are pivotal interactions with the host that can limit the invasion and proliferation of pathogens. In this section, we will discuss the role of the physical

barrier (e.g., mucous layer and epithelial cells) along with the oxygen gradient and components of the immune system, in the modulation of microbial resilience in the gut.

Oxygen Gradient

Since bacteria consistently sense the surrounding environment, the available oxygen becomes a key signal and energy source for their metabolism and fitness. Enteric bacterial composition and resilience are specifically related to the gut oxygen gradient since their metabolic activity can reduce free oxygen in the lumen, leading to the prevalence of an anaerobic environment [28]. For instance, the SCFA butyrate produced by *Clostridia* can boost aerobic respiration in epithelial cells by enhancing the beta-oxidation pathway and causing the lowering of the oxygen concentration [29]. The oxygen levels increased after Clostridia depletion, which can enable *S. typhimurium* proliferation [30]. In addition, it was demonstrated that, depending on the oxygen levels, Enterobacteriaceae can contribute to colonization resilience by competing with *S. entereditis* [28, 31]. Complementary, the resistance is lost when the capacity to respire oxygen under micro-aerophilic conditions is genetically ablated in *E. coli* [31]. Similarly, *Mucispirillum schaedler*, another microbiota component, competes for nitrate in the absence of oxygen, limiting the proliferation of *E. coli* and *S. typhimurium* which depend on nitrate metabolism to succeed during gut inflammation [32]. Hence, the capacity of the symbiont microbiota to generate a hypoxic environment in the intestine largely restricts the virulence potential and invasion of pathogenic players.

Mucus Layer

The intestinal barrier consists of an inner and an outer layer layers, the epithelial barrier, and the immune cells. Goblet cells secrete mucus, which consists of a combination of highly glycosylated proteins, with mucin 2 (MUC2) being the most abundant and crucial component for mucus layer organization in the colon [33]. Its importance was highlighted when studies demonstrated that mice lacking MUC2 spontaneously developed colitis [34], showed a predisposition to inflammation-dependent colorectal cancer development [35], and heightened susceptibility to *Citrobacter rodentium* and *Listeria monocytogenes* [36, 37, 38•]. These findings provide a plausible explanation for the development of inflammatory diseases in the absence or dysfunction of the mucus layer, which typically plays a crucial role in preventing pathogen-driven inflammation. Complementarily, microbiota components have been reported to play a fundamental role in mucus production. For instance, germ-free (GF) mice exhibit a thinner mucus layer [39] and the administration of a fiber-free diet to gnotobiotic mice hosting a simple microbiota set leads to higher *C rodentium* proliferation and epithelial invasion [40•]. The diet also exerts a direct effect on the mucus layer thickness. Gnotobiotic mice fed with a Western diet low in microbiota-accessible carbohydrates (MACs), fostered the growth of mucus-degrading bacteria, including *Akkermansia muciniphila* and *Bacteroides caccae.* As a result, these bacteria consumed the outer mucus layer, thereby reducing the space between the microbiota community and epithelial cells. Intrinsically, the host increased the MUC2 expression, however, it was not sufficient for avoiding pathogen invasion [41]. Only with *Bifidobacterium longum* administration could the outer mucus layer damage be reversed, possibly because of its potential capacity to stimulate mucus production [42]. Together, this evidence suggests an intrinsic balance between the functional state of the mucus layer and the microbiota composition.

The Epithelial Cells

Intestinal epithelial cells (IECs), which include goblet cells, as well as enteroendocrine and Paneth cells, possess specialized functions aimed at preserving the digestive and barrier functions of the epithelium [43]. The enteroendocrine population acts as a fundamental network between the central and enteric neuroendocrine systems by releasing a wide range of hormone regulators. As mentioned above, goblet cells secrete mucins, whereas Paneth cells are responsible for antimicrobial protein (AMPs) production, constituting a physical and biochemical barrier that prevents microbial contact with the epithelial surface [43, 44]. The most relevant and recognized AMPs produced by enterocytes are the C-type lectin regenerating islet-derived protein IIIγ (RegIIIγ), found throughout the small intestine and colon. Moreover, Paneth cells have been reported to secrete additional proteins such as defensins, lysozyme, and cathelicidins in the crypts of the small intestine [43, 45]. By disrupting the conserved features of microbial biology, AMPs allow the modulation of commensal and pathogenic bacteria in the intestinal tract. Microbiota components possess the capacity to regulate the production of AMPs, thus exerting an influence on microbial abundance [46] and playing a pivotal role in colonization resistance. A study demonstrated that microbiota depletion by antibiotics administration in mice caused a decrease in the RegIIIγ expression, which was restored after stimulation with a synthetic ligand for Toll-like receptor 7 (TLR7) [47]. This directly impacted the host's capacity to control vancomycin-resistant enterococci (VRE). Likewise, other studies have demonstrated that Nucleotide Binding Oligomerization Domain Containing 1 (NOD1) and NOD2 signaling

through receptor-interacting serine–threonine-protein kinase 2 (RIPK2) can limit *C. rodentium* expansion and colonization by stimulation of RegIIIγ production during the early stages of infection [48]. In addition, microbiota-derived peptidoglycans stimulate NOD2 and lead to crypt expression, which facilitates *L. monocytogenes* clearance in mice [49]. Epithelial cells also act as sentinels through the expression of pattern-recognition receptors (PRR), including members of the Toll-like receptor (TLR) [50], NOD-like receptor (NOD) [51], and Retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) [52]. Through signaling cascades that culminate in the production of several mediators, these receptors are pivotal for maintaining homeostasis between the host immune system and symbionts, recognizing pathogens, and initiating host defense and inflammation. The crosstalk between sensing molecules, the immune system, and microbiota resilience is discussed in detail in the next section.

Immune System Messengers

The intestinal microbiota also plays an essential role in orchestrating host immunity during homeostasis and disease. Cytokine signaling plays a vital role in host-microbiota interactions and serves to restrict pathogen invasion (Fig. 1). The primary producers of Interleukin (IL)-22 are lymphocytes, such as T helper (Th) 1, Th17, Th22, $CD8^+$ T cells, γδ T cells, natural killer cells (NK), and type 3 innate lymphoid (ILC3) cells [53]. This cytokine is expressed in response to proinflammatory cytokines, such as IL-1β, IL-6, Tumor Necrosis Factor (TNF)-α, and mainly IL-23, produced by myeloid cells upon perception of microbial signals [54]. It has been reported that IL-22 production by Th17 cells is triggered by the presence of segmented filamentous bacteria (SFB) and promotes lower susceptibility to *C. rodentium* infection [55]. Additionally, colonization of GF mice with human microbiota components promotes IL-22 production, enhancing host glycosylation and the consequent growth of *Phascolarctobacterium* species, which in turn compete with *C. difficile* for succinate in the gut [56••]. Several studies have reported the role of IL-22 in promoting intestinal barrier function and altering the composition of the gut microbiota [55, 57–59], however, it has also been shown that this cytokine may favor the proliferation of some pathogens, such as *S. tryphimurium,* over bacterial symbionts [60]. Notably, microbes can manipulate the host to achieve a competitive advantage within the intestinal microbiome community. *Bacteroides fragilis* can act via TLR2 activation on T helper (Th) cells to establish symbiosis with the host, which was proved by the fact that the TLR2 deletion in CD4 + T cells

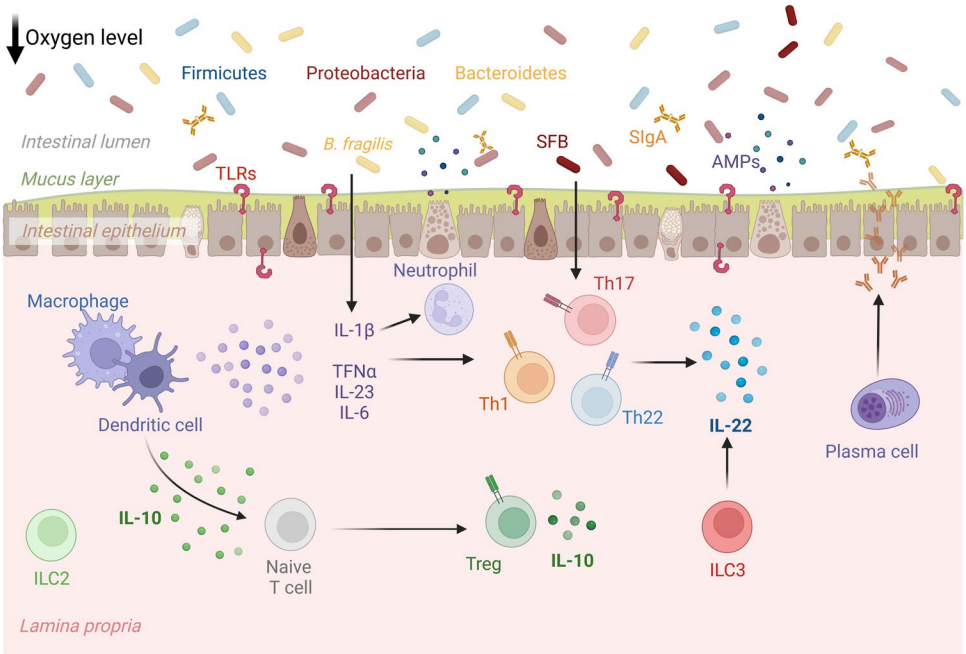

Fig. 1 Host-associated mechanisms of resilience. Several host features facilitate the diversity of mechanisms that cover the microbiota's resilience against pathogen invasions, including the low level of oxygen in the mucosa as a result of an interaction between commensals and epithelial cells; secretion of mucins by goblet cells compounding the mucus layer; secretion of AMPs and defensins by Paneth cells; cytokine production by innate immune cells that can activate and induce the differentiation of different types of lymphocytes, which together with ILCs produce key cytokines that control the exacerbated proliferation of microbiome components; secretion of IgA by plasma cells, which can also help controlling the expansion of prominent species in a balanced microbiota. AMPs: Antimicrobial peptides; ILCs: Innate lymphoid cells; IgA: Immunoglobulin A

drives an antimicrobial response that limits *B. fragilis* colonization [61]. Gut microbiota also enhances the priming of macrophages and IL-1β production to immediately respond to *S. tryphimurium* and *P. aeruginosa* infections, assisting neutrophil recruitment and further pathogen clearance [62]. A recent study showed that a mouse commensal *E. coli* isolate protected mice from *C. rodentium* infection and dextran sulfate sodium (DSS)-induced colitis by expansion IL-1B producing CX3CR1 + mononuclear phagocytes and IL-22-secreting type 3 innate lymphoid cells (ILC3) [63••]. A similar human commensal *E. coli* isolate also protected mice from infection and colitis [63••], revealing a surprising role for microbiota-mediated IL-1β secretion to endorse intestinal barrier repair.

Similarly, butyrate-producing bacteria can limit pathogen colonization by regulating tight junction protein expression via IL-10 signaling. IL-10 is secreted by several immune cells, the major producers of which are dendritic cells, macrophages, T cells, and ILC2 cells [64]. IL-10 can also promote intestinal Treg differentiation and maintenance, which is essential for preventing microbial-derived inflammation in the gut by controlling excessive effector T cell responses [65]. Studies have shown that diverse groups of symbionts can promote the expansion of Tregs from naïve T cells in the gut, thereby protecting mice from the inflammation caused by pathogenic invasion. For example, *B. fragilis* [66], *Bifidobacterium infantis* [67], and defined sets of bacteria including *Firmicutes* induce Treg expansion and reinforce intestinal barriers through several mechanisms [68]. Various studies have demonstrated differences in the microbiota composition between wild-type (WT) and IL-10-lacking mice. Using GF mice, Maharshak et al. [69] showed that IL-$10^{-/-}$ mice exhibited a decrease in microbiota complexity over time, however, this was not observed in wild-type littermates. Hence, *E. coli* is enhanced over time in IL-$10^{-/-}$ mice, converging with spontaneous inflammation and the initiation of colitis [69]. In summary, these studies highlighted the mechanisms employed by microbiota to promote cytokine production by immune components to maintain their colonization and resilience while facing pathogen invasion.

In addition to cytokines, the production of immunoglobulins is influenced by the gut microbiota, which can indirectly affect colonization fitness. Secretory immunoglobulin A (SIgA), produced by plasma cells, is the most prevalent isotype in the human intestinal lumen and is involved in the prevention of infections and maintenance of symbiont homeostasis. Fadlallah et al. [70] showed that co-dependent associations between commensals are disturbed in patients who exhibit deficiency in SIgA, which provides evidence for the participation of SIgA in the interactions between microbiota components [70]. Similarly, in mice, the binding of highly glycosylated SIgA to *Bacteroides* altered microbial metabolism and led to an indirect expansion of *Clostridiales*, culminating in impaired development of DSS colitis [71]. SIgA also induces the surveillance of *B. fragilis* in monocolonized mice [72] while promoting mutualistic associations between the host and possible pathogenic fungal symbionts by targeting and restraining virulent morphotypes. These evidence indicate the relevance of SIgA in modulating pathogen colonization and fostering ecological relationships between microbiota components [73].

Disruption of Microbiota Resilience by Pathogens

Despite multiple strategies developed through host-microbiota interactions, colonization resistance can be disrupted by pathogens. Through virulence programs, pathogens subvert the homeostasis of the healthy microbiota, impair barrier function, and trigger inflammation. The importance of pathogen virulence in combating microbiota resilience is emphasized by the integration of several environmental signals that dictate when and where to express virulence genes. For instance, the enhanced virulence of *C. rodentium* is essential for intestinal colonization in conventionally reared mice, but not in GF mice [20]. In addition, the proliferation of pathogens in diseases directly reflects the pathogen-microbiota interaction, since alterations in the physiological environment, such as oxygen levels and metabolic and nutritional settings, favor the growth of invading microbes over the commensals [74, 75]. The evasion and virulence strategies of pathogens and their consequences for health and disease are discussed in the next section.

Pathogen Evasion Strategies

As symbiont components, pathogens can successfully colonize the host through a virulence setting that modulates spatial niche construction and promotes their growth over the microbiota. Facultative anaerobic pathogens, including *S. typhimurium*, *C. rodentium*, and other Enterobacteriaceae, can create a physiologically challenging environment for symbiotic bacteria by modulating oxygen levels in the large intestine. As the majority of the microbes in the colon are fermenters and highly oxygen-sensitive, virulent programs that induce an increase in oxygen levels lead to a reduction in these components, facilitating pathogen invasion and growth [76]. For example, expression of the toxin type III secretion system (T3SS) by *C. rodentium* leads to crypt hyperplasia in mice, decreasing overall oxygen consumption through changes in epithelial metabolism [77]. Consequently, this increased oxygenation of the mucosa drives aerobic *C. rodentium* proliferation in the colon, favoring infection. It was recently reported that T3SS-mediated

intimate attachment also enables the oxidation of hydrogen peroxide by *C. rodentium*, which is produced by epithelial NADPH oxidase (NOX1) even before crypt hyperplasia [78••]. As mentioned previously, one of the inherent strategies of the microbiota to resist pathogen colonization is its capacity, together with the epithelium, for rapid nutrient consumption. However, some pathogens can circumvent this obstacle by evading microbiota resilience and colonizing the host. For example, enteropathogenic *E. coli* (EPEC) can obtain nutrients from infected host cells via host nutrient extraction (HNE). Through an inner membrane complex, EPEC can protrude the structure of membranous nanotubes directly into host cells and draw on their nutrients [79]. Conversely, other pathogens have evolved the capacity to use alternative nutrient sources, such as *C. rodentium*, which can use diet-derived metabolites produced by commensal bacteria for initial proliferation and T3SS-driven inflammation [80]. Triggering inflammation is also a widely used strategy employed by pathogens [81, 82]. For example, *S. typhimurium* uses the Spi1 T3SS to induce the expression of inflammatory signals in the ileum and cecum of mice. Through the host's generation of reactive oxygen and nitrogen species, *S. typhimurium* utilizes the byproducts, such as tetrathionate, nitrate, and oxidized sugars for respiration and proliferation [83, 84]. Together, this evidence exemplifies several specialized strategies to overcome the colonization resistance dictated by the microbiota (Fig. 2).

Microbiota Resilience Disruption

In addition to pathogen infection, other external stress factors such as severe dietary changes, antibiotics, and other medications can perturb the balanced ecosystem achieved by healthy microbiota. Consequently, the gut microbiome may return to its original shape. A resilient microbiota can return to its baseline equilibrium employing the various strategies discussed earlier, whereas a non-resilient microbiota is molded to acquire a new composition (Fig. 2). It is assumed that a healthy individual has a resilient microbiota that can rapidly return to its steady state after exposure to unavoidable environmental stressors [7, 10, 85]. An impaired ability to resist these challenges facilitates dysbiosis, which is associated with several chronic diseases. Specifically, in the gut, inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are intimately associated with the disruption of healthy microbiota. Although several factors, including genetics, can be associated with IBD pathogenesis, the composition of the gut microbiome is thought to be an essential determinant of host susceptibility to IBD, since it can contribute to aberrant immune responses through multiple mechanisms d [86, 87]. Similarly, the transfer of IBD-associated microbiota into healthy mice induces intestinal inflammation [88], while microbiota depletion by antibiotic administration enhances intestinal inflammation in IBD-susceptible mouse models. However,

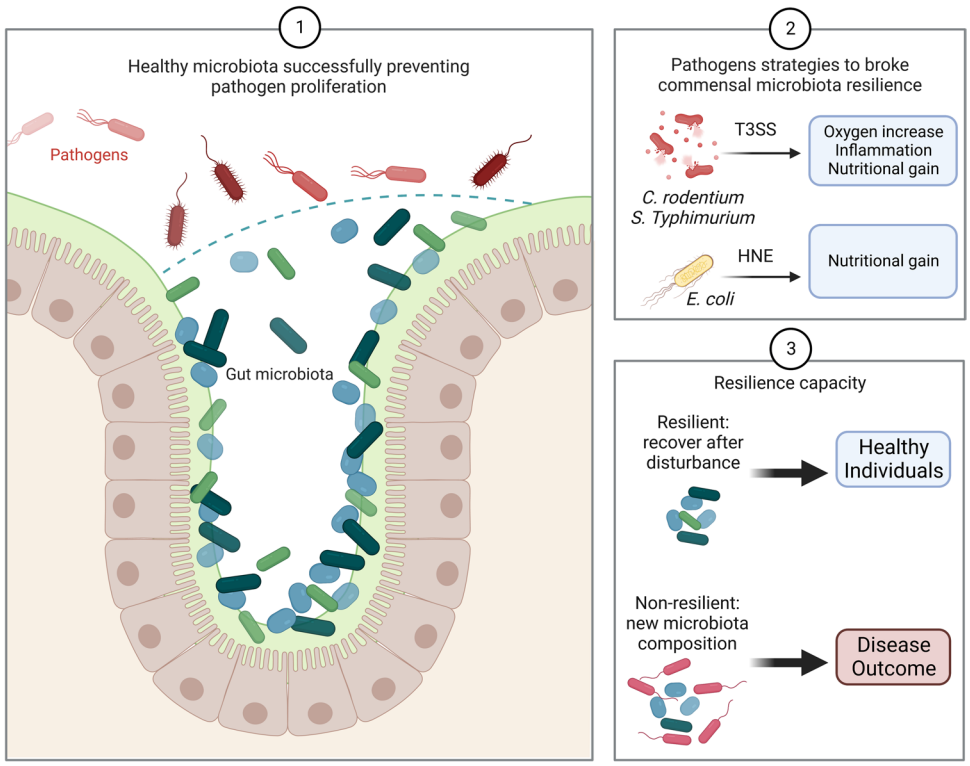

Fig. 2 The commensal microbiota colonization resistance is constantly challenged by external factors such as pathogens, which in turn develop strategies to modulate environmental factors, including oxygen levels and nutrient disposition. They also trigger inflammation, leading to physiological changes that impair the commensal's growth. However, a healthy microbiota can resist and recover from these attacks, as well as restore its original composition. In certain individuals, plausibly due to genetic alterations, the microbiota cannot be restored and the resilience is disrupted, establishing dysbiosis and leading to the development and worsening of the disease

the colonization of pathobionts, such as adherent-invasive *E. coli* (AIEC) [89••], *Enterococcus faecium* [90], enterotoxigenic *Bacteroides ragilis* [91], and multi-drug resistant *Klebsiella pneumoniae* (Kp) [92•] is related to IBD worsening in genetically susceptible individuals. Therefore, interventions that improve microbiome resilience are indispensable for disease amelioration. Understanding the features of resilient microbiota will assist in the conception of interventions aimed at enhancing resilience. In this way, dietary fibers can be a contributing factor in increasing microbiota diversity and, consequently, a more resilient one. Mice fed a fiber-enriched diet that was challenged with antibiotics and *C. difficile* returned to the pre-challenged composition, whereas mice fed a low-fiber diet did not [11], indicating that fibers have a direct effect on improving microbiota resilience in mice. Hence, the administration of probiotics containing species with anti-inflammatory features, such as *Lactobacillus rhamnosus* [93], or those that can improve the gut barrier, such as *Lactobacillus plantarum* [94], has been reported to be potential intervention strategies that can enhance microbiota resilience. Meanwhile, probiotic and dietary interventions that aim to boost certain species need to be carefully administered to avoid targeted components from becoming more prominent leading to a negative impact on the microbiome diversity [7]. Recently, Federici et al. [95••] demonstrated that IBD-associated Kp strains aggravate intestinal inflammation in colitis-prone, germ-free, and colonized mice, which is reversed using a lytic five-phage combination targeting Kp. They also assessed the proof-of-concept of Kp-targeting phages in an artificial human gut and healthy volunteers, demonstrating a feasible oral administration therapy that improves microbial resistance to pathobionts expansion [95••]. Together, these studies highlight the importance of colonization-resistant microbiota in health and disease and the emergence of combined therapies focused on reestablishing resilience.

Conclusion

In this review, we summarize the main strategies used by symbiotic bacteria to remain resilient against pathogen attacks throughout a host's life. The inherent ecological and physiological characteristics of symbionts has the ability to confer a high degree of equilibrium between all microbiota components. However, the modulation of the host's features, such as the mucosal barrier and immune system has been crucial for a closer host-microbiota relationship built through thousands of years of evolution. Its importance for human health has been highlighted in several studies showing the mechanisms underlying the disturbance of microbial resilience. However, a complete understanding of the role of microbiota resilience in health and disease remains a contentious subject, as experimental validation of models and further investigation in humans are required. In summary, as greater insights are acquired regarding microbiota resilience, innovative integrated interventions may be applied in the treatment of several microbiota-associated diseases.

Abbreviations *IBD*: Inflammatory bowel disease; *SCFA*: Short-chain fatty acids; *MUC2*: Mucin 2; *GF*: Germ-free; *MACs*: Microbiota-accessible carbohydrates; *IECs*: intestinal epithelial cells; *RegIIIγ*: Regenerating islet-derived protein IIIγ; *AMPs*: Antimicrobial proteins; *VRE*: Vancomycin-resistant enterococcus; *RIPK2*: Receptor-interacting serine–threonine-protein kinase 2; *TLR*: Toll-like receptor; *NOD*: NOD-like receptor; *RLR*: RIG-I like receptor; *PRR*: Pattern-recognition receptors; *SFB*: Segmented filamentous bacteria; *IL*: Interleukin; *Th*: T helper; *CX3CR1*: C-X3-C Motif Chemokine Receptor 1; *ILCs*: Innate lymphoid cells; *DSS*: Dextran sulfate sodium; *WT*: Wild-type; *SIgA*: Secretory immunoglobulin A; *T3SS*: The toxin type III secretion system; *NOX1*: NADPH oxidase; *EPEC*: Enteropathogenic *E. coli*; *HNE*: Host nutrient extraction; *AIEC*: Adherent-invasive *E. coli*; *Kp*: Klebsiella pneumoniae

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EMS: Writing—original draft; writing—review and editing.
NOSC: Conceptualization, lead; funding acquisition, supporting; lead; writing—original draft, lead; writing—review and editing, lead.

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Compliance with Ethical Standards

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- • Of importance
- •• Of major importance

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