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REVIEW

Healthy hosts rule within: ecological forces shaping the gut microbiota

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A balanced gut microbiota is important for human health, but the mechanisms that maintain homeostasis are incompletely understood. Recent insights suggest the host plays a key role in shaping its gut microbiota to be beneficial. While host control in the small intestine curbs bacterial numbers to avoid competition for simple sugars and amino acids, the host limits oxygen availability in the large intestine to obtain microbial fermentation products from fiber. Epithelial cells are major players in imposing ecological control mechanisms, which involves the release of antimicrobial peptides by small-intestinal Paneth cells and maintenance of luminal anaerobiosis by epithelial hypoxia in the colon. Harnessing these epithelial control mechanisms for therapeutic means could provide a novel lynchpin for strategies to remediate dysbiosis.

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INTRODUCTION

Since the first demonstration of causality by Koch's postulates,[1] the idea that microorganisms cause diseases has been a leading concept in pathogenesis. Frank pathogens can cause sickness in individuals with an intact immune system, which supports the idea that microbial virulence factors are the principal drivers of the disease process. Although the downstream host response to infection can contribute to the development of symptoms, disease caused by frank pathogens is not due to an underlying host defect. Therefore treating symptoms produced by the host immune response can provide benefit, but curing the disease requires eradicating its cause, the microbial pathogen.

The idea that microorganisms cause diseases is also a popular concept driving research on the contribution of the host-associated microbial community (microbiota) to disease.[2,3] The view that an imbalance in the microbial community (dysbiosis) is an underlying cause of sickness provides a rationale for establishing commensal Koch's postulates for microbiota research[4] and raises hope that administering fecal microbiota transplants (FMTs) to eradicate a microbial imbalance could be developed as a cure.[5,6] The latter approach is successful in treating antibiotic-associated colitis,[7] because here the FMT directly targets the underlying defect, namely an antibiotic-mediated disruption of the gut microbiota.[8] However, lasting benefits of FMT remain to be established for diseases associated with dysbiosis developing independently of antibiotic treatment.[9–11]

An alternative view holds that dysbiosis exacerbates disease, but that it is secondary to an underlying defect in the host,[8] which impairs control over the microbial ecosystem.[12] The defect in the host's ability to control the microbial ecosystem can lead to downstream consequences, such as changes in the microbial metabolite landscape, which can contribute to the development of symptoms. Thus, remediating dysbiosis with probiotics or FMTs can provide benefit, but curing the disease will require eradicating its cause by restoring host control over the microbial ecosystem.[12,13]

This review reports our current understanding of how the host maintains control over its microbial ecosystem. The main focus will be on the human gastrointestinal tract, because this site harbors the largest microbial community, whose disturbance is associated with many human illnesses, including inflammatory bowel diseases,[14] colorectal cancer,[15,16] athrosclerosis,[17] and even neurological disorders.[18,19]

HOST CONTROL AT ITS EXTREME

Ecological theory suggests that hosts are under strong natural selection to shape their microbiota to be beneficial.[13] Host control over the microbial community structure is particularly striking for the light organ of the bobtail squid, which is permissive for only a single-bacterial species, the luminous *Vibrio fischeri* (phylum *Proteobacteria*) (Fig. 1a).[20] The light organ acquires *V. fischeri* horizontally,[21] which suggests that the bobtail squid must select the correct bacterial species from some 1800 bacterial species present in seawater.[22] The underlying species–specific selection mechanisms are not fully resolved, but include a number of antimicrobial factors produced by the host.[23–25] Interestingly, luciferase, the enzyme catalyzing light production, is required for colonization of the light organ,[26] presumably because luminescence consumes oxygen, thereby protecting *V. fischeri* from bactericidal phenoloxidase activity, which is produced by the host to control the environemnt.[27] Through these mechanisms, the host limits access to its light organ to a single-bacterial species producing luminescence, which in turn provides benefit by supporting the bobtail squid's camouflaging behavior termed counterillumination.

Although, our body does not constrain any of its microbial communities to just a single-bacterial species, the female reproductive tract brings our ability to shape the microbiota

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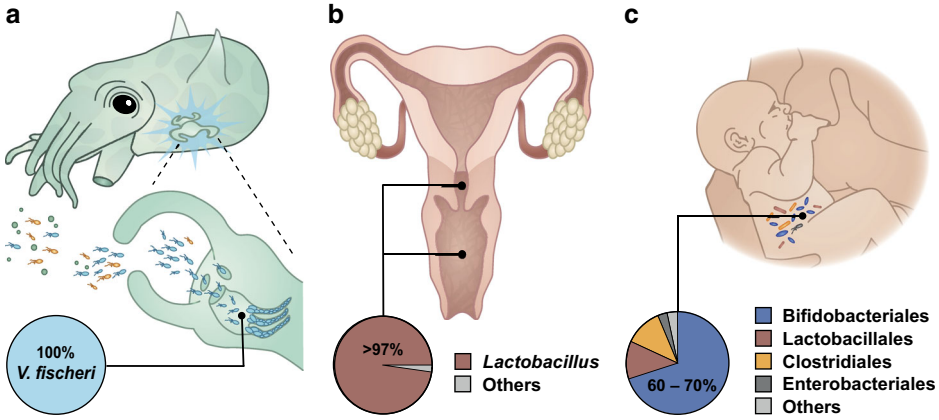

Fig. 1 Host control can steer the microbial community composition towards dominance of a single genus. **a** Antimicrobial factors produced by the bobtail squid limit colonization of its light organ to a single species, *Vibrio fischeri*.[20] **b** Host control mechanisms direct the composition of the cervical and vaginal microbiota in the majority of reproductive-aged women toward a dominance of *Lactobacillus* species.[28,29] **c** Maternal control imposed through milk oligosaccharides drives a dominance of *Bifidobacterium* species in the infant gut microbiota.[34]

composition into plain sight. In the majority of reproductive-aged women, >97.5% of the bacteria in the cervical and vaginal microbiota belong to one or more species of just a single genus, *Lactobacillus* (phylum *Firmicutes*) (Fig. 1b).[28,29] This dominance of a single genus illustrates that similar to the bobtail squid, the human host can keep its microbiota on a very short leash. The proposed mechanism selecting for a *Lactobacillus*-dominated microbiota is hormonal control by estrogen,[30] which coordinates α-amylase-mediated catabolism of host-derived glycogen into maltose and maltotriose. In turn these host-derived oligosaccharides promote fermentative growth by *Lactobacillus* species.[31] This host-mediated nutritional selection for a *Lactobacillus*-dominated vaginal microbiota is thought to provide benefit by imparting a barrier to infection with vaginal pathogens.[32]

Host control over microbes also becomes obvious during nursing, a maternal influence that profoundly shapes the composition of the colonic microbiota during infancy. Human milk oligosaccharides are complex carbohydrates that cannot be broken down by enzymes in the upper gastrointestinal tract of the infant and reach the colon,[33] where they foster development of a microbiota dominated by species belonging to the genus *Bifidobacterium* (phylum *Actinobacteria*), which account for up to 70% of the bacteria present in feces (Fig. 1c).[34] Consistent with the idea that human milk oligosaccharides selectively feed members of the genus *Bifidobacterium*, the infant-associated *B. longum* subspecies *infantis* contains a carbohydrate utilization gene cluster for fermentative breakdown of these nutrients,[35] which is absent from the genome of species that do not dominate the microbiota of breast-fed infants.[36] By shaping the composition of the gut microbiota during a critical period when the immune system is still developing, maternal control mediated through human milk oligosaccharides provides benefit for infant health.[37]

While the examples above illustrate that the host can profoundly shape the microbiota composition by imposing domination of a single genus (Fig. 1), host control over the microbiota composition is not apparent from fecal microbiota analysis of human adults, which provides no evidence for any bacterial species being under positive selection.[38] Once nutritional control mediated through milk oligosaccharides is relieved at weaning, the dominance of the genus *Bifidobacterium* gives way to a diverse microbial community, predominantly composed of obligate anaerobic bacteria belonging to the phyla *Firmicutes* and *Bacteroidetes*. On the species level, the human gut microbiota composition shifts strongly with changes in the diet,[39] thus supporting the idea that diet is one of the main drivers in shaping the gut microbiota.[40] In the absence of any blatant signs of host control over the microbiota in adults, mechanisms that maintain a balanced colonic microbial community during gut homeostasis have remained elusive. In the following sections we will review recent evidence suggesting that host control over the microbial ecosystem is also a prominent feature in the adult colon, but that its existence is masked by bacterial diversity needed for breaking down different dietary carbohydrates. Furthermore, the objective of host control over the microbiota changes fundamentally as contents move from the small intestine into the colon, which will be discussed in sequence.

SMALL INTESTINE: MICROBIAL POPULATION INCREASE MEETS HOST CONTROL

Facultative anaerobic bacteria belonging to the families *Lactobacillaceae* (phylum *Firmicutes*) and *Enterobacteriaceae* (Proteobacteria) dominate the microbiota in the small intestine, with bacterial densities gradually increasing from 10^1–10^3 bacteria/ml in the duodenum to 10^4–10^7 bacteria/ml in the ileum.[41] This bacterial community can de novo synthesize vitamin B-12 (cobalamin),[42,43] which is thought to be beneficial because humans lack this biosynthetic capacity and thus rely on an exogenous source. Gastric intrinsic factor secreted by the gastric mucosa binds dietary or microbiota-derived cobalamin and promotes its absorption in the ileum.[44]

While the small-intestinal microbiota might aid in supplying the host with cobalamin, its community size needs to be controlled because the small intestine is the main site for absorption of simple sugars, amino acids, fatty acids, and glycerol, nutrients that are either present in our diet or generated by host enzymes through digestion of proteins, carbohydrates or fat. Since microbes can also consume these diet-derived nutrients, a large microbial community in the small intestine would compete with the host for food and produce malnutrition. Thus, to ensure the microbiota remains beneficial, the host has to prevent bacterial overgrowth in the small intestine. The host curbs bacterial numbers in the small intestine through gastric acid secretion, bowel motility, secretion of immunoglobulin and bacteriostatic properties of pancreatic and biliary secretions. Any illness that impairs these host control mechanisms puts a person at risk for small-intestinal bacterial overgrowth, which can result in malnutrition and weight loss.[45]

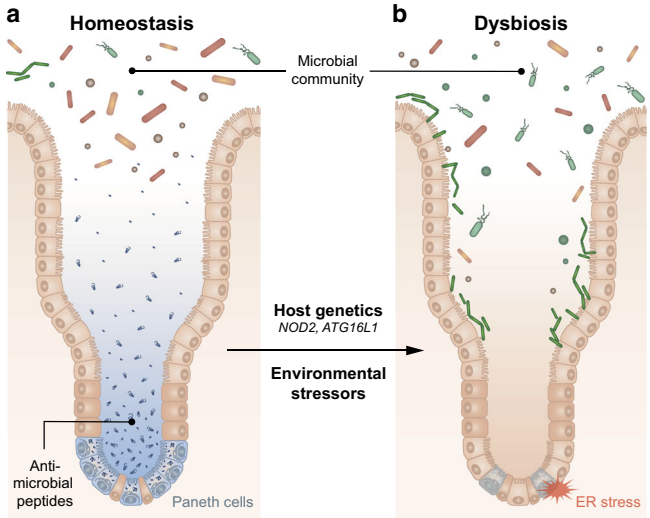

Fig. 2 Paneth cell-mediated host control in the small intestine. **a** Antimicrobial peptides secreted by Paneth cells in the small-intestinal crypts check bacterial growth in close proximity to the epithelial surface, thereby maintaining homeostasis in the small intestine. **b** Genetic and environmental factors can co-operate to trigger ER stress, which results in intestinal inflammation and Paneth cell dysfunction. The latter reduces antimicrobial peptide secretion, thereby inducing dysbiosis characterized by an outgrowth of bacteria that reside in close proximity to the epithelial surface, which in turn can exacerbate intestinal inflammation

Another mechanism by which the host keeps control over the microbiota in the small intestine is the secretion of antimicrobial peptides by Paneth cells, specialized secretory epithelial cells located in the small-intestinal crypts. Paneth cells secrete an antimicrobial cocktail of defensins, lysozyme, phospholipase A_2, and Reg3 lectins to contain gut microbes in close proximity to the mucosa (Fig. 2a).[46] Their intensive secretory activity renders the extensive endoplasmic reticulum (ER) network of Paneth cells vulnerable to ER stress. Disruption of normal Paneth cell function by ER stress accompanies ileal Crohn's disease, a form of inflammatory bowel disease.[47] One risk factor for developing Crohn's disease is childhood exposure to environmental factors present in geographical regions of high-disease incidence.[48] Animal experiments suggest such environmental factors include dietary emulsifiers,[49] a known trigger of ER stress in the intestinal epithelium.[50,51] Genome-wide association studies identify genetic polymorphisms in the *NOD2*[52] and *ATG16L1* genes[53] as risk factors for developing Crohn's disease. Interestingly, proteins encoded by the *NOD2* and *ATG16L1* genes are both functionally linked to ER stress,[54,55] suggesting the corresponding risk alleles might jeopardize Paneth cell function. Consistent with ER stress-induced Paneth cell dysfunction, patients with Crohn's disease exhibit decreased ileal synthesis of Paneth cell defensins,[56] a trait linked to the *NOD2* risk allele.[57] In turn, disruption of normal Paneth cell function contributes to dysbiosis observed during Crohn's disease (Fig. 2b).[58]

Direct evidence that Paneth cell-derived antimicrobial peptides shape the microbial community comes from experiments with transgenic mice expressing a human Paneth cell defensin, which results in the exclusion of segmented filamentous bacteria (phylum *Firmicutes*) from the microbial community.[59] Segmented filamentous bacteria are intimately associated with the plasma membrane of murine epithelial cells, but are not a common constituent of the human small-intestinal microbiota,[60] although it is not clear that synthesis of human Paneth cell defensin is responsible for their exclusion. However, Crohn's disease is associated with a dysbiotic expansion of adherent-invasive *Escherichia coli* (family *Enterobacteriaceae*), which reside in close proximity to the mucosal surface.[61] Thus, Paneth cell-derived antimicrobial peptides might serve to protect the epithelial surface, whereas impaired defensin synthesis accompanying Crohn's disease might result in enhanced colonization of this niche (Fig. 2b). Adherent-invasive *E. coli* reduce expression of *ATG16L1* in cultured epithelial cells, thereby impairing autophagy,[62] an ER repair mechanism.[63] This observation raises the possibility that dysbiosis enhances inflammation by exacerbating ER stress. The idea that dysbiosis exacerbates inflammation is supported by clinical data showing that antibiotic therapy can induce remission in active Crohn's disease.[64]

Graft-versus-host disease (GvHD) is another illness associated with a disruption of Paneth cell function. GvHD is linked to reduced luminal defensin secretion and dysbiosis, which further accelerates the underlying illness.[65,66] Interestingly, R-spondin 1-induced differentiation of intestinal stem cells into Paneth cells restores defensin secretion and prevents dysbiosis in a mouse model of GvHD.[67] These data provide a proof of principle that rebalancing the gut microbiota by reinstating epithelial control over the microbial ecosystem represents a feasible therapeutic approach for restoring homeostasis.

HEALTHY GUTS EXCLUDE OXYGEN: HOW THE HOST CONTROLS ITS COLONIC MICROBIOTA

As discussed above, host control in the small intestine is aimed at curbing bacterial numbers to avoid direct competition between host and microbiota for simple sugars and amino acids. In contrast, host control in the large intestine is no longer directed at limiting the size of the microbial community, as indicated by a steep rise in the bacterial density from 10^4–10^7 bacteria/ml in the ileum to 10^{11}–10^{12} bacteria/ml in the colon.[41] The large microbial community in the colon breaks down complex carbohydrates that cannot be digested by host enzymes in the upper gastrointestinal tract and reach the large bowel. In the absence of oxygen, obligate anaerobic bacteria catabolize complex carbohydrates into fermentation products, such as short-chain fatty acids, which are absorbed in the colon, thereby contributing to host nutrition.[68,69] However, in the presence of oxygen, facultative anaerobic bacteria catabolize fermentation products to carbon dioxide,[70] which is predicted to interfere with host nutrition. Thus, limiting oxygen availability in the colon helps the host to ensure the microbiota remains beneficial. To minimize the amount of oxygen emanating from the mucosal surface, the host maintains colonic epithelial cells (colonocytes) in a state of hypoxia (<1% oxygen).[71] This host control mechanism ensures a dominance of obligate anaerobic bacteria in the colon without restricting diversity of the microbiota on the species level.[72] The latter is functionally important, because bacterial diversity increases the probability of including species that can breakdown any given complex carbohydrate, thereby increasing the efficiency of obtaining short-chain fatty acids from a fiber-rich diet. Thus, while oxygen limitation in the colon controls the microbial ecosystem to ensure a dominance of obligate anaerobic bacteria,[73] a lack of constraints on species diversity explains why this important host control mechanism is easily overlooked when a detailed analysis of fecal microbiota composition is performed.[38]

The host maintains anaerobiosis in the large bowel through a virtuous cycle that involves monitoring the presence of microbiota-derived fermentation products. Specifically, short-chain fatty acids produced by the microbial community of obligate anaerobic bacteria in the colon promote maturation and expansion of regulatory T cells[74–78] and activate the epithelial butyrate-sensor PPAR-γ,[73] which is highly expressed in differentiated colonocytes.[79] Regulatory T cells and epithelial PPAR-γ-signaling act in concert to drive the energy metabolism of

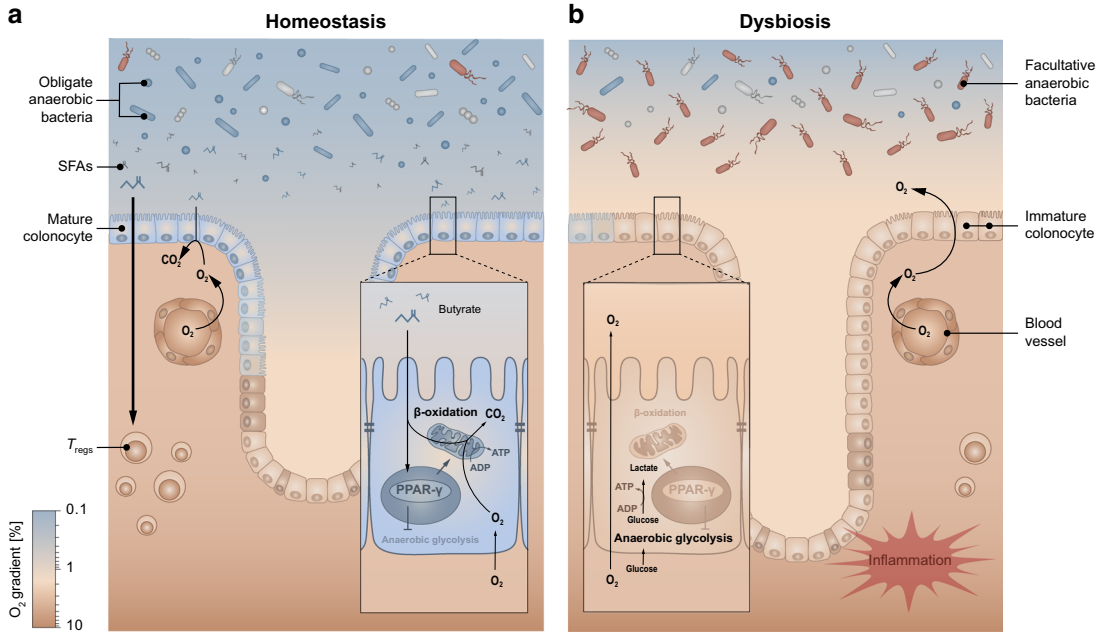

Fig. 3 Colonocyte-mediated host control in the large bowel. **a** Mature colonocytes obtain energy by PPAR-γ-activated mitochondrial β-oxidation of microbiota-derived butyrate (insert), a process that consumes oxygen (O_2) and renders the epithelial surface hypoxic (<1% O_2). Epithelial hypoxia drives anaerobiosis in the lumen, thereby ensuring a dominance of obligate anaerobic bacteria that convert fiber into short-chain fatty acids (SFAs), which serve host nutrition and suppress inflammation by promoting differentiation and expansion of regulatory T cells (T_{regs}). The color scale on the bottom left indicates O_2 levels. **b** Inflammation and epithelial repair can shift the energy metabolism of colonocytes towards anaerobic glycolysis (insert). The consequent increase in epithelial oxygenation impairs the host's ability to control the flow of oxygen into the intestinal lumen, which leads to dysbiosis characterized by a shift in the microbial community from obligate to facultative anaerobes

colonocytes toward oxygen consumption through β-oxidation, which renders the colonic surface hypoxic (Fig. 3a).[73] In turn, epithelial hypoxia limits the amount of oxygen diffusing into the intestinal lumen, thereby maintaining a dominance of obligate anaerobic bacteria that breakdown fiber into short-chain fatty acids. This virtuous cycle provides stability[73] and might contribute to microbiota resilience.[80,81]

An impaired ability of the host to limit the flow of oxygen into the gut lumen is associated with a shift in the microbial community from obligate to facultative anaerobes,[82] a common microbial signature of dysbiosis in the colon (Fig. 3b).[83] For example, an expansion of facultative anaerobic *Enterobacteriaceae* is observed during ulcerative colitis, a form of inflammatory bowel disease affecting the colon.[14] Based on this correlation, the "oxygen hypothesis" proposes that ulcerative colitis might be associated with a disruption in anaerobiosis.[84] Recent work on mouse models of ulcerative colitis provides direct support for this idea. Metagenomic analysis of changes in the gut microbiota observed in dextran sulfate sodium (DSS)-induced colitis identifies oxygen respiration as a dominant microbial signature associated with inflammation.[85] *Citrobacter rodentium* (family *Enterobacteriaceae*) triggers colonic crypt hyperplasia in mice, which mimics aspects of ulcerative colitis pathology.[86] Colonic crypt hyperplasia is the result of excessive epithelial repair responses, leading to crypt elongation, the appearance of undifferentiated epithelial cells at the luminal surface and a consequent reduction in the numbers of goblet cells, which results in a thinning of the mucus layer. Colonic crypt hyperplasia shifts the colonocyte metabolism toward anaerobic glycolysis, thereby elevating epithelial oxygenation, which in turn drives a luminal expansion of *C. rodentium* through aerobic respiration.[87] Similarly, aerobic respiration drives a luminal expansion of commensal *E. coli* during DSS-induced colitis.[85] Thus, an expansion of *Enterobacteriaceae* during ulcerative colitis might be a microbial signature of a dysfunctional epithelium that no longer limits the flow of oxygen into the colonic lumen.[88] The ensuing dysbiosis likely exacerbates intestinal inflammation, a conclusion supported by the clinical observation that ulcerative colitis can respond to antibiotic treatment.[64]

Above observations suggest that reestablishing anaerobiosis by restoring epithelial hypoxia could offer an alternative to FMTs for remediating dysbiosis. Unbeknownst to us, we might have already been harnessing this host control mechanism for therapeutic means for decades. Mesalazine, also known as 5-aminosalicylic acid (5-ASA), has been used for over 40 years as the first-line treatment for mild to moderate ulcerative colitis.[89–91] 5-ASA acts predominantly topical at the site of inflammation, especially within the colon,[92–94] presumably by activating PPAR-γ-signaling in colonocytes.[95] Since PPAR-γ-signaling is a strong driver of β-oxidation in colonocytes[73] (Fig. 3a), 5-ASA likely aids in reestablishing epithelial hypoxia, thereby restoring host control mechanisms that limit oxygen availability in the colon.

When patients with ulcerative colitis develop severe exacerbation and require hospitalization, corticosteroids are the mainstay of therapy, while 5-ASA no longer has any effect on disease of this severity.[96] This correlates with histopathological changes that include a loss of colonocytes (epithelial erosion),[97] the therapeutic target of 5-ASA.[95] Other histopathological indicators of severe acute ulcerative colitis include necrosis of tissue underlying areas of epithelial erosion (ulcers) and infiltration of neutrophils.[97] Neutrophils undergoing a respiratory burst render the mucosal surface hypoxic.[98] However, the respiratory burst generates alternative electron acceptors, such as nitrate and tetrathionate.[99] Mouse models of colitis show that nitrate and tetrathionate can drive a colonic expansion of facultative anaerobic *Enterobacteriaceae* through anaerobic respiration.[100–104]

Thus, colitis is generally accompanied by an expansion of *Enterobacteriaceae*, but the mechanisms driving this expansion might differ between mild to moderate ulcerative colitis and severe acute ulcerative colitis.

The picture emerging from these studies is that during homeostasis the host keeps control over the colonic ecosystem by limiting the availability of exogenous respiratory electron acceptors to maintain anaerobiosis and check the growth of facultative anaerobic bacteria (Fig. 3a). Loss of this host control mechanism during colitis triggers a dysbiotic shift in the microbial community from obligate to facultative anaerobes (Fig. 3b).[12] Epithelial PPAR-γ-signaling has emerged as a promising therapeutic target for restoring epithelial control over the colonic ecosystem to rebalance the microbiota.

CONCLUSIONS

The different digestive functions of the small and large intestines are each matched with a fitting host control mechanism that ensures the microbiota is compatible with and beneficial for host nutrition. An emerging theme throughout the gastrointestinal tract is the important role epithelial cells play in maintaining homeostasis by shaping the gut microbiota to be beneficial. The epithelial cell types exercising control over the microbiota differ between the small and large bowel. While Paneth cells secrete antimicrobial peptides to control the microbiota in the small intestine (Fig. 2),[58] colonocytes limit the flow of oxygen into the gut lumen to shape the microbiota composition in the large intestine (Fig. 3).[88] Since the human host already has ways to regulate the microbiota, reinstating epithelial control over the gut ecosystem offers an alternative to targeting the microbes themselves for remediating dysbiosis. Harnessing epithelial control for therapeutic means therefore represents a promising novel strategy for rebalancing the microbiota in a broad spectrum of human diseases.

AUTHORS CONTRIBUTIONS

M.X.B. and A.J.B. wrote the manuscript. S.R.P. generated scientific Illustrations.

ADDITIONAL INFORMATION

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