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Nutritional Modulation of Gut Microbiota - The Impact on Metabolic Disease Pathophysiology

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Abstract

The obesity epidemic afflicts over one-third of the United States population. With few therapies available to combat obesity, a greater understanding of the systemic causes of this and other metabolic disorders is needed to develop new, effective treatments. The mammalian intestinal microbiota contributes to metabolic processes in the host. This review summarizes the research demonstrating the interplay of diet, intestinal microbiota, and host metabolism. We detail the effects of diet-induced modifications in microbial activity and resultant impact on: 1) sensory perception of macronutrients and total energy intake, 2) nutrient absorption, transport, and storage, 3) liver and biliary function, 4) immune-mediated signaling related to adipose inflammation, and 5) circadian rhythm. We also discuss therapeutic strategies aimed to modify host-microbe interactions, including pre-, pro-, and post-biotics, as well as fecal microbiota transplantation. Elucidating the role of gut microbes in shaping metabolic homeostasis or dysregulation provides greater insight into disease development and a promising avenue for improved treatment of metabolic dysfunction.

Keywords

microbiota; high fat diet; metabolism; obesity

Introduction

The intestinal bacterial community, known as gut microbiota or their respective genomes, known as the gut microbiome, play a significant role in human health and disease, representing a new frontier in medical research. The recent explosion of this field has uncovered new, intimate links between microbial inhabitants and a number of critical metabolic processes required for growth and development. Moreover, gut microbes

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influence a growing list of human diseases, including metabolic disorders such as obesity and Type 2 diabetes. Recent research demonstrates the significant impact of diet on microbial assemblage and host-microbe interactions that significantly impact metabolic homeostasis. The newly gained knowledge in this field is expected to result in therapeutic strategies that target the gut microbiota for improved metabolic outcomes.

This review offers a comprehensive framework of the research investigating the influence of diet on the gut microbiota and the mechanisms regulating the impact of gut microbiota on metabolic and immune profiles of the host. We highlight the mechanisms leading to these alterations beginning in the intestine and elaborate on the downstream effects on peripheral hepatic, biliary, and adipose tissues. The influence of microbes on tissue functionality and metabolism has been linked to several pertinent disease states – obesity, non-alcoholic fatty liver disease, diabetes, and metabolic syndrome – and we explore the recent research involving these diseases. Stemming from these discoveries, interventional strategies to modulate the gut microbiota have become a new realm of innovation. We outline the current knowledge regarding pre- and pro-biotic therapies as well as fecal transplantation for disease treatment. Gut microbiota research is vast, however this review attempts to establish groundwork for the topic by detailing the pertinent interplay of the intestinal microbiota on the host and its translation into metabolic health and disease.

Obesity and Western Diet are associated with intestinal microbial dysbiosis

Obesity is a major health challenge in the United States, where it affects over one-third of the adult population [1] and contributes to increasing rates of stroke, Type 2 diabetes, metabolic disease as well as endometrial and colorectal cancer. Sedentary lifestyles, leading to less energy utilization, and the Western diet, high in saturated fats, are often regarded as the primary causes of the obesity epidemic [2, 3]. Research regarding the gut microbiota has convincingly established the involvement of a host-microbiome interaction in the development of weight gain and metabolic dysfunction. With the advent of advanced molecular approaches and high-throughput sequencing technologies, more is now understood about gut microbes and particular bacterial species that inhabit the gastrointestinal tract. Sequencing of the bacterial 16S rRNA genes have allowed for identification of previously unknown or underappreciated microbes that impact host physiology and obesity-related metabolic disorders. Additionally, several lines of evidence demonstrate the effect of intestinal microbial dysbiosis on development of obesity. For instance, obese and lean humans exhibited an altered community structure, with decreased abundance of Bacteroidetes and increased abundance of Firmicutes in fecal samples of obese subjects [4]. Similar patterns were seen between genetically obese (*ob/ob*) mice that displayed a 50% decrease in Bacteroidetes compared to their lean counterparts [5]. In mice fed a Western diet, the Mollicute class of Firmicutes was found to be in high abundance and transfer of these gut microbes to germ-free (GF) mice led to increased adiposity, supporting the hypothesis that microbiota alone can induce transferability of an obese-like phenotype by altering caloric availability and utilization in the host [6]. Conversely, a shift towards a higher abundance of distal-gut Bacteroidetes was induced in obese human subjects who underwent weight loss on a low-calorie, fat- or carbohydrate-restricted diet [7]. Vrieze *et al.* conducted a patient study in which patients with metabolic syndrome received fecal

transplantation from lean donors. While significant weight loss was not detected, transplant recipients displayed improved insulin sensitivity after hyperinsulinemic-euglycemic clamp, providing strong evidence that physiologic responses are transmissible via microbial community transplantation [8]. Roux-en-Y gastric bypass surgery is the most common and effective surgical intervention that significantly improves obesity and metabolic comorbidities in the United States [9]. This intervention distinctly alters the intestinal microbiota in humans and rodents, causing an increase in abundance of Gammaproteobacteria and Verrucomicrobia. GF mice conventionalized with fecal transplant from Roux-en-Y-treated mice displayed a decrease in weight and fat mass which was not seen in GF mice transplanted with fecal samples from control mice [10].

Taken together, the state of obesity and consumption of a Western diet have both been associated with microbial dysbiosis and it has been shown that altered diet may elicit changes on the gut microbiota that precede the development of host obesity. For example, animal and human studies show that an acute dietary switch results in dramatic shifts in the gut microbiota within the course of 24 hours [11, 12]. Turnbaugh's group also demonstrated that a diet mimicking a Western diet high in fat and sugar, impacted community structure regardless of the murine genotype tested, suggesting that diet can override host genetics in regards to gut microbiota [13]. In conclusion, diet, host genetics, and metabolic state are all drivers of gut microbial assemblage and the interaction between these factors is likely the major determinate of an individual's gut microbial ecology. The following sections will discuss the mechanisms behind host-microbe interactions in regulating obesity and associated metabolic disorders, highlighting effects on the gut, liver, and adipose tissue.

The gastrointestinal tract is the major site of host-microbe communication mediating host metabolic phenotypes

Studies employing the use of gnotobiotic mice have enabled researchers to understand the critical role of gut microbes in regulating nutrient sequestration and storage. In several reports, GF C57BL/6J mice on high-fat, obesogenic diets did not gain weight as compared to their specific pathogen free (SPF) counterparts despite higher energy intake, further indicating a link between the microbiota and metabolic disruption [14–16]. Mechanisms explaining this phenomenon in GF mice include 1) increased activity and peripheral metabolism, decreased energy availability through lack of SCFA production or impaired lipid absorption, 2) altered lipid and bile acid metabolism in the liver, 3) impaired lipid uptake in adipose tissue and altered immune-mediated responses, and 4) dysregulated circadian rhythm. Underlying the role of microbiota in metabolic processes is the finding that high-fat fed GF mice exhibit improved fasting and non-fasting glucose tolerance as well as decreased cholesterol levels compared to conventional counterparts [16]. Interestingly, GF mice displayed a significant increase in body weight two weeks after inoculation with cecal microbiota from genetically obese (*ob/ob*) mice versus microbiota from lean (+/+) littermates [7]. The results from these studies suggest obesogenic diet-induced changes in intestinal microbes can promote metabolic dysfunction. However, a study with GF mice of a different strain, C3H, displayed increased weight gain on high-fat diet (HFD) compared to conventionally-raised (ConvR) C3H mice and GF mice on a Western diet composed of

higher levels of sucrose and *trans*-fats. These mice did not have an increase in Angptl4 (angiopoietin-like protein 4), a lipoprotein lipase (LPL) inhibitor, as described in previous experiments using GF mice on a Western diet [14]. Although the HFD and Western diet had a similar ratio of macronutrients, the authors attribute the difference in weight gain to the variations in diet composition. Therefore, it was concluded that GF mice may not be resistant to diet-induced obesity, dependent upon the types of macronutrients in the diet [17]. These results reiterate the importance to further elucidate the connection between diet-induced microbiota and the host.

The influence of gut microbiota on diet-induced obesity and host metabolism begins with the sensory perception of food. At least two reports have demonstrated an interaction between microbes and sensory perception of dietary fat or nutritive sweeteners such as sucrose. GF mice consumed more calories from fat than their ConvR counterparts, which was linked to higher lingual cluster of differentiation 36 (CD36) expression, a fatty acid translocase important for long-chain fatty acid detection [18]. Interestingly, lingual CD36 is elevated in normal ConvR mice during fasting. This increase in oral sensitivity through CD36 promoted increased caloric intake from fat [19]. It is suspected that GF mice express a comparable response as fasted mice due to similarities in energy deprivation. GF mice also displayed higher intake of sucrose compared to conventionally-raised mice [20], similar to the previously described propensity towards higher energy intake [15].

Gut microbes play a major role in energy extraction from food through a variety of enzymatic activities. Several plant polysaccharides and complex carbohydrates are non-digestible by the host; however, their colonic microbial community successfully converts these dietary substances into monosaccharides and short chain fatty acids (SCFAs). Butyrate, a major SCFA produced by the microbiota, is used as the primary energy source for colonic epithelial cells, while propionate and acetate are necessary for lipogenesis and gluconeogenesis in the liver [21]. Differences in SCFA levels have been observed in obese and lean phenotypes of WT mice. For example, *ob/ob* mice have increased butyrate and acetate levels in their ceca and less energy, determined via bomb calorimetry, in their fecal samples compared to their lean counterparts [7]. The increase in Firmicutes, which includes several butyrate-producing microbes, likely contributes to this improved energy extraction in the *ob/ob* mice [22]. The abundance of SCFAs during obesogenic states contributes to host caloric salvage through fatty acid signaling of the G protein-coupled receptor Gpr41, expressed in the ileum and colon. Gpr41 promotes host adiposity and induction of peptide YY (PYY), a peptide hormone that slows gut motility and promotes satiety [23]. The lack of SCFAs and their signaling effects in GF mice results in decreased caloric absorption of indigestible food and less adiposity. These changes were reversible in GF mice co-colonized with polysaccharide-fermenting microbiota, *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*, compared to non-colonized GF mice on chow-diet [23].

Although SCFA production is seemingly linked to an obesogenic phenotype through the increase in extractable energy, studies have shown complementary SCFA mechanisms that promote lean metabolic profiles in ConvR mice. For instance, mice on HFD with an overexpression of Gpr43, a protein receptor signaled by SCFAs, causes reduced body weight gain and improved insulin sensitivity in adipose tissue. However, under antibiotic

treatment or GF conditions, these high-fat fed mice expressed phenotypes similar to WT controls on HFD alone [24]. Some of the beneficial effects of SCFA have been shown to be mediated through a peroxisome proliferator activated receptor gamma (PPAR γ)-dependent switch from lipogenesis to fatty acid oxidation via an AMP-activated protein kinase (AMPK)-dependent mechanism in liver and adipose tissue [25]. Activated AMPK promotes long-chain fatty acylCoA oxidation in peripheral tissues. Microbes also down-regulate the intestinal expression of fasting-induced adipose factor (Fiaf, also known as Angptl4), which otherwise inhibits LPL activity in peripheral metabolic tissues such as adipose tissue. Because LPL cleaves fatty acids from triglycerides (TG) contained in circulating TG-rich chylomicrons, Angptl4 reduction results in increased LPL activity, causing triglyceride accumulation in adipocytes [14]. These results indicate a dynamic metabolic pathway dependent upon the interaction of the microbiota and diet. It is difficult to elucidate the definitive effects from microbially-derived SCFAs as the results vary based on diet and microbial community, thus necessitating further research to understand the mechanisms driving the different metabolic phenotypes.

In addition to their role in increasing energy through SCFA, gut bacteria have also been implicated in increasing satiety, motility and fat absorption through the regulation of the enteric nervous system and enteroendocrine and absorptive cells in the small intestine. For instance, expression levels of cholecystokinin (CCK) and PYY are reduced in GF mice compared to conventional mice [18]. Thus, it is presumable that the lack of microbe-mediated stimulation of satiety hormone production and secretion may be linked to the observed increased food intake in GF mice. Energy acquisition is also regulated at the level of gastrointestinal motility. Bäckhed's group found that circulating GLP-1 levels were higher in GF mice, and that this was a compensatory response to slow intestinal transit increasing the likelihood of extracting energy from the diet [26].

Adequate lipid digestion and absorption in the upper small intestine requires several integrated processes that must occur including gut peptide hormone signaling and the coordination of pancreatic enzyme and bile acid secretion. To summarize, TGs from the diet are sensed in the upper small intestine signaling release of various gut peptide hormones to promote release of pancreatic lipases and bile to emulsify fat and liberate free fatty acids (FFA) for absorption by the enterocyte. The FFA may be converted back into triglycerides and subsequently stored in the enterocyte as lipid droplets, incorporated into chylomicrons, released into circulation, or utilized for energy. Microbe-mediated effects on fat absorption may occur through regulation of gut peptide hormones such as CCK. It was reported that GF mice displayed a reduced number of enteroendocrine cells, producers of these gut peptide hormones, in the distal small intestine, but not the proximal small intestine [18]. Therefore, it is unclear whether the lack of enteroendocrine cells, is the sole cause of decreased satiety peptide secretions [18]. Overall, microbes may directly influence fatty acid uptake and satiety responses either through regulation of enteroendocrine cell number or a direct regulation on gut peptide hormone production and secretion.

Lipid droplet formation and fatty acid accretion within the enterocyte is linked with microbial colonization. Intestinal lipid droplets are often used as a temporary storage site for fatty acids, and increase during high-fat feeding conditions. Gnotobiotic zebrafish displayed

increased numbers of lipid droplets in the enterocyte when colonized with Firmicutes and an increase in lipid droplet size when colonized with non-Firmicutes bacteria, namely *Chryseobacterium* and *Pseudomonas*, providing evidence of the direct effect bacteria have on lipid absorption [27]. In a separate study conducted in mice, research demonstrated that conventionalization of GF mice with jejunal contents initiated an early phase of innate immune defense responses followed by changes in nuclear receptor families that regulate lipid metabolism, switching from an oxidative to an anabolic state [28].

Similar findings have been shown for the microbial regulation of sugar absorption and transport. For instance, GF mice have increased expression of sweet signaling protein type 1 taste receptor 3 (T1R3) and glucose luminal transporter-1 (SGLT-1) in the intestine compared to conventional mice [20]. In addition, metagenomic sequencing of cecal microbial communities from mice fed Western diets displayed upregulated pathways involved in uptake and metabolism of simple dietary sugars from the intestine compared to microbial communities from mice fed carbohydrate-restricted or fat-restricted diets. The change in metabolic function coincides with the increase in abundance of Firmicutes in these mice, underscoring the important effects of bacterial communities on dietary processing of both fat and sugar, typical in a Western diet [6]. These analyses revealed changes in the gut microbiota are dependent on dietary factors present in the intestinal lumen. In summary, microbes have been shown to regulate energy extraction of the diet including non-digestible carbohydrates and dietary fat through several different mechanisms such as fatty acid receptor signaling, SCFA production, gut peptide hormone signaling, as well as enterocyte lipid droplet formation.

Intestinal microbiota alters liver function

The liver is a key player in metabolic pathways of lipogenesis and gluconeogenesis, as it is the hub of nutritive uptake and energy extraction from dietary substrates. In addition to regulation by the gut-liver axis, liver function is also highly regulated by the gut microbiota. For example, antibiotic treatment for two weeks using norfloxacin and ampicillin in *ob/ob* mice 1) reduced the bacterial cecal load, 2) changed gut microbial profiles 3) decreased hepatic lipogenesis and liver TG, and 4) increased liver glycogen and insulin sensitivity [29], highlighting a connection between microbial alteration and metabolic change in peripheral tissues. Liver TGs are reduced in the GF state, potentially due to lower availability of colonic SCFAs [21, 30]. Similar findings have been reported regarding cholesterol flux. Rabot *et al.* reported that resistance to hypercholesterolemia in GF mice on a HFD was due to an increase in hepatic cholesterol biosynthesis proteins as well as reverse cholesterol transporters, ABC-binding cassette subfamily G member 5 (ABCG5) and ABCG member 8 (ABCG8), which transport cholesterol from peripheral tissue to feces. Bacterial lipopolysaccharide (LPS), a component of bacterial cell walls, suppresses ABCG5 and ABCG8, detailing a mechanism by which microbes regulate cholesterol accumulation [16]. Microbial regulation of TG and cholesterol stored in the liver may have important implications for understanding of pathology of liver diseases, including nonalcoholic fatty liver disease (NAFLD) and the development of therapeutic regimens targeting the gut microbiota.

Different mechanisms have been proposed to explain HFD-mediated development of NAFLD, which is a result of hepatic dysfunction secondary to lipid accumulation. Tempol, an antioxidant that shifts the ratio of Firmicutes to Proteobacteria, and antibiotic treatment of HFD-fed mice decreased hepatic triglyceride levels and liver lipid droplets, compared to untreated HFD-fed controls. [31]. These changes were not noted in mice fed low-fat chow diet subjected to the same treatment conditions. In addition, antibiotic and tempol treatments increased tauro- β -muricholic acid, a bile acid that acted as an antagonist of the intestinal nuclear hormone receptor farnesoid X receptor (FXR), thereby decreasing hepatic cholesterol levels. Additionally, ceramides, sphingolipids involved in cell signaling and inducers of hepatic fatty acid synthesis genes sterol regulatory element-binding protein (SREBP)1 and cell death-inducing DFFA-like effector a (CIDEA), were also significantly reduced in these mice [31, 32].

Another mechanism of microbiota-induced hepatic dysfunction may originate from elevated gut microbe-derived endotoxin (i.e. lipopolysaccharide, LPS, and lipoteichoic acid, LTA) levels. Endotoxemia mediates inflammation in diabetics and NAFLD patients exhibiting insulin resistance. NAFLD and nonalcoholic steatohepatitis (NASH) patients in particular, express elevated microbially-derived LPS levels as well as inflammatory markers, CD14 and tumor necrosis factor- α (TNF- α) receptor II [33]. Previous studies demonstrate that HFD feeding and increased levels of free fatty acids activate CD14 receptors, which chaperone bacterial-derived LPS to stimulate toll-like receptor (TLR)4 and downstream NF κ B-mediated inflammation [34]. Thus, modulating CD14 and TLR signaling can drastically alter inflammatory responses leading to a decrease in tissue macrophage infiltration and pro-inflammatory cytokine expression [35]. These immune-mediated responses impact the pro-inflammatory milieu that maintains inflammatory insults and adversely impacts host metabolism [36]. Together, these data suggest that manipulation of the microbial community by shifting abundances and proportions of specific microbes may provide an avenue for treating NAFLD.

Intestinal microbiota influence host bile acid profiles

In addition to its role in regulating lipid flux, the liver also regulates the production and secretion of bile, which is important for proper lipid digestion and absorption in the proximal intestine. Primary bile acids, cholic and chenodeoxycholic acid, are synthesized from cholesterol and conjugated in the liver to taurine in mice and glycine in humans. HFD promotes bile acid secretion into the small intestine, where they are deconjugated by bacteria or metabolized into secondary bile acids. The increased bile acid pool within the small intestine can also result in an increased abundance of specific bile acids within the colon. For example, consumption of a milkfat-rich diet led to the increased intestinal delivery of taurocholic acid (TCA), a sulfur-containing bile acid, which supported a bloom of the pathobiont *Bilophila wadsworthia*, specifically in the distal colon. This hydrogen sulfide-producing microbe, associated with an induction of inflammatory intestinal immune responses, increased the development of colitis in genetically susceptible interleukin (IL)-10 deficient GF mice upon monoassociation with *B. wadsworthia* and exposure to milkfat diet [37]. This study nicely exemplified a direct interaction between host and microbe. Similarly, human consumption of animal-based diets increased the abundance of bile-resistant

microbes, such as *Alistipes*, *Bilophila*, and *Bacteroides* [11, 38]. Thus, host liver function can have a significant indirect impact on microbial structure and function by selectively altering bile production under specific dietary conditions, leading to an increase in the abundance of particular bacterial species that metabolize different types of bile. These changes in gut microbiota and bile acid metabolism may significantly affect disease development in the intestine.

Secondary bile acid formation in the intestine has been shown to be dependent on microbial metabolism; however, the bacterial community can directly regulate bile synthesis in the liver. FXR, a nuclear receptor expressed in both ileum and liver, antagonizes the expression of hepatic cholesterol 7 α hydroxylase (CYP7A1) the rate-limiting enzyme in bile synthesis. In studies comparing GF and ConvR mice, the lack of microbiota resulted in elevated taurine-conjugated α - and β -muricholic acid that were shown to down regulate FXR signaling in the intestine. This led to decreased FXR-mediated fibroblast growth factor (FGF)-15 signaling to the liver that would otherwise block cholesterol synthesis. Therefore, the lack of FGF-15 signaling resulted in increased bile acid production by GF mice. The increase in hepatic CYP7A1 and changes in bile composition were also established in mice treated with antibiotics, confirming the role of microbiota in influencing FXR and bile acid synthesis [39].

The impact of microbes on the bile acid profile is especially evident when comparing profiles between ConvR rats and GF or antibiotic-treated animals. For instance, the bile acid profile in GF and antibiotic-treated rats has an increased proportion of taurine-conjugated bile acids. In ConvR rats, conjugated bile acids dominate the hepatic profile while unconjugated acids dominate kidney and cardiac tissue, whereas in GF rats, all tissue profiles contained predominantly conjugated bile acids. GF mice lacking gut microbes and their enzymatic activity exhibit increased bile acid synthesis and reduced bile acid diversity. The global differences in bile acid profiles between GF and ConvR conditions may offer another mechanism by which microbiota impact whole body metabolism [40]. Indeed, TCA-mediated activation of the bile acid receptor TGR5 in peripheral brown adipose tissue (BAT) and muscle has been linked to increased mitochondrial oxidation and protection against HFD induced obesity [41]. In addition to activation of cell surface receptor TGR5, bile can act as intracellular signaling molecules by binding nuclear hormone receptors such as FXR. FXR and TGR5 have opposing activity, as the first impairs glucose homeostasis and the latter promotes glucagon-like peptide-1 (GLP-1) secretion from enterocytes to improve glucose tolerance.

Intestinal microbiota regulate xenobiotic metabolism and host metabolic pathways in the gut and the liver

The liver is central to xenobiotic metabolism due to its expression of numerous drug-metabolizing enzymes. Drug metabolism involves conversion of the primary drug into active forms through oxidation, hydrolysis, or reduction with phase I enzymes, such as the cytochrome p450 enzymes, followed by conjugation with phase II enzymes, such as sulfotransferases, into substances that can be excreted from the host. As the gut is the first site of drug interaction with the host, it is conceivable that microbial contact with the drug

likely affects its metabolism. Recent work has highlighted that the gut microbiota is a key contributor to regulating host drug metabolism as it is the first to interact with ingested xenobiotics prior to transport to the liver via portal circulation. For instance, Levi-dopa (L-dopa), a therapy designed to treat Parkinson's disease, was found to have reduced bioavailability in patients exhibiting *Helicobacter pylori* colonization of the stomach. Eradication of *H. pylori*, which has been correlated to the degradation of L-dopa, led to a significant increase in patient serum drug levels and efficacy [42]. Additionally, microbial metabolism of irinotecan, a topoisomerase inhibitor used to treat colorectal cancer, has been shown to induce gastrointestinal toxicity. Exploration into the mechanism of action revealed that microbial enzymes, in particular β -glucuronidase, led to prolonged drug toxicity. Blocking β -glucuronidase with an inhibitor greatly reduced the gastrointestinal side effects [43].

Beyond the direct involvement of gut microbes in xenobiotic processing in the intestine, alterations in enzymatic activity of the liver has been correlated with changes in gut microbial communities. Comparisons of GF and SPF mice have shown that several hepatic nuclear receptors and their downstream targets are upregulated in GF mice. Nuclear receptors, including constitutive androstane receptor (CAR) and pregnane X receptor (PXR), are responsible for regulating vast gene networks associated with liver functions including lipid and xenobiotic metabolism. The Pettersson group conducted microarray analysis on hepatic tissues comparing GF and SPF mice and found 112 genes to be differentially expressed, namely genes in endobiotic and xenobiotic pathways regulated by CAR. SPF mice expressed significantly reduced levels of CAR and several additional cytochrome P450 enzymes, a family of proteins primarily involved in metabolic processing of foreign and endogenous chemicals. GF mice injected with pentobarbital displayed significantly increased rates of drug metabolism with shorter recuperation times from the anesthetic compared to SPF counterparts [44]. Surprisingly, GF mice conventionalized with a complex microbial community for one to six weeks maintained similar xenobiotic activity as untreated GF mice, suggesting the absence of gut microbiota contributes to developmental effects on host metabolism. It is hypothesized that up-regulation of CAR and its targets is a result of the higher abundance of CAR activators in GF mice, including bile acids and steroid hormones, although the definitive reason remains unclear [44].

In depth analysis of specific xenobiotic effects of the microbiota revealed the contribution of certain bacterial communities on drug processing. GF mice have lower expression of *cyp3a11* and *cyp2c29*, which are activators of 6β - and 16β -hydroxylase, enzymes involved in oxidation of xenobiotics. Indeed, Claus *et al.* describes a positive relationship between the presence of *Eggerthella hongkongensis* and testosterone 6β -hydroxylase in ConvR mice. Conversely, progressive conventionalization of GF mice with soiled bedding obtained from ConvR mice led to an increase in the levels of 16β -hydroxylase, however 6β -hydroxylase was not restored to levels seen in ConvR counterparts. These results highlight the possible developmental abnormalities exhibited in GF mice that cannot be restored by the addition of gut microbes. However it is not clear whether the community utilized for conventionalization in this study contained *E. hongkongensis*, which could explain why 6β -hydroxylase was not induced. Regardless, these studies support the hypothesis that select gut

microbes may promote specific cytochrome activity within the host, resulting in increased activity of host xenobiotic metabolism [45]. Further supporting the role of microbes in drug metabolism, Haider *et. al* explained a mechanistic link between *Eggerthella lenta* and digoxin inactivation, a glycosidase used for cardiac disorders. It was discovered that some strains of the bacteria, in the presence of digoxin, express the cardiac glycosidase reductase (*cgr*) operon which encodes cytochrome c reductases, predicted to deactivate glycosidases [46]. More research is needed to understand the mechanisms involved in these host-microbe interactions and may implicate strategies to manipulate the gut microbiota for more efficacious drug therapies that could impact whole-body metabolism and alleviate the development of metabolic disorders.

Intestinal microbiota promotes obesity-associated inflammation and insulin resistance within adipose depots

Adipose tissue acts as a critical metabolic regulator of energy homeostasis as well as the inflammatory status of the host that underlies metabolic health versus disease. Several reviews detail the mechanisms involved in adipose tissue inflammation and insulin resistance [41, 47, 48]. Overall, these studies indicate that early inflammatory responses in obesity and metabolic syndrome are driven by nutritional intake, postprandial metabolic regulation, and microbe recognition phases that promote microbial-induced immune signaling pathways [36]. Immune-mediated signaling involved in excess dietary lipid intake and microbial dysbiosis are associated with multiple inflammatory-related complications including: insulin resistance, pancreatic beta cell dysfunction, NAFLD, and cardiovascular inflammation [47, 49–51]. A recent study profiling biomarkers of inflammation and immunity in one of the largest population-based cohort of normoglycemic, prediabetic, and diabetic patients revealed that diabetics exhibit significant increases in circulating immune cell populations, the blood clotting glycoprotein fibrinogen, and both anti- and pro-inflammatory cytokines, IL1RA and IL-18, respectively [52]. Human obese and obese diabetic peritoneal adipose depots also express increased levels of TLR4 and pro-inflammatory cytokines TNF- α and interleukin-6 (IL-6), further supporting the role of diet- and microbial-induced signaling pathways in host metabolic dysfunction [53].

The absence of gut microbiota and their beneficial fermentation products contribute to immunological defects noted in the GF state [54]. For instance, treatment of GF mice with SCFAs has been shown to induce regulatory T cell (Treg) development through a G-coupled protein receptor *Ffar2* (GPR43)-dependent mechanism [54]. Moreover, these signaling pathways elicit responses in adipose tissue to protect against HFD-induced obesity and insulin resistance via a PPAR γ -dependent switch from lipogenesis to fatty acid oxidation in adipocytes, as previously discussed [47, 49–51, 55].

Inflammatory signaling pathways activated in particular microenvironments mediate obesity-associated insulin resistance and metabolic syndrome. Hence, the nutritional microenvironment in the gut during HFD exposure or metabolic dysfunction modulates the gut microbiota and activation of specific signaling pathways to establish inflammatory profiles in peripheral tissues [56]. As previously described, obesity and metabolic dysfunction induces microbial dysbiosis characterized by a decrease in beneficial SCFA-

producing bacteria and an increase in pathogenic or opportunistic microbes. Bacterial-derived signals potentiate host responses via cell surface pattern-recognition receptors (PRR), such as innate immune TLRs, which play an integral role in intestinal host-microbe signaling pathways. While the intestine is a major site for these microbial-induced responses, adipocytes are essential effector cells in innate immune signaling that impact host metabolic phenotypes [53, 57].

HFD-induced obesity and associated metabolic disorders have been linked to high levels of circulating bacterial LPS, an endotoxin released from gram-negative bacteria [34, 58]. For example, a morbidly obese individual displayed a high abundance of endotoxin-producing *Enterobacter* that was greatly diminished after 23 weeks of stringent diet and 51.4 kilograms of weight loss. GF mice on either a HFD or chow diet were inoculated with fecal isolates of this obese individual's *Enterobacter* strain. The HFD-fed gnotobiotic mice gained weight similar to HFD-fed ConvR mice while the chow-fed gnotobiotic mice maintained a lean phenotype, emphasizing the critical interaction between diet and gut microbiota [59].

A potential mechanism explaining LPS entry into host circulation is through LPS-mediated TLR4 activation, which causes increased permeability of the epithelium via tight-junction dysfunction and intestinal inflammation. Thus, HFD-induced dysbiosis characterized by increased endotoxin-producing bacteria may promote the weakening of the intestinal barrier, resulting in the increased passage of LPS [60]. Once circulating in the periphery, LPS triggers TLR4 signaling, further inducing pro-inflammatory cytokine and chemokine expression profiles in adipocytes, contributing to host inflammation and metabolic dysfunction [48, 53]. This inflammatory state caused by activated TLR signaling pathways is mediated through macrophage infiltration of adipose tissue [61]. Adipose tissue macrophages (ATMs) elicit metabolic-disease-specific activation pathways distinct from classical activation that cause inflammation and insulin resistance in the host [56].

Microbes regulate intestinal and peripheral metabolism through circadian clock alterations

A novel link between gut microbes and circadian rhythm further underscores the role of our microbial partners in establishing metabolic health or disruption. Biological circadian clocks tuned to the Earth's 24-hour cycle of day and night help to coordinate metabolic homeostasis in nearly all forms of life (reviewed in Ref. [62, 63]). In humans and other animals, these molecular clocks anticipate regularly timed periodic events of energy supply versus demand (e.g. feeding vs. fasting, activity vs. sleep) and harmonize physiological responses across multiple tissues to maximize metabolic fitness. As modern human behaviors disconnect our daily activities from the natural cycle of day and night which our ancestors adapted to, a growing body of evidence suggests that new behaviors, such as jet lag and shift work, contribute to the increasing prevalence of metabolic disorders (reviewed in Ref. [64, 65]).

Feedback loops of transcriptional activators, including *Bmal1* (alternatively *Mop3* or *Arntl*) and *Clock*, and repressors, such as *Cryptochrome1/2* (*Cry1/2*) and *Period1-3* (*Per1-3*), form the primary drivers of circadian clocks in mammalian tissues [62]. Recent evidence suggests

that gut microbes help to establish proper levels of core clock gene expression in both the intestine and peripheral organs. Both antibiotic-treated and GF mice have reduced expression of *Bmal1* and *Cry1* and increased *Per1* and *Per2* within the intestinal epithelium [66]. GF mice also have altered levels of clock gene expression, including *Bmal1*, *Clock*, *Per2*, and *Cry1* in the liver and the hypothalamus [15]. HFDs can disrupt proper oscillation of core clock genes [67]. Notably, microbes appear to be necessary to transduce some of the disruptive effects of HFD, since these effects are partially abrogated in GF mice [15].

Though the full implications of microbial regulation of the core clock genes described above are yet to be revealed, work from Pierre Chambon's group [66] demonstrated a convincing mechanistic link between gut microbes, molecular circadian clock function, and metabolic disruption. In these studies, mice treated with antibiotics displayed metabolic abnormalities including weight gain, increased adiposity, and elevated blood glucose that corresponded with the alterations observed within the circadian clock. In addition to the core clock genes described above, ablation of the gut microbiota by antibiotics alters expression of intestinal *RevErba* and retinoid-related orphan receptor (*ROR*) α . The products of these genes, which normally oscillate in a circadian manner, encode two transcriptional regulators that compete for a promoter element, the RORE box. These RORE boxes are found in the promoters of many TLR genes in intestinal epithelial cells, such that the expression of these receptors also becomes rhythmic. During the dark period, when mice are mainly active, TLR gene expression rises, creating a time-dependent microbial signaling pathway that leads to activation of c-Jun N-terminal kinase (JNK) and I κ B kinase (IKK) β and repression of genes containing c-Jun binding sites. In antibiotic-treated mice, TLR gene expression is significantly decreased and becomes arrhythmic, which disrupts downstream TLR signaling through JNK and IKK β . A consequence of removing this regulatory cascade is the induction of *PPAR* α , normally repressed by active c-Jun, which leads to elevated expression of *Cyp11a1* and overproduction of corticosterone within intestinal cells, ultimately impacting host metabolic disruptions [66]. However, administration of LPS to antibiotic-treated mice restored normal levels of *RevErba* and *Ppara* transcripts in the intestine [66].

While the results of Mukherji *et al.* show that gut microbes are necessary to maintain stability of circadian rhythmicity of host cells, other work has shown that the microbiome itself also changes over a 24-hour period [15, 66, 68, 69]. Phylogenetic analyses of fecal microbiota in mice via 16S rRNA amplicon sequencing revealed that ~15% bacterial taxa oscillate over a 24-hour period [68, 69]. Firmicutes and Bacteroidetes, the two major phyla of gut bacteria, oscillate in antiphase with Firmicutes high during the feeding period and Bacteroidetes increasing in abundance during the fasting period [68]. Notably, mice fed a HFD exhibit less overall circadian rhythmicity in their microbiota, though dietary fat also promotes diurnal variations in certain taxa associated with increased risk of metabolic disorders [15, 68]. The driving force behind circadian oscillations of gut microbial communities may be feeding patterns, since timed feeding experiments shifted the phase of microbial abundances in WT mice and established microbial rhythmicity in the otherwise arrhythmic *Per1/2* knockout mouse [69], and partially restore bacterial oscillations in HFD-fed mice [68]. However, in the complete absence of enteral feeding, mice receiving parenteral nutrition still exhibit an oscillatory pattern within the gut microbiota, albeit a

dramatically altered microbial community, suggesting that other host-derived factors might be involved [15]. Fluctuations in the abundance of different bacteria over the course of the day create oscillations in the functional capacity of the gut microbiome [15, 69]. Notably, the production of microbial butyrate shows peaks and troughs corresponding to particular times of day [15]. Intriguingly, butyrate treatment in a hepanoid culture model promotes oscillation of *Bmal1* and *Per2*, and timed injection of butyrate into GF mice produces a time-dependent increase in the *Per2:Bmal1* mRNA ratio in the liver [15]. These results suggest that microbial metabolites may directly influence clock function.

If our gut microbial communities undergo their own daily cycles in parallel with our bodies, what happens to them when our circadian patterns are broken? Jet-lag can be simulated in mice by frequently shifting the timing of the onset of light and darkness. “Jet-lagged” mice fed a HFD develop a distinctive microbial community compared to non-disrupted mice [69, 70]. They also develop obesity and glucose intolerance, which can be recapitulated in GF mice colonized with “jet-lagged” microbiota. Furthermore, similar metabolic disruption appears in GF mice given fecal microbes from jet-lagged humans [69]. Thus, disruptions in microbial community structure and/or rhythmicity induced by losing track of time, so to speak, can have negative metabolic consequences for the host. Interestingly, broad-spectrum antibiotic therapy (vancomycin/ampicillin/kanamycin/metronidazole) could reverse the metabolic disorder observed by Thaïss *et al.* [69], whereas Mukherji *et al.* [66] reported that a nearly identical antibiotic treatment induced metabolic abnormalities. This apparently contradictory effect of antibiotic therapy underscores the need for experiments in which the direct effect of antibiotics can be measured and controlled.

Pre- and probiotics ameliorate obesity-associated metabolic disorders

As discussed above, extensive research has been conducted to understand the close interplay between the host and gut microbes as well as the microbial dynamics within the gut. Not only is it integral to understand microbial ecology and host-microbe interactions, but this information should also be leveraged to promote healthy metabolic phenotypes by modulating gut microbiota or the microbiome. Two major methods used to do so include the use of pre- and pro-biotics. Prebiotics are foods that promote growth of certain types of bacteria and include non-digestible carbohydrates such as inulin and oligofructose. Prebiotics are classified based on resistance to gastric acidity, passage through the small intestine without digestion, fermentation by bacteria, and promotion of healthy gut microbial communities. Probiotics, on the other hand, are live bacteria that beneficially impact host health that can be delivered as individual organisms or combinations such as VSL3, which contains 8 different bacterial species [71].

Several reports support a role for prebiotics in improving complications associated with metabolic disorders including obesity and insulin resistance [47]. Mechanisms found to support beneficial action of prebiotics include 1) increased expression of antimicrobial peptides; 2) SCFA production, stimulation of intestinal gluconeogenesis, and increased epithelial integrity; 3) increased release of gut peptide hormones including PYY and GLP1 to promote satiety and insulin sensitivity, respectively; and 4) restructured microbial communities including decreased relative abundance of pathogenic bacteria and increased

abundance of beneficial commensal bacteria (reviewed here and Ref. [47]). These mechanisms are discussed in more detail below.

One mechanism of prebiotic action is via the up-regulation of anti-microbial peptides. It was recently shown that a HFD reduced gene expression of Reg3 γ , an anti-microbial peptide targeting gram-positive bacteria, which was restored with supplementation of oligofructose [72]. Additionally, prebiotic treatment increased intectin expression, important for increasing epithelial cell turnover and maintaining epithelial integrity. Moreover, functional microbial analyses of clusters of orthologous genes (COGs) found that prebiotic treatment reduced HFD-mediated increases in the proportion of cell motility COGs. Together, these data suggest that prebiotic treatment may reduce the presence of LPS and lipoteichoic acid (LTA)-producing gram-positive bacteria and may protect against bacterial motility across the epithelium, leading to protection from HFD-induced insulin resistance and inflammation [72]. A separate mechanism was recently reported, whereby fructooligosaccharides (FOS) stimulated intestinal gluconeogenesis (IGN) [73]. Here it was found that FOS supplementation in mice fed high-fat, high-sucrose diet displayed improvements in glucose and insulin tolerance compared to control mice. This beneficial effect was lost in mice deficient in IGN, achieved through the intestinal-specific knockout of glucose-6-phosphatase catalytic subunit (G6Pc), a rate-limiting enzyme of gluconeogenesis. Therefore, it was concluded that IGN was necessary for prebiotic-mediated improvement in metabolic health. Importantly, associations between prebiotic foods as well as complex prebiotic formulations and improved metabolic indices have also been reported in human subjects. Participants fed Swedish brown beans displayed improved insulin sensitivity and increased circulating SCFAs [74]. Complex prebiotic formulations containing mixtures of wheat fiber and soluble fibers reduced inflammation, improved insulin sensitivity and significantly altered microbial structure in study participants with metabolic syndrome [75]. Specifically, the relative abundance of Enterobacteriaceae and Desulfovibrionaceae known to produce endotoxins were reduced with prebiotic therapy, while Bifidobacteriaceae was increased [75]. Altogether, these findings suggest that prebiotic therapy is effective in both animal models and humans and involve several mechanisms of action.

Probiotics, on the other hand, are live microorganisms found to beneficially impact host health. Probiotics can either be provided as individual organisms or as more complex communities such as VSL#3. The composition of probiotic formulations is important as each strain may differentially impact microbial structure or directly impact the host. This was nicely exemplified in a recent study conducted by Wang *et al.* [76] in which mice with HFD-induced metabolic syndrome were supplemented with one of three strains of bacteria: *Lactobacillus paracasei* CNCM I-4270, *L. rhamnosus* I-3690 and *Bifidobacterium animalis* subsp. *lactis* I-2494. Each strain independently reduced body weight, macrophage infiltration of adipose tissue, and improved glucose tolerance, but presumably through different mechanisms. For instance, *L. paracasei* and *L. rhamnosus* increased cecal acetate whereas *B. animalis* did not. *B. animalis* on the other hand, decreased TNF α expression in the liver and adipose tissue [76]. In addition to bacterial probiotics, attention has also been given to other microorganisms such as yeast. Intriguingly, the probiotic yeast *Saccharomyces boulardii* Biocodex, was shown to elicit improvements in the metabolic

profile of genetically obese and diabetic *db/db* mice. Daily gavage of the probiotic altered gut microbiota composition, including an increase in Bacteroidetes and decrease in Firmicutes, Tenericutes, and Proteobacteria, while there was a concurrent decrease in host adiposity and circulating inflammatory markers such as IL-6 and TNF α . Through correlation analyses, it was demonstrated that epididymal fat pad weight was negatively correlated with the genera Bacteroides but positively correlated with Odoribacter, Parabacteroides, Ruminococcus, and Prevotella, strains of bacteria previously associated with human obesity [77].

Modulation of gut microbes has a direct effect on fat metabolism and storage regulation via the LPL inhibitor Angptl4, a central player in adipocyte TG deposition [78]. A 10-week dietary intervention with the probiotic *Lactobacillus paracasei* F-19, in WT mice fed a HFD displayed increased circulating Angptl4 levels and significantly reduced adipocyte storage profiles. *In vitro* stimulation of colonic cell lines with specific gut microbes confirmed probiotic-mediated induction of Angptl4 mRNA expression via activation of PPAR signaling. In particular, PPAR γ and PPAR α are important for Angptl4-mediated signaling since PPAR downregulation via small interfering RNA (siRNA) compromised F19-stimulated Angptl4 expression. The impact of probiotics on the regulation of Angptl4 and thus, adiposity, were confirmed by mono-association of GF mice with F19, which increased Angptl4 serum protein levels [78]. Since Angptl4 is impacted by gut microbes and inhibition of Angptl4 increases adiposity and free fatty acid levels [14], changes in Angptl4 expression via nutritional modulation of gut microbiota provides an avenue for treatment of obesity and metabolic syndrome. Thus, probiotics may have the potential to ameliorate microbial dysbiosis as well as directly promote improvements in host metabolism through SCFA production or other aforementioned mechanisms.

However, the use of probiotics has been given less favorable attention due to lack of colonization of these beneficial microbes following consumption or ineffectiveness of providing one type of microbe alone [79]. It has been suggested that combinatorial probiotics such as VSL#3 or a combination of probiotic and prebiotic may prove to be a more effective treatment option. For instance, the commercially available probiotic formula VSL#3, containing *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Lactobacillus bulgaricus* has been shown to decrease the severity of NAFLD in obese children [80] as well as reduce the risk of hepatic encephalitis in patients with cirrhosis [81]. Overall, more research is needed to understand the best delivery method of pro- and prebiotic formulations to maximize their usefulness in the fight against obesity and associated metabolic disorders.

Alternative therapies are also emerging such as fecal microbiota transplant (FMT) and post-biotics. Although these therapies may be quite different in their source and complexity, both may be promising treatment options. For instance, FMT is the transfer of fecal slurries from an approved donor to a host recipient. This therapy has proved highly effective in patients with *Clostridium difficile* infection being protective in ~ 90% of cases [82]. As previously mentioned, Vrieze *et al.* demonstrated that FMT in men with metabolic syndrome reduced their symptoms related to insulin resistance [8]. More studies on the efficacy of FMT in

treating human obesity and metabolic disease are needed and will likely benefit from improved safety practices (reviewed in Ref. [83]).

The study of microbial metabolites and “post-biotics” is on the forefront of microbiome research as an alternative therapy to pre- and pro-biotics as well as FMT. Post-biotics include purified bacterial metabolites or other bacterial components that have a defined benefit to the host. Although the active use of post-biotics is in its infancy, several studies suggest that bacterial metabolites have a direct and positive impact on the host, such as SCFAs discussed previously. For instance, Rescigno and colleagues [84] found that while *ex vivo* culture with the probiotic *Lactobacillus plantarum* NCIMB8826 mounted an immune response, the culture supernatant from this bacterium protected against *Salmonella*-mediated TNF secretion from intestinal mucosal explants. The use of post-biotics would eliminate the need to administer live bacteria or complex communities containing potentially unknown pathogens that may be present in FMT therapies. It will be exciting to see how these products develop as effective therapies for human disease.

Conclusion

Further research is needed to understand host-microbe interactions as they relate to dietary intake and the development of obesity and metabolic syndrome. As discussed in this review several mechanisms are at play to explain the dynamic association between microorganisms that inhabit the GI tract and host metabolism. These mechanisms include 1) sensory perception of macronutrients and total energy intake, 2) nutrient absorption, transport, and storage, 3) liver and biliary function, 4) immune-mediated signaling related to adipose inflammation, and most recently 5) circadian rhythm. Each of these affected processes may influence the metabolic state and propensity of the host to gain excess weight and develop insulin resistance and metabolic syndrome. Current therapies are growing which include pre- and pro-biotic supplementation, FMT, and now also post-biotic treatments. However, it is still imperative that the research community focuses their efforts on better defining the mechanisms behind microbial regulation of metabolism as well as the therapies in order to combat the ever-increasing rate of obesity in the US.

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Figure 1. Mechanisms by which microbial alterations, induced by Western diet consumption, cause metabolic dysfunction in peripheral tissues of the host

ABCG, ATP-binding cassette sub-family G; SREBP1C, sterol regulatory element-binding protein 1; CIDEA – Cell death activator; SCFAs, Short-chain fatty acids; Gpr, G-coupled protein receptor; ANGPTL4, angiopoietin-type 4; LPS, lipopolysaccharide; LTA – lipoteichoic acid; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; TNFα, tumor necrosis factor alpha; LPL, lipoprotein lipase.

Figure 2. Mechanisms of diet-induced gut microbial regulation of intestinal, central and peripheral circadian clocks and metabolic outcome

(Top) Feeding patterns and other inputs produce day-night cycling of intestinal microbial communities and their associated metabolites, promoting proper circadian timing in the host.

(Bottom) High-fat Western diets create dysbiosis and alter oscillations of bacteria.

Dysregulation of host and microbial signaling molecules leads to desynchronization of clocks in multiple tissues and promotes metabolic disorder. SCFAs, Short-chain fatty acids; TLRs, Toll-like receptors; *Reverb*, Nuclear receptor subfamily 1, group D, member 1; *PPARa*, peroxisome proliferator-activated receptor; H₂S – Hydrogen sulfide