Gut microflora as a target for energy and metabolic homeostasis

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Purpose of review

Gut microbiota plays an important role in health and disease, but this ecosystem remains incompletely characterized and shows a wide diversity. This review discusses new findings that may explain how gut microbiota can be involved in the control of energy and metabolic homeostasis.

Recent findings

Over the past 5 years studies have highlighted some key aspects of the mammalian host–gut microbial relationship. Gut microbiota could now be considered a 'microbial organ' placed within a host organ. Recent data suggest that the modulation of gut microbiota affects host metabolism and has an impact on energy storage. Several mechanisms are proposed that link events occurring in the colon and the regulation of energy metabolism.

Summary

Gut microflora may play an even more important role in maintaining human health than previously thought. The literature provides new evidence that the increased prevalence of obesity and type 2 diabetes cannot be attributed solely to changes in the human genome, nutritional habits, or reduction of physical activity in our daily lives. One must also consider this important new environmental factor, namely gut microbiota. Scientists may take into consideration a key question: could we manipulate the microbiotic environment to treat or prevent obesity and type 2 diabetes? This opens up a new area in nutrition research.

Keywords

energy metabolism, gut microflora, lipopolysaccharide, microbiota, obesity, type 2 diabetes

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Introduction

Metabolic diseases such as obesity and type 2 diabetes result from a variable combination of genetic and environmental factors [1•]. Although it appears obvious that a mutation on a gene coding for a key molecular factor involved in the control of energy metabolism can lead to diabetes or obesity, the molecular events allowing environmental factors to provoke the same pathological consequences are poorly understood. Nowadays, the growing epidemic of obesity and type 2 diabetes has prompted the scientific community to develop or identify new therapeutic targets. The excessive energy intake, as well as the reduction of physical activity, are certainly two environmental factors classically associated with the development of metabolic diseases. When a population is overfed or subjected to the same nutritional stress, however, some individuals are less susceptible to diet-induced weight gain and hyperglycemia [2,3]. This observation suggests that other mechanisms are involved which are not directly related to the human genome. The intestinal flora was recently proposed as an environmental factor responsible for the control of body weight and energy metabolism. The aim of this review is to highlight how the modulation of gut microbiota affects the energy metabolism.

The human gut microbiota: we are not alone

The human gastrointestinal tract contains a diverse collection of microorganisms, the majority of which reside in the colon. The human gut contains around 10^{14} bacterial cells and up to 1000 species, which exceeds the largest microbial community associated with the human body [4]. Thus, it seems easy to view ourselves as an amalgam of genes embedded in our human genome and in the genomes of our microbial partners (microbiome), hence becoming the 'metagenome' [5•]. As a whole, the microbiome represents more than 100 times the human genome [6••,7]. What is becoming clear is that this microbiota and its microbiome provide us with genetic and metabolic attributes, sparing us from the need to evolve on our own.

This change involves several linked mechanisms, including defence against pathogens at the gut level, immunity (mediated through a number of signal molecules and metabolites), the development of the intestinal microvilli, the fermentation of nondigestible dietary fiber and related nutrients (resistant starch or oligosaccharides), the anaerobic metabolism of peptides and proteins, the biotransformation of conjugated bile acids, the degradation of oxalate-based complexes, and the synthesis of some

vitamins (e.g. B12 and K) [8]. Thus, the gut microbiota can be considered an 'exteriorized organ' which contributes to our homeostasis; its functions are multiple and largely diverse. Intuitively, the major part of the microbiota is present at a point in the gut where food products escaped digestion in the upper part of the gastrointestinal tract. Gut bacteria have genomic characteristics which allow them to use these 'providential' nutrients. As a feedback, they also intervene in host metabolism to provide energy through the production of metabolites absorbed by colonic host cells (short chain fatty acids), but also through more indirect ways, as explained further below. The vast majority of bacterial species within the gut are as yet uncultured and are not represented in studies using cultured-based microbiology. More recently, information on microbial diversity within this community has been expanded as a result of 16S rRNA-based analyses, as demonstrated by several studies highlighting the evolutionary and functional aspects of microbial diversity in the human gut [6••,9,10•,11•]. Most mechanistic and metagenomics studies have been performed in animal models. The latter help to eliminate many of the confounding variables (environment, diet and genotype), which would make such a proof of principle experiment impossible to perform and therefore to interpret in humans. Several new mechanistic studies performed in humans, however, will also be discussed in the present review.

Gut microbiota and energy balance

The biological functions controlled by the intestinal flora seem to relate to the effectiveness of energy harvest, by the bacteria, of the energy ingested but not digested by the host. The control of body weight depends on mechanisms subtly controlled over time. Less than 1% of excess in energy intake compared with the daily expenditure, however, can lead to a detrimental increase in body weight and metabolic complications in the long term (several years) [12]. Consequently, all the mechanisms influencing food-derived energy availability should contribute to the balance of body weight. Several studies from the group of J. Gordon (St Louis, Missouri, USA) have highlighted that gut microflora composition is involved in the regulation of energy homeostasis [5•,13,14,15••,16]. A few years ago, Backhed *et al.* [13] found that young conventionally reared mice have a 40% higher body fat content and 47% higher gonadal fat content than germ-free mice. Strikingly, this phenomenon was associated with a lower food intake in mice with the conventional microbiota than in their germ-free counterparts. In the same line, the authors demonstrated that germ-free mice colonized with the gut microflora derived from the conventional mice increased their fat mass by about 60% and developed insulin resistance within 2 weeks. The mechanisms of the apparent gain in weight implied, firstly, an increase in the intestinal glucose absorption; secondly, energy extraction from nondigestible food components (short chain fatty acids produced through the fermentation); and thirdly, concomitant higher glycemia and insulinemia, two key metabolic factors promoting lipogenesis. Interestingly, the conventionalization also brought about a general increase in the activity of the enzyme lipoprotein lipase (LPL), catalyzing the release of fatty acids from triacylglycerols associated with lipoproteins, which are then taken up by the muscle and adipose tissues. The authors proposed that such an increase was the consequence of suppressing the fasting-induced adipose factor (FIAF) in the gut. FIAF inhibits LPL activity, and therefore, decreasing FIAF in conventionalized germ-free mice leads to the accumulation of triacylglycerol in the adipose tissue. These experiments demonstrated for the first time that an environmental factor such as gut microbiota regulates energy storage [13].

Ley *et al.* [14] demonstrated, in a rodent model, that obesity can be associated with altered gut microflora. After the characterization of more than 5000 bacterial 16sRNA gene sequences from gut microbiota of genetically obese *ob/ob* mice and their lean counterparts, the authors pointed out that obese animals had a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. The observed alterations in the microbiota community may represent an unheralded contributing factor to the pattern of fuel partitioning between lean and obese mice.

Accordingly, these authors [15••] have also compared the distal gut microbiota of obese and lean humans. In order to investigate the relationship between gut microbial ecology and body fat mass in humans, they studied 12 obese volunteers assigned to a fat-restricted or a carbohydrate-restricted low-energy diet. They found that before therapy, obese people had lower Bacteroidetes and more Firmicutes than lean controls.

The results, obtained both in rodents and humans, suggest that obesity alters the composition of the gut microbiota, but they did not prove that the relative difference in bacterial strains distribution leads to different body weight evolution. To test this hypothesis, the same group performed a clear-cut experiment in which the gut microbiota from *ob/ob* mice was transferred to lean germ-free mice. They found that after only 2 weeks, lean mice colonized with the microbiota from obese mice had a modest fat gain, and extracted more energy from their food compared with the mice colonized with the gut microbiota from lean mice [5•]. Together, these data suggest that the differences between both groups of lean mice, in terms of fat and body weight gain, may be attributable to the change in gut microbiota.

This original idea that gut bacteria can contribute to the evolution of body weight is a matter of debate. It is not clear, however, whether a small modification in energy extraction can actually contribute to a meaningful difference in body weight within a short period of time, as suggested in gut flora transplantation studies. In fact, the difference in fat mass observed between the lean germ-free mice receiving the 'obese gut microbiota' and those given the 'lean gut microbiota' is so small that it could be accounted for entirely by the tiny differences in food intake rather than the energy extraction efficiency itself [16]. In addition, our group and others [17–21] have clearly shown that a food rich in fermentable nondigestible fibers decreases body weight, fat mass and the severity of diabetes. These fibers are highly fermented in the caeco-colon, promoting the development of some specific strains of bacteria able to use the fibers as an energy source, thus increasing the total amount of bacteria in the colon [22,23,24•]. This observation is not completely in favor of the hypothesis that the digestion of the fibres/polysaccharides by gut microbiota would support the gain in weight by increasing the supply of energy to the organism. It rather, supports the fact that a specific modulation of gut microbiota, even if not yet well characterized, may have beneficial consequences for the host. A last crucial point, which cannot depend only on the role played by the bacteria to harvest energy from nutrients escaping digestion in the upper part of the intestine, concerns a study showing that germ-free mice are more resistant to diet-induced obesity [25]. The authors maintained germ-free mice or conventionalized mice on a high-fat/high-carbohydrates diet (western diet). They found that conventionalized animals fed the western diet gained significantly more weight and fat mass than the germ-free mice, and showed higher glycemia and insulinemia. Strikingly, and opposite to the results previously observed in germ-free mice fed a normal chow diet, germ-free mice consumed similar amounts of western diet than the conventionalized mice and had a similar fecal energy output. All these data suggest that a bacterially related factor is responsible for the development of diet-induced obesity and diabetes.

Gut microbiota-related factor responsible for obesity and type 2 diabetes

Recently, a new hypothesis linking gut microflora to metabolic homeostasis has been proposed. Type 2 diabetes and obesity are closely associated to a low-tone inflammatory state in response to being fed a high-fat diet [26,27••]. We have been investigating whether a bacterially related factor may be responsible for the development of obesity, diabetes and inflammation induced by a high-fat diet. We found that the bacterial lipopolysaccharide from the Gram-negative intestinal microbiota would fulfil all the prerequisites to be eligible. Lipopolysaccharide is continuously produced in the gut through the lysis of Gram-negative bacteria and is physiologically absorbed and transported from the intestine toward target tissues by a lipoprotein-dependent mechanism [28,29]. Moreover, lipopolysaccharide triggers the secretion of proinflammatory cytokines when it binds to the complex of CD14/TLR4 at the surface of immune cells [30]. In support of this concept and by the modulation of the gut microflora by a change in dietary habits, we demonstrated that high-fat diet feeding resulted in a significant modulation of the dominant bacterial populations within the gut microflora. We observed a reduction in the number of bifidobacteria, *Eu. Recatle/Cl. Coccoides* group and *Bacteroides*-related mouse intestinal bacteria, which favored an increase in the Gram-negative/Gram-positive ratio. This profound modulation of gut microflora was associated with a significant increase in plasma lipopolysaccharide, fat mass and body weight gain, liver hepatic triglyceride accumulation, diabetes and inflammatory tone [31]. To demonstrate that bacterial lipopolysaccharide could act as a triggering factor, CD14 mutant mice were fed a high-fat diet. We found that, in the absence of the lipopolysaccharide receptor, mice resisted all the metabolic disorders induced by the high-fat dietary treatment. In line with our findings, recent studies have reported that plasma lipopolysaccharide is increased in *ob/ob* and *db/db* mice [32•]. Furthermore, polymyxin B treatment, which specifically eliminates Gram-negative bacteria, further quenches lipopolysaccharide and lessens hepatic steatosis [33]. Importantly, such a conclusion is also supported by an epidemiological study in humans [31] in which healthy individuals fed a fat-enriched diet were characterized by a higher fasting endotoxemia, independently of the other macronutrient intake (proteins or carbohydrates). Creely *et al.* [34••] recently reinforced the hypothesis that lipopolysaccharide may act as a gut microbiota-related factor involved in the development of type 2 diabetes and obesity in humans. The authors found that plasma lipopolysaccharide levels were significantly higher in the BMI, sex, and age-matched type 2 diabetes patients group than in the individuals without diabetes. Furthermore, fasting insulin significantly correlated with lipopolysaccharide level in the whole nondiabetic population, and this correlation remained when controled for sex, age, and BMI.

All these studies strongly suggest a potential role for a gut microflora derived factor (namely lipopolysaccharide) in the pathogenesis of obesity-related type 2 diabetes and the innate immune response.

Dietary modulation of gut microflora and metabolic consequences

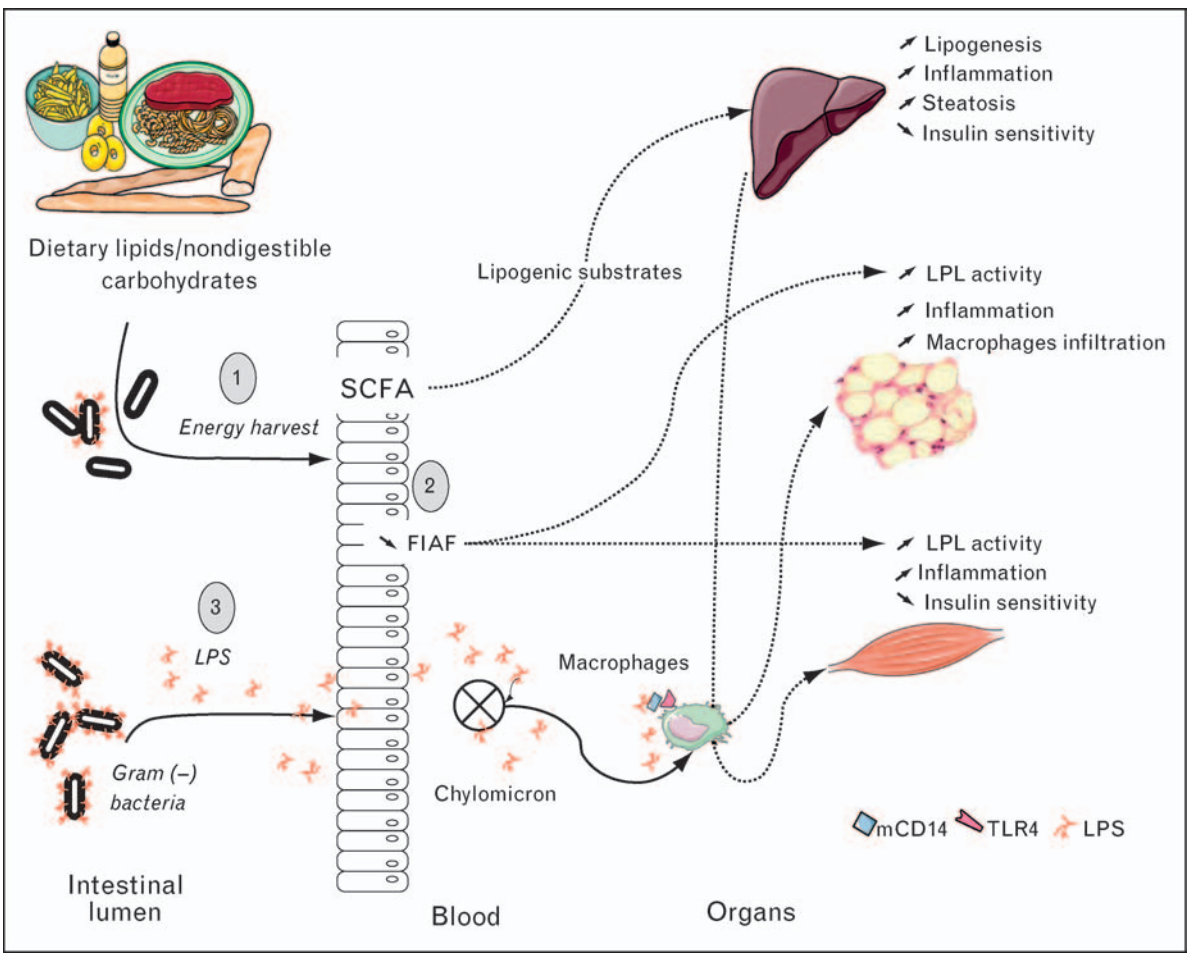
Among the tools used to modulate the gut microflora, prebiotics and probiotics are of the most importance, as recently reviewed by Macfarlane *et al.* [35••]. A prebiotic is "a selectively fermented ingredient that allows specific

changes, both in the composition of and/or the activity in the gastrointestinal microflora that confers benefits upon host well being and health'' [36]; it contains live flora given orally in quantities adequate to allow the colonization of the colon. Inulin-type fructooligosaccharides, when taken in the diet in relatively small amounts (5–20 g/day), have been clearly shown in human studies to stimulate growth of health-promoting species belonging to the genera *Bifidobacterium* spp. and *Lactobacillus* spp. [35••]. Since Bifidobacteria was found to reduce the intestinal endotoxin levels and improve mucosal barrier function [37,38•,39], then dietary supplementation with the prebiotic oligofructose restores the numbers of *Bifidobacterium* spp. in mice having a high-fat diet-induced altered gut microflora [40]. Mice fed the prebiotic dietary fibers exhibited normalized plasma lipopolysaccharide levels. This observation strongly correlated with a normal inflammatory tone, an improved glucose tolerance and normal glucose-induced insulin secretion in prebiotic fed mice. Therefore, these experimental data support the role of the gut microflora as a putative target to maintain or restore metabolic functions. Among the dietary interventions devoted to reducing body weight gain, food intake, hepatic steatosis and associated metabolic disorders in humans, several studies have already shown that an increase in Bifidobacteria by means of prebiotics seems to be clearly effective [20,41–43]. In addition to the modulation of energy and metabolism by gut microflora, one should bear in mind the possibility that the conversion of dietary components by intestinal bacteria may lead to the formation of a large variety of metabolites, which may have beneficial or adverse effects on human health, as largely described is recent reviews [44•,45,46•]. Other authors [47••] have elegantly discussed the role of the microbiota as a significant determinant of cardiovascular disease risk.

Conclusion

The recognition that gut microflora may play an important role in maintaining human health led the scientific

Figure 1 Schematic view of the complementary mechanisms explaining the metabolic shift towards energy storage and metabolic homeostasis



FIAF, fasting-induced adipose factor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; SCFA, short chain fatty acid.

community to consider the means by which gut microflora may be manipulated. Molecular methods for the quantification of bacteria have led to a major revision of the description of the human gut microbiota in the last 5 years, and will constitute an interesting tool for assessing microbiota complexity in the near future. The evidence that the gut microbiota composition can be different between healthy or obese and type 2 diabetes patients has led to gut microflora being thought of as a possible link and as an additional factor in the pathophysiology of metabolic diseases. Different and complementary mechanisms may be proposed, however, to explain the metabolic shift towards energy storage involving the gut microbiota in obese individuals (Fig. 1): firstly, the gut microbiota increases the capacity for an individual to harvest energy from the diet; secondly, the gut microbiota controls triacylglycerol fate (FIAF theory); and thirdly, the modulation of gut microbiota increases plasma lipopolysaccharide levels which trigger the inflammatory tone and the onset of obesity and type 2 diabetes. Nevertheless, a number of questions on how and why the composition of gut microbiota may be associated with obesity and other nutritional disorders will have to be answered. Finally, specific strategies for modifying gut microbiota (in favor of bifidobacteria?) may be a useful means to reduce the impact of high-fat feeding on the occurrence of metabolic diseases.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 778–779).

1 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin • resistance and type 2 diabetes. Nature 2006; 444:840–846.
This paper outlines the different mechanisms involved in the development of obesity and their relation to type 2 diabetes and insulin resistance.

2 Tappy L. Metabolic consequences of overfeeding in humans. Curr Opin Clin Nutr Metab Care 2004; 7:623–628.

3 Levin BE, Keesey RE. Defense of differing body weight set points in diet-induced obese and resistant rats. Am J Physiol 1998; 274:R412–R419.

4 Savage DC. Microbial ecology of the gastrointestinal tract. Annu Rev Microbiol 1977; 31:107–133.

5 Turnbaugh PJ, Ley RE, Mahowald MA, *et al.* An obesity-associated gut • microbiome with increased capacity for energy harvest. Nature 2006; 444: 1027–1031.
This paper outlines that the obese microbiome has an increased capacity to harvest energy from the diet.

6 Xu J, Mahowald MA, Ley RE, *et al.* Evolution of symbiotic bacteria in the distal •• human intestine. PLoS Biol 2007; 5:e156.
This paper illustrates the fact that the adaptation to the gut habitat is a dynamic process that includes the acquisition of genes from other microorganisms. These findings emphasize the importance of including the evolution of 'our' microbial genomes when considering the evolution of humans.

7 Xu J, Gordon JI. Inaugural article: Honor thy symbionts. Proc Natl Acad Sci USA 2003; 100:10452–10459.

8 Nicholson JK, Holmes E, Wilson ID. Gut microorganisms, mammalian metabolism and personalized healthcare. Nat Rev Microbiol 2005; 3:431–438.

9 Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 2006; 124:837–848.

10 Dethlefsen L, Eckburg PB, Bik EM, Relman DA. Assembly of the human • intestinal microbiota. Trends Ecol Evol 2006; 21:517–523.
This review presents promising tools and strategies that lead to a functional view of single populations within the microbial community in the human colon.

11 Gill SR, Pop M, Deboy RT, *et al.* Metagenomic analysis of the human distal gut • microbiome. Science 2006; 312:1355–1359.
This metagenomics analysis defines the gene content and encoded functional attributes of the gut microbiome in healthy humans.

12 Hill JO. Understanding and addressing the epidemic of obesity: an energy balance perspective. Endocr Rev 2006; 27:750–761.

13 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; 101:15718–15723.

14 Ley RE, Backhed F, Turnbaugh P, *et al.* Obesity alters gut microbial ecology. Proc Natl Acad Sci USA 2005; 102:11070–11075.

15 Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut •• microbes associated with obesity. Nature 2006; 444:1022–1023.
This study performed in obese individuals describes the composition of gut microbiota following a fat-restricted or a carbohydrate-restricted low-calorie diet.

16 Bajzer M, Seeley RJ. Physiology: obesity and gut flora. Nature 2006; 444: 1009–1010.

17 Cani PD, Neyrinck AM, Maton N, Delzenne NM. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1. Obes Res 2005; 13:1000–1007.

18 Cani PD, Daubioul CA, Reusens B, *et al.* Involvement of endogenous glucagon-like peptide-1(7–36) amide on glycaemia-lowering effect of oligofructose in streptozotocin-treated rats. J Endocrinol 2005; 185:457–465.

19 Cani PD, Knauf C, Iglesias MA, *et al.* Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. Diabetes 2006; 55:1484–1490.

20 Cani PD, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. Eur J Clin Nutr 2006; 60:567–572.

21 Keenan MJ, Zhou J, McCutcheon KL, *et al.* Effects of resistant starch, a nondigestible fermentable fiber, on reducing body fat. Obesity 2006; 14: 1523–1534.

22 Kleessen B, Hartmann L, Blaut M. Oligofructose and long-chain inulin: influence on the gut microbial ecology of rats associated with a human faecal flora. Br J Nutr 2001; 86:291–300.

23 Kolida S, Saulnier DM, Gibson GR. Gastrointestinal microflora: probiotics. Adv Appl Microbiol 2006; 59:187–219.

24 Kolida S, Meyer D, Gibson GR. A double-blind placebo-controlled study to • establish the bifidogenic dose of inulin in healthy humans. Eur J Clin Nutr 2007; 31 January [Epub ahead of print].
This intervention study determines the bifidogenic dose of fructooligosaccharides in healthy humans.

25 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; 104:979–984.

26 Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005; 115:1111–1119.

27 Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; •• 444:860–867.
A dense review collecting data supporting the link between inflammation, obesity, type 2 diabetes and insulin resistance.

28 Neal MD, Leaphart C, Levy R, *et al.* Enterocyte TLR4 mediates phagocytosis and translocation of bacteria across the intestinal barrier. J Immunol 2006; 176:3070–3079.

29 Vreugdenhil AC, Rousseau CH, Hartung T, *et al.* Lipopolysaccharide (LPS)-binding protein mediates LPS detoxification by chylomicrons. J Immunol 2003; 170:1399–1405.

30 Wright SD, Ramos RA, Tobias PS, *et al.* CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. Science 1990; 249:1431–1433.

31 Cani PD, Amar J, Iglesias MA, *et al.* Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007; 56:1761–1772.

32 Brun P, Castagliuolo I, Leo VD, *et al.* Increased intestinal permeability in obese • mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2007; 292:G518–G525.
This paper outlines the role of gut microbiota and endotoxemia in the development of nonalcoholic steatohepatitis in an obese mice model.

33 Pappo I, Becovier H, Berry EM, Freund HR. Polymyxin B reduces cecal flora, TNF production and hepatic steatosis during total parenteral nutrition in the rat. J Surg Res 1991; 51:106–112.

34 •• Creely SJ, McTernan PG, Kusminski CM, *et al.* Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab 2007; 292:E740–E747.
This paper is the first study performed in humans showing that type 2 diabetes is associated with increased endotoxemia, and that adipose tissue is able to initiate an innate immune response.

35 •• Macfarlane S, Macfarlane GT, Cummings JH. Review article: prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 2006; 24:701–714.
This is a complete overview of the current knowledge about prebiotics, with comprehensive and illustrative tables and figures.

36 Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995; 125:1401–1412.

37 Griffiths EA, Duffy LC, Schanbacher FL, *et al.* In vivo effects of bifidobacteria and lactoferrin on gut endotoxin concentration and mucosal immunity in Balb/c mice. Dig Dis Sci 2004; 49:579–589.

38 • Wang Z, Xiao G, Yao Y, *et al.* The role of bifidobacteria in gut barrier function after thermal injury in rats. J Trauma 2006; 61:650–657.
This paper relates the role of bifidobacteria in maintaining gut barrier function.

39 Wang ZT, Yao YM, Xiao GX, Sheng ZY. Risk factors of development of gut-derived bacterial translocation in thermally injured rats. World J Gastroenterol 2004; 10:1619–1624.

40 Cani PD, Neyrinck AM, Fava F, *et al.* Selective increases of bifidobacteria in gut microflora improves high-fat diet-induced diabetes through a mechanism associated with endotoxemia. Diabetologia (in press).

41 Archer BJ, Johnson SK, Devereux HM, Baxter AL. Effect of fat replacement by inulin or lupin-kernel fibre on sausage patty acceptability, postmeal perceptions of satiety and food intake in men. Br J Nutr 2004; 91:591–599.

42 Whelan K, Efthymiou L, Judd PA, *et al.* Appetite during consumption of enteral formula as a sole source of nutrition: the effect of supplementing pea-fibre and fructo-oligosaccharides. Br J Nutr 2006; 96:350–356.

43 Daubioul CA, Horsmans Y, Lambert P, *et al.* Effects of oligofructose on glucose and lipid metabolism in patients with nonalcoholic steatohepatitis: results of a pilot study. Eur J Clin Nutr 2005; 59:723–726.

44 • Flint HJ, Duncan SH, Scott KP, Louis P. Interactions and competition within the microbial community of the human colon: links between diet and health. Environ Microbiol 2007; 9:1101–1111.
This review focuses on the response of the bacterial community of the large intestine and its metabolic outputs to dietary change.

45 Louis P, Scott KP, Duncan SH, Flint HJ. Understanding the effects of diet on bacterial metabolism in the large intestine. J Appl Microbiol 2007; 102:1197–1208.

46 • Blaut M, Clavel T. Metabolic diversity of the intestinal microbiota: implications for health and disease. J Nutr 2007; 137:751S–755S.
This paper situates the role of gut microbiota in the conversion of nutrients and nonnutritive substances which lead to the formation of compounds that may have beneficial or adverse effects on human health.

47 •• Ordovas JM, Mooser V. Metagenomics: the role of the microbiome in cardiovascular diseases. Curr Opin Lipidol 2006; 17:157–161.
An excellent and clear review of the various mechanisms whereby gut microbiota can affect the occurrence of cardiovascular diseases.