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Emerging Aspects of Food and Nutrition on Gut Microbiota

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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 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 transfer²⁷ 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 maladaptation 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 stable⁴⁰ 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 Burkina 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 Burkina

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 States⁵² and Africa⁶³ 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 characterizing 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, acetylcarnitine, 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 H₂ 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 healthy¹³⁰ 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 intestine¹³⁶ 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 cellulose¹⁴⁶ 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 7 α -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 7 α -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 pH⁸⁹ and significantly lower fecal secondary bile acid production⁸³ 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 extract¹⁸⁰ 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*, *Burkholder-*

iales 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 ref 216). 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 gut²²⁴ and might induce competition for limited substrates that results in fluctuations of 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 development²²⁷ and therefore may be easily influenced by the consumption of probiotics (for example, daily supplementation of *Lactobacillus rhamnosus* GG²²⁸). 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 prausnitzii*, *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 colon²⁵⁸ (i.e., genera *Desulfovibrio*, *Desulfobacter*, *Desulfobulbus*, *Desulfomonas*, and *Desulfotomaculum*²⁵⁹) outcompete methanogenic archaea for H₂ due to their higher substrate affinity to produce hydrogen sulfide (H₂S),^{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 bacteria²⁶⁶ 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 *Bacteroidetes* 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.

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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

REFERENCES

- (1) Hooper, L.; Gordon, J. Commensal host-bacterial relationships in the gut. *Science* **2001**, *292*, 1115–1118.
- (2) Lederberg, J. Infectious history. *Science* **2000**, *288*, 287–93.
- (3) Dutton, R. J.; Turnbaugh, P. J. Taking a metagenomic view of human nutrition. *Curr. Opin. Clin. Nutr. Metab. Care* **2012**, *15*, 448–454.
- (4) Krajmalnik Brown, R.; Ilhan, Z. E.; Kang, D. W.; DiBaise, J. K. Effects of gut microbes on nutrient absorption and energy regulation. *Nutr. Clin. Pract.* **2012**, *27*, 201–214.
- (5) Tremaroli, V.; Bäckhed, F. Functional interactions between the gut microbiota and host metabolism. *Nature* **2012**, *489*, 242–249.
- (6) Turnbaugh, P.; Ley, R.; Mahowald, M.; Magrini, V.; Mardis, E.; Gordon, J. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **2006**, *444*, 1027–1031.
- (7) Kau, A. L.; Ahern, P. P.; Griffin, N. W.; Goodman, A. L.; Gordon, J. I. Human nutrition, the gut microbiome and the immune system. *Nature* **2011**, *474*, 327–336.
- (8) Arumugam, M.; Raes, J.; Pelletier, E.; Le Paslier, D.; Yamada, T.; Mende, D. R.; Fernandes, G. R.; Tap, J.; Bruls, T.; Batto, J.-M.; Bertalan, M.; Borruel, N.; Casellas, F.; Fernandez, L.; Gautier, L.; Hansen, T.; Hattori, M.; Hayashi, T.; Kleerebezem, M.; Kurokawa, K.; Leclerc, M.; Levenez, F.; Manichanh, C.; Nielsen, H. B.; Nielsen, T.; Pons, N.; Poulain, J.; Qin, J.; Sicheritz-Ponten, T.; Tims, S.; Torrents, D.; Ugarte, E.; Zoetendal, E. G.; Wang, J.; Guarner, F.; Pedersen, O.;

de Vos, W.; Brunak, S.; Doré, J.; Meta, H. I. T. C.; Antolín, M.; Artiguenave, F.; Blottiere, H.; Almeida, M.; Brechot, C.; Cara, C.; Chervaux, C.; Cultrone, A.; Delorme, C.; Denariac, G.; Dervyn, R.; Foerstner, K.; Friss, C.; van de Guchte, M.; Guedon, E.; Haimet, F.; Huber, W.; van Hylckama-Vlieg, J.; Jamet, A.; Juste, C.; Kaci, G.; Knol, J.; Lakhdari, O.; Layec, S.; Le Roux, K.; Maguin, E.; Mérieux, A.; Melo Minardi, R.; M'Rini, C.; Muller, J.; Oozeer, R.; Parkhill, J.; Renault, P.; Rescigno, M.; Sanchez, N.; Sunagawa, S.; Torrejon, A.; Turner, K.; Vandemeulebrouck, G.; Varela, E.; Winogradsky, Y.; Zeller, G.; Weissenbach, J.; Ehrlich, S. D.; Bork, P. Enterotypes of the human gut microbiome. *Nature* **2011**, *473*, 174–180.

(9) Sousa, T.; Paterson, R.; Moore, V.; Carlsson, A.; Abrahamsson, B.; Basit, A. W. The gastrointestinal microbiota as a site for the biotransformation of drugs. *Int. J. Pharm.* **2008**, *363*, 1–25.

(10) Wallace, B. D.; Redinbo, M. R. The human microbiome is a source of therapeutic drug targets. *Curr. Opin. Chem. Biol.* **2013**, *17*, 379–384.

(11) Rubio-Aliaga, I.; Kochhar, S.; Silva-Zolezzi, I. Biomarkers of nutrient bioactivity and efficacy: a route toward personalized nutrition. *J. Clin. Gastroenterol.* **2012**, *46*, 545–554.

(12) Ye, K.; Gu, Z. Recent advances in understanding the role of nutrition in human genome evolution. *Adv. Nutr.* **2011**, *2*, 486–496.

(13) Milton, K. The critical role played by animal source foods in human (*Homo*) evolution. *J. Nutr.* **2003**, *133*, 3886S–3892S.

(14) Aiello, L. C. Brains and guts in human evolution: the expensive tissue hypothesis. *Braz. J. Genet.* **1997**, *20*.

(15) Mann, N. Dietary lean red meat and human evolution. *Eur. J. Nutr.* **2000**, *39*, 71–79.

(16) Wrangham, R.; Conklin-Brittain, N. Cooking as a biological trait. *Comp. Biochem. Physiol. A: Mol. Integr. Physiol.* **2003**, *136*, 35–46.

(17) Aiello, L. C.; Wheeler, P. The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. *Curr. Anthropol.* **1995**, *36*, 199–221.

(18) Larsen, C. S. Animal source foods and human health during evolution. *J. Nutr.* **2003**, *133*, 3893S–3897S.

(19) Bäckhed, F.; Ley, R. E.; Sonnenburg, J. L.; Peterson, D. A.; Gordon, J. I. Host-bacterial mutualism in the human intestine. *Science* **2005**, *307*, 1915–1920.

(20) Ley, R.; Peterson, D.; Gordon, J. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* **2006**, *124*, 837–848.

(21) Ley, R.; Lozupone, C.; Hamady, M.; Knight, R.; Gordon, J. Worlds within worlds: evolution of the vertebrate gut microbiota. *Nat. Rev. Microbiol.* **2008**, *6*, 776–788.

(22) Ochman, H.; Worobey, M.; Kuo, C.-H.; Ndjango, J.-B. N.; Peeters, M.; Hahn, B.; Hugenholtz, P. Evolutionary relationships of wild hominids recapitulated by gut microbial communities. *PLoS Biol.* **2010**, *8*, e1000546.

(23) Muegge, B.; Kuczynski, J.; Knights, D.; Clemente, J.; González, A.; Fontana, L.; Henrissat, B.; Knight, R.; Gordon, J. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* **2011**, *332*, 970–974.

(24) Rechkemmer, G.; Rönna, K.; von Engelhardt, W. Fermentation of polysaccharides and absorption of short chain fatty acids in the mammalian hindgut. *Comp. Biochem. Physiol. A: Comp. Physiol.* **1988**, *90*, 563–568.

(25) Ley, R. E.; Hamady, M.; Lozupone, C.; Turnbaugh, P. J.; Ramey, R. R.; Bircher, J. S.; Schlegel, M. L.; Tucker, T. A.; Schrenzel, M. D.; Knight, R.; Gordon, J. I. Evolution of mammals and their gut microbes. *Science* **2008**, *320*, 1647–1651.

(26) Zaneveld, J.; Turnbaugh, P. J.; Lozupone, C.; Ley, R. E.; Hamady, M.; Gordon, J. I.; Knight, R. Host-bacterial coevolution and the search for new drug targets. *Curr. Opin. Chem. Biol.* **2008**, *12*, 109–114.

(27) Fraser-Liggett, C. M. Insights on biology and evolution from microbial genome sequencing. *Genome Res.* **2005**, *15*, 1603–1610.

(28) Lozupone, C. A.; Hamady, M.; Cantarel, B. L.; Coutinho, P. M.; Henrissat, B.; Gordon, J. I.; Knight, R. The convergence of

carbohydrate active gene repertoires in human gut microbes. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 15076–15081.

(29) El Kaoutari, A.; Armougom, F.; Gordon, J. I.; Raoult, D.; Henrissat, B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat. Rev. Microbiol.* **2013**, *11*, 497–504.

(30) Smillie, C. S.; Smith, M. B.; Friedman, J.; Cordero, O. X.; David, L. A.; Alm, E. J. Ecology drives a global network of gene exchange connecting the human microbiome. *Nature* **2011**, *480*, 241–244.

(31) Hehemann, J.-H.; Correc, G.; Barbeyron, T.; Helbert, W.; Czjzek, M.; Michel, G. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature* **2010**, *464*, 908–912.

(32) Le Chatelier, E.; Nielsen, T.; Qin, J.; Prifti, E.; Hildebrand, F.; Falony, G.; Almeida, M.; Arumugam, M.; Batto, J.-M.; Kennedy, S.; Leonard, P.; Li, J.; Burgdorf, K.; Grarup, N.; Jørgensen, T.; Brandslund, I.; Nielsen, H. B.; Juncker, A. S.; Bertalan, M.; Levenez, F.; Pons, N.; Rasmussen, S.; Sunagawa, S.; Tap, J.; Tims, S.; Zoetendal, E. G.; Brunak, S.; Clément, K.; Doré, J.; Kleerebezem, M.; Kristiansen, K.; Renault, P.; Sicheritz-Ponten, T.; de Vos, W.; Zucker, J.-D.; Raes, J.; Hansen, T.; Meta, H. I. T. C.; Bork, P.; Wang, J.; Ehrlich, S.; Pedersen, O.; Guedon, E.; Delorme, C.; Layec, S.; Khaci, G.; van de Guchte, M.; Vandemeulebrouck, G.; Jamet, A.; Dervyn, R.; Sanchez, N.; Maguin, E.; Haimet, F.; Winogradski, Y.; Cultrone, A.; Leclerc, M.; Juste, C.; Blottière, H.; Pelletier, E.; LePaslier, D.; Artiguenave, F.; Bruls, T.; Weissenbach, J.; Turner, K.; Parkhill, J.; Antolin, M.; Manichanh, C.; Casellas, F.; Boruel, N.; Varela, E.; Torrejon, A.; Guarner, F.; Denariáz, G.; Derrien, M.; van Hylckama Vlieg, J. E.; Veiga, P.; Oozeer, R.; Knol, J.; Rescigno, M.; Brechot, C.; M'Rini, C.; Mérieux, A.; Yamada, T. Richness of human gut microbiome correlates with metabolic markers. *Nature* **2013**, *500*, 541–546.

(33) Blaser, M. J.; Falkow, S. What are the consequences of the disappearing human microbiota? *Nat. Rev. Microbiol.* **2009**, *7*, 887–894.

(34) Eaton, S.; Konner, M.; Shostak, M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am. J. Med.* **1988**, *84*, 739–749.

(35) Eaton, S. B.; Konner, M. Paleolithic nutrition. A consideration of its nature and current implications. *N. Engl. J. Med.* **1985**, *312*, 283–289.

(36) Konner, M.; Eaton, S. B. Paleolithic nutrition: twenty-five years later. *Nutr. Clin. Pract.* **2010**, *25*, 594–602.

(37) Adlercreutz, H. Evolution, nutrition, intestinal microflora, and prevention of cancer: a hypothesis. *Proc. Soc. Exp. Biol. Med.* **1998**, *217*, 241–246.

(38) LaCroix, A. Z.; Guralnik, J. M.; Berkman, L. F.; Wallace, R. B.; Satterfield, S. Maintaining mobility in late life. II. Smoking, alcohol consumption, physical activity, and body mass index. *Am. J. Epidemiol.* **1993**, *137*, 858–869.

(39) Eaton, S.; Strassman, B.; Nesse, R.; Neel, J.; Ewald, P.; Williams, G.; Weder, A.; Eaton, S.; Lindeberg, S.; Konner, M.; Mysterud, I.; Cordain, L. Evolutionary health promotion. *Prev. Med.* **2002**, *34*, 109–118.

(40) Faith, J. J.; Guruge, J. L.; Charbonneau, M.; Subramanian, S.; Seedorf, H.; Goodman, A. L.; Clemente, J. C.; Knight, R.; Heath, A. C.; Leibel, R. L.; Rosenbaum, M.; Gordon, J. I. The long-term stability of the human gut microbiota. *Science* **2013**, *341*, 1237439.

(41) Jalanka-Tuovinen, J.; Salonen, A.; Nikkilä, J.; Immonen, O.; Kekkonen, R.; Lahti, L.; Palva, A.; de Vos, W. M. Intestinal microbiota in healthy adults: temporal analysis reveals individual and common core and relation to intestinal symptoms. *PLoS One* **2011**, *6*, e23035.

(42) Delgado, S.; Suárez, A.; Otero, L.; Mayo, B. Variation of microbiological and biochemical parameters in the faeces of two healthy people over a 15 day period. *Eur. J. Nutr.* **2004**, *43*, 375–380.

(43) Human Microbiome Project, C. Structure, function and diversity of the healthy human microbiome. *Nature* **2012**, *486*, 207–214.

(44) Eckburg, P. B.; Bik, E. M.; Bernstein, C. N.; Purdom, E.; Dethlefsen, L.; Sargent, M.; Gill, S. R.; Nelson, K. E.; Relman, D. A.

Diversity of the human intestinal microbial flora. *Science* **2005**, *308*, 1635–1638.

(45) Turnbaugh, P.; Hamady, M.; Yatsunenko, T.; Cantarel, B.; Duncan, A.; Ley, R.; Sogin, M.; Jones, W.; Roe, B.; Affourtit, J.; Egholm, M.; Henrissat, B.; Heath, A.; Knight, R.; Gordon, J. A core gut microbiome in obese and lean twins. *Nature* **2009**, *457*, 480–484.

(46) McNulty, N. P.; Yatsunenko, T.; Hsiao, A.; Faith, J. J.; Muegge, B. D.; Goodman, A. L.; Henrissat, B.; Oozeer, R.; Cools-Portier, S.; Gobert, G.; Chervaux, C.; Knights, D.; Lozupone, C. A.; Knight, R.; Duncan, A. E.; Bain, J. R.; Muehlbauer, M. J.; Newgard, C. B.; Heath, A. C.; Gordon, J. I. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. *Sci. Transl. Med.* **2011**, *3*, 106ra106.

(47) Yatsunenko, T.; Rey, F. E.; Manary, M. J.; Trehan, I.; Dominguez-Bello, M. G.; Contreras, M.; Magris, M.; Hidalgo, G.; Baldassano, R. N.; Anokhin, A. P.; Heath, A. C.; Warner, B.; Reeder, J.; Kuczynski, J.; Caporaso, J. G.; Lozupone, C. A.; Lauber, C.; Clemente, J. C.; Knights, D.; Knight, R.; Gordon, J. I. Human gut microbiome viewed across age and geography. *Nature* **2012**, *486*, 222–227.

(48) Song, S. J.; Lauber, C.; Costello, E. K.; Lozupone, C. A.; Humphrey, G.; Berg-Lyons, D.; Caporaso, J. G.; Knights, D.; Clemente, J. C.; Nakielnny, S.; Gordon, J. I.; Fierer, N.; Knight, R. Cohabiting family members share microbiota with one another and with their dogs. *eLife* **2013**, *2*, e00458.

(49) Zhang, C.; Zhang, M.; Wang, S.; Han, R.; Cao, Y.; Hua, W.; Mao, Y.; Zhang, X.; Pang, X.; Wei, C.; Zhao, G.; Chen, Y.; Zhao, L. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. *ISME J.* **2010**, *4*, 232–241.

(50) Ottman, N.; Smidt, H.; de Vos, W.; Belzer, C. The function of our microbiota: who is out there and what do they do? *Front. Cell. Infect. Microbiol.* **2012**, *2*, 104.

(51) Turnbaugh, P.; Ridaura, V.; Faith, J.; Rey, F.; Knight, R.; Gordon, J. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci. Transl. Med.* **2009**, *1*, 6ra14.

(52) Wu, G. D.; Chen, J.; Hoffmann, C.; Bittinger, K.; Chen, Y.-Y.; Keilbaugh, S.; Bewtra, M.; Knights, D.; Walters, W.; Knight, R.; Sinha, R.; Gilroy, E.; Gupta, K.; Baldassano, R.; Nessel, L.; Li, H.; Bushman, F. D.; Lewis, J. D. Linking long-term dietary patterns with gut microbial enterotypes. *Science* **2011**, *334*, 105–108.

(53) Jumpertz, R.; Le, D. S.; Turnbaugh, P. J.; Trinidad, C.; Bogardus, C.; Gordon, J. I.; Krakoff, J. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am. J. Clin. Nutr.* **2011**, *94*, 58–65.

(54) Aries, V.; Crowther, J. S.; Drasar, B. S.; Hill, M. L.; Williams, R. E. Bacteria and the aetiology of cancer of the large bowel. *Gut* **1969**, *10*, 334–335.

(55) Finegold, S. M.; Attebery, H. R.; Sutter, V. L. Effect of diet on human fecal flora: comparison of Japanese and American diets. *Am. J. Clin. Nutr.* **1974**, *27*, 1456–1469.

(56) De Filippo, C.; Cavalieri, D.; Di Paola, M.; Ramazzotti, M.; Poullet, J. B.; Massart, S.; Collini, S.; Pieraccini, G.; Lionetti, P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 14691–14696.

(57) Lin, A.; Bik, E. M.; Costello, E. K.; Dethlefsen, L.; Haque, R.; Relman, D. A.; Singh, U. Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. *PLoS One* **2013**, *8*, e53838.

(58) Dethlefsen, L.; Eckburg, P. B.; Bik, E. M.; Relman, D. A. Assembly of the human intestinal microbiota. *Trends Ecol. Evol.* **2006**, *21*, 517–523.

(59) Spor, A.; Koren, O.; Ley, R. Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat. Rev. Microbiol.* **2011**, *9*, 279–290.

(60) Holmes, E.; Li, J. V.; Marchesi, J. R.; Nicholson, J. K. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. *Cell Metab.* **2012**, *16*, 559–564.

- (61) Grenham, S.; Clarke, G.; Cryan, J. F.; Dinan, T. G. Brain-gut-microbe communication in health and disease. *Front. Physiol.* **2011**, *2*, 94.
- (62) Queipo-Ortuño, M.; Seoane, L.; Murri, M.; Pardo, M.; Gomez-Zumaquero, J.; Cardona, F.; Casanueva, F.; Tinahones, F. Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. *PLoS One* **2013**, *8*, e65465.
- (63) Ou, J.; Carbonero, F.; Zoetendal, E.; Delany, J.; Wang, M.; Newton, K.; Gaskins, H.; O'Keefe, S. Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans. *Am. J. Clin. Nutr.* **2013**, *98*, 111–120.
- (64) Faith, J. J.; McNulty, N. P.; Rey, F. E.; Gordon, J. I. Predicting a human gut microbiota's response to diet in gnotobiotic mice. *Science* **2011**, *333*, 101–104.
- (65) Duncan, S.; Lobley, G.; Holtrop, G.; Ince, J.; Johnstone, A.; Louis, P.; Flint, H. Human colonic microbiota associated with diet, obesity and weight loss. *Int. J. Obes.* **2008**, *32*, 1720–1724.
- (66) Ley, R.; Turnbaugh, P.; Klein, S.; Gordon, J. Microbial ecology: human gut microbes associated with obesity. *Nature* **2006**, *444*, 1022–1023.
- (67) Murphy, E.; Cotter, P.; Healy, S.; Marques, T.; O'Sullivan, O.; Fouhy, F.; Clarke, S.; O'Toole, P.; Quigley, E.; Stanton, C.; Ross, P.; O'Doherty, R.; Shanahan, F. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. *Gut* **2010**, *59*, 1635–1642.
- (68) Barcenilla, A.; Pryde, S. E.; Martin, J. C.; Duncan, S. H.; Stewart, C. S.; Henderson, C.; Flint, H. J. Phylogenetic relationships of butyrate-producing bacteria from the human gut. *Appl. Environ. Microbiol.* **2000**, *66*, 1654–1661.
- (69) Hold, G. L.; Schwiertz, A.; Aminov, R. I.; Blaut, M.; Flint, H. J. Oligonucleotide probes that detect quantitatively significant groups of butyrate-producing bacteria in human feces. *Appl. Environ. Microbiol.* **2003**, *69*, 4320–4324.
- (70) Duncan, S. H.; Belenguer, A.; Holtrop, G.; Johnstone, A.; Flint, H. J.; Lobley, G. E. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl. Environ. Microbiol.* **2007**, *73*, 1073–1078.
- (71) Russell, W. R.; Gratz, S. W.; Duncan, S. H.; Holtrop, G.; Ince, J.; Scobbie, L.; Duncan, G.; Johnstone, A. M.; Lobley, G. E.; Wallace, R. J.; Duthie, G. G.; Flint, H. J. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *Am. J. Clin. Nutr.* **2011**, *93*, 1062–1072.
- (72) Brinkworth, G. D.; Noakes, M.; Clifton, P. M.; Bird, A. R. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br. J. Nutr.* **2009**, *101*, 1493–1502.
- (73) Bäckhed, F.; Manchester, J. K.; Semenkovich, C. F.; Gordon, J. I. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 979–984.
- (74) Turnbaugh, P. J.; Bäckhed, F.; Fulton, L.; Gordon, J. I. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* **2008**, *3*, 213–223.
- (75) Million, M.; Maraninchi, M.; Henry, M.; Armougom, F.; Richet, H.; Carrieri, P.; Valero, R.; Raccach, D.; Viallettes, B.; Raoult, D. Obesity-associated gut microbiota is enriched in *Lactobacillus reuteri* and depleted in *Bifidobacterium animalis* and *Methanobrevibacter smithii*. *Int. J. Obes.* **2012**, *36*, 817–825.
- (76) de La Serre, C. B.; Ellis, C. L.; Lee, J.; Hartman, A. L.; Rutledge, J. C.; Raybould, H. E. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am. J. Physiol. Gastrointest. Liver. Physiol.* **2010**, *299*, G440–G448.
- (77) Hildebrandt, M. A.; Hoffmann, C.; Sherrill-Mix, S. A.; Keilbaugh, S. A.; Hamady, M.; Chen, Y.-Y.; Knight, R.; Ahima, R. S.; Bushman, F.; Wu, G. D. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* **2009**, *137*, 1716.
- (78) Ravussin, Y.; Koren, O.; Spor, A.; LeDuc, C.; Gutman, R.; Stombaugh, J.; Knight, R.; Ley, R.; Leibel, R. Responses of gut microbiota to diet composition and weight loss in lean and obese mice. *Obesity* **2012**, *20*, 738–747.
- (79) Flint, H. The impact of nutrition on the human microbiome. *Nutr. Rev.* **2012**, *70* (Suppl. 1), 3.
- (80) De Palma, G.; Nadal, I.; Collado, M.; Sanz, Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Br. J. Nutr.* **2009**, *102*, 1154–1160.
- (81) Sanz, Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult humans. *Gut Microbes* **2010**, *1*, 135–137.
- (82) Reddy, B.; Weisburger, J.; Wynder, E. Effects of high risk and low risk diets for colon carcinogenesis on fecal microflora and steroids in man. *J. Nutr.* **1975**, *105*, 878–884.
- (83) van Faassen, A.; Bol, J.; van Dokkum, W.; Pikaar, N. A.; Ockhuizen, T.; Hermus, R. J. Bile acids, neutral steroids, and bacteria in feces as affected by a mixed, a lacto-ovo-vegetarian, and a vegan diet. *Am. J. Clin. Nutr.* **1987**, *46*, 962–967.
- (84) Hentges, D. J. Does diet influence human fecal microflora composition? *Nutr. Rev.* **1980**, *38*, 329–336.
- (85) Maier, B. R.; Flynn, M. A.; Burton, G. C.; Tsutakawa, R. K.; Hentges, D. J. Effects of a high-beef diet on bowel flora: a preliminary report. *Am. J. Clin. Nutr.* **1974**, *27*, 1470–1474.
- (86) Hayashi, H.; Sakamoto, M.; Benno, Y. Fecal microbial diversity in a strict vegetarian as determined by molecular analysis and cultivation. *Microbiol. Immunol.* **2002**, *46*, 819–831.
- (87) Liszt, K.; Zwielerhner, J.; Handschur, M.; Hippe, B.; Thaler, R.; Haslberger, A. G. Characterization of bacteria, clostridia and Bacteroides in faeces of vegetarians using qPCR and PCR-DGGE fingerprinting. *Ann. Nutr. Metab.* **2009**, *54*, 253–257.
- (88) Kabeerdoss, J.; Devi, R. S.; Mary, R. R.; Ramakrishna, B. S. Faecal microbiota composition in vegetarians: comparison with omnivores in a cohort of young women in southern India. *Br. J. Nutr.* **2012**, *108*, 953–957.
- (89) Zimmer, J.; Lange, B.; Frick, J. S.; Sauer, H.; Zimmermann, K.; Schwiertz, A.; Rusch, K.; Klosterhalfen, S.; Enck, P. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *Eur. J. Clin. Nutr.* **2012**, *66*, 53–60.
- (90) Nicholson, J.; Holmes, E.; Kinross, J.; Burcelin, R.; Gibson, G.; Jia, W.; Pettersson, S. Host-gut microbiota metabolic interactions. *Science* **2012**, *336*, 1262–1267.
- (91) Stella, C.; Beckwith-Hall, B.; Cloarec, O.; Holmes, E.; Lindon, J. C.; Powell, J.; van der Ouderaa, F.; Bingham, S.; Cross, A. J.; Nicholson, J. K. Susceptibility of human metabolic phenotypes to dietary modulation. *J. Proteome Res.* **2006**, *5*, 2780–2788.
- (92) Mai, V.; Colbert, L. H.; Perkins, S. N.; Schatzkin, A.; Hursting, S. D. Intestinal microbiota: a potential diet-responsive prevention target in ApcMin mice. *Mol. Carcinog.* **2007**, *46*, 42–48.
- (93) Henderson, A. L.; Cao, W. W.; Wang, R. F.; Lu, M. H.; Cerniglia, C. E. The effect of food restriction on the composition of intestinal microflora in rats. *Exp. Gerontol.* **1998**, *33*, 239–247.
- (94) Michalsen, A.; Riegert, M.; Lüdtke, R.; Bäcker, M.; Langhorst, J.; Schwickert, M.; Dobos, G. J. Mediterranean diet or extended fasting's influence on changing the intestinal microflora, immunoglobulin A secretion and clinical outcome in patients with rheumatoid arthritis and fibromyalgia: an observational study. *BMC Complement. Altern. Med.* **2005**, *5*, 22.
- (95) Armougom, F.; Henry, M.; Viallettes, B.; Raccach, D.; Raoult, D. Monitoring bacterial community of human gut microbiota reveals an increase in *Lactobacillus* in obese patients and *Methanogens* in anorexic patients. *PloS One* **2009**, *4*, e7125.
- (96) Carey, H. V.; Walters, W. A.; Knight, R. Seasonal restructuring of the ground squirrel gut microbiota over the annual hibernation cycle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2013**, *304*, 42.

- (97) Chacko, A.; Cummings, J. H. Nitrogen losses from the human small bowel: obligatory losses and the effect of physical form of food. *Gut* **1988**, *29*, 809–815.
- (98) Cummings, J.; Macfarlane, G. The control and consequences of bacterial fermentation in the human colon. *J. Appl. Bacteriol.* **1991**, *70*, 443–459.
- (99) McNeil, N. I. The contribution of the large intestine to energy supplies in man. *Am. J. Clin. Nutr.* **1984**, *39*, 338–342.
- (100) Salzman, N. H.; Underwood, M. A.; Bevins, C. L. Paneth cells, defensins, and the commensal microbiota: a hypothesis on intimate interplay at the intestinal mucosa. *Semin. Immunol.* **2007**, *19*, 70–83.
- (101) Mukherjee, S.; Vaishnav, S.; Hooper, L. Multi-layered regulation of intestinal antimicrobial defense. *Cell. Mol. Life Sci.* **2008**, *65*, 3019–3027.
- (102) Yokota, A.; Fukiya, S.; Islam, K. B.; Ooka, T.; Ogura, Y.; Hayashi, T.; Hagio, M.; Ishizuka, S. Is bile acid a determinant of the gut microbiota on a high-fat diet? *Gut Microbes* **2012**, *3*, 455–459.
- (103) van Passel, M. W.; Kant, R.; Zoetendal, E. G.; Plugge, C. M.; Derrien, M.; Malfatti, S. A.; Chain, P. S.; Woyke, T.; Palva, A.; de Vos, W. M.; Smidt, H. The genome of *Akkermansia muciniphila*, a dedicated intestinal mucin degrader, and its use in exploring intestinal metagenomes. *PLoS One* **2011**, *6*, e16876.
- (104) Ruas-Madiedo, P.; Gueimonde, M.; Fernández-García, M.; de los Reyes-Gavilán, C. G.; Margolles, A. Mucin degradation by *Bifidobacterium* strains isolated from the human intestinal microbiota. *Appl. Environ. Microbiol.* **2008**, *74*, 1936–1940.
- (105) Flint, H.; Bayer, E.; Rincon, M.; Lamed, R.; White, B. Polysaccharide utilization by gut bacteria: potential for new insights from genomic analysis. *Nat. Rev. Microbiol.* **2008**, *6*, 121–131.
- (106) Kurokawa, K.; Itoh, T.; Kuwahara, T.; Oshima, K.; Toh, H.; Toyoda, A.; Takami, H.; Morita, H.; Sharma, V. K.; Srivastava, T. P.; Taylor, T. D.; Noguchi, H.; Mori, H.; Ogura, Y.; Ehrlich, D. S.; Itoh, K.; Takagi, T.; Sakaki, Y.; Hayashi, T.; Hattori, M. Comparative metagenomics revealed commonly enriched gene sets in human gut microbiomes. *DNA Res.* **2007**, *14*, 169–181.
- (107) Flint, H. J. Polysaccharide breakdown by anaerobic microorganisms inhabiting the mammalian gut. *Adv. Appl. Microbiol.* **2004**, *56*, 89–120.
- (108) Flint, H.; Duncan, S.; Scott, K.; Louis, P. Interactions and competition within the microbial community of the human colon: links between diet and health. *Environ. Microbiol.* **2007**, *9*, 1101–1111.
- (109) Louis, P.; Scott, K. P.; Duncan, S. H.; Flint, H. J. Understanding the effects of diet on bacterial metabolism in the large intestine. *J. Appl. Microbiol.* **2007**, *102*, 1197–1208.
- (110) Pryde, S.; Duncan, S.; Hold, G.; Stewart, C.; Flint, H. The microbiology of butyrate formation in the human colon. *FEMS Microbiol. Lett.* **2002**, *217*, 133–139.
- (111) Eastwood, M. A.; Hamilton, D. Studies on the adsorption of bile salts to non-absorbed components of diet. *Biochim. Biophys. Acta* **1968**, *152*, 165–173.
- (112) Lupton, J. R.; Coder, D. M.; Jacobs, L. R. Long-term effects of fermentable fibers on rat colonic pH and epithelial cell cycle. *J. Nutr.* **1988**, *118*, 840–845.
- (113) Cummings, J. H.; Hill, M. J.; Jivraj, T.; Houston, H.; Branch, W. J.; Jenkins, D. J. The effect of meat protein and dietary fiber on colonic function and metabolism. I. Changes in bowel habit, bile acid excretion, and calcium absorption. *Am. J. Clin. Nutr.* **1979**, *32*, 2086–2093.
- (114) Stephen, A. M.; Wiggins, H. S.; Cummings, J. H. Effect of changing transit time on colonic microbial metabolism in man. *Gut* **1987**, *28*, 601–609.
- (115) Burkitt, D. P.; Walker, A. R. P.; Painter, N. S. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. *Lancet* **1972**, *2*, 1408–1412.
- (116) Englyst, K. N.; Liu, S.; Englyst, H. N. Nutritional characterization and measurement of dietary carbohydrates. *Eur. J. Clin. Nutr.* **2007**, *61*, S19–S39.
- (117) Candela, M.; Maccaferri, S.; Turrone, S.; Carnevali, P.; Brigidi, P. Functional intestinal microbiome, new frontiers in prebiotic design. *Int. J. Food Microbiol.* **2010**, *140*, 93–101.
- (118) Gibson, G.; Probert, H.; Loo, J.; Rastall, R.; Roberfroid, M. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr. Res. Rev.* **2004**, *17*, 259–275.
- (119) Costabile, A.; Klinder, A.; Fava, F.; Napolitano, A.; Fogliano, V.; Leonard, C.; Gibson, G. R.; Tuohy, K. M. Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebo-controlled, crossover study. *Br. J. Nutr.* **2008**, *99*, 110–120.
- (120) Mitsou, E. K.; Panopoulou, N.; Turunen, K.; Spiliotis, V.; Kyriacou, A. Prebiotic potential of barley derived β -glucan at low intake levels: a randomised, double-blinded, placebo-controlled clinical study. *Food Res. Int.* **2010**, *43*, 1086–1092.
- (121) Bouhnik, Y.; Raskine, L.; Simoneau, G.; Vicaut, E.; Neut, C.; Flourie, B.; Brouns, F.; Bornet, F. R. The capacity of nondigestible carbohydrates to stimulate fecal bifidobacteria in healthy humans: a double-blind, randomized, placebo-controlled, parallel-group, dose-response relation study. *Am. J. Clin. Nutr.* **2004**, *80*, 1658–1664.
- (122) François, I. E.; Lescroart, O.; Veraverbeke, W. S.; Marzorati, M.; Possemiers, S.; Evenepoel, P.; Hamer, H.; Houben, E.; Windey, K.; Welling, G. W.; Delcour, J. A.; Courtin, C. M.; Verbeke, K.; Broekaert, W. F. Effects of a wheat bran extract containing arabinoxylan oligosaccharides on gastrointestinal health parameters in healthy adult human volunteers: a double-blind, randomised, placebo-controlled, cross-over trial. *Br. J. Nutr.* **2012**, *108*, 2229–2242.
- (123) Ramirez-Farias, C.; Slezak, K.; Fuller, Z.; Duncan, A.; Holtrop, G.; Louis, P. Effect of inulin on the human gut microbiota: stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. *Br. J. Nutr.* **2009**, *101*, 541–550.
- (124) Harmsen, H. J. M.; Raangs, G. C.; Franks, A. H.; Wildeboer-Veloo, A. C. M.; Welling, G. W. The effect of the prebiotic inulin and the probiotic *bifidobacterium longum* on the fecal microflora of healthy volunteers measured by FISH and DGGE. *Microb. Ecol. Health Dis.* **2002**, *14*, 212–220.
- (125) Tuohy, K. M.; Finlay, R. K.; Wynne, A. G.; Gibson, G. R. A human volunteer study on the prebiotic effects of HP-inulin—faecal bacteria enumerated using fluorescent in situ hybridisation (FISH). *Anaerobe* **2001**, *7*, 113–118.
- (126) Scott, K. P.; Martin, J. C.; Chassard, C.; Clerget, M.; Potrykus, J.; Campbell, G.; Mayer, C.-D.; Young, P.; Rucklidge, G.; Ramsay, A. G.; Flint, H. J. Substrate-driven gene expression in *Roseburia inulinivorans*: importance of inducible enzymes in the utilization of inulin and starch. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108* (Suppl. 1), 4672–4679.
- (127) Tuohy, K.; Kolida, S.; Lustenberger, A.; Gibson, G. The prebiotic effects of biscuits containing partially hydrolysed guar gum and fructo-oligosaccharides – a human volunteer study. *Br. J. Nutr.* **2001**, *86*, 341–348.
- (128) Scholtens, P. A.; Alles, M. S.; Bindels, J. G.; van der Linde, E. G.; Tolboom, J. J.; Knol, J. Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. *J. Pediatr. Gastroenterol. Nutr.* **2006**, *42*, 553–559.
- (129) Knol, J.; Scholtens, P.; Kafka, C.; Steenbakkers, J.; Gro, S.; Helm, K.; Klarczyk, M.; Schöpfer, H.; Böckler, H. M.; Wells, J. Colon microflora in infants fed formula with galacto- and fructo-oligosaccharides: more like breast-fed infants. *J. Pediatr. Gastroenterol. Nutr.* **2005**, *40*, 36–42.
- (130) Davis, L. M.; Martínez, I.; Walter, J.; Hutkins, R. A dose dependent impact of prebiotic galactooligosaccharides on the intestinal microbiota of healthy adults. *Int. J. Food Microbiol.* **2010**, *144*, 285–292.
- (131) Rossi, M.; Corradini, C.; Amaretti, A.; Nicolini, M.; Pompei, A.; Zanoni, S.; Matteuzzi, D. Fermentation of fructooligosaccharides and inulin by bifidobacteria: a comparative study of pure and fecal cultures. *Appl. Environ. Microbiol.* **2005**, *71*, 6150–6158.
- (132) De Vuyst, L.; Leroy, F. Cross-feeding between bifidobacteria and butyrate-producing colon bacteria explains bifidobacterial com-

petitiveness, butyrate production, and gas production. *Int. J. Food Microbiol.* **2011**, *149*, 73–80.

(133) Abell, G. C.; Cooke, C. M.; Bennett, C. N.; Conlon, M. A.; McOrist, A. L. Phylotypes related to *Ruminococcus bromii* are abundant in the large bowel of humans and increase in response to a diet high in resistant starch. *FEMS Microbiol. Ecol.* **2008**, *66*, S05–S15.

(134) Walker, A. W.; Ince, J.; Duncan, S. H.; Webster, L. M.; Holtrop, G.; Ze, X.; Brown, D.; Stares, A. D.; Scott, P.; Bergerat, A.; Louis, P.; McIntosh, F.; Johnstone, A. M.; Lobley, G. E.; Parkhill, J.; Flint, H. J. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J.* **2010**, *5*, 220–230.

(135) Koropatkin, N. M.; Cameron, E. A.; Martens, E. C. How glycan metabolism shapes the human gut microbiota. *Nat. Rev. Microbiol.* **2012**, *10*, 323–335.

(136) Zoetendal, E. G.; Raes, J.; van den Bogert, B.; Arumugam, M.; Booiijink, C. C.; Troost, F. J.; Bork, P.; Wels, M.; de Vos, W.; Kleerebezem, M. The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. *ISME J.* **2012**, *6*, 1415–1426.

(137) Booiijink, C. C.; Boekhorst, J.; Zoetendal, E. C.; Smidt, H.; Kleerebezem, M.; de Vos, W. M. Metatranscriptome analysis of the human fecal microbiota reveals subject-specific expression profiles, with genes encoding proteins involved in carbohydrate metabolism being dominantly expressed. *Appl. Environ. Microbiol.* **2010**, *76*, S533–S540.

(138) Gosalbes, M. J.; Durbán, A.; Pignatelli, M.; Abellan, J. J.; Jiménez-Hernández, N.; Pérez-Cobas, A. E.; Latorre, A.; Moya, A. Metatranscriptomic approach to analyze the functional human gut microbiota. *PLoS One* **2011**, *6*, e17447.

(139) Kolmeder, C. A.; de Been, M.; Nikkilä, J.; Ritamo, I.; Mättö, J.; Valmu, L.; Salojärvi, J.; Palva, A.; Salonen, A.; de Vos, W. M. Comparative metaproteomics and diversity analysis of human intestinal microbiota testifies for its temporal stability and expression of core functions. *PLoS One* **2012**, *7*, e29913.

(140) Xu, J.; Bjursell, M. K.; Himrod, J.; Deng, S.; Carmichael, L. K.; Chiang, H. C.; Hooper, L. V.; Gordon, J. I. A genomic view of the human-Bacteroides thetaiotaomicron symbiosis. *Science* **2003**, *299*, 2074–2076.

(141) Sonnenburg, E. D.; Zheng, H.; Joglekar, P.; Higginbottom, S. K.; Firbank, S. J.; Bolam, D. N.; Sonnenburg, J. L. Specificity of polysaccharide use in intestinal bacteroides species determines diet-induced microbiota alterations. *Cell* **2010**, *141*, 1241–1252.

(142) Chassard, C.; Goumy, V.; Leclerc, M.; Del'homme, C.; Bernalier-Donadille, A. Characterization of the xylan-degrading microbial community from human faeces. *FEMS Microbiol. Ecol.* **2007**, *61*, 121–131.

(143) Martens, E. C.; Koropatkin, N. M.; Smith, T. J.; Gordon, J. I. Complex glycan catabolism by the human gut microbiota: the Bacteroidetes Sus-like paradigm. *J. Biol. Chem.* **2009**, *284*, 24673–24677.

(144) Thomas, F.; Hehemann, J.-H.; Rebuffet, E.; Czejek, M.; Michel, G. Environmental and gut bacteroidetes: the food connection. *Front. Microbiol.* **2011**, *2*, 93.

(145) Bolam, D. N.; Koropatkin, N. M. Glycan recognition by the Bacteroidetes Sus-like systems. *Curr. Opin. Struct. Biol.* **2012**, *22*, S63–S69.

(146) Robert, C.; Bernalier-Donadille, A. The cellulolytic microflora of the human colon: evidence of microcrystalline cellulose-degrading bacteria in methane-excreting subjects. *FEMS Microbiol. Ecol.* **2003**, *46*, 81–89.

(147) Salyers, A. A.; West, S. E.; Vercellotti, J. R.; Wilkind, T. D. Fermentation of mucins and plant polysaccharides by anaerobic bacteria from the human colon. *Appl. Environ. Microbiol.* **1977**, *34*, S29–S33.

(148) Mahowald, M. A.; Rey, F. E.; Seedorf, H.; Turnbaugh, P. J.; Fulton, R. S.; Wollam, A.; Shah, N.; Wang, C.; Magrini, V.; Wilson, R. K.; Cantarel, B.; Coutinho, P. M.; Henrissat, B.; Crock, L. W.; Russell, A.; Verberkmoes, N. C.; Hettich, R. L.; Gordon, J. I. Characterizing a model human gut microbiota composed of members of its two

dominant bacterial phyla. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 5859–5864.

(149) Hinsberger, A.; Sandhu, B. K. Digestion and absorption. *Curr. Paediatr.* **2004**, *14*, 605–611.

(150) Pihl, B.; Glotzer, D.; Patterson, J. Absorption of medium-chain fatty acids by the dog colon. *J. Appl. Physiol.* **1966**, *21*, 1059–1062.

(151) Jørgensen, J. R.; Fitch, M. D.; Mortensen, P. B.; Fleming, S. E. In vivo absorption of medium-chain fatty acids by the rat colon exceeds that of short-chain fatty acids. *Gastroenterology* **2001**, *120*, 1152–1161.

(152) Jørgensen, J.; Holtug, K.; Jeppesen, P.; Mortensen, P. Human rectal absorption of short- and medium-chain C2–C10 fatty acids. *Scand. J. Gastroenterol.* **1998**, *33*, S90–S94.

(153) Jeppesen, P. B.; Mortensen, P. B. The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. *Gut* **1998**, *43*, 478–483.

(154) Marchesi, J. R.; Holmes, E.; Khan, F.; Kochhar, S.; Scanlan, P.; Shanahan, F.; Wilson, I. D.; Wang, Y. Rapid and noninvasive metabonomic characterization of inflammatory bowel disease. *J. Proteome Res.* **2007**, *6*, S46–S51.

(155) De Weirtdt, R.; Possemiers, S.; Vermeulen, G.; Moerdijk-Poortvliet, T. C.; Boschker, H. T.; Verstraete, W.; Van de Wiele, T. Human faecal microbiota display variable patterns of glycerol metabolism. *FEMS Microbiol. Ecol.* **2010**, *74*, 601–611.

(156) Hill, M. J. Bile acids and colorectal cancer: hypothesis. *Eur. J. Cancer Prev.* **1991**, *1* (Suppl. 2), 69–74.

(157) Reddy, B. Diet and excretion of bile acids. *Cancer Res.* **1981**, *41*, 3766–3768.

(158) Kurdi, P.; Kawanishi, K.; Mizutani, K.; Yokota, A. Mechanism of growth inhibition by free bile acids in lactobacilli and bifidobacteria. *J. Bacteriol.* **2006**, *188*, 1979–1986.

(159) Floch, M. H.; Binder, H. J.; Filburn, B.; Gershengoren, W. The effect of bile acids on intestinal microflora. *Am. J. Clin. Nutr.* **1972**, *25*, 1418–1426.

(160) Islam, K. B.; Fukiya, S.; Hagio, M.; Fujii, N.; Ishizuka, S.; Ooka, T.; Ogura, Y.; Hayashi, T.; Yokota, A. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. *Gastroenterology* **2011**, *141*, 1773–1781.

(161) Jones, B. V.; Begley, M.; Hill, C.; Gahan, C. G.; Marchesi, J. R. Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13580–13585.

(162) Ridlon, J.; Kang, D.-J.; Hylemon, P. Bile salt biotransformations by human intestinal bacteria. *J. Lipid Res.* **2006**, *47*, 241–259.

(163) Hylemon, P. B.; Harder, J. Biotransformation of monoterpenes, bile acids, and other isoprenoids in anaerobic ecosystems. *FEMS Microbiol. Rev.* **1998**, *22*, 475–488.

(164) Swann, J. R.; Want, E. J.; Geier, F. M.; Spagou, K.; Wilson, I. D.; Sidaway, J. E.; Nicholson, J. K.; Holmes, E. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108* (Suppl.1), 4523–4530.

(165) Devkota, S.; Wang, Y.; Musch, M. W.; Leone, V.; Fehlner-Peach, H.; Nadimpalli, A.; Antonopoulos, D. A.; Jabri, B.; Chang, E. B. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in IL10^{−/−} mice. *Nature* **2012**, *487*, 104–108.

(166) Baron, E. J.; Curren, M.; Henderson, G.; Jousimies-Somer, H.; Lee, K.; Lechowicz, K.; Strong, C. A.; Summanen, P.; Tunér, K.; Finegold, S. M. *Bifidobacterium wadsworthia* isolates from clinical specimens. *J. Clin. Microbiol.* **1992**, *30*, 1882–1884.

(167) Laue, H.; Cook, A. M. Biochemical and molecular characterization of taurine:pyruvate aminotransferase from the anaerobe *Bifidobacterium wadsworthia*. *Eur. J. Biochem.* **2000**, *267*, 6841–6848.

(168) Laue, H.; Denger, K.; Cook, A. M. Taurine reduction in anaerobic respiration of *Bifidobacterium wadsworthia* RZATAU. *Appl. Environ. Microbiol.* **1997**, *63*, 2016–2021.

(169) Laue, H.; Friedrich, M.; Ruff, J.; Cook, A. M. Dissimilatory sulfite reductase (desulfoviridin) of the taurine-degrading, non-sulfate-reducing bacterium *Bifidobacterium wadsworthia* RZATAU contains a fused DsrB-DsrD subunit. *J. Bacteriol.* **2001**, *183*, 1727–1733.

- (170) Hardison, W. G. Hepatic taurine concentration and dietary taurine as regulators of bile acid conjugation with taurine. *Gastroenterology* **1978**, *75*, 71–75.
- (171) Evans, D. F.; Pye, G.; Bramley, R.; Clark, A. G.; Dyson, T. J.; Hardcastle, J. D. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* **1988**, *29*, 1035–1041.
- (172) Fallingborg, J.; Christensen, L. A.; Ingeman-Nielsen, M.; Jacobsen, B. A.; Abildgaard, K.; Rasmussen, H. H. pH-profile and regional transit times of the normal gut measured by a radiotelemetry device. *Aliment. Pharmacol. Ther.* **1989**, *3*, 605–613.
- (173) Thomas, L. A.; Veysey, M. J.; French, G.; Hylemon, P. B.; Murphy, G. M.; Dowling, R. H. Bile acid metabolism by fresh human colonic contents: a comparison of caecal versus faecal samples. *Gut* **2001**, *49*, 835–842.
- (174) Walker, A. W.; Duncan, S. H.; McWilliam Leitch, E. C.; Child, M. W.; Flint, H. J. pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. *Appl. Environ. Microbiol.* **2005**, *71*, 3692–3700.
- (175) Duncan, S.; Louis, P.; Thomson, J.; Flint, H. The role of pH in determining the species composition of the human colonic microbiota. *Environ. Microbiol.* **2009**, *11*, 2112–2122.
- (176) Wong, J. M.; de Souza, R.; Kendall, C. W.; Emam, A.; Jenkins, D. J. Colonic health: fermentation and short chain fatty acids. *J. Clin. Gastroenterol.* **2006**, *40*, 235–243.
- (177) Windey, K.; De Preter, V.; Verbeke, K. Relevance of protein fermentation to gut health. *Mol. Nutr. Food Res.* **2012**, *56*, 184–196.
- (178) Hosseini, E.; Grootaert, C.; Verstraete, W.; Van de Wiele, T. Propionate as a health-promoting microbial metabolite in the human gut. *Nutr. Rev.* **2011**, *69*, 245–258.
- (179) Danielsson, H.; Gustafsson, B. On serum-cholesterol levels and neutral fecal sterols in germ-free rats; bile acids and steroids. *Arch. Biochem. Biophys.* **1959**, *83*, 482–485.
- (180) Carr, T. P.; Weller, C. L.; Schlegel, V. L.; Cuppett, S. L.; Guderian, D. M., Jr.; Johnson, K. R. Grain sorghum lipid extract reduces cholesterol absorption and plasma non-HDL cholesterol concentration in hamsters. *J. Nutr.* **2005**, *135*, 2236–2240.
- (181) Martínez, I.; Wallace, G.; Zhang, C.; Legge, R.; Benson, A. K.; Carr, T. P.; Moriyama, E. N.; Walter, J. Diet-induced metabolic improvements in a hamster model of hypercholesterolemia are strongly linked to alterations of the gut microbiota. *Appl. Environ. Microbiol.* **2009**, *75*, 4175–4184.
- (182) Reddy, B.; Mastromarino, A.; Wynder, E. Further leads on metabolic epidemiology of large bowel cancer. *Cancer Res.* **1975**, *35*, 3403–3406.
- (183) Holt, R. R.; Heiss, C.; Kelm, M.; Keen, C. L. The potential of flavanol and procyanidin intake to influence age-related vascular disease. *J. Nutr. Gerontol. Geriatr.* **2012**, *31*, 290–323.
- (184) Habauzit, V.; Morand, C. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: an update for clinicians. *Ther. Adv. Chronic Dis.* **2012**, *3*, 87–106.
- (185) Scalbert, A.; Morand, C.; Manach, C.; Rémésy, C. Absorption and metabolism of polyphenols in the gut and impact on health. *Biomed. Pharmacother.* **2002**, *56*, 276–282.
- (186) Manach, C.; Donovan, J. L. Pharmacokinetics and metabolism of dietary flavonoids in humans. *Free Radical Res.* **2004**, *38*, 771–785.
- (187) Crozier, A.; Del Rio, D.; Clifford, M. N. Bioavailability of dietary flavonoids and phenolic compounds. *Mol. Aspects Med.* **2010**, *31*, 446–467.
- (188) Spencer, J. P.; Schroeter, H.; Rechner, A. R.; Rice-Evans, C. Bioavailability of flavan-3-ols and procyanidins: gastrointestinal tract influences and their relevance to bioactive forms in vivo. *Antioxid. Redox Signal.* **2001**, *3*, 1023–1039.
- (189) Scalbert, A.; Williamson, G. Dietary intake and bioavailability of polyphenols. *J. Nutr.* **2000**, *130*, 2073S–2085S.
- (190) Bosscher, D.; Breynaert, A.; Pieters, L.; Hermans, N. Food-based strategies to modulate the composition of the intestinal microbiota and their associated health effects. *J. Physiol. Pharmacol.* **2009**, *60* (Suppl.6), 5–11.
- (191) Hollman, P. C.; Katan, M. B. Dietary flavonoids: intake, health effects and bioavailability. *Food Chem. Toxicol.* **1999**, *37*, 937–942.
- (192) Tuohy, K. M.; Conterno, L.; Gasperotti, M.; Viola, R. Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. *J. Agric. Food Chem.* **2012**, *60*, 8776–8782.
- (193) Moco, S.; Martin, F.-P. J.; Rezzi, S. Metabolomics view on gut microbiome modulation by polyphenol-rich foods. *J. Proteome Res.* **2012**, *11*, 4781–4790.
- (194) van Duynhoven, J.; Vaughan, E. E.; Jacobs, D. M.; Kemperman, R. A.; van Velzen, E. J.; Gross, G.; Roger, L. C.; Possemiers, S.; Smilde, A. K.; Doré, J.; Westerhuis, J. A.; Van de Wiele, T. Metabolic fate of polyphenols in the human superorganism. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108* (Suppl. 1), 4531–4538.
- (195) Gardana, C.; Canzi, E.; Simonetti, P. The role of diet in the metabolism of daidzein by human faecal microbiota sampled from Italian volunteers. *J. Nutr. Biochem.* **2009**, *20*, 940–947.
- (196) Bolca, S.; Possemiers, S.; Maervoet, V.; Huybrechts, L.; Heyerick, A.; Vervaeke, S.; Depypere, H.; De Keukeleire, D.; Bracke, M.; De Henaew, S.; Verstraete, W.; Van de Wiele, T. Microbial and dietary factors associated with the 8-prenylnaringenin producer phenotype: a dietary intervention trial with fifty healthy post-menopausal Caucasian women. *Br. J. Nutr.* **2007**, *98*, 950–959.
- (197) Shinohara, K.; Ohashi, Y.; Kawasumi, K.; Terada, A.; Fujisawa, T. Effect of apple intake on fecal microbiota and metabolites in humans. *Anaerobe* **2010**, *16*, 510–515.
- (198) Juśkiewicz, J.; Milala, J.; Jurgoński, A.; Król, B.; Zduńczyk, Z. Consumption of polyphenol concentrate with dietary fructo-oligosaccharides enhances cecal metabolism of quercetin glycosides in rats. *Nutrition* **2011**, *27*, 351–357.
- (199) Jurgoński, A.; Juśkiewicz, J.; Kowalska, K.; Zduńczyk, Z. Does dietary inulin affect biological activity of a grapefruit flavonoid-rich extract? *Nutr. Metab.* **2012**, *9*, 31.
- (200) Li, F.; Hullar, M. A.; Schwarz, Y.; Lampe, J. W. Human gut bacterial communities are altered by addition of cruciferous vegetables to a controlled fruit- and vegetable-free diet. *J. Nutr.* **2009**, *139*, 1685–1691.
- (201) Vendrame, S.; Guglielmetti, S.; Riso, P.; Arioli, S.; Klimis-Zacas, D.; Porrini, M. Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. *J. Agric. Food Chem.* **2011**, *59*, 12815–12820.
- (202) Guglielmetti, S.; Fracassetti, D.; Taverniti, V.; Del Bo', C.; Vendrame, S.; Klimis-Zacas, D.; Arioli, S.; Riso, P.; Porrini, M. Differential modulation of human intestinal bifidobacterium populations after consumption of a wild blueberry (*Vaccinium angustifolium*) drink. *J. Agric. Food Chem.* **2013**, *61*, 8134–8140.
- (203) Tzounis, X.; Rodriguez-Mateos, A.; Vulevic, J.; Gibson, G. R.; Kwik-Urbe, C.; Spencer, J. P. Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study. *Am. J. Clin. Nutr.* **2011**, *93*, 62–72.
- (204) Hervet-Hernández, D.; Pintado, C.; Rotger, R.; Goñi, I. Stimulatory role of grape pomace polyphenols on *Lactobacillus acidophilus* growth. *Int. J. Food Microbiol.* **2009**, *136*, 119–122.
- (205) Lee, H. C.; Jenner, A. M.; Low, C. S.; Lee, Y. K. Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Res. Microbiol.* **2006**, *157*, 876–884.
- (206) Tzounis, X.; Vulevic, J.; Kuhnle, G. G.; George, T.; Leonczak, J.; Gibson, G. R.; Kwik-Urbe, C.; Spencer, J. P. Flavanol monomer-induced changes to the human faecal microflora. *Br. J. Nutr.* **2008**, *99*, 782–792.
- (207) Puupponen-Pimiä, R.; Nohynek, L.; Meier, C.; Kähkönen, M.; Heinonen, M.; Hopia, A.; Oksman-Caldentey, K. Antimicrobial properties of phenolic compounds from berries. *J. Appl. Microbiol.* **2001**, *90*, 494–507.
- (208) Puupponen-Pimiä, R.; Nohynek, L.; Hartmann-Schmidlin, S.; Kähkönen, M.; Heinonen, M.; Määttä-Riihinen, K.; Oksman-Caldentey, K. M. Berry phenolics selectively inhibit the growth of intestinal pathogens. *J. Appl. Microbiol.* **2005**, *98*, 991–1000.

- (209) Rodríguez Vaquero, M. J.; Alberto, M. R.; Manca de Nadra, M. C. Antibacterial effect of phenolic compounds from different wines. *Food Control* **2007**, *18*, 93–101.
- (210) Duda-Chodak, A. The inhibitory effect of polyphenols on human gut microbiota. *J. Physiol. Pharmacol.* **2012**, *63*, 497–503.
- (211) Selma, M. V.; Espín, J. C.; Tomás-Barberán, F. A. Interaction between phenolics and gut microbiota: role in human health. *J. Agric. Food Chem.* **2009**, *57*, 6485–6501.
- (212) FAO/WHO. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria; available at http://www.fao.org/es/ESN/food/foodandfoo_probio_en.stm.
- (213) Prithy, R.; Yoshinori, M. Recent advances in the role of probiotics in human inflammation and gut health. *J. Agric. Food Chem.* **2012**, *60*, 8249–8256.
- (214) Tuohy, K. M.; Robert, H. M.; Smejkal, C. W.; Gibson, G. R. Using probiotics and prebiotics to improve gut health. *Drug Discov. Today* **2003**, *8*, 692–700.
- (215) Lourens-Hattingh, A.; Viljoen, B. C. Yogurt as probiotic carrier food. *Int. Dairy J.* **2001**, *11*, 1–17.
- (216) Saxelin, M.; Lassig, A.; Karjalainen, H.; Tynkkynen, S.; Surakka, A.; Vapaatalo, H.; Järvenpää, S.; Korpela, R.; Mutanen, M.; Hatakka, K. Persistence of probiotic strains in the gastrointestinal tract when administered as capsules, yoghurt, or cheese. *Int. J. Food Microbiol.* **2010**, *144*, 293–300.
- (217) Lebeer, S.; Vanderleyden, J.; De Keersmaecker, S. C. Genes and molecules of lactobacilli supporting probiotic action. *Microbiol. Mol. Biol. Rev.* **2008**, *72*, 728–764.
- (218) Marco, M. L.; Bongers, R. S.; de Vos, W. M.; Kleerebezem, M. Spatial and temporal expression of *Lactobacillus plantarum* genes in the gastrointestinal tracts of mice. *Appl. Environ. Microbiol.* **2007**, *73*, 124–132.
- (219) Marco, M. L.; de Vries, M. C.; Wels, M.; Molenaar, D.; Mangell, P.; Ahrne, S.; de Vos, W. M.; Vaughan, E. E.; Kleerebezem, M. Convergence in probiotic *Lactobacillus* gut-adaptive responses in humans and mice. *ISME J.* **2010**, *4*, 1481–1484.
- (220) Marco, M. L.; Peters, T. H.; Bongers, R. S.; Molenaar, D.; van Hemert, S.; Sonnenburg, J. L.; Gordon, J. I.; Kleerebezem, M. Lifestyle of *Lactobacillus plantarum* in the mouse caecum. *Environ. Microbiol.* **2009**, *11*, 2747–2757.
- (221) Sanders, M. E.; Marco, M. L. Food formats for effective delivery of probiotics. *Annu. Rev. Food Sci. Technol.* **2010**, *1*, 65–85.
- (222) Kim, S. W.; Suda, W.; Kim, S.; Oshima, K.; Fukuda, S.; Ohno, H.; Morita, H.; Hattori, M. Robustness of gut microbiota of healthy adults in response to probiotic intervention revealed by high-throughput pyrosequencing. *DNA Res.* **2013**, *20*, 241–253.
- (223) Filteau, M.; Matamoros, S.; Savard, P.; Roy, D. Molecular monitoring of fecal microbiota in healthy adults following probiotic yogurt intake. *PharmaNutrition* **2013**, *1*, DOI: 10.1016/j.phanu.2013.05.002.
- (224) Sonnenburg, J. L.; Chen, C. T.; Gordon, J. I. Genomic and metabolic studies of the impact of probiotics on a model gut symbiont and host. *PLoS Biol.* **2006**, *4*, e413.
- (225) Martin, F.-P. J.; Wang, Y.; Sprenger, N.; Yap, I. K. S.; Lundstedt, T.; Lek, P.; Rezzi, S.; Ramadan, Z.; van Bladeren, P.; Fay, L. B.; Kochhar, S.; Lindon, J. C.; Holmes, E.; Nicholson, J. K. Probiotic modulation of symbiotic gut microbial-host metabolic interactions in a humanized microbiome mouse model. *Mol. Syst. Biol.* **2008**, *4*, 157.
- (226) Lozupone, C. A.; Stombaugh, J. I.; Gordon, J. I.; Jansson, J. K.; Knight, R. Diversity, stability and resilience of the human gut microbiota. *Nature* **2012**, *489*, 220–230.
- (227) O'Sullivan, A.; He, X.; McNiven, E. S.; Haggarty, N. W.; Lönnerdal, B.; Slupsky, C. M. Early diet impacts infant rhesus gut microbiome, immunity, and metabolism. *J. Proteome Res.* **2013**, *12*, 2833–2845.
- (228) Cox, M. J.; Huang, Y. J.; Fujimura, K. K.; Liu, J. T.; McKean, M.; Boushey, H. A.; Segal, M. R.; Brodie, E. L.; Cabana, M. D.; Lynch, S. V. *Lactobacillus casei* abundance is associated with profound shifts in the infant gut microbiome. *PLoS One* **2010**, *5*, e8745.
- (229) Bull-Ottersson, L.; Feng, W.; Kirpich, I.; Wang, Y.; Qin, X.; Liu, Y.; Gobejishvili, L.; Joshi-Barve, S.; Ayvaz, T.; Petrosino, J.; Kong, M.; Barker, D.; McClain, C.; Barve, S. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of *Lactobacillus rhamnosus* GG treatment. *PLoS One* **2013**, *8*, e53028.
- (230) Park, D. Y.; Ahn, Y. T.; Park, S. H.; Huh, C. S.; Yoo, S. R.; Yu, R.; Sung, M. K.; McGregor, R. A.; Choi, M. S. Supplementation of *Lactobacillus curvatus* HY7601 and *Lactobacillus plantarum* KY1032 in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. *PLoS One* **2013**, *8*, e59470.
- (231) Nakamura, S.; Hongo, R.; Moji, K.; Oku, T. Suppressing effect of partially hydrolyzed guar gum on transitory diarrhea induced by ingestion of maltitol and lactitol in healthy humans. *Eur. J. Clin. Nutr.* **2007**, *61*, 1086–1093.
- (232) Livesey, G. Tolerance of low-digestible carbohydrates: a general view. *Br. J. Nutr.* **2001**, *85* (Suppl. 1), S7–S16.
- (233) Oku, T.; Nakamura, S. Digestion, absorption, fermentation, and metabolism of functional sugar substitutes and their available energy. *Pure Appl. Chem.* **2002**, *74*, 1253–1261.
- (234) Beards, E.; Tuohy, K.; Gibson, G. Bacterial, SCFA and gas profiles of a range of food ingredients following in vitro fermentation by human colonic microbiota. *Anaerobe* **2010**, *16*, 420–425.
- (235) Lian-Loh, R.; Birch, G. G.; Coates, M. E. The metabolism of maltitol in the rat. *Br. J. Nutr.* **1982**, *48*, 477–481.
- (236) Beards, E.; Tuohy, K.; Gibson, G. A human volunteer study to assess the impact of confectionery sweeteners on the gut microbiota composition. *Br. J. Nutr.* **2010**, *104*, 701–708.
- (237) Abou-Donia, M. B.; El-Masry, E. M.; Abdel-Rahman, A. A.; McLendon, R. E.; Schiffman, S. S. Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. *J. Toxicol. Environ. Health A* **2008**, *71*, 1415–1429.
- (238) Gostner, A.; Blaut, M.; Schäffer, V.; Kozianowski, G.; Theis, S.; Klingenberg, M.; Dombrowski, Y.; Martin, D.; Ehrhardt, S.; Taras, D.; Schwiertz, A.; Kleessen, B.; Lührs, H.; Schaubert, J.; Dörbath, D.; Menzel, T.; Scheppach, W. Effect of isomalt consumption on faecal microflora and colonic metabolism in healthy volunteers. *Br. J. Nutr.* **2007**, *95*.
- (239) Payne, A.; Chassard, C.; Lacroix, C. Gut microbial adaptation to dietary consumption of fructose, artificial sweeteners and sugar alcohols: implications for host-microbe interactions contributing to obesity. *Obes. Rev.* **2012**, *13*, 799–809.
- (240) Bafana, A.; Devi, S. S.; Chakrabarti, T. Azo dyes: past, present and the future. *Environ. Rev.* **2011**, *19*, 350–371.
- (241) Van den Mooter, G.; Samyn, C.; Kinget, R. Azo polymers for colon-specific drug delivery. *Int. J. Pharm.* **1992**, *87*, 37–46.
- (242) Yang, L.; Chu, J. S.; Fix, J. A. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. *Int. J. Pharm.* **2002**, *235*, 1–15.
- (243) Chung, K. T.; Stevens, S. E., Jr.; Cerniglia, C. E. The reduction of azo dyes by the intestinal microflora. *Crit. Rev. Microbiol.* **1992**, *18*, 175–190.
- (244) Brown, J. P. Reduction of polymeric azo and nitro dyes by intestinal bacteria. *Appl. Environ. Microbiol.* **1981**, *41*, 1283–1286.
- (245) Bragger, J. L.; Lloyd, A. W.; Soozandehfar, S. H.; Bloomfield, S. F.; Marriott, C.; Martin, G. P. Investigations into the azo reducing activity of a common colonic microorganism. *Int. J. Pharm.* **1997**, *157*, 61–71.
- (246) Rafii, F.; Franklin, W.; Cerniglia, C. Azoreductase activity of anaerobic bacteria isolated from human intestinal microflora. *Appl. Environ. Microbiol.* **1990**, *56*, 2146–2151.
- (247) Rafii, F.; Cerniglia, C. Reduction of azo dyes and nitroaromatic compounds by bacterial enzymes from the human intestinal tract. *Environ. Health Perspect.* **1995**, *103* (Suppl. 5), 17–19.
- (248) Xu, H.; Heinze, T. M.; Paine, D. D.; Cerniglia, C. E.; Chen, H. Sudan azo dyes and Para Red degradation by prevalent bacteria of the human gastrointestinal tract. *Anaerobe* **2010**, *16*, 114–119.

- (249) Pan, H.; Feng, J.; He, G. X.; Cerniglia, C.; Chen, H. Evaluation of impact of exposure of Sudan azo dyes and their metabolites on human intestinal bacteria. *Anaerobe* **2012**, *18*, 445–453.
- (250) Carbonero, F.; Benefiel, A. C.; Alizadeh-Ghamsari, A. H.; Gaskins, H. R. Microbial pathways in colonic sulfur metabolism and links with health and disease. *Front. Physiol.* **2012**, *3*, 448.
- (251) Florin, T.; Neale, G.; Gibson, G.; Christl, S.; Cummings, J. Metabolism of dietary sulphate: absorption and excretion in humans. *Gut* **1991**, *32*, 766–773.
- (252) Lewis, S.; Cochrane, S. Alteration of sulfate and hydrogen metabolism in the human colon by changing intestinal transit rate. *Am. J. Gastroenterol.* **2007**, *102*, 624–633.
- (253) Florin, T. H. J.; Neale, G.; Goretzki, S.; Cummings, J. H. The sulfate content of foods and beverages. *J. Food Compos. Anal.* **1993**, *6*, 140–151.
- (254) Magee, E. A.; Curno, R.; Edmond, L. M.; Cummings, J. H. Contribution of dietary protein and inorganic sulfur to urinary sulfate: toward a biomarker of inorganic sulfur intake. *Am. J. Clin. Nutr.* **2004**, *80*, 137–142.
- (255) Forsberg, C. W. Sulfide production from cysteine by *Desulfovibrio desulfuricans*. *Appl. Environ. Microbiol.* **1980**, *39*, 453–455.
- (256) Nava, G. M.; Carbonero, F.; Ou, J.; Benefiel, A. C.; O'Keefe, S. J.; Gaskins, H. R. Hydrogenotrophic microbiota distinguish native Africans from African and European Americans. *Environ. Microbiol. Rep.* **2012**, *4*, 307–315.
- (257) Gibson, G.; Cummings, J.; Macfarlane, G.; Allison, C.; Segal, I.; Vorster, H.; Walker, A. Alternative pathways for hydrogen disposal during fermentation in the human colon. *Gut* **1990**, *31*, 679–683.
- (258) Nava, G.; Carbonero, F.; Croix, J.; Greenberg, E.; Gaskins, H. Abundance and diversity of mucosa-associated hydrogenotrophic microbes in the healthy human colon. *ISME J.* **2012**, *6*, 57–70.
- (259) Gibson, G. R. Physiology and ecology of the sulphate-reducing bacteria. *J. Appl. Microbiol.* **1990**, *69*, 769–797.
- (260) Lovley, D. R.; Dwyer, D. F.; Klug, M. J. Kinetic analysis of competition between sulfate reducers and methanogens for hydrogen in sediments. *Appl. Environ. Microbiol.* **1982**, *43*, 1373–1379.
- (261) Elferink, J. W. H. S. O.; Visser, A.; Pol, L. W. H.; Stams, A. J. M. Sulfate reduction in methanogenic bioreactors. *FEMS Microbiol. Rev.* **1994**, *15*, 119–136.
- (262) Linden, D. R. Hydrogen sulfide signaling in the gastrointestinal tract. *Antioxid. Redox Signal.* **2013**, DOI: 10.1089/ars.2013.5312.
- (263) Christl, S. U.; Gibson, G. R.; Cummings, J. H. Role of dietary sulphate in the regulation of methanogenesis in the human large intestine. *Gut* **1992**, *33*, 1234–1238.
- (264) Florin, T.; Woods, H. Inhibition of methanogenesis by human bile. *Gut* **1995**, *37*, 418–421.
- (265) Florin, T. H.; Jabbar, I. A. A possible role for bile acid in the control of methanogenesis and the accumulation of hydrogen gas in the human colon. *J. Gastroenterol. Hepatol.* **1994**, *9*, 112–117.
- (266) Nakamura, N.; Lin, H.; McSweeney, C.; Mackie, R.; Gaskins, H. Mechanisms of microbial hydrogen disposal in the human colon and implications for health and disease. *Annu. Rev. Food Sci. Technol.* **2010**, *1*, 363–395.
- (267) Gibson, G.; Cummings, J.; Macfarlane, G. Competition for hydrogen between sulphate-reducing bacteria and methanogenic bacteria from the human large intestine. *J. Appl. Bacteriol.* **1988**, *65*, 241–247.
- (268) Hartmann, P.; Chen, W.-C.; Schnabl, B. The intestinal microbiome and the leaky gut as therapeutic targets in alcoholic liver disease. *Front. Physiol.* **2012**, *3*, 402.
- (269) Yan, A. W.; Fouts, D. E.; Brandl, J.; Stärkel, P.; Torralba, M.; Schott, E.; Tsukamoto, H.; Nelson, K. E.; Brenner, D. A.; Schnabl, B. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* **2011**, *53*, 96–105.
- (270) Mutlu, E.; Keshavarzian, A.; Engen, P.; Forsyth, C.; Sikaroodi, M.; Gillevet, P. Intestinal dysbiosis: a possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. *Alcohol. Clin. Exp. Res.* **2009**, *33*, 1836–1846.
- (271) Mutlu, E.; Gillevet, P.; Rangwala, H.; Sikaroodi, M.; Naqvi, A.; Engen, P.; Kwasny, M.; Lau, C.; Keshavarzian, A. Colonic microbiome is altered in alcoholism. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2012**, *302*, G966–G978.
- (272) McNiven, E. M. S.; German, J. B.; Slupsky, C. M. Analytical metabolomics: nutritional opportunities for personalized health. *J. Nutr. Biochem.* **2011**, *22*, 995–1002.
- (273) Llorach, R.; Garcia-Aloy, M.; Tulipani, S.; Vazquez-Fresno, R.; Andres-Lacueva, C. Nutrimental strategies to develop new biomarkers of intake and health effects. *J. Agric. Food Chem.* **2012**, *60*, 8797–8808.