Gut Microbiota: Modulation of Host Physiology in Obesity

Many factors are involved in weight gain and metabolic disturbances associated with obesity. The gut microbiota has been of particular interest in recent years, since both human and animal studies have increased our understanding of the delicate symbiosis between the trillions of microbes that reside in the GI tract and the host. It has been suggested that disruption of this mutual tolerance may play a significant role in modulating host physiology during obesity. Environmental influences such as diet, exercise, and early life exposures can significantly impact the composition of the microbiota, and this dysbiosis can in turn lead to increased host adiposity via a number of different mechanisms. The ability of the microbiota to regulate host fat deposition, metabolism, and immune function makes it an attractive target for achieving sustained weight loss.

The growing epidemic of obesity (17) and its associated complications of cardiovascular disease, hyperlipidemia, non-alcoholic fatty liver disease, and Type 2 diabetes mellitus present an increasing burden on the healthcare system worldwide. Since 1980, the prevalence of obesity has increased 75% (57, 75), with estimates that in 2014 ~375 million women and 266 million men were reported to be obese worldwide (17). Simplistically, obesity results from imbalance between energy consumption and expenditure. In reality, however, the development of obesity is due to a complex interaction of genetic, environmental, cultural, behavioral, and microbial factors.

The human gut microbiota is a diverse array of microorganisms, including bacteria, archaea, fungi, and viruses that colonize the surfaces of the gastrointestinal (GI) tract (69). Under normal homoeostatic conditions, a physicochemical barrier of mucus, epithelial tissue, and regulatory components of the innate and adaptive immune system maintain a constant bidirectional communication between microbes and the host that results in mutual benefit. Disturbances in the microbial community can result in a compromised intestinal barrier, dysregulated immune system, and altered tissue metabolism, mechanisms which have been implicated in development of obesity. In this review, we discuss the factors that determine gut microbial composition, proposed mechanisms linking the gut microbiota with obesity, and potential interventions to combat obesity through manipulation of gut microbial communities.

Early Life Modulators of the Gut Microbiota

The gut microbiota is a delicate balance of organisms influenced by several factors including age, mode of delivery, infant feeding mode (e.g., breast milk vs. formula) (60), and use of antibiotics (25). Age is particularly important, and the gut microbiota composition may differ at different time points within the same individual (46). Vertical transmission of the microbiota from pregnant mother to offspring establishes the infant gut microbiota, with colonization beginning at or just before birth, as the meconium of full-term neonates has been shown to contain bacteria. Vaginally delivered infants have microbiomes that resemble the mothers’ vaginal tract, whereas infants delivered by Caesarean section have microbiotas consisting largely of skin microbes, including *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* (16, 28, 46). These differences may lead to long-term health consequences, as evidenced by a 46% increase in obesity risk at 7 years of age for children who were born by Caesarean delivery (54).

Prenatal and postnatal exposures to microbial modulators, such as diet and antibiotics, may also affect the infant microbiome and the predisposition to obesity. For instance, maternal antibiotic usage was associated with an 84% higher risk in obesity in their children (54). Meanwhile, in primates, an obesity-inducing diet during pregnancy reduced the diversity of the intestinal microbiota of the offspring, even after a switch to a healthy diet at weaning (48). Postnatal antibiotic exposure can
Diet as a Modulator of Gut Microbiota

Diet has a major role in modulating the composition and metabolic output of the gut microbiota and represents an important therapeutic strategy in the management of obesity. The effect of diet on the microbiota and obesity predisposition can begin even before the introduction of solid foods, as breast-fed infants have a significantly reduced risk of obesity later in life compared with formula-fed infants (56). Although the exact mechanisms for such an effect remain unclear, human milk, comprised of indigestible glycans, oligosaccharides, glycolipids, and glycoproteins, appears to create an environment conducive to a healthy microbiota and body weight later in life (58, 66).

The effect of diet on the microbiota is also evident on a global scale. For instance, the high-fiber diet of Burkino Faso children was associated with greater microbial richness, higher amounts of Prevotella, and lower amounts of Bacteroidetes compared with the microbiotas of European children eating a diet much lower in fiber (21). Irrespective of age, Western diets, consisting of high amounts of processed simple sugars, have been linked to microbial dysbiosis and the obesity epidemic. Metagenomic studies have also found that obesity is associated with low bacterial gene richness (43), whereas energy-restriction increases richness (19).

Both short-term and long-term dietary influences have been shown to affect the gut microbial diversity and function (20, 86). A recent study supporting this concept shows that lack of microbiota-accessible carbohydrates, as often seen with Western diets, can lead to a potentially irreversible loss in microbial diversity over generations (73).

The assessment of microbial composition in response to diet is helpful, but, given the inter-individual variability and the redundancy in microbial functions, it becomes imperative to concurrently assess changes in microbial function. Wu and colleagues characterized the gut microbiota and metabolome of individuals consuming a vegan or omnivorous diet in Western society. They found little difference in microbial community composition, but significant differences in the microbial metabolome (87) highlight the importance of assessing changes in microbial function.

The interactions of diet and the microbiota during obesity are also shaped by host genetics. For example, mice lacking the TLR5 gene have an altered gut microbiota, which promotes hyperphagia and an obese phenotype (81). In humans, the gut microbiota appears to be highly individualized, although its composition and function can be used with other host parameters to predict acute dietary responses (91). These studies highlight the potential role of gut microbiota in mediating host response to diet and their therapeutic utility in regulating metabolic response.

Exercise as a Microbiota Modulator

Regular exercise can significantly alter the gut microbiota. Recent studies indicate that exercise can initiate changes in the microbiota in a healthy state or in unfavorable circumstances, including consumption of a Western diet (39), exposure to oncogenic substances (14), and experimental diabetes (42). In relation to obesity, we recently demonstrated that exercise training and a high-sugar, high-fat diet orthogonally alter the gut microbiota (37). Evans et al. also showed changes in the microbiota by exercise training, both alone and in combination with a high-sugar, high-fat diet (30). Notably, exercise training in mice reduced levels of Erysipelotrichaceae and Turicibacteraceae, families of bacteria that are associated with obesity, bile acid regulation, and gut inflammation (30). Changes in the microbiota by exercise training have also been associated with improvements in metabolic parameters, including the reduction of circulating leptin (62). Detailed mechanisms for how exercise-induced changes in the microbiota occur are still unclear but could involve interactions between host and microbial metabolism, including cross feeding of metabolites (18). Further research is needed to determine whether exercise affects the human microbiota during obesity and whether the magnitude of weight loss and metabolic changes are linked to these changes.

The Gastrointestinal Mucus Layer, Epithelial Barrier, and Immune System: Gatekeepers and Active Signalers of the Gut Microbiota During Obesity

The mucus layer of the GI tract provides the most distinct microbial-host interface, consisting of an outer, non-adherent mucus layer colonized by commensal microbes and an inner, adherent layer closest to the epithelium that remains largely sterile. In mice, diet-induced obesity results in degradation of the outer mucus layer and change in bacterial niches with translocation to the inner mucus layer or epithelium (31). Although the
mucus layer and spatial organization of microbes is much more difficult to characterize in humans, there is strong evidence of a relationship between mucus-degrading bacteria, host adiposity, and obesity-related conditions. For instance, the mucus-degrader *Akkermansia muciniphila* is negatively associated with adiposity and metabolic dysfunction (70), whereas other mucus-associated bacteria, such as *Ruminococcus gnavus*, are positively correlated with similar outcomes (41). Functionally, *A. muciniphila* contains a large collection of enzymes capable of degrading O-linked oligosaccharides, whereas *R. gnavus* contains enzymes that allow it to both cleave and consume terminal sialic acids on the mucus structure (76). Downstream, *A. muciniphila* can improve host metabolism and the immune system through numerous mechanisms, including, but not limited to, SCFA production, host endocannabinoid release (31), and regulation of lipid metabolism (47). Despite colonizing the same area, *R. gnavus* has vastly different downstream effects on host physiology, as it has been strongly correlated with both gut inflammation and serum triglycerides in mice and humans (35, 41). These data suggest an important role of the mucus layer and its associated microbiota in obesity, and provide rationale for a potential therapeutic role for mucus-degrading bacteria in the management of obesity and associated metabolic disorders.

In addition to its effects on mucus layer, the gut microbiota also alters expression of host genes that impact nutrient absorption and metabolism (36). For instance, germ-free mice fed a Western diet were resistant to diet-induced obesity and demonstrated elevated levels of fasting-induced adipose factor (Fiaf), a circulating inhibitor of lipoprotein lipase. Meanwhile, germ-free mice colonized with microbiota from wild-type mice displayed suppression of Fiaf and greater deposition of triglycerides in adipose tissue (88). More research is necessary to determine which microbes carry the most influence on Fiaf expression and whether these are the same microbes that are typically present or absent in greater numbers in obese individuals. AMP-activated protein kinase (AMPK) represents another mechanism by which the microbiota regulates host metabolism. Germ-free mice have elevated levels of activated AMPK, increased mitochondrial fatty acid oxidation, decreased glycogen storage, and they remained lean despite being fed a high-calorie diet (4).

The microbiota may also be partially responsible for reduced barrier integrity and systemic endotoxemia during obesity. For instance, a high-fat diet in mice was shown to induce phosphorylation of the myosin light chain and localization of occludin into the cytoplasm of intestinal epithelial cells. This change in barrier function was correlated with the rise in endotoxin in the blood throughout the diet, suggesting that barrier disruption within the gut is at least partially responsible for diet-induced endotoxemia (22). Endotoxemia also occurs in obese humans and may contribute to metabolic disturbances. For example, it was shown that obese, insulin-resistant individuals had higher levels of circulating LPS than their more insulin-sensitive counterparts (10). In rats, diet-induced endotoxemia was shown to contribute to leptin-resistance in vagal nerves, indicating a possible mechanism for endotoxin-induced metabolic disturbances (22). Despite this intriguing data, more research is needed (especially in humans) to determine the mechanisms related to low-grade endotoxemia and whether this phenomenon contributes significantly to increased adiposity.

If the mucosal and epithelial barrier of the gut is compromised, commensal microbes are also able to act locally on the underlying GI immune system (11). Antigen-presenting cells (e.g., dendritic cells and macrophages) throughout the gut express pathogen recognition receptors (PRRs), including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domains (NOD)-like receptors (NLRs), which continually respond to antigenic stimuli, including the microbiota (12). During obesity, intestinal immune activation and inflammatory processes induced by the commensal microbiota can lead to enhanced adiposity and altered metabolism. For example, in wild-type mice, ileal TNF-α expression increased significantly at weeks 6 and 16 during exposure to high-sugar, high-fat diet, and was strongly associated with weight gain and metabolic disturbances, including an increase in fasting glucose (27). However, in germ-free mice exposed to the same diet, there was attenuation of intestinal inflammation, adipose gain, and metabolic disturbances. In another study, intestinal epithelial-specific deletion of MyD88, a downstream component of TLR signaling, partially inhibited diet-induced obesity and associated metabolic disturbances in mice. Meanwhile, upon transfer of the microbiota from MyD88 KO animals to germ-free animals, the obese phenotype was attenuated (32).

Together, these data provide evidence that alterations in gut microbiota by obesity can cause gastrointestinal barrier disruption, GI immune system activation, and bacterial translocation, all of which may lead to altered metabolism within the host. Future studies are needed to elucidate the mechanistic underpinnings of these phenomena to further understand how they relate to obesity.
Microbial Mechanisms Regulating Energy Homeostasis and Inflammation

The metabolic activity of gut microbiota can regulate energy balance via mechanisms that affect energy harvest from diet as well as modulate genes that affect energy storage/expenditure and inflammation. In this section, we will highlight some of the metabolites produced or altered by the microbiota that have been implicated in obesity.

Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) are mainly produced by gut microbiota as fermentation products of complex polysaccharides, including dietary fibers such as inulin and pectin, and endogenous substrates like mucins (55). Overall, the nature of fermentation and the SCFA profile within the gut is dependent on the composition of the gut microbiota, interactions between microbes and the host (i.e., composition of mucin oligosaccharides), and amount/type of fermentable carbohydrate consumption. Following absorption, butyrate serves as a source of energy for the colonic epithelial cells, whereas propionate and acetate mainly act as substrates for gluconeogenesis and lipogenesis in the gut and the liver (24, 72). Prior to metabolism, SCFAs are also able to interact with free fatty acid receptors (FFARs) located in the intestine and various other tissues.

With regard to obesity, SCFAs came into light when seminal studies showed that the microbial community of genetically obese mice was enriched for genes capable of harvesting energy from complex plant-derived polysaccharides (80). Germ-free, FFAR3−/− mice colonized with Bacteroidetes thetaiotaomicron and Methanobrevibacter smithii were leaner compared with conventionally raised wild-type littermates, implying a role of FFAR3 and the gut microbiota in the regulation of host energy harvest (67). Such effects may be traced to FFAR3-induced release of peptide YY, a hormone derived from the enteroendocrine cells that slows intestinal transit and hence contributes to increased caloric extraction from the diet (67). Meanwhile, microbiota transfer from obese mice to lean, germ-free mice led to increased hepatic triacylglycerol accumulation (72), possibly through increased fermentation to SCFAs and thus energy harvest. In humans, it has been shown by more than one group that SCFAs are elevated in the feces of obese individuals (33, 71, 77).

Despite these energy-harvesting capabilities, which may exacerbate adipogenesis, SCFAs appear to have a complex and pleiotropic role in obesity. SCFAs can also induce satiety, sensitize cells to insulin, and reduce inflammation in the pancreas, muscle, and adipose tissue, among others. One example is SCFA-induced leptin secretion via FFAR3, which regulates appetite and energy metabolism (90). Meanwhile, stimulation of the FFAR2 receptors in the gut mediates release of glucagon-like peptide (GLP-1) to improve insulin secretion (78), whereas signaling in neutrophils suppresses inflammation (49). SCFAs can also directly modulate the adaptive immune system independent of FFARs. Most notably, SCFAs can directly modulate the metabolic phenotype of T-cells by inhibiting histone deacetylases (3, 92). Butyrate and acetate can also stimulate goblet cells to release Muc2, an essential component of the mucus layer that helps maintain the intestinal barrier and tolerance to foreign antigens (9). In humans, metagenome-wide association studies have identified butyrate-producing bacteria that are negatively associated with obesity and subsequent insulin resistance. For instance, Qin et al. (61) and Karlsson et al. (38) report lower proportions of butyrate-producing Clostridial, including Roseburia and Faecalibacterium prausnitzii, in obese individuals.

These conflicting data present a paradox for delegating these SCFAs into “good” or “bad” regarding the pathogenesis of obesity. Dichotomously, SCFAs not only may enhance energy harvest and contribute to excess lipogenesis in the liver, but also concurrently reduce inflammation, sensitize tissues to insulin, and contribute to satiety. Discrepancies in these findings may be related to categorizing SCFAs under one umbrella term, when, in reality, each metabolite has distinct metabolic effects. For instance, acetate displays more obesogenic potential, since it acts as a primary substrate for hepatic and adipocyte lipogenesis, compared with propionate or butyrate, which primarily serve as substrates for other metabolic processes (13). Moreover, excess SCFA concentration in feces, alone, likely does not represent bodily turnover and metabolism of these molecules. Thus future research requires a more detailed understanding of the transport, metabolism, and signaling of SCFAs in obesity and other chronic diseases.

Bile Acids

Bile acids (BAs) are synthesized in the liver from cholesterol, stored in the gall bladder, and released into the small intestine to aid in digestion of triglycerides. Upon release, the gut microbiota further metabolize BAs through deconjugation, dehydroxylation, and dehydrogenation. BA transformation by the gut microbiota has been shown to initiate dramatic changes in the BA pool size with subsequent effects of host physiology (64). Meanwhile, BAs can initiate changes in the diversity and...
composition of the gut microbiota, and thus can contribute to microbe and host physiology (63).

BAs (and their regulation by the microbiota) can significantly alter glucose/lipid metabolism and inflammation in the host. Such action primarily occurs through BA activation of the nuclear farnesoid X receptor (FXR) and cytoplasmic G-protein-coupled BA receptor TGR5 (82). Within the gut, BAs can act through TGR5 on enteroendocrine cells and stimulate the production of GLP-1, an incretin hormone implicated in improved glucose metabolism and satiety (8). Stimulation of TGR5 by BAs has also been linked to other metabolic actions outside of the GI tract. In particular, activation of TGR5 by BAs initiates the browning of adipose tissue and increases skeletal muscle energy expenditure through cAMP-dependent type 2 iodothyronine deiodinase, an enzyme that activates thyroid hormone (85). Activation of FXR by BAs, meanwhile, can initiate the release of fibroblast growth factors FGF19 and FGF21, both of which have insulin-sensitizing and hypolipidemic effects (15). BA activation of FXRs can also modulate TLRs on intestinal myeloid cells, thus implicating BAs in the regulation of innate immunity toward an anti-inflammatory state (34).

There are also negative consequences of microbial transformation of BAs. For instance, the dehydroxylation from primary to secondary BAs by the microbiota can lead to secondary BA accumulation in the colon. Secondary BAs, which are particularly high in individuals on Western diets, can activate numerous downstream signals involved in disease states (63). In relation to obesity, Yoshimoto et al. recently found that the secondary bile acid deoxycholic acid (DCA) has a primary role in obesity-associated hepatocellular carcinoma (89).

Endocannabinoids

The endocannabinoid (eCB) system has been proposed to regulate gut barrier function during obesity, in addition to regulating feeding behavior and metabolism (53). The eCB lipids, AEA (anandamide or N-arachidonyl ethanolamine) and 2-AG (2-arachidonoylglycerol), are widely expressed in tissues that control energy balance (muscle, gut, liver, adipose tissue, pancreas, hypothalamus) (50). They exert most of their functions by activating CB1 and CB2, two G-protein-coupled receptors expressed throughout the GI tract. The eCB system tends to be activated during obesity in both mice and humans, with an increase in both eCBs and their receptors (7, 29). In vitro work with Caco-2 cells suggests that expression of tight-junction proteins and transepithelial electrical resistance are CB1-dependent. These findings are consistent with in vivo work, since leptin-deficient, genetically obese mice treated with CB1 antagonists exhibit improved barrier function, reduced adipose tissue mass, and reduced metabolic endotoxemia, independent of food intake (2, 53). Moreover, the gut microbiota has been shown to modulate colonic CB1 mRNA. Conventionally raised mice have significantly lower CB1 expression in the colon compared with germ-free mice, and genetically obese mice fed prebiotic fiber have reduced CB1 expression in the colon compared with genetically obese mice fed control diets (53). These results suggest that the eCB system might link the microbiota and low-grade, systemic inflammation.

Shaping the Microbiota to Combat Obesity

Gut microbial ecology can be reshaped by several targeted and non-targeted interventions, including prebiotics, probiotics, fecal microbiota transplant, and surgical interventions (FIGURE 1).

Prebiotics

Prebiotics have been defined as nondigestible compounds that, after metabolism by the gut microbiota, modulate the composition and metabolic activity of micro-organisms to confer physiological benefits to the host (6). Gut microbiota adapt to the available dietary and host nutrients either by shifting relative composition or changing microbial function (40). For instance, in adult humans, dietary polysaccharide and resistant starch increased levels of Ruminococcus bromii and...
Eubacterium rectale, two bacterial strains that are capable of metabolizing insoluble carbohydrates to SCFAs (84). The beneficial role of prebiotics in obesity remains to be elucidated, but the addition of inulin (a soluble, fermentable fiber) to diets of obese individuals has shown to decrease LPS in the blood, likely through changes in butyrate and butyrate-producing bacteria (44). In future studies, prebiotics targeting specific bacterial functions may have a role in management of obesity.

**Live Bacterial Therapeutics**

Live bacterial therapeutics (LBPs) have also shown potential for improving host physiology in obesity. Although it remains debatable whether they are able to permanently colonize the GI tract, transiently altering gut microbial community dynamics with LBPs has proven effective. For instance, various strains of *Lactobacilli* or *Bifidobacteria* have proven effective at promoting weight loss (26, 51). *Lactobacillus plantarum* has been shown to reduce adipocyte size and overall adiposity in mice (59), whereas *Lactobacillus rhamnosus* GG has been shown to increase weight loss in women in combination with a moderately energy-restricted diet (68). A 2015 study found that *Bifidobacterium psuedoacetatalatum* reduces obesity-associated inflammation in mice with diet-induced obesity (52). Consumption of traditional fermented foods, which naturally contain large amounts of beneficial microbes, has also been shown to promote weight loss and improvement in metabolic disease parameters (39).

**Roux-en-Y Gastric Bypass**

Roux-en-Y gastric bypass (RYGB), an effective treatment for weight loss in morbidly obese individuals, has been associated with alterations in gut microbiota in both human and mouse models. The reported changes in gut microbiota include increased abundance of Gamma Proteobacteria (a facultative anaerobe) and decreased Firmicutes (93). When this altered microbial community is transplanted into germ-free mice, improvements in metabolic parameters are observed, suggesting that weight loss following surgery may be due in part to alteration in the gut microbiota (45). Specifically, there is an increase in *Faecalibacterium prausnitzii* in obese patients with Type 2 diabetes after surgery, and levels of this organism are negatively correlated with inflammatory markers. This again indicates that this species may contribute to the improvement in insulin sensitivity following gastric bypass, possibly through increased butyrate production (11, 38). Perhaps the largest contributor to improved health after RYGB is the alteration in bile acid flow, which can in turn dramatically alter signaling through downstream release of GLP-1 and FGF-19 (74).

**Fecal Microbiota Transplant**

Fecal microbiota transplantation (FMT) from lean donors to obese recipients with metabolic syndrome resulted in improved peripheral insulin sensitivity, enhanced gut microbial diversity, and increased numbers of butyrate-producing *Eubacterium hallii* (83). Although FMT is not currently accepted for the treatment of obesity, the ability to transfer the metabolic phenotype in mice and humans may support a future role of FMT in management of obesity and associated metabolic conditions in humans.

**Conclusion and Future Perspectives**

In this review, we outlined how the gut microbiota, directly or indirectly, influences the pathogenesis of obesity. The importance of the gut microbiota in host health is evidenced by the strong relationship of the gut microbiota to host adiposity and metabolism. Therefore, modulation of gut microbiota represents an important opportunity for management of obesity. We envision that advances in metagenomic analysis will unravel new details relative to the composition and functionality of gut microbiota, whereas targeted repletion of specific bacteria will become a more widely used therapeutic application to combat obesity. Based on the different microbiota compositions, there is also potential for development of specific biomarkers to identify individuals at risk for development of obesity and stratification to personalized treatment options, including diet and lifestyle modifications, prebiotics, probiotics, or bariatric surgery.

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