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Emerging Aspects of Food and Nutrition on Gut Microbiota

Xuan He,[†,‡] Maria L. Marco,[‡] and Carolyn M. Slupsky*[,†,‡]

[†]Department of Nutrition and [‡]Department of Food Science and Technology, University of California, Davis, California 95616, United States

ABSTRACT: The human gastrointestinal tract contains a highly complex ecosystem that harbors various microorganisms, which together create a unique environment within each individual. There is growing awareness that dietary habits are one of the essential factors contributing to the microbial diversity and community configuration that ultimately affects human health. From an evolutionary perspective, human dietary history can be viewed as a central factor in the selection of the gut microbial community and stabilization of the mutualistic host−microbial interaction, that together drive host phenotype. Herein, current knowledge concerning the influence of major dietary macrostructure and individual food ingredients is presented. This knowledge will provide perspectives for personalized gut microbiota management and, ultimately, movement toward an era of personalized nutrition and medicine.

KEYWORDS: *gut microbiome, diet, nutrition, food, colon, dietary fiber*

INTRODUCTION

We live in an intimate relationship with microorganisms that are present on the surfaces and cavities of the human body. During birth, or shortly thereafter, microbes from the mother's skin and milk, the air, and inanimate objects enter the virtually germ-free system of the neonate and proliferate to a dramatic extent. The gastrointestinal (GI) tract is the most densely populated microbial ecosystem of the mammalian host. Bacterial cells are most abundant, but other types of microbes are also present in the GI tract, such as archaea, viruses, protozoa, and fungi. The intestinal lumen alone harbors 10 times more bacterial cells than eukaryotic cells in the entire human body, an amount equivalent to approximately 1 kg of human mass.[1] This fact leads us to view ourselves as "super-organisms", being composed of our cells as well as microbial cells that are dependent on each another for survival.[2]

Food is a major source of energy that promotes growth and development, immunity, and tissue repair, as well as homeostatic regulation. It is also an important energy source for gut microbiota.[3,4] Although most nutrient absorption occurs in the small intestine, the colon harbors the majority of bacterial colonists. The colon can be viewed as the major site for "co-metabolic" activity, which enhances the efficiency of the energy harvest from foods[5,6] and influences the synthesis, bioavailability, and function of nutrients,[4] vitamins,[7,8] and drugs.[9,10] Thus, the functional interaction between microbes and their host explains individual variability of nutrient metabolism and bioavailability.[11] Understanding the relationship between the gut microbiome and diet is important for the development of next-generation therapeutic foods that target these microbes in health-promoting ways and will ultimately usher us toward an era of personalized nutrition and medicine.

In this paper, current knowledge of the gut microbiome from the perspective of human dietary history and the coevolutionary relationship with the host will be broadly reviewed. The impact of major dietary components as well as single food ingredients that favor changes in the gut microbiome will be explored.

LIVING WITH THE PAST: EVOLUTIONARY HISTORY OF DIET AND THE GUT MICROBIOME

Dietary transition during human history has been suggested to play a central role in the evolution of mankind.[12,13] Unlike the diets of other higher primates, which consist of mainly fiber-rich plants supplemented with insects and a small amount of animal flesh,[13] humans consume easily digested, energy-dense food. This distinction has resulted in substantial differences in the human GI tract including a smaller gut volume, longer small intestine, smaller cecum and colon, and faster gut passage rate.[13−15] The discovery of fire and use of cooking techniques are also contributed to the evolution of human GI physiology by softening food texture, elevating calorie density, and reducing toxins.[16] These differences are encompassed within the "expensive tissue hypothesis",[14,17] which suggests that a reduction in the of size of an energetically expensive GI tract yields a corresponding increase in the size of an energetically expensive brain, which in humans may have been facilitated by improvements in diet (Figure 1).

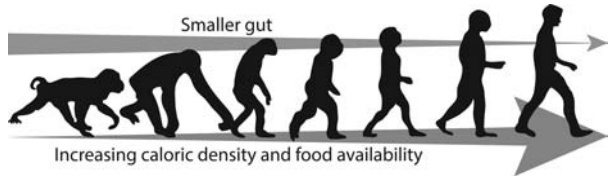

Figure 1. Human evolution is connected with changes in diet. Throughout human dietary history, there was a gradual shift toward high-quality, energy-dense, easily absorbed food that was coupled with the use of fire in cooking. At the same time, the size of the gut decreased.

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Another major advancement in human evolution was the shift from hunting and gathering to agriculture involving the domestication of animals and crops. Domesticated plants provided more calories than nondomesticated plants, which consequently drove the dietary pattern to focus more on a limited variety of foods, with a reduction in nutrient diversity.[18] Today, economics, agriculture, and culture are strong forces that shape food availability, variety, and quality. With the advent and spread of global food production, additional changes in the human diet have occurred. Mass food production has allowed people to focus more intensively on the consumption of a few staples.

The acquisition of a conserved and stable microbial consortium is constrained by the host GI tract morphology and long-term diet history.[19−22] A recent study examined the gut microbiome of 39 different mammalian species (including humans), grouping them into herbivores (fore-gut and hind-gut fermenters), carnivores, and omnivores.[23] Comparisons between the groups revealed only three bacterial genera are significantly associated with the overall mammalian phylogenetic tree, namely *Prevotella*, *Barnesiella*, and *Bacteroides*.[23] Although there were differences in the anatomy and function of the gut in each group, as well as a varied rate of microbial fermentation among the hosts,[24] herbivores appeared to be enriched in functional enzymes essential to the biosynthesis of amino acids, whereas carnivores were enriched in enzymes involved with branched-chain amino acid degradation.[23] Herbivores also harbored a more diverse microbial community than carnivores.[25] Notably, a gut microbiome that is low in diversity is less resilient to various disturbances from diet.[7] These results support the notion that, over time, the intestinal microbial community has coevolved with the host.[20,26]

Part of the coevolution of the gut microbiota with its host involves horizontal gene transfer[27] to gain function and adapt to new environmental conditions. For example, the acquisition of carbohydrate-active enzymes (CAZymes), both glycoside hydrolases and glycosyltransferases, in human gut microbiota is largely due to horizontal gene transfer rather than functional gene expansion.[28] Indeed, the human genome lacks the large repertoire of glycoside hydrolases and polysaccharide lyases to digest a wide variety of plant material, whereas the distal gut microbiome provides diverse CAZymes that cleave the many glycosidic linkages present in complex dietary polysaccharides (reviewed in ref 29). More recently, a comparative genomic analysis demonstrated the high prevalence of horizontal gene transfer in the human gut microbiome.[30] Therefore, horizontal gene transfer contributes to the complexity of the metabolic function of the gut microbiome, allowing the host and its resident microbiota to adapt to changing environmental conditions. Thus, the ability of a host to acclimatize to environmental shifts is dictated by the co-metabolic capabilities of both the gut microbes and the host. For instance, in Japanese communities where nonsterile, uncooked seaweed is regularly consumed, the genome of the human gut symbiont *Bacteroides plebeius* has retained β-porphyranase, a beneficial enzyme capable of digesting algal cell walls from *Zobellia galactanivorans*.[31] Indeed, low microbial complexity (or gene richness) has been associated with a Western diet and sedentary lifestyle and potentially could contribute to disorders associated with excessive weight gain.[32]

Studies on intestinal microbiota raise questions as to whether consuming a modern diet that is hyperhygienic and highly processed results in reduction of microbial functional maturity by preventing the exchange of beneficial genes between gut microbiota and microbes from the diet and environment. In addition, the increasing use of sanitization and antibiotics in food processing may contribute to a profound impact on the gut microbiome (reviewed in ref 33). The activity and composition of the gut microbiome is also affected by an individual's attitudes, taste preference, and dietary habits that are likewise influenced by culture, the global food industry, and media. Furthermore, there is growing evidence that the human diet has undergone profound simplification since industrialization, which has occurred too recently on an evolutionary time scale for the human genome to adapt.[34−36] This maladaption to the modern diet has been hypothesized to be the underlying evolutionary origin of "civilization diseases," such as cardiovascular disease, in the 21st century.[34,36−39]

INFLUENCE OF GLOBAL DIET ON THE GUT MICROBIOME

The gut microbiome is remarkably stable[40] and shares a high degree of functional capability across all human healthy individuals; however, intestinal bacterial communities are diverse and variable from person to person.[41−43] For example, intraindividual variability of the fecal microbiota is consistently lower than between-subject (interindividual) variability.[43,44] Recent discoveries of greater similarities in gut microbiota between monozygotic and dizygotic twin adults[45,46] or between family members[45,47] versus unrelated individuals highlight the powerful impact of shared environment, lifestyle, and diet as a whole on intestinal microbial configuration.[48] Interestingly, in mice, genetics was shown to play less of a role than diet on the gut microbial community.[49] Age and health are also associated with alterations to the intestinal microbiota that might explain interindividual differences as well.[50]

In general, dietary effects on the intestinal microbiota can occur on short and long time frames. An acute influx of energy and nutrients is assumed to induce bacterial blooms in a short time frame. As expected, short-term dietary modulation in a humanized gnotobiotic mouse model resulted in a significant shift within the microbiome in a single day.[51] A similar change in fecal microbiome within a day of a dietary change was confirmed in a controlled-feeding study of 10 healthy volunteers.[52] Likewise, in as short as 3 days, dramatic changes in the community composition of the gut microbiome occurred with alterations in calorie content of the diet (2400 vs 3400 kcal/day) for several individuals.[53]

Long-term, diet-driven structural and functional differences in the microbial community are apparent in populations from different geographic areas with very distinct dietary patterns. Studies employing culture-based and culture-independent methods found significant global differences in the fecal microbiota from individuals in different cultures.[54−56] For example, children from Burkino Faso practice a diet with high fiber and low animal protein and fat, consisting mainly of cereals, legumes, and vegetables. Italian children practice a typical Western-style diet characterized by high animal protein, simple sugars, starch, and fat with less vegetables and fiber than the diet in Burkina Faso. The microbial composition of children from Burkina Faso revealed higher levels of *Prevotella* and *Xylanibacter* (Bacteroidetes), *Treponema* (Spirochaetes), and *Butyrivibrio* (Firmicutes), which were absent in the Italian children.[56] A similar observation was reported in a comparison of Bangladeshi and American children. Bangladeshi children, who consumed a diet similar to that of children from Burkino

Faso, exhibited a significantly greater bacterial diversity and distinct microbial community composition enriched in *Prevotella*, *Butyrivibrio*, and *Oscillospira* and depleted in *Bacteroides* in comparison with American children.[57] Both children and adults from the United States have very different microbiota from rural communities in Malawi and Venezuela. A typical U.S. diet that is rich in protein differs from the diets of Malawians and Venezuelan populations that are dominated by maize, cassava, and other plant-derived polysaccharides. The major change in macronutrient composition may contribute to the higher bacterial diversity of those in Malawi and Venezuela compared to adults living in U.S. metropolitan areas.[47]

Comparative studies between different geographic regions have been challenged with multiple dependent factors such as socioeconomic status, genetics, dietary habits, age, hygiene, food quality, pathogen exposure, history of antibiotic use, body composition (host phenotype), stress, physical activity, and other environmental conditions.[7,58−62] Despite ethnic and geographical variation, both comparative[47,56,57] and controlled feeding studies conducted in the United States[52] and Africa [63] revealed similar patterns of the *Bacteroides*−*Prevotella* balance based on diet.

Global macronutrient profiles are recognized to modulate the intestinal microbial community. In a study charactering human fecal samples from 98 individuals, Wu et al. found that saturated fat and animal protein decreased microbial diversity and enriched the abundance of *Bacteroidetes* and *Actinobacteria*, whereas a plant-based diet with high carbohydrates increased microbial diversity and was linked with *Firmicutes* and *Proteobacteria* abundance.[52] In a recent study, gnotobiotic mice colonized with 10 human intestinal bacterial species were provided diets containing various percentages of protein (from casein), fat (from corn oil), polysaccharides (from starch), and sucrose.[64] Intriguingly, the authors were able to explain over half of the variation in species abundance in the fecal microbiome depending on the food ingested, even when the mice were fed more complex diets.[64]

Recent evidence suggests that extreme changes in carbohydrate intake will lead to a shift in the composition of human gut microbiota. Although reports of the relative proportion of *Bacteroidetes* and *Firmicutes* with respect to carbohydrate intake are contradictory in several studies,[65−67] certain genera and bacterial families are associated with levels of carbohydrate consumption. For example, in human obese subjects, a declining carbohydrate intake induced a marked progressive decrease of a butyrate-producing subgroup of Clostridial cluster XIVa (*Roseburia* spp. and *Eubacterium rectale*)[68,69] as well as bifidobacteria.[65,70] A reduced-carbohydrate, high-protein diet resulted in decreased proportions of butyrate and total short-chain fatty acid by reducing butyrate-producing bacteria such as the *Roseburia*/*Eubacterium rectale* group.[71] Likewise, *Bifidobacterium* levels decreased in mice fed a low-carbohydrate, high-fat "Atkin's style diet" compared with their counterparts consuming a high-carbohydrate, high-fiber, and low-fat diet.[72]

More detailed documentation of diet-induced specific changes on the gut microbial relative abundance was reviewed by Krajmalnik-Brown et al.[4] Although many inconsistent results have been observed regarding the impact of diet on phylum-wide changes in gut microbiota composition and energy-harvesting capacity, many have suggested that the complex relationship might involve the severity of obesity, microbial adaptation to diet over time and perhaps an age−microbial interaction. Notably, the high-fat, low-fiber diet has also been recognized as a well-established model of obesity;[51,73−77] thus, the impact of differences in caloric consumption and subsequent response from host metabolic perturbations through weight change needs to be considered. Studies on experimental animals need to control for body mass and composition, which will allow a better comparison of the gut microbiota without the confounding effects of weight/adiposity.[78]

Although it appears that the overall macronutrient profile affects general patterns of fecal microbiota, understanding the responses of intestinal microbial communities to major dietary composition presents an additional set of challenges. For example, a carbohydrate-rich diet is often accompanied with elevated dietary fiber intake and a low percentage of protein and fat; hence, the microbial composition should respond to the complex profile of the dietary structure instead of the shifting of a single dietary component. If not specifically controlled, dietary factors will affect the gut microbiome in both energy intake and relative proportion of macronutrients in the diet. Recently, interest in microbial response to major dietary composition has re-emerged in many reviews.[3,4,79] In this section, we will explore the complex influence of dietary structure on the gut microbiome including gluten-free diet, vegetarian/vegan diet, and food restriction.

Gluten-free Diet. To determine the effect of a gluten-free diet on the gut microbiome, a crossover study involving 10 healthy subjects consuming a conventional diet without any restriction, except for gluten-containing products, resulted in a reduction in bacterial populations that are generally regarded as beneficial for human health such as *Bifidobacterium* and *Lactobacillus*, as well as an increase in opportunistic pathogens such as *Escherichia coli* and total Enterobacteriaceae.[80] The observed changes might be explained by the associated reduction in polysaccharide intake that may have prebiotic action for certain bacteria. Provision of a gluten-free but polysaccharide- and probiotic-rich food intake could avoid this situation and provide better support to balance gut microbiota.[81]

Vegetarian and Vegan Diet. Several small-scale culture-based studies examined the effect of a vegetarian diet on the composition of the human gut microbiota.[82,83] However, results from these studies offer no clear consensus.[84] A crossover study reported that a Western-style diet high in meat facilitates the growth of *Bacteroides*, *Bifidobacterium*, *Peptostreptococcus*, and *Lactobacillus* spp. compared to a vegetarian diet.[82] Similarly, elevated *Bacteroides* spp. levels were observed in a 4 week high-beef diet.[85] Dietary modulation of 12 healthy male subjects with either mixed Western, lacto-ovo vegetarian, or vegan diet in a 20 day crossover study revealed significantly lower fecal lactobacilli and enterococci in the vegetarian diet than in the other two diets.[83]

Hayashi et al. reported a predominance of bacteria from the Clostridium cluster XVIII, in addition to high levels of bacteria from Clostridium clusters IV and XIVa in the fecal microbiome of a strict vegetarian woman.[86] However, Liszt et al.[87] and Kabeerdoss et al.[88] report that the proportions of Clostridium clusters IV and XIVa are lower in vegetarians. The inconsistent findings from these studies might be due to the use of different experimental methods, the limited number of individuals in these studies, or poorly matched control groups.[89] The stool pH was lower among 250 subjects on strict vegan or vegetarian diets with equal numbers of age- and gender-matched control subjects compared to individuals consuming ordinary omniv-

orous diets, and this likely inhibited the growth of *E. coli* and Enterobacteriaceae in vegetarian/vegan subjects.[89]

Furthermore, it has been established that microbial−mammalian co-metabolites may be measured in urine that may provide information concerning intestinal microbial metabolic activities.[90] Clear metabolic differences in urine associated with the vegetarian and omnivorous diets have been observed, with creatine, carnitine, acetylacarnitine, and trimethylamine-*N*-oxide (TMAO) being elevated in a high-meat diet and *p*-hydroxyphenylacetate (a microbial−mammalian co-metabolite) increased in a vegetarian diet.[91]

Fasting and Food Restriction. A 40% calorie restriction in mice for 9 weeks revealed small changes in fecal anaerobic populations using fluorescent in situ hybridization (FISH) and denaturing gradient gel electrophoresis (DGGE).[92] Similarly, using conventional anaerobic culture of rat feces,[93] small changes in fecal anaerobic bacterial populations with no significant difference in the bacterial cellular fatty acid profile were observed after caloric restriction.[93] Patients with rheumatoid arthritis who participated in an intermittent modified 8-day fasting therapy (total maximum energy intake of 300 kcal/day) also exhibited no changes in the fecal bacterial counts of clostridia, bifidobacteria, *Candida*, *E. coli*, *Enterococcus*, or *Lactobacillus*.[94]

Interestingly, the *Lactobacillus* spp. and archaeon *Methanobrevibacter smithii* counts were elevated in anorexia patients compared with healthy controls, and this difference was associated with the increased efficiency in removal of excess H_2 from the human GI tract.[95] In hibernating ground squirrels, the relative proportion of Firmicutes was decreased relative to Verrucomicrobia and Bacteroidetes after several months of fasting.[96] Follow-up studies need to address the impact of food restriction in both the short- and long-term scale and the global significance of these changes in the intestinal microbiota.

GATHERING AT THE COLON: NUTRIENT−GUT MICROBIOTA INTERACTIONS

In normal healthy individuals, the large intestine receives contents that escape from the terminal ileum, which are subsequently mixed and retained for 20−140 h to provide an opportunity for microbes to ferment a range of undigested dietary substances. The transition time through the colon strongly influences the gut microbial community, which has been correlated with stool weight and excretion of bacterial dry matter. Although few data exist on the nutrients that enter the colon from the small intestine, generally, about 85−90% of dietary sugar and starch, 66−95% of protein, and almost all fat are absorbed before entering the large intestine depending on genetics and other dietary factors[4,97−99] (Figure 2). It is well established that dietary intake of nondigestible material, in combination with host-derived peptides,[100,101] bile acids,[102] and mucin,[103,104] influences microbial anaerobic fermentation activity and microbial population in the colon.

Increasing evidence supports that shifts in the microbial composition occur in response to changes in the content of the diet. Such changes can be expected to result from differential effects of substrates on stimulating or inhibiting microbial growth. Perhaps one of the greatest challenges in nutrition is to interrogate the interaction between the complex food matrices that integrate a wide range of biologically active compounds. This raises the question of whether there are specific dietary ingredients that have stronger selective forces on microbial diversity and configuration of functional communities than

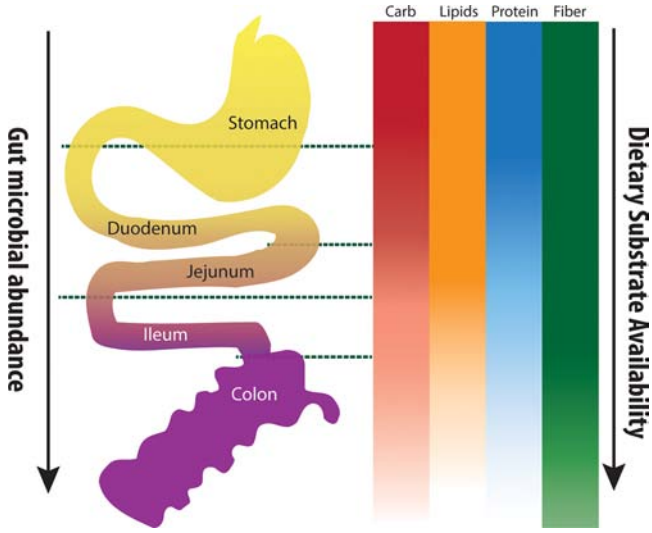

Figure 2. Schematic representation of gut microbial abundance and dietary substance concentration in the major sections of the GI tract.

others. A summary of each dietary ingredient under broad categories will be discussed below.

Dietary Fiber. Dietary fiber and complex carbohydrates consist of nonstarch polysaccharides, such as resistant starch and oligosaccharides, as well as edible indigestible plant components (including cellulose, xylan, and pectin) that are resistant to digestion by endogenous enzymes in the small intestine and become the primary source of microbial fermentation, particularly in the large intestine.[105−109] The effect of dietary fiber has long been proposed to contribute to human health through prebiotic enhancement of certain beneficial microbes that produce butyrate,[110] absorb bile acids,[111] decrease colon pH,[112] and promote GI motility via shortening of the mean transit time.[113−115] However, not all dietary fibers have the same effect, which is dependent on their physicochemical characteristics.[116] The prebiotic effect of indigestible polysaccharides on gut microbiota has previously been broadly discussed.[107,117,118]

Several human dietary intervention studies have shown that intake of certain types of dietary fibers can significantly modify the gut microbiota observed in feces. For example, consumption of whole-grain breakfast cereal for 3 weeks significantly increased fecal bifidobacteria and lactobacilli compared to wheat bran alone; however, no difference was observed in fecal short-chain fatty acids (SCFAs).[119] Introduction of barley β-glycan in the diet (0.75g/day) elevated fecal *Bifidobacterium* and *Bacteroides* counts in older healthy human subjects (≥50 years), whereas only the *Clostridium perfringens* count increased in the younger group.[120]

Typically, consumption of nondigestible carbohydrates such as wheat bran arabinoxylan oligosaccharides, short-chain fructooligosaccharides (FOS), and soybean oligosaccharides and galactooligosaccharides (GOS) induces enrichment of human fecal bifidobacteria.[121,122] Inulin has been shown to stimulate the growth of *Bifidobacterium adolescentis*, *Bifidobacterium longum*, *Bifidobacterium bifidum* and the butyrate-producing bacteria *Faecalibacterium prausnitzii* and *Roseburia inulinivorans*.[123−126] Similarly, *Bifidobacterium* spp. levels significantly increased upon consumption of biscuits containing partially hydrolyzed guar gum and FOS for 21 days, whereas *Bacteroides* spp., *Clostridium* spp., and *Lactobacillus*−*Enter-*

ococcus spp. remained at similar levels.[127] GOS alone or combined with FOS are often supplemented in infant formula to favor the growth of bifidobacteria spp.,[128,129] and the bifidogenic response of GOS has been shown to be dose-dependent.[130] Interestingly, Rossi et al. reported that only 8 of the total 55 *Bifidobacterium* strains were able to grow on long-chain inulin in vivo,[131] suggesting that not all bifidobacteria species benefit in the same way from the presence of these substrates as their energy source. Indeed, the specificity of polysaccharide use by the gut microbiota supports the underlying cross-feeding interaction between gut microbiota (reviewed in ref 132).

Various types of resistant starch demonstrate substrate specialization of the gut microbiome. For example, the impact of type 2 (native granular) resistant starch is associated with enrichment of *Ruminococcus bromii*,[133] whereas type 3 (retrograded amylose) resistant starch elevates both *E. rectale* and *R. bromii* in healthy[130] and overweight subjects.[134] Type 4 (chemically modified) resistant starch significantly differs from types 2 and 3 and has been shown to induce a profound phylum-level change and elevate *B. adolescentis* and *Parabacteroides distasonis*.[130] Furthermore, the variability observed in these studies[130,134] suggests that the host-specific environment affects the composition of the gut microbiome.

The fermentation profile depends on the glycosidic linkage type of the dietary substrate as well as the functional capability of the gut microbiota (reviewed in ref 135). Metatranscriptome analysis revealed a functional enrichment of genes associated with carbohydrate uptake and metabolism in the small intestine[136] and feces.[137,138] A fecal metaproteomic analysis from three healthy subjects over a period of 6−12 months revealed a common functional core enriched in carbohydrate transport and degradation.[139] In particular, the ability to degrade complex polysaccharides has been identified in a range of bacteria.[107] In particular, the *Bacteroides* phylum contains a large repertoire of genes that exhibit broad capacities to degrade a great diversity of plant-derived polysaccharides.[140−142] Microbial sequencing projects revealed that starch utilization systems are highly abundant and conserved in the phylum Bacteroidetes (reviewed in refs 143−145). In contrast, members from the *Firmicutes* phylum exhibit a wide range of functionalities; for example, *Ruminococcus*, which is in the order of Clostridiales, can degrade cellulose[146] and pectin,[147] whereas *E. rectale* and *Eubacterium eligens* have fewer polysaccharide-degrading enzymes and are enriched with more ATP binding cassette (ABC) transporters and phosphotransferase (PTS) systems than the Bacteroidetes.[148] Although many microbes have the ability to ferment undigestible dietary components, diet-induced microbial changes seem to favor the groups that have a stronger survival advantage and perhaps specifically depend on host-derived factors such as pH and bile acid profiles.

Dietary Lipids, Bile Acids, and Cholesterol. The human colon has not often been considered to be a site of fat absorption; however, the small intestine absorbs only approximately 95% of dietary lipids after consumption of a typical Western diet.[149] Furthermore, some studies have suggested that colonic absorption of medium-chain fatty acids takes place in dogs,[150] rats,[151] and humans[152,153] and that glycerol accumulates in the colon when fat absorption is disturbed in the small intestine.[154] Accumulation of glycerol has been shown to alter the *Lactobacillus* and *Enterococcus* communities in the gut.[155]

A diet high in animal fat and low in dietary fiber stimulates the synthesis and enterohepatic circulation of primary bile acids.[113,156] Although the majority of bile acids are recycled in the ileum, some of them escape the enterohepatic circulation in the intestine and become substrates for microbial metabolism in the colon.[157] Bile acids restrict the growth of several microbes.[158,159] Accordingly, only the microbes that are able to tolerate the physiologic concentrations of bile acids survive in the gut; thus, bile acids appear to exert strong selective pressure on gut microbial structure and function. For example, administration of cholic acid to mice induces phylum-level population shifts of the relative abundance of *Firmicutes* and *Bacteroidetes*[160] that resembles microbial changes observed by feeding a high-fat diet alone.[51,67,74,77]

Gut microbiota detoxify primary bile acids via deconjugation, in which well-conserved bile salt hydrolases release the amino acids glycine and taurine.[161,162] The free primary bile acids are then converted into various types of secondary bile acids such as deoxycholic acid and lithocholic acid by the 7α-dehydroxylation reaction.[163] A detailed list of bacteria with genes encoding bile salt hydrolase activity is reviewed by Ridlon et al.[162]

In general, the conjugated bile acid profile is heavily dependent on microbial activity. The bile acid distribution profile in multiple compartments of germ-free animals shows less diversity and is smaller in size compared with conventional counterparts.[164] Dietary lipid composition can also modulate bile acid profile, in particular, increasing taurocholic acid that, as a consequence, promotes the growth of *Bilophila wadsworthia*,[165] a Gram-negative opportunistic pathogen.[166] *B. wadsworthia* utilizes taurine as a source of sulfite,[167] which serves as the terminal electron acceptor for the respiratory chain.[168,169] The concentrations of bile acids and their conjugation status to glycine or taurine between individuals may be influenced by diet, as people eating a meat-rich diet tend to have more taurine-conjugated bile acids in their bile acid pool than those eating a vegetarian diet.[170]

It has been recognized that the production of secondary bile acids is pH dependent. The proximal colon is more acidic than the distal colon,[171,172] which results in an elevated activity of 7α-dehydroxylase in the cecum versus the left colon.[173] Subjects consuming diets high in resistant starch showed a significantly decreased stool pH compared with subjects consuming a low resistant starch diet. A decrease in pH (from 6.5 to 5.5) is associated with an elevated production of SCFAs, which selectively regulate the intestinal microbial community, with a tendency to suppress *Bacteroides* spp.[174] and promote butyrate-producing Gram-positive bacteria such as *E. rectale*.[175] Similarly, subjects on a vegan or vegetarian diet showed significantly more acidic stool pH[89] and significantly lower fecal secondary bile acid production[83] than omnivores. Higher consumption of animal protein is one possible explanation of higher fecal pH value in an omnivorous diet, as proteolytic putrefactive bacteria are able to increase stool pH by producing alkaline metabolites. Thus, increases in SCFAs result in a more acidic colonic pH, a decreased solubility of bile acids, an indirect increased absorption of minerals, and a reduction of ammonia absorption, which indirectly alters the composition of gut microbiota.[176,177]

Importantly, 50−70% of acetate (the principal SCFA in the colon) taken up by the liver becomes the primary substrate for cholesterol synthesis, whereas propionate inhibits cholesterol synthesis in hepatic tissue (reviewed in refs 176 and 178). The

role of cholesterol on gut microbiota was first elucidated using germ-free rats. Danielsson et al. demonstrated that germ-free rats exhibit a higher serum cholesterol level than their conventional counterparts.[179] More recently, the characterization of the gut microbiota in a hamster model of hypercholesterolemia showed that dietary intervention with grain sorghum lipid extract[180] modulated the gut microbial composition, with bifidobacteria being positively associated with increases in HDL cholesterol level and the family Coriobacteriaceae being associated with non-HDL cholesterol.[181] Together, high intake of dietary fat, in particular animal fat, and cholesterol not only changes the composition of bile acids and neutral sterols in the colon but also modifies the gut microbiota, which consequently transforms these compounds into secondary bile acids and cholesterol metabolites.[182]

Polyphenol-Containing Foods. Polyphenols present in a wide range of plant-based foods have received great interest owing to their antioxidant capacity and potential protective effect in reducing cardiovascular disease risk through improvement in vascular function and modulation of inflammation.[183,184] The interpretation of the influence of polyphenols on cardiovascular health in dietary intervention studies can be complicated due to dynamic bioavailability during the processes of absorption, metabolism, distribution, and excretion. Generally, the absorption of dietary polyphenols (i.e., the parent compounds) is widely dependent on the type and structure of the compound (reviewed in refs 185−189) and is often slow and largely incomplete in the small intestine. Therefore, significant quantities of polyphenols are retained in the colon. In addition, the nonabsorbed polyphenols are subjected to biotransformation via the activity of enzymes from various microbial groups (reviewed in refs 187 and 190). Consequently, the microbiota-derived metabolites of polyphenols are better absorbed in the gut,[191] which then become an important factor in the health effect of polyphenol-containing foods. Important plant polyphenols and their microbial derivatives are listed in ref 192. Many of the studies that assess bioavailability and effects of polyphenols have evaluated the balance between the enterohepatic circulating levels, residence time in plasma, and urine excretion rate of the parent phenolic compounds and their microbial-derived metabolites using metabolomic techniques.[193,194] Importantly, although endogenous enzyme and transporter activities in the small intestine as well as transformation of polyphenols are subject to a wide interindividual variability, the functional capability of the gut microbiota is important to partially explain the variation of bioavailability among the population.[195,196]

Assessing the properties of a single dietary constituent from the polyphenol family alone without dietary fiber is difficult due to the complex dietary food matrix present in a flavonoid-rich diet. For example, regular consumption of apples (two per day for 2 weeks) increased the numbers of fecal bifidobacteria and decreased the *C. perfringens* count.[197] Similarly, the concomitant dietary presence of apple polyphenols and FOS increased SCFA production.[198] In contrast, compared to consumption of an inulin-containing diet alone, including a grapefruit flavonoid-rich extract decreased both production of SCFAs and the bifidobacteria population.[199] Furthermore, a randomized crossover intervention study in which subjects consumed high levels of cruciferous vegetables for 14 days revealed an alteration of the fecal microbial community profile compared with a low-phytochemical, low-fiber diet, including a higher abundance of *Eubacterium hallii*, *Phascolarctobacterium faecium*, *Burkholderiales* spp., *Alistipes putredinis* and *Eggerthella* spp.[200] The observed changes could also be explained by the increase in dietary fiber that is enriched in cruciferous vegetables.[200] Overall, the direct effects of fiber blur the ability to judge the specific effects of individual dietary ingredients on gut microbiota. These dietary ingredients (polyphenols and fiber) may act in an additive or a synergistic manner, exerting their effects on gut microbiota.

The prebiotic-like flavonol-rich foods have been demonstrated to modify the composition of gut microbiota. Six week consumption of a wild blueberry drink that was high in polyphenols (in particular, anthocyanins) was shown to increase the proportion of *Bifidobacterium* spp. compared to the placebo group;[201] however, a high interindividual variability in response to the dietary treatment was also observed.[202] Similarly, the daily consumption of a high-cocoa flavonol drink (494 mg/day) for 4 weeks significantly enhanced the growth of fecal bifidobacterial and lactobacilli populations, but decreased the *Clostridia histolyticum* counts relative to those consuming a low-cocoa flavonol drink (23 mg/day).[203] Furthermore, unabsorbed dietary phenolics and their metabolites selectively inhibit pathogen growth and stimulate the growth of commensal bacteria. For example, grape pomace phenolic extract (1 mg/mL) increases *Lactobacillus acidophilus* CECT 903 growth in liquid culture media.[204] In addition, upon bacterial incubation, tea phenolics were shown to suppress the growth of potential pathogens such as *Clostridium* spp. (*C. perfringens* and *C. difficile*) and Gram-negative *Bacteroides* spp., whereas commensal anaerobes such as *Bifidobacterium* spp. and *Lactobacillus* spp. were less affected.[205] Similarly, the flavanol monomer (+)-catechin significantly increases the growth of the *Clostridium coccoides*−*Eubacterium rectale* group, *Bifidobacterium* spp., and *E. coli* and significantly inhibits the growth of *C. histolyticum* group in vitro.[206] To date, there is a wide range of phenolic compounds that have been demonstrated to have antimicrobial properties,[207−210] and many have been previously reviewed.[211] Although many of the studies highlighting the beneficial role of plant polyphenols through regulation by gut microbiota appear promising, there are limitations in the results that can be drawn regarding the ability of flavonoids to influence the growth of selected intestinal bacterial groups using a batch-culture model. More comprehensive human intervention studies will be essential in the future to provide insight into the potential influence of dietary polyphenols and their aromatic bacterial metabolites on intestinal microbial communities and their activities.

Probiotics in Foods. Probiotics are defined as viable microorganisms that, when consumed in sufficient amounts, confer a health benefit on the host.[212,213] To date, most of the commonly used probiotics are limited to strains of certain *Lactobacillus* and *Bifidobacterium* species (reviewed in ref 214). Survival during passage through the GI tract is generally considered as the essential feature for probiotics to preserve their active functions in the colon. Indeed, the probiotic strains must overcome biological barriers, including resisting gastric and bile acid secretion and tolerating intestinal lysozyme and toxic metabolites produced during digestion (reviewed in ref 215). Various studies found that at least a fraction of probiotic bacteria can be detected in stool for between 1 and 3 weeks after consumption (for example, see ref216). Probiotic *Lactobacillus* strains were also found to adapt for survival in the gut and possess gut-inducible genes that are responsive at different sites in the intestine.[217,218] Interestingly, provision of

the probiotic *Lactobacillus plantarum* to mice fed a Western-style diet and to humans resulted in similar gene expression profiles of this strain.[219,220] As probiotics are delivered via various food vehicles, the complex food matrix should also be viewed as an important factor that may alter the probiotic activity in the gut. To date, only a few animal and clinical studies have addressed the functional roles of food on probiotic-conferred health benefits.[221]

The mechanisms of probiotic effects on health are only partially understood but likely function either directly through interactions with host intestinal epithelial and immune cells or indirectly by modulating the indigenous intestinal microbiota. In regard to the latter, several studies have concluded that probiotic consumption does not result in global modifications of the intestinal microbiota in healthy individuals.[46,222,223] However, probiotics might confer modest but significant changes to the functional activities of local intestinal bacterial populations. When examined at the meta-transcriptional level, intake of a probiotic fermented milk was associated with the up-regulation of microbial genes corresponding to plant polysaccharide metabolism.[46] Similarly, administration of probiotics was shown to induce crosstalk between the probiotics from the diet and the individual bacterial species in the gut[224] and might induce competition for limited substrates that results in fluctuations tof the metabolic profile of the host.[225]

The gut microbiome of healthy adults is highly resilient (colonization resistant), where the stable native microbiota prohibits the succession of microbes from the diet.[226] In addition, the effect of probiotics on the gut microbiome appears to differ depending on host phenotypes such as age, health status, and chronic conditions. For example, the infant gut microbiome is highly diverse and dynamically changes during development[227] and therefore may be easily influenced by the consumption of probiotics (for example, daily supplementation of *Lactobacillus rhamnosus* GG[228]). In individuals with irritable bowel syndrome (IBS), probiotic consumption resulted in an increase in the numbers of Bacteroidetes in the intestine.[229] Moreover, intake of two *Lactobacillus* strains by diet-induced obese mice altered microbial composition and decreased expression of inflammatory genes in the adipose tissue while increasing levels of fatty acid oxidation in the liver.[230] Further studies are needed to investigate the effects of assorted probiotic supplements on the gut microbiome with respect to various host life stages and phenotypes.

Artificial Sweeteners (Non/Low-Digestible Sugar Substitutes). The premise behind substituting sugar with artificial sweeteners is to maintain the palatability of food at the same time as lowering energy intake. However, a sufficiently high ingestion of non/low-digestible sugar substitutes stimulates the growth of gut microbiota and can induce transitory diarrhea in humans.[231,232] In particular, the great proportion of non/low-digestible sugar substitutes (including many kinds of oligosaccharides and sugar alcohols that are not or only partially absorbed from the small intestine) that reach the distal intestine are subject to fermentation by the colonic microbiota, offering approximately 2 kcal/g of energy.[233,234] Although discovering and characterizing these compounds within foods is relatively new, it is of interest to note that many of these food ingredients are common in our daily diet. For example, the disaccharide alcohol maltitol is considered a common replacement for sucrose. Urinary and fecal excretions of sorbitol and maltitol after 24 h in conventional rats were shown to be minimal compared with germ-free rats.[235] Likewise, maltitol consumption significantly increased production of SCFAs in addition to nine tested fecal microbes after a 6 week trial, including bifidobacteria, *Bacteroides*, *Clostridium*, lactobacilli, eubacteria, *Atopobium*, *Fusobacterium prausnizii*, *Ruminococcus flavefaciens*, and *R. bromii*.[236] A 12 week administration of Splenda, composed of 1.1% of the artificial sweetener sucralose, increased fecal pH and reduced the amount of fecal bifidobacteria, lactobacilli, *Bacteroides*, clostridia, and total aerobic bacteria in a rat,[237] whereas isomalt, a widely used low-energy sweetener, was considered to be bifidogenic in a human study.[238] Overall, artificial sweetener fermentation by gut microbiota remains either unexplored or poorly documented, some of which are highlighted in a review by Payne et al.[239]

Food Coloring/Azo Compounds. Azo compounds are widely used as coloring agents in foods, beverages, and food packaging.[240] In addition, azo polymer coatings have been specifically designed for colon-selective drug delivery due to the presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure.[241,242] Indeed, azo dyes can be metabolized under anaerobic conditions by intestinal microbial processes and, as a result, produce the reductive cleavage products aromatic amines (usually colorless). The majority of the toxic effects of azo dyes are exerted through aromatic amines produced by their colonic degradation.[240,243−245] Raffi et al. reported that isolated intestinal bacteria in an anaerobic culture system were able to decolorize the dyes in the supernatant, suggesting that some of the azoreductase activities are extracellularly released.[246,247] Xu et al. demonstrated a variable degree of efficiency in the reduction of Sudan azo dyes and Para Red by 35 prevalent human intestinal microbes in vitro.[248] In contrast, Sudan azo dyes and their metabolites selectively inhibit the growth of some human intestinal microorganisms,[249] which may suggest a potential impact on gut microbiome after long-term exposure. In summary, although there are tantalizing glimpses into the effect of azo dyes on microbes in vitro, more data from animal and human studies are keenly awaited.

Sulfur-Containing Foods. In the colon, sulfur is present in either inorganic form (such as sulfates and sulfites) or organic form (such as dietary amino acids and host mucins).[250] The human GI tract poorly absorbs sulfate, and there is little sulfatase activity in the mucosa of the GI tract; therefore, free sulfate in the colon is likely to be of dietary origin.[251] Dietary sulfate drives the activity of sulfate-reducing bacteria that couple oxidative phosphorylation with reduction of sulfate to produce sulfide.[252] The total inorganic sulfur intake (sulfite and sulfate) is much higher in the Western diet in comparison to a typical African rural diet.[253,254] Highly processed foods that are high in sulfate include bread, soy flour, dried fruits, and brassicas, as well as sausage, beers, ciders, and wines.[253] Dietary sulfite primarily originates from preservatives in processed and dried food as well as beverages.[254] Sulfur-containing amino acids such as cysteine can be found in dietary protein and are a source of sulfur for colonic sulfate-reducing bacteria *Desulfovibrio desulfuricans*.[255] Native Americans who consume a diet high in resistant starch and low in animal products harbor significantly distinct sulfate-reducing bacterial populations and more diverse and different methanogenic archaea than Americans consuming a typical Western diet.[256]

Substrate competition for hydrogen among methanogenic archaea, sulfate-reducing bacteria, acetogenic bacteria, and other

species likely occurs in the colon.[257] Because hydrogen is an essential component for the survival of colonic methanogens, removal of the substrate (hydrogen) terminates methanogenesis. Given an adequate supply of sulfate, sulfate-reducing bacteria that are more abundant in the right colon[258] (i.e., genera *Desulfovibrio*, *Desulfobacter*, *Desulfobulbus*, *Desulfomonas*, and *Desulfotomaculum*[259]) outcompete methanogenic archaea for H_2 due to their higher substrate affinity to produce hydrogen sulfide (H_2S),[260−262] an end-product of dissimilatory sulfate reduction.[263] As a result, the mucosal microbiome may be shaped in part through the availability of toxic sulfide compounds and the differential susceptibility of mucosalistic microbes to the toxins.[250] Furthermore, the activity of methanogenic bacteria can also be disrupted by bile acids.[264,265] In brief, methane production was thought to occur only when sulfate-reducing bacteria were not active.[257] If sulfate is limited and hydrogen is in relative excess, methanogenic bacteria or perhaps acetogenic bacteria[266] will become essential.[267] Therefore, the levels of sulfate present in the colon are critical for determining which bacterial group gains a better survival advantage.[263,267]

Alcohol. Many people consume alcoholic beverages; however, few studies exist on the effect of alcohol consumption on the gut microbiome of healthy individuals. For individuals who consume alcohol to excess, abnormal gut microbiota and bacterial overgrowth can potentially initiate or worsen alcohol-induced impaired gut barrier function (i.e., gut leakiness) and contribute to endotoxemia in patients with alcoholic fatty liver disease.[268] Yan et al. demonstrated a 3 week acute effect following alcohol administration in mice that resulted in bacterial overgrowth, as well as an expansion of *Bacteroidetes* and *Verrucomicrobia* bacteria while decreasing *Firmicutes*, with no difference observed after only 1 day or 1 week.[269]

Chronic alcohol consumption induces changes in gut community profiles. For example, daily alcohol consumption for 10 weeks in a rat alters the colonic mucosa-associated bacterial microbiota fingerprint pattern.[270] Similarly, chronic ethanol feeding for 8 weeks increased fecal pH and decreased abundance of both *Bacteriodetes* and *Firmicutes* phyla with a remarkable expansion of *Proteobacteria* and *Actinobacteria* phyla in mice.[229] In a human trial, chronic alcohol consumption resulted in the alteration of the mucosa-associated colonic bacterial composition in a subset of alcoholics, with lower median abundances of *Bacteroides* and higher *Proteobacteria*. Furthermore, measurement of serum endotoxin suggests a change in microbial function, rather than abundance, which may lead to increased levels of gut-derived pro-inflammatory factors in chronic alcohol consumption. It is noted that the inability to detect clear differences between alcoholics with and without liver disease suggests that chronic alcohol consumption, rather than the disease physiology, is the most important event that appears to alter microbiota composition.[271]

FUTURE PERSPECTIVES

It is now well established that host diet alters the gut microbiome. Changes in the gut microbiota composition are also considered an important factor in health and disease. Dietary assessment has provided us with a window to discover a way to reconfigure the gut microbiome. In this regard, the nutritional manipulation of the gut microbiome serves as a basis for formulating therapeutic approaches that are feasible and acceptable to the general population as a promising way to promote health in the era of personalized nutrition and medicine.

Understanding the impact of foods and nutrients on host−microbe coevolution supports the essential role of a mutualistic relationship for intestinal homeostasis, but there remain challenges for nutritionists and scientific investigators alike to determine the "ideal" diet. This review collectively maintains the emerging view that diet supports a specific bacterial community structure and further suggests that a suboptimal dietary composition/quality may promote the development of diseases through introducing intestinal microbial dysbiosis. Major shifts in intestinal microbial composition are often observed when dietary differences between groups are extreme. Only a few population-wide studies are available to date, but some of them support a role of food diversity as a potential mechanism for altering gut microbial diversity. Although it is difficult to determine the causality of observed fecal microbiota shift with respect to many lifelong changes, generally, an adequate control over influential factors is important for the success of clinical studies to eliminate the drastic effects of unnecessary confounding variables. Many of the studies reviewed here rely on the assumption of equivalence between the term "fecal microbiome" and "intestinal (mucosal) microbiome". Further studies are necessary to elucidate more clearly the exact impact of the selection of different diets on qualitative changes in the gut microbiota.

Some nutrients that have been studied, such as dietary fiber, are a possible option for the maintenance of intestinal homeostasis and improvement of gut health, whereas others may contribute an opposite effect. Therefore, future research must be focused on looking to improve the effectiveness of diets with an underlying long-term "targeted approach" that allows improvement of intestinal microbial composition and functional activities. In other instances, when dietary differences are small and on a short time scale, gut microbiota changes are not as obvious, but that is not to say that changes do not occur. An alteration of the gut microbiota at lower taxonomic levels is still likely to have important functional consequences for the host. Notably, gut microbiota varies dramatically from individual to individual in lower taxonomic levels. Even small dietary changes may have impacts on the gut microbiota and altered metabolic activities in the microbial profile that are not easily detected by the phylogenetic/taxonomic methods.

Metabolic alterations induced by diet may result in varying the microbial capability of synthesizing substances in the intestinal tract. It appears that measurement of bacterial enzyme activities may be a more sensitive indicator of diet-induced changes in the gut microbiota than taxonomic-based methods. Arguably, absolute microbial population densities are more important than the relative proportion, because these determine the absolute production rates and concentrations of metabolites and signals of microbial origins. Rates of production of fermentation products need to be measured as an index of microbial community function. Further research into the characterization and metabolic activity of the gut microbiota may provide the key to the influence of the environment on colonic health and disease. Integrating the gut microbiome data with clinical nutritional assessment, food consumption monitoring, and host phenotyping measurements in future investigations are needed to focus on the identification of metabolic impacts that mediate the effect of diet on gut microbiota as well as their synergistic effect on host immune function, metabolism, and homeostasis.[272,273]

Although the highly complex relationship of food and health remains to be further explored, recent research advances in a variety of different disciplines provide promising new approaches to improve our understanding. The growing demand for "healthy food" is stimulating innovation and new product development in the food industry. The knowledge gained through further inquiry into the interaction between host, food, and the gut microbiota will help us understand the importance of environmental factors, particularly dietary patterns, on human health. Although more extensive research needs to be conducted before definitive conclusions can be reached regarding the impact of diet on the gut microbiome, we are confident this rapidly expanding research is opening new areas for exploration. We expect that in the near future microbiota composition might serve as a biomarker in disease diagnosis. Overall, the optimal goal is to use diet to balance host metabolic homeostasis and employ a specific dietary design to shift and maintain a "healthy" gut microbial composition.

AUTHOR INFORMATION

Corresponding Author

*(C.M.S.) E-mail: cslupsky@ucdavis.edu. Phone: (530) 752-6804.

Notes

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ABBREVIATIONS USED

GI, gastrointestinal; CAZymes, carbohydrate-active enzymes; TMAO, trimethylamine-*N*-oxide; FISH, fluorescent in situ hybridization; DGGE, denaturing gradient gel electrophoresis; SCFAs, short-chain fatty acids; FOS, fructooligosaccharides; GOS, galactooligosaccharides

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