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Review Article

The gut microbiome in obesity

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Obesity is worldwide epidemic given its rapid growth in global prevalence. Among the risk factors contributing to obesity, human gut microbiome recently emerges with unprecedented intimacy in host metabolism and inflammation. With the advances in sequencing technology, more and more detailed understandings towards the intricate relationships linking gut microbiome and obesity have been continuously disclosed. Herein, we review studies resolving associations between gut microbiome and obesity, and then mechanistic studies tackling the roles played by gut microbes in obesogenic physiology.

Introduction

Obesity is a worldwide public health problem continuing to rise rapidly, affecting more than 107.7 million children and 603.7 million adults around the globe and accounting for over 60% of deaths related to high body-mass index (BMI).[1] If the rising trends persist, global obesity prevalence is estimated to reach 18% in men and over 21% in women by 2025.[2] Furthermore, 20% of the world's adult population are projected being obese by 2030 along the progressing trajectory.[3] Obesity is strongly associated with the incidence of several adverse comorbidities, such as cardiovascular disease, type 2 diabetes, and cancer,[4] leading to a significant economic and social burden of pandemic magnitudes.

Obesity is considered as a complex and multifactorial disease mainly attributable to risk factors of genetic, behavioral, socioeconomic, and environmental origins.[5,6] Among them, the association and causative role played by gut bacteria in obesity represents one of astonishing findings over the past decade.[7] This notice can be traced back to the observation of significantly more body fat in conventionally raised than germ-free mice.[8] Following that, a pioneering discovery demonstrated differential gut bacterial compositions in genetically obese (*ob*/*ob*) mice compared to lean (*ob*/+) and wild-type (+/+) siblings under the same polysaccharide-rich diet,[9] by summarizing

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the reduced relative abundance of Bacteroidetes and increased Firmicutes in obesity. To distinguish the effect of gut bacteria from genetic modification, Turnbaugh et al. transplanted lean and obese microbiome to germ-free recipients, and found a significantly greater increase in total body fat in mice colonized by obese microbiota than lean microbiota.[10] This landmark study not only witnessed the increased capacity for host energy harvest by obese microbiota, but also opened avenues for scientific efforts looking at the gut microbiome in obesity later on.

The enormous number of microbial cells in the human gastrointestinal tract was documented a half century ago,[11] while their mutualism to human host was recognized ten more years ago[12] and acknowledged of equal importance as a forgotten organ.[13] Since then, attention to this field has increased rapidly, leading to the vibrant growth of discussion and publications. As a result, discordant use of specific terms can be sporadically found among literature at the cost of confusion and even misinterpretation.[14] Therefore, it is necessary to define the terminology ahead of a systematic discussion. Here, we refer the term "microbiota" to the taxonomic composition of microorganisms (mostly bacteria) in a specified sampling site or location, "metagenome" to the genetic contents and coding capacity of microbiota, and "microbiome" to the collection of taxonomic, genomic information, and other abiotic factors in a microbial community. Current studies of gut microbiota majorly focus on bacteria. Other coexistent microorganisms (e.g., virus, phage and fungi) are principally ignored.

Given the massive availability of literature, studies tackling the complex relationships between gut microbes and obesity cannot be fully covered in one paper. Therefore, following the chronological progress of related research, we set topics and selected papers considered representative to each section, and apologize to the authors of studies that are relevant but not included herein. Being such an important public health issue with vibrant research activities, the gut microbiome in obesity has been comprehensively reviewed with relentless efforts from different perspectives.[15–18] In this review, we begin with discussing association studies on the index for obesity susceptibility, factors altering gut microbiota, and obesogenic microbiota. The second part encompasses mechanistic understandings of the microbial role in the metabolisms of bile acids, indigestible polysaccharides and metabolic endotoxemia, all of which are involved in the development of obesity (Fig. 1).

Association studies

A short history

As early as the 1980s, the gut microbiota has been associated with obesity in human[19] and rats[20] by utilizing culture-dependent methods, which only sees pieces of microbes in the gut. In the 1990s, the application of culture-independent molecular techniques based on 16S ribosomal RNA (rRNA) genes (e.g., competitive PCR, real-time PCR, fluorescent in situ hybridization, denaturing/temperature gradient gel electrophoresis, and restriction fragment length polymorphisms)[21] expanded our knowledge to the human gut microbiota, dominated by bacteria of Bacteroidetes and Firmicutes.[12] However, those methods still have respective limitations that restrict related studies to a labor-intensive and time-consuming scale with only acceptable resolution. Until the early 2000s, this research field was revolutionized by the introduction of next-generation sequencing (NGS), improving the diagnosis of microbiota to a further finer and more comprehensive viewpoint in a cost-effective and time-efficient fashion.[22]

Stories all begin from comparison and observation, and the gut microbiome in obesity is no exception. In addition to above mentioned microbiome transplantation experiments performed in mice,[9,10] transplantation from an overweight adult twin to germ-free mice led to rapid increases in body and fat mass, while mice receiving the lean twin microbiome maintained normal weight.[23] Similarly, transplanting gut microbiome from patients after Roux-en-Y gastric bypass gave rise to a reduced fat deposition in germ-free mice.[24] These results collectively emphasized that obesity-related phenotypes such as increased body mass and decreased adiposity are transmissible from people to mice using personalized microbiome.

The Firmicutes to Bacteroidetes ratio

As for the bacterial groups in play, comparing the gut microbiota of obese and lean people revealed higher Firmicutes and lower Bacteroidetes proportion in obesity, and an inverse profile was found in people after 1-year diet therapy[25] and gastric bypass.[26] The diminished proportion of Bacteroidetes was also observed in obese subjects compared to people of normal BMI and anorexic patients, but Firmicutes exhibited no differential abundance.[27] A further extensive metagenomics study resolving the gut microbiome in obese and lean twins discovered lower bacterial diversity and Bacteroidetes proportion but higher Actinobacteria in obese than lean individuals,[28] while proportional difference in Firmicutes was not significant. As a result, the ratio of Firmicutes to Bacteroidetes relative abundance (i.e., the F/B ratio) was seemingly a biomarker indicative to obesity susceptibility. However, with the rapid accumulation of data, meta-analyses looking at the human gut microbiome and obesity could not find a clear trend between the F/B ratio and obesity status,[29,30] suggesting that the complexity of how gut microbiome modulate obesity is way more than a simple imbalance status of these commensal phyla.

Gut microbiota alteration by diet and antibiotics

Given the intuitive fact that gut microbes live on food ingested by host, validating the effects of diet on gut microbiota is important. As resistin-like molecule β (RELMβ) deficient mouse is resistant to high-fat-diet induced obesity, a sophisticated study compared the gut microbiota of RELMβ deficient with wild-type mice when fed freely on high-fat diet. Results showed that, although RELMβ deficient mice remained relatively lean, both groups shared similar alteration in gut microbial composition, suggesting the effects of diet being more influential on gut microbiota

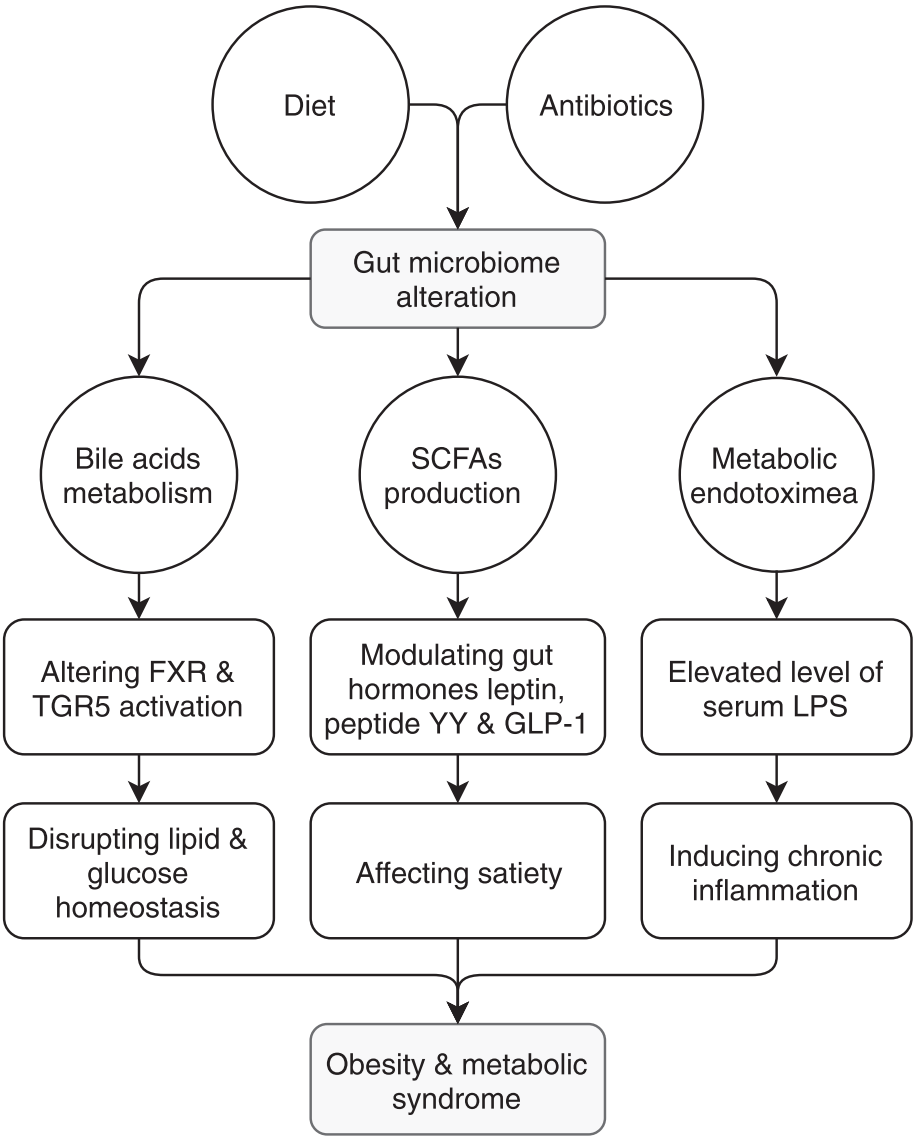

Fig. 1 Association between altered gut microbiome and downstream metabolic consequences mediating the development of obesity and metabolic syndrome. FXR, farnesoid X receptor; GLP-1, glucagon-like peptide; LPS, lipopolysaccharide; SCFAs, short-chin fatty acids; TGR5, G-protein-coupled bile acid receptor 1.

than obesity phenotype.[31] In the meantime, the long-term effects of antibiotics on gut microbiota also received attention according to the prevalent use of antibiotics in treating bacterial infection. A 7-day clindamycin intervention in humans irreversibly modified the *Bacteroides* community for up to two years after administration without any sign of recovery.[32] Another result demonstrated that a short-term antibiotic exposure of ciprofloxacin substantially reduced the human gut microbial diversity.[33] Although the microbiota largely restored to its pretreatment state within four weeks, several taxa seemingly failed to recover by six months after intervention.

Antibiotics, microbiota and obesity

With the notion that antibiotics alter gut microbiota, associations between these alterations with consequent phenotypes were also reported. The combination of norfloxacin and ampicillin improved glycemic control in *ob*/*ob* and diet-induced obese mice,[34] suggesting the therapeutic potentials of antibiotics for managing obesity. However, an early-life subtherapeutic antibiotic exposure was found to alter gut microbiome and increase adiposity in mice.[35] Similarly, mice at birth were more vulnerable to low-dose penicillin compared to four-week-old counterparts as suggested by increased adiposity,[36] indicating that there is a critical time window for antibiotics to impose a long-term effect on host phenotype. The accompanying transplantation of penicillin-selected microbiota to germ-free mice induced obesity phenotype, established the causal role by gut microbiota in the development of obesity. In humans, obesity was reportedly associated with antibiotic therapy.[37,38] Childhood obesity was linked to antibiotics exposure in infancy,[39,40] and this association was correspondingly found in Finnish pre-school children by metagenomics.[41]

Dysbiotic gut microbiota in obesity

The constant role played by gut microbes in the human physiology links our health to a balanced gut microbiota. On the other hand, an imbalanced gut microbiota, or dysbiosis, has thus been associated with multiple conditions like inflammatory bowel disease,[42] *Clostridium difficile* infection,[43] autoimmune disorders,[44] and obesity.[45] Dysbiotic microbiota of obesity was extensively discussed with myriad literature, and in particular the F/B ratio would be the very first index derived from it,[25] of which a larger value implicates a higher obesity susceptibility in host. An energy-balance study revealed that a 20% increase in Firmicutes and a 20% decrease in Bacteroidetes were associated with an additional energy harvest of 150 kcal per day.[46] Other than the two human commensal phyla Firmicutes and Bacteroidetes, several bacterial groups at deeper taxonomic levels (e.g., family, genus and even species) were reportedly associated with dysbiosis in obesity. At the family level, Prevotellaceae[26] and Enterobacteriaceae[47] enriched in obesity, but Christensenellaceae[48] enriched in subjects with low BMI. Among bacterial genera, the endotoxin-producing *Enterobacter*[49] was overabundant in morbidly obese patients and suggestively to induce obesity. *Lactobacillus* increased after a weight-loss program in adolescents[50] but also abounded in obese and overweight children.[51,52] *Bacteroides* was prominent among obese individuals and its abundance positively correlated with BMI.[53] The genus *Roseburia* was seemingly beneficial to obesity as it increased in feces when obese subjects consumed more indigestible polysaccharides.[54] A negative correlation was revealed between BMI and *Bifidobacterium*.[51] Similarly, *Oscillospira*,[48] *Erwinia*, *Succinivibrio*[55] and *Alistipes*[56] were more abundant in subjects with normal weight than obesity. For bacterial species, *Blautia hydrogenotorophica*, *Coprococcus catus*, *Eubacterium ventriosum*, *Ruminococcus bromii* and *Ruminococcus obeum* were significantly associated with Japanese obese individuals, while *Bacteroides faecichinchillae*, *Bacteroides thetaiotaomicron*, *Blautia wexlerae*, *Clostridium bolteae* and *Flavonifractor plautii* were associated with lean people[57] (BMI $<$20). In addition, *Akkermansia muciniphila* was a gut commensal bacterium giving hope to fight obesity.[58]

However, association studies have limitations by nature, among which the largest concern is that the observed dysbiotic microbiota are merely the consequence rather than the cause of diseases[59] (or interventions). Also, the immense diversity of microbial biology leads to species-level[60] and even strain-level[61] differential roles in weight gain and obesity development. Therefore, microbiome studies focused on the mechanistic understanding and causative association linking gut microbes to obesity is gaining traction.[7,62]

Mechanistic studies

Bile acids metabolism

Bile acids tightly mediate the absorption of dietary fat in small intestine, of which the primary form is synthesized from cholesterol in liver and conjugated with glycine or taurine. In the intestine, primary bile acids are converted into secondary form by bacterial deconjugation and dihydroxylation.[63] In addition to the digestive function, bile acids was known to inhibit the growth of various gut bacteria[64] including probiotic lactobacilli and bifidobacteria by disrupting their membrane integrity.[65] Bile acids also act as ligands for the nuclear farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor 1 (TGR5),[66] suggesting a strong role in host lipid and glucose homeostasis (Fig. 1). The experiment remodeled gut microbiome in the *Fxr*-null and wild-type mice demonstrated that the microbiota promotes diet-induced obesity through FXR signaling.[67] Transplanting the microbiota from *Fxr*-null mice fed with high-fat diet led to a less weight gain in germ-free mice than transferring that from wide-type counterparts,[68] indicating that the diet-induced obesity is mediated by gut microbiota in a FXR-dependent fashion. As for TGR5, its activation by bile acids has been reported to control glucose homeostasis by inducing the release of intestinal glucagon-like peptide-1.[69] Later studies using *Tgr5*-deficient mice revealed the role of TGR5 in anti-obesity effects after bariatric surgery.[70,71]

Indigestible polysaccharides metabolism

Bacteria in the anaerobic distal gut rumen utilize indigestible polysaccharides (i.e., fiber) as growth substrates through microbial fermentation[72] and generate short-chain fatty acids (SCFAs), including acetate, propionate and butyrate, as major end-products. These SCFAs are estimated to contribute about 80—200 kcal/d to human[73] and ultimately absorbed in different organs. Reduced intake of dietary carbohydrates (e.g., structural polysaccharides, plant-derived oligosaccharides and resistant starch) was associated with decreases in fecal concentration of butyrate and butyrate-producing bacteria in obese individuals.[54] A study with similar design revealed significant reductions in fecal butyrate, total SCFAs and bifidobacteria counts when obese subjects had a low-fiber diet.[74] A low-fiber diet has been shown to enhance pathogen susceptibility by establishing a microbiota feeding on colonic mucus in host.[75]

The SCFAs from microbial fermentation were suggested to lower pH and alter microbiota in colon by creating a niche favoring the growth of butyrate-producing bacteria.[76] Besides the intrinsic function of being an energy source and modulating colonic pH, SCFAs also act as signaling molecules to activate at least two G-protein coupled receptors, Gpr41 and Gpr43,[77] and promote downstream secretion of leptin[78] by adipocytes, and peptide YY (PYY)[79] and glucagon-like peptide (GLP-1)[80] by enteroendocrine cells to regulate host satiety (Fig. 1). Therefore, a high-fiber diet is beneficial to obesity management through gut bacterial modulation on SCFAs production and downstream singling pathways.

Metabolic endotoxemia

Obesity has long been characterized by chronic inflammation and that inflammation was ascribed to obesity-related

insulin resistance.[81] The link between obesity and chronic inflammation remained elusive until Cani et al. discovered metabolic endotoxemia,[82] a high-fat diet-induced elevation of plasma lipopolysaccharide (LPS). They demonstrated that high-fat diet increased LPS-containing bacteria abundance, induced metabolic endotoxemia, and triggered downstream inflammation through LPS receptor CD14. Upon LPS binding, CD14 and its co-receptor Toll-like receptor 4 (TLR4) activate the nuclear factor κB (NF-κB) inflammatory pathway, and thus enhance transcription of several proinflammatory cytokines implicated in the pathogenesis of chronic inflammation in obesity and other metabolic diseases (Fig. 1).[83] In healthy humans, metabolic endotoxemia was found to reduce 35% of systemic insulin sensitivity,[84] associated with their energy intake,[85] and could be induced after a high-fat or high-carbohydrate meal.[86]

Conclusions

Studying the etiology of obesity has come a long way since we noticed its growing prevalence. In comparison with those renowned risk factors like diet, lifestyle and socioeconomic status, gut microbiota emerges as a relative new factor with a much more intimate role in play. Although attempts to summarize the intricate relationships between gut microbiota and obesity by compositional data remains inclusive, what we consumed (i.e., diet and antibiotics) has been unequivocally proved to impact our gut microbiota, which turns out to influence host metabolism and inflammation. A recent study has reported that prebiotics were beneficial to overweight and obese children by lowering their body weight, fat deposition and serum level of interleukin 6 and triglyceride, along with increased *Bifidobacterium* spp. and decreased *Bacteroides vulgatus*.[87] Therefore, modulating gut microbiota through diet and food supplements is not only a theoretically effective approach to alleviate the symptoms associated with obesity, but also represents a potential therapeutic avenue to obesity.

Disclosures

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jfma.2018.07.009.

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