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The human gut microbiome in health and disease: time for a new chapter?

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ABSTRACT The gut microbiome, composed of the colonic microbiota and their host environment, is important for many aspects of human health. A gut microbiome imbalance (gut dysbiosis) is associated with major causes of human morbidity and mortality. Despite the central part our gut microbiome plays in health and disease, mechanisms that maintain homeostasis and properties that demarcate dysbiosis remain largely undefined. Here we discuss that sorting taxa into meaningful ecological units reveals that the availability of respiratory electron acceptors, such as oxygen, in the host environment has a dominant influence on gut microbiome health. During homeostasis, host functions that limit the diffusion of oxygen into the colonic lumen shelter a microbial community dominated by primary fermenters from atmospheric oxygen. In turn, primary fermenters break down unabsorbed nutrients into fermentation products that support host nutrition. This symbiotic relationship is disrupted when host functions that limit the luminal availability of host-derived electron acceptors become weakened. The resulting changes in the host environment drive alterations in the microbiota composition, which feature an elevated abundance of facultatively anaerobic microbes. Thus, the part of the gut microbiome that becomes imbalanced during dysbiosis is the host environment, whereas changes in the microbiota composition are secondary to this underlying cause. This shift in our understanding of dysbiosis provides a novel starting point for therapeutic strategies to restore microbiome health. Such strategies can either target the microbes through metabolism-based editing or strengthen the host functions that control their environment.

KEYWORDS gut microbiome, gut microbiota, dysbiosis, ecological guilds

Advances in high-throughput sequencing in the first decade of the 21st century kicked off studies on host-associated microbial communities (the microbiota) using culture-independent approaches. By providing detailed insights into the microbiota composition, this methodology launched a new discipline focused on exploring the human microbiome during health and disease (1). Microbiome research touches many aspects of human health since changes in the fecal microbiota composition suggest that a microbiome imbalance (dysbiosis) is associated with major causes of morbidity and mortality (2), ranging from cardiovascular disease (3) to colorectal cancer (4, 5), diabetes (6), chronic kidney disease (7), chronic liver disease (8), and even neurological disorders(9) (Fig. 1). Changes in the fecal microbiota are relevant because they reflect alterations in the composition of the colonic microbiota, which is by far the largest community inhabiting our body (10) and an important source of microbial metabolites that affect human health (11). Therefore, understanding the mechanisms that maintain gut homeostasis and the ecological causes for its disruption during gut dysbiosis is essential to answer central questions in human microbiome research.

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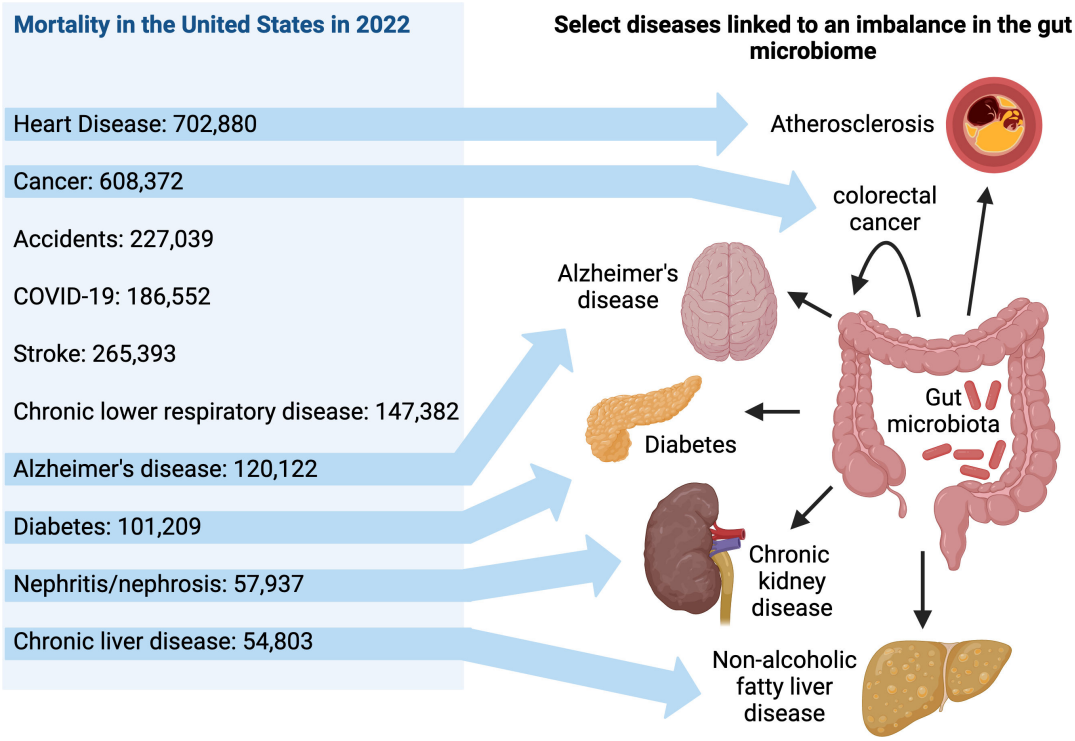

FIG 1 A gut microbiome imbalance is associated with major causes of human morbidity and mortality. Left panel: Leading causes of human mortality in the United States reported by the centers for disease control and prevention (2). Numbers indicate deaths recorded in 2022. Right panel: Select diseases linked to a change in the fecal microbiota composition.

INTO DARKNESS

Studies performed prior to the advent of modern microbiome research had revealed that host-associated microbial communities of invertebrates contain abundant core species that are characteristic for a homeostatic host-associated microbial community. Perhaps, the most striking example is the light organ of the bobtail squid, which selects for a single bacterial species, *Vibrio fisheri* (12). These observations gave rise to the idea that a first step in defining a "healthy" colonic microbiota is the identification of abundant core species that we all share (13). Dysbiosis could then be defined as a change in the core species content, commonly featuring a decrease in microbial diversity, an absence of beneficial microbes or the presence of potentially harmful microorganisms (14).

However, this vision collapsed when the analysis of fecal microbiota from volunteers revealed marked interpersonal differences in bacterial species content (15, 16). Unlike invertebrates, where the same bacterial species are associated with hosts collected from different geographical locations (17), the fecal microbiota of individuals from different households exhibits only 2%–3% overlap at the species level, which makes it impossible to identify abundant core species that are common to the colonic microbiota of humans (15, 16). A selection of abundant core species by the host no longer seemed to be a concept relevant for the human gut microbiota, thus upending the species-based definitions of gut homeostasis and gut dysbiosis. In the absence of abundant core species, gut homeostasis could no longer be defined by determining the microbial species composition of the colonic microbiota. Consequently, gut dysbiosis could no longer be defined as a change in the species composition either (18, 19). Since the terms could not be defined, it was questioned whether homeostasis and dysbiosis even existed (18, 20).

With a theoretical framework becoming more elusive, the microbiome field turned to discovery-driven research to develop concepts about gut homeostasis (21). The development of more advanced approaches, such as metagenomics,

metatranscriptomics, and metabolomics, nourished the hope that a possible way out of the conceptual crisis would be to scale up discovery-driven research because by generating enough data, hypotheses about what constitutes gut homeostasis would emerge eventually (22). This approach was embraced by the human microbiome project, which generated 42 terabytes of multi-omics data by 2019 (23, 24). But even this large-scale nation-wide effort did not reveal which features in microbiota data sets define gut homeostasis or the disruption thereof (25).

The fact that scientists still do not agree on what constitutes a healthy microbiome or how to define an impaired one (25) has plunged microbiome theory into darkness. If the outcome of the human microbiome project is any indication, continuing down the path of scaling up discovery-driven research to produce ever larger data sets is not likely to succeed in establishing a conceptual framework for microbiome research. One cannot help but think that the sole reliance on discovery-driven research has steered the microbiome ship off course.

DISTILLING MICROBIOTA COMPLEXITY DOWN TO ITS ECOLOGICAL ESSENCE

To explore where human microbiome research strayed off course, let us first scrutinize the premise that discovery-driven research is necessary because a theoretical framework is largely still lacking in microbiome studies (21). The dominant influence the host exerts on the microbiota composition is obvious in invertebrate models (26), where the host epithelium selects for abundant core species (17, 27, 28). This concept was rejected as a theoretical framework relevant for human microbiome research because the human colonic microbiota does not contain abundant core species (15, 16). But what if the goal is not to select for core species in the colonic microbiota but for ecological guilds, which are groups of microorganisms that exploit environmental resources in a similar way (29)? An ecological guild groups together microbial species that significantly overlap in their niche requirements without regard to their taxonomic position. Therefore, a selection for ecological guilds is not expected to result in a selection for abundant core species common to the human colonic microbiota.

Microbiologists traditionally define ecological guilds based on their energy metabolism (30). This property is relevant for understanding the composition of microbial consortia because microorganisms that produce the largest amount of energy have the shortest generation times (31) and come to dominate microbial communities. Energy is produced in redox reactions where the transfer of electrons from a carbon-based donor, such as glucose, to an electron acceptor, such as oxygen (O_2), is captured in form of adenosine triphosphate (ATP) through either substrate level phosphorylation or oxidative phosphorylation. The amount of ATP generated from an organic compound (i.e., from a carbon-based donor) increases with the redox potential of the electron acceptor, which is highest for oxygen. This thermodynamic hierarchy of electron acceptors dictates that microbes that use oxygen dominate microbial communities under oxic conditions (32, 33). These microorganisms belong to one of two ecological guilds: (i) the aerobic microbes, which cannot grow in the absence of oxygen, or (ii) the facultatively anaerobic microbes, which can also grow under anaerobic conditions (34, 35). In contrast, nutrient-rich anoxic environments are dominated by an ecological guild termed the primary fermenters (36). Primary fermenters break down organic compounds into fermentation products using endogenous electron acceptors, such as pyruvate or phosphoenolpyruvate. These fermentation products are broken down further by secondary fermenters (37), sulfate-reducing bacteria (38), iron-reducing bacteria (39), and methanogens (40, 41), but representatives of these ecological guilds are minority species within nutrient-rich anoxic environments. The theorem that a hierarchy of electron acceptor utilization governs the abundance of ecological guilds in microbial communities is known as the microbial redox tower.

The use of ecological guilds allows for comparative studies among the fecal microbiota from different individuals even when there is no direct overlap in species composition. During homeostasis, the colonic microbiota is dominated by bacterial

species belonging to the class *Actinomycetia* in breast-fed infants (42), whereas members of the classes *Bacteroidia* and *Clostridia* dominate in adults (1). The class-level change in the colonic microbiota composition during weaning is driven by an abrupt shift in the dietary input. *Bifidobacterium longum* subspecies *infantis* (*B. infantis*), a member of the *Actinomycetia,* is a primary fermenter that specializes in catabolizing human milk oligosaccharides, a component of breast milk (43). Human milk oligosaccharides are poorly absorbed in the ileum and reach the colon, where they drive intestinal domination of *B. infantis* in breast-fed infants (42). After weaning, fermentable carbohydrates in the diet select for primary fermenters that display a taxonomic affinity for the classes *Bacteroidia* and *Clostridia*. In a first approximation, poorly absorbed fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) present in the diet are preferentially fermented by *Clostridia* species (44, 45), whereas *Bacteroidia* species specialize in breaking down undigested complex carbohydrates (i.e., fiber) into fermentation products (46). Importantly, despite marked changes in taxonomic identity, the colonic microbiota of breast-fed infants and of healthy adults are both homeostatic communities dominated by the same ecological guild: the primary fermenters. Other ecological guilds that are present exhibit a low abundance, which includes secondary fermenters belonging to the class *Clostridia* (47), sulfate-reducing bacteria belonging to the class *Deltaproteobacteria* (48), methanogens belonging to the domain *Archaea* (49), as well as iron-reducing bacteria and facultatively anaerobic bacteria belonging to the classes *Bacilli* (50, 51) and *Gammaproteobacteria* (52).

In short, although homeostasis can feature marked shifts in abundant taxonomic groups within the colonic microbiota, the ecological guild composition remains dominated by primary fermenters that best suit the host's dietary input (Fig. 2). Thus, whereas dietary input can rapidly and reproducibly change the taxonomic composition of the gut microbiota (53), homeostasis is maintained so long as primary fermenters continue to dominate.

HIDING IN PLAIN SIGHT: A THEORETICAL FRAMEWORK FOR HUMAN GUT MICROBIOME RESEARCH

In contrast to gut homeostasis, the dominance of primary fermenters is challenged in impaired colonic microbial communities by facultatively anaerobic microbes (54, 55), an ecological guild that represents less than 1% of the fecal microbiota during homeostasis (1) (Fig. 2). An elevated relative abundance of facultatively anaerobic *Bacillus* and/or *Gammaproteobacteria* species is seen in patients with cardiovascular disease (3), colorectal cancer (5), cancer-associated cachexia (56), radiation enteritis during radiotherapy (57), Alzheimer's disease (58), type 1 diabetes (59), chronic kidney disease (7), chronic liver disease (60), inflammatory bowel disease (61), graft vs host disease (62), severe malnutrition (63), and chronic inflammation during aging (64). This increased abundance of facultatively anaerobic bacteria is one of the most consistent and robust ecological patterns observed in the fecal microbiota of patients with chronic human diseases (54, 65) (Fig. 1). Thus, a guild-based comparison of homeostatic and impaired microbial communities reveals a shift in abundant ecological guilds.

In summary, by focusing on trophic strategies, the ecological guild conceptual framework offers a different perspective on the composition of the colonic microbiota than metrics based on species richness or taxonomic identity. The concept of ecological guilds is attractive because it provides a way to distill taxonomically complex communities, such as the gut microbiota, into more manageable ecological units. Even though the human colonic microbiota does not contain abundant core species (15, 16), sorting species into ecological guilds reveals that disruption of gut homeostasis is characterized by a shift from a community dominated by primary fermenters to intestinal domination by facultatively anaerobic bacteria. Such a change in abundant ecological guilds can be explained by the microbial redox tower (66, 67), a microbiological concept that rests on aggregated scientific knowledge accumulated since the 1960s. This raises the question

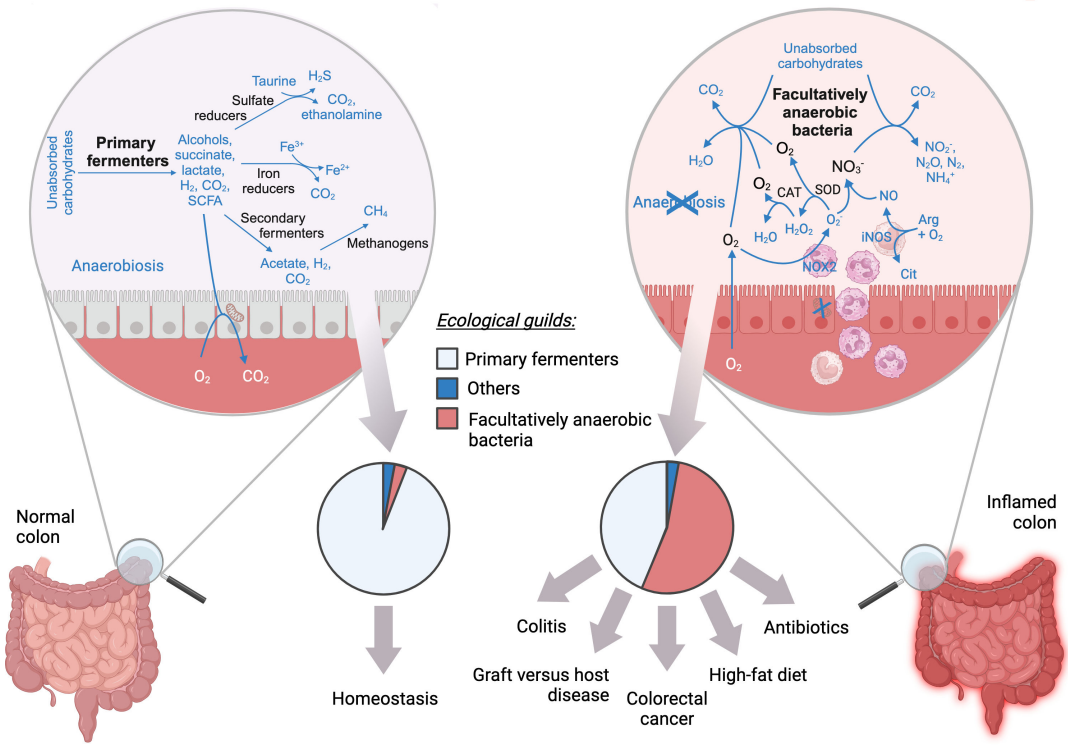

FIG 2 The gut microbiome in health and disease. Comparison of the healthy colon (bottom left) and the inflamed colon (bottom right). The area of magnification shows a schematic of the ecological guild composition characteristic of the normal colon (left) and the inflamed colon (right). The pie charts below indicate the abundance of ecological guilds during homeostasis (left) or in individuals with the indicated diseases (right). O_2, oxygen; H_2, hydrogen; CO_2, carbon dioxide; CH_4, methane; Fe^{3+}, ferric iron; Fe^{2+}, ferrous iron; H_2S, hydrogen sulfide; SCFA, short-chain fatty acids; NO, nitric oxide; Arg, arginine; Cit, citrulline; O_2^-, superoxide; H_2O_2, hydrogen peroxide, H_2O, water; NO_3^-, nitrate; NO_2^-, nitrite; N_2O, nitrous oxide; N_2, nitrogen; NH_4, ammonium; SOD, superoxide dismutase; CAT, catalase; iNOS, inducible nitric oxide synthase; NOX2, phagocyte NADPH oxidase.

whether the elusive theoretical framework for gut microbiome sciences (21, 68) is an already well-established microbiological theorem that is hiding in plain sight.

GUT HOMEOSTASIS AND THE ECOLOGICAL CAUSES FOR ITS DISRUPTION

Let us first explore whether the concept of the microbial redox tower helps explain how the host maintains gut homeostasis. Sorting species into ecologically meaningful categories suggests that homeostasis in the colon is characterized by a dominance of primary fermenters, an ecological guild composition that is typical for nutrient-rich anoxic environments (69). This observation would suggest that the host maintains gut homeostasis by actively sheltering primary fermenters from atmospheric oxygen. Consistent with this idea, a comparison of cecal environments in conventional and germ-free mice reveals that both luminal environments feature anaerobic conditions, suggesting that anaerobiosis is maintained by the host independently of the microbiota (70). The underlying mechanism is high mitochondrial oxygen consumption in the epithelium of the large intestine that renders the mucosal surface hypoxic (<1% O_2) (71), thereby limiting the diffusion of oxygen into the intestinal lumen (72, 73). In turn, the anaerobic conditions maintained in the intestinal lumen through epithelial hypoxia promote the growth of primary fermenters best suited for breaking down those components of our diet that escape digestion and absorption by host enzymes in the small intestine (42–46). Fermentation products produced by primary fermenters are then absorbed by the host for nutrition (74). Providing shelter from atmospheric oxygen, so that unabsorbed components of our diet can be broken down into fermentation products that aid host nutrition, represents an ancient agreement between us and primary fermenters in our colon. This mutually beneficial arrangement represents a state

of gut homeostasis that is preserved by host functions involved in upholding epithelial hypoxia in the large intestine (75–77).

Homeostasis becomes disrupted when the dominance of primary fermenters in the colonic microbiota is challenged by facultatively anaerobic bacteria (54), a change in the ecological guild composition that more closely resembles oxic environments (34). The theorem of the microbial redox tower predicts that such a change in the ecological guild composition involves thermodynamic filtering by electron acceptors, such as oxygen. Oxygen can become available when the colonic epithelium shifts its energy metabolism from high oxygen consumption through oxidative phosphorylation in the mitochondria to a conversion of glucose into lactate (aerobic glycolysis) (72). A shift from mitochondrial oxygen consumption to aerobic glycolysis elevates epithelial oxygenation, which enhances the diffusion of oxygen into the intestinal lumen (75). This metabolic reprogramming of epithelial cells is observed during high-fat diet (78, 79), infectious colitis (80, 81), chemical-induced colitis (82), in mouse models of colorectal cancer (83), graft vs host disease (84), as well as after antibiotic treatment (72, 85). In turn, increased diffusion of oxygen into the lumen (73) fuels the growth of facultatively anaerobic microbes in the large intestine through aerobic respiration (72, 80–83), thereby increasing the abundance of this ecological guild (Fig. 2).

Oxygen can also become available through the detoxification of reactive oxygen species that are generated when phagocytes migrate into the intestinal lumen during conditions of intestinal inflammation (86). The phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase initially depletes oxygen to generate reactive oxygen species (O_2 + NADPH → O_2^- $NADP^+$), which produces microenvironmental hypoxia at sites of inflammation (87). However, detoxification of superoxide radicals (O_2^-) by superoxide dismutase ($2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$) and of hydrogen peroxide (H_2O_2) by catalase ($2H_2O_2 \rightarrow O_2 + 2H_2O$) liberates oxygen to drive an increase in the luminal abundance of facultatively anaerobic bacteria through aerobic respiration (86).

A second respiratory electron acceptor contributing to thermodynamic filtering in oxic environments is nitrate (NO_3^-), which has a redox potential that is second only to oxygen (35). Nitrate becomes available in the colonic environment when homeostasis is disrupted by inflammatory responses. Colonic inflammation is accompanied by elevated synthesis of inducible nitric oxide synthase (iNOS), a host enzyme producing nitric oxide (NO), which reacts with superoxide radicals (O_2^-) generated by NADPH oxidases to form host-derived nitrate in the intestinal lumen (88–91). Elevated luminal concentrations of host-derived nitrate in the colon (92–94) increase the abundance of facultatively anaerobic bacteria through anaerobic nitrate respiration in mouse models of infectious colitis (92, 93), ulcerative colitis (95), high-fat diet (78), antibiotic treatment (72, 96), cancer-associated cachexia (56), and colorectal cancer (97).

Although the host is the source of oxygen and nitrate present in the colonic lumen, the availability of these electron acceptors is modulated by diet and the microbiota. High fat intake, for instance, can increase epithelial oxygenation in the colon by reducing mitochondrial activity (78). Similarly, the depletion of short-chain fatty acid-producing microbes results in the loss of epithelial hypoxia by reducing mitochondrial oxygen consumption (71, 72). Furthermore, when a facultatively anaerobic microbe enters the ecosystem, the availability of respiratory electron acceptors is shaped by competition with resident members of this ecological guild (85, 98–100).

Collectively, these data support the idea that colonic homeostasis is disrupted when host functions that shelter primary fermenters from oxic environments become weakened. The resulting shift from an anoxic to an oxic environment sets the stage for colonic domination by facultatively anaerobic microorganisms (75–77, 101–103) (Fig. 2), a hallmark of the compositional changes in the fecal microbiota that are linked to many chronic human illnesses (3–9) (Fig. 1). These insights suggest that it would be timely to incorporate the ecological guild concept into pipelines for analyzing metagenomic or metatranscriptomic data sets, e.g., by flagging changes in the abundance of respiratory genes (44, 104).

DYSBIOSIS: TO BE OR NOT TO BE, THAT IS THE QUESTION

Although a disruption of colonic homeostasis features a change in the ecological guild composition, it is not warranted to revive the concept that dysbiosis can be defined by compositional changes in the gut microbiota. The focus on compositional changes is rooted in a microbe-centric view of the term microbiome, which was originally defined as the collection of all microbes and their genes (105). This narrow definition of the microbiome limits definitions of dysbiosis to microbial features (14), which remains controversial (18, 19). Furthermore, the absence of abundant core species in the gut microbiota deprives us of a unit of measurement to quantify health. The question is whether the term dysbiosis should be rejected (18, 19) or whether its definition should be revisited after correcting the actual problem, which is defining the term microbiome too narrowly (106).

There is a growing consensus that microbes and their genes comprise only one part of our microbiome, which is defined ecologically as the microbiota and its host environment (107, 108). Broadening the definition of the term microbiome is not mere semantics. Including the host environment in the definition introduces the idea that a microbiome imbalance might not be triggered by changes in the microbiota composition, but by an underlying change in the host environment (106). In the colon, for instance, homeostasis is maintained by host functions that limit the availability of oxygen and nitrate to create an anoxic environment favoring the growth of primary fermenters that are best suited for the host's dietary input (66, 109, 110). A weakening of these host functions results in an increased availability of host-derived electron acceptors in the colonic lumen, which represents a shift toward an oxic environment (77, 106, 109). The transition from primary fermenters to facultatively anaerobic microbes is a useful biomarker for an underlying weakening of host functions involved in maintaining homeostasis (65). Based on an ecological microbiome definition (107, 108), these host functions, along with the environmental parameters they control, are an integral part of the microbiome. Importantly, the part of the microbiome that triggers a disruption of gut homeostasis is a change in the host environment, whereas changes in the microbiota composition merely serve as a biomarker for this underlying cause (65, 75). Thus, it has been proposed that dysbiosis should not be defined based on species richness or taxonomic identity, but that it generally represents a state of weakened host control over the microbial environment (77, 101, 103, 106, 109). This ecological definition of dysbiosis is no longer subject to the fatal limitations that haunt classifications based on taxonomic composition (18, 19). Furthermore, parameters such as the luminal concentration of oxygen or nitrate in the colon can be measured, at least in theory, to determine a normal range in healthy individuals and diagnose gut dysbiosis in individuals in whom these concentrations rise above the normal range.

TOWARD TRANSLATING MICROBIOME RESEARCH INTO CLINICAL INTERVENTIONS

The picture emerging from this analysis is that adopting the microbial redox tower as a theoretical framework goes a long way in helping to understand what constitutes a healthy gut microbiome and how to define gut dysbiosis (77). This theorem suggests that increased luminal concentrations of oxygen and nitrate, a hallmark of dysbiosis in the colon, drive changes in the microbiota composition, which, in turn, can exacerbate the disease (103). Whereas thermodynamic filtering by respiratory electron acceptors is a common driver for changes in the fecal microbiota composition associated with numerous important human illnesses (Fig. 1), the causative effects these compositional changes have on disease progression differ for each condition. Increased luminal concentrations of nitrate, for example, can boost the production of uremic toxins by facultatively anaerobic *Enterobacteriaceae* (78), which exacerbates cardiovascular disease (111, 112). In mouse models of colorectal cancer, increased luminal concentrations of oxygen or nitrate can accelerate polyp formation by driving a bloom of facultatively anaerobic *Escherichia coli* strains that produce the toxin colibactin (83, 97). In

immunocompromised individuals, increased oxygen availability induced by prophylactic antibiotics sets the stage for intestinal domination by facultatively anaerobic opportunistic pathogens, such as *Enterobacteriaceae* (72) or *Candida albicans* (85), which is a common cause of invasive bloodstream infections in these patients (113, 114).

With a framework of aggregated scientific knowledge now at hand, discovery-driven research can be replaced by formulating and testing meaningful hypotheses. An obvious hypothesis to test is the idea that the negative consequences of dysbiosis on health can be mitigated by either blocking microbial respiratory pathways that drive compositional changes or strengthening host functions that limit access to oxygen and nitrate in the lumen. Below, we describe recent work testing this hypothesis using mouse models.

Respiratory pathways that drive a dominance of facultatively anaerobic bacteria during dysbiosis in the colon employ several enzymes that contain a molybdenum (Mo)-containing cofactor (molybdopterin) in their active site (115). Tungsten (W) can replace molybdenum in molybdopterin, resulting in the inactivation of the cofactor in *Gammaproteobacteria* (116), a taxon that has been implicated in exacerbating intestinal inflammation in mouse colitis models (117, 118). A contribution of microbes to intestinal inflammation is relevant for ulcerative colitis, where genetic risk factors and environmental risk factors cooperate to generate inappropriate mucosal immune responses that are driven by the microbiota (119). The fecal microbiota composition in patients with ulcerative colitis features an elevated abundance of facultatively anaerobic bacteria, including *Gammaproteobacteria* (61). In mouse models of ulcerative colitis, sodium tungstate (Na_2WO_4) administration selectively blunts an expansion of *Gammaproteobacteria* by blocking their respiratory metabolism, which in turn reduces intestinal inflammation (118).

The gut microbiota is among the environmental factors implicated in the pathogenesis of colorectal cancer (120), the third most diagnosed cancer worldwide (121). One of the pathobionts implicated in causing colorectal cancer in a mouse model are colibactin-producing *E. coli*, a facultatively anaerobic bacterium that exhibits an elevated fecal abundance in patients with colorectal cancer (5). Metabolism-based editing of the microbiota with sodium tungstate blocks a bloom of colibactin-producing *E. coli* in a mouse model of colorectal cancer, thereby reducing polyp formation (97). These examples illustrate that negative consequences of gut dysbiosis on host health can be mitigated by blocking microbial respiratory pathways that drive a dominance of facultative anaerobic bacteria in the colon and should be explored as potential therapeutic interventions.

An alternative to targeting microbes with metabolism-based interventions is to devise therapeutic strategies that activate host functions to limit microbial access to oxygen. One host pathway involved in maintaining epithelial hypoxia in the colon is epithelial peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling (72). During homeostasis, the microbiota-derived short-chain fatty acid butyrate activates epithelial PPAR-γ signaling to maintain high mitochondrial oxygen consumption in the colonic epithelium, which, in turn, preserves epithelial hypoxia (71, 72). Conversely, an increase in epithelial oxygenation features a reduction in epithelial PPAR-γ signaling and decreased mitochondrial oxygen consumption (72). Epithelial hypoxia can be restored by treatment with 5-amino salicylic acid (5-ASA), a PPAR-γ agonist (122) that is poorly absorbed in the small intestine (123) and acts on the colonic epithelium (82). By reducing the bioavailability of oxygen in the lumen, treatment with 5-ASA blocks excessive growth of colibactin-producing *E. coli* in the colon, thereby preventing colorectal cancer formation in a mouse model (83).

Anaerobiosis in the colon also limits the growth of facultatively anaerobic fungi. Increased epithelial oxygenation during antibiotic treatment (71, 72) sets the stage for a bloom of the facultatively anaerobic *Candida albicans*, an opportunistic fungal pathogen. An intestinal bloom of *C. albicans* during antibiotic therapy is the most common etiology of candidemia in patients with hematologic malignancies (114), which carries a high mortality rate (124–127). Treatment with 5-ASA restores epithelial hypoxia during

antibiotic treatment, thereby restoring anaerobiosis to limit an intestinal bloom of the facultatively anaerobic *C. albicans* in a mouse model (85). Thus, a strengthening of host functions that limit access to oxygen in the colonic lumen can alleviate some of the negative consequences linked to a colonic bloom of facultatively anaerobic microbes, such as colibactin-producing *E. coli* or *C. albicans*.

Metabolic reprogramming of the colonic epithelium has also been linked to the production of uremic toxins (78). Uremic toxins are metabolites exclusively produced by the gut microbiota, which have been implicated in the pathogenesis of chronic kidney disease (128, 129) and cardiovascular disease (111, 112). One of these uremic toxins is trimethylamine-*N*-oxide (TMAO), which is produced in the liver through oxidation of microbiota-derived trimethylamine (TMA) by flavin monooxygenases (130). TMA is produced by the gut microbiota from carnitine or choline present in red meat (112). TMAO is elevated in the plasma of patients with cardiovascular disease (111, 112, 131), chronic kidney disease (132), and type 2 diabetes (133). The latter is a common cause of chronic kidney disease (134). The fecal microbiota of patients diagnosed with these conditions commonly feature an elevated abundance of *Gammaproteobacteria* species, such as *E. coli* (3, 6, 7, 135). Mice on a high fat diet, which is a risk factor for type 2 diabetes and cardiovascular disease (136), exhibit an elevated *E. coli* abundance in the feces (137) and an increased luminal concentration of host-derived nitrate generated by low-grade mucosal inflammation (78). In the presence of host-derived nitrate, *E. coli* becomes a prominent producer of TMA within the gut microbiota because nitrate stimulates choline catabolism (78). However, an increase in the TMAO serum levels in mice receiving a high-fat diet supplemented with choline can be prevented by blocking nitrate production with aminoguanidine (78), a chemical inhibitor of the host enzyme iNOS (138). This work suggests that therapeutic interventions that limit the availability of host-derived nitrate in the colonic lumen can prevent the production of harmful metabolites during gut dysbiosis.

Adverse consequences of gut dysbiosis are not limited to an increased abundance of facultatively anaerobic microbes but can also be associated with a reduced abundance of primary fermenters. For example, a low abundance of *Clostridia* species in the fecal microbiota can result from impaired microbiota recovery after antibiotic treatment when anaerobiosis is disrupted because a diet rich in saturated fatty acids reduces epithelial PPAR-γ signaling (79). *Clostridia* species are the main source in the colonic microbiota of sorbitol dehydrogenase, the enzyme catalyzing the first step in sorbitol catabolism (44). Sorbitol is an alcoholic sugar that is poorly absorbed by the small intestine, resulting in a low caloric content that makes it suitable as a low-calorie sweetener in "sugar-free" foods (139). When *Clostridia* species are depleted, sorbitol accumulates in the intestinal lumen (45), resulting in osmotic diarrhea (140). Through this mechanism, a high-fat diet-induced impairment of microbiota recovery after antibiotic treatment produces sorbitol intolerance (44), the third most common cause of carbohydrate intolerance (141). Activation of epithelial PPAR-γ signaling by treatment with 5-ASA restores epithelial hypoxia even in the face of high fat intake, thereby promoting microbiota recovery after antibiotic treatment to prevent the development of prolonged sorbitol intolerance in a mouse model (44). In short, a strengthening of host functions that limit access to oxygen in the colonic lumen helps erase some of the adverse effects on host health that are linked to a reduced abundance of primary fermenters during gut dysbiosis.

In conclusion, by shining light on the ecological causes of gut dysbiosis, the theorem of the microbial redox tower opens a new chapter in the development of intervention strategies, which can target either microbial energy metabolism or host functions that limit access to electron acceptors. Mouse models suggest that these strategies could be adapted to a wide spectrum of conditions, such as colorectal cancer (83, 97), chronic kidney disease (78), cardiovascular disease (78), sorbitol intolerance (44), opportunistic *Candida* infections (85), ulcerative colitis (118), and perhaps many others. More work is needed to translate these preclinical data into clinical interventions, which will require

microbiome researchers to embrace the microbial redox tower and its implications for understanding gut homeostasis and gut dysbiosis. Given the importance of the colonic microbiota for human health, the development of these intervention strategies represents an impactful sector within the field of human microbiome research.

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