Host–Microbiota Mutualism in Metabolic Diseases

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The intestinal microbiota is a plastic ecosystem that is shaped by environmental and genetic factors, interacting with virtually all tissues of the host. Many signals result from the interplay between the microbiota with its mammalian symbiont that can lead to altered metabolism. Disruptions in the microbial composition are associated with a number of comorbidities linked to the metabolic syndrome. Promoting the niche expansion of beneficial bacteria through diet and supplements can improve metabolic disorders. Reintroducing bacteria through probiotic treatment or fecal transplant is a strategy under active investigation for multiple pathological conditions. Here, we review the recent knowledge of microbiota’s contribution to host pathology, the modulation of the microbiota by dietary habits, and the potential therapeutic benefits of reshaping the gut bacterial landscape in context of metabolic disorders such as obesity.

Keywords: microbiota, obesity, metabolism, dysbiosis, diet, probiotics, fecal transplant, co-metabolism

INTRODUCTION

The intestinal microbiota is a highly dynamic ecosystem in which hundreds of bacterial species and other microorganisms coexist along with their neighboring mammalian cells. Estimated numbers vary across studies, but it is believed that there are at least as many bacteria as host cells in humans, if not drastically more (1). The most abundant phyla in humans and rodent models are Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes, sharing functional structure among hosts species despite having low taxonomic identity (2). Environmental factors such as early microbial exposure and lifestyle, as well as host genetics, shape its composition and function (3, 4). The gut microbiota in turn affects the host metabolic phenotype, contributes to food and drug metabolism, and helps the immune system to develop (5). From the first observation that obese individuals have a distinct gut microflora compared to lean people (6), and the following efforts to elucidate the function of this altered microbiota (7), the past 10 years have seen a growing body of evidence on the impact of the gut microflora on the host. By transplanting the gut microbiota to germ-free (GF) animals, it has become possible to directly assess the causality of microbiota composition with diseases. In this review, we focus on the relationship between gut microbiota composition and host pathophysiology, and on how shaping the microbiota can be beneficial to promote host health and combat metabolic disorders.

DEREGULATION OF THE GUT MICROBIOTA AND THE METABOLIC SYNDROME

Microbiota Compositional Changes in Metabolic Disorders

The gut microbiota is sensitive to external cues that can reshape it to new stable compositions, resulting sometimes in a deranged, or dysbiotic gut flora. Dysbiotic states are often associated with...
metabolic alterations in both humans and rodent models such as obesity (6), type 2 diabetes (8), non-alcoholic fatty liver disease (NAFLD) spectrum (9), and dyslipidemia (10). These metabolic traits are often clustered in metabolic syndrome patients (11); it is, therefore, relevant, but challenging, to distinguish the implication of the gut microbiota with each of these pathologies separately.

Germ-free mice are extensively used as a model for studying the importance of the dysbiotic gut flora. Interestingly, GF mice are resistant to obesity following high-fat diets (HFD), and their colonization leads to an increased adiposity along with decreased insulin sensitivity (12) and altered lipid metabolism (13). Nevertheless, when colonization occurs from an obese dysbiotic donor, recipient mice gain even more adiposity and increase their systemic inflammation (14). Considering that HFD challenges elicit heterogeneous responses in terms of weight gain and glucose homeostasis, the differences in the pre-HFD gut microbiota–host interactions in mice can be predictive of the diet outcome (15), where final HFD-driven microbial differences are determinant to transfer these acquired phenotypes following microbiota transplantation and diet challenge (16). Specifically, Le Roy et al. show that GF mice populated with microbiota from two donors similarly obese but discordant in glycemia phenocopy their response to HFD, with a similar increase in the body weight but hyperglycemia and steatosis only in one group. This suggests that components of the gut microbiota can influence liver steatosis and hyperglycemia independently from their effect on adiposity and systemic inflammation.

Dysbiotic microbial composition can be, at least in the case of the obesogenic microbiota, resilient over time. Whereas dieting rapidly reverses the metabolic defects associated with HFD, the dysbiosis provoked in mice after a 4-week HFD persists up to 21 weeks after returning to normal chow diet (17). Importantly, this persistent post-HFD dysbiotic microbiota is not sufficient to drive obesity by itself, but can induce weight gain and glucose intolerance upon exposure to a second HFD stimulus. This two-step obesogenic mechanism relies on a reduced bioavailability of flavonoids (dietary compounds that can promote brown adipose tissue activation and increase energy expenditure) due to the combination of their scarcity in high-fat food and increased flavonoid-degrading ability of the obese microbiota (17). Weight gain upon second exposure to calorie-rich food is a common problem in dieting individuals. Human data are, therefore, needed to assess the plasticity of the microbiota in obese individuals and determine an ideal diet length and composition that would be accomplished with complete and lasting microbial reshaping (17). Another evidence that dysbiosis by itself may not be sufficient to drive metabolic defects comes from the observation that transplant of dysbiotic microbiota to healthy conventional mice neither causes metabolic dysfunctions nor alters the hepatic metabolism (18).

Microbiome analysis on two independent human cohorts described an intestinal microbial signature predicting the glycemic status (19, 20). The stratification of the microbiota analysis for metformin medication highlighted a commonly deregulated pathway in untreated type-2 diabetes (T2D) patients, characterized by decreased abundance of bacteria such as Roseburia spp. and Subdoligranulum spp., which produce butyrate, a known regulator of hepatic function through intestinal gluconeogenesis (8). Indeed, the metformin in part improves T2D by rescuing the decreased butyrate production through reshaping the microbiota, since microbial transplant from metformin-treated patients was sufficient to improve glucose control in GF mice (21, 22). Of note, other studies using meta-analyses, however, called for the need of large human cohorts to further generalize the predictive power of the microbiota (23–25).

Microbiota-Driven Regulation of Metabolism

Absence of microbiota in GF mice or through antibiotic treatment improves glucose and lipid metabolism (12, 13, 26, 27), protecting against diet-induced metabolic diseases. These improvements can, at least in part, be explained by increased activity of the thermogenic fat depots (26, 27), and can be reversed by microbial recolonization of the microbiota-depleted animals (27). Cold exposure, the most potent environmental trigger for brown and beige fat development and activation (28), drastically reshapes microbiota composition. Transplantation of this cold-adapted microbiota to GF mice is sufficient to induce tolerance to cold, improve insulin sensitivity, increase energy expenditure, and lower their fat content, largely due to increased brown and beige fat activity in the cold-microbiota transplanted mice (26, 29).

The complexity of the gut microbiota is reflected in its interplay with the host, with a great variety of signaling cues and relay organs (summarized in Table 1). Bile acids (BAs) are released after a meal directly in the proximal intestinal lumen and help lipid absorption by enterocytes. Since around 95% of BAs are reabsorbed in the distal intestine, the total BA pool is relatively stable across the enterohepatic circulation. The gut microbiota metabolizes primary BAs produced by the liver giving rise to secondary BAs, and this microbiota–liver cross talk is responsible of the BA pool (30). BAs act as signaling molecules through intracellular farnesoid X receptor with effect on the overall metabolism (31–35) and membrane-bound G-coupled bile acid receptor (TGR5). TGR5 stimulates intestinal glucagon-like peptide 1 (GLP1) production, brown fat activity, and improves hepatic metabolism in obese animals (36, 37). Interestingly, BAs signaling on intestinal cells can trigger their antimicrobial action (38), suggesting a negative feedback loop. In addition, it was suggested that the brown adipose tissue can also intervene into the gut microbiota–liver regulation of BA pool, since changes in cholesterol metabolism due to the brown adipose tissue activity during cold exposure can increase BAs biosynthesis and drive compositional changes in the gut microbiota (39).

Short chain fatty acids (SCFAs) derive from bacterial fermentation of dietary fibers. They can enter circulation and signal through their cognate receptors to many organs (52, 53) including the central nervous system, which in turn regulates other tissues (40). The SCFA acetate can act in the gut–brain communication, by directly suppressing appetite through hypothalamic activation (41). Conversely, evidence suggested that increased acetate levels in HFD microbiota relay into the parasympathetic nervous system activation driving ghrelin secretion and glucose-stimulated
insulin secretion, leading to hyperphagia and metabolic syndrome (42). Other SCFAs are also involved in energy regulation through the gut–brain axis after being sensed in the portal vein and signaling to the autonomous nervous system (54). The gut microbiota also produces or controls the synthesis of other neuroactive signals that can affect the enteric and central nervous system, like g-aminobutyric acid (43) and serotonin (44), both of which could influence appetite and energy balance (55, 56). The contribution of the microbiota-produced neuropeptides to these mechanisms is under active investigation (57).

A group of receptors that senses bacteria-derived metabolites and has been implicated in metabolism is the toll-like receptor family, with TLR2 and TLR4 being particularly important (58). Lipopolysaccharide (LPS), a component of the bacterial wall of Gram-negative species, plays a major role in metabolism pathophysiology. Metabolic endotoxemia, in part caused by increased LPS production, is a common consequence of high caloric diets and can affect host metabolism by inducing systemic inflammation and adipose tissue fibrosis, as well as decreasing thermogenesis and hepatic glucose metabolism (45–47). Accordingly, genetic inactivation of TLR4 in hematopoietic cells protects from NAFLD occurrence in mice housed with the people involved in their study, in HFD-fed mice, time restriction is associated with a decrease of obesogenic taxa and an increase in beneficial bacteria, thus improving host metabolism (64, 65) (Figure 1).

### Table 1: List of Microbe-Derived Signals that Impacts Host Metabolism

| Signal                          | Target organ                                     | Effect                                          | Reference |
|---------------------------------|--------------------------------------------------|-------------------------------------------------|-----------|
| Bile acids (BAs)                | Adipose tissue, intestine, liver                 | Hepatic metabolism, bacterial regulation, lipid metabolism | (36, 38) |
| Short chain fatty acids (SCFAs) | Adipose tissue, brain, intestine, liver, muscle  | Lipid metabolism, regulation of appetite        | (40–42)  |
| Neuroactive molecules [g-aminobutyric acid (GABA), serotonin] | Central and peripheral nervous system | Regulation of appetite                         | (43, 44) |
| Lipopolysaccharide (LPS)        | Adipose tissue, liver, brain                     | Systemic inflammation, hepatic glucose metabolism, adipose tissue fibrosis | (45–47)  |
| Trimethylamine N-oxide          | Adipose tissue, liver, kidney                    | Higher atherosclerosis risk, reduced beige fat  | (48, 49) |
| Branched-chain amino acids (BCAAs) | Adipose tissue, endothelium, skeletal muscle | Adipogenesis, lipid trafficking, lipogenesis, and insulin resistance | (12, 13, 26, 27, 50, 51) |

LPS, BAs, SCFAs, BCAAs, trimethylamine N-oxide, and neuroactive molecules are major known signals of microbial origin that can affect different metabolic organs listed together with the proposed model of action.

### DIETARY INTERVENTIONS AND THERAPEUTIC POTENTIAL OF MICROBIOTA RESHAPING

#### Feeding Patterns and Microbiota Compositional Fluctuations

Different lifestyles are associated with changes in microbiota composition, which can result in different efficacy in energy extraction from food and, therefore, impact host metabolism (7, 12). The general microbial composition, as well as the abundance of multiple taxa, undergoes circadian oscillations (66–68). This rhythmicity is dictated by the feeding pattern of the host controlled by its own circadian clock, as genetic depletion of the clock machinery, or its disruption due to jet lag induces dysbiosis and loss of diurnal cycling. In turn, the microbiota too can influence the circadian fluctuation of intestinal epithelial cells (69) and affect intestinal and hepatic metabolism through rhythmic patterns of attachment to the mucosa and metabolomic changes (70). The timing of meals, therefore, influences acute compositional fluctuations in the gut microbiota and modulate microbial-dependent effects on the host. For instance, time-restricted feeding (limiting food access to 10–11 h/day) reduces body weight and improves well-being in overweight individuals (71). While the authors did not explore the subsequent changes in the microbiota of the people involved in their study, in HFD-fed mice, time restriction is associated with a decrease of obesogenic taxa and an increase in beneficial bacteria, thus improving host metabolism (67).
**Dietary Fibers and Prebiotics**

Diet composition is one of the most important factors that shape the gut microbiota. Diets rich in saturated fatty acids are associated with insulin resistance and adipose inflammation (72), whereas polyunsaturated fats have an insulin-sensitizing role (73). Both kinds of dietary lipids affect metabolism through compositional changes in the gut microbiota and signaling of microbial byproducts to the host (74). Protein intake and protein–carbohydrate ratio also impact the production of multiple bacterial metabolites (75). Carbohydrates constitute an important source of energy for the microbiota and, as mentioned above, their byproducts—the SCFAs influence host metabolism. The reduced fiber intake in western diets is associated with reduced bacterial richness and metabolic disorders (76), both of which can be rescued in overweight individuals by dieting (77, 78). Increased fiber consumption leads to improved postprandial glucose metabolism in response to whole grain-based meals (79) and is associated with an increase in *Prevotella* abundance (80) and a higher ratio of *Prevotella* over *Bacteroides*, the two main genera of the *Bacteroidetes* phylum. During fiber-rich diet, *Prevotella* appears to positively interact with species from the *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Archaea* phyla to form a niche of bacteria involved in carbohydrate fermentation (81). This contributes to an improved glucose metabolism through increased hepatic glycogen storage (81).

Administration of oligofructose in obese mice regulates appetite, reduces obesity, and the related metabolic disturbances. These improvements are associated with 100-fold increase in the abundance of *Akkermansia muciniphila*, increased growth of *Bifidobacteria*, and *Lactobacilli*, and expression of antimicrobial peptides by the host (82, 83). Studies on healthy and obese individuals demonstrate expansion in *Bifidobacterium* species and *Faecalibacterium prausnitzii* during prebiotic treatment. Prebiotics can also induce satiety by regulating the SCFAs (84) and increasing Peptide YY and GLP1 production by the L cells in the ileon and the colon (85–87). In turn, these enteroendocrine hormones inhibit the hypothalamic orexigenic (hunger-inducing) regions and stimulate the anorexigenic (satiety-inducing) neurons (85–88). Fiber-rich diets also impact the interaction between the microbiota and the intestinal mucosal layer, a barrier that separates the epithelium from direct contact with bacteria, constituting a first level of defense against pathogen infection (89). Prebiotic treatment promotes production of the glucagon-like peptide-2, which increases mucosal barrier function and reduces endotoxin-driven inflammation in obese mice (90). Conversely, disruption or ablation of the mucose layer leads to intestinal inflammation, colitis, and even cancer (91–93). In absence of dietary fibers, the mucus layer is dramatically reduced due to expansion of a mucin-degrading bacterial niche. This causes susceptibility to enteric pathogens (94) and increases the predisposition toward metabolic disorders. Indeed, monoclonization with *Bacteroides thetaiotaomicron*, a mucin degrader in absence of other available sources of energy, causes impaired glucose tolerance through decreased hepatic glycogen storage (81). Conversely,
fiber-rich diets in humans promote the presence of species from the *Xylanibacter, Prevotella, Butyrivibrio,* and *Treponema* genera, preventing the colonization of intestinal pathogens like *Enterobacteriaceae* (95, 96). A vertical study in mice addressed the long-term effects on microbial changes in response to a low fiber diet. Whereas reverting to a fiber-rich diet within a single generation mostly restores the microbial composition, the loss of microbial taxa under fiber-low diets is not reversible after several generations (97). These results suggest that in addition to the dietary changes, it may be necessary to reintroduce beneficial taxa that are currently lost in the Western microbiota in order to prevent the diseases associated with it.

**Probiotics**

Probiotics are live bacteria, usually present in fermented foods, whose intake improves metabolic health. Their supplementation in diet has been associated with protective effects against irritable bowel syndrome (IBS), ulcerative colitis, allergic diseases, and obesity in both rodents and humans. They are mostly Gram-positive bacteria belonging either to the *Lactobacillus* or *Bifidobacterium* genera, although a Gram-negative, non-pathogenic, *Escherichia coli* strain has also a probiotic effect (98). The mechanism of action of probiotics is quite heterogeneous and depends on the specific strain used. The anti-obesity effects include reducing metabolic endotoxemia (99–101), improving endothelial dysfunction in obese mice (102, 103), improving hepatic steatosis (104), and limiting free fatty acids available to the host (105). This wide range of effects is mediated by multiple, mutually linked mechanisms like increased intestinal adhesion and colonization that limit the colonization of less beneficial bacteria, production of metabolites such as SFCA and poly-unsaturated fatty acids (106, 107), release of antibacterial molecules called bacterocins (108), and strengthening of the intestinal epithelial integrity and the intestinal mucus layer (109). Recently, in addition to “traditional” probiotic species, *A. muciniphila* has gained a lot of interest. Abundance of this species is inversely correlated with body weight and insulin resistance, and its increase is another effect of metformin treatment (110). Daily supplementation of *A. muciniphila* in mice ameliorates HFD-induced metabolic dysfunctions (111), and prevents the increased intestinal absorptive surface and caloric uptake during cold exposure (26). Even pasteurized, *A. muciniphila* potently reduces body weight gain and insulin resistance in obese mice, due to an outer membrane protein called Amuc_1100, which activates TLR2 and restores intestinal gut barrier function (112). Since *A. muciniphila* is a strict anaerobic species, the discovery that it can exert its protective function against metabolic disorders after pasteurization makes it a more manageable and therapeutically interesting tool.

**Fecal Transplants**

Another way to restore a dysbiotic state and reintroduce beneficial taxa is through fecal microbiota transplant (FMT) from a healthy donor. It is currently mainly used to restore intestinal balance in patients affected by recurrent *Clostridium difficile* infections, with a success rate up to 94% and without adverse effects (113). Since dysbiotic states are clinically similar regardless of the origin, this therapy is currently being tried also for non-infectious intestinal pathologies, like intestinal bowel disease and IBS (114, 115), with first few randomized trials that suggest, at least for IBS, a recovery in bacterial richness after transplantation and an attenuation of the symptoms (114, 116). In the context of the metabolic syndrome, a first human trial on obese Caucasian male subjects showed an increase in peripheral insulin sensitivity in patients receiving allogenic gut microbiota, as well as a tendency to increased hepatic insulin sensitivity (117). Subsequent analyses on this and other cohorts of human patients undergoing FMT (118) have suggested that the stimulation of the recipient microbiota with the donor one has an important impact on the efficiency of the microbial transfer and its persistence in the host and that, therefore, the outcome of FMT depends on the composition of both microbiota (119, 120). With FMT being suggested also for a plethora of other pathologies including anxiety, depression, and even autism (116, 121), increasing our knowledge on the function and the interaction of the gut microflora within itself and with the host will, therefore, be paramount in order to design microbiota-based therapies.

**PERSPECTIVES**

Dissecting how bacterial cues are sensed and act on host physiology is essential to either modulate the microbiota or mimic its signals in a therapeutic perspective. Nevertheless, the known variability of microbial ecosystems in humans is currently a constraint for standard treatments. We can envision an approach where the advances in gut microbiota profiling applied to personalized medicine could allow the definition of pipelines for treatments aiming at re-establishing a healthy microflora. These considerations can potentially overcome the current obstacles in single taxa reintroduction or fecal microbiota transfer and could rely on sequential treatments to reopen ecological niches for beneficial bacteria.

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The authors reviewed literature, conceived, and wrote the manuscript and artwork.

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84. Salazar N, Dewulf EM, Neyrinck AM, Bindels LB, Cani PD, Mahillon J, et al. Inulin-type fructans modulate intestinal *Bifidobacterium* species populations and decrease fecal short-chain fatty acids in obese women. *Clin Nutr* (2016) 35:501–7. doi:10.1016/j.clnu.2015.12.001

85. Ramirez-Farias C, Slezek K, Fuller Z, Duncan A, Holtrop G, Louis P. Effect of inulin on the human gut microbiota: stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. *Br J Nutr* (2009) 101:541–50. doi:10.1017/S0007114508019880

86. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr* (2009) 89:1751–9. doi:10.3945/ajcn.2009.27465

87. Cani PD, Leibson C, Van de Wiele T, Guist Y, Ehrard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* (2009) 58:1091–103. doi:10.1136/gut.2008.165886

88. Johansson ME, Gustafsson JK, Holmen-Larsson J, Jabbar KS, Xia L, Xu H, et al. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut* (2014) 63:281–91. doi:10.1136/gutjnl-2012-303207

89. Fu J, Wei B, Wen T, Johansson ME, Liu X, Bradford E, et al. Loss of intestinal core 1-derived O-glycans causes spontaneous colitis in mice. *J Clin Invest* (2011) 121:1657–66. doi:10.1172/JCI45538

90. Van der Sluis M, De Koning BA, De Bruijn AC, Velcich A, Meijerink JP, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* (2013) 10:482–8. doi:10.1073/pnas.1219451110

91. Hsieh CY, Osaka T, Moriyama E, Date Y, Kikuchi J, Tsuneda S. Strengthening of the intestinal epithelial tight junction by *Bifidobacterium bifidum*. *Physiol Rep* (2015) 3:e12327. doi:10.14814/phy2.12327

92. Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, et al. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* (2014) 63:727–35. doi:10.1136/gutjnl-2012-303839

93. Everard A, Belzer C, Geurs S, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* (2013) 109:9066–71. doi:10.1073/pnas.1219451110

94. Plover H, Everard A, Druart C, Depommier C, Van Hul M, Geurts S, et al. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat Med* (2016) 23:107–13. doi:10.1038/nm.4236

95. Gough E, Shai B, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis* (2011) 53:994–1002. doi:10.1093/cid/cir632

96. Hallaer SJ, Boshoven AW, Gunther S, Christensen AH, Petersen AM. Can a faecal microbiota transplantation cure irritable bowel syndrome? *World J Gastroenterol* (2017) 23:4112–20. doi:10.3748/wjg.v23.i42.4112

97. Lane ER, Zisman TL, Suskind DL. The microbiota in inflammatory bowel disease: current and therapeutic insights. *J Inflamm Res* (2017) 10:63–73. doi:10.2147/JIR.S116088

98. Muzzo S, Masaka T, Naganuma M, Kishimoto T, Kitazawa M, Kurokawa S, et al. *Bifidobacterium*-rich fecal donor may be a positive predictor for successful fecal microbiota transplantation in patients with irritable bowel syndrome. *Gastroenterology* (2017) 152:961–70. doi:10.1053/j.gastro.2016.12.0313

99. Schlossing S, Arumugam M, Sunagawa S, Mitreva M, Tap J, Zhu A, et al. Genomic variation landscape of the human gut microbiome. *Nature* (2013) 493:45–50. doi:10.1038/nature11711

100. Li SS, Zhu A, Benes V, Costea PI, Hercol R, Hildebrand F, et al. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. *Science* (2016) 352:586–9. doi:10.1126/science.aad8852

101. de Groot PF, Frissen MN, de Clercq NC, Nieuwdorp M. Fecal microbiota transplantation in metabolic syndrome: history, present and future. *Gut Microbes* (2016) 7:825–67. doi:10.1080/19490976.2017.1293224

102. Mauricio MD, Serna E, Fernandez-Murga ML, Portero J, Aldasoro M, Valles SL, et al. *Bifidobacterium pseudocatenulatum* CECT 7765 supplementation restores altered vascular function in an experimental model of obese mice. *Int J Med Sci* (2011) 8:44–51. doi:10.7915/jims.18354

103. Toral M, Gomez-Guzman M, Jimenez R, Romero M, Sanchez M, Urrilla MP, et al. The probiotic *Lactobacillus casei* strain IM38 ameliorates high-fat diet-induced blood glucose intolerance and obesity. *Clin Sci (Lond)* (2014) 127:33–45. doi:10.1042/CS20130339

104. Li Z, Jin H, Oh SY, Ji GE. Anti-obese effects of two Lactobacilli and two Bifidobacteria on ICR mice fed on a high fat diet. *Biochem Biophys Res Commun* (2016) 480:222–7. doi:10.1016/j.bbrc.2016.10.031

105. Chung HJ, Yu JG, Lee IA, Liu MJ, Shen YF, Sharma SP, et al. Intestinal removal of free fatty acids from hosts by Lactobacilli for the treatment of obesity. *FEBS Open Bio* (2016) 6:64–76. doi:10.1111/1758-081X.12104

106. Matsuki T, Pedron T, Regnault B, Mulet C, Hará T, Sansonetti PJ. Epithelial cell proliferation arrest induced by lactate and acetate from *Lactobacillus casei* and *Bifidobacterium breve*. *PLoS One* (2013) 8:e63053. doi:10.1371/journal.pone.0063053

107. Aoki R, Kamikado K, Suda W, Takii H, Mikami Y, Suganuma N, et al. A proliferative probiotic *Bifidobacterium* strain in the gut ameliorates progression of metabolic disorders via microbiota modulation and acetate elevation. *Sci Rep* (2017) 7:43522. doi:10.1038/srep43522

108. Martinez FA, Bakiunas EM, Converti A, Cotter PD, de Souza Oliveira RP. Bacterial production of short-chain fatty acids improves glucose homeostasis in diet-induced obese mice. *Gut Microbes* (2016) 3:e12327. doi:10.14814/phy2.12327

109. Hoekstra PH, Wijngaard IE, Stiggelbout AM, van Vliet ML, Benoist MM, et al. Microbiota transfer therapy alters gut ecosystem and improves insulin sensitivity in individuals with metabolic syndrome. *J Inflamm Res* (2017) 8:253–67. doi:10.1080/19490976.2017.1293224

110. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota transfer therapy alters gut ecosystem and improves insulin sensitivity in inflammatory bowel disease. *Frontiers in Endocrinology* | www.frontiersin.org 8 October 2017 | Volume 8 | Article 267
gastrointestinal and autism symptoms: an open-label study. *Microbiome* (2017) 5:10. doi:10.1186/s40168-016-0225-7

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