Genes Nutr (2011) 6:241–260
DOI 10.1007/s12263-011-0230-1

REVIEW

Obesity and the gut microbiota: does up-regulating colonic fermentation protect against obesity and metabolic disease?

Lorenza Conterno · Francesca Fava · Roberto Viola · Kieran M. Tuohy

Received: 16 March 2011 / Accepted: 20 April 2011 / Published online: 11 May 2011

Abstract Obesity is now considered a major public health concern globally as it predisposes to a number of chronic human diseases. Most developed countries have experienced a dramatic and significant rise in obesity since the 1980s, with obesity apparently accompanying, hand in hand, the adoption of "Western"-style diets and low-energy expenditure lifestyles around the world. Recent studies report an aberrant gut microbiota in obese subjects and that gut microbial metabolic activities, especially carbohydrate fermentation and bile acid metabolism, can impact on a number of mammalian physiological functions linked to obesity. The aim of this review is to present the evidence for a characteristic "obese-type" gut microbiota and to discuss studies linking microbial metabolic activities with mammalian regulation of lipid and glucose metabolism, thermogenesis, satiety, and chronic systemic inflammation. We focus in particular on short-chain fatty acids (SCFA) produced upon fiber fermentation in the colon. Although SCFA are reported to be elevated in the feces of obese individuals, they are also, in contradiction, identified as key metabolic regulators of the physiological checks and controls mammals rely upon to regulate energy metabolism. Most studies suggest that the gut microbiota differs in composition between lean and obese individuals and that diet, especially the high-fat low-fiber Western-style diet, dramatically impacts on the gut microbiota. There is currently no consensus as to whether the gut microbiota plays a causative role in obesity or is modulated in response to the obese state itself or the diet in obesity. Further studies, especially on the regulatory role of SCFA in human energy homeostasis, are needed to clarify the physiological consequences of an "obese-style" microbiota and any putative dietary modulation of associated disease risk.

Keywords Obesity · Microbiota · SCFA · Fiber · Prebiotics · Probiotics

L. Conterno (✉) · F. Fava · K. M. Tuohy
Nutrition and Nutrigenomics Group, Research and Innovation Centre, FEM-IASMA, 38010 S. Michele a.A, Trento, Italy
e-mail: lorenza.conterno@iasma.it

R. Viola
Research and Innovation Centre, FEM-IASMA, 38010 S. Michele a.A, Trento, Italy

Introduction

Obesity is now considered among the top public health issues worldwide. In many countries, obesity rates reported before 1980 were below 10%, whereas nearly half of the Organization for Economic Co-operation and Development (OECD) countries now report 50% or more of the population as being overweight, with the percentage obese reaching 20 to 30% (OECD 2010). Obesity has a dramatic impact on the body, with major changes in energy metabolism and regulatory mechanisms leading to type 2 diabetes, cardiovascular disease (CVD), hormone-linked cancers, and gastrointestinal diseases including inflammatory bowel disease and colon cancer. Characteristic physiological perturbation in terms of hormonal imbalances (e.g., elevated leptin and insulin) and chronically elevated glucose and blood lipids (TAG, cholesterol) occur in congruence with oxidative stress and chronic systemic inflammation, which itself leads to cellular damage in diverse body tissues including the liver, pancreas, vascular system, and the intestinal mucosa. Obesity therefore is a key risk factor for numerous chronic diseases including CVD, the metabolic syndrome, type 2 diabetes, and certain cancers (Pi-Sunyer 2009).

Data collected about this new epidemic of obesity are revealing a complicated network of contributory factors including genetics, age, diet, and nutritional environment. However, the rapid increase in obesity over such a short time frame makes a novel genetic cause per se unlikely and strongly favors modified environmental factors over the past 30 years. Such environmental factors include dietary habit, exercise or energy expenditure, and lifestyle. Indeed, there appears to be a strong correlation between Westernization in terms of diet and lifestyle and obesity. Reduced energy expenditure of modern lifestyles and a Western-style diet prevalent in developed nations are both implicated as causative factors in obesity and are likely to work in synergy to increase obesity rates at the population level (Lieberman 2003; Keim et al. 2004). A shift from more traditional diets, rich in whole-plant foods like whole-grain cereals, fruits, and vegetables, e.g., those of traditional Chinese, Japanese, rural African, and hunter-gatherer populations or aboriginal peoples in Australia and south America, to modern Western-style diets rich in refined carbohydrates, fat, and red/processed meats and low in fiber and whole-plant foods, is strongly correlated with increased body weight, obesity, and the diseases of obesity (O'Dea 1991; Ravussin et al. 1994; Williams et al. 2001; Novotny et al. 2009; Willcox et al. 2009). The same is seen in Europe, where poor adherence to a "Mediterranean style diet" and reduced intake of fiber, fruit, and vegetables is presaging increased body weight and obesity even in countries that traditionally have lower rates of obesity such as Italy (Celi et al. 2003; di Giuseppe et al. 2008; Baldini et al. 2009; De Filippo et al. 2010). This divergence from traditional whole-plant food-based diets and concomitant increases in body weight and diabetes in particular has been reported in genetically diverse populations from different corners of the world again strongly discounting genetics as the major cause for the current wave of obesity.

A more recently appreciated characteristic of obesity is an aberrant intestinal microbiota composition in obese individuals, which appears to be linked to the obese state itself and yet susceptible to dietary modulation (for recent reviews, see Bäckhed 2010; Ley 2010; Tuohy et al. 2010). Whether this aberrant microbiota composition plays an etiological role in obesity or is a consequence of the diet in obesity remains to be determined with evidence from different laboratories, models systems, and human studies supporting either hypothesis (Ley et al. 2006; Duncan et al. 2007). However, this in itself is not surprising considering the complex interplay between the resident human intestinal microbiota and diverse mammalian physiological systems including the immune system, endocrine system, and importantly, energy homeostasis and lipid metabolism. Also the fact that diet, especially dietary fiber, is already known to modify microbial profiles and fermentative output of the gut microbiota would make a low-fiber Western-style obesogenic diet a likely candidate for impacting on gut microbiota composition and activity (Tuohy et al. 2009a, b; De Filippo et al. 2010). Further, recent metagenomic studies are suggesting that many metabolic functions within the gut microbiota are shared between diverse species, suggesting that ecological function may not be as closely linked to bacterial phylogenetics as we have assumed in the past and that although certain groups of indicator organisms may predict either a healthy microbiota (e.g., the bifidobacteria and lactobacilli) or one more likely to be associated with disease (e.g., elevated numbers of enterobacteria), when trying to correlate a phenotypic trait as globally pervasive as energy metabolism, it may not be surprising that different studies show different results in terms of microbial populations correlating with obesity (Cummings et al. 2004).

In the following text, we present a review of studies showing that the gut microbiota, both in composition and metabolic activity, appears to be different in obese compared with lean individuals and discuss the different mechanisms suggested to link aberrant intestinal microbiota profiles with obesity and the diseases of obesity (Table 1). We discuss these recent observations with respect to mechanistic nutritional studies linking colonic fermentation and microbial metabolites, in particular the short-chain fatty acids, acetate, propionate, and butyrate to the regulation of mammalian energy metabolism and body composition.

Is the gut microbiota altered in obesity?

Evidence from germ-free animals

Some of the earliest data linking the mammalian gut microbiota with obesity and particularly, energy homeostasis and fat storage come from studies conducted in germ-free animals. These are animals raised and maintained in the complete absence of contact with living microorganisms and as such do not undergo natural physiological successional development in terms of immune education, mucosal architecture, mammalian–microbiota co-metabolic pathways (e.g., bile acid turnover or xenobiotic metabolism), and as we are finding out, energy metabolism and storage, which occur in free-living vertebrates concomitantly with gut microbiota successional development. However, they do serve as a very useful tool to elucidate fundamental mechanisms underpinning microbial communication and interactions with mammalian physiology at the systems level under controlled conditions not attainable using conventional models or in human studies. Bäckhed et al. (2004) found that transplant of gut microbiota from conventional animals (animals raised under normal, microbiota

associated conditions) into germ-free mice (C57BL/6) led to 60% increased body fat and insulin resistance within 14 days despite reduced food intake and a 40% reduction in muscle mass. Colonization with the common mammalian anaerobic commensal *Bacteroides thetaiotaomicron* alone also led to a 23% increase in the total body fat. This bacterial species has a very high capacity of degrading plant polysaccharides, the major constituent of dietary fiber, which are not broken down by host-encoded enzymes. The study showed that conventionalization promoted increased monosaccharide uptake from the gut, increased delivery of monosaccharides to the liver, increased transactivation of lipogenic enzymes, and increased LPL activity leading to higher uptake of fatty acids and triglyceride accumulation. These authors were the first to show that acquisition of a gut microbiota impacts on fat deposition, clearly linking microbial activities in the intestine with mammalian energy homeostasis and obesity.

Turnbaugh et al. in 2006 showed that germ-free animals colonized with the gut microbiota from obese animals showed greater body weight and fat mass than germ-free animals colonized with the microbiota derived from lean animals. The obese donor was found to be populated by a microbiota with a higher proportion of *Firmicutes* than the lean donor. The recipients showed a gut microbiota profile similar to their obese donor 2 weeks after colonization. However, even if the initial body mass of the recipient and the chow consumption during the 2 weeks was not statistically different, mice colonized with the obese microbiota showed a higher increase (47%) in body fat, than their lean recipient littermates (27%). Furthermore, using massive metagenomic sequencing, these authors showed that the gut microbiota of obese animals had a greater capacity to extract energy from the diet than the microbiota of lean animals. In fact, the obese microbiome showed an enzyme profile high in glycoside hydrolases and other enzymes responsible for transport and metabolism of the glycosides involved in the generation of fermentation end products like butyrate and acetate (Turnbaugh et al. 2006). In confirmation, cecal concentrations of short-chain fatty acids (SCFA), important energy sources absorbed by the host, accounting for about 10% of daily energy intake (Macfarlane and Gibson 1997), were higher in obese animals compared to lean (Turnbaugh et al. 2006). In a study by Samuel and Gordon (2006), gnotobiotic wild-type mice colonized with *Methanobrevibacter smithii* and/or *B. thetaiotaomicron* showed that co-colonization with these two bacterial species increases the feed conversion efficiency and changes the specificity of bacterial polysaccharide fermentation, driving the host to a significant increase in body fat compared with mice colonized with either one of the bacterial species alone. This study showed the important role cross-feeding plays in the energy economy of the colonic microbiota, and the consequences of microbiota modulation or changes in microbiota composition within the gut may wrought on mammalian physiology at the whole organism level.

Evidence from genetic models of obesity

Genetic predisposition to obesity in *ob/ob* mice, due to mutation of the gene coding for leptin, the obesity hormone responsible for regulating food intake and appetite in the hypothalamus, appears to shape a peculiar gut microbiota specialized for enhanced dietary energy recovery. This microbiota was characterized by an up-regulated metabolic machinery with an enhanced capacity for energy extraction from food (Ley et al. 2005; Turnbaugh et al. 2006). Ley et al. (2005) found that these obese *ob/ob* mice possessed a gut microbiota distinct from their lean ob/+ and +/+ siblings at the phylum level with a 50% reduction in the abundance of *Bacteroidetes* and a concomitant increase in *Firmicutes*. This groundbreaking study was one of the first to show that a single genetic mutation in a mammalian gene responsible for regulating food intake could impact on the composition of the mammalian gut microbiota. A later study using the Zucker *fa/fa* rat model of obesity, which more closely mimics common diet-induced obesity in humans where obesity is induced by resistance to leptin rather than lack of functioning leptin protein, found that in rats too, obesity was characterized by a gut microbiota profile distinct from lean phenotype littermates. Using a combination of FISH and DGGE for a broad picture of microbiota composition and relative abundance, Waldram et al. (2009) found that total bacterial numbers and numbers of the *Actinobacteria*, *Bifidobacterium*, and *Atopobium/Coriobacterium* were significantly lower in the obese *fa/fa* rats and that obese animals displayed elevated numbers of the *Firmicutes* groups *Eubacterium rectale/Blautia coccoides* and lactobacilli/enterococci compared with lean counterparts. The lean *fa/−* were characterized by a higher number of *Eubacterium rectale/Blautia coccoides* and lactobacilli/enterococci than the −/− rats. Moreover, these authors using an NMR-based metabolomics approach showed that many of the metabolites responsible for differentiating obese from lean animals derived from combined host–gut microbiota metabolic pathways. In fact, the obese phenotype was characterized by higher amount of urine acetate but lower hippurate, creatinine, and also trimetylammine-N-oxide (TMAO). Bifidobacterial numbers in the cecum were positively correlated with hippurate and dimethylglycine in the urine. The plasma analysis discriminated the obese rats as having higher concentrations of acetoacetate, LDL, and VLDL and lower concentrations of glycine and glutamate than lean rats. Murphy et al. (2010) confirmed that the gut microbiota of *ob/ob*

mice and high-fat-fed wild-type animals, as discussed in more detail later, displayed a microbiota with elevated abundance of *Firmicutes* and reduced abundance of *Bacteroidetes* compared with lean animals. Although they also confirmed that *Actinobacteria* were dominant members of the gut microbiota in these animals, changes wrought by diet or obesity itself in this bacterial phylum varied greatly between individuals masking any group effects. However, they also found that the energy-harvesting potential of the microbiota appeared to be dissociated from changes within the gut microbiota at the phylum level, contrary to the Turnbaugh findings, and suggested that the energy-harvesting potential of the microbiota was more related to diet and that it also changed over time, with fecal acetate, the main SCFA fermentation end product, decreasing over the 15-week experimental period.

Evidence from diet-induced models of obesity

Recent studies have also shown that diets designed to bring on obesity and the diseases of obesity in animal models can also impact on the composition and activity of the gut microbiota. These studies are shedding new light on the complex interaction between nutrient intake (both quantity and quality), the gut microbiota, and host energy metabolism in regulating susceptibility to metabolic disease and excess body weight gain. Diet-induced obesity more closely resembles the situation in humans, where diet under the prevailing genetic constraints of a given individual drives energy storage, body fat accumulation on the one hand and thermogenesis and energy expenditure on the other. Dumas et al. (2006) studied the crosstalk between mammalian and microbiotal metabolism in dietary-induced impaired glucose homeostasis and non-alcoholic fatty liver disease (NAFLD) in the 129S6 mouse model. Using an NMR-based metabolomics approach, they observed changes in plasma and urine metabolic profiles, which differentiated animals that develop non-alcoholic fatty liver disease, insulin resistance, and later obesity on high-fat diets from lean and healthy animals. Many of the metabolites associated with disease derived from microbiota–host co-metabolism of choline, including a reduction in plasma concentrations of phosphatidylcholine and elevated urinary excretion of methylamines (dimethylamine, trimethylamine, and trimethylamine-*N* oxide). The authors suggested that on high-fat diets, this mouse model, 129S6, developed NAFLD and insulin resistance due to conversion of choline into methylamines by their intestinal microbiota, leading to choline deficiency, mimicking the disease-inducing effects of low-choline diets.

Cani et al. (2007a) found that mice on a high-fat (10% w/w), low-fiber diet developed obesity with a significant concomitant "die-off" in saccharolytic bacteria within the gut microbiota. Moreover, diet-induced aberrant gut microbiota could be related to increased intestinal permeability and uptake of the inflammatory bacterial cell wall fragment lipopolysaccharide (LPS), also called endotoxin, which induced a state of chronic systemic inflammation typified by elevated TNF-alpha, IL-1, IL-6, and PAI-1 in the blood, and fat deposition in the liver, which contributed to the development of insulin resistance and subsequent obesity and type 2 diabetes. They later found that this situation could be reversed using the prebiotic fiber oligofructose, via upregulation of the gut hormone glucagon-like peptide-2 (GLP-2), an important regulator of intestinal permeability, and improved intestinal function, and which in rodents at least, can impact on satiety (discussed later in more detail) (Cani et al. 2009).

Turnbaugh et al. (2008) found that a high-sugar, high-fat Western-style diet leads to a "bloom" in *Mollicutes* class of the *Firmicutes*, reducing the *Firmicutes* community species richness, together with concomitant reduction in other bacterial groups including the *Bacteroidetes*. KEGG pathway metabolic reconstruction, using metagenomic sequencing of the whole cecal microbiota, revealed that the *Mollicutes* have the ability to import the refined sugars characterizing the Western diet, such as glucose, fructose, and sucrose and to use them to produce SCFA.

Recently, Murphy et al. (2010) observed that feeding mice a high-fat diet also causes the increased *Firmicutes* and reduced *Bacteroidetes* obese-type microbiota described previously by Turnbaugh, Ley, and Gordon in *ob/ob* mice and in obese humans. In both wild-type and *ob/ob* mice, Murphy found that high-fat feeding induced obesity and an obese-type microbiota. Surprisingly, despite an initial increased dietary energy conversion by the microbiota in obese animals, in both *ob/ob* and high-fat fed wild-type animals, energy harvesting as measured by SCFA production in the cecum and energy content of feces appeared to be divorced from microbiota profile after prolonged exposure to the experimental diet. Fecal energy (as measured by bomb calorimetry) and concentrations of fecal acetate, quantitatively the main short-chain fatty acid produced by the gut microbiota, decreased in both *ob/ob* animals and obese high-fat fed animals between weeks 7 and 15 of the experiment, while in lean animals, fecal energy content and concentrations of SCFA remained stable.

Evidence from human studies

The human gut microbiota also appears modified in obesity. A group of 12 obese human subjects showed a gut microbiota highly populated by *Firmicutes* accompanied by lower abundance of *Bacteroidetes* and a diet-induced modulation of this obese-type microbiota profile shifting toward higher relative abundance of *Bacteroides* and decreased abundance

of *Firmicutes* upon weight loss with low-calorie diets (either because of fat reduction or carbohydrate reduction) (Ley et al. 2006). *Bacteroidetes* abundance was in direct correlation with the body weight loss percentage and not with the change of calorie content of the diets. Although each individual was unique in terms of bacterial species populating their intestine, the dominance of *Firmicutes* and *Bacteroidetes* was maintained. In agreement with this study, Turnbaugh et al. (2009a, b) and later Nadal et al. (2009) also observed the relatively lower abundance of *Bacteroidetes* accompanied by a greater relative abundance of *Firmicutes* in the gut microbiota of obese humans. In addition, the *Bacteroidetes* populations showed a reduced heterogeneity in the obese gut microbiota (Turnbaugh et al. 2009a). The obese microbiota was enriched for genes encoding energy harvesting–related enzymes. Dominance of *Firmicutes* was observed in both obese and normal weight groups in a recent human study by Zhang et al. (2009). The obese gut microbiota had a relatively increased abundance of the *Bacteroidetes* family *Prevotellacee*, which are important H_2 producers. The Archae, mostly from the Methanobacteriales order, were also significantly more abundant in these obese subjects compared with lean. Other than showing a clearly distinct gut microbiota, the obese subjects were populated by a H_2-producing–H_2-consuming consortium that was hypothesized to contribute significantly in the obese process through increased energy yield from non-digestible dietary components. Armougom et al. (2009) found that a group of obese patients had lower *Bacteroidetes*, but also *Firmicutes* compared with the lean controls, and that elevated abundance of *Lactobacillus* species within the *Firmicutes* was characteristic of obesity. In adolescents (average age 15), the *Firmicutes Clostridium histolyticum*, *C. lituseburense*, and *E. rectale-C. coccoides* diminished, while *Bacterioides/Prevotella* increased after a weight loss of more than 4 kg (Nadal et al. 2009). Also in obese adolescents, Santacruz et al. (2009) revealed that following a low-calorie diet designed for weight loss, those individuals ($n = 23$) who lost the most weight had a distinct gut microbiota compared with those who were less successful in weight loss. Subjects in the high weight loss group (weight loss higher than 4 kg) had a higher average count of total fecal bacteria before dietary intervention compared with the low-weight loss group, characterized by higher numbers of *Bacterioides fragilis*, *Clostridium leptum*, and *Bifidobacterium catenulatum*, together with a lower numbers of *C. coccoides*, *Lactobacillus, Bifidobacterium, B. breve*, and *B. bifidum* as determined by qPCR. Thus, it appears that the composition of the gut microbiota in obesity can impact on weight loss in humans following low-calorie diets and contribute to "success" rates on an individual basis, where success rates for weight-reducing diets are typically low, about 15% (Ayyad and Andersen 2000).

Other studies have failed to record an association between low abundance of *Bacteriodetes* within the gut microbiota and obesity in humans. In fact, a higher count of *Bacterioides*, together with *Clostridium* and *Staphylococcus*, was recorded in overweight women, in comparison with the lean women during pregnancy (Collado et al. 2008) or in a group of overweight/obese humans compared with the lean subjects who were populated by *Methanobrevibacter* (Schwiertz et al. 2010). The same overweight/obese group also showed higher fecal concentrations of total SCFA, in particular propionate, compared with the lean control group. A link between obesity and carriage of *Staphylococcus aureus* in feces was noted in a group of obese children (Kalliomaki et al. 2008) whose infant feces contained higher numbers of *S. aureus* than that of lean children. The same study also revealed higher bifidobacterial counts in the infant feces of those childen who upon reaching the age of 7 were within the normal weight range.

Bifidobacteria appeared to be sensitive to carbohydrate dietary intake since their count decreased in obese patients after either high-protein, medium carbohydrate or high protein, low carbohydrate (Duncan et al. 2007). Together with reduced bifidobacterial counts, a significant decrease in total SCFA, particularly acetate, butyrate, and valerate, concentrations in feces was measured after decreasing the carbohydrate intake in these obese subjects. The same dietary intervention showed that *Roseburia* and *Eubacterium* numbers decreased in feces and this too was correlated with the deceased dietary carbohydrate even if the population level of the clostridial cluster XIVa group did not appear to be affected. *Roseburia* and *Eubacterium* group were also shown to be positively correlated with weight loss (Sotos et al. 2008). Both these bacterial groups play important roles in the production and interspecies cross-feeding interactions, which determine final concentrations and relative proportions of the different SCFA in feces.

As mentioned earlier, Murphy et al. (2010) studied the relative impact of genetically induced obesity (in the *ob/ob* mouse model) and diet-induced obesity (wild-type mice fed a high-fat diet) on the gut microbiota and its metabolic output. They confirmed a progressive increase in the relative abundance of *Firmicutes* in both *ob/ob* and high-fat-fed wild-type animals observed previously by the Gordon group. In genetically obese animals, the phylum *Bacteroidetes* abundance decreased over time. In terms of "energy harvesting" by the gut microbiota, *ob/ob* animals after 7 weeks (but not 11 or 15 weeks) showed lower fecal energy content than the other groups but also produced more feces. No difference in fecal energy output as determined by bomb calorimetry was observed between the wild-type animals on different diets. SCFA production decreased over time in all groups, with higher cecal concentrations generally observed in the *ob/ob* and high-fat-fed

animals. Although propionate and butyrate concentrations were not determined in feces due to assay sensitivity, acetate was always higher in the genetically obese animals. This in part agrees with Turnbaugh's observation that *ob/ob* animals display reduced fecal energy content but elevated cecal SCFA concentrations as a result of enhanced energy-harvesting potential of the obese gut microbiota (Turnbaugh et al. 2006) and observations in other human obese/lean comparison studies. Schwiertz et al. (2010) reported that in a comparative study of 30 lean, 35 overweight, and 33 obese human subjects, fecal SCFA concentrations were elevated in the obese in agreement with the observations in *ob/ob* mice, but that the established obese-type microbiota *Firmicutes*/*Bacteroidetes* ratio was reversed in obese humans with *Bacteroidetes* being more abundant in the obese compared with lean subjects. Brinkworth et al. (2009) investigated the impact of 8 weeks dietary intervention with two very different energy-restrictive diets designed to induce weight loss (a low-carbohydrate, high-fat diet and a low-fat, high-carbohydrate, high-fiber diet) on the gut microbiota and their metabolic activity in overweight and obese individuals. Subjects on the low-carbohydrate high-fat diet had lower fecal output, lower fecal concentrations of total SCFA and butyrate, and reduced numbers of fecal bifidobacteria compared with subjects on the high-carbohydrate and fiber, low-fat diet. The authors considered this low-carbohydrate, high-fat microbiota profile a detrimental modulation of the gut microbiota, and one possible contributory to gastrointestinal disease. However, these diet-induced changes within the gut microbiome of obese individuals occurred either under uncontrolled dietary environments (Schwiertz et al. 2010) or energy-restrictive conditions over a relatively short period of time (Brinkworth et al. 2009). It would be interesting to determine whether a similar modulation of fecal SCFA excretion occurs in overweight individuals on high-calorie or calorie-sufficient controlled diets of varying macronutrient composition over a longer period of time.

In summation, even if a consistent specific pattern in the bacterial populations has not been found in all obese versus lean human studies, in most studies, bacterial profiles of the obese gut microbiota were different to those found in the lean individuals, and differences were observed in bacterial populations or microbial metabolites upon dietary intervention with diets designed to modify body weight. This may not be surprising considering that many metabolic activities are shared between diverse bacterial species (e.g., many different groups of bacteria are involved in both carbohydrate fermentation and the deconjugation of bile acids and the enterohepatic circulation of bile acids). For a given individual, what is important is that the gut microbiota appears to be altered in obesity or on obese-type diets, that this aberrant microbiota can impact on different physiological mechanisms regulating body energy metabolism, lipid homeostasis, and immune function, and that dietary components can be used to modulate this aberrant microbiota and their interactions with the host. However, despite strong data from animal studies, the ability of diet to modulate gut microbial activities for improved human energy homeostasis remains to be confirmed in well-powered human intervention studies.

Cellular mechanisms linking the colonic microbiota, fermentation, and mammalian energy metabolism

On analysis of data from animal experiments, germ-free, genetic models of obesity and nutritional models of obesity alike, and from the limited number of human studies, it is difficult to get a coherent picture of whether the gut microbiota plays an etiological role in the epidemic of new obesity sweeping the developed world or whether it is a consequence of diet in obesity, or both. However, these studies clearly illustrate the importance of the microbiotal metabolic output and direct physiological interactions at the cellular level between microorganisms and mammals in global energy metabolism. Animal studies in particular have shown that the gut microbiota impacts on a number of important physiological processes and metabolic pathways responsible for regulating mammalian energy homeostasis that either alone or more likely in combination contribute to regulating body composition and human obesity.

Increased glucose uptake from the small intestine

Germ-free animal studies have shown that intestinal colonization with the gut microbiota or the common anaerobic human commensal, *B. thetaiotaomicron*, induces the expression of sodium/glucose transporter-1 (SGLT1) in the small intestine (Hooper et al. 2001). This results in a doubling of glucose absorption from the intestine of these ex-germ-free animals. In addition, these studies also showed an increase in vasculature and blood supply to the intestine in ex-germ-free animals, showing that colonization of the intestine with commensal bacteria is an important step in mucosal maturation (Stappenbeck et al. 2002). Increased glucose absorption as a result of intestinal colonization and mucosal maturation may therefore be particularly important in infants, where microbial colonization of the sterile gut occurs shortly after birth.

Contribution of SCFA directly to energy metabolism

It has been estimated that SCFA produced in the colon principally upon fermentation of non-digestible carbohydrates by the resident microbiota contributes about 10% of

daily energy requirements in man (Macfarlane and Gibson 1997). The main SCFA are acetate, propionate, and butyrate, in that order. Butyrate is an important energy source for the colonic mucosa and plays a role in epigenetic control of gene expression through the inhibition of histone deacetylase, thus modifying DNA methylation (Meijer et al. 2010). As described below, acetate acts as a substrate for hepatic de novo lipogenesis via acetyl-coA and fatty acid synthase (FAS), while propionate down-regulates lipogenesis. Additionally, acetate also acts as a substrate for hepatic cholesterol biosynthesis, a process that in rats at least is blocked by inhibition of the cholesterol biosynthesis rate-limiting enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) by propionate. Thus, the ratio of acetate/propionate produced, mainly from carbohydrate fermentation in the colon, plays a critical role in regulating lipid and cholesterol metabolism in our bodies (Favier et al. 1995).

De novo lipogenesis in the liver

Hepatic de novo lipogenesis is the process whereby the body converts excess glucose into lipids for storage. Increased glucose absorption from the intestine as a result of conventionalization of germ-free animals leads to increased hepatic lipogenesis through the activation of carbohydrate response element–binding protein (ChREBP)-activated genes or by increased insulin concentrations activating sterol response element–binding protein-1 (SREBP-1). Colonization also leads to an up-regulation of acetyl-CoA carboxylase (Acc1) and fatty acid synthase (FAS) enzymes involved in lipogenesis (Bäckhed et al. 2004). In conventional animals and in human hepatocytes, SCFA have been shown to impact on lipogenesis, with acetate as lipogenic substrate and propionate inhibiting lipogenesis through reduced expression of FAS in particular. A number of factors impact on the ratio of acetate to propionate and subsequent regulation of de novo lipogenesis including better absorption of propionate across the colonic mucosa compared with acetate, and the fact that the liver appears to preferentially clear propionate from the portal vein compared with acetate (90% of propionate in the portal vein is removed following one pass through the liver compared with 75% of portal acetate) and that the fermentation of different fibers or non-digestible carbohydrates by the colonic microbiota have been shown to give different concentrations of SCFA in vitro and in acute feeding studies in healthy individuals (Dankert et al. 1981; Peters et al. 1992; Vogt et al. 2004). Thus, high concentrations of propionate regulate both acetate uptake from the colon and *fas* gene expression in the liver, controlling de novo lipogenesis at both substrate supply and enzyme activity levels (Agheli et al. 1998; Daubioul et al. 2002; Fava et al. 2006).

Fat storage and serum triglycerides

The gut microbiota has been suggested to alter fat storage through the regulation of FIAF (fasting-induced adipose factor, also known as angiopoietin-like 4 protein, ANGPTL4, or PPARγ angiopoietin-related PGAR), an inhibitor of lipoprotein lipase (LPL). FIAF, produced by brown and white fat, liver and intestine, inhibits LPL, regulating fatty acid oxidation in both muscle and adipose tissue. LPL promotes release of fatty acids from circulating chylomicrons and VLDL, which results in their storage as triglycerides in the adipose tissue. FIAF inhibition of LPL therefore reduces fat storage. FIAF is suppressed in germ-free animals colonized with either a conventional mouse gut microbiota or *B. thetaiotaomicron* (Bäckhed et al. 2004). Thus, it has been proposed that suppression of FIAF in conventionalized germ-free animals may be a mechanism by which conventionalization leads to increased fat deposition and obesity. Fleissner et al. (2010) on the contrary found that intestinal production of Fiaf/Angptl4 did not play a role in gut microbiota–mediated effects on fat storage. Intestinal expression of Fiaf/Angptl4 was elevated in both germ-free and conventional C3H mice on either high-fat or Western-style diets, without effecting circulating levels of the protein. In this report, germ-free mice on a high-fat diet had higher body weight than conventional animals on the same diet, in contrast to earlier reports of obesity and increased body fat induced by conventionalization. However, the authors did note dramatic effects of diet on the gut microbiota, with the microbiota of conventional mice fed either high-fat or Western-style diets showing a relative enrichment for *Firmicutes*, mainly due to high abundance of a single family, the *Erysipelotrichaceae*, and lower relative abundance of *Bacteroidetes*, as was observed by Ley, Bäckhed, Turnbaugh in the Gordon group (Ley et al. 2005, 2006; Turnbaugh et al. 2006, 2008, 2009a; Turnbaugh and Gordon 2009). Recently, the probiotic strain *Lactobacillus paracasei* ssp. *paracasei* F19, a *Firmicutes* originally isolated from the human small intestine, was shown to reduce fat storage in mice fed a high-fat diet (20%) through increased circulating levels of FIAF. Mice supplemented with *L. paracasei* F19 showed a significant increase in lipoprotein VLDL triglyceride load but no change in cholesterol profiles (TC, VLDL, LDL, HDL). However, total body fat was significantly reduced in probiotic-supplemented animals as measured by MRI, and circulating levels of FIAF were significantly higher in this group. Co-culture of the intestinal cell line HCT116 with selected gut bacteria showed that the probiotic lactobacilli, *L. rhamnosus* GG and *L. paracasei* F19 and to a lesser extent the *Bifidobacterium animalis* subsp. *lactis* Bb12, stimulated FIAF gene expression after 6 h unlike the commensal *Bacteroides thetaiotaomicron*. *Bacteroides* and

bifidobacteria are anaerobic bacteria and their relative failure to induce FIAF may indicate a necessity for active growth and metabolic activity. F19 also stimulated FIAF production in cell lines LoVo, HT29, and SW480. The active factor appeared to be present in cell-free supernatants of F19 and to be resistant to heat inactivation. Expression of FIAF appeared to be regulated by PPARγ and PPARα, as siRNA to these transcription factors markedly reduced F19-induced gene expression. Colonization of germ-free animals with F19 also resulted in increased circulating ANGPTL4. Suppression of these receptors did not always compromise FIAF expression as also observed previously by Bäckhed et al. (2004).

Enterohepatic circulation of bile acids

Bile acids are released into the small intestine upon ingestion of fatty meals to aid lipid uptake via emulsification and micelle formation. These cholesterol derivatives are reabsorbed in the ileum but if deconjugated or hydroxylated by the gut microbiota are rendered less hydrophobic limiting their absorption across the mucosa and driving their excretion in feces. Bile acids excreted in feces must be replaced by new bile acids synthesized from cholesterol in the liver and can thus impact on blood cholesterol levels. Certain diets, including those supplemented or naturally high in fiber or polyphenols, can increase excretion of bile acids, although the relative contribution of direct bile acid binding in the small intestine and subsequent protection from re-absorption or up-regulation of the deconjugative activities of the gut microbota remains to be determined. Fukasawa et al. (2010) investigated the mechanisms underpinning the observed hypolipidemic effect of the prebiotic, short-chain fructooligosaccharides or FOS. Using a nutrigenomics-based approach, these authors examined hepatic gene expression in rats fed a diet supplemented with the FOS for 2 weeks compared with an isoenergetic diet. DNA microarray analysis of hepatic gene expression revealed modified regulation of genes involved in lipid metabolism, organic acid metabolism, amino acid and derivative metabolic processes, and genes related to proliferation, differentiation, and programmed cell death. Hepatic expression of proliferator-activated receptor-α (PPAR-α) and farnesoid X receptor (FXR) ligand-activated transcription factors was activated. These transcription factors are involved in fatty acid oxidation, lipoprotein, bile acid and amino acid metabolism, glucose homeostasis, and bile acid homeostasis, lipoprotein and glucose metabolism, respectively. PPAR-α is thought to be activated by endogenous long-chain unsaturated fatty acids, eicosanoids and prostaglandins (themselves regulated by SCFA), and dietary fatty acids, including conjugated linoleic acid (CLA), and FXR is a bile acid receptor. Thus, prebiotic modulation of the gut microbiota may have wrought these changes in hepatic gene expression and therefore modified lipid, glucose, and bile acid homeostasis by the production of particular profiles of bile acids and their interaction with the transcription factor FXR or upon SCFA production via PPAR-α. FOS and other fructans, specifically oligofructose and inulin, have been confirmed to improve blood lipid profiles in hyperlipidemic subjects, in a recent metanalysis of human studies (Brighenti 2007).

Modulating mammalian lipid and energy metabolism using probiotic microorganisms

Although yoghurt and milk drinks fermented with lactic acid bacteria have long been studied for their ability to regulate human body weight among other health effects, the scientific evidence of efficacy is equivocal. One recent human intervention in 87 overweight individuals (24.2–30.7 kg/m^2, abdominal visceral fat area (81.2–178.5 cm^2) found that 200 g/day of a probiotic (*Lactobacillus gasseri* SBT2055) fermented milk significantly reduced body weight, abdominal fat area, and subcutaneous fat area, while no change in these parameters was observed with a control non-probiotic fermented milk over a 12-week period. High molecular weight adiponectin was elevated in the serum of both groups after fermented milk intervention (Kadooka et al. 2010). Similarly, in a 10-year follow-up study, Luoto et al. (2010) found that perinatal probiotic intervention with *Lactobacillus rhamnsus* GG was associated with restraining of excessive infant weight gain during the first years of life in 159 mother/child pairings.

Yin et al. (2010) examined the impact of four bifidobacterial strains of human origin in a rat model of diet-induced obesity. Compared with rats on a high-fat diet without probiotic supplementation, dietary supplementation with one of the bifidobacterial strains reduced body weight, another increased body weight, while two other bifidobacterial strains had no effect on body weight. Interestingly, all bifidobacterial strains showed improvements in lipid and cholesterol markers, with reduced serum and hepatic triglycerides and at least a trend toward reduced serum and liver cholesterol. Adding bifidobacteria to the diet did not effect blood glucose or insulin. Importantly, this study shows that the anti-obesity effects of probiotics may be strain-specific (going some way to explain lack of effect in body weight management in certain studies).

Wall et al. (2009) found that enteric microbiota or bacteria of enteric origin could alter fatty acid composition in murine and porcine liver and adipose tissue when added as feed along with dietary fat. Oral administration of a

probiotic *Bifidobacterium breve* strain capable of producing conjugated linoleic acid (CLA) from dietary linoleic acid could influence fat composition in the different mammalian tissues. BALB/c mice, immunodeficient mice (SCID), and weanling pigs were fed linoleic acid–supplemented diets with or without *B. breve* NCIMB 702258. The combination of dietary linoleic acid and probiotic microorganism led to increased cis-9, trans-11 CLA in the livers of mice and pigs, and higher concentrations of PUFA omega-3 (n-3) fatty acids eicosapentaenoic acid and docosahexaenoic acids were found in adipose tissue. Mucosal inflammatory markers (including TNF-alpha, IL-6, and INF-gamma) were reduced in pigs upon probiotic/linoleic acid feeding compared with control linoleic acid diet, which may be of relevance in obesity and the diseases of obesity. CLA has also been shown to alleviate nonalcoholic fatty liver disease (Nagao et al. 2005). In an earlier study, Lee et al. (2006), with the human-derived probiotic *Lactobacillus rhamnosus* PL60 strain that produces t10, c12-CLA, reduced body weight without reducing energy intake in high fat–induced obese mice. Probiotic dietary supplementation reduced white fat mass and there appeared to be a normalization of hepatic steatosis. These studies show that the most likely explanation for probiotic-induced regulation of body fat involves modulation of bile acid and cholesterol metabolism under a prevailing high-fat dietary environment possibly through the up-regulation of PPAR and FXR transcription factors in the liver. CLA is an known ligand of PPAR transcription factors involved in the regulation of nutritional-induced inflammatory processes, and probiotic modulation of the enterohepatic circulation of bile acids or binding of cholesterol in the intestine and subsequent increased fecal excretion may impact on activation of the bile acid–induced FXR transcription factor. This in turn would impact on downstream gene expression under FXR regulation involved in lipid absorption and de novo lipogenesis. However, these studies need to be confirmed, and few data in humans exists.

Muscle fatty acid oxidation and thermogenesis

Conventionalization of germ-free animals shows that the intestinal microbiota reduces the expression of adenosine monophosphate–activated protein kinase (AMPK) in the liver and muscle, which plays a key role in fatty acid beta-oxidation (Bäckhed et al. 2007). Muscle tissue in particular exhibits increased rates of fatty acid oxidation in germ-free animals fed a Western-style diet compared with conventional counterparts, with elevated AMP, AMPK, and phosphorylated acetyl-CoA carboxylase leading to increased carnitine palmitoyl transferase activity (Bäckhed et al. 2007). This leads to increased fatty acid oxidation in muscle and may help maintain lean phenotype in germ-free animals exposed to a high-fat/Western-style diet. Under natural ecological conditions, where the intestine is colonized by a gut microbiota from birth, oral acetate, or vinegar, ingestion has long been associated with improvements in blood lipid, cholesterol, and glucose levels and in the regulation of satiety. Recently, Kondo et al. (2009) confirmed that acetate delivered by oral gavage to high-fat fed mice inhibited accumulation of body fat and hepatic fat deposition without changing food intake. They found that acetate induced hepatic gene expression of PPARα and of fatty acid oxidation and thermogenesis-related proteins, acetyl-CoA oxidase, carnitine palmitoyl transferase-I (CPT-1), and uncoupling protein-2 (UCP-2) via a α2-5′ AMP-activated protein kinase mediated mechanism. As acetate is the main SCFA produced from fermentation of carbohydrate in the colon, it would be interesting to see whether similar results are mediated upon fiber or prebiotic up-regulation of colonic fermentation. Gao et al. (2009) found that supplementing the diet of high-fat fed mice with sodium butyrate (5% w/w) reduced body weight in obese animals, maintained weight in lean animals and protected against insulin resistance. Butyrate enhanced adaptive thermogenesis, a key regulator of energy homeostasis and fatty acid oxidation. Brown adipose tissue (BAT) is responsible for adaptive thermogenesis in response to diet. Adipocyte size was smaller in BAT in the butyrate-fed group, while gene expression and protein levels of two key genes involved in thermogenesis, PGC-1α and UCP-1, were upregulated. Butyrate supplementation also increased the proportion of type I oxidative fibers in muscle tissue, which are relatively rich in mitochondria, store energy as triglycerides and are more resistant to fatigue. AMPK and p38 were activated in the liver of butyrate-fed animals suggesting that these two kinases may contribute to the increased PGC-1α activity induced by butyrate since they are known to extend PGC-1α half-life through phosphorylation and enhance its transcription activity. Fatty acid oxidation in muscle mitochondria increased in the butyrate-fed animals as measured by the oxidation of ^{14}C-labeled palmitic acid with concomitant increased expression of PPAR-δ, a promoter of fatty acid oxidation in muscle, and PGC-1α controlled genes CPT1b and COX-1 (cytochrome c oxidase I). In a second experiment, butyrate was also found to reduce body weight and body fat percentage, and to improve markers of insulin resistance when fed to obese animals. Together, these data suggest a possible role for butyrate in controlling body weight and markers of the metabolic syndrome, mainly through increased energy expenditure and thermogenesis. Butyrate in this case was delivered directly in the diet at high levels and it remains to be seen whether similar up-regulation of thermogenesis is achievable through increased colonic fermentation of fiber and indeed in

humans. However, recent microbial ecology studies comparing the gut microbiota and colonic fermentation between groups of individuals following high-fiber "traditional" whole-plant food diets compared with Western-style low-fiber diets are showing that high dietary fiber diets are associated with considerably higher fecal SCFA concentrations. For example, De Filippo et al. (2010) found significantly lower concentrations of total SCFA in children in Italy following a Western-style low-fiber diet compared with age-matched children in Burkina Faso following a more traditional high-fiber African diet. Concentrations of fecal propionate and butyrate were nearly four times higher in the Burkina Faso children. Interestingly, fecal microbiota 16S rRNA community sequencing analysis showed that the *Enterobacteriaceae* appeared to be in significantly higher abundance in the European children, while the African children had higher abundance of *Actinobacteria* (mainly bifidobacteria) and *Bacteroidetes* and a relative depletion in *Firmicutes*. These studies also support epidemiological data showing an inverse association between fiber intake and obesity.

SCFA regulate satiety and thus food intake, through control of gut hormone expression

SCFA produced upon carbohydrate fermentation in the colon regulate gut hormones including peptide YY (PYY) and glucagon-like peptide (GLP), which in turn regulate production and release of digestive enzymes and satiety, our feeling of fullness. The human brain and gut are connected via an endocrine network of signaling hormones that oversees energy homeostasis, regulating feelings of hunger and satiety, regulating food intake and transit times through the different sections of the gastrointestinal tract. The pancreas secretes insulin in reply to GLP-1, promoting satiety and slowing gastric emptying. GLP-1 and PYY are expressed mainly in intestinal L cells and are released systemically in response to G-coupled receptors (Darzi et al. 2011). Two G-coupled receptors have been identified, which have SCFA as ligands, FFA2 and FFA3 (formally GPR43 and GPR41, respectively) (Stoddart et al. 2008). Although both are activated by all three major SCFA, FFA3 is preferentially activated by propionate and butyrate, and the receptors are expressed in a range of human tissues including the intestinal epithelium, immune cells including neutrophils and adipocytes (Darzi et al. 2011). Propionate has been shown to induce circulating leptin in mice via activation of FFA3 in adipocytes (Xiong et al. 2004). In the colon, FFA2 and FFA3 are found in L cells together with the anorexigenic gut hormones, PYY, which regulates intestinal motility and thus the availability of food for digestion and nutrient absorption from the gut, and GLP-1 excreted by L cells, which regulates satiety. In rats and pigs, luminal administration of SCFA solutions induce PYY and reduce upper gut motility (Cherbut et al. 1998; Cuche et al. 2000) implicating FFA3 in gut hormone regulated intestinal motility and satiety control.

The activity of the endocrine cells of the intestine also appears to be under the influence of the microbiota resident in the intestine of zebrafish (Bates et al. 2006) and rats (Uribe et al. 1994; Cani et al. 2007b). When oligofructose has been introduced with the diet, a contemporary increase in bifidobacteria and L cells has been observed in the rat colon. Similarly, prebiotic carbohydrates have been shown to modify the gut microbiota and increase GLP-1 and 2 production in *ob/ob* mice (Cani et al. 2009). In addition, gut hormone PYY has been shown to be released in response to gut microbiota metabolic stimulus. Intestinal permeability is underregulated by GLP-2, which also upregulates glucose transport from the intestine (Drucker 1999).

Parnell and Reimer (2009) showed that high-level (21 g/day) oligofructose intake could reduce body weight over a 12-week period in overweight healthy adults ($n = 24$) compared with a placebo group. This weight reduction was accompanied by reduced ghrelin and increased production of PYY but not GLP-1, in the oligofructose group compared with control, consistent with reduced food intake in the prebiotic-supplemented group. Prebiotic intervention also improved fasting glucose and insulin levels. The same authors later showed that oligofructose at 10 and 20% diet reduces blood cholesterol and triglycerides via upregulation of cholesterol excretion via bile and inhibited TAG accumulation in the liver in a FAS-independent manner (Parnell and Reimer 2010). So et al. (2007) found that resistant starch (RS), starch that resists digestion in the upper gut but acts as a main carbohydrate source for colonic fermentation and SCFA production, could impact on satiety and body composition in rats compared with non-RS, which is readily digested and absorbed in the upper gut and therefore does not usually contribute greatly to colonic fermentation. The Authors used ^{1}H-magnetic resonance imaging (MRI) to measure whole body composition and fat deposition in the liver and manganese-enhanced MRI to investigate hypothalamic neural activity involved in appetite control in response to up-regulation of colonic fermentation by dietary RS. Mice on either diet had similar body weights after the 8-week intervention but significantly different fat distribution, with the RS-fed animals having lower total body adiposity, subcutaneous and visceral fat, and intrahepatocellular lipids than the animals fed the RS diet. Similarly, plasma leptin, adiponectin (an inflammatory molecule produced by adipocytes), and blood insulin/glucose ratio were all significantly lower in the RS fed animals. RS–fed animals had larger adipocytes with lower insulin-stimulated glucose uptake than

adipocytes from the RS-fed animals, both indicative of obesity and metabolic disease. Manganese-enhanced MRI of the hypothalamus appetite centers of these animals showed that ventromedial hypothalamic nucleus and paraventricular hypothalamic nucleus had significantly greater uptake of Mn^{2+} in the RS–fed animals compared with the RS-fed animals, indicating that RS feeding decreased neuronal activity responsible for appetite control, enhancing satiety in these animals. Thus, SCFA produced by the colonic microbiota appear to be both energy source and signaling molecules important for regulating food intake and gastrointestinal transit times.

Gut microbiota, "leaky-gut", and inflammation

Intestinal mucosal permeability is in large part governed by the extent to which epithelial cells adhere to each other. This occurs through a complex system of junction proteins (tight junction, adherens junction, gap junction, and desmosomes). In particular, the tight junctions are made of a heteropolymer membrane integral proteins including occludine and claudin (Tsukita 2001), ZO-1 (Stevenson et al. 1986). The junction, in particular the tight junction barrier, is responsible for charge (cation) and size selectivity paracellular mechanisms modulating the passage of the intestinal contents (microbes and metabolites) into the blood stream. If the barrier mechanism malfunctions, the gut contents "leak" into the circulatory system. This leads to the passage of pathogens, but also toxins and allergens including LPS (Barbara 2006; Guttman et al. 2006) together with other metabolic products, which can affect other distant organ functions (Maes 2008; Maes and Leunis 2008; Sandek et al. 2008; Vaarala et al. 2008). Butyrate has been shown to reduce mucosal permeability, increasing transepithelial electrical resistance, and impeding PEG translocation in heat-damaged rat colon (Venkatraman et al. 1999); therefore, colonic bacterial fermentation leading to high production of butyrate has been suggested to exert a positive effect on restoring mucosal barrier function. In addition, certain members of the gut microbiota, including strains of *Lactobacillus plantarum* (Anderson et al. 2010), *Escherichia coli* (Ukena et al. 2007), and *Bifidobacterium lactis* (Putaala et al. 2008), are capable of directly enhancing the expression of tight junction proteins occludine and ZO-1, leading to fortification of the intestinal barrier.

Diabetes, the metabolic syndrome, and obesity are metabolic diseases characterized by low-grade systemic inflammation (Hotamisligil and Erbay 2008). Immune responses are part of the complex interplay between different host physiological processes that respond to host nutritional stimuli. Cytokines like tumor necrosis factor-α (TNF-α), IL-1, and IL-6 are associated with the inflammatory processes that occur in obesity and lead to the development of insulin resistance (Hotamisligil et al. 1996). Bacterial LPS is an important structural component of Gram-negative bacterial cell walls, such as those of *Bacteroidetes* and the *Enterobacteriaceae*, and is highly inflammatory, being a pathogen-associated molecular pattern recognized by the innate immune system. Cani et al. (2007a) found that mice injected with LPS showed increased weight gain and insulin resistance without effecting the energy intake. They also found that animals fed a high-fat diet showed a similar physiological and inflammatory response and had elevated plasma LPS. The same study showed that mice deficient for the Toll-like receptor 4 (TLR-4) co-receptor CD14 responsible for innate immune system recognition of LPS were protected from LPS, and high-fat diet-induced inflammation, weight gain, and insulin resistance. Serum amyloid A (SAA) proteins have been proposed as mediators of inflammation and metabolism. SAA are elevated in obesity and there is a suggestion that this is in response to LPS (Yang et al. 2006). This protein has been proposed as link between chronic inflammation and obesity. In mice, SAA3 is elevated in both the adipocytes and intestinal cells if bacteria are present. Based on observations in germ-free, conventionally raised, and Myd88 −/− mice, LPS from bacterial cell wall may (Reigstad et al. 2009) activate SAA (and TNF-α) production from the colonic cells through the signal cascade (Kaway and Akira 2006) TLR4–Myd88–NF-κB, with NF-κB finally regulating the expression of SAA in the nucleus. LPS stimulus could arise from either direct contact with the epithelium cells or by leakage of LPS across the intestinal mucosa. Cani et al. (2007c) demonstrated that mice fed a high-fat diet supplemented with the prebiotic oligofructose had reduced plasma concentrations of the cytokines TNF-α, IL-1, and INF-γ recognized as tight junction disruption promoters, compared with control animals on high-fat diet alone via up-regulation of GLP-2 production from intestinal L cells as discussed previously. GLP-2 is known to be up-regulated by SCFA. In addition, after observing higher plasma LPS content in humans on energy-rich diets, it has been suggested that a diet rich in fat may cause metabolic inflammation by contributing to uptake of LPS from the intestinal lumen (Amar et al. 2008; Cani et al. 2007c). This mechanism was clarified by Ghoshal et al. (2009) showing that dietary fat translocated from the intestine to the blood stream as triglycerides by the chylomicrons also carries LPS from the intestine.

The high-fat diets have also been shown to influence the composition of the gut microbiota (as discussed previously). de La Serre et al. (2010) recently determined that it is the appearance of inflammation that leads to with hyperphagia and obesity in rats on high-fat diets rather than changes within the composition of the gut microbiota per se. Using the Spargue-Dawley outbred rats that display

heterogeneity in obese phenotype on high-fat diets, with some individuals being prone to obesity (DIO-P) and others resistant to obesity (DIO-R), the authors found that high-fat feeding had a dramatic and similar impact on the composition of the gut microbiota in both rat phenotypes compared with rats on a low-fat diet. High-fat feeding increased the relative proportions of both *Bacteroidiales* and *Clostridiales* irrespective of obesity and mucosal inflammation (de La Serre et al. 2010). Obese animals did, however, show elevated *Enterobacteriaceae* (important producers of inflammatory LPS) compared with both obesity-resistant high-fat-fed animals and low-fat-fed animals. Hyperphagia, significantly higher body weight, and adiposity index were observed in the DIO-P animals compared with DIO-R and control low-fat-fed animals. Obesity only occurred upon up-regulation of mucosal inflammatory markers, myeloperoxidase activity as a measure of inflammation and neutrophil infiltration of ileal mucosa and TLR4 activation as measured by immunolocalization of the TLR4/MD2 complex within and along the basolateral region of enterocytes indicating bacterial translocation and plasma LPS elevation. Intestinal alkaline phosphatase (IAP) dephosphorylates LPS reducing the toxicity of the lipid A region of the LPS molecule and is recognized as a local mucosal defence factor possibly acting through regulation of TLR4 recognition of LPS from the microbiota (Chen et al. 2011). In the DIO-P animals, IAP activity was reduced in the duodenal mucosa after 8 weeks of high-fat feeding, while both ileal p-MLC expression and cytoplasmic occludin immunoreactivity were significantly increased in DIO-P after 12 weeks high fat compared with the other groups. Although not measured in this present study, IAP expression is inhibited by inflammatory cytokines IL-1β and TNF-α (known to be elevated in metabolic endotoxemia and obesity) and is induced by the SCFA butyrate (Malo et al. 2006), likely to be in short supply in high-fat low-fermentable fiber diets, such as the one used by de La Serre et al. (2010) Gut permeability as measured by FITC-labeled dextran appearance in plasma was observed in DIO-P high-fat-fed animals after 10 weeks. Together, these data point toward a high-fat-induced modulation of the gut microbiota, which in obesity prone animals, leads to mucosal inflammation, compromises mucosal defences and increases gut permeability and elevates plasma LPS, which then goes on to trigger body weight gain and obesity. The trigger of mucosal inflammation in these animals, which then compromises the mucosal barrier, remains to be determined, although modified IAP expression in response to diet or microbiota modulation (e.g., SCFA concentrations) and increased inflammatory response to LPS either at the mucosal surface or upon carriage across the gut wall by dietary fat are promising candidates.

Conclusions

Although most studies show differences in the composition of the gut microbiota between lean and obese individuals, a clear "obese-type" microbiota fingerprint or profile does not appear to be defined at the phylogenetic level. Although some of this discrepancy may be accounted for by methodological differences, for example, deep 16S rRNA gene community sequencing as opposed to more direct enumeration methods like qPCR and FISH, it is possible that this heterogeneity may also reflect the fact that metabolic function within a given gut microbiome may be commonly shared between different bacterial species, even distantly related bacterial species.

The interactions between the gut microbiota, nutrient intake, energy harvesting, weight gain, and host metabolism appear to be quite intricate. Animal studies have shown that the gut microbiota can increase glucose uptake from the small intestine, produce SCFA directly contribute to energy metabolism, control lipid generation in the liver, control fat storage, and serum triglycerides concentration. The gut microbiota link with the liver metabolism is well established through the enterohepatic circulation of bile acids and their deconjugation in the colon and also modulation of liver metabolic activities and lipid handling by SCFA produced by the gut microbiota upon carbohydrate fermentation in the colon. SCFA also play a role in satiety and control of food intake by regulating the gut hormone expression. Probiotics, in particular the bifidobacteria, and especially *Bifidobacterium breve*, may influence liver lipid and cholesterol markers and modify the bodies handling of dietary lipids such as linoleic acid. A number of studies also show that this important group of gut bacteria, often considered a marker of a healthy gut microbiota, are inversely associated with obesity. SCFA, pre-, and probiotics are also linked to the regulation and reduction of inflammation in obesity, while high-fat diets have been linked to inflammation through increased LPS leakage from the gut.

Apparent contradiction between germ-free studies (showing that the gut microbiota increases energy recovery from diet and thus contributes to obesity) and studies in conventional animals and humans, which show that up-regulation of colonic fiber fermentation can lead to reduced energy intake, body weight control, and protection from the diseases of obesity, may not on second glance be in fact contradictory. The germ-free models describe a xenobiotic situation more akin to early successional development of the gut micobiota and intestinal colonization in infants, where appropriate successional development of the gut microbiota is linked to increased body weight, health in the infant and later in life, especially in breast fed, term infants,

Table 1 Gut microbiota–obesity links based on experimental evidence (modified from Tuohy et al. 2009b)

Model	Design	Evidence	Proposed mechanism	References
C57bl6/J Germ-free mice	Conventionalization of wild-type and *Fiaf* −/−germ-free mice with murine gut microbiota or with *Bacteroides tetaiotaomicron*	Conventionalization or monoassociation of germ-free mice led to increased body fat with less food intake compared with germ-free animals	Gut microbiota suppression of *Fiaf* and relief of LPL inhibition and a resulting increased deposition of triglycerides in adipocytes	Bäckhed et al. (2004)
C57bl6/J *ob/ob* mice	*Ob/ob* versus lean wild-type cecal 16S rRNA gene fragment sequence	A 50% reduction in the relative abundance of *Bacteroidetes* and a proportional increase in *Firmicutes* abundance in obese gut microbiota compared with the lean-type microbiota	Lack of functioning leptin and resultant obesity-modified gut microbiota enhancing dietary energy recovery	Ley et al. (2005)
Human adults	16S rRNA gene sequence library of gut microbiota in obese subjects on weight reduction diets (low carbohydrate or low fat, $n = 12$)	Relative proportion of *Bacteroidetes* increased compared with *Fimicutes* and correlated with percentage of weight loss	The gut in obesity exerts ecological pressure promoting a higher relative abundance of *Firmicutes*	Ley et al. (2006)
Germ-free and *ob/ob* C57bl6/J mice	Sequenced metagenome of cecal *ob/ob* and lean wild-type mice sequenced ($n = 2$)	Increased *Firmicutes* and reduced *Bacteroidetes* prevalence in the obese compared with lean animals. *ob/ob* microbiome enriched in sequences encoding polysaccharide-degrading enzymes and other genes involved in energy recovery from diet	The obese gut microbiota with enhanced potential to extract energy from diet	Turnbaugh et al. (2006)
C57bl6/J Mice and CD14−/− mutant strain	Metabolic, inflammatory and microbiological differences (FISH) between high-fat-fed obese or rodent lean chow-fed mice	High-fat feeding and obesity decimates intestinal microbiota–*Bacteroides*-mouse intestinal bacteria, *Bifidobacterium*, and *Eubacterium rectale–Clostridium coccoides* groups all significantly lower than in control animals	High-fat diet-induced die-off of gut microbiota leads to elevated plasma LPS leading to metabolic endotoxemia, possibly through compromised mucosal barrier function	Cani et al. (2007c)
C57bl6/J mice	C57bl6/J mice-fed high-fat diet with or without the prebiotic oligofructose or cellulose, microbiota enumerated by FISH	Prebiotic supplementation of high-fat diet stimulates bifidobacterial numbers, reduces metabolic endotoxemia and metabolic disease. Bifidobacterial numbers were inversely proportional to plasma LPS	Prebiotics may reduce intestinal permeability and reduce metabolic endotoxemia via reduced plasma LPS	Cani et al. (2007c)
Human adults	Fecal bacterial composition of obese ($n = 16$) on different diets; maintenance, high-protein–medium carbohydrate, high protein/low carbohydrate. Microbiota enumerated by FISH	*Roseburia spp.* and *Eubacteium rectale* subgroup, and bifidobacteria decrease with the high-protein/low-carbohydrate diet, accompanied by a decrease in fecal butyrate	Gut microbiota and fecal butyrate concentrations change in relation to the presence of dietary fermentable carbohydrate	Duncan et al. (2007)
C57bl6/J *ob/ob* mice	Cecal microbiota of mice under high-fat low-fiber diet, and antibiotics. Microbiota enumerated by qPCR and DGGE	Antibiotic reduced LPS cecal content in *ob/ob* and high fat High-fat diet increased intestinal permeability and LPS uptake leading to metabolic endotoxemia	Obese/high-fat modified microbiota contributes to increased gut wall permeability and metabolic endotoxemia, which can be reversed by antibiotics	Cani et al. (2008)
Human pregnant	Comparison of the fecal microbiota (flow cytometry FISH, and qPCR) of overweight ($n = 18$) and normo-weight ($n = 36$) during first and third trimesters	*Bacteroides* and *Staphylococcus aureus* were counted in higher numbers in overweight compared with normo-weight pregnant women	Overweight can lead to aberrant gut microbiota during pregnancy inclining toward aberrant gut microbiota development in the infant and promoting subsequent obesity	Collado et al. (2008)

Table 1 continued

Model	Design	Evidence	Proposed mechanism	References
Human adults	Fecal microbiota difference (measured by FISH), between lean and obese, and obese upon weight loss	No difference in *Bacteroides* populations between lean or obese, or upon weight loss in obese. Diet-correlated decrease in *Firmicutes* (*Roseburia, E. rectale*), and bifidobacteria in obese on weight loss	Diets conceived for weight loss purpose of obese subject change the composition of gut-hosted microbiota	Duncan et al. (2008)
Human children	Retrospective study of fecal microbiota profile (FISH, flow cytometry, and qPCR) of infants presenting with either obesity or normal weight at age 7 years (25 out of 49)	The obese children showed at infancy a fecal microbiota lower in bifidobacteria but higher in *Staphylococcus aureus* compared with infant who remained lean at 7 years	Aberrant gut microbiota development during infancy contributes to obesity risk at childhood	Kalliomaki et al. (2008)
Male Sprague–Dawley rats	Induction of excess of body weight in pups in over-nutrition and normal nutrition condition with microbiota enumerated by FISH and plate count	Obesity resulted from overfed small litters who had reduced *Bacteroides* and increased enterococci and lactobacilli compared with normo-weight, conventionally housed and fed animals	Postnatal nutrition has obesity-inducing potential by impacting the gut microbiota development	Mozes et al. (2008)
Germ-free C57BL/6 J mice	Conventional under Western-style or high-carbohydrate diets and conventionalized with obese-type microbiota from Western-style or high-carbohydrate diets. The colon microbiota was examined by PCR-based 16S rRNA gene fragment sequencing and functional analysis	Western-style diet and associated obesity induced *Firmicutes* bloom characterized by increased abundance of in a single phylogenetic clade within the *Mollicutes* class; relative abundance of *Bacteroidetes* decreased. Conventionalization of lean germ-free mice with *Mollicutes*-dominated microbiota lead to higher body weight gain than with lean-type microbiota. Western diet/*Mollicutes*-modulated microbiota have a higher capacity for intake and fermentation of simple sugars	Western-style diet selects for a particular gut microbiota with increased capacity for energy recovery from diet	Turnbaugh et al. (2008)
Human adults	qPCR analysis of the gut microbiota of obese, anorexic, and lean human adults	Lower *Bacterioidetes* in obese patients and obese microbiota enriched in *Lactobacillus*	Gut microbiota displays distinct pattern in obesity	Armougom et al. (2009)
Mice	Wild-type and RELMβ KO mice from a normal to a high-fat diet. Microbial evaluation by 16S rDNA deep sequencing using 454	Gut microbiota from normal diet (*Bacterioidetes* more abundant than *Firmicutes*, mostly *Clostridia* genus with lower abundance of Tenericutes, Proteobacteria) shifted after high-fat diet to higher proportion of *Firmicutes* (mostly *Clostridiales*) and lower *Bacteriodetes* (*Bacteriodacee, Prevotellaceae, Rickenellaceae,* the more affected orders) together with a bloom of Proteobacteria (*Desulfuvibrionaceae*) Change also in amino acid and carbohydrate metabolism, which were less abundant after high-fat feeding	Impact of dietary fat on the gut microbiota composition and metabolism: changes induced by obesity or direct from fat	Hildebrandt et al. (2009)

Table 1 continued

Model	Design	Evidence	Proposed mechanism	References
Human adolescents	Fecal microbiota (FISH and IgA-coating bacteria) of obese adolescents before and after restricted calorie diet and physical activity regime ($n = 39$, 10 weeks)	*C. histolyticum*, *E. rectale-C. coccoides* groups decreased count with weight loss; *Bacteroides-Prevotella* increased upon weight loss of >4 kg; IgA-coating bacteria decreased in those who lost >6 kg	Potential link between diet, gut microbiota, immunity, and host metabolic processes involved in obesity	Nadal et al. (2009)
Human adolescents	Fecal microbiota (qPCR) of overweight adolescents ($n = 36$) under calorie-restricted diet and physical activity	Total bacterial were higher, as were *Bacterioides fragilis* and *Clostridium leptum* and *Bifidobacterium catenulatum* in the obese population in which intervention was more effective. *C. coccoides*, *Lactobacillus*, *Bifidobacterium, B. bifidus*, and *B. breve* were lower. The weight loss dietary intervention affected also *B. longum*	Differences in the gut microbiota are correlated with a high effective response to weight loss inducing intervention	Santacruz et al. (2009)
Humans adults	Intestinal microbiota (qPCR) and feces SCFA of lean ($n = 30$), overweight ($n = 35$), and obese ($n = 33$) humans	Higher proportion of Bacterioidetes in overweight and obese. *Ruminococcus flavefaciens* subgroup reduced in overweight and obese *Clostridium leptum* group, *Methanobrevibacter* and *Bifidobacterium* all reduced in overweight and obese Higher amount of SCFA in obese, more propionate in overweight and obese	SCFA concentration elevated in obese feces with significant differences in the composition of gut microbiota between lean and obese at phylum and sub-phylum levels	Schwiertz et al. (2010)
Human female twins and their mothers	Adult female monozygotic and dizygotic twin pairs concordant for obesity and their mothers ($n = 31$, 23 and 46, respectively) Gut microbiota described by 16s rRNA gene sequencing	Lower abundance of *Bacteroidetes*, but higher *Actinobacteria* (no change in *Firmicutes*) in obese. Reduced species diversity in obese. Metabolic pathways and functional genes altered in obesity. Functional heterogeneity associated with the relative amount of *Bacteroidetes*. Microbiota enriched in *Firmicutes*/*Actinobacteria* exhibited more less diverse functions	Modulated functional microbiome with metagenomic differences in carbohydrate, lipid, and amino acid metabolism	Turnbaugh et al. (2009a)
Zucker *fa/fa*, fa/+ and +/+ rats	Cecal microbiota composition (FISH and DGGE) in Zucker genotypes on normal diet correlated with ^{1}H-NMR metabolomics of urine and blood	Microbiota of obese *fa/fa* animals distinct from non-obese genotypes. Total bacteria, bifidobacteria, lactobacilli, and *Atopobium* species, all significantly lower in obese ceca. Distinct urine and plasma metabolite profiles associated with obesity and obese-type microbiota	Gut microbiota of the Zucker genetic model of obesity linked to energy metabolism and obesity in these animals	Waldram et al. (2009)
Humans post-gastric bypass (PGB) surgery	Fecal microbiota from 3 lean, 3 morbidly obese, and 3 PGB surgery patients upon weight loss describe after PCR-based 16S rRNA gene fragment sequencing and qPCR for methanogens	*Bacterioidetes* (*Prevotellaceae*) more abundant in obese *Firmicutes* dominant in lean and obese but reduced in PGB, PGB had increased Gammaproteobacteria Methanogenic functional group elevated in obese	Increased methanogenesis, enhancing fermentation through relief of end-product inhibition increases production of acetate absorbed at the human gut contributing to enhanced energy recovery	Zhang et al. (2009)

Table 1 continued

Model	Design	Evidence	Proposed mechanism	References
Human children	Obese and non-obese Indian children (11–14 years: *n*: 28) fecal microbiota enumerated by 16S rRNA target by qPCR	*Bacterioides-Prevotella*, *Lactobacillus acidophilus, Eubacterium rectale* were not significantly different in obese and non-obese. High number of *Faecalibacterium prausnitzii* characterized the obese children	Evident alteration of gut microbiota in obese children	Balamurugan et al. (2010)
Sprague–Dawley rat	Obesity-prone (DIO-P) and resistant (DIO-R) rats under high-fat diet were examined for 16S rRNA qPCR microbiota, TLR4, and LPS	Reduced total bacterial count with higher relative proportions of *Bacterioidales* and *Clostridiales* after high-fat feeding. Greater abundance of *Enterobacteriales* in DIO-P Increased intestinal permeability and plasma LPS upon high-fat feeding	Change in microbiota induced by high-fat diet and inflammation development associated with obesity	de La Serre et al. (2010)
Germ-free (GF) and conventional (CV) mice	Fecal microbiota and *Fiaf/Angptl4* in GF and CV male adult mice on low-fat diet (LFD), a high-fat diet (HFD), or a commercial Western diet (WD)	*Bacteroidetes* relative amount was lower in on both HFD and WD in favor of *Firmicutes*. One species of *Firmicutes* was predominated: the Erysipelotrichaceae Higher expression of *Fiaf/Angptl4* at intestinal level in HFD and WD	Concluded that the absence of gut microbiota does not provide a general protection from diet-induced obesity, that intestinal production of intestinal Fiaf/Angptl4 and gut microbiota are not linked together in fat storage. Diet composition highly affects gut microbiota	Fleissner et al. (2010)
C57bl6/J *ob/ob* mice	Feces of *ob/ob* (low-fat diet) compared to wild type (low-fat and high-fat diet HF) for their metagenomic profile (16S rRNA tags pyrosequencing) in relation to low-fat and high-fat diet. SCFA analysis	*Firmicutes* more abundant in *ob/ob* and HF wild mice. *Bacteriodes* significantly decrease in *ob/ob*. *Actinobacteria* increased in *ob/ob* and HF mice from 7 to 11 weeks. Protobacteria decline in HF mice. Bifidobacteria decline in *ob/ob* and HF at 11 weeks SCFA concentrations and fecal energy content higher in obese at week 7 but lower upon adaptation to diet	High-fat diet may have more influence gut microbiota composition than host genotype. Diet and obesity-induced changes in microbiota energy harvesting change upon adaptation to high-fat diet	Murphy et al. (2010)
Human pregnant	Feces from overweight (*n* 16) and normal weight (*n* 34) pregnant women analyzed by qPCR, together with monitoring of body weight and biochemical parameters from plasma	Overweight women had more abundant fecal *Enterobacteriacee, E. coli*, and *Staphylococcus* and lower counts of *Bifidobacterium* and *Bacterioidetes* in comparison with normal weight subjects. *A. muciniphila* and *Bifidobacterium* were higher in subjects with normal weight gain, compared with those with excessive weight gain. *C. leptum* and *Staphylococcus* counts correlated with excessive weight gain. Higher amount of folic acid and Fe in normal weight subject	Gut microbiota associated with body weight and body weight gain, pregnancy important metabolites, beneficial health effect on woman and infant	Santacruz et al. (2010)
Mice	Wild-type and Apoa-I knocked out mice intolerant to glucose, under fat or normal diet, DGGE-DNA fingerprint and 16S rRNA pyrosequencing	Bifidobacteriacea disappeared after high-fat diet and Desulfovibrionacea prevailed in the glucose impaired/obese group	High impact of diet on the microbiota composition, potentially capable to induce metabolic syndrome	Zhang et al. (2010)

whereas low body weight, preterm infants are more likely to have higher body weight in later life.

However, the discussed mechanisms and their involvement with the gut microbiota and obesity axis have to be further explored, in particular to establish the role of colonic fermentation in human energy homeostasis. The combination of the metagenomic and metabolomic approaches appears to offer a very powerful tool for the elucidation of underlying metabolic interactions between the gut microbiota and its host and ultimately to elucidate the cause or effect relationship between the aberrant gut microbiota in obesity and the diseases of obesity.

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