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MEETING REVIEW

Thinking Outside the Cereal Box: Noncarbohydrate Routes for Dietary Manipulation of the Gut Microbiota

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ABSTRACT The gut microbiota is a diverse and dynamic ecological community that is increasingly recognized to play important roles in host metabolic, immunological, and behavioral functioning. As such, identifying new routes for manipulating the microbiota may provide valuable additional methods for improving host health. Dietary manipulations and prebiotic supplementation are active targets of research for altering the microbiota, but to date, this work has disproportionately focused on carbohydrates. However, many other resources can limit or shape microbial growth. Here, we provide a brief overview of the resource landscape in the mammalian gut and review relevant literature documenting associations between noncarbohydrate nutrients and the composition of the gut microbiota. To spur future work and accelerate translational applications, we propose that researchers take new approaches for studying the effects of diet on gut microbial communities, including more-careful consideration of media for *in vitro* experiments, measurement of absolute as well as relative abundances, concerted efforts to articulate how physiology may differ between humans and the animal models used in translational studies, and leveraging natural variation for additional insights. Finally, we close with a discussion of how to determine when or where to employ these potential dietary levers for manipulating the microbiota.

KEYWORDS diet, fats, heavy metals, microbiota, physiology, polyphenols, protein

The human microbiota make up a large and diverse community that is increasingly recognized as playing a critical role in human biology (1). Many aspects of physiology are now understood to be directly or indirectly modulated by the microbiota, particularly in the gut but also elsewhere in and on our bodies (2–4). Because of the relevance to biomedical science, there is growing interest in manipulating the gut microbiota to correct imbalances and promote healthy functioning (5–7). Such efforts are pursued in both academic and industry settings, with a large focus on diet, whether at the scale of single supplement prebiotics (8), foods rich in probiotic organisms (9), or cultural differences in nutrient intake (10). It is certainly logical to attempt to use diet manipulations to shape the gut microbiota, as diet directly affects nutritional niches in the gut, thereby altering the competitive landscape for gut microbes (11). Indeed, diet has been found to be a major driver of gut microbial composition (12, 13). However, the question remains of how to best use diet to manipulate the gut microbiota.

To date, dietary interventions targeting the gut microbiota have focused largely on carbohydrates, primarily fiber components, and their fermentation to short-chain fatty acids. This emphasis on carbohydrates, and in particular indigestible carbohydrates, derives from a simple calculus: the densest populations of microbes (for most animals) reside in the distal gut, these microbes require nutrients to grow and reproduce, and diet-derived indigestible carbohydrates reach the distal gut more reliably than do diet-derived lipids and proteins (14–16). The gut microbial production of short-chain

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fatty acids is important for the host, providing 60% to 70% of the energy used by gut epithelial cells and up to 30% of the host's total energy (17). However, it remains unclear what fraction of the short-chain fatty acids benefiting the host is derived from carbohydrate fermentation, as short-chain fatty acids are also produced from microbial protein fermentation (18, 19). Moreover, it is unknown how much of the gut microbiota's own energy pool is produced through carbohydrate fermentation.

Other factors beyond carbohydrate availability are known to shape overall microbial load and/or patterns of competition among specific members of the gut microbiota; these may therefore have direct consequences for human health. Aerobic and anaerobic respiration, protein fermentation, and chemosynthesis are continually taking place (17, 20), and all microbial metabolism requires more than carbon substrates. The microbiota have been shown to be responsive to other dietary components (Table 1), for example, fat and protein (21), as is discussed more extensively later in this piece. Indeed, there is evidence that other elements may be more important than carbon for host management of the microbiota (e.g., nitrogen [22–24]). As such, provisioning or depleting noncarbohydrate microbial resources, limiting or otherwise, would provide additional, potentially even more efficacious, routes for manipulating the gut microbiota.

Here, we propose that the field of microbiome research should expand thinking about dietary interventions. We intend not to undermine the value of carbohydrate-focused work but instead to extend the toolkits of researchers and clinicians by highlighting additional targets for research. We begin by briefly outlining the nutrient environment experienced by the microbiota and the mechanisms shaping that landscape. Next, we discuss noncarbohydrate resources in the gut that are likely contenders to impact the microbiota and new approaches for studying the effects of these resources. Finally, to emphasize the value of expanded approaches to dietary interventions, we also address what the outcome of such interventions could be, including alterations to both the metabolic and nonmetabolic contributions of microbiota to the host.

HOST DIGESTIVE PHYSIOLOGY AND THE RESOURCE ENVIRONMENT OF THE GUT MICROBIOTA

The mammalian gut microbiota as a whole is dominated by obligate anaerobes from the *Firmicutes* and *Bacteroidetes* phyla. However, gut microbial abundance, composition, and function differ radially and longitudinally across regions in response to fine-scale differences in the resource environment (1, 25).

Radial variation in the microbiome is driven by host immune defense, mucus production, epithelial sloughing, and environmental gradients in nutrients and oxygen (26, 27). Lateral communities, adhering to the epithelium or mucosal layers, are generally less diverse and less densely colonized than luminal bacterial communities (27–29). The microbes that are present are more likely to be oxygen tolerant and specialize in the metabolism of protein than luminal microbes (26). Due to their relatively high dependence on host secretions rather than diet-derived nutrients, epithelial and mucosal adherent microbial communities are generally more stable over time than luminal microbial communities (27) and likely more resistant to manipulation via diet. Because of their stability, and the fact that surveying these communities is invasive and therefore impractical for temporal tracking of the effects of a dietary intervention on the gut microbiome, we focus here on the luminal microbial community.

Across mammals, longitudinal variation in the gut microbiota is driven largely by host gut ecophysiology. Diet directly impacts the presence of macronutrients, micronutrients, and phytochemicals in the lumen and, over evolutionary time, has also shaped the basic structure of the gut and related host-derived environmental factors like pH, passage rate, and enzyme production. At the broadest level, this is evident in the differences between foregut and hindgut fermenters. Ruminant and pseudoruminant animals, such as cows, sloths, and colobus monkeys, have independently evolved specialized multichambered stomachs that allow microbial fermentation to occur prior to the passage of chyme into the small intestine, where the majority of host digestion and absorption occurs. In these gastric fermentation chambers, conditions are main-

TABLE 1 Select experimental findings on microbial responses to dietary interventions showing that dietary elements beyond fiber often contribute to microbial variation

Resource(s)	Finding(s)	Host	Reference
Fat	Consumption of high-saturated-fat diet increased relative abundance of *Bilophila wadsworthia* and promoted inflammation in genetically susceptible mice via bile acid alterations	Mouse	83
Fat	High-fat diets altered the gut microbial community, but these responses were idiosyncratic based on fat source	Mouse	112
Fat	High-fat-diet-associated small intestinal microbial community altered lipid digestion even when mice were fed a low-fat diet	Mouse	109
Fat	Switch to Westernized diet produced relative increases in *Firmicutes* and decreases in *Bacteroidetes*, a decrease in microbial diversity, and a greater increase in body fat than in controls	Mouse	110
Fat, fiber	Bacterial communities in mice fed low-fat/high-fiber diets or high-fat/high-sugar diets differed in composition but were mostly resilient to diet changes; in contrast, viral communities responded rapidly to switch between diets	Mouse	111
Fat, fiber	Microbial responses to introduction of high-fat/low-fiber or low-fat/high-fiber diets were documented within 24 h but were insufficient to overcome interindividual variability	Human	13
Fat, sugar	High-fat/high-sugar and low-fat/high-fiber diets shaped the gut microbiota consistently across mice with different genotypes and metabolic/immune phenotypes; blending the diets led to proportional changes in the gut microbiota	Mouse	12
Iron	Infant iron supplementation increased enterobacterial and *Clostridium* abundances, including many pathogens	Human	38
Iron	Child iron supplementation altered the gut microbiota, with a relative increase in enterobacteria and decrease in lactobacilli, even without changing human iron status	Human	146
Protein	Higher dietary casein levels increased total microbial DNA; some taxa, including members of the *Clostridia* and the sulfate reducer *Desulfovibrio*, decreased	Mouse	120
Protein	Gut microbial community was responsive to dietary fat content but not protein/sucrose ratio; host adiposity and survival were shaped by protein/sucrose ratio	Mouse	121
Protein	Increasing protein levels led to higher total microbial loads and changes in composition, including *Bacteroidaceae* absolute abundance	Mouse	24
Protein	High-protein diets changed fecal short-chain-fatty-acid concentrations, most notably reducing butyrate levels while also reducing the proportion of some *Firmicutes* and members of the *Bacteroides*	Human	122
Protein	Changes in dietary protein or fiber amt did not alter the microbial community at the phylum level, but high-protein diets were associated with an increase in *Oscillibacter* and a decrease in *Collinsella aerofaciens*	Human	123
Protein, fiber	Microbial relative-abundance and diversity responses to altered protein and fiber levels were more significant than responses to changes in fat or energy density across a range of diets	Mouse	23
Protein, fat	Short-term human diet interventions involving high-protein/high-fat diets resulted in rapid changes in the microbiota, including increases in bile-tolerant bacteria like *Bilophila wadsworthia* and members of the *Bacteroides*, with concurrent reductions in some *Firmicutes*	Human	21
Protein, fiber, fat, sugars	Microbiota changes and associated inflammation were consistently recorded in response to various levels of multiple fiber and protein sources but not digestible carbohydrates or most fats	Mouse	189

tained to encourage efficient microbial metabolism of cellulose, including relatively high pH and relatively low passage rates for individual particles. In contrast, hindgut fermenters, like horses and rhinoceroses, have physiological adaptations to promote microbial residence and fermentation distal to the stomach and small intestine in an enlarged hindgut and a well-developed cecum. In both cases, these animals, which forage primarily on plant materials but lack the enzymes required to break down cellulose and hemicellulose themselves, actively promote microbial growth and fermentation and in turn gain a substantial fraction of their total energy budget from the absorption and metabolism of microbiota-derived volatile fatty acids. In contrast, animals with simple guts synthesize the enzymes required to digest the majority of

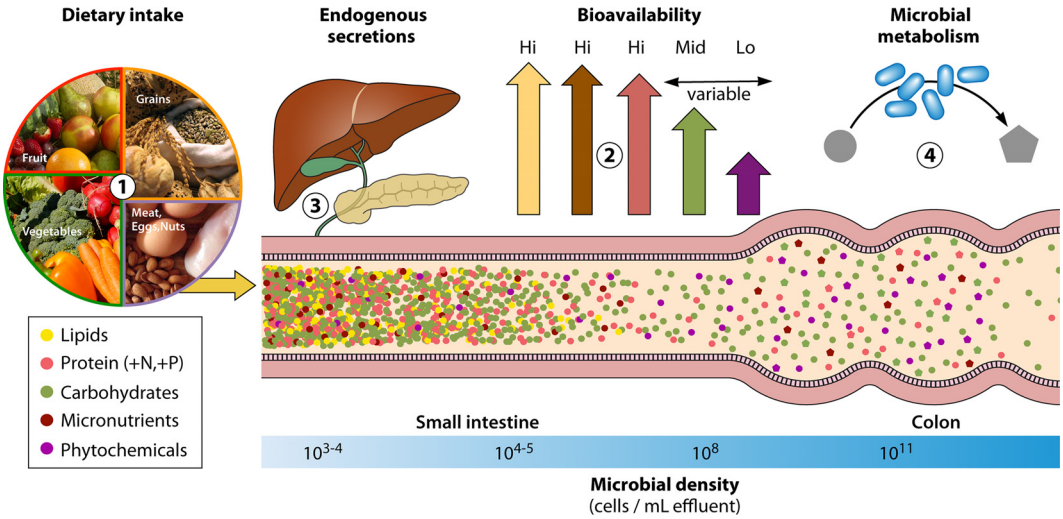

FIG 1 Nutrient landscape of the gut as shaped by host and microbial processes. Gut microbial absolute and relative abundances are expected to be sensitive to the nutrients available within the gut lumen. Nutrient composition in the gut lumen is, in turn, dependent on (i) dietary intake of macronutrients, micronutrients, and phytochemicals; (ii) the bioavailability of those nutrients within the small intestine, which alters the fraction of ingested nutrients reaching the densest microbial communities in the colon; (iii) endogenous secretions such as bile acids and digestive enzymes that alter competitive dynamics among gut microbial taxa and/or modulate bioavailability; and (iv) microbial metabolism of nutrients, producing metabolites that may have downstream effects on competitive dynamics within the gut microbiota.

their diet and exhibit a range of adaptations that serve to restrict the largest populations of microbes to the colon, ensuring that the host retains first access to nutrients.

Humans exemplify this first-pass resource access strategy. Gut microbial density increases exponentially along the human gastrointestinal tract, with 10^2 to 10^3 microbes per ml of effluent in the stomach, 10^3 to 10^5 in the proximal small intestine, 10^8 in the ileum, and 10^{11} in the colon (1, 30, 31). Concomitant with this increase in microbial density are gradients in oxygen, pH, antimicrobial peptides (AMPs), and immunoglobulins (1). These gradients are the outcome of coevolution between humans and the human gut microbiota, a shared history marked by cooperation but also competition, in which humans have maximized the fraction of ingested nutrients serving our own metabolism by isolating primary digestion from the bulk of the microbial community.

Ultimately, the ecological niches available for microbial colonization are determined by the interaction of host physiology and dietary ecology, with diet being more readily modifiable than physiology. Below, we review how diet interacts with host physiology to shape gut microbial communities, with the goal of highlighting some properties of diet that serve as promising targets for therapeutic manipulation.

HOST DIET AND NUTRIENT AVAILABILITY IN THE HUMAN GUT

Nutrient availability in the gut is largely a function of four distinct processes: (i) dietary intake, (ii) host uptake of diet-derived nutrients, (iii) host endogenous secretions, and (iv) microbial metabolism of diet-derived, endogenous, and microbiota-derived compounds (Fig. 1). The broad relevance of dietary intake is clear, as most resources in the gut, as in the rest of the body, are ultimately acquired via diet. However, downstream processing of diet-derived compounds, by both host and microbiota, contributes importantly to the resource environment of the lumen. We focus here on these other processes shaping nutrient availability.

Host uptake of diet-derived nutrients. Given that the densest and most diverse gut microbial populations in humans reside in the distal gut, in considering the effect of diet on the nutrient environment, it is critical to consider the fraction of diet-derived nutrients that actually reaches the colon.

Distinct pathways exist for the digestion of carbohydrates, proteins, and fats, but their absorption is not equally efficient. Free dietary lipids are almost completely

absorbed by the terminal ileum, although fats contained within plant cell walls may remain inaccessible to digestion unless cell walls are ruptured by processing (32, 33). In contrast, dietary proteins and dietary carbohydrates show high degrees of variability in bioavailability based on their chemical form (16). Denaturation of proteins via heat or acid causes the protein structure to unfold, promoting bioavailability; for instance, there is a 2-fold increase in the ileal digestibility of egg protein served raw (51% to 65%) versus cooked (91% to 94%) (34, 35). In humans, most protein-rich foods are routinely cooked, and approximately 80 to 90% of proteins are absorbed in the small intestine (36). The bioavailability of carbohydrate also depends on its structure, with simple sugars being readily absorbed in the small intestine, complex polysaccharides (e.g., cellulose, lignin, pectin, and oligosaccharides) resisting digestion in the small intestine, and starch being either highly digestible or resistant, depending on its form (15, 37). Starch, the most common carbohydrate in the human diet, exists in a native state that is resistant to digestion by amylases, but here too, cooking produces consistent and significant increases in ileal digestibility ranging from 28% to 109% for substrates tested in humans (16).

The small intestine is also the site of vitamin, mineral, and metal absorption. Most water-soluble vitamins (e.g., vitamin C) are readily absorbed via active transport in the jejunum, while protein-bound B vitamins and fat-soluble vitamins (e.g., vitamins A, D, E, and K) are primarily absorbed further along the small intestine. Minerals are absorbed in the small intestine via either active transport in the proximal small intestine or passive diffusion around tight junctions in the distal small intestine. Divalent metals such as iron can be transported from the duodenal lumen via the divalent metal transporter or enter enterocytes in the form of heme via endocytosis, although not all dietary iron is taken up (38). Other diet-derived compounds, such as phytochemicals and chemical by-products of food processing, exhibit various degrees of absorption in the small intestine. Many common compounds, such as plant-derived polyphenols (39), are known to pass through the mammalian small intestine largely intact. Such poorly absorbed compounds may be especially likely to affect the microbiome because they concentrate in the colon as digestible nutrients and water are removed.

Ultimately, dietary material depleted of macronutrients and micronutrients passes into the colon, where water and electrolytes are recovered directly and residual nutrients become substrates for microbial metabolism. The mammalian colon has a limited ability to absorb diet-derived nutrients directly, but volatile short-chain fatty acids produced during microbial fermentation of carbohydrates and proteins diffuse into enterocytes, where they serve as important metabolic fuel for both local and systemic energy metabolism. Nutrients may be salvaged after processing in the large intestine through coprophagy, but this process is common only in some nonhuman species (40).

Host endogenous secretions. In addition to diet-derived nutrients, the intestinal lumen is also rich in products produced by the host. For instance, epithelial cells are sloughed constantly, having the highest turnover rate of any fixed-cell population in the body. Upon entry into the intestinal lumen, these shed cells become substrates for both host and microbial metabolism (41). Epithelial cell life cycles interact with nutritional factors, with luminal nutrients directly modulating the rate of intestinal cell proliferation (42, 43).

Beyond the luminal nutrients introduced by epithelial cell sloughing, the host gut actively secretes compounds that modulate the gut microbiota via nutritional or antimicrobial effects. Goblet cells located along the entire intestinal tract secrete a continuous layer of mucus, composed of mucin glycoproteins (primarily MUC2) and trefoil peptides. Mucus serves as a critical barrier between the epithelium and the gut lumen, whose production is modulated by both host genetics and diet (44–46). However, mucus is also both a habitat and a nutrient source that differentially promotes the growth of specific microbial taxa. Although commensal bacterial genomes are generally rich in glycan-degrading enzymes (47, 48), some bacterial taxa (e.g., *Akkermansia muciniphila* [49] and *Ruminococcus gnavus* [50]) produce specialized gly-

cosidases that confer an enhanced ability to metabolize MUC2 oligosaccharides. Gut microbiota composition can further alter patterns of oligosaccharide glycosylation (51), and the activity of mucolytic bacteria like *A. muciniphila* may actually stimulate mucus production in the host (52).

The host gut also produces a range of antimicrobial compounds to restrict microbial growth and prevent invasion into the mucosa. For instance, intestinal epithelial cells secrete IgA into the lumen via the polymeric immunoglobulin receptor (53), releasing an estimated 3 to 5 g daily (54). Paneth cells secrete a wide range of antimicrobial peptides (AMPs) that disrupt gut microbial cell membrane integrity and/or cellular function, including α-defensins and lysozymes (55). Jointly, IgA and AMPs regulate the growth of commensal gut bacteria, exerting selective effects that shape gut microbial community structure (56, 57). However, the extent to which diet shapes IgA and AMP production in the lumen remains to be determined.

Animals also secrete bile acids with robust direct (58, 59) and indirect (60) bactericidal properties. Bile is released into the duodenal lumen in response to ingestion of fats and serves to emulsify dietary lipids. Roughly 95% of bile acids released into the small intestine are reabsorbed in the ileum for recycling, but approximately 400 to 800 mg of bile acids daily escapes enterohepatic circulation (61). Residual bile acids can reach high-millimolar concentrations in the colon, where differential resistance to the antimicrobial effects of bile acids contributes to shaping gut microbial structure and function (62–65). Given any differential sensitivity of gut microbial taxa, dietary-fat-induced variation in bile acid production can be expected to influence gut microbial community structure and function.

Microbial metabolism of luminal compounds. The gut microbiome harbors a metabolic capacity that far exceeds our own (66). Microbes can transform carbohydrates in ways that extend beyond fermentation. For instance, some microbes can degrade host-produced glycans such as intestinal mucus and human milk oligosaccharides, releasing nutrients into the lumen and exposing the residual glycan structure to further degradation by other members of the commensal community (67–69). The colonic gut microbiota can metabolize a wide variety of noncarbohydrate dietary compounds that resist digestion in the small intestine, including proteins (18, 70), polyphenols such as lignans (71, 72), and xenobiotic compounds like polycyclic aromatic hydrocarbons (73). Gut bacteria can also synthesize numerous macronutrients and micronutrients, including essential amino acids like lysine. Indeed, isotopic labeling studies in humans have found microbiota-derived lysine to contribute substantially to the plasma lysine and body protein pools, even on nitrogen-adequate diets (74, 75). Such activities can modify the resource environment of the gut, independent of and in conjunction with host action, with further consequences for gut microbial structure and function.

Bile acids offer a prime example of the ecological consequences of noncarbohydrate microbial metabolism. As mentioned above, bile acids that escape enterohepatic circulation and pass into the colon can possess strong antimicrobial properties. A key line of gut bacterial defense is to manipulate the antimicrobial properties of the primary bile acids produced by the host via deconjugation or transformation into secondary bile acids with altered chemical properties. Deconjugation involves the action of bile salt hydrolases (BSHs) that hydrolyze the bond linking the bile acid to the amino acid conjugate, which in humans is either taurine or glycine. BSH activity appears unique to the gut environment (76) and can show high redundancy within carrier taxa (e.g., *Lactobacillus plantarum* carries 4 functional BSH genes [77]), in which it may confer a survival advantage by reducing the stronger detergent properties of the conjugated forms. BSH activity is encoded in multiple Gram-positive and archaeal taxa but appears less widely distributed among Gram-negative bacteria, with functional BSH genes detected to date only among *Bacteroides* strains (62). Interestingly, taurine versus glycine conjugation of bile acids appears to depend on habitual diet, with animal-rich diets increasing the rate of taurine conjugation and plant-based diets enriching for glycine conjugation (78, 79). The higher rate of taurine conjugation on animal-rich diets

is presumably due to an increased availability of taurine, which is derived exclusively from animal tissue and which humans have lost the ability to synthesize efficiently (80, 81). Thus, diet might shape gut microbial community structure via BSH both by changing the abundance of microbes possessing hydrolase activity and by modulating luminal concentrations of free taurine and glycine, which can be used as sources of nitrogen and carbon to enhance growth (82).

Notably, gut microbial responses to taurine versus glycine conjugation can also impact human health directly. For instance, because taurine catabolism releases sulfite in addition to ammonia and carbon dioxide, taurine deconjugation may select for sulfidogenic bacteria such as *Bilophila wadsworthia*, with downstream consequences for intestinal inflammation (83). In addition, germination of the nosocomial enteric pathogen *Clostridium difficile* from spores is maximized in the presence of taurocholic acid and glycine (84); indeed, most clinical isolates of *C. difficile* appear to require the taurine conjugate to germinate (85). Together, such data suggest a microbiota-mediated link between taurine-rich diets and the risk of gastrointestinal pathology.

Gut bacteria also transform host-produced primary bile acids into secondary forms with altered chemical properties. Cholic acid (CA) and chenodeoxycholic acid (CDCA) together represent 80% of the primary bile acid pool in humans (86) and are transformed by microbial metabolism into the two most abundant secondary bile acids in the human gut, deoxycholic acid (DCA) and lithocholic acid (LCA), respectively (87). Conversion of primary to secondary bile acids typically involves 7α-dehydroxylation, a multistep biochemical pathway found exclusively in anaerobic gut bacteria, most notably among members of *Clostridia* cluster XIVa (87–90). Correspondingly, the antibiotic-induced reduction in bacterial taxa capable of 7α-dehydroxylation shifts the fecal bile acid pool from secondary to primary bile acids (84, 91). Gut bacteria are also capable of oxidizing and epimerizing other hydroxy groups in the primary bile acid structure, altogether yielding more than 20 secondary structures (62). As a result of this microbial activity, the fecal bile acid pool consists almost exclusively of unconjugated and secondary bile acids (87).

Bacteria capable of transforming primary to secondary bile acids might benefit by outcompeting or inhibiting taxa more sensitive to secondary bile acids (62), with downstream effects on host health. For instance, *Clostridium scindens* and *Clostridium hiranonis* show 10-fold-higher 7α-dehydroxylating activity than other *Clostridia*, a phenotype linked to the production of an NAD(H)-dependent 3-dehydro-4-bile acid oxidoreductase encoded by the *baiCD* gene cluster (92, 93). This 7α-dehydroxylating activity is thought to underlie the protection conferred by these taxa against *C. difficile* colonization (94, 95), an effect potentially mediated by the inhibitory effect of secondary bile acids on *C. difficile* germination (84, 96). Notably, symptomatic *C. difficile* infection in humans was recently associated with negative or low *baiCD* gene cluster abundance, and a case study reported that successful treatment of recurrent *C. difficile* infection via fecal microbiota transplant (FMT) was associated with a shift from a *baiCD*-negative status pre-FMT to a *baiCD*-positive status post-FMT (91). Similarly, experimental administration of *C. scindens* was recently shown to confer resistance to *C. difficile* infection, with effects dependent on the synthesis of secondary bile acids (95).

Microbial processing of mucus is another example of the complex metabolic capacity of the gut microbiota. Although the capacity to degrade mucin is phylogenetically widespread (97), *in vivo* stable isotope experiments have found that there is significant interspecific and intraspecific variation in mucin foraging (98). There is also differential uptake of various components of mucin, with most cells incorporating mucin-sourced nitrogen, likely via its circulation in the free ammonium pool and incorporation during amino acid synthesis, while only a small proportion of the community takes up mucin-sourced carbon through direct metabolism of mucin oligosaccharides (98). Mucus serves as an important resource for the gut microbiota, especially when dietary resources are reduced. For example, mucin metabolism increases under dietary fiber deprivation (99), leading to a thinner mucosal layer and increased pathogen suscepti-

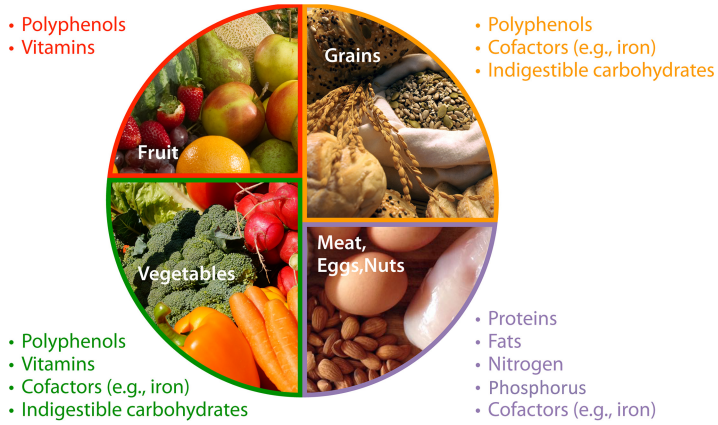

FIG 2 Many resources relevant to microbial growth and function are naturally sourced from the typical human diet. Identifying what specific resources drive microbial differences in humans whose diets vary is a complicated endeavor, however. Here, we show how the USDA MyPlate-recommended diet components include various microbially relevant resources such that changing diet broadly may not allow researchers to ascribe causality to microbial changes. Further theory on limiting resources and controlled experiments isolating individual aspects of diet are necessary to develop a dynamic range of manipulations and to understand the degree to which host physiology modulates microbial responses to diet.

bility. Correspondingly, mucus-degrading bacteria are relatively more abundant in hibernating or fasting animals (100, 101).

Ultimately, as these examples attest, the resource landscape of the distal gut lumen is a complex function of host physiology, nutritional ecology, and microbial activities. However, the system reacts to dietary levers in ways that, with additional research encompassing a range of substrates, we may ultimately be able to control precisely.

NONCARBOHYDRATE DIETARY COMPONENTS AND THE GUT MICROBIOTA

Much research effort has focused on relating variation in the gut microbiota to differences in diet. Diet dissimilarities between countries (102, 103), seasons (104, 105), and lifestyles (106, 107) are all associated with variation in the gut microbiota. More broadly, contrasts, and similarities, between animal species in their gut microbiota are also ascribed to diet (108). However, isolating what specific aspects of diet drive gut microbial composition and function is a complex and multifaceted problem. Gut microbial taxa may respond to differences in macronutrients, micronutrients, and elemental availability, all in various intersecting manners. Does a change following altered protein intake reflect responsiveness to protein availability? The macronutrient(s) replacing or replaced by protein? Nitrogen availability? Iron or other minerals found in protein-rich food? Most experiments unfortunately do not allow for ascribing causality precisely. Here, we briefly review some recent experimental work exploring the relationship between the noncarbohydrate fraction of diet and the gut microbiota and highlight some of the dietary constituents that we expect contribute to gut microbial responses (Fig. 2).

As many studies have found differences in the gut microbiota and health outcomes of Western and non-Western populations, much research has been performed in humans and mice using Western-style high-fat diets (12, 13, 83, 109, 110) or other altered-fat diets (111, 112). The gut microbiota is typically found to respond to changes in dietary fat, perhaps unsurprisingly since the gut microbiota is known to contribute to host metabolism of fats (21, 109, 113, 114). The effect of increased fat consumption can often be specifically tied to changes in bile acid production and metabolism (83, 109, 115, 116). Interruption of microbial bile acid metabolism by antibiotics or dietary shifts has been associated with negative health outcomes, including inflammation (117) and *C. difficile* infection (94, 95). As such, alterations to dietary fat consumption and thus bile acid production are expected to serve as meaningful tools for manipulating the gut microbiota, particularly in the context of disease. In most humans consuming Western-

style diets, this may mean focusing on reducing fat intake, altering the proportional intake of fats from different sources (118, 119), and/or combatting downstream microbial effects through alternative diet changes.

Less research has been conducted on dietary protein levels than on fats or carbohydrates. However, work that has been carried out has shown significant responses in the gut microbiota following increases in protein intake (21, 23, 120–123). Indeed, changes in protein levels have been found to be one of the most significant predictors of gut microbial responses in studies that compare populations (13) or multiple dietary manipulations (23, 120). It has been proposed that this is because nitrogen is a limiting nutrient in the gut (24), and therefore, nitrogen availability would determine overall biomass in the system (24) and also set the terms for competition over other resources like carbohydrates (23). Nitrogen is commonly limiting in environmental microbial communities (124–127) as well as for animal hosts (128). Nevertheless, how particular forms of nitrogen (e.g., protein, amino acid, and free circulating ammonium [129]) contribute to microbial dynamics in the gut requires further study. Microbes both utilize and produce amino acids, for example, modulating the availability of the essential amino acid tryptophan, with downstream implications for inflammation, disease, and nervous system signaling (18, 130–132). Dietary sources will need to be considered alongside host secretions like mucus (98) and urea (133) as well as microbial biosynthesis of nitrogen-rich products (75) that can also play a prominent role in gut nitrogen dynamics. Overall, due to the theoretical and empirical support for nitrogen limitation, it seems likely that changing dietary protein will be a powerful tool for manipulating the gut microbiota.

Beyond the macronutrients, there are many other components of diet that matter for host nutrition and likely also gut microbial growth and functioning. For example, phosphorus is another element that is commonly limiting for microbes in the environment (126, 134–136) and has been shown to limit gut bacterial growth *in vitro* (137), but its role *in vivo* has not yet been studied. Better understood are trace metals, which are essential micronutrients for animals and can also contribute to gut microbial dynamics (138). Most research has focused on the importance of metal-based molecules for pathogen colonization and growth (38, 139–141) or their antimicrobial functions (142), but the competition for metals observed in pathogens (143) can also affect commensals (129, 137, 144, 145). Iron supplementation can alter gut microbial composition, most notably with increases in potential pathogens, even without changing host iron levels (38, 146). Zinc deficiency or excess has also been shown to produce altered gut microbial profiles and metabolism (147, 148). Similarly, polyphenols from plant sources, including tea, wine, and berries, can also modulate the gut microbiota by depleting sensitive taxa, promoting the growth of resistant taxa, and/or manipulating host-microbe interactions in a manner linked to positive health outcomes (149–152), including attenuated development of obesity and glucose intolerance in mice fed a high-fat/high-sugar diet (150, 153). Characterizing differences in nonmacronutrient dietary components accurately is challenging in observational studies, particularly ones that rely on dietary recall or population-wide trends. Therefore, relationships between these aspects of diet and gut microbial communities likely have gone undetected in many studies. Nevertheless, the underlying biology implies that they may prove to be rich untapped drivers of the microbiota.

Diet also impacts substrates for microbial respiration. While these molecules are not typically sourced directly from the diet, their availability as well as their usage are in part determined by host metabolism of diet. Various electron acceptors have been found to play an important role in pathogenesis, providing a unique metabolic niche that few strains can utilize to colonize (154–158). More generally, changes in electron acceptor availability underlie competition between respiring bacteria and fermenters and contribute to community dynamics following antibiotic disturbance (159). Similarly, competition between acetogens, methanogens, and sulfate-reducing bacteria for hydrogen gas, an end product of carbohydrate fermentation (160), likely dictates the levels of these organisms in the human gut (161), as has been shown in ruminants (162, 163).

The availability of sulfate will also determine the abundance of sulfate reducers like *Desulfovibrio piger* (164, 165), although the potentially toxic effects of their metabolism, mediated by the sulfide end product, will be shaped by the abundance of methanogens which can utilize the hydrogen in H_2S and thereby detoxify it (166).

Various other molecules and substrates likely play a role in microbial community dynamics in the gut. Numerous therapeutic and diet-derived xenobiotics are known to change gut microbial growth *in vivo* (167) and *in vitro* (168). For instance, a recent *in vitro* screen of more than 1,000 nonantibiotic drugs found that 24% of drugs with human targets inhibited the growth of at least 1 of the 40 human gut bacterial strains tested (168). Resource availability may also determine the ability of gut bacteria to make signaling molecules or other molecules mediating microbial interactions. Diet and microbial metabolism can affect gut pH (169) or redox state (159) and have further downstream effects on microbial composition. Although an in-depth review of all relevant conditions is not possible here, we hope that these examples highlight the diversity of diet-associated properties beyond fermentable carbohydrates that impact the gut microbiota.

RECOMMENDATIONS FOR FUTURE RESEARCH

As outlined in the section above, various noncarbohydrate diet interventions can be expected to manipulate the gut microbiota. We would argue, however, that adjustments to the way that we analyze such manipulations will help identify and refine appropriate substrates of focus above and beyond just testing more resource types. Although there are numerous potential pathways to enhance the detection and mechanistic characterization of dietary levers, we offer four initial recommendations for new tacks to studying dietary properties that shape and can potentially manipulate the gut microbiota.

First, we propose that *in vitro* studies should utilize more-diverse media to ensure that all aspects of nutrient limitation might be captured. Minimal media are typically carbon limited and thus are most likely to identify interactions based on carbon. Studies with complex media most often use modified Gifu anaerobic medium (MGAM), a rich medium with high success for isolating gut strains (170) but one mismatched to the gut with regard to the abundance of various substrates. For example, at a very simple level, MGAM has a much lower carbon-to-nitrogen ratio (i.e., much higher nitrogen availability) than the mammalian gut (24). Varying nutrient availability even among rich media can result in highly differential growth (171), and more-thorough assays, including variation in the concentrations as well as kinds of nutrients available, should be done to identify nutrient requirements of different taxa. However, if a single medium is to be used, it should be designed to more closely hew to conditions found in the gut.

Second, we propose that research more often include measurements of changes in absolute abundance. Amplicon sequencing produces compositional data, which have many statistical limitations (172, 173). Recent work by Vandeputte and colleagues (174) demonstrated that variation in absolute abundance underpins changes in host phenotype more so than variation in relative abundance. However, only a small fraction of research on gut microbial responses to diet incorporates absolute-abundance data. It has been shown that changes in dietary protein altered overall concentrations of fecal bacteria in mice (24), supporting the inference that nitrogen is limiting in the gut. In contrast, while adding an indigestible carbohydrate (porphyran) to mouse diets allowed colonization by an exogenous strain of *Bacteroides*, there was not an overall increase in the number of bacteria (175); that is, the new strain ousted an equal number of other bacteria, a distinction not evident from relative-abundance data alone. Between these two studies, we can observe that some dietary manipulations (like changes in protein content) change the total biomass of the ecosystem, whereas others (like the addition of porphyran) change only community composition. Each may be a worthwhile goal, but they are nevertheless distinct. Appreciating and tailoring experiments to capture these differences will be necessary for interventions targeting specific health outcomes.

Third, we recommend more prudence when translating data from mouse research to humans. The mouse gastrointestinal tract differs in important ways from that of humans from mouth to anus and as such likely harbors a unique resource environment. For example, mice have lower ratios of small intestine to large intestine length (176) and area (177), which may decrease nutrient uptake proximal to the bulk of the microbial community, thereby dampening resource limitations present in humans. Mouse studies frequently report microbial community structural and functional profiles based on endpoint cecal samples; these profiles are unlikely to be recapitulated in humans, who lack an enlarged, functionally separate cecum (176). More generally, the mouse microbiota is not identical to that of humans (178); thus, humanized mice (i.e., germfree mice colonized by a human gut microbial community) are considered a closer alternative (179). However, humanized mice retain the anatomical differences from humans and also have numerous physiological differences from conventional mice, including a deficient immune system (180), which may make them less appropriate for use in studies of disease. It is also important to note that the environment experienced by mice in experiments differs from typical human conditions. Most notably, mouse diets do not vary under standard husbandry, so the introduction of a new diet or diet component may represent a more significant disturbance than when a human introduces a new food atop their normally variable diet. As omnivorous mammals, mice are ecologically similar to humans in many ways and have a long history of coresidence with humans. Moreover, given that laboratory mice have been reared for hundreds of generations in direct contact with humans and consuming highly processed (milled and cooked) diets, it is possible that mice and humans exhibit a degree of convergent adaptation in digestion that remains unexplored. Certainly, given the exceptional genetic, environmental, and microbiological control possible with mice, and the depth of systemic understanding arising from their frequent use in biological studies (181), mice will remain critical experimental models for studies of the microbiota. However, we would advocate that researchers should keep the differences outlined above in mind and seek to treat them more transparently.

Finally, we encourage leveraging variability in responses to more clearly understand the nuances inherent in dietary interventions. It is likely not the case that the same nutrients will be limiting in every gut due to individual host variation in diet or physiology. Focusing on individual responses will provide a clearer picture of what nutrients can shape the gut microbial community and in what contexts. For example, studies targeting resistant starch as a possible prebiotic have observed variable responses, with nearly half of individuals showing limited responses in gut microbial structure or microbial function, as measured by short-chain-fatty-acid concentrations (182). Similarly, some individuals have been found to pass most added resistant starch intact, whereas others have microbial communities that ferment >95% of it (123). With more-extensive studies of what defines a responsive community, it may be possible to design personalized interventions tailored to an individual's baseline microbial community composition and functional potential.

MANIPULATIONS TO WHAT END?

While many resources can shape the composition and function of the gut microbiota, different resource manipulations will be appropriate depending on the context. The goal of intervention to either promote or eliminate particular microbially mediated host phenotypes should determine the area of focus. In general, such phenotypes can be considered to belong to either of two categories: nutritional and nonnutritional contributions of the gut microbiota.

Unsurprisingly, nutritional contributions of the gut microbiota can be manipulated by altering the nutrients available in the lumen. Microbes break down diet components to grow and in so doing may produce metabolites taken up by the host, such as short-chain fatty acids but also amino acids, lactate, and ammonia (11, 17). Microbial symbionts can also produce nutrients that are missing from or insufficient in the diet, including essential vitamins (183) and amino acids (75). Changing diets can produce

alterations to these metabolic pathways, resulting in changes in host provisioning (e.g., see reference 110). Focusing diet interventions on substrates that are necessary in the metabolic process of interest, and in particular those substrates that are limiting to the process, will allow for greater dynamic control over microbial metabolic provisioning. However, it is important to note that the gut microbiota can also compete with the host for resources (184) or hurt the host when overproducing certain metabolites (185), so increasing populations through provisioning will not always be beneficial.

Beyond nutritional contributions, the gut microbiota shapes the physiology of many other host organ systems. The gut microbiota plays a crucial role in colonization resistance (186), it modulates the immune system (4), and it produces or alters host production of signaling molecules, with effects on organs as distant as the brain (187, 188). Manipulating the gut microbiota through diet to promote these functions is less straightforward, at least when it comes to determining what manipulations to use. Substrates necessary to promote the growth of species of interest or to make the signaling molecules involved will need to be identified first either through *in vitro* screens or through more-expansive measurements of functioning in diet intervention studies. The effects of dietary changes on immune functioning or signaling may be more complicated than those on metabolism. For instance, increasing mucosal secretions to support a physical barrier and colonization resistance may involve any or all of the following: promoting growth of bacterial taxa (e.g., *Firmicutes*) that produce the short-chain fatty acid butyrate, whose uptake promotes mucus secretion (45); limiting the growth of taxa that catabolize mucus (e.g., *Bacteroidetes*) (98); promoting the growth of mucin degraders (e.g., *Verrucomicrobia*) that nevertheless stimulate robust barrier function (52); altering cross-feeding interactions among gut bacteria at the mucus barrier (69); or fostering a complex gut microbiota that interacts with various aspects of host biology to improve overall immunity.

More broadly, to support host health, it will be necessary to determine what a healthy gut microbial community looks like. Of course, the answer will not necessarily be the same for all individuals, but in the absence of a particular functional target, general structural guidelines will be necessary before beginning interventions. Some diets, for example, those including protein supplementation, could increase the overall bacterial load (24, 189), but it remains unknown what constitutes an ideal bacterial load for a human gut. Similarly, while low diversity is often considered a marker for community imbalance, there is little observational or experimental evidence documenting ideal diversity levels or their functional implications (190). Better defining of the goals in microbial manipulation will require answering these questions and others, with particular attention paid to both the evolutionary context in which our relationship to the microbiota arose as well as how contemporary contexts may differ. Gut microbial profiles that were healthy historically and those most improving health among traditional subsistence, developing, and industrialized populations can all be expected to differ. Rational attempts to engineer the gut microbiota via diet will need to appreciate these differences and to capitalize on existing variation to accelerate the pace of discovery.

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