Commentary

Role of Intestinal Microbiome in Lipid and Glucose Metabolism in Diabetes Mellitus

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ABSTRACT

Purpose: The contribution of intestinal bacterial strains (gut microbiota) in human metabolism and obesity is being increasingly recognized. The goal of this article was to provide a commentary on the clinical usefulness of these data.

Methods: We performed a review of the currently available articles on PubMed.

Findings: Because most of the data are based on germ-free animal research, translation to human disease may be difficult. However, changes in the intestinal bacterial composition and subsequent altered diversity have been associated with the presence of chronic low-grade inflammation, a known feature of insulin resistance and type 2 diabetes mellitus.

Implications: It is still not proven whether intestinal bacteria play a causal role in glucose and lipid metabolism. Intervention studies including fecal transplantation and supplementation of single bacterial strains in humans might provide more insight. Moreover, prospective cohorts of healthy subjects using fecal samples collected at baseline can help to identify causally involved specific intestinal bacterial strains that drive aberrant human metabolism. Ultimately, it would be a great asset if potential diagnostic and therapeutic targets could be derived from this novel player in human cardiometabolism. (*Clin Ther*. 2015;37:1172–1177) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: glucose, lipids, metabolism, microbiome, diabetes.

INTRODUCTION

With the dramatically increasing number of patients with type 2 diabetes mellitus (T2DM), researchers are continuously attempting to identify new options for therapeutics and diagnostics. Over the past decade, an increasing amount of evidence has emerged on the relationship between the intestinal microbiome and the presence of obesity and diabetes mellitus. The microbiome of the adult human gut has not only 10 times the number of cells in our own body,[1] but it also vastly outnumbers the size of the human genome by ~100 times. The intestinal microbiota provides us with physiologic capacities such as synthesis of a range of vitamins, particularly vitamins B and K.[2] Moreover, it is likely that the major role of the intestinal bacteria is based on regulation and training of our (innate and adaptive) immune system and, via this route, affects our metabolism.[3,4] With hindsight, it is somewhat surprising that only 15 years have passed since this "external endocrine organ" started to gain acclaim as a regulator of obesity, low-grade inflammation, insulin resistance, and diabetes mellitus. Various links have been proposed between the intestinal microbiome, obesity, and altered glucose and lipid metabolism. Moreover, its role in

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low-grade inflammation and effects on energy expenditure have been increasingly recognized.[4–6] Thus, the purpose of the present review was to summarize the available clinical data and focus on the diagnostic and therapeutic role of intestinal microbiota in human glucose and lipid metabolism.

MATERIALS AND METHODS

We performed a review of the currently available articles on PubMed.

RESULTS

Energy Harvest from Diet and Obesity

A significant subset of the intestinal bacteria has the capacity to extract calories out of otherwise indigestible components in the diet[1,7] and, in that way, influence our energy balance and metabolism. This scenario was elegantly shown by using colonization of adult germ-free mice using feces harvested from conventionally raised mice; this fecal transplant induced a 60% increase in fat within 10 to 14 days, with a concomitant change in insulin sensitivity. The difference in increased fat was believed to be driven by microbial fermentation of dietary polysaccharides otherwise indigestible by the host that are broken down in monosaccharides and short-chain fatty acids (SCFAs), including butyrate. The SCFAs are thought to function both as signaling molecules by which microbes regulate transcription of host genes (epigenetic modulation), as well as mechanisms of lipid and glucose metabolism by supplying substrate for gluconeogenesis and lipogenesis in the liver.[8] In addition, function of the gut microbiome seems to be directly linked to the richness (or diversity) of bacterial strains in the intestine. In a study of obese and nonobese Danish subjects, those with low bacterial richness were found to be overall more overweight, insulin-resistant with dyslipidemia, and characterized by a more pronounced inflammatory phenotype compared with individuals having a more diverse microbiota composition.[9]

Dietary intervention improves the low bacterial diversity and composition that correlate with improvement of metabolic markers such as lipids and homeostasis model assessment.[10] In this respect, the changes in bacterial diversity were associated with alterations in SCFA-producing bacterial strains. Interestingly, SCFA such as butyrate can function as a ligand for Gpr41, a G protein–coupled receptor expressed by a subset of enteroendocrine cells in the gut epithelium, thus affecting satiety, dietary intake, and postprandial glucose and lipid metabolism. Gpr41 signaling modulates the secretion of glucagon-like peptide-1, which is involved in intestinal transit time and seems to be a physiologic regulator of appetite and food intake.[11,12] With regard to the role of Gpr41 signaling on energy balance, Samuel et al found that conventionally raised *Gpr 41 –/–* mice were significantly leaner and had less weight gain compared with their wild-type littermates.[13] This effect could be partly attributed to the gut microbiota; fecal transplantation studies in wild-type germ-free mice using bacteria of the human distal gut microbiota from the *Gpr 41 –/–* mice improved postprandial glucose metabolism via SCFA in mice.[14] Similarly, it has been suggested that bariatric Roux-en-Y gastric bypass affects dietary intake via glucagon-like peptide-mediated pathways. Indeed, transfer of the gut microbiota from Roux-en-Y gastric bypass–treated mice to wild-type, germ-free mice resulted in weight loss and decreased fat mass and altered SCFA in the recipient animals compared with recipients of feces from mice that had sham surgery.[15] Although these data underscore a role for gut microbiota and specifically SCFA butyrate in (postprandial) regulation of energy metabolism, clinical relevance is currently lacking. In this respect, we are currently investigating the effect of oral butyrate supplementation on gluconeogenesis and lipolysis in patients with metabolic syndrome.

Chronic Low-Grade Inflammation and Insulin Resistance in Obesity

Insulin resistance in obesity goes hand in hand with low-grade systemic inflammation, however the etiology of these low-grade inflammation processes remains partly unresolved.[16] A prospective study recently showed that endotoxemia is a predictor of development of metabolic syndrome and T2DM in obese subjects.[17] Dietary fats lead to an increase in the absorption and excretion from lipopolysaccharides (LPS) by intestinal/epithelial cells via increased induction of chylomicrons. LPS has an affinity for chylomicrons and seems to be co-transported along with other dietary fats.[18] When mice were fed a high-fat diet for 4 weeks, they exhibited an increased proportion of LPS-containing microbiota in the intestine and a concomitant increase of LPS in plasma. Artificially induced "metabolic endotoxemia" with intravenous LPS led to an increase in fasted glycemia, insulinemia, and whole-body, liver, and adipose tissue weight gain similar to mice fed a high-fat diet.[19] Moreover, 8 weeks

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of high-fat dietary intervention showed an increase in Toll-like receptor 4 (TLR4) activation, associated with ileal inflammation, and an increase in plasma LPS.[20] Similarly, knockout mice in TLR2, TLR4, and TLR5 are characterized by metabolic syndrome once they are put on a high-fat diet, underscoring the potential role of TLR in the development of metabolic syndrome.[21–23]

Myeloid differentiation factor 88 (MyD88) is a central adaptor molecule for the majority of TLRs, which are the most studied pathogen recognition receptors, and MyD88 knockout mice are characterized by increased bacterial translocation. Evidence thus indicates that MyD88 plays a key role in the shaping of the microbiome and energy homeostasis via its interactions with gram-negative intestinal bacterial strains.[24,25] Moreover, intestinal epithelial MyD88 can also function as a sensor that regulates host metabolism via energy expenditure and SCFAs.[26] In this respect, it was recently found that postprandial dyslipidemia and endotoxemia are correlated in obese insulin-resistant subjects, underscoring the relation between intestinal-derived endotoxemia and lipid metabolism.[27,28] Obese patients and patients with T2DM have a moderate decrease in intestinal microbiota diversity with changes of the 2 dominant bacterial divisions, the *Bacteroidetes* and the *Firmicutes*. Moreover, metagenome-wide association studies showed that patients with insulin resistance as well as T2DM had a decrease in important butyrate-producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia* species) and an increase in Gram-negative, LPS-containing pathogens such as *Escherichia coli*.[29]

The current hypothesis is that either lysis of Gram-negative bacteria resulting in increased LPS load or direct translocation of Gram-negative intestinal bacteria subsequently triggers proinflammatory cytokines and results in insulin resistance. The reduction in SCFA-producing bacteria might facilitate bacterial translocation due to impaired intestinal barrier function, accelerating low-grade endotoxemia. This endotoxemia subsequently fuels visceral white adipose tissue (WAT) inflammation, as mice fed a high-fat diet exhibited an infiltration of large numbers of $CD8^+$ T cells and accumulation of macrophages in WAT. Furthermore, immunologic and genetic depletion of $CD8^+$ T cells diminished infiltration of macrophages and inflammation in the visceral adipose tissue of mice fed a high-fat diet.[30,31] Because LPS has been shown to promote the accumulation of macrophages in WAT,[32] these data suggest that an altered (trained) innate immune response of macrophages might be crucial in the development of bacterial translocation and subsequent chronic inflammation.[33] In this regard, it is noteworthy that the DNA of intestinal bacteria has been found in mesenteric visceral adipose tissue of mice fed a high-fat diet. Indeed, bacterial DNA load in plasma was shown to be an independent marker of development of T2DM.[34] These results thus suggest a causal connection between malfunctioning of the innate immune system and development of metabolic syndrome; however, human data are still lacking.

Causal Role of Gut Microbiota in Glucose and Lipid Metabolism: A Role for SCFA?

As described earlier, insulin resistance is correlated with obesity and low-grade inflammatory conditions attributed in part to changes in intestinal microbiota. However, the question remains whether these changes are causal or merely a consequence of obesity. Causal evidence comes from mouse studies; 1 of the earliest metabolic studies of germ-free mice indicated that fecal transplantation using stool harvested from conventionally raised mice induced weight gain and increased insulin resistance within 14 days.[8] A follow-up study showed that when fecal microbiota was transplanted from adult female twin pairs discordant for obesity into germ-free mice, it induced a phenotype in the murine recipient similar to that of the fecal donor. Furthermore, co-housing mice harboring an obese twin's microbiota with mice containing the lean co-twin's microbiota prevented the formation of the obesity-associated phenotype.[35] We recently reported a similar effect in humans showing that in obese male subjects with metabolic syndrome, fecal microbiota transplantation from lean donors induced improved insulin sensitivity and lipid metabolism by increasing SCFA-producing bacterial strains both in the small and the large intestines.[36] In this respect, it is interesting to note that intestinal microbiota promote absorption of dietary lipids from the intestinal lumen by intestinal lipoprotein lipase inhibition via the expression of ANGPTL4.[8]

Another way to dissect causation from causality is to study the effect of antibiotics on gut microbiota composition. Insulin-resistant *ob/ob* mice treated with norfloxacin and ampicillin had significantly affected fasting glycemia as well as oral glucose tolerance test results. Similarly, we found that in obese male subjects with metabolic syndrome who were randomized to

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receive either 7 days of amoxicillin (targeting Gram-negative/anaerobic bacteria) or 7 days of vancomycin (targeting Gram-positive bacteria), deterioration in insulin resistance was seen in the vancomycin group but not in the amoxicillin group. The reduction in insulin resistance was associated with a concomitant decrease in secondary bile acids (a by-product of intraluminal bacterial dehydroxylation of primary bile acids) and a markedly decreased population of SCFA-producing bacteria within the *Firmicutes* phylum.[37] Apart from their role in lipid absorption and cholesterol homeostasis, bile acids seem to play an important regulating role in metabolism by functioning as signaling molecules. Among their signaling targets are TGR5 (activated by secondary bile acids) and the nuclear receptor farnesoid X receptor.[38,39] Murine studies have shown that secondary bile acid–induced TGR5 signaling increases energy expenditure in brown adipose tissue via activation of 2 iodothyronine deiodinase, mediated by increasing the production of cyclic adenosine monophosphate.[40] TGR5 also directly affects secretion of glucagon-like peptide-1,[41] an incretin that improves postprandial glucose handling.[42]

Another factor that affects incretin release are SCFAs.[12] Based on stable isotope fluxes, it is estimated that SCFA turnover accounts for ~7% of total resting energy expenditure, with an approximate production of 8 g per day of SCFA butyrate in the intestine.[43] The SCFA produced may serve as an energy source for the intestinal epithelium and the liver, as they are absorbed and transported mainly via the portal vein. Stable isotope–based studies in mice showed that the gut-derived SCFAs acetate, propionate, and butyrate play important roles as substrates for glucose, cholesterol, and lipid metabolism.[44] The SCFAs propionate and butyrate have the ability to activate intestinal gluconeogenesis (IGN). Butyrate can increase IGN directly via an increase in cyclic adenosine monophosphate. Propionate, conversely, increases IGN via a gut–brain neural circuit involving GPR41 signaling.[45] Increased IGN leads to increased glucose concentration in the portal vein, which results in decreased hunger and food intake.[46] Reduced intestinal levels of SCFA with a subsequent increase in indigestible carbohydrate excretion in the feces were found in germ-free–raised mice, demonstrating a crucial role of intestinal bacteria in the production of these SCFAs.[47]

Obesity is also associated with a reduction in the SCFA butyrate-producing *Akkermansia muciniphila* strain in the intestine, whereas oral gavage with *A muciniphila* improved low-grade inflammation, the gut barrier, and gut peptide secretion.[48] Thus, modulation of the gut microbiota (by an increase in the *Akkermansia* species population) may contribute to the antidiabetic effects of metformin, thereby providing a new mechanism for the therapeutic effect of this agent in patients with T2DM.[49]

Finally, the gut microbiota modulates brown adipose tissue activation, as the absence of gut microbiota stimulates both hepatic and brown adipose tissue lipolysis while inhibiting lipogenesis.[50] These findings are in agreement with data showing that pure supplementation of butyrate can prevent fat accumulation in the liver and subsequent insulin resistance in mice. The mechanism of butyrate action may be related to promotion of energy expenditure and induction of mitochondrial uncoupling.[51] It is thought that the NLRP6 and NLRP3 inflammasomes and the effector protein interleukin-18 negatively regulate fatty liver disease (nonalcoholic fatty liver disease/nonalcoholic steatohepatitis progression), as well as multiple aspects of metabolic syndrome via modulation of the gut microbiota. Various mouse models revealed that inflammasome deficiency–associated changes in the configuration of the gut microbiota are associated with exacerbated hepatic steatosis and inflammation through influx of TLR4 and TLR9 agonists into the portal circulation, leading to enhanced hepatic tumor necrosis factor-α expression that drives the progression of non-alcoholic steatohepatitis.[52] Clearly, the effects of the intestinal microbiota on host metabolism are complex, and the quantitative contribution of the bile acids SCFA and as-yet unknown bacterial metabolites must be established.

DISCUSSION

There are many ways to further study causality and magnitude of the metabolic effects of the intestinal microbiota and translate these findings into clinical therapeutics. An attractive option is the prospective collection of fecal samples in otherwise healthy subjects, of whom a substantial amount will convert from obesity to metabolic syndrome; this topic was studied in the HELIUS (Healthy Life in an Urban Setting) study (Stronks, 2013). From a more therapeutic angle, one might consider replenishing missing intestinal bacterial strains to efficiently process dietary compounds such as protein and carbohydrates, which are known to affect postprandial glycemic profiles in insulin-resistant subjects (Belinova, 2014). Conversely, supplementation of specific intestinal bacteria or their metabolites (including sodium

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butyrate) might beneficially influence metabolism and thus reverse insulin resistance and increase energy expenditure; a study on this topic is ongoing at our department. Finally, using targeted vaccination to boost the immune system against intestinal microbiota may be a novel therapeutic option for the regulation of metabolism and the prevention of cardiometabolic disease. Further research in humans is needed to confirm the causality of intestinal microbial strains in human metabolism, but even more importantly, experimental findings on correlations between microbial communities and specific cardiometabolic phenotypes should be corroborated by more detailed mechanistic investigations and, ideally, therapeutic intervention studies in humans.

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CONFLICTS OF INTEREST

AMC hospital owns several patents in the field; Dr. Nieuwdorp is on the scientific advisory board of Seres Health and of Caelus Pharmaceuticals. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Bäckhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. *Science*. 2005;307:1915–1920.
2. Hill MJ. Intestinal flora and endogenous vitamin synthesis. *Eur J Cancer Prev*. 1997;6:S43–S45. http://www.ncbi.nlm.nih.gov/pubmed/9167138. Accessed January 9, 2015.
3. Honda K, Littman DR. The microbiome in infectious disease and inflammation. *Annu Rev Immunol*. 2012;30:759–795.
4. Nieuwdorp M, Gilijamse PW, Pai N, Kaplan LM. Role of the microbiome in energy regulation and metabolism. *Gastroenterology*. 2014;146:1525–1533.
5. Hartstra AV, Bouter KE, Bäckhed F, Nieuwdorp M. Insights into the role of the microbiome in obesity and type 2 diabetes. *Diabetes Care*. 2014;38:159–165.
6. Khan MT, Nieuwdorp M, Bäckhed F. Microbial modulation of insulin sensitivity. *Cell Metab*. 2014;20:753–760.
7. Flint HJ, Bayer EA, Rincon MT, et al. Polysaccharide utilization by gut bacteria: potential for new insights from genomic analysis. *Nat Rev Microbiol*. 2008;6:121–131.
8. Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004;101:15718–15723.
9. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*. 2013;500:541–546.
10. Cotillard A, Kennedy SP, Kong LC, et al. Dietary intervention impact on gut microbial gene richness. *Nature*. 2013;500:585–588.
11. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007;87:1409–1439.
12. Wichmann A, Allahyar A, Greiner TU, et al. Microbial modulation of energy availability in the colon regulates intestinal transit. *Cell Host Microbe*. 2013;14:582–590.
13. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci U S A*. 2008;105:16767–16772.
14. Tolhurst G, Heffron H, Lam YS, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes*. 2012;61:364–371.
15. Liou AP, Paziuk M, Luevano JM, et al. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Sci Transl Med*. 2013;5:178ra41.
16. Mehta NN, McGillicuddy FC, Anderson PD, et al. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. *Diabetes*. 2010;59:172–181.
17. Sun L, Yu Z, Ye X, et al. A marker of endotoxemia is associated with obesity and related metabolic disorders in apparently healthy Chinese. *Diabetes Care*. 2010;33:1925–1932.
18. Ghoshal S, Witta J, Zhong J, et al. Chylomicrons promote intestinal absorption of lipopolysaccharides. *J Lipid Res*. 2009;50:90–97.
19. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56:1761–1772.
20. De La Serre CB, Ellis CL, Lee J, et al. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol*. 2010;299:G440–G448.
21. Caricilli AM, Picardi PK, de Abreu LL, et al. Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice. *PLoS Biol*. 2011;9:e1001212.
22. Shi H, Kokoeva MV, Inouye K, et al. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest*. 2006;116:3015–3025.
23. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010;328:228–231.
24. Fitzgerald KA, Palsson-McDermott EM, Bowie AG, et al. Mal (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. *Nature*. 2001;413:78–83.
25. Hosoi T, Yokoyama S, Matsuo S, et al. Myeloid differentiation factor 88 (MyD88)-deficiency increases risk of diabetes in mice. *PLoS One*. 2010;5:e12537.

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26. Everard A, Geurts L, Caesar R, et al. Intestinal epithelial MyD88 is a sensor switching host metabolism towards obesity according to nutritional status. *Nat Commun*. 2014;5:5648.
27. Harte AL, Varma MC, Tripathi G, et al. High fat intake leads to acute postprandial exposure to circulating endotoxin in type 2 diabetic subjects. *Diabetes Care*. 2012;35:375–382.
28. Clemente-Postigo M, Queipo-Ortuño MI, Murri M, et al. Endotoxin increase after fat overload is related to postprandial hypertriglyceridemia in morbidly obese patients. *J Lipid Res*. 2012;53:973–978.
29. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*. 2012;490:55–60.
30. Nishimura S, Manabe I, Nagasaki M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med*. 2009;15:914–920.
31. Feuerer M, Herrero L, Cipolletta D, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med*. 2009;15:930–939.
32. Caesar R, Reigstad CS, Bäckhed HK, et al. Gut-derived lipopolysaccharide augments adipose macrophage accumulation but is not essential for impaired glucose or insulin tolerance in mice. *Gut*. 2012;61:1701–1707.
33. Saeed S, Quintin J, Kerstens HH, et al. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science*. 2014;345:1251086.
34. Amar J, Serino M, Lange C, et al. Involvement of tissue bacteria in the onset of diabetes in humans: evidence for a concept. *Diabetologia*. 2011;54:3055–3061.
35. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*. 2013;341:1241214.
36. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012;143:913–916.e7.
37. Vrieze A, Out C, Fuentes S, et al. Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *J Hepatol*. 2014;60:824–831.
38. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. *J Biol Chem*. 2003;278:9435–9440.
39. Makishima M, Okamoto AY, Repa JJ, et al. Identification of a nuclear receptor for bile acids. *Science*. 1999;284:1362–1365. http://www.ncbi.nlm.nih.gov/pubmed/10334992. Accessed January 2, 2015.
40. Watanabe M, Houten SM, Mataki C, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*. 2006;439:484–489.
41. Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochem Biophys Res Commun*. 2005;329:386–390.
42. Thomas C, Gioiello A, Noriega L, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metab*. 2009;10:167–177.
43. Pouteau E, Nguyen P, Ballèvre O, Krempf M. Production rates and metabolism of short-chain fatty acids in the colon and whole body using stable isotopes. *Proc Nutr Soc*. 2003;62:87–93.
44. Den Besten G, Lange K, Havinga R, et al. Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. *Am J Physiol Gastrointest Liver Physiol*. 2013;305:G900–G910.
45. De Vadder F, Kovatcheva-Datchary P, Goncalves D, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell*. 2014;156:84–96.
46. Mithieux G, Misery P, Magnan C, et al. Portal sensing of intestinal gluconeogenesis is a mechanistic link in the diminution of food intake induced by diet protein. *Cell Metab*. 2005;2:321–329.
47. Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*. 2009;461:1282–1286.
48. Everard A, Belzer C, Geurts L, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*. 2013;110:9066–9071.
49. Shin NR, Lee JC, Lee HY, et al. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut*. 2014;63:727–735.
50. Mestdagh R, Dumas ME, Rezzi S, et al. Gut microbiota modulate the metabolism of brown adipose tissue in mice. *J Proteome Res*. 2012;11:620–630.
51. Gao Z, Yin J, Zhang J, et al. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes*. 2009;58:1509–1517.
52. Henao-Mejia J, Elinav E, Jin C, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature*. 2012;482:179–185.

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