REVIEW

The gut microbiota at the intersection of diet and human health

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Diet affects multiple facets of human health and is inextricably linked to chronic metabolic conditions such as obesity, type 2 diabetes, and cardiovascular disease. Dietary nutrients are essential not only for human health but also for the health and survival of the trillions of microbes that reside within the human intestines. Diet is a key component of the relationship between humans and their microbial residents; gut microbes use ingested nutrients for fundamental biological processes, and the metabolic outputs of those processes may have important impacts on human physiology. Studies in humans and animal models are beginning to unravel the underpinnings of this relationship, and increasing evidence suggests that it may underlie some of the broader effects of diet on human health and disease.

Controversy regarding what constitutes a healthful diet has persisted since the advent of nutrition as a scientific discipline and establishment of government nutritional guidelines (*1*). The emergence of the gut microbiota as a key regulator of health and disease has further complicated this issue. A mutualistic relation exists between diet and the gut microbiota so that dietary factors are among the most potent modulators of microbiota composition and function. Intestinal microbes in turn influence the absorption, metabolism, and storage of ingested nutrients, with potentially profound effects on host physiology.

The human gut microbiota consists of trillions of microbial cells and thousands of bacterial species. The specific compositional features differ among individuals, and although the mature microbiota is fairly resilient, it can be altered within individuals by both internal and external stimuli. Interindividual variability and the plasticity of the gut microbiota have hindered efforts to identify a "healthy" microbiota, although markers of microbial stability, such as richness and diversity, are often used as indicators of gut health because of their inverse association with chronic disease and metabolic dysfunction (*2*). Microbiota plasticity also creates a distinct opportunity; by manipulating various external factors, the potential exists to reshape the architecture and biological outputs of gut microbes for improved human health.

Diet is an important external factor affecting the gut microbiota, and diet's ability to alter microbial ecology was first recognized more than a century ago (*3*). Transient diet-induced alterations occur independently of body weight and adiposity and are detectable in humans within 24 to 48 hours after dietary manipulation (*4*). The effects of diet on microbial ecology are unsurprising when one considers that gut microbes, like their human hosts, use ingested nutrients as fuel for fundamental biological processes. Thus, changes to host dietary patterns alter bacterial metabolism and favor species most suited to use consumed fuel sources. What was not predicted after the initial observations a century ago, and has only come to light in recent decades, is the important effect that diet-induced changes in microbial structure have on human physiology and disease processes.

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Nutrients

Microbiota-accessible carbohydrates

When studied in isolation, each of the major macronutrients and numerous micronutrients have been shown to modify the gut microbiome. Among the macronutrients, the effects of dietary carbohydrates (CHO) are best characterized. Simple CHO such as sucrose, both alone and as part of a Western-style high-fat high-sugar diet, cause rapid microbiota remodeling and metabolic dysfunction in experimental animals (*5*, *6*). Complex CHO exhibit a diverse array of monosaccharide linkages, many of which are indigestible by humans. Gut microbes, on the other hand, possess several hundredfold more CHO-degrading enzymes and thus use indigestible CHO as their primary energy source. The term "fiber" is commonly used to describe these indigestible CHO, although this designation is problematic given that some fibers are not used by gut microbes (such as cellulose), whereas other readily fermented CHO fall outside of the definition of fiber (such as resistant starches). Sonnenburg and colleagues (*7*) recently proposed the term "microbiota-accessible carbohydrate," or MAC, to describe CHO that are metabolically available to gut microbes, and we use that terminology hereafter.

Several lines of evidence indicate that alterations in dietary MACs have important effects on microbiota composition and function. Agronomic and nomadic hunter-gatherer societies that consume high levels of MACs display greater microbial richness and diversity as compared with those of industrialized societies (*8*, *9*). Diets high in MACs alter microbiota composition in humans within days or weeks (*10*, *11*). Mice fed a diet low in MACs experience decreases in numerous taxa, and loss of diversity is compounded over several generations of offspring and not recovered after reintroduction of MACs (*7*, *9*). Reductions in bacterial abundance with low MAC intake are not observed uniformly across all bacterial taxa because certain bacterial species that typically consume dietary glycoproteins can also use glycoproteins of the intestinal mucus layer as an alternative energy source. Over-grazing of the mucus layer by these species may be an important consequence of MAC restriction, as chronic foraging has been shown to compromise barrier integrity and enhance inflammation and pathogen susceptibility in animal studies (*12*, *13*).

Another consequence of MAC restriction is a reduction in short chain fatty acid (SCFA) production. SCFAs, the primary end products of bacterial fermentation, represent an excellent example of mutualism between humans and their bacterial symbionts. MACs provide a critical energy source for gut bacteria, and the consequent production of SCFAs benefits the host by serving as both recovered energy from otherwise inaccessible carbohydrates as well as potent regulatory molecules with vast physiological effects (Fig. 1). SCFAs signal via the central nervous system and several G protein–coupled receptors (GPCRs) to modulate a range of physiological processes, including energy homeostasis, lipid and carbohydrate metabolism, and suppression of inflammatory signals (*14*, *15*). Two SCFAs, butyrate and propionate, also act as histone deacetylase inhibitors, suggesting that they can epigenetically influence host gene expression (*16*). Thus, decreased SCFA production and increased mucus foraging represent two microbiota-dependent consequences of low MAC intake, and it is tempting to speculate that these processes underlie the long-recognized health benefits of high-fiber diets. It should be noted that the extent of mucus foraging in humans, and its importance in human disease processes, have not been directly examined. Furthermore, despite the protective effects of SCFAs observed in preclinical models, obese humans and genetically obese mice display increased fecal and caecal concentrations of SCFA (*17*), suggesting that they may contribute to enhanced energy harvest. Thus, energy balance status of an individual may determine whether the beneficial effects of SCFA signaling on metabolism outweigh the additional calories harvested (*18*).

It is important to recognize that MACs represent a diverse group of oligo- and polysaccharides with considerable structural heterogeneity and diverse effects on microbial ecology. A specific subset of MACs have been termed "prebiotic," which originally described a class of oligosaccharides that selectively enhance growth of *Bifidobacterium* and *Lactobacillus* (*19*). These canonical prebiotics, primarily fructo- and galactooligosaccharides of varying chain lengths, have been shown to alter members of the human gut microbiota and modulate inflammation and

markers of metabolic syndrome (*20*, *21*). Despite promising data on oligosaccharide use for appetite regulation and obesity-related complications, therapeutic efficacy of these prebiotics in treating gastrointestinal conditions is variable (*22*). Several studies have shown that restricting oligosaccharides and other fermentable sugars [a low-FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet] alleviates symptoms of irritable bowel syndrome (*23*).

Technological advances that allow for holistic examination of microbial responses to dietary components have led to a recent expansion of the prebiotic concept (*24*). Although selective use of a dietary substrate by specific microbial populations is still required, the list of potential substrates and microbial targets is more inclusive. For example, candidate prebiotic substrates now include nonpolysaccharide dietary components such as polyunsaturated fats, conjugated linoleic acid, and phytochemicals/phenolics (*24*, *25*). Likewise, prebiotics may be selectively used by bacteria other than *Bifidobacterium* and *Lactobacillus*, provided the net effects on host health are beneficial. As a result of these expanded inclusion criteria, studies that characterize distinct host-microbe-substrate interactions are of particular interest.

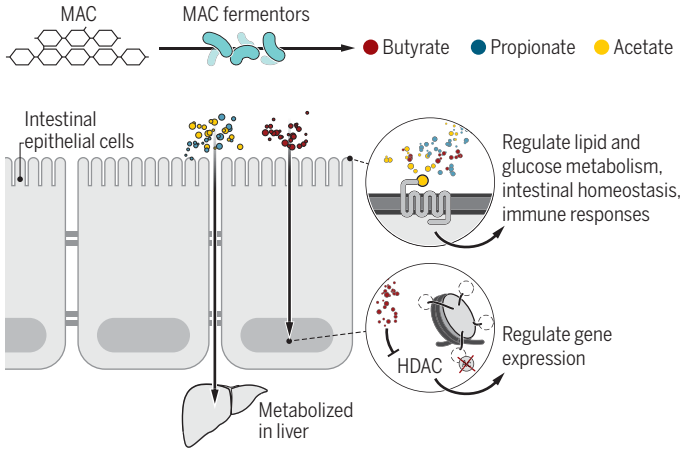

Fig. 1. MAC fermentors produce SCFAs that can have multiple interactions with host tissues. Butyrate is taken up by epithelial cells and used as a primary source of energy for these cells. Butyrate (and to a lesser degree, propionate) can block histone deacetylases (HDAC) to regulate gene expression. All of the SCFAs can bind with varying affinities to G protein receptors in the intestines and other cells to regulate energy metabolism, intestinal homeostasis, and immune responses. Acetate and propionate are primarily metabolized in the liver, where propionate is used as a substrate for gluconeogenesis and acetate is used as an energy source and for fatty acid synthesis.

Dietary fats

An increase in dietary fat also substantially alters microbiota composition. Experimental mice fed a high-fat diet (40 to 80% total caloric intake) exhibit decreases at the phyla-level in Bacteroidetes and increases in Firmicutes and Proteobacteria. These changes were observed in mice resistant to weight gain, implying a direct effect of dietary lipids on the microbiota (*26*, *27*). Germ-free (GF) mice are protected from the metabolic consequences of high-fat diets, suggesting that gut microbes may be important mediators of lipid-induced metabolic dysfunction (*28*). The metabolic protection in GF mice may be due to enhanced fat oxidation or reduced absorption in the small intestine (*29*). Microbes in the small intestine were recently found to be highly susceptible to fat load and essential for lipid digestion and absorption (*17*). These data suggest that regional specificity of microbiota composition may have important functional consequences and highlight the need for spatially distinct analyses along the gastrointestinal tract. Importantly, not all studies have found that GF mice are protected from the metabolic consequences of high-fat feeding, and the cholesterol content of the diet may be an important determining factor (*30*). As with carbohydrates, lipid-mediated effects on the microbiota are dependent on the lipid type and source. For example, mice fed an isocaloric diet rich in long-chain saturated fats derived primarily from meat products displayed greater insulin resistance and adipose tissue inflammation as compared with that of mice fed a high–fish oil diet. These metabolic disturbances were accompanied by reductions in phylogenetic diversity in the saturated fat–fed mice, and receipt of transplanted microbiota from mice fed fish oil abrogated saturated fat–induced inflammation (*31*). Furthermore, transgenic mice that constitutively produce ω3 polyunsaturated fatty acids possess a microbiome with enhanced phylogenetic diversity that offers protection against the metabolic consequences of a high-saturated-fat, high-sugar diet (*32*).

One mechanism by which gut microbes may mediate the metabolic consequences of high-fat intake is through translocation of lipopolysaccharide (LPS), a cell-wall component of gram-negative bacteria. Increases in circulating LPS have been reported in humans after a high-fat meal, with exacerbated effects in obese individuals (*33*). Once in circulation, LPS elicits a potent inflammatory response via Toll-like 4 receptor signaling, which has been implicated in the development of cardiovascular and metabolic disease (*34*). Although existing data that link circulating LPS to cardiometabolic disturbances are compelling, progress in this area has been hindered by the inability of available assays to distinguish between stimulatory and non-stimulatory LPS, as well as by circulating inhibitors that reduce accuracy of LPS quantification (*35*). Furthermore, although circulating LPS has been reported in obese individuals and correlates with markers of metabolic disease, a direct causal role in human disease has not been examined (*36*).

Primary bile acids are produced in the liver from cholesterol and facilitate the digestion of dietary lipids. Once generated, primary bile acids are secreted into the small intestine, where they facilitate the solubilization and absorption of lipids. Microbial alterations to primary bile acids include hydrolysis of conjugated amino acids, 7α/β-dehydroxylation, and oxidation and epimerization of hydroxyl groups at various positions (Fig. 2) (*37*). GF mice display increased abundance and reduced diversity of bile acids compared with that of conventional mice (*38*), and enrichment of specific secondary bile acids has been observed in colorectal cancer cases (*39*). In addition to their canonical role in aiding lipid digestion, bile acids act as dynamic signaling molecules via the farnesoid X receptor (FXR) and the G protein–coupled bile acid receptor 1 (TGR5). Like SCFAs, bile acids have been shown to regulate energy homeostasis, glucose metabolism, and innate immunity (*40*). More recent data suggest that gut microbes also have direct effects on FXR and TGR5 expression and signaling (*40*, *41*). Thus, the gut microbiota helps regulate bile acid composition, abundance, and signaling, and this regulation may have important implications not only for lipid digestion and absorption but also for the development and prevention of metabolic disease. Several bile acid–directed therapeutics are currently being examined for obesity-related conditions, and as the clinical utility of these therapeutics is tested, it will be important to consider microbiota composition in determining interindividual efficacy and safety.

Dietary protein

Dietary proteins also modulate microbial composition and metabolite production, with amino acids providing gut microbes essential carbon and nitrogen. Amino acid catabolism yields numerous metabolites that affect host physiology (Fig. 3). For example, although SCFAs are derived mainly from MAC fermentation, they are also by-products of bacterial metabolism of amino acids. The relative contribution of amino acid metabolism to total SCFA production is unclear, but total protein and fiber intake are influencing factors. Additional metabolites of amino acid catabolism include branched chain fatty acids, indoles, phenols, ammonia, and amines, all of which can affect human health. For example, phenols, indoles, and amines can combine with nitric oxide to form genotoxic N-nitroso compounds that are associated with gastrointestinal

cancers in human populations (*42*). By contrast, indolepropionic acid, a microbial metabolite of tryptophan, maintains intestinal homeostasis and protects from experimental colitis (*43*). Indole-3-acetate, another bacterially derived tryptophan metabolite, was recently shown to reduce hepatocyte and macrophage inflammation (*44*). The source of dietary protein also determines the nature of microbiota-dependent metabolic outputs. This is perhaps best exemplified by production of the compound trimethylamine oxide (TMAO) from the amino acid L-carnitine, which is abundant in animal but not vegetable protein. TMAO is predictive of cardiovascular events in various populations (*45*) and has been implicated in the development of fatty liver disease (*46*). A recently developed inhibitor of TMAO production reduced platelet aggregation and thrombus formation in experimental animals, enhancing the potential of TMAO-directed therapies (*47*). Collectively, these data highlight that the vast effects of microbiota-derived amino acid metabolites on host physiology are only now beginning to emerge and represent an area ripe for future research.

Micronutrients

In addition to major macronutrients, the gut microbiota regulates both synthesis and metabolic output of various micronutrients. The B vitamins, for example, can be synthesized by more than 100 bacterial species, and analysis of the synthesis pathways involved suggests that bacteria cooperatively exchange B vitamins to ensure survival (*48*). The relation between vitamins and the microbiota appears to be bidirectional because several vitamins supplied by the host shape microbial composition and provide critical functions within bacteria. Riboflavin, for example, regulates bacterial extracellular electron transfer and redox status (*49*), and vitamin D and its receptor help regulate intestinal inflammation, in part by shaping microbial ecology (*50*). Like vitamins, metals are required cofactors for numerous mammalian and bacterial physiological processes and can dramatically alter the microbiota. Zinc deficiency, which is a strong risk factor for potentially fatal childhood diarrhea in developing countries, enhances populations of pathogenic bacteria (*51*). Iron is an essential micronutrient for pathogen growth, and restricting iron intake is an effective form of nutritional immunity against pathogen establishment. Human breastmilk transmits lactoferrin, an iron-binding glycoprotein, to protect the undeveloped infant gut from pathogen colonization, and iron supplementation in infants can increase pathogen growth and intestinal inflammation (*52*). Despite observed bacteriogenic effects of iron, supplementation in experimental mice was recently found to suppress virulence of the rodent enteric pathogen *Citrobacter rodentium*, essentially converting the pathogen to a commensal microbe (*53*). High salt intake has been implicated in the cardiovascular consequences of Western diets. Recent data suggest that the hypertensive effects of high-salt diets in experimental animals and humans are mediated by reduced levels of *Lactobacillus* and subsequent increases in proinflammatory T helper 17 cells (*54*). Collectively, the interactions identified thus far between the microbiota and micronutrients, as well as the myriad other interactions that undoubtedly await discovery, represent an important avenue of future research. The data also highlight the importance of monitoring micronutrient composition in microbiota-focused dietary intervention studies and beget the need for clinical trials in populations at risk for vitamin and mineral deficiencies.

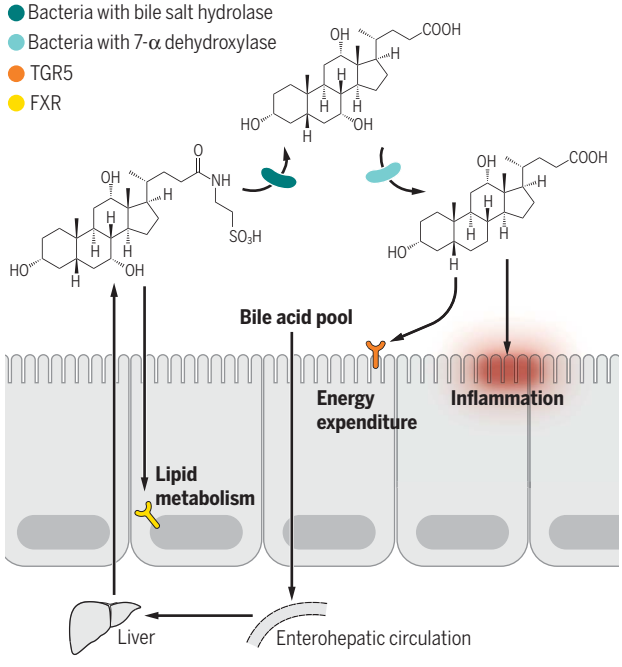

Fig. 2. Gut bacteria play an important role in bile acid modification. Primary bile acids deposited into the small intestine are deconjugated and dehydroxylated by enzymes from bile-modifying bacteria. These changes influence total bile acid pools available for reabsorption and recycling through enterohepatic circulation. In addition, bile acids can act as regulatory molecules by binding to cell surface or nuclear receptors, influencing host factors such as energy expenditure and lipid metabolism.

Food additives

The impact of food additives on the gut microbiota and intestinal homeostasis represents another understudied area with potential implications for human health. Although microbial and health consequences of Western diets are typically attributed to macronutrient composition, several studies suggest that the detrimental effects may be driven by food additives. For example, administration of two dietary emulsifiers, polysorbate-80 and carboxymethyl cellulose, induced obesity, intestinal inflammation, and metabolic dysfunction in the absence of other dietary manipulations in mice. The microbiota was both required and sufficient for these effects as GF mice were protected from detrimental consequences, and microbiota transfer from emulsifier-treated mice was sufficient to recapitulate the metabolic derangements (*55*). These results are particularly striking given the wide range of foods in which these emulsifiers are found (such as gluten-free and reduced-fat products, ice cream, wine, and pickles), and that the doses used in the study are well within the amount consumed by humans. In addition to emulsifiers, non-nutritive sweeteners (NNS) have been linked to gut-associated metabolic alterations. In a series of experiments that used rodents and humans, NNS consumption induced glucose intolerance in a microbiota-dependent manner (*56*). However, the collective data regarding the effects of NNS on the gut microbiota and metabolic function are equivocal, and it is important to recognize that NNS represent a broad class of substances with tremendous structural and functional diversity. Thus, the physiological effects of a particular NNS should not be generalized, and additional human intervention studies examining the impact of individual NNS are needed.

Dietary patterns

One obvious limitation to studying the health effects of individual nutrients is that those nutrients are rarely consumed in isolation; thus, experimental manipulation of an individual macronutrient invariably alters intake of other macronutrients that may have metabolic effects unto themselves. For example, high-fat diets are commonly low in fiber, and it may be this latter feature, and its downstream effects on the microbiota, that drives some of the metabolic consequences of the diet rather than the elevated fat content by itself. Given the limitations of studying nutrients in isolation, there is increasing focus away from this experimental reductionism and toward examining the health effects of broader dietary patterns.

Ketogenic diet

The ketogenic diet is characterized by very low CHO consumption (5 to 10% of total caloric intake), sufficient to enhance ketone production. It was originally developed as a treatment for refractory childhood epilepsy, and response of the gut microbiota to a ketogenic diet appears to play a role in the efficacy of this intervention in epileptic children (*57*). Animal data suggest that the neuroprotective effects are mediated through modulation of specific gut bacteria that enhance

hippocampal γ-aminobutyric acid/glutamate levels (*58*). In recent years, the benefits of ketogenic diets have extended beyond seizure control, and the diets are commonly adopted for weight loss and have been shown to enhance longevity and reduce disease onset in experimental animals (*59*). Conversely, some human studies that examined ketogenic diets suggest negative impacts on microbial ecology and gut health. However, these studies were conducted in small cohorts with specific metabolic conditions (*60*, *61*), limiting generalization to larger populations. Because modified versions of ketogenic diets are rapidly growing in popularity, it is necessary to examine their long-term safety and impacts on the gut microbiota and intestinal environment.

Paleolithic diet

The Paleolithic diet, which seeks to mimic the dietary patterns of pre-agricultural societies, is often implemented as a high-protein/low-CHO diet for weight loss by individuals in Western societies. Clinically, the Paleolithic diet is being explored for management of inflammatory bowel disease (IBD), and although initial findings were promising, the study was conducted in a small cohort, and additional nutrient supplementation was required to curtail iron and vitamin D deficiencies (*62*). Although there is a paucity of intervention studies that examine microbiota-specific effects of replacing a Western diet with a Paleolithic diet, comparative studies between industrialized populations and modern-day hunter-gatherer societies have provided some insight. The Hadza, a hunter-gatherer tribe whose lifestyle has been described as mimicking that of Paleolithic communities, experience few metabolic diseases that plague industrialized societies, and their microbiota is characterized by greater microbial diversity (*9*, *63*). However, it is difficult to ascribe these microbiota and health benefits to lower CHO intake by itself because the Hadza diet is rich in plant-derived MACs, and their microbiota contains a high abundance of CHO-metabolizing bacteria (*63*). Furthermore, diets of Western societies lack many of the traditional foods and seasonal variation of the Hadza, highlighting the limited parallels between traditional hunter-gatherer diets and modern-day Paleolithic diets adopted by individuals in Western societies.

Vegan/vegetarian diets

Plant-rich diets have long been a key feature of dietary recommendations, and vegan/vegetarian diets are associated with positive health outcomes and reduced disease risk (*64*). These beneficial effects may extend to the gut microbiota. Plant-based foods constitute the primary source of dietary MACs, and the microbiota of individuals who consume vegetarian or predominantly plant-based diets exhibit greater capacity for MAC fermentation. However, some intervention and cross-sectional studies have observed only modest microbiota differences between omnivores and vegetarians and suggest that the effects of dietary pattern on the microbiota are greatest at the genus and species level and relatively minimal on broader compositional features, such as diversity and richness (*65*–*67*). Despite the absence of global microbiota compositional shifts, the species-level changes appear sufficient to alter metabolic outputs because SCFA production is typically increased in vegetarians. The extent to which these microbial metabolic outputs mediate the beneficial effects of vegetarian diets is unclear.

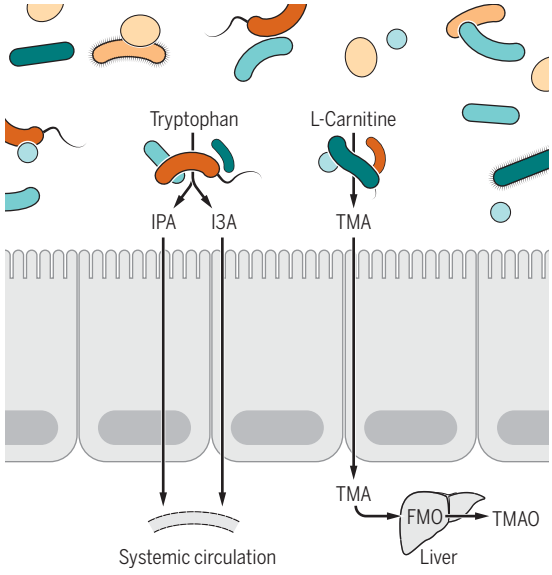

Fig. 3. Interactions between amino acids and the gut microbiota. Microbial metabolism of the amino acid carnitine produces trimethylamine (TMA), which is subsequently oxidized in the liver to TMAO in a reaction catalyzed by flavin-containing monooxygenase (FMO). Increased levels of circulating TMAO have been linked to metabolic disease. Gut microbes metabolize the amino acid tryptophan into various substances, including indolepropionic acid (IPA) and indole-3-acetic acid (I3A), both of which can enter the general circulation. The metabolic effects of IPA, I3A, and other microbially derived amino acid metabolites are only now beginning to emerge.

In addition to providing MACs, plant-based foods provide a diverse source of phytochemicals, biologically active small molecules with the potential to affect human health. Within the plant, many phytochemicals are glycosylated, reducing their bioavailability and bioactivity when consumed. As a result, phytochemicals often reach the lower intestinal tract and can have direct antimicrobial and anti-inflammatory effects in the gut. In addition, phytochemicals can be modified by microbial enzymes into metabolites with increased bioavailability and altered bioactivity (*68*). A prominent example includes the bioconversion of naturally occurring soy isoflavones to equol (*69*), which exhibits increased bioavailability compared with that of the parent compounds. Thus, microbe-mediated alterations in phytochemical bioavailability may represent an additional mechanism underlying the beneficial effects of plant-based diets.

Mediterranean diet

The Mediterranean diet emphasizes consumption of a variety of foods (fruits, vegetables, legumes, unsaturated fats, and limited red meat intake) rather than the exclusion of particular food groups or confinement to specific macronutrient ratios. Numerous epidemiologic studies and clinical trials have demonstrated that following a Mediterranean diet reduces the risk of all-cause mortality and multiple chronic diseases (*64*, *70*). Although only a few of these studies have examined the effects on microbiota composition, existing data indicate that the Mediterranean diet elicits favorable microbiota profiles and metabolite production, with microbial diversity paralleling levels of dietary adherence (*71*–*73*). For example, closer adherence to the Mediterranean dietary pattern was associated with lower ratios of Firmicutes:Bacteroidetes and higher fecal SCFA detection (*73*). Collectively, these studies suggest that emphasis should be placed on sufficient inclusion of a variety of plant-based foods rather than exclusion of animal-based food and supports the concept that diet diversity is a driver of microbiota stability.

Microbiota-targeted diets

A number of microbiota-targeted diets have recently emerged with the growing public awareness of the gut microbiota and its potential to influence human health. Although the scientific premise of many of these diets is logically rooted in prevailing paradigms, they fail to acknowledge the many gaps in our knowledge regarding diet-microbiome-host interactions. The specific carbohydrate diet (SCD) restricts complex carbohydrates and refined sugar under the premise that these compounds are malabsorbed in the gastrointestinal tract, leading to bacterial overgrowth and gut dysbiosis. Like the low-FODMAPs diet, there is some evidence to suggest that individuals with IBD experience benefits when following a SCD (*74*), although long-term adherence to this restrictive diet is difficult. A derivative of the SCD is the gut and psychology syndrome (GAPS) diet, which expands beyond dietary exclusion of specific foods by adding foods claimed to have gut-healing potential. This includes consumption of nutrient-rich bone broth to regenerate the intestinal lining and antimicrobial foods such as garlic to reduce pathogen loads. Although this diet is frequently prescribed by alternative medicine practitioners for conditions ranging from autism to depression, there is only anectotal rather than scientific evidence to support that adherence produces the intended effects on health outcomes. A study supporting the use of a similar diet was recently retracted from the journal *PLOS ONE* because of several issues, including the absence of a control group, inadequate description of methods, and lack of microbiota analysis (*75*). Last, although not a diet in itself, there is a common belief that probiotic-containing fermented foods modify the

gut microbiota and confer host health benefits. However, fermented foods rarely contain adequate amounts of specific probiotic organisms. Moreover, there is limited evidence for the role of probiotics as modulators of the human gut microbiota, and recent data suggest that even supplemental quantities of probiotics exert limited effects on human gut ecology (*76*) and may even be detrimental with regard to recolonization of the microbiota after antibiotic use (*77*). With the exception of yogurt, benefits of fermented foods have not been clinically tested, and studies examining the effects of yogurt for weight management are equivocal (*78*). Evidence suggests that acetic acid, a metabolic by-product of fermentation, suppresses appetite and reduces postprandial insulin response and glucose excursions (*79*). In addition, some fermented foods have higher nutrient content and elevated B vitamins as compared with those of nonfermented forms of the same food (*80*), suggesting that any added benefits may be due to microbial metabolites rather than the microbes themselves.

Perspectives and future directions

Data collected over the past decade have identified the gut microbiota as an important factor defining interindividual variation in disease risk and dietary response. The ascension of the gut microbiota as a key regulator of human physiology has generated tremendous excitement within and beyond the scientific community, as exemplified by the exponential increase in microbiota-focused publications and by the growth of the probiotic market into a multibillion-dollar industry. The rapidity of this ascension, however, poses a substantial challenge in that commercialization and popularity of microbiota-targeted therapies have accelerated despite the fact that fundamental questions regarding the microbiota and its relation to diet and human health remain unresolved. For example, much of the current data linking the microbiota to disease processes have been generated in animal models, and human feeding studies are needed to confirm their relevance before they can be translated to practical nutrition advice.

The plasticity of the microbiota makes microbiome-targeted interventions an attractive approach for disease prevention and treatment. However, despite reported alterations of the gut microbiota in response to short-term dietary interventions, long-term dietary patterns are associated with stable microbiota conformations that are difficult to alter (*81*–*83*). Additionally, diet-responsive members of the microbiota often represent a small proportion of the total community, necessitating a better understanding of whether changes in tractable populations are sufficient to elicit physiological outcomes in the host. Last, the degree of microbiota plasticity, and thus the potential for response to microbiota-directed interventions, may be dependent on baseline microbial populations (*76*) and past dietary patterns (*82*). For example, recent data from mice colonized by human bacteria indicate that diets associated with reduced microbial diversity may have impaired responsiveness to dietary interventions, requiring reexposure to diet-responsive microorganisms (*82*). Thus, identifying presence of key diet-responsive microorganisms may be important in predicting success of dietary interventions in humans.

Although plasticity offers an opportunity for microbiota-targeted therapeutics, it represents a double-edged sword in that it also catalyzes deleterious effects of external stressors, such as an unhealthful diet. Dysbiosis, an alteration in the composition of the microbiota associated with a disease state, has been linked with poor diet and numerous chronic diseases. However, determination of an absolute, rather than comparative, definition of dysbiosis remains a fundamental unresolved question. The recently proposed "Anna Karenina hypothesis" suggests that dysbiosis is not a definitive pattern but rather the loss of microbiota stability, resulting in dispersion from the norm (*84*). This indicates the need to define a healthy microbiota, which is problematic on an individual basis, given that factors such as environment, genetics, past diet, exercise, and geography all play a role in shaping the microbiota, and these individual influences may or may not translate to tangible health outcomes.

Despite current unresolved questions that limit practical and clinical translation of microbiota research, several new developments promise continued advancement of the field. Integration of proteomic and metabolomic data with existing DNA-based methods of microbiota assessment could circumvent the need to define healthy versus unhealthy microbial populations as more accurate functional profiling emerges. To this end, the Integrated Human Microbiome Project was recently launched to functionally characterize human cohorts in various life stages and at the onset of specific disease states (*85*). Additionally, new bioinformatics tools and modeling algorithms are improving our ability to apply microbiota data to human outcomes. Examples of recent successes include the development of algorithms that incorporate microbiota profiles to predict post-dieting weight gain (*86*) and develop personalized diet recommendations for control of postprandial glycemic responses (*87*). These examples demonstrate how realization of the potential for microbiota-diet interactions could change future approaches to nutrition.

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