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The Gut Microbiota: The Gateway to Improved Metabolism

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Abstract

Obesity is an emerging global epidemic with profound challenges to world healthcare economies and societies. Traditional approaches to fight obesity have not shown promise in promoting a decline in obesity prevalence. The gut microbiota are becoming widely appreciated for its role in regulating metabolism and thus represents a target for new therapies to combat obesity and associated co-morbidities. In this review, we provide an overview of altered microbial community structure in obesity, dietary impact on the gut microbiota, host-microbe interactions contributing to the disease, and lastly improvements in microbial assemblage after bariatric surgery and with therapies targeting the gut microbiome.

Keywords

Microbiota; Microbiome; Obesity; Metabolism; Bariatric Surgery; RYGB; Enteroendocrine Hormones; Lipid Absorption; Circadian Rhythm; Probiotics; Prebiotics; Synbiotics

Introduction: Obesity and the Gut Microbiota

The rise of obesity and its related comorbidities in ‘westernized’ countries over the past four decades presents an emerging global epidemic with profound challenges to world healthcare economies and societies. In the past 35 years, the rate of adult obesity has risen by 75% globally^{1,2}. This number was greater among children^{3,4}. Stratified assessment of Body Mass Index (BMI) further demonstrates disproportionate increases among the most severely obese (35 kg/m^2), compared with the lesser obese (30 kg/m^2), illustrating the scale of the problem. Unfortunately, obesity and its comorbidities⁵, including metabolic syndrome, diabetes, and heart disease, have detrimental effects on quality of life and substantial costs to individuals and societies. Thus, the need for understanding the complexity of pathophysiological events and elucidating effective interventions remain urgent.

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The etiology of obesity is multifactorial, including the complex interaction of genetics and environment, which encompasses diet, developmental factors, lifestyle (eg. hedonistic tendencies, altered sleep patterns), and antibiotic use. Intestinal microbes are impacted by all of these factors in their community structure and function and in turn initiate host-microbe interactions that may disrupt metabolic and immune homeostasis. Strikingly, fecal microbiota transplant (FMT) of microbes under environmental stressors, like diet and obesity, can induce a similar phenotype in recipients ⁶. Indeed, the gut microbiome is by definition a microbial organ - vital to intestinal and systemic functions – one that we cannot live without, but also an organ that is transplantable (i.e., via FMT). This technique is commonly used for *Clostridium difficile* infection and has only recently been studied for use in other conditions, including obesity. However, other therapies targeting the microbiome, such as pre- and pro-biotics, may confer modest, yet positive, improvements for symptoms associated with obesity and its comorbidities.

Although an extreme measure reserved for the morbidly obese, one of the most effective strategies to decrease obesity is bariatric surgery which profoundly changes the gut microbiota, energy balance, and alters physiological and endocrine metabolic states ⁷. It is expected that by changing metabolic set points, desired weight can be achieved. Therefore, understanding the mechanisms behind bariatric surgery and associated changes in the gut microbiota may be leveraged to develop new therapies to fight the obesity epidemic. In this review, we explore these concepts by providing an overview of altered microbial structure and function in obesity, host-microbe interactions driving obesity, dietary influence on the microbiome, improvements in metabolism and microbial structure with RYGB, the host-microbe interactions driving obesity, and lastly current therapies targeting the gut microbiome to facilitate positive metabolic outcomes.

Paradigms in Gut Microbiota During Obesity

Obesity-Driven Alterations in Gut Microbiota

The human body contains staggering numbers of microbes, including thousands of bacterial species, in addition to many eukaryotes, Achaea, protists, and viruses, which collectively contain an estimated 5 million genes that have profound metabolic and immunomodulatory effects upon the mammalian host ⁸. The community of microbes is termed the microbiota, while their collective genes are called the microbiome. Both the state of obesity and westernized diets are associated with microbial dysbiosis, which is a deviation from microbial organization that would otherwise promote optimal metabolic homeostasis. Dysbiotic microbiota in obesity is characterized by decreased diversity in the microbial community and by an increased ratio of the phylum Firmicutes to the phylum Bacteroidetes ⁹. The change in Firmicutes and Bacteroidetes ratio occurs in both mice and humans, and weight loss restores microbial composition ^{9–11}. Interestingly, 3 genres of bacteria are often overrepresented under obesity in humans, including *Bacteroides* and *Prevotella* (both Bacteroidetes) or *Ruminococcus* (Firmicutes) ¹². In addition to composition, major functional differences are observed in metabolic capacity of the microbial community. For instance, decreases in SCFA producers, such as from the phylum Actinobacteria and blooms in pathogenic bacteria from the phylum Proteobacteria, occur in

obesity¹³. In addition to bacteria, recent work demonstrates the microbiota metabolic networks include yeast and archaea, which synergistically produce and utilize metabolites collectively with bacteria¹⁴. While this area is still relatively unexplored, recent work suggests yeast species abundance is lower under obesity, and supplementation with *Saccharomyces cerevisiae* improves metabolic parameters and adiposity^{15–17}.

When dysbiotic communities of bacteria are transferred to naïve germ-free mice, the recipient mice develop increased adiposity, demonstrating a direct impact of the microbes on advancing fat storage in the mammalian host⁶. While some bacteria are associated with excess adiposity, others have been directly implicated in improving metabolic syndrome and atherosclerosis, such as *Akkermansia muciniphila*^{18,19}, which are often found to be underrepresented in obesity. Administration of *A. muciniphila* during obesity was shown to improve glucose tolerance¹⁹. Schneeberger *et al* found that among 27 genes that regulate inflammation and metabolism in white adipose tissue under high fat feeding, 20 genes negatively correlate with the relative abundance of *A. muciniphila*. Additionally, *Bifidobacterium spp.* also negatively correlated with 6 of 27 genes. Positive correlations were observed with *Bilophila wadsworthia* in 14 of 27 genes, and this microbe is known to expand under high milk fat diets and subsequently stimulate inflammatory responses²⁰. Together these observations suggest certain microbes might regulate aspects of peripheral metabolism related to obesity and metabolism, but further investigations to determine strong proof of causality are required.

Another line of evidence that supports the notion microbes might closely regulate host metabolism and body weight is found through the study of acute malnutrition in childhood. In contrast to overfed and obese individuals, work by Gordon and colleagues²¹ followed severely malnourished children for 2 years. Through compositional modeling, they demonstrated the microbiota normally develop with the growing child, but with malnutrition, the microbiota “maturity” remains stunted and lags behind host development. Even after common therapeutic food interventions, the immaturity of the microbiota persisted. Intriguingly, it was found that the microbiota remains immature even under less severe malnourished states and that microbiota maturity correlated with anthropometric measurements of the children²¹. These findings strongly support the notion of the gut microbiota functioning as a vital organ, and its development and growth throughout life may have important unknown implications for human health. Understanding the role of microbial development under states of hyper-alimentation may provide insights into dysfunctional microbial-host metabolic interactions that lead to excessive fat storage.

Dietary Impact on the Gut Microbiota

While host phenotype influences the composition of the microbial communities, diet also notably has an immediate and dramatic impact on microbial structure that mimics communities seen in obese individuals. For instance, Turnbaugh *et al* observed in humans that a diet rich in animal-derived fat and protein resulted in significant changes in the gut microbiota in as little as a day, and of particular note, blooms in hydrogen-sulfide producing bacteria such as *Bilophila wadsworthia* were also observed²². Later his group found that diet has a greater impact on altering microbial assemblage than genetic background in

mice²³. In this study, five different inbred mouse strains, four genetic knockout strains relevant to host-microbe interactions (e.g., ob/ob, NOD2, MyD88^{-/-}, and Rag1^{-/-}), and 200 outbred mice were placed on high-fat, high-sugar diets or diets rich in plant polysaccharides. In each experiment, the western diet had profoundly altered community structure, regardless of strain differences or gene deficiencies²⁴. More recently, Sonnenburg's group nicely demonstrated that diets low in microbe-accessible carbohydrate (MAC) and high in simple sugars result in loss of bacterial diversity and extinction of specific microbial groups which is compounded over generations²⁵. The generational loss of bacterial diversity could only be remedied with fecal microbiota transplant from control mice maintained on the MAC-rich diet, but not by diet alone. This study provides a model for the rapid and drastic impact of our food supply, containing readily-available processed high-fat and high-sugar food, on the progressive loss of bacterial diversity over the past several decades. This theory postulates that our bodies are not equipped to reciprocate and adapt to the sudden insult on our gut microbiota, thereby leading to the development of obesity. Based on the results from this study, suitable therapies to combat the loss of bacterial diversity might include probiotic supplementation or fecal microbiota transplant.

High fat (HF) diets also transform the metagenomes of the bacteriophage community, also known as the "phageome." It was demonstrated by Howe and Ringus *et al.*²⁶ that HF diets can shift the "phageome" independent of observed alterations in their bacterial host pattern. The impact of diet on viral communities was also rapid, occurring within 24 hours. In addition, the change in the viral metagenomes by high fat diet was not reversible after washout, suggesting that diet-mediated changes in the phage community are persistent, similar to the aforementioned findings in bacteria²⁶. Further research in this area is needed to better understand the regulation and function of the phageome, its impact on gut microbial ecology, and more importantly consequences for the host.

Restructuring of Gut Microbiota in Bariatric Surgery

Surgical intervention, although largely invasive, is the most effective weight loss strategy for obesity. Roux-en-Y (RYGB) is the most common and the most effective, promoting a 20–40% weight loss compared to 15–30% loss of body weight with gastric banding²⁷. RYGB includes the formation of a small pouch, made of the upper stomach that is then attached to a region of jejunum approximately 75 cm distal to the stomach (termed a gastrojejunostomy). The resulting limb (including the distal stomach) carries bile, gastric juice, and pancreatic juices alone, without nutrients, another 125 cm distal from the gastrojejunostomy, collectively delaying the mixture of digestive juices from nutrients for approximately 200 cm up upper GI tract. It is becoming increasingly apparent that bariatric surgery, particularly RYGB, may involve multiple mechanisms beyond simply physical restrictions to nutrient intake and absorption through reduced stomach size and decreased absorptive capacity. It is plausible that new treatments will be discovered based on the mechanisms underlying bariatric surgery efficaciousness. Intriguing data suggests the mechanisms involved may include altered gut microbial function⁷ and interactions of the microbiome with the hosts bile acid pool^{28,29}.

Anatomical rearrangement triggers the dramatic restructuring of the intestinal microbiota and host-microbe interactions that may contribute to weight loss after bariatric surgery. For example, RYGB in mice resulted in the rapid restructuring of gut microbiota as early as one week compared to sham controls⁷. The early changes in microbial composition occur under the same time frames that improvement in glucose tolerance and reduced insulin resistance are observed³⁰, in contrast to body weight and adiposity changes that occur over weeks and months, suggesting microbial alterations may be involved in the resetting of metabolic set points that are distinct from adiposity. Specifically, RYGB results in a decrease in the Firmicutes to Bacteroidetes ratio, which includes increases in Bacteroidales, Enterobacteriales, as well as increases in Gammaproteobacteria (*E. coli*) and Verrucomicrobia⁷ as a relative percentage of the microbial community. Interestingly, the Verrucomicrobia genus *Akkermansia muciniphila* utilizes host secretion of mucin as a fuel source and has been inversely correlated with body weight¹⁹. As previously discussed, oral administration of live *Akkermansia muciniphila* restores insulin sensitivity in high fat fed animals¹⁹. Following RYGB in diabetic rodents, the level of *A. muciniphila* in the small bowel increased significantly compared with sham obese controls³¹. Intriguingly, in that study, the increase in *A. muciniphila* was positively related to the release of GLP-1, an important intestinal incretin, suggesting this microbe could be modulating peripheral glucose handling through modulated insulin tolerance. In humans following RYGB, an inverse correlation in the relative percentage of *E. coli*, *Bacteroides*, and *Prevotella* with circulating leptin levels were found, an important adipose factor released at higher levels under obesity³². Finally, the increases in Proteobacteria observed following RYGB have reached 50-fold, and together with other models suggest Proteobacteria may influence insulin sensitivity^{33,34}. A direct role for the microbial community in mediating host metabolism following RYGB was confirmed with fecal microbiota transplant from bariatric surgery donors into recipients, which conferred protection from obesity³⁵. Altogether, these studies provide strong evidence that the gut microbiota may significantly contribute to the effectiveness of RYGB surgery, paving the way for focused investigations into altering the microbiota in a similar manner for the treatment of obesity.

The direct role for microbes in improving metabolism following RYGB remain under investigation, but other indirect roles include microbial changes to the bile acid composition, bile-acid activation of the ileal and colonic bile acid receptors, and regulation of gut peptide enteroendocrine hormones, such as GLP-1 and PYY. Current evidence suggests the composition of bile acids influence the microbiota assemblage through antimicrobial function^{28,29}, since bile acids are detergents and influence the membrane chemistry. Reciprocally, bacteria influence bile acid composition by deconjugation and fermentation of primary bile acids into secondary and tertiary bile acids, which have differential effects upon host metabolism. Primary bile acids are associated with improved metabolism, while secondary bile acids are potentially carcinogenic and not associated with metabolic improvement^{36,37}. Therefore, bile acids and microbial compositions are inseparably associated and continually interacting in the gut. Novel work demonstrated that bile acid-altered microbial communities in turn influence host metabolism, establishing a cross-talk between bile acids and the intestinal microbiome that influences host metabolism³⁸. In addition to altering bacterial viability and growth, and aiding in the absorption of luminal

dietary lipids and lipid vitamins, bile acids directly modulate host metabolism through host bile acid receptors^{28,39}. Bile acid interactions with the G protein-coupled bile acid receptor 1 (GPBAR1 or TGR5) and farnesoid X Receptor (FXR) regulate peripheral energy expenditure and counteract obesity and diabetes. Upon activation by bile acids, TGR5 specifically stimulates the release of GLP-1, GLP-2 and PYY from enteroendocrine cells as well as expression of various transport proteins and biosynthetics, resulting in improved glycemic control. Enteroendocrine cells also contain toll-like receptors and sense bacteria in the intestinal lumen⁴⁰. Following RYGB, elevated circulating levels of GLP-1 and PYY are reported^{41,42}. PYY is normally released postprandial to increase energy expenditure and decrease food intake. In healthy individuals, PYY release following feeding is proportionate to caloric consumption, acting directly on the hypothalamus and vagal afferents to slow feeding behavior⁴³. It remains unclear if elevated PYY and GLP-1 following RYGB are in response to altered microbial populations, bile acid pools, or a combination. Regardless, changes in intestinal enteroendocrine signaling following RYGB have profound effects on host metabolism and multiple lines of evidence now strongly support the involvement of the microbiota.

Host-Microbe Interactions Driving Obesity

The observation that GF mice are resistant to diet-induced obesity has created a foundation for understanding the contribution of microbes and host-microbe interactions to the development of obesity and its co-morbidities. Several mechanisms to explain microbe-mediated obesity have been proposed, including 1) short chain fatty acid (SCFA) production, 2) regulation of food intake and sensory perception of food, 3) nutrient absorption, 4) circulation of microbe-derived enterotoxins like LPS and reduced production of angiopoietin like 4 (angptl4) resulting in increased fatty acid uptake in liver and adipose tissue ¹³, 5) and peripheral control of circadian rhythm which is intimately links metabolic coordination between the brain and peripheral organs ^{44,45}.

One metabolic function of microbes is the production of SCFAs, including acetate, propionate, and butyrate from otherwise indigestible fibers. SCFAs can act as energy sources for the intestinal epithelium and liver and mouse models of obesity demonstrate elevated SCFA in luminal content and lower energy content in feces ⁴⁶. However, SCFAs have many reported beneficial effects on metabolism and improved glucose tolerance. For instance, diets supplemented with fructooligosaccharides, butyrate, and propionate decreased weight gain and improved glucose tolerance in rats compared to controls. It was shown that these positive effects were mediated through stimulation of intestinal gluconeogenesis, as mice deficient in the catalytic subunit of glucose-6 phosphatase, displayed impaired glucose tolerance ⁴⁷. Thus, conflicting evidence exists regarding the negative consequences of increased energy availability through SCFA production given the potential positive impact of SCFAs on metabolism.

Obesity is also related to peripheral inflammation, especially in adipose tissue. The gut microbiota influences gut permeability, which may lead to entry of microbial ligands, including lipopolysaccharides (LPS), into the blood stream and periphery, where they can induce insulin resistance and prevent peripheral uptake of fat^{48–50}. Intriguingly, bioactive

Microbial regulation of metabolism is mediated in part through the sensory perception of food, gastrointestinal motility, and nutrient absorption, as these are altered in GF mice. For instance, GF mice have increased preference for sugar-sweetened liquids and fat emulsions but lack the machinery to process the nutrients. Swartz *et al.*⁵⁴ found that GF mice consume more sucrose solution concurrent with increased expression of type 1 taste receptor 3 (TIR3) expression and sodium glucose luminal transporter 1 (SGLT1) in the small intestinal epithelium compared to conventional mice⁵⁴. Anorexigenic gut peptide hormones, including PYY and CCK, are also regulated by gut microbes facilitating control of food intake. While GF mice have increased expression of lingual fatty acid translocase (CD36), expression of gut peptide hormones including PYY, CCK, and GLP-1 were reduced in the intestinal epithelium, as well as decreased numbers of EECs in the ileum⁵⁵. In contrast, to these gut peptide hormones, Backhed's group reported that GF mice have elevated GLP-1 which slows gastric motility and increases intestinal transit time as a compensatory mechanism to allow for enhanced nutrient absorption⁵⁶. Given the role of enteroendocrine hormone signaling in nutrient absorption, dysregulation of these hormones may explain why germ free mice have elevated levels of triglycerides and total lipids in their stool after high fat diet feeding⁵⁷. Interestingly, conventionalization of GF zebrafish increases lipid accumulation in the intestinal epithelium⁴⁴. Taken together, these findings suggest that gut microbes facilitate hormonal cues to regulate sensory perception of food, dietary intake, as well as nutrient absorption. However, the exact mechanisms behind microbial regulation of carbohydrate and lipid absorption and the extent to which microbe-induced nutrient absorption significantly contributes to obesity have not been well characterized.

The difference in bile ‘acid metabolism speaks to the marked difference in liver function between GF and conventional mice. Indeed, GF mice have decreased liver lipid content and altered expression of gene networks including those involving xenobiotic metabolism and circadian rhythm⁵⁹. At the hub of xenobiotic gene networks are two nuclear hormone

receptors, constitutive androstane receptor (CAR) and pregnane X receptor (PXR), which are implicated in regulating whole body metabolism. Activation of CAR has been shown to decrease body weight and improve insulin sensitivity, whereas PXR activation has been positively associated with obesity^{60–62}. Thus, it is tempting to speculate that CAR-mediated metabolic activity in GF mice may contribute to their resistance to high fat diet-induced obesity. However, this connection has not been thoroughly investigated in the current literature.

Gut microbes have been found to control circadian function. This has important implications for fighting obesity, as the disruption of the natural cycle of day and night (e.g., jet lag, shift work and sleep apnea) contributes to the increasing prevalence of metabolic disorders¹³. Circadian rhythms are regulated by molecular clocks that coordinate regularly timed events (i.e., states of feeding vs fasting) and the necessary physiological responses to enhance metabolic efficiency. Thus, circadian rhythm is intimately linked to the regulation of food intake, activity, and whole body metabolism involving clocks located in the brain as well as peripheral metabolic tissues. The circadian transcriptional program is under the control of two major transcriptional activators, Bmal and Clock, which are counter-regulated by repressors, Period 1–3 and Cryptochrome 1/2. Consumption of high-fat diets represses diurnal variation of these gene transcripts and impairs normal circadian function⁶³. It has recently been shown that these changes are dependent on the gut microbiota, as GF mice and antibiotic-treated mice have reduced expression of Bmal and Clock and increased expression of Per1–3, and Cry1/2 in the intestinal epithelium⁶⁴. It was later demonstrated by Leone *et al.*⁴⁵ that diurnal variation in the circadian gene program is also blunted in the liver of GF compared to SPF mice.

In addition to host circadian rhythm, microbes themselves display circadian behavior⁴⁵. Strikingly, community structure of the gut microbiota as well as butyrate exhibits diurnal variation over a 24-hour period under normal feeding conditions and is diminished under high fat feeding. To ensure these changes were not due to times of feeding, stool was collected from mice on total parenteral nutrition (TPN) and compared to mice fed enterally. Although differences existed in the relative abundance of specific microbes (e.g., increase in Verrucomicrobia in TPN group), diurnal shifts were still evident, indicating that microbial abundance may fluctuate based on host cues, such as the release of mucin or other epithelial proteins and secretions. Altogether these findings suggest that the regulation of host circadian function is dependent on the activity of the gut microbiota and conversely, the circadian behavior of the gut microbiota is dependent on host physiology^{13,45}. Identifying the host-microbe interactions that facilitate microbial control of circadian rhythm may lead to therapies targeting the gut microbiota to restore the metabolic consequences of disrupted sleep, common in obesity.

Treatments targeting microbiome to fight obesity and metabolic syndrome

The host-microbiome field is moving toward improving metabolism and weight maintenance through modulating gut microbial communities using a variety of supplements such as pre- and pro-biotics, synbiotics, FMT, and postbiotics. Prebiotics are foods or dietary supplements that encourage the growth of saccharolytic bacteria that metabolize non-

digestible carbohydrates such as inulin and oligofructose. Several criteria must be met for a supplement to be considered a prebiotic and these include: resistance to gastric acidity, non-digestible by the host in the small intestine, bacterial fermentation, and promotion of beneficial bacteria ⁶⁵.

Prebiotics

Prebiotics have recently been shown to improve complications associated with metabolic disorders including obesity and insulin resistance ⁶⁶. Various mechanisms have been identified to explain these beneficial effects including SCFA production, stimulation of intestinal gluconeogenesis, epithelial integrity, release of hormones PYY and GLP1 to promote satiety and insulin sensitivity, increased expression of antimicrobial peptides, and alteration of gut microbial community structure ⁶⁶.

Gene expression of the antimicrobial peptide, Reg3γ, was reduced after HFD feeding but restored upon delivery of oligofructose ³⁵. Prebiotic supplementation also increased intestinal expression, which promotes epithelial cell turnover and maintenance. Fructooligosaccharide (FOS) treatment in mice fed a Western diet, exhibited improved glucose and insulin tolerance compared to controls. The therapeutic effect of FOS was lost in mice deficient in glucose-6-phosphatase catalytic subunit (G6Pc), thereby shutting down intestinal gluconeogenesis. These findings implicate that intestinal gluconeogenesis is necessary for FOS-mediated glucose and insulin sensitivity ⁴⁷. Similar results have been shown in humans. For example, participants fed brown beans ⁶⁷ or prebiotics containing wheat fiber and soluble fiber. ⁶⁸ displayed improved insulin sensitivity. Taken together, these findings support the use of prebiotic therapy in both animals and humans for improved metabolic health.

Probiotics

Another commonly used approach and widely studied supplement is the use of probiotics, that are live microorganisms delivered individually or in combinations such as VSL#3, that positively impact health outcomes in the host ⁶⁵. It is important to consider the composition of probiotic formulations as each strain may have a different impact on microbial structure/function or on the host immune response, for instance. Wang et al. ⁶⁶ demonstrated in mice that three strains of bacteria including *Lactobacillus Paracasei* CNCM I-4270, *L. rhamnosus* I-3690 and *Bifidobacterium animalis* subsp *Lactis* I-2494 independently decreased body weight and improved glucose tolerance but through different mechanisms (reviewed in ¹³). Daily gavage of the probiotic yeast *Saccharomyces boulardii* or Biocodex, elicited changes in gut microbiota, reflecting a less obesogenic state, as well as improved the metabolic profile of genetically obese and diabetic db/db mice ¹⁷.

A common concern with probiotics use is the lack of colonization following supplementation ⁶⁹. In addition, mixed strain probiotics like VSL#3 or a symbiotic, which is the combination of a probiotic and prebiotic, may be more effective than single microbial isolates alone. VSL#3 contains 7 different strains belonging to the genus *Bifidobacterium* and *Lactobacillus* and has been shown to improve NAFLD in children ⁷⁰ and reduce the risk of hepatic encephalopathy in patients with cirrhosis ⁷¹. Due to the complexity in formulating

pro- and prebiotic supplements, more research is needed to maximize their effectiveness for ameliorating metabolic disorders associated with obesity.

Fecal Microbiota Transplant (FMT)

Other alternative therapies include fecal microbiota transplant (FMT) and post-biotics. FMT is the transfer of fecal slurries to a recipient from an approved donor. While FMT is effective in ~90% cases of *Clostridium difficile* infection⁷², its use for other diseases in humans is still under investigation. Intriguingly, FMT from bariatric patients results in an improved metabolic profile in mice⁷³. Unfortunately, few reports exist for use of FMT in relation to metabolic disease. However it was shown by Vrieze *et al.* that FMT improved symptoms related to insulin resistance in men with metabolic syndrome⁷⁴. Along with further study for metabolic disease, well-defined safety practices are needed for the use of FMT (reviewed in⁷⁵).

Postbiotics

More recently, research has focused largely on metabolomics and the introduction of “postbiotics” which are new formulations containing purified microbial metabolites or bacterial components that have a defined benefit to the host, as opposed to live bacteria in probiotics. Postbiotics may become a popular treatment option, because this targeted approach involves small, bioactive molecules that have a defined and specific function, without the potential adverse side effects live bacteria may promote. For example, ex vivo culture with the probiotic *Lactobacillus plantarum* NCIMB8826 elicited an undesired immune response, but the culture media protected against *Salmonella*-mediated TNF secretion from intestinal mucosal explants⁷⁶. The use of postbiotics would bypass adverse effects promoted by unknown processes triggered by probiotic formulations or potential pathogens delivered via FMT.

Summary

Obesity and metabolic disease delve from various underlying causes, including genetics and environmental factors, making appropriate and effective treatments difficult to identify. The emergency of high throughput sequencing has recently made it possible to examine the intestinal microbiome in the context of obesity. Understanding how the microbiota structure and function changes under states of obesity as well as bariatric surgery may resolve the role of the microbiome in regulating host metabolic set-points, likely including interactions with the endocrine and nervous systems. The use of 16s rRNA amplicon sequencing is now routinely performed by many labs, but offers only limited information regarding the microbial members present under certain conditions such as obesity, malnutrition, and RYGB surgery. It does not provide information regarding the function of key microbial species that drive host outcome. Without this information it is difficult to determine which strains to examine for potentially vital host-microbe interactions. The complex and individualized nature of obesity presents another obstacle in understanding how we can utilize the microbial organ. Which organ and what pathways do we target and how do we determine this on an individual basis? However, with further advances in the field and employment of available technologies, such as metagenomics and metabolomics, keystone

microbes should be better identified and interaction with the host understood. This will allow for the creation of a database of potential pathobionts to target in order to modulate the microbial community. Conversely, these techniques can also be applied to beneficial microbes to understand how we can utilize them for developing more effective prebiotic, probiotic, or postbiotic therapies.

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Key Points

1. Shifts in the gut microbiome are inseparably associated with the development of obesity and comorbidities.
2. Transfer of dysbiotic microbial communities confers disease phenotypes in recipients, supporting a central role for microbe-mediated regulation of metabolism.
3. Bariatric surgery, the most effective treatment for morbid obesity, results in rapid changes in the gut microbiota, with concurrent improvements in metabolic parameters
4. Deeper understanding of host-microbe interactions may hold promise in the treatment of obesity, which remains a global epidemic.