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REVIEW

Connection between gut microbiome and the development of obesity

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Abstract

The potential role of the gut microbiota in various human diseases has attracted considerable attention worldwide. Here, we discuss the vital role of the intestinal microbiota in the development of obesity. First, we describe how the gut microbiota promotes fat accumulation. Additionally, a high-fat diet leads to structural instability among in the gut microbiota, further leading to an increase in endotoxins, which aggravates obesity. We then discuss how gut microbiota metabolites, including short-chain fatty acids and lipopolysaccharides, affect the host. Finally, we review several strategies for regulating the intestinal flora.

Keywords Obesity · Gut microbiota · Fat accumulation · LPS · SCFAs · Strategies

Introduction

The global prevalence of obesity is increasing to various degrees depending on geography, ethnicity, age, and sex [1]. Host-microbial interactions have been documented in studies of obesity-related diseases [2]. In the context of the global obesity epidemic, it is of great interest to understand how microbial metabolomes alter human energy metabolism. The intestine hosts the densest and one of the most diverse microbial communities in the human body [3]. The gut microbiota plays a vital role in the development of obesity as microbes can harvest energy from indigestible dietary substances [4, 5]. Moreover, metabolites of the intestinal flora have different effects on the host. Gas, heat, and short-chain fatty acids (SCFAs) are the main byproducts of bacterial fermentation of indigestible carbohydrates in the gut, and intestinal microflora SCFAs have been reported to have a beneficial effect on host metabolism and appetite [6]. Lipopolysaccharides (LPS), which is often referred to as an endotoxin, is commonly found in the human intestine and has a strong affinity for chylomicron lipoproteins. Dietary lipids are transported through the intestinal wall, passing through the gastrointestinal mucosa and binding to destructive lipoproteins. Metabolic endotoxemia is a form of systemic inflammation in which bacteria appear to mediate the risk of

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metabolic disease [7]. Although the gut microbiota changes in obesity, the role of Toll-like receptor (TLP) ligands in inducing insulin resistance, the effects of LPS cycling pathways, and the limitations of current permeability tests and other potentially useful markers, are well understood, additional research is needed to elucidate how such changes in the intestinal flora occur [8]. Obesity causes increased levels of proinflammatory cytokines in macrophages and infiltration of expanded adipose tissues. Indeed, obesity is thought to be an inflammatory state characterized by a positive correlation between fat mass and the expression of TNF-α and other proinflammatory cytokines [9]. In this review, we discuss the gut microbiota as a potential target for reducing obesity. We also describe methods for regulating the intestinal flora, including fecal microbiota transplantation, bariatric surgeries, antibiotic treatment, natural product regulation, probiotics uses, and dietary alteration.

The gut microbiota facilitates fat accumulation

Zhao used Koch's postulates to explain the association and causality link between the gut microbiota and obesity [10]. Diet is a powerful environmental factor that shapes the composition of the intestinal flora. The main causes of obesity are reduced exercise and increased intake of high-energy foods. In addition, various gene polymorphisms have been shown to play a role in the pathogenesis of obesity [11, 12], and specific proteins and hormonal factors in human cells play roles in regulating metabolism and body weight [13]. Although the composition of the human gut microbiota changes transiently following dietary changes, it is relatively stable over long periods in adults.

The gut microbiota is also considered a regulator of energy homeostasis. According to the literature, exposure of the intestinal microbiota to certain environmental insults can result in impairment of energy homeostasis impairment and the eventual development of obesity [14]. Numerous studies have focused on the effects of the gut microbiota on obesity, and the relationship between obesity and these microflora [15, 16]. For example, animal experiments have shown that fluctuations in the microbiota can cause changes in the production or secretion of fat molecules, which affect energy storage (fat mass) and balance [17, 18]. The gut microbiota is necessary for the decomposition of dietary polysaccharides, and studies comparing conventionally (CONV-R) and sterile (GF) fed mice have shown that the intestinal flora is an environmental regulator of fat storage [19]. Intestinal microbes increase the monosaccharide absorption in the intestinal lumen, which subsequently induces fat production in the liver. Insulin and glucose also induce the expression of lipogenic enzymes in the liver. Host glycoside hydrolase cannot cleave to the glycosidic bonds of polysaccharides, and a transplanted microbial population not only enhances the absorption of polysaccharides but also regulates the host genes that affect fat cell accumulation [19, 20].

Fasting-induced adipocytokine (FIAF), a circulating lipoprotein lipase inhibitor, is essential for microbial-induced triglyceride deposition in adipocytes, and according to Fredrik, a lack of FIAF significantly reduced the total fat content [19]. However, the intestinal flora can promote lipoprotein lipase (LPL) expression by inhibiting FIAF gene expression to promote triacylglycerol storage in adipocytes [21]. The intestinal flora decomposes substances that cannot be digested by the host and converts them into SCFAs, which can promote fat accumulation.

Adenosine monophosphate–activated protein kinase (AMPK), which plays a key role in systemic energy balance, is an evolutionary sensor of cellular energy status [22]. In addition, AMPK coordinates nutrient and hormonal signals in both peripheral tissues and the hypothalamus. AMPK is directly phosphorylated by acetyl-CoA carboxylase (Acc; conversion of acetyl-CoA to malonyl-CoA) to stimulate fatty acid oxidation in peripheral tissues; Acc phosphorylation, which reduces fat accumulation, inhibits its activity, resulting in decreased levels of malonyl-CoA. In turn, malonyl-CoA inhibits carnitine: palmitoyltransferase-1 (Cpt1), accelerating the rate-limiting step of long-chain fatty acyl-CoA entry into mitochondria, and a decrease in malonyl-CoA leads to increased Cpt1 activity and fatty acid oxidation [23]. Changes in the structure of the gut microbiota may reduce AMPK in the liver and muscle, and thereby inhibit AMPK-dependent fatty acid oxidation [20], which can lead to fat accumulation.

SCFAs are not only an important source of energy for host intestinal epithelial cells but also an important signaling molecule for at least two G protein–coupled receptors(GPCRs),—the binding partners of GPR41 and GPR43 [24]. Samuel et al. showed that there is less fat accumulation in the bodies of GPR41 knockout mice colonized with *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii* than in wild-type mice colonized by the same bacterial species [25]. Furthermore, serum levels of peptide YY (PYY) were found to increase significantly after colonization of both wild-type sterile mice and GPR41 knockout mice. PYY inhibits food absorption, intestinal movement, pancreatics and intestinal secretion, and gastrointestinal emptying [26]. Loss of GPR41 signaling and decreased levels of serum levels of PYY promote intestinal peristalsis and reduce energy procurement from food (Fig. 1).

Extensive experimental evidence suggests that the gut microbiota plays an indispensable role in promoting host fat synthesis and accumulation. Therefore, we hypothesized that a high-fat diet (HFD) can cause obesity due to intestinal microbiotal activity.

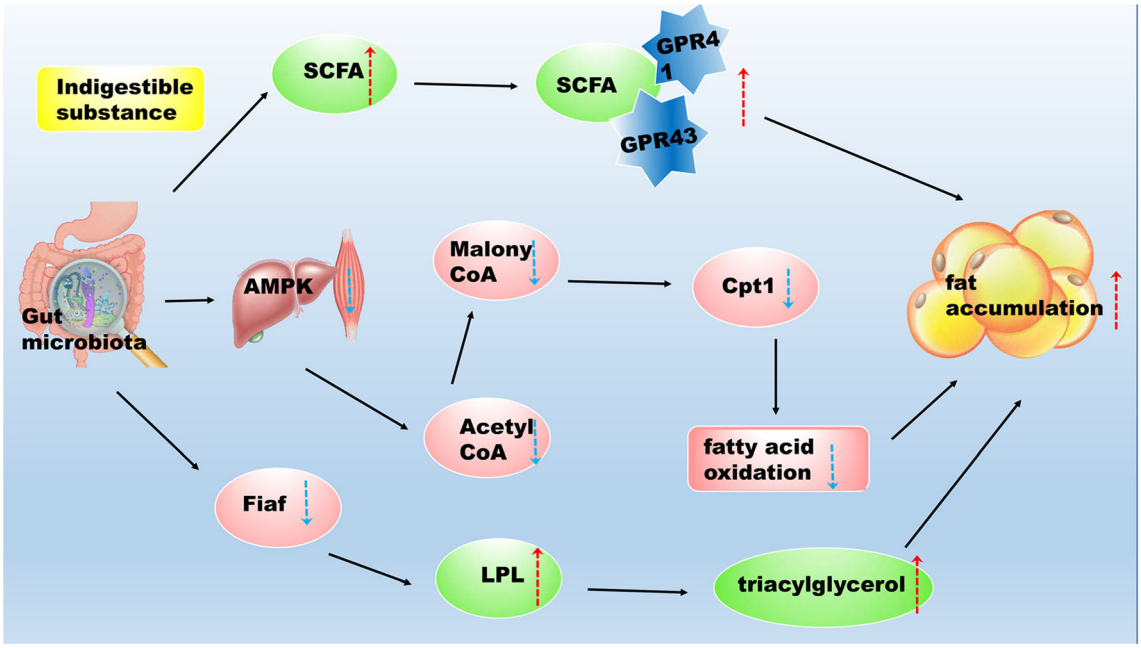

Fig. 1 Fat accumulation

The role of gut microbiota metabolites in the development of obesity

SCFAs regulate host metabolism and appetite

Gas, heat, and SCFAs are the main byproducts of bacterial fermentation of indigestible carbohydrates in the gut [6]. The bacterial fermentation process can be regarded as a system for collecting energy from undigested substances, such as energy that cannot be absorbed in the small intestine, and as a major source of energy for certain bacteria [27] [28, 29]. SCFAs, primarily propionate, butyrate, and acetate, are produced after bacterial fermentation, and they are present in a molar ratio of approximately 20:20:60 [30]. In animal models, fermentable soluble carbohydrates (FC) have been shown to increase the cecal content of SCFAs [31].

Intestinal microflora SCFAs are reported to be beneficial for host metabolism, and the associated molecular mechanisms are highlighted here. SCFA concentrations are ~ 400 μM, in portal blood, ~ 100 mM in the gut lumen, and ~ 100 μM in peripheral tissues [30]. Because of this concentration gradient, SCFAs have relatively different functions in different tissues. Butyrate promotes fatty acid oxidation and thermogenesis by increasing phosphorylation of peroxisome proliferator–activated receptor-gamma coactivator-1α (PGC-1α) and AMPK in the liver and muscle and the expression of PGC-1α and mitochondrial uncoupling protein-1 (UCP-1) in brown adipose tissues [32]. Butyrate and propionate activate intestinal gluconeogenesis through the intestine-brain circuit, thereby promoting glucose control and metabolic benefits reflected by body weight [33]. Acetate reduces appetite by activating the tricarboxylic acid (TCA) cycle to alter the expression profile of the hypothalamic appetite-regulating neuropeptide [34]. Different studies have shown that GPCRs act as receptors for SCFA target molecules in the host [35, 36].

GPCRs, which initiate signaling cascades, are molecular information transducers of sugars, proteins, lipids, and peptides for the cell, causing cells to open ion channels; secrete substances; and regulate gene expression at the transcriptional level [37]. GPR43 receptors are expressed in a variety of different cell types, including neutrophils, adipocytes, peripheral blood mononuclear cells, B lymphocytes, eosinophils, and pancreatic β-cells [38]; GPR41 receptors are present in human adipocytes and cell of the sympathetic nervous system [39]. After binding to 3-carbon fatty acids, the receptors have different affinities for SCFA binding; human GPR41 exhibits greater affinity toward butyrate and propionate, whereas GPR43 binds with greater affinity to butyrate, acetate, and propionate [40]. SCFAs are effective signaling molecule that can be induced, for example, by interaction with GPR41 and GPR43 receptors, which are subclasses of GPCRs, as sensory receptors for nutrients to elicit glucose-stimulated insulin secretion from pancreatic β-cells [41]. Thus, SCFAs promote energy metabolism through their effects on receptor-mediated pathways of cellular metabolism. GPR41 and GPR43 co-localized with L cells, which secrete the pancreatic glucagon-like peptide-1 (GLP-1) peptide YY3–36, glucagon-like peptide-2 (GLP-2), and oxyntomodulin in the colon, resulting in receptor activation by microbiota SCFA ligands and promoting the release of at least GLP-1 and PYY [42]. Regarding obesity, these peptide hormones promote satiety-induced glucose disposal. In addition, sympathetic ganglia

and intestinal neurons activate the GPR41 receptor in the intestine, improving sympathetic outflow and gut gluconeogenesis, and thereby increasing energy expenditure and reducing hepatic glucose production [41].

CS Byrne studied the role of acetate and the abundance of SCFAs in appetite regulation in mice [34]. Recent observations have revealed that dietary supplementation with FC inulin can significantly reduce weight gain and energy intake [43]. Furthermore, researchers have used positron emission tomography–computed tomography to study the effects of colonic and intravenous infusion of C-acetate in vivo, and found that although most C-acetate tracers were absorbed by the liver and heart, a small amount passed through the blood-brain barrier (approximately 3%) and was absorbed by the brain [44]. The team then proved that after intraperitoneal injection, acetate induces the activation of hypothalamic neurons in the arcuate nucleus, indicating that acetate is an anorexia semaphore.

The same research team recently studied appetite regulation using propionate and found that GLP-1 and PYY in human colon cells can be significantly stimulated by propionate [45] through a new inulin propionate system in which propionate is bound to inulin (a carrier molecule) via an ester bond, which was also described by this group. The ester bond is broken by bacterial fermentation, which causes the propionate to be delivered directly to the colon. The researchers found that inulin propionate decreased energy intake by approximately 14% in the buffet and significantly improved postprandial GLP-1 and PYY after acute administration. Furthermore, they demonstrated that inulin propionate markedly reduced weight gain in overweight adults after a 24-week supplementation period (Fig. 2).

Endotoxins produced by the gut microbiota

The diversity of the gut microbiota is vast, for example, the genes in the microbiota are observed to be 500 times more abundant than those present in the entire mammalian genome [46]. The intestinal bacteria mainly include Gram-negative bacteria, i.e., *Bacteroidetes* and *Proteus*; however, Gram-positive bacteria, including *Actinobacteria* and *Firmicutes*, are also present. *Bacteroidetes* (20–25%) and *Proteus* (5–10%), together with *Actinobacteria* (3%) and *Firmicutes* 0(60–65%), constitute approximately 97% of the gut microbiota. The proportion of *Firmicutes* which includes more than 200 genera are the highest, the most important genera of which are *Clostridium*, *Bacillus*, and *Mycoplasma* [47]. Large differences in the gut microbiota are important because they provide the host with a better ability to break down food; thus, substantial heterogeneity is a vital feature of the gut microbiota because it allows better food degradation by the host. Certain bacterial strains produce potentially toxic substances, such as capsular polysaccharide. Such toxins may directly damage the gastrointestinal mucosa, causing harmful molecules to enter the bloodstream and thereby disrupting homeostasis, accelerating disease development, and even jeopardizing the life of the host [48]. Those bacteria generally colonize the host intestine without causing symptoms, and they generally prolong food degradation. A microbially prolonged metabolic capacity results in the provision of vitamins, antioxidants, and SCFAs to the host [49, 50].

LPS is a cell wall component of Gram-negative bacteria that is also released by the microbiota. Because it affects the secretion of proinflammatory cytokines, LPS has been identified as a trigger for insulin resistance [51]. LPS consists of a lipid A tail (a hydrophobic region) and an O-antigen core regions (a hydrophilic region); thus, LPS is an amphiphilic molecule. Of the two regions, the lipid A portion is associated with the immunomodulation and toxicity of LPS [52]. In addition, the *Firmicutes*:*Bacteroidetes* ratio is higher in very obese individuals than in "healthy obese" and lean individuals [53, 54]. Experiments have shown that transplantation of microorganisms from obese mice to sterile mice is correlated with greater weight gain than transplantation of microbes from control mice [15]. This evidence suggests that such attributes of the microbiome are both quantitative and qualitative and can explain the varying abundance levels of *Firmicutes* observed in different studies. Interestingly, an HFD (high-fat diet) is associated with elevated plasma LPS levels in mice and decreased levels of Gram-positive *Bifidobacterial* in the gut [55, 56]. *Akkermansia muciniphila* reconstitution has also been shown to improve glucose tolerance and insulin action, and studies have shown that the abundance of this bacterium is reduced in obesity [57].

LPS has been detected at low concentrations (1 to 200 pg ml1), in healthy animals and human blood, indicating that a small amount of LPS can pass through the intestinal epithelial barrier. The increased concentration of endotoxin in the blood is referred to as metabolic endotoxemia in obese individuals or as postprandial homeostasis, in order to highlight the effects of this state on metabolism rather than this state serving as an indicator of infectious disease [58]. In mice, obesity is associated with increased levels of Gram-negative (LPS in the cell wall) and certain Gram-positive bacteria (*Firmicutes*) in the gut and decreased levels of other Gram-positive bacteria (*Bifidobacterium*) and elevated plasma LPS levels [56]. Cani [51] first reported that under conditions of continuous HFD feeding for 4 weeks, the structure of the dominant bacterial population in the intestinal microbiota of mice would be altered. Regarding the newly recognized Gram-negative operational taxonomic unit, the *Cytophaga-Flavobacterium-Bacteroides* gate, the number of *Bacteroides*-like bacteria in the intestines of mice was significantly reduced after HFD feeding. The populations of *Clostridium perfringens* and *Bifidobacteria* in the intestines

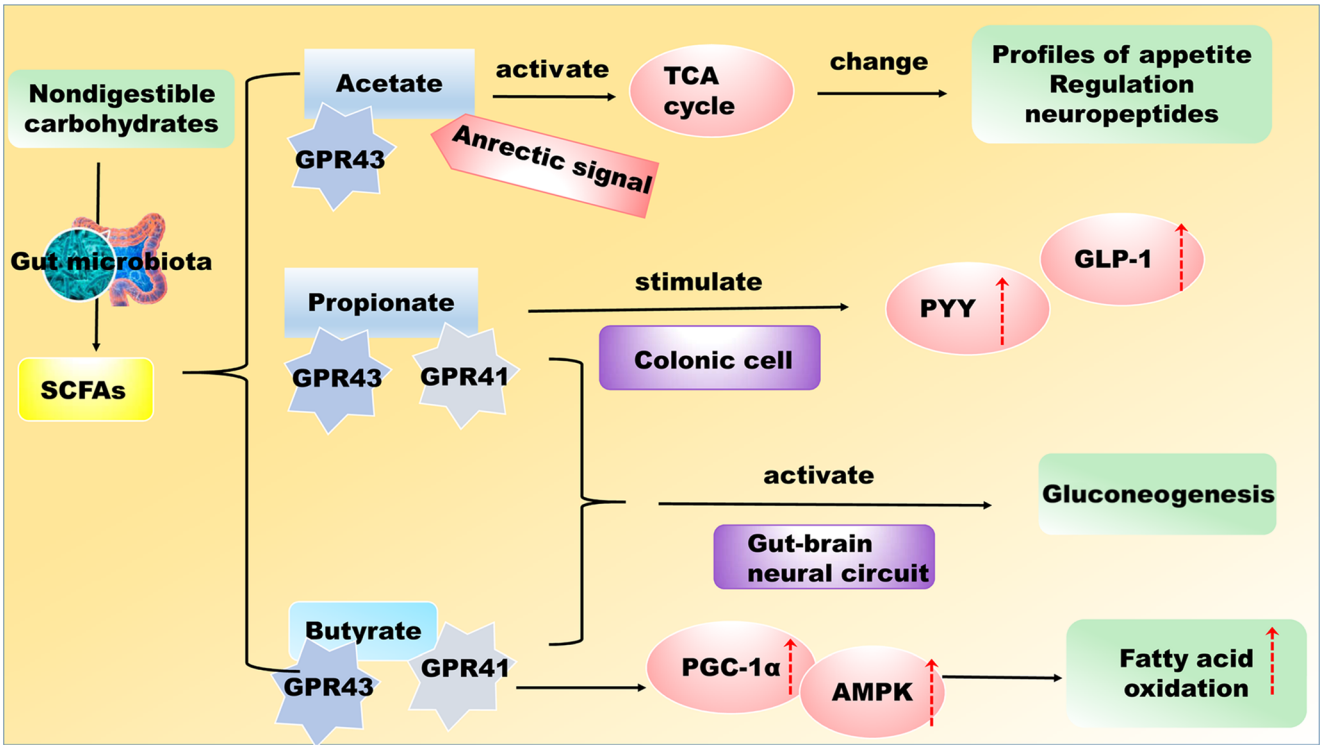

Fig. 2 SCFAs regulate host metabolism and appetite

of animals fed an HFD were significantly lower than those in the control group, and these corresponding bacterial families are mainly Gram-positive. Additionally, the researchers assessed whether exogenous LPS could be absorbed. Studies have shown that in individious fed an HFD, exogenous LPS, and endogenous LPS are involved in causing endotoxemia [59]. LPS is has also been proposed be present in the bloodstream because passive diffusion of LPS through the intestinal mucosa results in impaired tight junction integrity of intestinal epithelial cells and increased intestinal permeability. Although the underlying mechanism is currently unknown, we know that changes in intestinal permeability are likely to trigger metabolic endotoxemia, which may be related to obesity-related metabolic diseases.

LPS is involved in aggravating obesity-related inflammation

In a mouse experiment, LPS induced a systemic inflammatory state via translocation from intestinal epithelial cells to the blood and tissues, which is the origin of the concept of metabolic endotoxemia [60]. LPS binds to CD14 and serves as a ligand for TLR4. TJs, which regulate paracellular permeability, are responsible for the gut barrier, and numerous extracellular factors may increase permeability and impair barrier function, including dietary, such as alcohol and lipids, pathogens, and inflammatory [61]. For instance, alcohol-induced TJ destruction has been shown to increase entry of LPS from the intestinal lumen into the circulation [62]. Conversely, among TLRs, TLR5 may slow the development of metabolic syndrome as studies have shown that mice genetically deficient in TLR5 are more prone to this condition [63, 64]. Furthermore, TLR5 has been demonstrated to be involved in a mechanism that interferes with the development of inflammation, thereby controlling metabolic disorders such as hyperphagia, insulin resistance, hyperlipidemia, hypertension, and obesity. Zonulin, which regulates gastrointestinal permeability, is a protein of the haptoglobin family that is liberated by intestinal epithelial cells and the liver. According to current data, gastrointestinal permeability increases as levels of zonulin and occludin increase; this increase causes the antigen to enter the intestinal environment, which triggers oxidative stress and inflammatory responses as well as immune responses [65]. Major changes in intestinal function or increased intestinal permeability affecting bacterial structure can be reflected by endotoxemia [7]. Studies have shown that inflammatory cytokines, LPS levels, and oxidative stress markers are reduced in mice treated with probiotics, and improved gastrointestinal barriers functions and TJs were also found. The corresponding mechanism is related to elevated levels of GLP-2 [60, 66], which has an important role in maintaining gut quality by reducing inflammation, maintaining intestinal mucosal integrity, reducing apoptosis, providing cellular protection, and stimulating intestinal cell proliferation [67].

Based on the above discussion, we can speculate that the key characteristics of diet-induced obesity-related metabolic disorders are inflammation caused by intestinal dysfunction and fat accumulation (Fig. 3). Because of this inflammatory response mechanism in obese individuals, inflammation can be modulated to reduce the risk of obesity-related disorders [68]. Studies have also shown that circulating endotoxin in the body increases the risk of type 2 diabetes. For example, plasma samples from 25 middle-aged type 2 diabetic patients contained higher concentrations of endotoxin than those from matched control [69]. In approximately 6600 participants, the risk of type 2 diabetes during follow-up increased by factor of 1.5 in individuals with endotoxin concentrations in the upper quartile; endotoxin concentrations were significantly higher in patients with type 2 diabetes than those in healthy individuals and predicted the development of type 2 diabetes during a 10 years of follow-up [70]. Thus, the pathogenesis of circulating endotoxins can help elucidate the pathogenesis of obesity-related metabolic diseases.

Strategies for regulating the gut microbiota

Because the gut microbiota and obesity affect one another, proper regulation of the intestinal flora may reduce obesity. In fact, adjustment of the gut microbiota is often recommended as an effective strategy for the treatment of obesity, which can be achieved using various approaches. Below, we discuss methods and drugs used to regulate the gut microbiota and provide new ideas for the treatment of obesity.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT), also known as "bacteriotherapy," is the administration of a fecal suspension from a healthy person to the gastrointestinal tract (GIT) of another person to cure a specific disease. This concept dates back to the fourth century in China, when Ge Hong used this method to treat food poisoning or severe diarrhea [71]. The hypothesis behind FMT is that the metabolic phenotype can be transferred. For example, transplantation of the gut microbiota from conventionally raised (CR) mice to GF mice normalizes glucose and lipid metabolism. The FMT was used clinically for the first time of in 1958 to treat pseudomembranous colitis [72]. The concept has recently become popular for treating severe recurrent infection with *Clostridium difficile*, with a success rate of more than 80% globally [73]. Moreover, FTM has been shown to be effective for the treatment of GIT as well as non-GIT diseases caused by microbial dysbiosis. A pilot study of FMT involving the transfer of intestinal microbiota via a postpyloric enteral feeding tube from lean human donors to subjects with metabolic syndrome showed an increase in peripheral insulin sensitivity after 6 weeks [74]. Thus, given its potential, if a legal framework and standard protocols are instituted, the exact mecha-

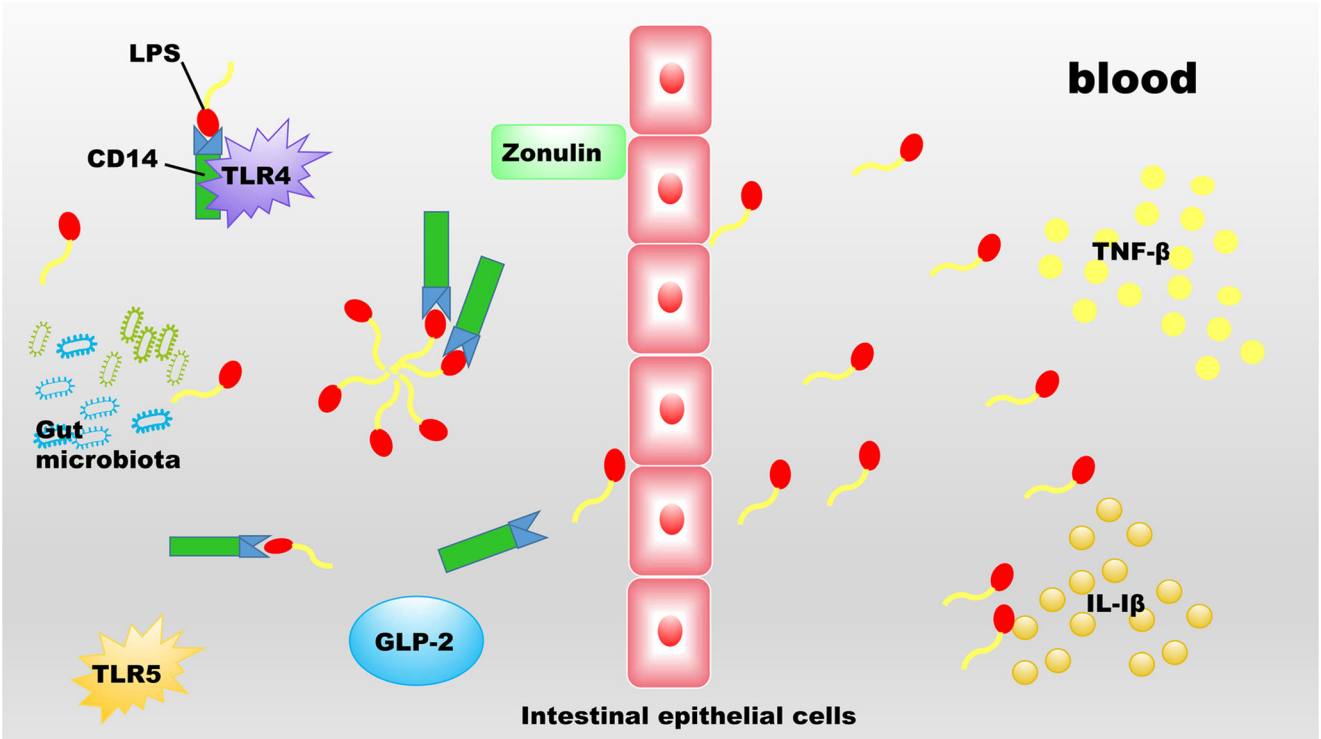

Fig. 3 Lipopolysaccharide-mediated inflammation

nism of the procedure is elucidated, and a stable and durable engraftment protocol is optimized, FMT may facilitate the design a personalized medicine approach to treat obesity and other metabolic disorders in the future.

Bariatric surgeries: gastric bypass

Procedures that alter bowel physiology and anatomy (e.g., Roux-en-Y gastric bypass [RYGB]) also change the relative proportions of gut microbiota, and which results in altered postoperative energy metabolism. These procedures also cause rapid adaptation of the microbiota [53]. The proportion of H2-utilizing methanogenic Archaea have been reported to be significantly higher in obese subjects than that in normal or obese subjects who underwent RYGB; however, higher levels of *Firmicutes* and lower levels of *Gammaproteobacteria* were observed in individuals of normal and obese weight but the opposite pattern was observed in RYGB subjects [75]. Recent studies have shown that metabolic conversion (epimerization, dihydroxylation, and de-conjugation) of bile acids does not differ from the duodenum to the colon. However, in the cecum, where biotransformation primarily occurs, researchers observed a profound change in the composition of the microbiota unique to each type of surgery. In summary, despite a specific ecological imbalance after surgery, bile acid metabolism in the intestinal lumen is still highly active, suggesting that the intestinal microbiota is resilient after these operations [76]. One of the striking findings is that regulation of the intestinal microbiota after bariatric surgery does not completely follow the phenotype. In fact, the type of bacteria associated with weight reduction (before surgery) changes only slightly after bariatric surgery, despite many metabolic improvements, indicating that other mechanisms are responsible for the metabolic improvement observed after surgery. This observation also shows that low microbial richness cannot predict the presence, absence, or even the magnitude of the response to the RYGB procedure [77].

Antibiotic treatments

During the past few decades, the composition of the gut microbiota in humans has changed, with some species increasing and others decreasing in numbers, but importantly, an overall reduction in the diversity of the intestinal microflora has been reported. One major factor causing this reduction is the increased use of antibiotics. Although changes in microflora vary among individuals, some lost taxa are not recovered, even many months after postantibiotic therapy, resulting in an overall loss of diversity due to antibiotic use [14]. A recently observed trend is the positive correlation between the use of antibiotics and increased weight in humans, particularly in malnourished children, neonates, and adults; however, the exact underlying mechanisms are not known [78]. One suggested mechanism is that certain antibiotics (e.g., avoparcin, a drug similar to vancomycin) exert a positive selective pressure on certain bacteria (e.g., lactobacilli) that are resistant to glycopeptides and are found at high concentrations in the feces of patients treated with vancomycin. One study reported a decreased incidence of diabetes in mice treated with a combination of antibiotics and a hydrolyzed casein diet. Another study in humans found that the sugar anabolic capabilities of treated subjects increased but became less balanced than those of nontreated groups [79]. Regardless, the exact mechanism remains unclear because most studies have mainly focused on the effect of antibiotic treatment on the composition and diversity of the gut microbiota.

Natural products regulate the intestinal microflora

Natural products can effectively ameliorate disturbances in the intestinal flora. Natural polysaccharides can reduce the side effects of HFDs by promoting more efficient energy metabolism in the intestinal microbiota, and natural sugar can therefore be used to develop functional foods for metabolic diseases such as obesity. Numerous studies have shown that regular consumption of natural polysaccharides is necessary to prevent or control obesity [80]. Additionally, an analysis based on the decomposition and absorption functions of microbes suggested that chitooligosaccharide treatment of the intestine can effectively regulate the metabolic pathway of the intestinal microbiota [81]. *Ganoderma lucidum* is a traditional Chinese medicinal mushroom that is presumed to have antidiabetic effects, and water extracts of *G. lucidum* were reported to reduce body weight inflammation and insulin resistance in mice fed an HFD [82, 83]. Moreover, grape polyphenols (GPs) significantly increased *Akkermansia muciniphila* levels and reduced the proportion of thick-walled bacteria and *Bacteroides*, which is consistent with previous studies. Overall, such changes in the microbial community structure can regulate diet-induced obesity and its associated metabolic diseases. These data suggest that GPs act in the gut, reducing intestinal and systemic inflammation, altering the intestinal microflora structure, and improving metabolic outcomes. Therefore, the intestinal microflora may be a bridge connecting the mechanism of action of polyphenols that are not absorbed [84].

Probiotics

As the gut microbiota plays important roles in energy harvesting and metabolism, scientists have hypothesized that in subjects who lose certain microbial groups, deliberate restoration or administration of these microbes may be beneficial [85].

The regular use of probiotic beverages in newborns has been shown to improve metabolism in rodent models as well as in humans [86]. Manipulating microbial populations via probiotic uses in the presence of an HFD can reduce intestinal inflammation, improve intestinal barrier integrity, and increase the abundance of beneficial bacteria, and these improvements are linked to weight loss [67]. However, how the microbiota and probiotics interact with the host to alter intestinal permeability in different regions of the gut and how this leads to weight gain and obesity are unclear. Obesity amelioration in animals and humans resulting from use of probiotics has been reported. For example, *Bifidobacterium*-containing probiotics increased gut barrier function, reduced endotoxemia, and increased metabolism in a rat models involving an HFD [87, 88]. Similar metabolic improvements have been shown with *Lactobacillus* treatment in animal models of obesity [89]. The proposed underlying mechanism may involve conjugated linoleic acid production, increased fatty acid oxidation, and decreased LPL activity. In humans, well-controlled studies on the effects of probiotics are scarce; however, a recent meta-analysis based on the results of 17 randomized trials in humans, 14 studies of animal models, and 51 studies on farm animals demonstrated a strain-dependent effect of "*Lactobacillus*" probiotics on weight management [90]; thus, *L. acidophilus* probiotics were shown to be associated with weight gain, whereas *L. plantarum* and *L. gasseri* were linked to weight loss. Thus, although it may seem promising, the therapeutic use of probiotics is highly controversial and not yet recommended because probiotic administration alone is not the solution to the problem of obesity.

Dietary changes

Diet has been revealed to be an important factor in defining and shaping the gut microbiota of mammals [91]. The ratio of *Firmicutes* to *Bacteriodetes* was reported to be 10.9/1 in healthy adults [92]. Long-term dietary patterns seem to have a major impact on shaping the human gut microbiota [93]. Dietary changes have been shown to affect the composition of the gut microbiota within 24 h of implementation [94]. The long-term effects of successive generations of mice fed low-fiber diets indicate that certain fiber-fermenting bacteria are gradually disappeared and that these bacteria cannot be recovered through fiber-rich diets [95], thus proving that prolonged diet restrictions may have a potentially serious impact on regulating microbial diversity. Long-chain fatty acids (LCFAs) commonly found in Western diets have been observed to be are involved in enhancing the differentiation and proliferation of T helper 1 (Th1) and/or Th17 cells, and reducing SCFAs in the gut, thus favoring a potentially adverse proinflammatory environment in obesity and its associated comorbidities [96]. In addition, bacteria of the phylum *Firmicutes* and their associated metabolites have been proven to increase the number of lipid droplets of a sizes associated with other bacterial types, suggesting that there are distinct mechanisms by which microbial species fatty acid absorbs in the host [97]. Supplementation of bacterium *Bacteroides uniformis* CECT 7771 in mice with HFD-induced obesity led to a reduction in dietary fat absorption in enterocytes, supporting the notion that specific components of the human microbiota may interfere with dietary lipid absorption, although the mechanism or specific bacterial components mediating this effect were not investigated [98]. Overall, all studies have shown that diet plays a vital role in shaping the host gut microbiota and changing dietary habit may be an efficient strategy to prevent obesity by altering the composition of the gut microbiota.

Conclusion

The gut microbiota breaks down substances that the stomach and intestines cannot decompose through different mechanisms, allowing nutrients to be more easily absorbed. An HFD leads to an imbalance in the structure of the gut microbiota that results in increased endotoxins, which aggravates obesity. Gut microbial SCFAs play a beneficial role in host metabolism. LPS induces a systemic inflammatory state by translocating from intestinal epithelial cells to the blood and tissues. As the gut microbiota may be a potential new target for relieving obesity, strategies for regulating intestinal flora should be further investigated.

Authors' contributions Cuiting Zhi had the idea for the article and drafted it. Jingqing Huang and Jin Wang performed the literature search. Cuiting Zhi, Yan Bai, Jiao Guo, and Zhengquan Su critically revised the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Abbreviations LPS, lipopolysaccharides; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1β; LPL, lipoprotein lipase; AMPK, adenosine monophosphate–activated protein kinase; SCFAs, short-chain fatty acids; FIAF, fasting-induced adipocyte factor; Cpt1, carnitine palmitoyl transferase-1; GPCRs, G protein–coupled receptors; TLR, Toll-like receptor; GLP, glucagon-like peptide; CD, clusters of differentiation; PGC-1α, receptor-gamma coactivator-1α; UCP-1, mitochondrial uncoupling protein-1; PYY, peptide YY; HFD, high-fat diet; TCA cycle, tricarboxylic acid cycle; LCFAs, long-chain fatty acids; Th., T helper

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