Published in final edited form as:
Nutr Clin Pract. 2012 April ; 27(2): 201–214. doi:10.1177/0884533611436116.

Effects of Gut Microbes on Nutrient Absorption and Energy Regulation

Rosa Krajmalnik-Brown, PhD[1], **Zehra-Esra Ilhan**[1], **Dae-Wook Kang, PhD**[1], and **John K. DiBaise, MD**[2]

[1]Biodesign Institute at Arizona State University, Tempe, Arizona

[2]Mayo Clinic, Scottsdale, Arizona

Abstract

Malnutrition may manifest as either obesity or undernutrition. Accumulating evidence suggests that the gut microbiota plays an important role in the harvest, storage, and expenditure of energy obtained from the diet. The composition of the gut microbiota has been shown to differ between lean and obese humans and mice; however, the specific roles that individual gut microbes play in energy harvest remain uncertain. The gut microbiota may also influence the development of conditions characterized by chronic low-level inflammation, such as obesity, through systemic exposure to bacterial lipopolysaccharide derived from the gut microbiota. In this review, the role of the gut microbiota in energy harvest and fat storage is explored, as well as differences in the microbiota in obesity and undernutrition.

Keywords

microbiome; metagenome; obesity; malnutrition; absorption; energy metabolism

Malnutrition can be defined as either the inadequate or excessive consumption of dietary substances ultimately leading to the development of undernutrition or obesity, respectively, and their corresponding health sequelae. Selective pressures throughout evolution appear to have programmed animals to protect energy stores. In part, the obesity epidemic may be related to these physiologic biases such that, although the availability and stability of the food supply have improved over the past several centuries, humans remain physiologically predisposed to protect energy stores through the accumulation of adipose tissue. Therefore, as diets have changed and energy-dense foods have become readily available, obesity rather than undernutrition has become the primary concern in developed nations.

The microbes present within the gastrointestinal tract (ie, gut microbiota) have coevolved with the human host to perform a number of functions the host would otherwise be unable to accomplish on its own. Although incompletely understood, the gut microbiota is implicated in a variety of host functions involving intestinal development and function, micronutrient synthesis, and drug metabolism. Accumulating evidence suggests that the gut microbiota

Corresponding Author: John K. DiBaise, MD, Mayo Clinic, Division of Gastroenterology, 13400 East Shea Blvd, Scottsdale, AZ 85259; dibaise.john@mayo.edu.

Financial disclosure: Supported in part by grant R01DK090379 (to RKB and JKD) from the National Institute of Diabetes and Digestive and Kidney Diseases.

also plays an important role in the harvest, storage, and expenditure of energy obtained from the diet. The preponderance of the evidence demonstrates that germ-free mice are protected against obesity and that the transfer of gut microbes from conventionally raised animals to germ-free animals results in dramatic increases in body fat content and insulin resistance. Moreover, the composition of the gut microbiota has been shown to differ between lean and obese humans and mice and to change rapidly in response to dietary factors. The gut microbiota may also influence the development of conditions characterized by chronic low-level inflammation, such as obesity and type 2 diabetes, through systemic exposure to bacterial lipopolysaccharide derived from the intestinal microbiota.

To better define our nutrition status, an understanding of our microbial differences and their origins is necessary. In this review, the role of the gut microbiota in energy harvest and fat storage will be explored as will differences in the microbiota in obesity and undernutrition. Finally, potential mechanisms for modifying the gut microbiota as a therapeutic strategy for undernutrition, obesity, and other metabolic disorders will be examined.

Development and Plasticity of the Commensal Gut Microbiota

The gut microbiota can be classified into 3 domains based on molecular phylogeny (ie, 16S ribosomal ribonucleic acid [rRNA] sequence similarities and differences): Eukarya, Bacteria, and Archaea. Recall that Eukarya consists of organisms with cells that contain complex structures enclosed within membranes, most notably the nucleus. In contrast, Bacteria are the predominant members of the gut microbiota. The sequencing of 16S rRNA genes from amplified bacterial nucleic acids extracted from fecal material or mucosal samples using high-throughput techniques has greatly improved the ability to identify and classify bacteria.[1] Using these techniques, the gastrointestinal tract in an individual adult human has been estimated to contain approximately 500 to 1000 distinct bacterial species.[2,3] Two divisions of Bacteria, *Bacteroidetes* and *Firmicutes*, dominate, accounting for >90% of all phylotypes, whereas a single hydrogen-consuming methanogen, *Methanobrevibacter smithii*, dominates the Archaea domain.[3]

Infancy is characterized by microbial plasticity, whereby the rapid colonization by groups of microbes can change in response to events such as illness, medications, or changes in diet. The age-related mechanisms involved in the development of the adult human microbiota are poorly understood. Current evidence suggests that the gastrointestinal microbiota is established within the first few years of life in a process that is influenced by a variety of host (genetics) and external factors (diet, environmental exposures).[4,5]

In the newborn, most bacterial species are acquired during the birthing process. Birth by vaginal delivery or caesarean section (C-section) affects the newborn's initial microbial profile. The vaginal microbial communities appear to change during pregnancy to provide newborns with beneficial microbes; at the time of delivery, the vagina is dominated by *Lactobacillus* and *Prevotella* spp.[6] Vaginally delivered newborns are initially colonized with the same microbiota as their mothers and only later develop the distinct microbial communities found as adults. In contrast, infants born by C-section harbor microbial communities that initially resemble those of the skin, comprising *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp,[5,6] and maintain differences in their gut microbiota for several months after birth. These differences in the microbial communities resulting from the method of delivery may have important implications for infant development and health, including the observation of an increased susceptibility to certain pathogens and atopic diseases in babies delivered by C-section.[7,8]

Most important in the transformation of the microbiota from the infant to the adult type are effects of the microbiota itself, developmental changes in the gut environment, and the

transition to an adult diet.[9] The specific concentration and type of bacteria within the gastrointestinal tract are influenced by microhabitat variations throughout the gut involving such factors as pH, oxygen content, and exposure to bile, pancreatic secretions, and nutrients. The microbial habitats of the host select for a group of microbial communities from the microbiota available for colonization, and host genetics influence the composition of the microbiota by influencing the environmental conditions of the habitats.[10] Bacterial counts rise from the proximal to the distal end of the gastrointestinal tract, and a gradual transition from aerobic to anaerobic organisms occurs in more distal segments of the gut. Once across the ileocecal valve, bacterial counts rise from 10^7–10^9 organisms/mL in the terminal ileum to approximately 10^{10}–10^{12} organisms/mL in the colon.[11]

Diet is one of the most important determinants of microbial diversity within the gut.[12] A recent study comparing the gut microbiome of rural children in Burkina Faso with children in Italy showed that *Bacteroidetes* were far more abundant in the microbiomes of African children and that the specific types that were increased were well suited to harvest energy from their plant-rich diet.[13] These findings raise the possibility that microbiomes vary geographically with their hosts, in part because they are adapted to local diets. Other dietary factors that have occurred over the past few decades that have likely affected the human gut microbiome include differences in overall energy intake and the relative proportions of the different macronutrients and micronutrients in the diet, as well as differences in food modification and preparation.

Although the gut microbiota is thought to remain fairly stable throughout the lifetime of an individual,[14] transient changes may occur, and some factors can lead to long-term changes in the human gut microbiota. In particular, antibiotics have a dramatic effect on the gut microbiota, and restoration to its prior diversity varies among individuals.[15] Changes in diet may also cause significant, and potentially long-term, alterations in the gut microbiota. Jumpertz et al[16] recently showed that in as short as 3 days, the gut microbiota structure in humans can be drastically altered by variations in calorie intake (from 2400–3400 kcal/d). A study of mice recipients of microbiome transplantation also showed that switching from a low-fat, plant polysaccharide diet to a high-fat, high-sugar Western diet altered gut community structure and metabolic function within 1 day.[17] Aging itself also has an effect on the stability of gut microbial communities. Aging is associated with reduced immune function, increased disease and use of medications, and changes in nutrition—all of which may modify the gut microbiota.[18] Nevertheless, the general intraindividual stability of the gut microbiota is largely based on recognition and tolerance of the infant-acquired microbiota by the gut immune system, which, by being exposed to and sampling microbial antigens, identifies these as normal.[19] In contrast to the intraindividual stability described, interindividual differences in intestinal microbiota show more diversity, as do differences between luminal (ie, stool) and mucosal (ie, epithelial) compositions.[3] Importantly, comparative studies of the gut microbiota of monozygotic and dizygotic twins have emphasized the influence of host genotype over diet, age, and lifestyle,[20] although conflicting information exists.[21]

Despite these interindividual differences in gut microbiota, findings from a recent study provide further insights between human fecal microbiomes across different geographic populations by identifying 3 robust clusters referred to as “enterotypes.”[22] The enterotypes were found to be mostly driven by species composition; however, functional differences were also important, reflecting a possible impact on symbiotic interrelations with the human host. Interestingly, host properties such as body mass index, age, and gender did not explain the observed enterotype clusters. The presence of these 3 enterotypes was recently confirmed[23] and was shown to be linked to long-term (but not short-term) dietary patterns, particularly protein and animal fat vs carbohydrates.

Role of Microorganisms in Energy Regulation

Production of Short-Chain Fatty Acids and Hydrogen Metabolism

The stomach and proximal small intestine are responsible for most nutrient digestion and absorption in humans. In an otherwise healthy individual without prior surgical resection of the small bowel, about 85% of carbohydrates, 66%–95% of proteins, and all fats are absorbed before entering the large intestine.[24,25] The indigestible carbohydrates and proteins that the colon receives represent from 10%–30% of the total ingested energy[26,27] and, without the activity of the colonic microbiota, would generally be eliminated via the stool without further absorption because the human large intestine has limited digestive capability.

In the colon, microorganisms ferment starch (including resistant starch), unabsorbed sugars, cellulosic and noncellulosic polysaccharides,[28] and mucins[29] into short-chain fatty acids (SCFAs)[30] and gases such as CO_2, CH_4, and H_2.[31,32] The type and quantity of SCFA and gases produced in the gut depend on multiple factors,[32] including age, diet,[33] especially the availability of nondigested carbohydrates,[34] the gut microbial community composition,[35] gut transit time,[36] pH of the colon,[37] and the segment of the colon.[38] The major SCFAs produced as a result of carbohydrate and protein fermentation are acetate, propionate, and butyrate.[28] In addition to the major SCFAs, formate, valerate, caproate, isobutyrate, 2-methyl-butyrate, and isovalerate can be produced during the breakdown of branched-chain amino acids.[28]

Microorganisms in the gut work in symbiosis; the manner in which they interact with each other and with their environment will determine the final metabolic and environmental outcome. Because much of the gut is anaerobic, disposal of H_2 strongly influences microbial interactions. As illustrated in Figure 1, fermentation breaks down complex organic compounds producing SCFA and H_2. H_2 is then excreted in the breath[39] and/or consumed (oxidized) by 3 groups of microorganisms: methanogens, acetogens (homo-acetogens), and/or sulfate reducers, all of which coexist in the colon in differing proportions.[40] These H_2-based interactions are critical for fermentation to proceed because accumulation of H_2 in the colon inhibits further fermentation.[30] Our group and others have verified the enrichment of H_2-oxidizing methanogens in obese compared with normal-weight individuals.[41–43] Of the homo-acetogens detected in the human gut,[44–46] many belong to the *Firmicutes* phylum, and this may partly explain why an increase in *Firmicutes* has been demonstrated in obesity.[47] Sulfate-reducing bacteria (SRB) may be present within the gut even when sulfate is absent as an electron acceptor. In this case, they act as fermenters and, in some instances, may function as H_2-producing acetogens, [48] which convert acetate to CO_2 and H_2.

With reference to the 3 enterotypes described previously,[22] each enterotype was defined by the variation of 3 genera: *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2), and *Ruminococcus* (enterotype 3).[22] The key microorganisms within each enterotype are involved in degradation of polymers such as plant carbohydrates. The principal microorganisms in enterotypes 1 and 2 interact with other community members to achieve sugar or mucin degradation and are intimately involved in H_2 transfer and disposal. Interestingly, the enriched genera within each enterotype were shown to use different routes to generate energy from fermentable colonic substrates, suggesting that they could be triggered by the 3 distinct pathways for hydrogen disposal described above. Indeed, despite their low abundance, the sulfate reducer, *Desulfovibrio*, and methanogen, *Methanobrevibacter*, were found to be enriched in enterotypes 1 and 3, respectively.

Absorption of Monosaccharides and SCFA by the Host Epithelium

Monosaccharides are directly absorbed by the intestinal epithelium via monosaccharide transporters.[49,50] In a healthy individual consuming a typical Western diet, about 100–200 mM SCFAs are produced per day in the large intestine,[51,52] of which about 90%–95% are absorbed in the colon.[25] The molar ratio of acetate to propionate and to butyrate varies around 40:40:20 to 75:15:10 depending on the diet consumed.[26,28,53] The absorption of SCFA is an efficient process involving passive diffusion or ion exchange.[51,54]

Absorbed SCFAs are used as energy for the colonocytes or transported to various peripheral tissues for further metabolism.[32] Butyrate is the colonic epithelial cells' preferred nutrient for their metabolism and development.[51,52] Substantial amounts of propionate traverse the colonocyte and are transported to the liver,[55] where it serves as a substrate for gluconeogenesis or regulates cholesterol synthesis.[55,56] Acetate is the principal SCFA in the blood and is an important energy source to peripheral tissues, including the liver, where acetate is used for lipogenesis and cholesterol synthesis.[26,51] SCFAs absorbed in the colon contribute 6%–10% of the entire energy requirements in humans, and their contribution likely increases in humans who ingest more dietary fiber.[26,57] Although SCFAs account for a relatively small portion of energy acquisition, their impact on energy balance in humans is significant because of other roles they play in energy regulation as discussed in the following sections.[56]

SCFAs and Obesity

The abundance of SCFAs and their concentration in the colon has recently been associated with the health of humans[31,32,58] and, pertinent to this review, linked to obesity.[59,60] Transplantation of the gut microbiome from obese and lean mice to germ-free mice resulted in higher acetate and butyrate production in obese microbiome recipients.[61] In humans, Schwiertz et al[35] reported a greater concentration of total SCFAs, particularly propionate, in fecal samples of obese adults compared with their lean counterparts. These observations are supported by a study conducted in obese and normal-weight children.[60] Although fecal acetate, glucose, and lactate concentrations were relatively similar in both groups, butyrate, propionate, and intermediate fermentation compounds such as formate and isobutyrate were significantly higher in the obese children.

Host-Microbial Mutualism in Energy Harvest

Microbes in the large intestine allow the host to salvage energy from otherwise indigestible carbohydrates and proteins by providing a variety of enzymes required for their metabolism.[62,63] For example, *Bacteroides thetaiotaomicron* (*B theta*), a prominent commensal gut microbe, produces 226 predicted glycoside hydrolases and 15 polysaccharide lyases, whereas the human genome only contains 98 potential glycoside hydrolases.[63,64] Therefore, the gut microbiota provides the human host an ability to degrade plant polysaccharides, enhancing the host's energy balance. The genes involved in the metabolism of starch, sucrose, glucose, galactose, fructose, arabinose, mannose, and xylose, as well as fucose from host mucus, are enriched in the distal colon microbiome.[2] Cluster of Orthologous Groups (COG) analysis has shown that the gut microbiome is dominated by genes that drive production of acetate, butyrate, lactate, and succinate.[2] The gut microbiome is also enriched in genes that code for amino acid and vitamin synthesis and enzymes that detoxify xenobiotics such as β-glucosidase.[2]

Enrichment of some bacterial genes in the gut microbiome has recently been linked to obesity. In an obese microbiome, *Eubacterium rectale* (a *Firmicutes*) genes that encode for primary fermentation enzymes that digest dietary polysaccharides, α- and β-galactosidases that generate acetate and butyrate, and ABC transporters were all found to be enriched.[61]

Another study involving monozygotic and dizygotic twins showed a higher abundance of *Bacteroidetes* and an enrichment of genes related to carbohydrate metabolism in lean individual microbiomes, whereas *Firmicutes* dominated the obese microbiome, which was enriched with genes related to nutrient transporters.[21] In addition to a transporter-related mechanism, members of *Firmicutes* such as the *Ruminococcus* genus can also degrade cellulose and produce acetate, succinate, and ethanol.[65]

Fat Storage: Lipoprotein Lipase Activity and Gut Microorganisms

Intestinal microbes affect energy balance through metabolites they produce by regulating gene expression via complex mechanisms initiated by monosaccharides and SCFAs (Figure 2).[64] The gut microbiota induces monosaccharide cellular uptake[66] and stimulates hepatic triglyceride production (lipogenesis) by activating the transcription factors, carbohydrate response element binding protein (ChREBP), and sterol response element binding protein (SREBP).[50,67] The product of hepatic lipogenesis, triacylglycerols, are secreted from the liver to the bloodstream in the form of very low-density lipoprotein (VLDL) and chylomicrons and influence host nutrient balance and insulin resistance.

SCFAs also act as signaling molecules that interact with the G-protein-coupled receptors, Gpr41 and Gpr43, expressed on adipocytes and intestinal epithelium.[68–70] Propionate and butyrate have higher activity than acetate toward the Gpr41 receptor; however, all 3 SCFAs share equal potency toward GPR43.[68,71] Following Gpr41 activation, SCFAs stimulate leptin expression, which suppresses appetite.[70] Samuel et al[72] emphasized the role of Gpr41 as a key regulator between microbial-host communications. In their investigation, mice deficient in Gpr41 (*Gpr41−/−*) weighed significantly less than germ-free and wild-type mice when both types of mice were colonized by gut microbes.[72] It was speculated that the weight gain in the wild-type mice was due to an increased expression of the gut-derived hormone, peptide YY (PYY), which inhibits gut motility, thereby allowing more intestinal epithelial contact time in which to extract and absorb energy.[72,73] Although Gpr43 binding by SCFAs is known to inhibit inflammatory responses,[74] it also participates in energy regulation. Xiong et al[70] observed an increase in both leptin expression and adipogenesis via interactions with Gpr43 in the adipose tissue of mice.[75]

Energy balance is also associated with another key modulator, fasting-induced adipocyte factor (Fiaf). Reduced expression of Fiaf induces the activity of circulating lipoprotein lipase (LPL),[50] which hydrolyzes circulating triacylglycerols to free fatty acid (FFA) at various peripheral tissues.[76] The distribution of FFA deposit is not well known, but a high ratio of adipose tissue to muscle-LPL activity directs more FFA to adipose tissues, while a low ratio induces more FFA deposit to muscles.[77,78] The expansion of adipose tissue, in turn, results in an inability to store surplus FFA, which raises blood FFA levels and contributes to insulin resistance.[79] Backhed et al[80] showed that *B theta* monocolonized mice increased their body fat because of bacterial suppression of Fiaf.[22] Germ-free (GF) knockout mice lacking Fiaf (*Fiaf−/−*) have also been shown to be susceptible to diet-induced obesity because of a lower expression of the peroxisomal proliferator-activated receptor coactivator (Pgc-1α) that increases expression of genes regulating fatty acid oxidation.

Adipocytes have an important role in obesity as a source of hormones, such as leptin and adiponectin.[81] Adipocytes sense the increase of SCFA levels produced by intestinal microbe fermentation and respond by inducing leptin production. Leptin signals the brain to regulate the appetite and energy expenditure, thereby tightly connecting host energy balance.[82] Adiponectin is associated with adenosine monophosphate-activated protein kinase (AMPK), an enzyme that monitors cellular energy status and stimulates fatty acid oxidation in peripheral tissues. Increased AMPK activity was shown to prevent GF mice from diet-induced obesity.[80] In obesity, the level of adiponectin decreases,[83] causing a deactivation of

AMPK and leading to a reduction in fatty acid oxidation and an increased influx of free fatty acids into the liver.[84]

Gut Microbes and Undernutrition

Worldwide, nearly a billion people suffer from undernutrition of varying degrees.[85] Undernutrition may present with a spectrum of clinical manifestations ranging from asymptomatic micronutrient deficiencies to severely symptomatic protein-energy malnutrition in the forms of kwashiorkor and marasmus. Importantly, undernutrition contributes in some manner to over half the deaths occurring annually in the nearly 10 million children younger than age 5 years.[86] Even the children who survive periods of undernutrition can suffer long-term sequelae, including growth retardation and neurodevelopmental deficits.[87] Furthermore, the exposure to undernutrition in utero may lead to large and long-term negative mental and physical sequelae.[88] Although food availability, socioeconomic factors, and genetics influence the development of undernutrition, the underlying mechanisms remain poorly defined. The gut microbiota may contribute to the risk and pathogenesis of undernutrition through effects on nutrient metabolism and immune function. In addition, under-nutrition in childhood could affect the development of the gut microbiome and its metabolic capabilities, leading to metabolic dysfunction and contributing to the sequelae of undernutrition. Very little is known about the microbial diversity in undernutrition. Further study in this area is critical because identifying how undernutrition affects the gut microbiota will likely have important implications for improving its clinical consequences. Furthermore, modifying the gut microbiota may be used as a strategy to counter undernutrition.

Gut Microbes and Obesity

Abundance of Microbial Divisions and Important Functions in the Host

The development of metagenomics and high-throughput sequencing has expanded our knowledge of the microbial composition and gene content of the gut microbiome and has led to insights into the role of the gut microbiota in health and disease.[36] Major differences in the abundance of major phyla, reduction in bacterial diversity, and changes in bacterial gene expression and, therefore, the metabolic function of the distal gut have been detected in association with numerous disease states, including obesity.[17,89] Based on a recent metagenomics study, 75% of microbial genes associated with obesity belonged to *Actinobacteria* and 25% to *Firmicutes*, whereas 42% of genes associated with leanness belonged to *Bacteroidetes*.[17]

Comparisons of the dominant phyla from obese and lean gut microbiomes have produced conflicting results. Although some studies involving mouse models[61,89] and humans[21,90] have demonstrated a significant increase in the ratio of *Firmicutes* to *Bacteroidetes* in the obese microbiome, others[16,43,91,92] have not observed a change in this ratio or the abundance of any specific phyla. For example, 16S rDNA sequencing performed on genetically obese (*ob/ob*) and lean mice revealed major differences in the microbial community structure between obese and lean mice at the phyla level.[89] Specifically, genetically obese (*ob/ob)* mice had at least a 50% reduction of *Bacteroidetes* and a significant increase of *Firmicutes*.[89] In another study, obese mice exhibited more *Firmicutes* (71%) and less *Bacteroidetes* (26%) than *ob/+* and *+/+* mice despite similar chow consumption and energy expenditure.[90] Phylum-level alterations between obese and lean microbiomes have also been observed with human studies. Reduction of *Bacteroidetes*[41,93] and increase in *Actinobacteria*[21] and *Prevotella*[93] were observed with obesity. In contrast, when a group of anorexic individuals was compared with lean and obese individuals, the abundance of *Firmicutes* did not correlate with obesity.[41] These phylogenetic differences

may arise from many variables, including diet, sample handling, sequencing techniques, and data analysis tools.

Interestingly, the shifts in gut microbiota based on body mass index (BMI) at the division level do not always correlate with the shifts at lower (more defined) taxonomic levels such as the genus level. For example, a reduction in *Bacteroidetes* does not mean there cannot be an increase in the *Bacteroides* genus. Indeed, *Bacteroides* strains known to degrade plant polysaccharides were found to be more abundant in obese adults[35] but were not significantly different between obese and nonobese Indian children.[94] Another plant polysaccharide (cellulose) degrader, *Ruminococcus* spp,[65] which belongs to *Firmicutes*, and *Bifidobacterium* were present in lower abundance in obese individuals.[35,95] Higher counts of the *Lactobacillus* genus were observed in some obese individuals[41,95] in contrast to no difference between obese and non-obese Indian children.[94] Abundance of the *Prevotella* genus, an H_2-producing genus, did not correlate with obesity among children; however, it was more abundant in obese adults.[43] Finally, fecal counts of *Faecalibacterium prausnitzii* were higher in obese than in nonobese children.[94]

M smithii, the dominant archaeon in the human gut, is associated with increased energy harvest and adiposity.[96] Two scenarios may help to explain the differences in the abundance of *M smithii* noted in obese and lean microbiomes. In the first scenario in which *M smithii* is more abundant in the obese microbiome than in the lean microbiome,[35,42,43] it may be hypothesized that obese individuals produce more SCFAs due to an increased efficiency of the fermentation process caused by the increased concentration of *M smithii*. In the second scenario in which underweight individuals harbor more *M smithii* than obese individuals,[41,95] it may be hypothesized that a lower calorie intake stimulates enhanced energy extraction through more efficient fermentation and SCFA production via *M smithii*.

Diet and Its Effect on Gut Microorganisms

The effect of diet on the pathogenesis of obesity is a key contributing factor; however, the impact of diet on the gut microbiome structure remains poorly understood. Studies using high-throughput sequencing to compare variations in microbial community composition in animals and humans following different diets[13,97] suggest that differences in the diet modify the relative abundance of gut microorganisms. High-fat, high-sugar (ie, Western-type diet), or high-plant polysaccharide-containing diets have been shown to significantly alter the microbiome composition at different phylogenetic levels.

Genetically modified mouse models that display obesity-resistant or obesity-prone phenotypes when fed a high-fat diet have been employed to better identify the effect of diet on gut microbial composition independent of the obese state. When fed a high-fat diet, the microbiomes of both Sprague-Dawley rats[98] and RELMβ knockout (KO) mice,[99] which do not become obese despite ingesting a high-fat diet, were found to be enriched in *Clostridiales* in the *Firmicutes* phylum. The relative abundance of *Bacteroidales* in the *Bacteroidetes* phylum was also higher in rodents fed with a high-fat diet, independent of the phenotype.[98] From the *Proteobacteria* phyla, *Enterobacteriales* were significantly more abundant in obesity-prone rats than obesity-resistant and low-fat-fed animals; however, the total number of bacteria based on 16S rDNA copy numbers was lower in rats that were fed a high-fat diet.[98] A high-fat diet significantly reduced phylogenetic orders, including *Bacteroidaceae*, *Prevotellaceae*, and *Rickenellaceae*,[99] while transiently increasing *Bifidobacterium* and *Actinobacteria* orders (see Table 1). These studies confirm the strong correlation between high-fat diet and the variations in gut microbial community composition.

Carbohydrate intake also alters the gut microbiome composition. *Bifidobacterium* levels decreased in normal-weight mice that were switched from a high- to a low-carbohydrate diet, and the fecal *Lactobacilli*, often associated with the obese phenotype, did not change as a result of either diet.[100] Low carbohydrate accompanied by high protein in the diet led to significant reduction in the *Roseburia*/*E rectale* group, which might negatively affect host health by leading to a reduction in butyrate production.[58]

As would be expected, the introduction of a diet high in both fat and sugar (ie, Western diet) also results in changes in the gut microbiome. Mice that underwent transplantation with human gut microbiota and were switched from a low-fat plant polysaccharide diet to a Western diet exhibited a higher abundance of *Bacilli* (mainly *Enterococcus*) and *Erysipelotrichi* from *Firmicutes* and less *Bacteroidetes*.[17] In a study in which mice became obese following consumption of a Western diet, pyrosequencing also demonstrated an increase in *Firmicutes* owing mostly to a bloom in the *Mollicutes* class.[97] The impact of Western and plant polysaccharide-rich diets on the gut microbiota was investigated in a study of children in the European Union and Burkina Faso, Africa. African children consuming a high-fiber, polysaccharide diet had a higher *Bacteroidetes/Firmicutes* ratio in their gut microbiota than did European Union children consuming a high-fat, high-protein diet. Although *Actinobacteria* were found to be more abundant in African children, *Proteobacteria* were more abundant in European children. African children also had an enriched reservoir of the genera *Prevotella* and *Xylanibacter* accompanied by high SCFA production. The nutrient-rich, fiber-poor Western diet reduced the diversity of the gut microbiota, whereas the fiber-rich diet was associated with an increased diversity of the gut microbiota, resulting in a concomitant increase in the diversity of enzymes that can produce a variety of SCFAs.[13]

Shifts in gut microbial composition due to dietary variations have been observed at different phylogenetic levels. At the phylum level, the abundance of 2 major phyla, *Bacteroidetes* and *Firmicutes*, in response to changes in the diet has not been clearly established. Many studies with different diet regimens in both mice and humans have shown mixed findings. For example, in a weight loss intervention study with obese individuals, the *Bacteroidetes/Firmicutes* ratio did not change following 4 weeks of low-carbohydrate followed by another 4 weeks of medium-carbohydrate weight loss diets.[91] In contrast, Turnbaugh et al[97] showed a reduced abundance of *Bacteroidetes* following a low-carbohydrate weight loss diet, and Duncan et al[101] found that a low-carbohydrate, high-protein diet also reduced the abundance of *Bacteroidetes*.

Gut Microbes, Endotoxemia, Systemic Inflammation, Innate Immunity, and Obesity

Endotoxin (lipopolysaccharide [LPS]), derived from the cell wall of gram-negative bacteria, circulates at low concentrations in the blood of healthy individuals. The presence of genetic and diet-induced obesity and other metabolic disorders has been associated with a substantial increase in LPS concentrations in the blood, a condition termed *metabolic endotoxemia*.[102,103] Obesity and a number of other metabolic disorders are characterized by chronic, systemic, low-grade inflammation, possibly related to this metabolic endotoxemia.

Consumption of a high-fat meal in both animals and humans results in both changes to the gut microbiota composition, as previously described, and significant increases in endotoxin concentrations.[104,105] It has been suggested that the increases in systemic endotoxin levels may result from increased intestinal permeability caused by the compositional changes in the microbiota.[103] Endotoxemia may then contribute to the low-grade inflammation, insulin resistance, adipocyte hyperplasia, and decreased β-cell function that characterize the

metabolic syndrome. Further supporting this hypothesis is a recent study in which antibiotics were administered to both high-fat-fed and *ob/ob* mice.[106] Reduced levels of endotoxemia and cecal LPS content were found as were a decrease in intestinal permeability, reductions in glucose intolerance, body weight gain and fat mass development, and a decrease in markers of inflammation, oxidative stress, and infiltration of macrophages into visceral adipose tissue. A recent report suggests that these effects may be mediated, at least in part, by interactions between LPS and adipose tissue metabolism through endocannabinoid-driven adipogenesis.[107]

The innate immune system also appears to play a role in both regulating the gut microbiota and, by extension, influencing the development of metabolic disorders. Toll-like receptors (TLRs) are highly expressed transmembrane proteins in the innate immune system that recognize structurally conserved molecules derived from microbes. TLR4, which recognizes LPS, knockout mice have been shown to be resistant to LPS and diet-induced weight gain.[106] Similarly, loss of function mutations in TLR4 prevent diet-induced obesity and insulin resistance.[108] Mice genetically deficient for TLR5, which recognizes bacterial flagellin, exhibit hyperphagia, features of metabolic syndrome, and significant changes in the composition of the gut microbiota.[109] Furthermore, transfer of the gut microbiota from TLR5-deficient mice to wild-type, germ-free mice was shown to confer features of the metabolic syndrome. Finally, removal of the expression of TLR2, which recognizes a number of microbial products, was shown to protect mice from diet-induced adiposity, insulin resistance, hypercholesterolemia, and hepatic steatosis and was also associated with attenuation of adipocyte hypertrophy.[110] Notably, members of the phyla *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were more abundant in mutant mice than in wild-type mice,[111] consistent with previous studies suggesting that the relative proportion of *Bacteroidetes* is reduced in obese mice and humans.

Weight Reduction and Gut Microorganisms

The gut microbiome is responsive to weight loss.[90] Weight loss programs involve not only calorie restriction and changes in the macronutrient composition of the diet but are also generally accompanied by an increase in physical exercise, another factor influencing gut microbiota composition and further complicating our knowledge of the direct effects of diet changes on the gut microbiota. Following a 10-week weight loss program supplemented with exercise, adolescents who achieved both high weight loss and low weight loss demonstrated increased counts of *Bacteroides fragilis* and *Lactobacillus* and decreased counts *of Clostridium coccoides* and *Bifidobacterium longum*.[112] Another study from the same group showed reduced counts of *Clostridium histolyticum*, *E rectale*, and *C coccoides* and increased *Bacteroides-Prevotella* associated with weight loss >4 kg.[113]

Gastric Bypass Surgery and Gut Microorganisms

The mechanisms of action of surgical weight loss procedures are incompletely understood but clearly are more complex than their typical division into restrictive and malabsorptive. The alterations in bowel anatomy and physiology that occur following certain operations such as the Roux-en-Y gastric bypass (RYGB) cause changes to the gut microbiota that may have relevance for energy harvest and storage postoperatively,[43,114,115] and these bariatric operations may represent good models to study adaptations of the intestinal microbiota to dietary variations, metabolism, and systemic inflammation.[93]

Quantification of bacteria based on culture-dependent methods in the bypassed stomach and proximal gastric pouch revealed bacterial overgrowth and an increase in the pH in the functioning proximal stomach following RYGB.[114] Using both Sanger sequencing and high-throughput sequencing, our group demonstrated altered microbial composition of the distal

gut following RYGB.[43] In comparison with obese and normal-weight control groups, individuals who underwent bariatric surgery and achieved successful weight loss harbored proportionally more *Gammaproteobacteria* and less *Clostridia* and *Verrucomicrobia*. In another recent study, when microbiome composition changes following RYGB were monitored using quantitative polymerase chain reaction (qPCR)–based methods over 6 months at 3-month intervals, *Bacteroides* and *Prevotella* counts decreased and approached the counts from healthy, normal-weight control individuals even though the RYGB individuals had not achieved normal body weight.[93] In contrast, at 3 and 6 months after the surgery, *Bifidobacterium* and *Lactobacillus/Leuconostoc/Pediococcus* counts decreased. *Bifidobacterium* levels in RYGB patients were lower at 6 months than the normal-weight control group,[93] a finding that corresponds well with the lower abundance of *Bifidobacterium* generally found in obese individuals.[95]

Microorganisms With Antiobesity Effects

Recent studies in mice and humans suggest that the dietary inclusion of beneficial bacteria (ie, probiotic agents) with antiobesity effects may also help to reduce body weight.[116–118] *Lactobacillus* species, *Lactobacillus rhamnosus* PL60 and *Lactobacillus plantarum* PL62, were reported to reduce the fat content of mice adipose tissue based on their ability to produce conjugated linoleic acid (CLA).[119,120] CLA has been shown to reduce body fat in animal and human studies[121–123]; however, humans do not produce significant levels of CLA from linoleic acid.[119] Thus, CLA needs to be provided by direct uptake of dietary sources of CLA such as dairy products[124] or probiotic bacteria, such as *Lactobacillus* species, that continuously digest dietary linoleic acid to CLA in the large intestine.[119] Moreover, because dietary CLA is mainly absorbed in the small intestine, gut microbe-generated CLA may also contribute to mucosal homeostasis in the large intestine because of CLA's anti-inflammatory effects.[125] Rosberg-Cody et al[126] obtained a significantly higher CLA level in adipose tissue in mice when a recombinant *Lactobacillus* strain that harbors the linoleic acid isomerase gene was administered. *Lactobacillus gasseri* and *L plantarum* have also been shown to reduce adipose tissue mass and size in mice.[118,127]

Bifidobacterium species appear to have a similar antiobesity role as *Lactobacillus* species.[128–130] *Bifidobacterium breve* and *Bifidobacterium dentium* are efficient CLA producers,[128,131] and mice fed a high-fat diet showed a suppression of body weight accumulation when administrated *B breve*.[117] Isolated *Bifidobacterium* L66-5 also induced weight loss in mice.[132] Yin et al[132] observed that 4 strains of *Bifidobacterium* reduced liver lipid deposition but, interestingly, each species caused a different pattern of body weight change. In addition to *Lactobacillus* and *Bifidobacteria* species, other CLA producers of the genera *Propionibacterium*, *Enterococcus*, and *Pediococcus* warrant testing for possible antiobesity effects.[133,134] *Roseburia* and *Bacteroides/Prevotella* species also appear to be candidates for further study based on findings from a study that revealed an inverse correlation between those species and obesity-related metabolic parameters.[116]

Modifying the Gut Microbiome: Insights on Host Energy Regulation

Gut microorganisms are capable of extracting energy from nondigested food, interfering with gene expression, and ultimately changing host body weight and adiposity. Theoretically, energy extraction from dietary intake may be regulated by manipulation of the gut microbiome during malnutrition. A critical aspect in the regulation of energy through microorganisms involves the need for a better understanding of host-microbe and microbe-microbe relationships. Interspecies interactions are of particular importance in energy regulation. For instance, germ-free mice colonized with *B theta* with and without *M smithii* showed increased energy harvest and greater adiposity in the mice co-colonized with *B theta* and *M smithii*.[42] Samuel and Gordon,[42] Samuel et al,[96] and Hansen et al[135] suggested that

targeting hydrogen-consuming species, especially *M smithii*, with the goal of increasing SCFA production, could be one adjunctive approach to the treatment of undernutrition by helping the host extract the most possible energy from the limited diet.[96] Manipulating the abundance of targeted groups of microorganisms using probiotics and prebiotics or their combination (ie, synbiotics) has the potential to shift the abundance of microbial groups and, therefore, to control host body weight.

Probiotics are classically defined as living, nonpathogenic microbes that, when ingested in sufficient amounts, stimulate beneficial effects in the host, typically by multifactorial mechanisms.[136,137] The impact of probiotic supplementation on host energy regulation remains insufficiently investigated at present and often has demonstrated conflicting results. A clinical study conducted with infants who received either a mixture of pre/pro-biotic or placebo showed weight gain only in infants who received the pro/prebiotic mixture.[138] In contrast, identification of lipid-lowering properties of many *Lactobacillus*[127,139] and *B breve*[140,141] strains during diet-induced obesity suggests that pro-biotics may lower host adiposity and weight. Delzenne and Reid[142] suggest there is not enough evidence to suggest a link between obesity and probiotics, and the results attained from animal studies do not always correspond to human metabolism.

Prebiotics are nondigestible substances that, when ingested, stimulate microbial growth of specific bacteria within the colon, particularly bifidobacteria and lactobacilli, that are associated with health benefits to the host.[137,143] The prebiotics most commonly studied in the area of weight regulation are oligofructose and inulin. In addition to the prebiotic dosage, differing degrees of polymerization (DP) appear to affect the degree of microbial community and metabolic changes—changes that seem to be based on differences in fermentability within particular colon segments.[144] Inulin has a high DP between 3 and 60 and is produced by extraction from chicory roots, whereas oligofructose has a low DP between 2 and 20 and results from enzymatic degradation of inulin. The ingestion of oligofructose has been demonstrated to result in a reduction of food intake[145] and a decrease in body weight[146] in mice, as well as weight loss and satiety in humans.[147,148] Weight loss due to oligofructose supplementation has been associated with colonic fermentation of oligofructose and production of peptide YY[146,147] and glucagon-like peptide 1 (GLP-1).[149,150]

Inulin consumption has been shown to lead to an enrichment of *Bifidobacterium* in infants[149] and, in particular, *Bifidobacterium adolescentis* in adults.[151] In infants, inulin consumption showed a reduction of *Clostridia* and coliforms.[150] Unfortunately, the reports of the impact of inulin administration on gut metabolism have not been readily reproducible. In vivo experiments showed inulin stimulated the production of SCFAs in adults[152] and also in infants[150]; however, it has also been reported that inulin does not change SCFA concentration.[153] Inulin administration to healthy subjects has been shown to result in a reduction of lipogenesis and plasma triacylglycerol concentrations.[154] Clearly, further study in this area is needed.

The effects of dietary fiber on energy regulation remain controversial, and the use of dietary fiber to treat obesity appears to have modest benefit.[155] The beneficial effects of dietary fiber, both soluble and insoluble forms, have generally been attributed to increases in satiation and satiety. A microbial mechanism has also been postulated. Although not considered to be prebiotic in the classical sense, dietary fiber consumption has been shown to result in the production of colonic SCFAs and recently was demonstrated to have beneficial effects on endotoxemia, inflammatory cytokine production, and obesity-related inflammation as well as glucose and lipid metabolism.[156]

Conclusion

Malnutrition may manifest as either obesity or undernutrition. Microorganisms play an important role in nutrient and energy extraction and energy regulation. To date, the specific roles that individual gut microbes play in energy harvest remain uncertain. A better understanding of host-microbe and microbe-microbe interactions may lead to the development of novel adjunctive treatment strategies for obesity and undernutrition. This will undoubtedly be an important area of nutrition research in the years to come.

References

1. Macfarlane S, Macfarlane GT. Bacterial diversity in the human gut. Adv Applied Microbiol. 2004; 54:261–289.
2. Gill SR, Pop M, DeBoy RT, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006; 312(5778):1355–1359. [PubMed: 16741115]
3. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. Science. 2005; 308(5728):1635–1638. [PubMed: 15831718]
4. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLOS Biol. 2007; 5(7):1556–1573.
5. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. Am J Clin Nutr. 1999; 69(5):1035S–1045S. [PubMed: 10232646]
6. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA. 2010; 107(26):11971–11975. [PubMed: 20566857]
7. Watson J, Jones RC, Cortes C, et al. Community-associated methicillin-resistant *Staphylococcus aureus* infection among healthy newborns—Chicago and Los Angeles County, 2004 [Reprinted from *MMWR*. 2006;55:329–332). JAMA. 2006; 296(1):36–38.
8. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disesase: meta-analyses. Clin Exp Allergy. 2008; 38(4):634–642. [PubMed: 18266879]
9. Koenig JE, Spor A, Scalfone N, et al. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci USA. 2011; 108:4578–4585. [PubMed: 20668239]
10. Ley RE, Hamady M, Lozupone C, et al. Evolution of mammals and their gut microbes. Science. 2008; 320(5883):1647–1651. [PubMed: 18497261]
11. Berg RD. The indigenous gastrointestinal microflora. Trends Microbiol. 1996; 4(11):430–435. [PubMed: 8950812]
12. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006; 118(2):511–521. [PubMed: 16882802]
13. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci USA. 2010; 107(33):14691–14696. [PubMed: 20679230]
14. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science. 2009; 326(5960):1694–1697. [PubMed: 19892944]
15. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci USA. 2011; 108:4554–4561. [PubMed: 20847294]
16. Jumpertz R, Duc Son L, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr. 2011; 94(1):58–65. [PubMed: 21543530]
17. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med. 2009; 1(6):6ra14.
18. Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. Ageing Res Rev. 2010; 9(2):107–116. [PubMed: 19874918]

19. Ouwehand A, Isolauri E, Salminen S. The role of the intestinal microflora for the development of the immune system in early childhood. Eur J Clin Nutr. 2002; 41(suppl 1):32–37.
20. Zoetendal EG, Akkermans ADL, Akkermansvan Vliet WM, de Visser JAGM, de Vos WM. The host genotype affects the bacterial community in the human gastrointestinal tract. Microb Ecol Health Dis. 2001; 13(3):129–134.
21. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature. 2009; 457(7228):480–487. [PubMed: 19043404]
22. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome (vol 473, pg 174, 2011). Nature. 2011; 474(7346):174–180. [PubMed: 21508958]
23. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011; 334(6052):105–108. [PubMed: 21885731]
24. Chacko A, Cummings JH. Nitrogen losses from the human small bowel: obligatory losses and the effect of physical form of food. Gut. 1988; 29(6):809–815. [PubMed: 2838402]
25. Cummings JH, Macfarlane GT. The control and consequences of bacterial fermentation in the human colon. J Appl Bacteriol. 1991; 70(6):443–459. [PubMed: 1938669]
26. Bergman EN. Energy contribution of volatile fatty-acids from the gastrointestinal tract in various species. Physiol Rev. 1990; 70(2):567–590. [PubMed: 2181501]
27. Parker DS. Measurement of production-rates of volatile fatty-acids in cecum of conscious rabbit. Br J Nutr. 1976; 36(1):61–70. [PubMed: 949469]
28. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. Proc Nutr Soc. 2003; 62(1):67–72. [PubMed: 12740060]
29. Nakamura N, Lin HC, McSweeney CS, Mackie RI, Gaskins HR. Mechanisms of microbial hydrogen disposal in the human colon and implications for health and disease. Ann Rev Food Science Tech. 2010; 1:363–395.
30. Gibson GR, Macfarlane GT, Cummings JH. Sulfate reducing bacteria and hydrogen metabolism in the human large-intestine. Gut. 1993; 34(4):437–439. [PubMed: 8491386]
31. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev. 2001; 81(3):1031–1064. [PubMed: 11427691]
32. Wong JMW, de Souza R, Kendall CWC, Emam A, Jenkins DJA. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol. 2006; 40(3):235–243. [PubMed: 16633129]
33. Murphy EF, Cotter PD, Healy S, et al. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. Gut. 2010; 59(12):1635–1642. [PubMed: 20926643]
34. Campbell JM, Fahey GC, Wolf BW. Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats. J Nutr. 1997; 127(1):130–136. [PubMed: 9040556]
35. Schwiertz A, Taras D, Schafer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity. 2009; 18(1):190–195. [PubMed: 19498350]
36. Lewis SJ, Heaton KW. Increasing butyrate concentration in the distal colon by accelerating intestinal transit. Gut. 1997; 41(2):245–251. [PubMed: 9301506]
37. Walker AW, Duncan SH, Leitch ECM, Child MW, Flint HJ. 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(7):3692–3700. [PubMed: 16000778]
38. Macfarlane GT, Gibson GR, Cummings JH. Comparison of fermentation reactions in different regions of the human colon. J Appl Bacteriol. 1992; 72(1):57–64. [PubMed: 1541601]
39. Marthinsen D, Fleming SE. Excretion of breath and flatus gases by human consuming high-fiber diets. J Nutr. 1982; 112(6):1133–1143. [PubMed: 6283045]
40. Nava GM, Carbonero F, Croix JA, Greenberg E, Gaskins HR. Abundance and diversity of mucosa-associated hydrogenotrophic microbes in the healthy human colon. ISME J. 2012; 6(1):57–70. [PubMed: 21753800]
41. Armougom F, Henry M, Vialettes B, Raccah 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(9):e7125. [PubMed: 19774074]

42. Samuel BS, Gordon JI. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proc Natl Acad Sci USA. 2006; 103(26):10011–10016. [PubMed: 16782812]
43. Zhang H, DiBaise JK, Zuccolo A, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci USA. 2009; 106(7):2365–2370. [PubMed: 19164560]
44. Bernalier A, Willems A, Leclerc M, Rochet V, Collins MD. *Ruminococcus hydrogenotrophicus* sp nov, a new H-2/CO_2-utilizing acetogenic bacterium isolated from human feces. Arch Microbiol. 1996; 166(3):176–183. [PubMed: 8703194]
45. Liu CX, Finegold SM, Song YJ, Lawson PA. Reclassification of *Clostridium coccoides*, *Ruminococcus hansenii*, *Ruminococcus hydrogenotrophicus*, *Ruminococcus luti*, *Ruminococcus productus* and *Ruminococcus schinkii* as *Blautia coccoides* gen. nov., comb. nov., *Blautia hansenii* comb. nov., *Blautia hydrogenotrophica* comb. nov., *Blautia luti* comb. nov., *Blautia producta* comb. nov., *Blautia schinkii* comb. nov and description of *Blautia wexlerae* sp nov., isolated from human faeces. Int J Syst Evol Microbiol. 2008; 58:1896–1902. [PubMed: 18676476]
46. Robert C, Del'Homme C, Bernalier-Donadille A. Interspecies H-2 transfer in cellulose degradation between fibrolytic bacteria and H-2-utilizing microorganisms from the human colon. FEMS Microbiol Lett. 2001; 205(2):209–214. [PubMed: 11750804]
47. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444(7122):1022–1023. [PubMed: 17183309]
48. Fuchs G. CO_2 Fixation in acetogenic bacteria-variations on a theme. Fems Microbiology Rev. 1986; 39(3):181–213.
49. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PC, Gordon JI. Molecular analysis of commensal host-microbial relations hips in the intestine. Science. 2001; 291(5505):881–884. [PubMed: 11157169]
50. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004; 101(44):15718–15723. [PubMed: 15505215]
51. Cook SI, Sellin JH. Review article: short chain fatty acids in health and disease. Aliment Pharmacol Ther. 1998; 12(6):499–507. [PubMed: 9678808]
52. McNeil NI, Cummings JH, James WPT. Short chain fatty-acid absorption by human large intestine. Gut. 1978; 19(9):819–822. [PubMed: 30683]
53. Rubinstein R, Howard AV, Wrong OM. In vivo dialysis of faeces as a method of stool analysis, IV: organic anion component. Clin Sci. 1969; 37(2):549–564. [PubMed: 5359007]
54. Fleming SE, Choi SY, Fitch MD. Absorption of short-chain fatty-acids from the rat cecum in vivo. J Nutr. 1991; 121(11):1787–1797. [PubMed: 1941187]
55. Reilly KJ, Rombeau JL. Metabolism and potential clinical-application of short-chain fatty-acids. Clin Nutr. 1993; 12:97–105.
56. Venter CS. Effects of dietary propionate on carbohydrate and lipid-metabolism in healthy-volunteers. Am J Gastroenterol. 1990; 85(5):549–553. [PubMed: 2159696]
57. McNeil NI. The contribution of the large-intestine to energy supplies in man. Am J Clin Nutr. 1984; 39(2):338–342. [PubMed: 6320630]
58. Russell WR, Gratz SW, Duncan SH, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr. 2011; 93(5):1062–1072. [PubMed: 21389180]
59. Arora T, Sharma R. Fermentation potential of the gut microbiome: implications for energy homeostasis and weight management. Nutr Rev. 2011; 69(2):99–106. [PubMed: 21294743]
60. Payne AN, Chassard C, Zimmermann M, Muller P, Stinca S, Lacroix C. The metabolic activity of gut microbiota in obese children is increased compared with normal-weight children and exhibits more exhaustive substrate utilization. Nutr Diabetes. 2011; 1:e12. [PubMed: 23154580]
61. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444(7122):1027–1031. [PubMed: 17183312]
62. Tilg H, Moschen AR, Kaser A. Obesity and the microbiota. Gastroenterology. 2009; 136(5):1476–1483. [PubMed: 19327360]
63. Sonnenburg JL, Xu J, Leip DD, et al. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. Science. 2005; 307(5717):1955–1959. [PubMed: 15790854]

64. Xu J, Bjursell MK, Himrod J, et al. A genomic view of the human–*Bacteroides thetaiotaomicron* symbiosis. Science. 2003; 299(5615):2074–2076. [PubMed: 12663928]
65. 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(1):81–89. [PubMed: 19719585]
66. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005; 307(5717):1915–1920. [PubMed: 15790844]
67. Towle HC. Glucose and cAMP: adversaries in the regulation of hepatic gene expression. Proc Natl Acad Sci USA. 2001; 98(24):13476–13478. [PubMed: 11717416]
68. Brown AJ, Goldsworthy SM, Barnes AA, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem. 2003; 278(13):11312–11319. [PubMed: 12496283]
69. Le Poul E, Loison C, Struyf S, et al. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. J Biol Chem. 2003; 278(28): 25481–25489. [PubMed: 12711604]
70. Xiong YM, Miyamoto N, Shibata K, et al. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. Proc Natl Acad Sci USA. 2004; 101(4):1045–1050. [PubMed: 14722361]
71. Dass NB, John AK, Bassil AK, et al. The relationship between the effects of short-chain fatty acids on intestinal motility in vitro and GPR43 receptor activation. Neurogastroenterol Motil. 2007; 19(1):66–74. [PubMed: 17187590]
72. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA. 2008; 105(43):16767–16772. [PubMed: 18931303]
73. Cuche G, Cuber JC, Malbert CH. Ileal short-chain fatty acids inhibit gastric motility by a humoral pathway. Am J Physiol Gastrointest Liver Physiol. 2000; 279(5):G925–G930. [PubMed: 11052989]
74. Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009; 461(7268):1282–1286. [PubMed: 19865172]
75. Hong YH, Nishimura Y, Hishikawa D, et al. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. Endocrinology. 2005; 146(12):5092–5099. [PubMed: 16123168]
76. Preiss-Landl K, Zimmermann R, Hammerle G, Zechner R. Lipoprotein lipase: the regulation of tissue specific expression and its role in lipid and energy metabolism. Curr Opin Lipidol. 2002; 13(5):471–481. [PubMed: 12352010]
77. Greenwood MRC. The relationship of enzyme-activity to feeding-behavior in rats: lipoprotein-lipase as the metabolic gatekeeper. Int J Obes (Lond). 1985; 9:67–70.
78. Kern PA. Potential role of TNF alpha and lipoprotein lipase as candidate genes for obesity. J Nutr. 1997; 127(9):S1917–S1922.
79. Coppack SW, Evans RD, Fisher RM, et al. Adipose-tissue metabolism in obesity: lipase action in vivo before and after a mixed meal. Metab Clin Exp. 1992; 41(3):264–272. [PubMed: 1542265]
80. Backhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci USA. 2007; 104(3):979–984. [PubMed: 17210919]
81. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004; 145(5):2273–2282. [PubMed: 14726444]
82. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001; 414(6865):799–806. [PubMed: 11742412]
83. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab. 2007; 92(3):1023–1033. [PubMed: 17164304]

84. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002; 8(11):1288–1295. [PubMed: 12368907]
85. Grover Z, Ee LC. Protein energy malnutrition. Pediatr Clin North Am. 2009; 56(5):1055–1068. [PubMed: 19931063]
86. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. Refer WHOCHE. WHO estimates of the causes of death in children. Lancet. 2005; 365(9465):1147–1152. [PubMed: 15794969]
87. Bhutta ZA, Ahmed T, Black RE, et al. Maternal and child undernutrition 3—what works? Interventions for maternal and child undernutrition and survival. Lancet. 2008; 371(9610):417–440. [PubMed: 18206226]
88. Roseboom TJ, Painter RC, van Abeelen AFM, Veenendaal MVE, de Rooij SR. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. Maturitas. 2011; 70(2):141–145. [PubMed: 21802226]
89. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA. 2005; 102(31):11070–11075. [PubMed: 16033867]
90. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444(7122):1022–1023. [PubMed: 17183309]
91. Duncan SH, Lobley GE, Holtrop G, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes. 2008; 32(11):1720–1724.
92. Mai V, Draganov PV. Recent advances and remaining gaps in our knowledge of associations between gut microbiota and human health. World J Gastroenterol. 2009; 15(1):81–85. [PubMed: 19115471]
93. Furet J-P, Kong L-C, Tap J, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss links with metabolic and low-grade inflammation markers. Diabetes. 2010; 59(12):3049–3057. [PubMed: 20876719]
94. Balamurugan R, George G, Kabeerdoss J, Hepsiba J, Chandragunasekaran AMS, Ramakrishna BS. Quantitative differences in intestinal *Faecalibacterium prausnitzii* in obese Indian children. Br J Nutr. 2010; 103(3):335–338. [PubMed: 19849869]
95. Million M, Maraninchi M, Henry M, et al. Obesity-associated gut microbiota is enriched in *Lactobacillus reuteri* and depleted in *Bifidobacterium animalis* and *Methanobrevibacter smithii*. Int J Obes (Lond). 2011 Aug 9. [Epub ahead of print]. 10.1038/ijo.2011.153
96. Samuel BS, Hansen EE, Manchester JK, et al. Genomic and metabolic adaptations of *Methanobrevibacter smithii* to the human gut. Proc Natl Acad Sci USA. 2007; 104(25):10643–10648. [PubMed: 17563350]
97. Turnbaugh PJ, Baeckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008; 3(4):213–223. [PubMed: 18407065]
98. de La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, Raybould HE. 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(2):G440–G448. [PubMed: 20508158]
99. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology. 2009; 137(5):1716–1724. [PubMed: 19706296]
100. Brinkworth GD, Noakes M, Clifton PM, Bird AR. 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(10):1493–1502. [PubMed: 19224658]
101. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. 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(4):1073–1078. [PubMed: 17189447]
102. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007; 56(7):1761–1772. [PubMed: 17456850]

103. Brun P, Castagliuolo I, Di Leo V, et al. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol. 2007; 292(2):G518–G525. [PubMed: 17023554]
104. Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. Am J Clin Nutr. 2007; 86(5): 1286–1292. [PubMed: 17991637]
105. Amar J, Burcelin R, Ruidavets JB, et al. Energy intake is associated with endotoxemia in apparently healthy men. Am J Clin Nutr. 2008; 87(5):1219–1223. [PubMed: 18469242]
106. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008; 57(6):1470–1481. [PubMed: 18305141]
107. Muccioli GG, Naslain D, Backhed F, et al. The endocannabinoid system links gut microbiota to adipogenesis. Mol Syst Biol. 2010; 6:392. [PubMed: 20664638]
108. Tsukumo DM, Carvalho-Filho MA, Carvalheira JB, et al. Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. Diabetes. 2007; 56(8):1986–1998. [PubMed: 17519423]
109. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010; 328(5975):228–231. [PubMed: 20203013]
110. Himes RW, Smith CW. Tlr2 is critical for diet-induced metabolic syndrome in a murine model. FASEB J. 2010; 24(3):731–739. [PubMed: 19841034]
111. Kellermayer R, Dowd SE, Harris RA, et al. Colonic mucosal DNA methylation, immune response, and microbiome patterns in Toll-like receptor 2-knockout mice. FASEB J. 2011; 25(5): 1449–1460. [PubMed: 21228220]
112. Santacruz A, Marcos A, Warnberg J, et al. Interplay between weight loss and gut microbiota composition in overweight adolescents. Obesity. 2009; 17(10):1906–1915. [PubMed: 19390523]
113. Nadal I, Santacruz A, Marcos A, et al. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. Int J Obes. 2009; 33(7): 758–767.
114. Ishida RK, Faintuch J, Paula AMR, et al. Microbial flora of the stomach after gastric bypass for morbid obesity. Obes Surg. 2007; 17(6):752–758. [PubMed: 17879574]
115. Woodard GA, Encarnacion B, Downey JR, et al. Probiotics improve outcomes after Roux-en-Y gastric bypass surgery: a prospective randomized trial. J Gastrointest Surg. 2009; 13(7):1198–1204. [PubMed: 19381735]
116. Neyrinck AM, Possemiers S, Druart C, et al. Prebiotic effects of wheat arabinoxylan related to the increase in *Bifidobacteria*, *Roseburia* and *Bacteroides/Prevotella* in diet-induced obese mice. PLoS One. 2011; 6(6):e20944. [PubMed: 21695273]
117. Kondo S, Xiao JZ, Satoh T, et al. Antiobesity effects of *Bifidobacterium breve* strain B-3 supplementation in a mouse model with high-fat diet-induced obesity. Biosci Biotechnol Biochem. 2010; 74(8):1656–1661. [PubMed: 20699581]
118. Takemura N, Okubo T, Sonoyama K. *Lactobacillus plantarum* strain No. 14 reduces adipocyte size in mice fed high-fat diet. Exp Biol Med. 2010; 235(7):849–856.
119. Lee HY, Park JH, Seok SH, et al. Human originated bacteria, *Lactobacillus rhamnosus* PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. Biochim Biophys Acta Mol Cell Biol Lipids. 2006; 1761(7):736–744.
120. Lee K, Paek K, Lee HY, Park JH, Lee Y. Antiobesity effect of trans-10,cis-12-conjugated linoleic acid-producing *Lactobacillus plantarum* PL62 on diet-induced obese mice. J Appl Microbiol. 2007; 103(4):1140–1146. [PubMed: 17897219]
121. Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. J Nutr. 2000; 130(12): 2943–2948. [PubMed: 11110851]
122. Smedman A, Vessby B. Conjugated linoleic acid supplementation in humans: metabolic effects. Lipids. 2001; 36(8):773–781. [PubMed: 11592727]

123. West DB, Delany JP, Camet PM, Blohm F, Truett AA, Scimeca J. Effects of conjugated linoleic acid on body fat and energy metabolism in the mouse. Am J Physiol Regul Integr Comp Physiol. 1998; 275(3):R667–R672.

124. Chin SF, Liu W, Storkson JM, Ha YL, Pariza MW. Dietary sources of conjugated dienoic isomers of linoleic acid, a newly recognized class of anticarcinogens. J Food Compost Anal. 1992; 5(3): 185–197.

125. Bassaganya-Riera J, Reynolds K, Martino-Catt S, et al. Activation of PPAR gamma and delta by conjugated linoleic acid mediates protection from experimental inflammatory bowel disease. Gastroenterology. 2004; 127(3):777–791. [PubMed: 15362034]

126. Rosberg-Cody E, Stanton C, O'Mahony L, et al. Recombinant lactobacilli expressing linoleic acid isomerase can modulate the fatty acid composition of host adipose tissue in mice. Microbiology (UK). 2011; 157:609–615.

127. Kang JH, Yun SI, Park HO. Effects of *Lactobacillus gasseri* BNR17 on body weight and adipose tissue mass in diet-induced overweight rats. J Microbiol. 2010; 48(5):712–714. [PubMed: 21046354]

128. Coakley M, Ross RP, Nordgren M, Fitzgerald G, Devery R, Stanton C. Conjugated linoleic acid biosynthesis by human-derived *Bifidobacterium* species. J Appl Microbiol. 2003; 94(1):138–145. [PubMed: 12492934]

129. Rosberg-Cody E, Ross RP, Hussey S, et al. Mining the microbiota of the neonatal gastrointestinal tract for conjugated linoleic acid-producing bifidobacteria. Appl Environ Microbiol. 2004; 70(8): 4635–4641. [PubMed: 15294796]

130. Barrett E, Ross RP, Fitzgerald GF, Stanton C. Rapid screening method for analyzing the conjugated linoleic acid production capabilities of bacterial cultures. Appl Environ Microbiol. 2007; 73(7):2333–2337. [PubMed: 17277221]

131. Wall R, Ross RP, Shanahan F, et al. Metabolic activity of the enteric microbiota influences the fatty acid composition of murine and porcine liver and adipose tissues. Am J Clin Nutr. 2009; 89(5):1393–1401. [PubMed: 19357220]

132. Yin YN, Yu QF, Fu NA, Liu XW, Lu FG. Effects of four *Bifidobacteria* on obesity in high-fat diet induced rats. World J Gastroenterol. 2010; 16(27):3394–3401. [PubMed: 20632441]

133. Oh DK, Hong GH, Lee Y, Min SG, Sin HS, Cho SK. Production of conjugated linoleic acid by isolated *Bifidobacterium* strains. World J Microbiol Biotechnol. 2003; 19(9):907–912.

134. Sieber R, Collomb M, Aeschlimann A, Jelen P, Eyer H. Impact of microbial cultures on conjugated linoleic acid in dairy products: a review. Int Dairy J. 2004; 14(1):1–15.

135. Hansen EE, Lozupone CA, Rey FE, et al. Pan-genome of the dominant human gut-associated archaeon, *Methanobrevibacter smithii*, studied in twins. Proc Natl Acad Sci USA. 2011; 108:4599–4606. [PubMed: 21317366]

136. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics: approaching a definition. Am J Clin Nutr. 2001; 73(2):361S–364S. [PubMed: 11157342]

137. Collins MD, Gibson GR. Probiotics, prebiotics, and synbiotics: approaches for modulating the microbial ecology of the gut. Am J Clin Nutr. 1999; 69(5):1052S–1057S. [PubMed: 10232648]

138. Underwood MA, Salzman NH, Bennett SH, et al. A randomized placebo-controlled comparison of 2 prebiotic/probiotic combinations in preterm infants: impact on weight gain, intestinal microbiota, and fecal short-chain fatty acids. J Pediatr Gastroenterol Nutr. 2009; 48(2):216–225. [PubMed: 19179885]

139. Lee SJ, Cho SJ, Park EA. Effects of probiotics on enteric flora and feeding tolerance in preterm infants. Neonatology. 2007; 91(3):174–179. [PubMed: 17377402]

140. Kondo S, Xiao J-Z, Satoh T, et al. Antiobesity effects of *Bifidobacterium breve* strain B-3 supplementation in a mouse model with high-fat diet-induced obesity. Biosci Biotechnol Biochem. 2010; 74(8):1656–1661. [PubMed: 20699581]

141. Choi I, Kim Y, Park Y, Seog H, Choi H. Anti-obesity activities of fermented soygerm isoflavones by *Bifidobacterium breve*. Biofactors. 2007; 29(2–3):105–112. [PubMed: 17673827]

142. Delzenne N, Reid G. No causal link between obesity and probiotics. Nat Rev Microbiol. 2009; 7(12):901. [PubMed: 19915580]

143. Gibson GR, Beatty ER, Wang X, Cummings JH. Selective stimulation of *Bifidobacteria* in the human colon by oligofructose and inulin. Gastroenterology. 1995; 108(4):975–982. [PubMed: 7698613]

144. van de Wiele T, Boon N, Possemiers S, et al. Inulin-type fructans of longer degree of polymerization exert more pronounced in vitro prebiotic effects. J Appl Microbiol. 2007; 102:452–460. [PubMed: 17241351]

145. Cani PD, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. Eur J Clin Nutr. 2006; 60(5):567–572. [PubMed: 16340949]

146. Delmee E, Cani PD, Gual G, et al. Relation between colonic proglucagon expression and metabolic response to oligofructose in high fat diet-fed mice. Life Sci. 2006; 79(10):1007–1013. [PubMed: 16757002]

147. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr. 2009; 89(6):1751–1759. [PubMed: 19386741]

148. Cani PD, Lecourt E, Dewulf EM, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. Am J Clin Nutr. 2009; 90(5):1236–1243. [PubMed: 19776140]

149. Delzenne NM, Cani PD, Daubioul C, Neyrinck AM. Impact of inulin and oligofructose on gastrointestinal peptides. Br J Nutr. 2006; 93(suppl 1):S157–S161. [PubMed: 15877889]

150. Yap WKW, Mohamed S, Jamal MH, Diederick M, Manap YA. Changes in infants faecal characteristics and microbiota by inulin supplementation. J Clin Biochem Nutr. 2008; 43(3):159–166. [PubMed: 19015750]

151. 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(4):541–550. [PubMed: 18590586]

152. van Nuenen MHMC, Meyer PD, Venema K. The effect of various inulins and *Clostridium difficile* on the metabolic activity of the human colonic microbiota in vitro. Microb Ecol Health Dis. 2003; 15(2–3):137–144.

153. Kruse HP, Kleessen B, Blaut M. Effects of inulin on faecal bifidobacteria in human subjects. Br J Nutr. 1999; 82(5):375–382. [PubMed: 10673910]

154. Letexier D, Diraison F, Beylot M. Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. Am J Clin Nutr. 2003; 77(3):559–564. [PubMed: 12600843]

155. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. Nutr Rev. 2001; 59:129–139. [PubMed: 11396693]

156. Al-Lahham S, Roelofsen H, Rezaee F, et al. Propionic acid affects immune status and metabolism in adipose tissue from overweight subjects. Eur J Clin Invest. 2011 Aug 23. [Epub ahead of print]. 10.1111/j.1365-2362.2011.02590.x

157. Mahowald MA, Rey FE, Seedorf H, et al. Characterizing a model human gut microbiota composed of members of its two dominant bacterial phyla. Proc Natl Acad Sci USA. 2009; 106(14):5859–5864. [PubMed: 19321416]

158. Walker AW, Ince J, Duncan SH, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J. 2011; 5(2):220–230. [PubMed: 20686513]

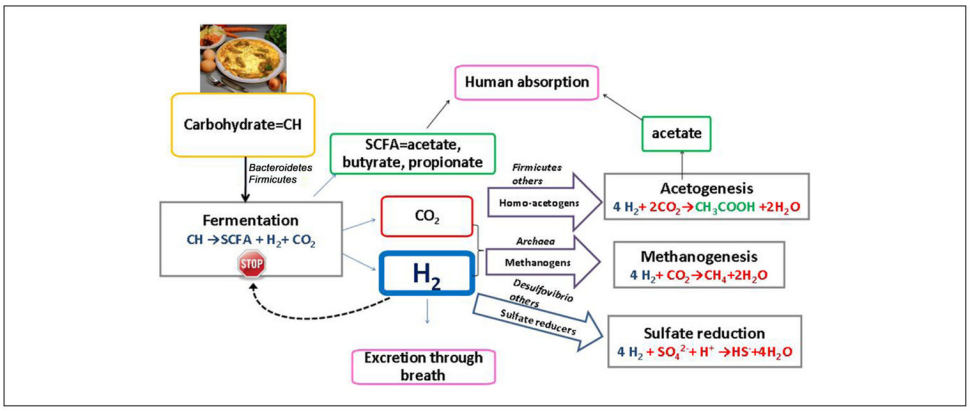

Figure 1.
Microbial H_2-producing and consuming reactions in the human intestine. SCFA, short-chain fatty acid.

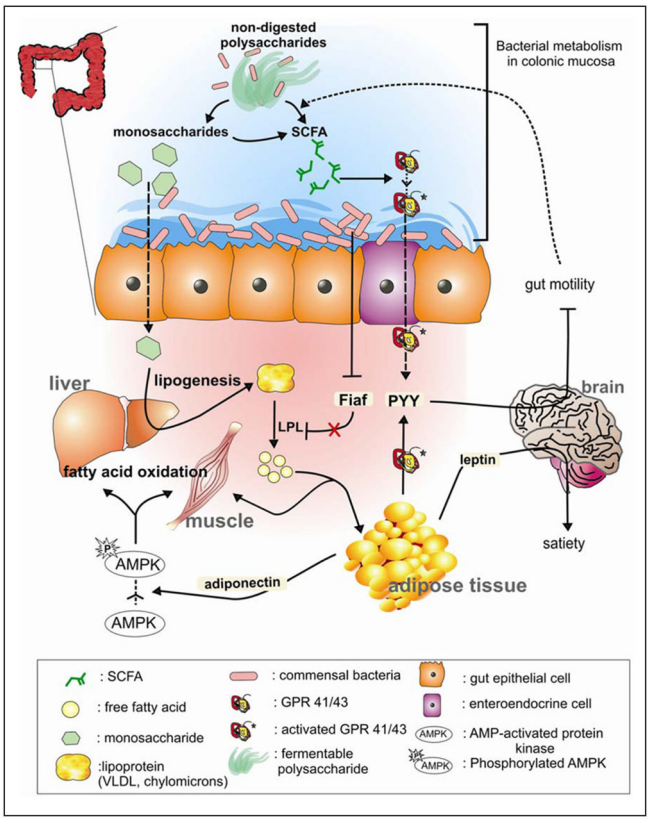

Figure 2.

The gut microbiome has a regulatory function on host energy metabolism. By breaking down nondigestible polysaccharides, gut microorganisms produce monosaccharides and short-chain fatty acids (SCFAs). SCFAs bind to GPR 41/43 receptors and stimulate peptide YY (PYY) production, which inhibits gut motility and allows gut microbes to digest more polysaccharides. Gut microbes also regulate energy metabolism by reducing the expression of fasting-induced adipocyte factor (Fiaf) from gut epithelial cells. Suppressed Fiaf release results in the degradation of lipoproteins and deposition of free fatty acids in adipose tissues. The adiposity in liver and skeletal muscles is also regulated by microorganisms through the changes of phosphorylated adenosine monophosphate-activated protein kinase (AMPK) levels. LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

Table 1

Impact of the Diet on the Abundance of the Gut Microbiota

Donor	Sample	Phenotypic Changes	Diet	Important Changes in Microbiota
Sprague-Dawley rats[98]	Cecal	Increase in body fat on obesity prone rats	High fat	*Bacteroidales* ↑ *Clostridiales* ↑
Mice[97]	Fecal	Increase in body fat	Western	*Eubacterium dolichum* ↑
RELMβ KO and wild-type mice[99]	Fecal	Tendency to obesity in wild-type mice RELMβ KO mice not affected	Chow to high fat	*Clostridiales* ↑ *Mollicutes* ↑[a] *Desulfovibrionaceae* ↑ *Bacteroidaceae* ↓ *Prevotella* ↓ *Rickenellaceae* ↓
ob/ob mice[33]	Fecal and cecal	Increase in body weight	High fat	*Bifidobacteria* ↑ *Actinobacteria* ↑ *Proteobacteria* ↓
Gnotobiotic mice (obese human microbiome)[17]	Fecal	Increase in adiposity	Low fat to Western[b]	*Bacilli* (*Enterococcus*) ↑ *Erysipelotrichi* ↑
Gnotobiotic mice (co-colonization)[157]	Cecal	NA	Western to low- fat, high-plant polysaccharide	*Eubacterium rectale* ↓ *Bacteroides thetaiotaomicron* =
Normal-weight individuals[100]	Fecal	Stable weight	Low carbohydrate High carbohydrate	*Bifidobacterium* ↓ Fecal *Lactobacillus* = Fecal *Lactobacillus* =
Normal-weight individuals[58]	Fecal	Stable weight	Low carbohydrate, high protein	*Roseburia/E rectale* ↓
Obese men[158]	Fecal	NA	Resistant starch in comparison with NSP Weight loss diet	*E rectale* ↑ *Ruminococcus bromii* ↑ *Oscillibacter valericigenes* ↑ *Bacteroides* =*Faecalibacterium prausnitzii* = *Collinsella aerofaciens* ↓
Obese men[101]	Fecal	NA	High protein, low carbohydrate to medium carbohydrate	*Roseburia/Eubacterium* ↑ *Bifidobacterium* ↑
Children[13]	Fecal	NA	High fiber, polysaccharide	*Prevotella* ↑ *Xylanibacter* ↑

KO, knockout; NA, not available; NSP, nonsugar polysaccharide; ↑, increase; ↓, decrease; =, no change observed.

[a] Significantly less important.

[b] Western diet refers to high-sugar and high-fat diet.