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Review

The links between gut microbiota and obesity and obesity related diseases

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ABSTRACT

The obesity epidemic has become a global public health crisis in recent years and is continuing to worsen at an alarming rate. However, the pathophysiological mechanisms involved in the development of obesity and obesity-related diseases are still being unraveled. In the past ten years, the gut microbiota has been identified as a crucial player affecting the onset and progression of obesity and obesity-related diseases, especially with respect to changes in its composition and metabolites during obesity progression. Herein, we summarize the roles and mechanisms of gut microbiota's composition and metabolite changes in the gut play in obesity and obesity related diseases. Furthermore, we discuss potential therapeutic treatments that can be used to modulate the gut microbiome composition and target the relevant metabolic pathways of obesity and obesity-related metabolic diseases.

1. The obesity related diseases

Obesity has become a global epidemic and public health crisis, especially in last decades, and the incidence of obesity is continuing to rise at an alarming rate. Nearly two billion adults throughout the world are considered overweight, more than half of whom are classified as obese [1,2]. Furthermore, the exacerbation of the global obesity epidemic has been linked to increasing incidence of serious health risk factors and conditions, including insulin resistance, type 2 diabetes (T2D) [3], nonalcoholic fatty liver disease (NAFLD) [4], atherosclerosis [5], and certain cancers [6]. Consequently, obesity is the leading cause of morbidity, mortality, and healthcare expenditure. Obese patients also have a significantly higher risk of death and severe complications from COVID-19 compared to normal-weight ones [7]. For example, approximately 85% of hospitalized patients with obesity required mechanical ventilation, 62% of whom died from complications related to COVID-19 [8]. Given the significant health complications that obesity can ensue, disrupting the progression of the obesity epidemic is vital for controlling the development of other related metabolic diseases.

To date, many strategies have been developed to treat obesity and related diseases. Bariatric surgery has been a highly popular and successful strategy in treating obesity and its comorbidities [9–11]. However, strategies for the diagnosis, screening, and successful management of obesity and obesity-related diseases are limited partly by that we have not completely understanding its pathophysiology. In fact, consuming a high-caloric diet and substitution of leisurely physical activities with sedentary activities are the main risk factors for obesity and obesity-related diseases, which ultimately results in excess energy stored in the body [12]. Excess lipid consumption from high-caloric diets results in the accumulation of lipids in subcutaneous and visceral adipose tissue, which can cause adipose tissue unable to store excess energy as triglycerides, leading the excess lipids to enter systemic circulation. Excess systemic circulation and absorption of lipids into non-adipose tissues, which cannot readily undergo fatty acid oxidation (FAO) to increase the availability of fatty acid, causing the ectopic fat storage [13]. Furthermore, the accumulation of excess triglycerides in adipocytes contributes to the production and release of pro-inflammatory cytokines and adipokines, which can promote insulin resistance, NAFLD incidence and progression, and the development of obesity-related cancers [14–19].

The human gut microbiota has been suggested to play a critical role in obesity and its comorbidities via affecting the adiposity and glucose

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metabolism [20–23]. In addition, during the past few decades, researches about the role of the gut microbiome in modulating obesity and related metabolic diseases has rapidly increased. Many studies have aimed to uncover the role of gut microbiota imbalance in these metabolic changes [24]. Diet is the main factor influencing the imbalance of the gut microbiota [22,24]. Therefore, this review article serves to summarize the recent advances in the understanding of the relationships between the gut microbiome and obesity and obesity-related diseases that have propelled the obesity therapy field forward from association to causative results. Herein, we discuss the roles of both the gut microbiota composition and metabolites changes in the pathophysiological mechanisms of obesity and obesity-related metabolic disorders. These metabolites include those which are produced by dietary components bacteria, such as short-chain fatty acids (butyrate and propionate), indole derivatives, and polyamines (primarily putrescine, spermidine, spermine) as well as the metabolites which are biochemically modified by gut bacteria and produced by the host (i.e. secondary bile acids and ATP). Furthermore, we highlight some potential therapeutic treatments that can serve to regulate the gut microbiome composition and target the relevant metabolic pathways that promote the development of obesity and obesity-related metabolic diseases.

2. Gut microbiota

The human gut microbiota is a complex ecosystem that resides within the gut and is estimated to be composed of approximately 10^{14} bacterial cells from 400 to 500 different bacterial species per gramme of colonic content. Healthy individuals harbor ~195 bacterial strains, 101 species of which represent their fecal microbiota [25]. Each section of the gastrointestinal (GI) tract contains varying compositions and amounts of bacteria per gram content. For example, the stomach and duodenum contain an estimated 10–10^{13} cells, the small intestine 10^{4}–10^{7} cells, and the large intestine 10^{11}–10^{12} cells. The gut microbiota also forms a synergistic relationship with the host [26,27], harvesting additional nutrients and energy from diet and protecting the host from infiltration by pathogens [28]. Therefore, the composition of the microbiota is heavily influenced by diet (Table 1). In heath, the gut microbiota is characterized by its diversity and stability, a reduction of which can cause the disease and aging process [29]. In obesity, Bacteroidales genera, for example, *Lactobacillus* spp., *Bifidobacterium* spp., *Bacteroides* spp., and *Enterococcus* spp., as well as the ratio of Firmicutes to Bacteriodetes and the Enterobacteriaceae species are upregulated, while *Clostridia*, including *Clostridium leptum*, and *Enterobacter* spp. are downregulated [30–33].

The gut microbiota composition can affect the human body's ability to acquire nutrients and regulate energy usage; as such, it plays an important role in the occurrence and development of obesity and related diseases [38,39]. Importantly, the composition is different between infants and adults as well as between obese and lean individuals. For example, calorie-restricted diets can reduce the ratio of Firmicutes to Bacteroidetes bacteria in the gut [34], and vegetarian diets have been shown to upregulate *Bacteroides* spp. and downregulate *Acteroides* spp., *Bifidobacterium* spp., and *Escherichia coli*, as well as Enterobacteriaceae and Firmicutes bacteria [35–37]. Given this, targeting the gut microbiome may provide a potential therapeutic approach in the treatment of obesity [40].

Table 1
Dietary structure affects the composition of the gut microbiota.

Type of diet	Upregulated	Downregulated	Ref.
Calorie-restricted	——	Firmicutes to Bacteroidetes ratio	[34]
Vegetarian Diet	Bacteroides	*Acteroides* spp. *Bifidobacterium* spp. *Escherichia coli* *Enterobacteriaceae* spp. Firmicutes	[35–37]
High-Fat Diet	Firmicutes to Bacteriodetes ratio *Lactobacillus* spp. Enterobacteriaceae Bacteroidales *Bacteroides* spp. *Bifidobacterium* spp. *Enterococcus* spp.	*Clostridia* *Clostridium leptum* *Enterobacter* spp.	[30–33]

2.1. Composition of infants' microbiota and factors affecting homeostasis

The composition of the gut microbiome and the factors affecting its homeostasis are different between infants and adults. In infants, the gut microbiota establishment is a dynamic process. The earliest intestinal microbiota colonization is thought to occur during birth [41]. However, bacteria have been found on the human placentae, indicating that mother-to-infant commensal bacterial transmission may occur during gestation. In newborns, the gut microbiome comprises *Enterococcus*, *Escherichia/Shigella*, *Streptococcus*, and *Rothia* bacteria. The gut microbiome of infants aged 1 and 6 months has been characterized by *Bifidobacterium* and *Collinsella* colonization [42,43]. Metagenomic sequencing on fecal samples of Swedish infants, however, demonstrated a more abundant gut microbiota colonization [44]. Infants 4 months of age harbor bacteria of the *Bifidobacterium*, *Lactobacillus*, *Collinsella*, *Granulicatella*, and *Veillonella* genera, while the speciation of the gut microbiota of 12-month-old infants is more similar to adults. Even so, the microbiome is not fully established until at least 2 years old, and it does not reach the complexity of the adult microbiome until the age of 3 [45,46].

The factors that promote gut microbiome maturation during early-life constitute the mother's intestinal microbiota, delivery mode, feeding, antibiotic administration, and dietary changes [44,47]. The mother's gut microbiota has a direct connection with subsequent microbiota colonization of the infant. *Bifidobacteria* is the predominant bacteria in the infant microbiome and is transmitted from the mother to the infant through breast milk and the infants' fecal matter [42]. Interestingly, the delivery mode can affect the differences in the composition of the gut microbiota in infants, and these differences will last at least 6 months after birth. For example, after delivering vaginally, data have shown that the gut microbiota of infants between 3 months and 6 months were enriched with *Bacteroides*. However, other species, such as *Hungatella*, were found to be abundant in infants delivered by Cesarean sections [48]. Feeding is another crucial factor that can determine the diversity of intestinal microbial colonization. Unlike breastfeeding, formula feeding will facilitate a greater development of infants' microbiomes [49,50]. In addition, administration of antibiotics can rapidly alter the diversity of the gut microbiota composition, decreasing the levels of healthy bacteria in a short period of time [51,52]. Dietary changes, such as the introduction of complementary diets, also can potentially affect the diversity of the intestinal microbial composition [53].

2.2. Composition of the adult microbiota and factors affecting homeostasis

Compared to infants' gut microbiomes, healthy adults have relatively stable gut microbial communities, except for the elderly population, who have relatively unstable and less abundant intestinal microbiomes [54]. Metagenomic sequencing of healthy adult feces found that the dominant flora in the gut microbiota are Firmicutes and Bacteroidetes [55]. Other species of bacteria, such as *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, as well as methanogenic archaea and multiple phages, also colonize the gut of healthy adults [56]. In addition to the variations in diversity between age groups, gut microbial diversity also varies from person to person. However, gut bacteria perform relatively consistent physiological functions in healthy adult bodies,

including metabolism, fermentation, methanogenesis, lipopolysaccharide biosynthesis, and oxidative phosphorylation [57,58]. Therefore, maintaining intestinal flora homeostasis is particularly important for maintaining proper human health.

Although healthy adults have relatively balanced intestinal microbiome compositions, many factors including host genetics, diet, drugs, infections, and diurnal rhythm will disturb this homeostasis [59]. For instance, studies have indicated that humans with diet-derived obesity have variable gut microbiota deviations from those of normal-weight humans [60]. Administration of antibiotics and other xenobiotics can also immediately impact the metabolic homeostasis, diversity, and gene expression profile of the gut microbiome [61,62]. Moreover, exposure to antibiotics for a long time period will induce the activation of antibiotic resistance genes as well as changes in microbial composition [63,64]. In healthy adults, a stable intestinal microbial community is essential for maintaining immune system homeostasis by enabling resistance to pathogenic infection [65]. However, pathogenic infection dramatically disrupts the structure of the gut microbiota [66]. Lastly, diurnal rhythm is another factor that influences the day-night rhythm homeostasis of the gut microbiota [67], as disturbing the feeding rhythm will lead to intestinal flora disturbance, which is often accompanied by metabolic disorders, including obesity [68].

2.3. Dysbiosis

The gut microbiota can be described as a fascinating 'new organ' that affects nutrient acquisition and energy regulation and plays a fundamental role in obesity and related diseases. The gut microbiota constitutes approximately 1 kg of the total body weight. Most researches in animals and humans have demonstrated that the gut microbiota composition differs depending on body mass. In mice, a high-fat diet was shown to increase endotoxemia [69], reducing both gram-negative (e.g. *Bacteroides*-related bacteria) and gram-positive bacteria (e.g., *Eubacterium rectale, Clostridium coccoides,* and *Bifidobacterium*), which was consistent with a human dietary intervention study that demonstrated weight loss in obese individuals was accompanied by Bacteroidetes abundance increase [70]. In humans, high-throughput sequencing of microbial ribosomal RNA and DNA showed that Bacteroidetes (Gram--negative) and Firmicutes (Gram-positive) are the two most dominant bacterial phyla in most individuals [71], whereas *Methanobrevibacter smithii,* is the most dominant of the Archaea domain. Other phyla include Proteobacteria, Actinobacteria (Gram-positive), Fusobacteria, and Verrucomicrobia [72]. In addition, the number of human microbiome genes are at least 100 times as many genes as the human genome [73], and each individual has 500,000–600,000 bacterial genes and most individuals shared half of them [74].

During the last 10 years, the elucidation of the microbiome role in the development and progression of obesity and related diseases has gained significant attention [75,76]. Changes to the composition of the gut microbiota have been related to obesity, such that the intestinal microbiome in obese patients tends to be more available in harvesting energy from the diet compared to normal weight patients. The gut microbiota composition is even different depending on the level of obesity (Table 2). Specifically, notable decreases in the composition of the *Akkermansia, Faecalibacterium, Oscillibacter*, and *Alistipes* genera of bacteria have been observed in obese people compared to normal-weight people[77]. Higher levels of *Lactobacillus reuteri* are associated with obesity, leading to a significant weight gain, while *Bifidobacterium animalis*, *Methanobrevibacter smithii* and other species of *Lactobacillus* are higher in abundance in normal-weight individuals, while the levels of *M. smithii* are decreased in the obese group compared to normal-weight individuals [78]. These differences in the composition of gut microbiota could be an early diagnostic markers in treating T2DM in high-risk patients [79]. Many studies have also found that the gut microbiota could affect glucose metabolism in the body [80], while some other microbial species, such as *Bacteroides faecalis*, could promote the progression of diabetes [81].

Table 2
Compositional changes of the gut microbiota in obesity and related diseases.

	Upregulated	Downregulated	Ref.
Overweight pregnant women	Obese women: *Bacteroides, Staphylococcus aureus, Enterobacteriaceae, Escherichia coli, Staphylococcus* Excessive weight gain: *Escherichia coli, C. leptum, Staphylococcus* Mild weight gain: *Clostridium Bifidobacterium*	Excessive weight gain: *Akkermansia muciniphila, Bifidobacterium*	[87, 88]
Overweight and obese	*Staphylococcus aureus,* Firmicutes-to-Bacteroidetes ratio; *Lactobacillus* spp. *(Lactobacillus reuteri, Lactobacillus), E. coli, Prevotellaceae, Archaea,* Firmicutes	*Bacteroides vulgatus, M. smithii*	[70, 89–92]
Pre-pregnancy and infant	Infants whose mothers are overweight: *Akkermansia muciniphila, Staphylococcus aureus, Clostridium histolyticum,* Infants of mothers with excessive weight gains: *Clostridium histolyticum, Staphylococcus aureus*	*Bacteroides-Prevotella*	[93]
Overweight/ obese women in metabolic disorder group	*E. rec*-to-*Bacto* ratio, *E rectale-C coccoides,* Gram-negative, Firmicutes/acteroidetes ratio	——	[94]

Metabolites such as butyrate produced from intestinal microbes may be beneficial for enhancing the metabolism of humans by increasing mitochondrial activity, preventing metabolic endotoxemia, and activating the gluconeogenesis in intestinal via regulation of the expression of gene and/or hormone production [82]. One study on every-other-day fasting (EODF) was shown to selectively activate beige fat. Li et al. found that shaping the composition of gut microbiota by EODF, causing increases in the formation of the beiging stimuli acetate and lactate, could enable the activation of adipose tissue browning, leading to treatment of metabolic diseases [83]. Therefore, the activation of beige adipocyte thermogenesis might serve as a promoting strategy for the treatment of obesity and related diseases [84]. However, in human, there are currently no known pharmacological method of inducing such thermogenesis. Bacteroides 2 (Bact2) enterotype is also an predominate type in the obese individuals, which is linked to systemic inflammation and disease. However, obese patients after taking statins have a lower prevalence of this dysbiosis than those not, suggesting that statins might improve the gut microbiota profile of obese individuals [85]. In general, the abundance of intestinal microbiota and the number of biogenic genes are essential for the body health [20,86].

3. Metabolites produced by the gut microbiota

A significant amount of data from studies in animal models and humans suggests that obesity and related diseases are associated with profound gut dysbiosis [95–97], which results in changes to the production of metabolites derived from the microbiota. In addition, the gut microbiota creates a homeostatic imbalance within the host toward adiposity, inflammatory response, oxidative stress, and metabolic dysfunction [98,99]. These organisms produce a diversity of metabolites from both exogenous dietary substrates and endogenous host compounds [100], including short-chain fatty acids (SCFAs), indole derivatives, and polyamines (e.g., putrescine, spermidine, spermine), as

well as other metabolites, such as secondary bile acids, ATP, and other metabolites, which are biochemically modified by gut bacteria and produced by the host (Fig. 1).

SCFAs produced by the gut microbiota activate receptors on the surface of neutrophils, macrophages, and dendritic cells, which promotes IL-18 (from GPR43/GPR109a-dependent activation of inflammasome), IL-22 (from GPR43-dependent ILC3 activation), anti-inflammatory IgA (from GPR43-dependent B cells activation), and GLP1 (from the of GPR41 and GPR43 receptor activation) production. In addition, expression of genes involved in intestinal gluconeogenesis (IGN) is activated by a gut-brain neural circuit involving FFAR3 or a cAMP-dependent mechanism. SCFAs inhibit histone deacetylase (HDAC) by activating G protein-coupled receptors (GPCRs). Exogenous tryptophan obtained from diet is mainly metabolized through the kynurenine pathway, and its rate-limiting enzymes include IDO in the mucosa and immune cells and TDO in the liver. In the 5-hydroxytryptamine (5-HT) pathway, tryptophan is converted to 5-hydroxytryptophan by tryptophan hydroxylase and then metabolized to 5-HT by IDO, which stimulates gastrointestinal motility. Indole is metabolized into indole sulfate by CYP2E1 and sulfotransferases in the liver, resulting in IS accumulation, which can cause renal dysfunction. Indole can also induce intestinal endocrine L cells to release GLP-1, inhibit insulin secretion and appetite, and slow down gastric emptying. In addition, several tryptophan metabolites activate aryl hydrocarbon receptor (AhR) and produce IL-22 to maintain mucosal reactivity. CYP, Cytochrome P450 family; I3A, Indole-3-aldehyde; ILA, Indole-3-lactic acid; IAA, Indole-3-acetic acid; IPA, indole-3-propionic acid; IS, Indoxyl sulfate; QA, quinolinic acid; TDO, tryptophan 2,3-dioxygenase; IDO, Indoleamine 2,3-dioxygenase;.

3.1. Metabolites produced by dietary components bacteria

3.1.1. Short-Chain Fatty Acids (SCFAs)

The gut microbiota generates a significant amount of energy and nutrients for the body through anaerobic microbes fermenting non-digestible carbohydrates in the cecum [101]. SCFAs (fatty acids with 6 carbons or less) including acetic acid, isobutyric acid, formic acid, isovaleric acid, propionic acid, butyric acid, and valeric acid, are some metabolites produced by these fermentation reactions, as are amino acids and vitamins [26,102]. Acetate, propionate, and butyrate are the most abundant SCFAs in the intestinal tract [103]. Commonly, *Bacteroides thetaiotaomicron* are the main producers of acetate, while *Faecalibacterium prausnitzii* is one of the main producers of butyrate.

The increase in the concentration of SCFAs in plasma [104] and the concomitant decrease in feces [105] can be linked to obesity and metabolic disorders. In addition, SCFAs can activate the carbohydrate responsive element-binding protein (CHREBP) and the sterol regulatory element-binding transcription factor-1 (SREBP1) to induce lipogenesis and increase triglyceride stores through molecular pathway. They also can suppress fasting-induced adipocyte factor (FIAF) expression to inhibit the lipoprotein lipase activity, thereby leading triglycerides to accumulate in adipocytes [106]. Once produced by the bacteria, SCFAs are absorbed into the bloodstream and bind to GPCRs, which participate in cellular signaling mechanisms, including those involved in lipid, glucose, and cholesterol metabolism [101]; gut inflammation; and neurogenesis [107]. Early mechanistic studies indicated that SCFAs produced by the gut microbiota can trigger cell-specific signal cascade by binding to Gpr41 (FFAR3) and GPR43 (FFAR2) receptors to stimulate the production of glucagon-like peptide-1 (GLP-1) in L cells [108,109], further suggesting that not only can SCFA-GPCR interactions modulate host adiposity and glucose tolerance, but also GPR43 is capable of dual signaling through Gq and Gi pathways, whereas GPR41 signals exclusively through the Gi pathway [110].

IL-18 secreted by intestinal epithelial cells, which is stimulated by the binding of butyric acid to GPR109A, can activate immunosuppression and help to maintain intestinal homeostasis. Butyric acid can also function as an inhibitor of histone deacetylases (HDACs) and has anti-inflammatory functions [111]. In addition, De Vadder et al. discovered that the products of the fermentation of soluble fiber by the gut microbiota propionate and butyrate can activate the expression of genes

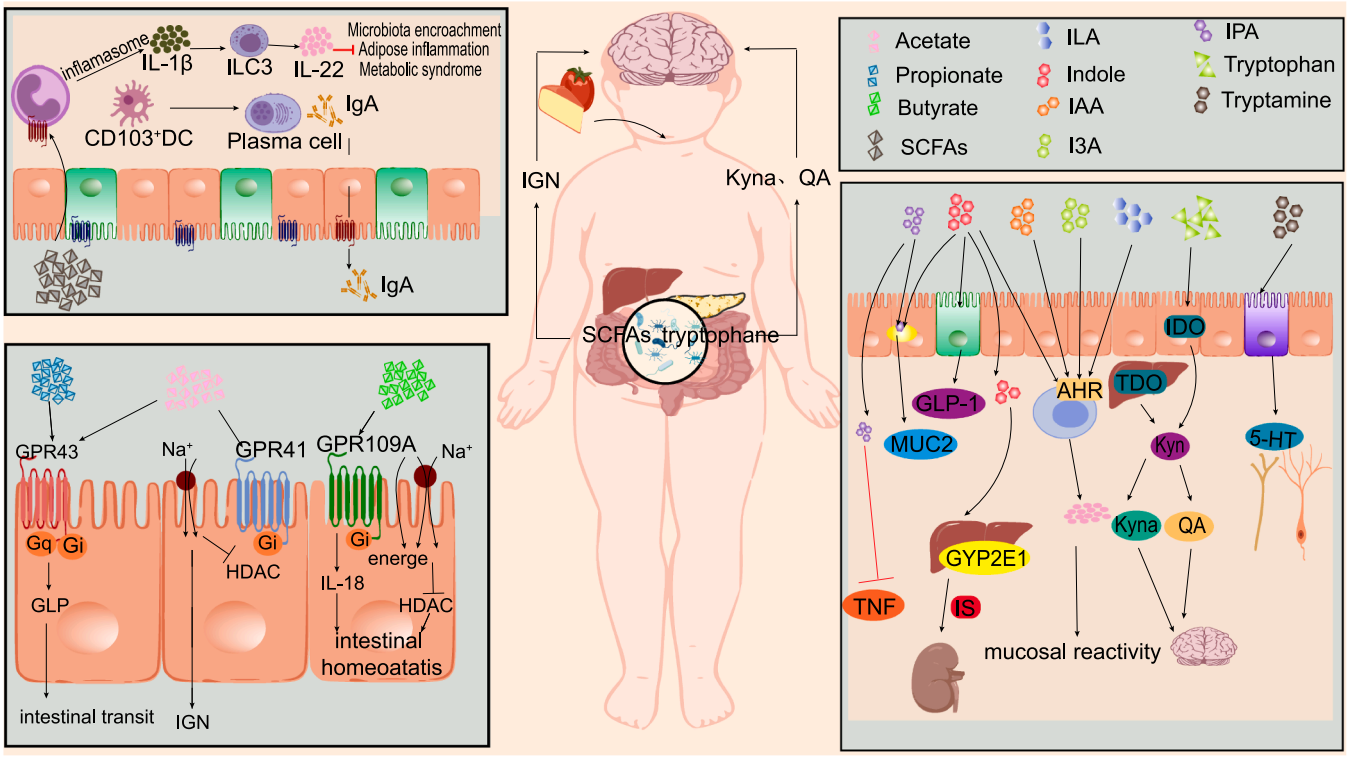

Fig. 1. The Effects of SCFAs and Indole derivatives on hosts.

involved in intestinal gluconeogenesis (IGN) in a cAMP-dependent manner or a gut-brain neural circuit, in which the fatty acid receptor FFAR3 was involved [112]. Moreover, microbiota-derived acetate serves as a precursor for lipogenic acetyl-CoA and fatty acids for de novo lipogenesis (DNL) in liver; therefore, the excess production of acetate has contributed to an increasing rate of obesity and non-alcoholic fatty liver diseases [113–116]. Zou et al. found that binding of microbiota-generated, fiber-derived SCFAs to free fatty acid receptors markedly suppressed high fat diet-induced metabolic syndrome through restoring IL-22-mediated enterocyte function by microbiota [117]. Interestingly, the crosstalk between the gut microbiota and immune system also enabled the regulation of metabolic homeostasis in healthy animals. Chagwedera et. al reported that *Lactobacillus johnsonii* Q1–7 selective deficiency contributed to decreased food intake and body mass in $Tsc1^{f/f}$ $CD11c^{Cre}$ mice via activating mTORC1 signaling in CD11c cells to regulate *L. johnsonii* Q1–7-specific IgA production [118]. In clinical studies, the abundance of the phylum Bacteroidetes increased while the SCFA-producing and 7α-dehydroxylating Firmicutes decreased in patients with NAFLD [119,120].

3.1.2. Indole derivatives

Indole and its derivatives, which are secreted by certain commensal bacteria, such as *Escherichia coli*, *Lactobacillus*, *Bacteroides*, can mediate intra- and interspecies communication among bacteria, as well as synergistic communication between the host and the bacteria [121]. The indole and its metabolites production require the bacterial enzyme tryptophanase (TnaA) to catabolize dietary tryptophan into indole and its derivatives. Tryptophan, which is an essential aromatic amino acid, can be acquired from our common diet, such as oats, poultry, fish, milk and cheese [122]. Commonly, indole metabolites in the digestive tract can be reaching millimolar concentrations and up to 200 μM in tissues, urine, and blood after excreting into the feces or absorbed by the host. Indole in liver is metabolized by CYP2E1 to 3-indoxyl sulfate (3-IS) and ultimately excreted through urine; low urinary 3-IS concentrations is a indicator of dysbiosis [123]. In addition, indole and its derivatives, such as indole-3-lactic acid (ILA), indole-3-aldehyde (I3A), indole-3-acetic acid (IAA), and indole-3-propionic acid (IPA), can act as ligands that bind to aryl hydrocarbon receptors (AhRs) [124], which are transcription factors that play a vital protective and anti-inflammatory roles, mainly via regulation of IL-22 and natural lymphoid in the intestines [125,126].

Preclinical and clinical studies have indicated that the capacity of the microbiota to metabolize tryptophan into AhR agonizts decreased can be an vital characterization of metabolic syndrome [127]. Deactivation of the AhR pathway caused the decrease of GLP-1 and IL-22 production, which result in insulin resistance and liver steatosis by increasing intestinal permeability and lipopolysaccharide (LPS) translocation [128]. Using the AhR agonizts or *Lactobacillus reuteri*, which naturally produces AhR ligands to treatment human, have been shown to improve intestinal barrier function and secrete the incretin hormone GLP-1, which can reverse metabolic disorders, such as intestinal barrier dysfunction and low-grade inflammation [127]. Oral administration of indole was shown to prevent LPS-induced cholesterol metabolism abnormal and alleviate liver inflammation in mice [129]. Natividad et al. [127] and Mallmann et al. [130] found that both genetic and pharmacological approaches to inhibit indoleamine 2,3-dioxygenase (IDO) and the rate-limiting enzyme activity in the kynurenine (Kyn) pathway, can improve HFD-induced obesity and metabolic alteration [131]. Further studies determined that this inhibitory mechanism was a result of the inactivation of IDO caused by binding of AhR agonizts [132]. Furthermore, IDO overactivation was linked to an increase in the concentration of various metabolites, including xanthurenic acid, kynurenic acid, 3-hydroxynurenine, 3-hydroxyanthranilic acid, and quinolinic acid, as well as decreases in the concentration of tryptophan in plasma [133]. Serotonin (5-HT), another tryptophan metabolite, is also involved in obesity treatment, as it affects appetite and satiety. It also inhibits the thermogenesis of brown adipose tissue, causing fat accumulation [134]. These results were confirmed by the human data, as the concentrations of the end-product of serotonin metabolism, 5-hydroxyindole-3-acetic acid, are higher in patients with metabolic disorders relative to those who do not suffer from metabolic disorders [135,136].

3.2. Metabolites produced by the host and biochemically modified by gut bacteria

3.2.1. Secondary bile acids

Bile acids, which are the end product of cholesterol metabolism, are played vital role in dietary fat digestion and absorption [137,138]. In addition, as signaling molecules they play important roles in modulating host lipid metabolism, glucose/insulin metabolism, and inflammation, as they orchestrate blood glucose, lipid, and energy metabolism [139,140]. The composition of bile acid pool, which is a function of bile acids metabolism by the microbiota in the intestine, as unique enzymes that modify bile acids in the gut expressed by the gut microbiota [141]. Shaping the bile acid pool and regulating the bile acid-activated receptors (BARs) activity can trigger various metabolic signals. Therefore, the composition of the gut microbiota in turn be regulated by bile acids [142]. Mechanistically, bile acids are preferential ligands of farnesoid X receptors (FXR), pregnane X receptors, and GPCRs, all of which can result in metabolic alteration if their activities are dysregulated [137,141]. For example, obeticholic acid, one of the semi-synthetic FXR agonist was shown to improve the NASH patient after 72 weeks of treatment in a randomized, controlled clinical trial (RCT) [143]. Another example indicated that short-term treatment NASH patients with the FGF19 analog NGM282 resulted in a reduction of steatosis [144]. However, there are no clinical study performed to treat patients with NAFLD or NASH via modifying FXR signaling by the gut microbiota. The most abundant metabolites in the gut microbiome, including the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), have been shown to modulate host energy homeostasis and metabolism by activating TGR5 [142,145]. In clinic, studies have also found that the bile acid composition of the gut microbiota was affected by treatment with the anti-diabetic medication acarbose in T2D patients [143]. In addition, compared to a normal diet, the levels of bile acid in the intestinal lumen and serum was obviously increased and the bile acid profiles including disproportionate increases in the levels of primary bile acids and secondary bile acids were also altered by an HFD [146]. Wu et al. showed that deficiency of the gut microbiome alleviated HFD-induced metabolic syndrome by modulating CYP7A1 expression in the alternative bile acid synthesis pathway in hamsters, indicating that CYP7A1 might serve as a potential target to modulate diet-induced obesity [147].

Treatment the ob/ob mice with the bile acid sequestrant colesevelam increased the secretion of GLP-1 and also improved glycemia in an FXR-dependent manner, revealing that the FXR-GLP-1 could be a potential pharmacological target for T2D [148]. Treatment with antibiotic upregulated the expression of CYP7B1, increased the release of tauro-β-muricholic acid (TβMCA), and suppressed the intestinal FXR signaling in hamsters, thereby improving HFD-induced glucose intolerance and hepatic steatosis [147]. A high-protein diet in pig increased the abundance of *Eubacterium* species in the gut, which are capable of metabolizing bile acids via 7α-dehydroxylation, causing higher levels of the secondary bile acids DCA and LCA [149]. Methionine restriction attenuated insulin resistance triggered by HFD as well as stabilized the periodic fluctuations in the expression of both genes associated with lipidolysis and bile acid synthetic interrupted by HFD, thereby alleviating the blood lipid profile [150]. A recent study revealed that mixes of extruded legumes and cereals modulated lipid profiles and increased bile acids fecal excretion [151]. This research drives us to understand the nutritional and physiological function of extruded legumes and cereals dietary mixtures. Moreover, common buckwheat (*Fagopyrum esculentum* Moench) improved HFD-induced NAFLD associated with

dyslipidemia in mice [152]. Common buckwheat supplementation significantly regulated the biosynthesis of primary bile acid and altered the gut microbiome structure, ameliorating lipid metabolism [153]. These studies suggested that common buckwheat could be a potential functional food in the NAFLD and hyperlipidemia prevention.

3.2.2. *Taurine, ATP, polysaccharide A (PSA)*

In addition to the bile acids, several other metabolites are produced by the host are all involved in immune regulation of the host. ATP, which is secreted by a subset of intestinal bacteria, activates the P2X and P2Y receptors, while PSA activates LR2 on DCs and Tregs. In addition, ATP can promote inflammation by rapidly binding to activated ATP receptors in an autocrine or paracrine manner, including ionic P2X receptors and metabolic P2Y receptor subtypes, which amplify T cell receptor signals in lymphocytes and promote the activation of inflammatory bodies in macrophages and DC. At present, seven specific ionic receptors of ATP have been identified in mammals: purinergic 2X receptors 1–7 (P2X1R–P2X7R) [154]. There are also eight metabolic GPCRs with ATP as the preferred agonist: P2Y1 receptor (P2Y1R), P2Y2R, P2Y4R, P2Y6R, P2Y11R, P2Y12R, P2Y13R, and P2Y14R [155]. Extracellular ATP is the only agonist of P2X. The combination between ATP and P2X leads to an influx of Na^{+} and Ca^{2+} and an efflux of K^{+}. Taurine, as an essential amino acid for the human body, accounts for more than 50% of free amino acids in immune cells. It also plays an critical role in intestinal microorganisms metabolism [156]. Taurine was found to improve T cell proliferation, promote the single-chain fatty acids production, and reduce the LPS concentration, thereby regulating intestinal microecology [157]. PSA activated the expression of TLR2 on the surface of DC and promote the production of IL-10 by T cells [158]. PSA directly binding to TLR2 expressed on FoxP3 +Tregs further increased the production of IL-10 [159]. In addition, PSA also exhibited protective effects against mouse colitis by inducing IL-10 production, which inhibited the mucosal effector T cells activity, especially TH17 cells [160](Fig. 2).

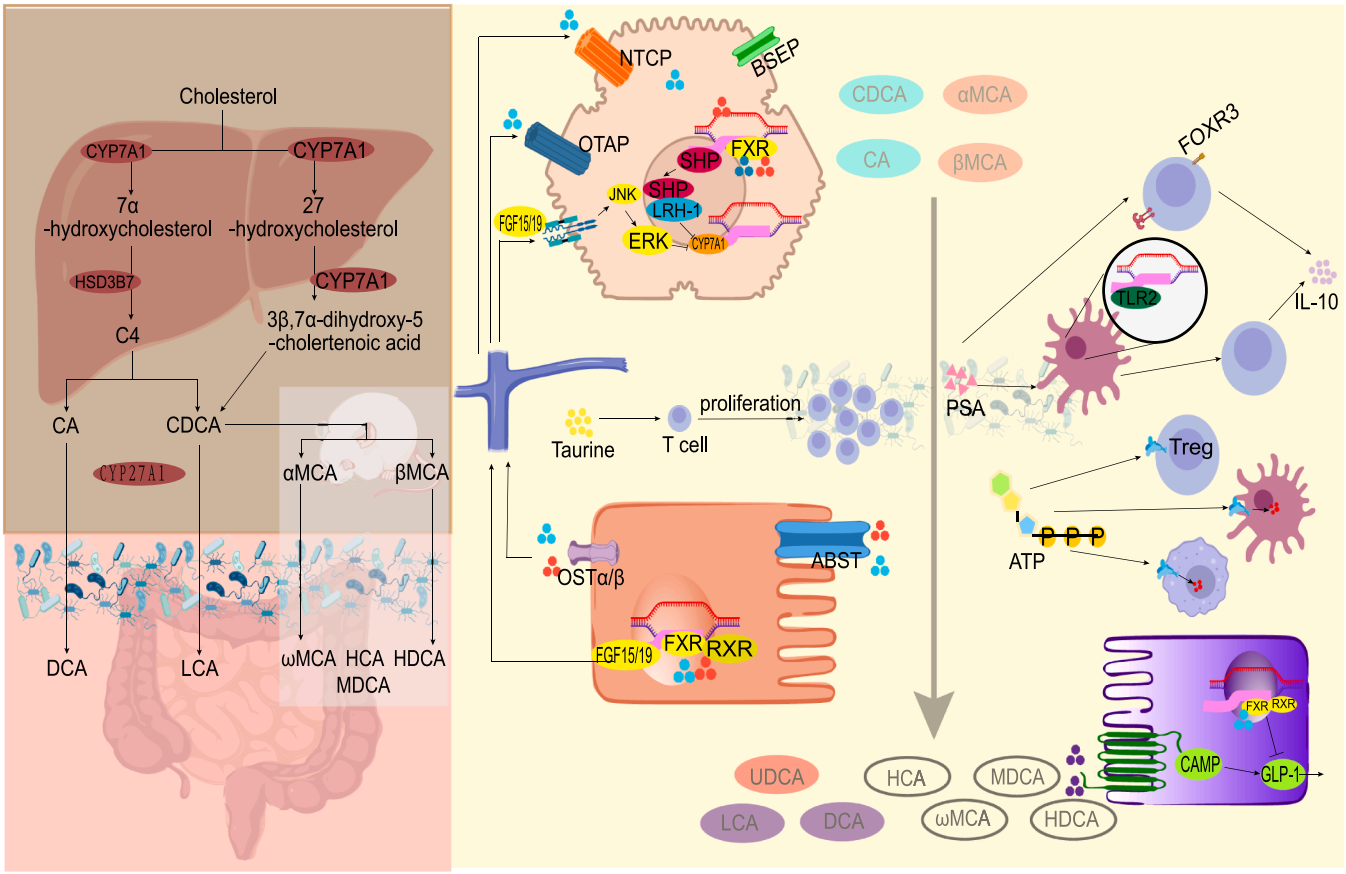

Fig. 2. Metabolites produced by the host and biochemically modified by gut bacteria.
The biosynthetic pathways of primary bile acids in hepatocytes (top left) and secondary bile acids in the intestine (bottom left). Primary bile acids (CDCA, CA and α/βMCA) are synthesized in the liver, transported to the bile duct through the bile salt export pump (BSEP) transporter, and transformed into secondary bile acids (UDCA, LCA, DCA, etc.) by intestinal microorganisms. Bile acid is transported back to liver by enterohepatic circulation through several transporters on hepatocytes (NTCP and OATP) and ileal enterocytes (ASBT, OST). In ileal enterocytes (bottom middle), FXR is activated by CDCA and CA, resulting in the transcription of FGF15/19 to the liver and then binding to the FGFR4/β-klotho receptor complex on the surface of hepatocytes (top middle), activating the JNK/ERK signaling cascade and inhibiting the CYP7A1 expression. In hepatocytes, the bile acid binding to the FXR-RXR heterodimer complex result in the nuclear receptor SHP transcription and the SHP binding to LRH-1, thereby inhibiting the CYP7A1 expression. In colonic L cells (bottom right), the activation of FXR inhibited the synthesis of GLP-1, while the activation of the plasma membrane receptor TGR5 by LCA and DCA engendered an increase in the intracellular levels of cAMP and the expression and release of GLP-1. PSA can activate the expression of TLR2 on the surface of DC or directly combine with TLR2 expressed by FoxP3 + Treg to promote the production of IL-10. ATP activates P2X and P2Y receptors and promotes inflammation (top right). SHP, small heterodimer partner; LRH-1, liver receptor homolog-1; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; FGF15/19, fibroblast growth factor 15/19; FXR, farnesoid X receptor; RXR, retinoid X receptor; NTCP, sodium taurocholate co-transporting polypeptide; OATP, organic anion-transporting polypeptide; OST, organic solute transporter; TGR5, G protein-coupled membrane receptor 5.

4. Therapeutic potential of the gut microbiota

The gut microbiota has become a target for live bacterial cell-based biotherapies, such as probiotic biotherapies, for various chronic diseases, including metabolic syndrome and diabetes. These biotherapies create a healthy gut environment by balancing bacterial populations and promoting their favorable metabolic action. Currently, dietary intervention and drugs are the predominant intervention strategies for balancing the composition of the gut microbiota and are discussed further below [86].

4.1. Dietary intervention

Diet and dietary components have profound effects on the composition of the gut microbiota and are among the most important contributors to alterations in bacteria flora [161]. Research has indicated that carbohydrate-restricted or fat-restricted, low caloric, diet-induced weight loss was related with increased the gene richness of gut bacterial and reduced the chronic systemic inflammation [162]. Specific diets were linked to certain gut bacterial communities; for example, *Prevotella*, a fiber-rich diet, while *Bacteroides* was associate with protein-rich diet [162]. Different types of foods, for example, caffeine, omega-3 polyunsaturated fatty acids, and green tea may increase the richness of gut bacterial and restore the *Firmicutes* to *Bacteroidetes* ratio [163]. In addition, the intestinal bacterial composition many also be promoted by the fruits, vegetables, extra virgin olive oil and so on [164]. Another therapeutic strategy is to use probiotics, such as species of *Bifidobacterium* and *Lactobacillus*, and prebiotics, such as lactulose, inulin, fructooligosaccharides and galactooligosaccharides, to alter the gut microbiota composition [165,166].

Many other diets rich in prebiotics, such as the Mediterranean diet, can positively influence the stability of the gut microbiota [161]. In clinic, Zimmer et.al found that compared to an omnivore diet-fed subjects, the fecal microbiota of the vegetarian and vegan diet-fed ones showed significantly lower microbial counts of *Bacteroides*, *Bifidobacterium*, *Escherichia coli*, and Enterobacteriaceae bacteria. As the undigestible polysaccharides can be fermented into SCFAs by the gut microbiota in a vegetarian/vegan diet, which is typically associated with a higher carbohydrate and fiber content [37]. A depleted gut microbial biodiversity in people consuming a Western diet has been associated with an increased obesity and related diseases incidence, such as coronary vascular disease, metabolic syndrome, and NAFLD [167]. In addition to diet, physical exercise also can modulate the composition of the gut microbiota by enabling an increase in the abundance of health-promoting bacteria, such as *Staphylococcus hominis* and *Akkermansia muciniphila* [168]. Researchers have also developed microbiota-directed interventions to treat obesity related diseases in recent years. For example, fecal microbiota transplantation (FMT) from lean male donors to metabolic syndrome males could significant improve the insulin sensitivity and increase the diversity of intestinal microbia [169].

4.2. Drugs

4.2.1. Probiotics

Altering the microflora of people with obesity to increase the population of beneficial microorganisms or probiotics has been demonstrated to be a promoting measure to combat obesity and related diseases. Probiotics exhibit anti-obesity effects through the regulation of intestinal microflora, reduction of insulin resistance, and improving satiety [170,171]. More specifically, because of their low pathogenicity and high barrier to antibiotic resistance, *Lactobacillus* and *Bifidobacterium* species have been applied in animal models of obesity [172] and have led to reductions in weight and fat accumulation to varying degrees [173]. *Bifidobacterium* reduced inflammation, insulin sensitivity, fat accumulation, and serum levels of cholesterol and triglycerides predominantly by reducing intestinal permeability. In addition, administering probiotics containing *Lactobacillus* strains to obese animals effectively reduced body fat mass and improved both lipid distribution and blood glucose homeostasis by stimulating fatty acid oxidation or inhibiting lipoprotein lipase activity [174].

In humans, some strains of *Lactobacillus* have been tested. For instance, compared to the children who were exposed to a placebo, the probiotic *L. rhamnosus* facilitated the modulation of the child's weight gain during the first few years of life and during the initial phase of excessive weight gain, but this was not the case later in life [173]. Other probiotics such as *Lactobacillus gasseri* SBT2055 and BNR17 species were administered to those obese individuals for 12 weeks. *Lactobacillus. gasseri* SBT2055 lowered abdominal adiposity and body weight, while *L. gasseri* BNR17 group not [175,176]. In addition, among obese children with insulin resistance, weight loss was significant after taking *Aspergillus flavus* CECT7765 [177]. In adults, *Lactobacillus* and *Bifidobacterium* promoted significant reductions in body weight, BMI, waistline size, and fat [178]. Oral supplementation with probiotics appeared to improve atherogenic indices by reducing the concentration of low-density lipoproteins (LDL) and total cholesterol [179]; and improve body composition, body weight, and abdominal visceral adipose tissue [175]. Probiotics have also been recognized for having antibacterial properties and promoting barrier and immunomodulatory functions [178]; therefore, probiotics can function to regulate the composition of intestinal microflora for improving obesity and obesity-related diseases.

4.2.2. Antibiotics

In obese mice, vancomycin treatment was shown to improve metabolic abnormalities associated with obesity. Plasma TNF-α levels in diet-induced obese mice treated with vancomycin were lower than those in the diet-induced obese control group [180]. Vancomycin has also been shown to alter the composition of intestinal microflora of human males with metabolic syndrome, thereby reducing peripheral insulin sensitivity in the patients [181]. Therefore, there is great potential for antibiotics use to prevent and treat obesity.

4.2.3. Prebiotics

Prebiotics are an indigestible food ingredient that can have a beneficial effect on the host by selectively stimulating the growth or activity of certain bacteria in the colon, which can help to improve the health of the host [174]. Tons of studies in animal models have shown that various supplementation of diets with fructooligosaccharides and galactooligosaccharides could change the intestinal microorganisms composition [108] and promote the growth of beneficial *Bifidobacterium* and *Lactobacillus* [182]. This microflora regulation can improve intestinal barrier function and significantly reduce body weight and total fat. In one study, injection of fructooligosaccharides into DIO rats led to reductions in fat and weight gain and significantly increased *Bifidobacteria* and lactic acid bacteria [183]. These effects were achieved by reducing food intake, appetite and fatty acid storage. In addition, improved intestinal barrier integrity led to improved glucose tolerance and insulin resistance in mice [174,184]. In humans, prebiotics have also been shown to be involved in weight loss and metabolic parameters improvement, including insulin resistance [185].

4.3. Fecal microbiota transplant (FMT)

Fecal microbiota transplantation (FMT) is an approach used to treat certain diseases by reconstructing the intestinal flora and involves transplanting the fecal fluid of treated healthy people into the intestines of diseased patients. Although FMT has been extensively studied in humans, several studies on FMT in mice have been conducted. For example, despite aseptic mice being resistant to diet-induced obesity, FMT from obese mice to aseptic mice endowed the aseptic mice with a metabolic phenotype [186]. Since a metabolic phenotype can be transferred to germ-free (GF) mice through intestinal microflora, it was

speculated that FMT might effectively improve the homeostasis of lipids and glucose [183]. In a pilot study with humans, intestinal microflora was transferred from emaciated human donors to those recipients who are under metabolic syndrome by delaying enteral feeding tubes. Compared to the peripheral insulin sensitivity before FMT, insulin sensitivity increased in the patients with metabolic syndrome six weeks after beginning treatment [187]. Therefore, FMT might serve as a new method for treating obesity and related metabolic disorders in the future.

5. Conclusion

Although our knowledge about how the gut microbiota affects obesity is still rudimentary, the rate at which new discoveries are emerging is impressive. As outlined, there is overwhelming evidence that the composition of the gut microbiota and metabolites impact the progression of obesity and obesity-related diseases. The composition and characteristics of the gut microbiota, as well as the factors affecting their homeostasis, are different not only between adults and infants but also between stages of infancy. Importantly, gut microbiota metabolites, including the metabolites that not only are biochemically modified by gut bacteria and produced by the host and but also that are produced by bacteria from dietary components, play a vital important role in the development of obesity and related diseases. These metabolites are heavily involved in the onset and progression of obesity. Thus, targeting the composition of both the gut microbiota and the metabolites produced by these organisms and the host using dietary intervention and drugs are intervention strategies for treating and preventing metabolic diseases, including obesity. Probiotics intervention is the most direct and effective method to intervene obesity and obesity related diseases in clinic because they can selectively increase the number of microorganisms and improve the intestinal microecological environment of intestinal bacteria under an obese state. Probiotics can regulate the balance of the gut microbiota and improve obesity and metabolic-related indicators, such as body mass and blood glucose and lipid levels. Thus, it is feasible to improve the symptoms of obesity and metabolic diseases by using probiotics to change the structure of the gut microbiota and improve the chronic inflammatory response in the intestines of obese people. Overall, our review highlights the importance that the gut microbiota plays in the development of disease, including obesity, as it represents a critical modifiable factor to think about when discovering precision medicine strategies for the prevention and/or treatment obesity and related diseases.

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CRediT authorship contribution statement

X. J. Feng conceived and drafted the manuscript. **X. J. Feng, J. F. Geng and Q. Q. Ni** wrote the manuscript, **W. Sun** made the figures, **L.G. Li** reviewed and modified the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

References

[1] D.J. Hoffman, T.L. Powell, E.S. Barrett, D.B. Hardy, Developmental origins of metabolic disease, Physiol. Rev. 101 (2020) 739–795.
[2] V.K. Ridaura, J.J. Faith, F.E. Rey, J. Cheng, A.E. Duncan, A.L. Kau, N.W. Griffin, V. Lombard, B. Henrissat, J.R. Bain, M.J. Muehlbauer, O. Ilkayeva, C. F. Semenkovich, K. Funai, D.K. Hayashi, B.J. Lyle, M.C. Martini, L.K. Ursell, J. C. Clemente, W. Van Treuren, W.A. Walters, R. Knight, C.B. Newgard, A.C. Heath, J.I. Gordon, Gut microbiota from twins discordant for obesity modulate metabolism in mice, Science 341 (6150) (2013), 1241214.
[3] T.R. Wu, C.S. Lin, C.J. Chang, T.L. Lin, J. Martel, Y.F. Ko, D.M. Ojcius, C.C. Lu, J. D. Young, H.C. Lai, Gut commensal Parabacteroides goldsteinii plays a predominant role in the anti-obesity effects of polysaccharides isolated from Hirsutella sinensis, Gut 68 (2) (2019) 248–262.
[4] H. Charles-Messance, K. Mitchelson, E. De Marco Castro, F.J. Sheedy, H. M. Roche, Regulating metabolic inflammation by nutritional modulation, J. Allergy Clin. Immunol. 146 (2020) 706–720.
[5] M. Mongraw-Chaffin, M.C. Foster, C.A.M. Anderson, G.L. Burke, N. Haq, R. R. Kalyani, P. Ouyang, C.T. Sibley, R. Tracy, M. Woodward, D. Vaidya, Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk, J. Am. Coll. Cardiol. 71 (17) (2018) 1857–1865.
[6] L.R. Howe, K. Subbaramaiah, C.A. Hudis, A.J. Dannenberg, Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer, Clin. Cancer Res. 19 (22) (2013) 6074–6083.
[7] A. Petersen, K. Bressem, J. Albrecht, H.M. Thieß, J. Vahldiek, B. Hamm, M. R. Makowski, A. Niehues, S.M. Niehues, L.C. Adams, The role of visceral adiposity in the severity of COVID-19: highlights from a unicenter cross-sectional pilot study in Germany, Metabolism 110 (2020), 154317.
[8] N. Stefan, A.L. Birkenfeld, M.B. Schulze, D.S. Ludwig, Obesity and impaired metabolic health in patients with COVID-19, Nat. Rev. Endocrinol. 16 (7) (2020) 341–342.
[9] G. Mingrone, S. Panunzi, A. De Gaetano, C. Guidone, A. Iaconelli, G. Nanni, M. Castagneto, S. Bornstein, F. Rubino, Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial, Lancet 386 (9997) (2015) 964–973.
[10] K.J. Neff, G. Baud, V. Raverdy, R. Caiazzo, H. Verkindt, C. Noel, C.W. le Roux, F. Pattou, Renal function and remission of hypertension after bariatric surgery: a 5-year prospective cohort study, Obes. Surg. 27 (3) (2017) 613–619.
[11] K. Sarkhosh, N.J. Switzer, M. El-Hadi, D.W. Birch, X. Shi, S. Karmali, The impact of bariatric surgery on obstructive sleep apnea: a systematic review, Obes. Surg. 23 (3) (2013) 414–423.
[12] F.L. Stigler, R.H. Lustig, J.I. Ma, Mechanisms, pathophysiology, and management of obesity, N. Engl. J. Med. 376 (15) (2017) 1491.
[13] H.E. Bays, P.H. Jones, T.A. Jacobson, D.E. Cohen, C.E. Orringer, S. Kothari, D. E. Azagury, J. Morton, N.T. Nguyen, E.C. Westman, D.B. Horn, W. Scinta, C. Primack, Lipids and bariatric procedures part 1 of 2: scientific statement from the National Lipid Association, American Society for Metabolic and Bariatric Surgery, and Obesity Medicine Association: full report, J. Clin. Lipidol. 10 (1) (2016) 33–57.
[14] B. Cha, J.H. Yu, Y.J. Jin, Y.J. Suh, J.W. Lee, Survival outcomes according to body mass index in hepatocellular carcinoma patient: analysis of nationwide cancer registry database, Sci. Rep. 10 (1) (2020) 8347.
[15] C.A. Alarcón Rojas, M.T. Alvarez-Bañuelos, J. Morales-Romero, H. Suárez-Díaz, J. C. Hernández-Fonseca, G. Contreras-Alarcón, Breast cancer: metastasis, molecular subtypes, and overweight and obesity in Veracruz, Mexico, Clin. Breast Cancer 19 (1) (2019) E166–E171.
[16] C.A. Alarcón Rojas, M.T. Alvarez-Bañuelos, J. Morales-Romero, H. Suárez-Díaz, J. C. Hernández-Fonseca, G. Contreras-Alarcón, Breast cancer: metastasis, molecular subtypes, and overweight and obesity in Veracruz, Mexico, Clin. Breast Cancer 19 (1) (2019) e166–e171.
[17] X. Tang, S. Liu, D. Chen, Z. Zhao, J. Zhou, The role of the fat mass and obesity-associated protein in the proliferation of pancreatic cancer cells, Oncol. Lett. 17 (2) (2019) 2473–2478.
[18] L.J. Bou Malhab, W.M. Abdel-Rahman, Obesity and inflammation: colorectal cancer engines, Curr. Mol. Pharmacol. 14 (2021).
[19] J. Luo, M. Hendryx, J.E. Manson, J.C. Figueiredo, E.S. LeBlanc, W. Barrington, T. E. Rohan, B.V. Howard, K. Reding, G.Y. Ho, D.O. Garcia, R.T. Chlebowski, Intentional weight loss and obesity-related cancer risk, JNCI Cancer Spectr. 3 (4) (2019) pkz054.
[20] E. Le Chatelier, T. Nielsen, J. Qin, E. Prifti, F. Hildebrand, G. Falony, M. Almeida, M. Arumugam, J.M. Batto, S. Kennedy, P. Leonard, J. Li, K. Burgdorf, N. Grarup, T. Jørgensen, I. Brandslund, H.B. Nielsen, A.S. Juncker, M. Bertalan, F. Levenez, N. Pons, S. Rasmussen, S. Sunagawa, J. Tap, S. Tims, E.G. Zoetendal, S. Brunak, K. Clément, J. Doré, M. Kleerebezem, K. Kristiansen, P. Renault, T. Sicheritz-Ponten, W.M. de Vos, J.D. Zucker, J. Raes, T. Hansen, c. MetaHIT, P. Bork, J. Wang, S.D. Ehrlich, O. Pedersen, Richness of human gut microbiome correlates with metabolic markers, Nature 500 (7464) (2013) 541–546.
[21] C. Bárcena, R. Valdés-Mas, P. Mayoral, C. Garabaya, S. Durand, F. Rodríguez, M. T. Fernández-García, N. Salazar, A.M. Nogacka, N. Garatachea, N. Bossut,

F. Aprahamian, A. Lucia, G. Kroemer, J. Freije, P.M. Quirós, C. López-Otín, Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice, Nat. Med. 25 (8) (2019) 1234–1242.
[22] M.A. Stanislawski, D. Dabelea, L.A. Lange, B.D. Wagner, C.A. Lozupone, Gut microbiota phenotypes of obesity, NPJ Biofilms Microbiomes 5 (1) (2019) 18.
[23] L.A. Velloso, F. Folli, M.J. Saad, TLR4 at the crossroads of nutrients, gut microbiota, and metabolic inflammation, Endocr. Rev. 36 (3) (2015) 245–271.
[24] L. Abenavoli, L. Boccuto, A. Federico, M. Dallio, C. Loguercio, L. Di Renzo, A. De Lorenzo, Diet and non-alcoholic fatty liver disease: the Mediterranean way, Int. J. Environ. Res. Public Health 16 (17) (2019).
[25] J.J. Faith, J.L. Guruge, M. Charbonneau, S. Subramanian, H. Seedorf, A. L. Goodman, J.C. Clemente, R. Knight, A.C. Heath, R.L. Leibel, M. Rosenbaum, J. I. Gordon, The long-term stability of the human gut microbiota, Science 341 (6141) (2013), 1237439.
[26] J. Liang, M. Zhang, X. Wang, Y. Ren, T. Yue, Z. Wang, Z. Gao, Edible fungal polysaccharides, the gut microbiota, and host health, Carbohydr. Polym. 273 (2021), 118558.
[27] H. Tilg, N. Zmora, T.E. Adolph, E. Elinav, The intestinal microbiota fuelling metabolic inflammation, Nat. Rev. Immunol. 20 (1) (2020) 40–54.
[28] H.Y. Cheng, M.X. Ning, D.K. Chen, W.T. Ma, Interactions between the gut microbiota and the host innate immune response against pathogens, Front. Immunol. 10 (2019) 607.
[29] F. Shanahan, The colonic microbiota in health and disease, Curr. Opin. Gastroenterol. 29 (1) (2013) 49–54.
[30] C.B. de La Serre, C.L. Ellis, J. Lee, A.L. Hartman, J.C. Rutledge, H.E. Raybould, Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation, Am. J. Physiol. Gastrointest. Liver Physiol. 299 (2) (2010) G440–G448.
[31] D. Chen, Z. Yang, X. Chen, Y. Huang, B. Yin, F. Guo, H. Zhao, J. Huang, Y. Wu, R. Gu, Effect of Lactobacillus rhamnosus hsryfm 1301 on the gut microbiota and lipid metabolism in rats fed a high-fat diet, J. Microbiol. Biotechnol. 25 (5) (2015) 687–695.
[32] K.A. Kim, W. Gu, I.A. Lee, E.H. Joh, D.H. Kim, High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway, PLoS One 7 (10) (2012), e47713.
[33] M.K. Hamilton, G. Boudry, D.G. Lemay, H.E. Raybould, Changes in intestinal barrier function and gut microbiota in high-fat diet-fed rats are dynamic and region dependent, Am. J. Physiol. Gastrointest. Liver Physiol. 308 (10) (2015) G840–G851.
[34] C. Zhang, S. Li, L. Yang, P. Huang, W. Li, S. Wang, G. Zhao, M. Zhang, X. Pang, Z. Yan, Y. Liu, L. Zhao, Structural modulation of gut microbiota in life-long calorie-restricted mice, Nat. Commun. 4 (2013) 2163.
[35] C. De Filippo, D. Cavalieri, M. Di Paola, M. Ramazzotti, J.B. Poullet, S. Massart, S. Collini, G. Pieraccini, P. Lionetti, Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa, Proc. Natl. Acad. Sci. USA 107 (33) (2010) 14691–14696.
[36] M.S. Kim, S.S. Hwang, E.J. Park, J.W. Bae, Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation, Environ. Microbiol. Rep. 5 (5) (2013) 765–775.
[37] J. Zimmer, B. Lange, J.S. Frick, H. Sauer, K. Zimmermann, A. Schwiertz, K. Rusch, S. Klosterhalfen, P. Enck, A vegan or vegetarian diet substantially alters the human colonic faecal microbiota, Eur. J. Clin. Nutr. 66 (1) (2012) 53–60.
[38] R.X. Ding, W.R. Goh, R.N. Wu, X.Q. Yue, X. Luo, W. Khine, J.R. Wu, Y.K. Lee, Revisit gut microbiota and its impact on human health and disease, J. Food Drug Anal. 27 (3) (2019) 623–631.
[39] M. Régnier, M. Van Hul, C. Knauf, P.D. Cani, Gut microbiome, endocrine control of gut barrier function and metabolic diseases, J. Endocrinol. 248 (2) (2021) R67–R82.
[40] P. Lee, B.R. Yacyshyn, M.B. Yacyshyn, Gut microbiota and obesity: an opportunity to alter obesity through faecal microbiota transplant (FMT), Diabetes Obes. Metab. 21 (3) (2019) 479–490.
[41] H. Wopereis, R. Oozeer, K. Knipping, C. Belzer, J. Knol, The first thousand days – intestinal microbiology of early life: establishing a symbiosis, Pediatr. Allergy Immunol.: Off. Publ. Eur. Soc. Pediatr. Allergy Immunol. 25 (5) (2014) 428–438.
[42] M.M. Grönlund, Ł. Grześkowiak, E. Isolauri, S. Salminen, Influence of mother's intestinal microbiota on gut colonization in the infant, Gut Microbes 2 (4) (2011) 227–233.
[43] S. Dogra, O. Sakwinska, S.E. Soh, C. Ngom-Bru, W.M. Brück, B. Berger, H. Brüssow, N. Karnani, Y.S. Lee, F. Yap, Y.S. Chong, K.M. Godfrey, J. D. Holbrook, Rate of establishing the gut microbiota in infancy has consequences for future health, Gut Microbes 6 (5) (2015) 321–325.
[44] F. Bäckhed, J. Roswall, Y. Peng, Q. Feng, H. Jia, P. Kovatcheva-Datchary, Y. Li, Y. Xia, H. Xie, H. Zhong, M.T. Khan, J. Zhang, J. Li, L. Xiao, J. Al-Aama, D. Zhang, Y.S. Lee, D. Kotowska, C. Colding, V. Tremaroli, Y. Yin, S. Bergman, X. Xu, L. Madsen, K. Kristiansen, J. Dahlgren, J. Wang, Dynamics and stabilization of the human gut microbiome during the first year of life, Cell Host Microbe 17 (5) (2015) 690–703.
[45] E. Avershina, K. Lundgård, M. Sekelja, C. Dotterud, O. Storrø, T. Øien, R. Johnsen, K. Rudi, Transition from infant- to adult-like gut microbiota, Environ. Microbiol. 18 (7) (2016) 2226–2236.
[46] T. Yatsunenko, F.E. Rey, M.J. Manary, I. Trehan, M.G. Dominguez-Bello, M. Contreras, M. Magris, G. Hidalgo, R.N. Baldassano, A.P. Anokhin, A.C. Heath, B. Warner, J. Reeder, J. Kuczynski, J.G. Caporaso, C.A. Lozupone, C. Lauber, J. C. Clemente, D. Knights, R. Knight, J.I. Gordon, Human gut microbiome viewed across age and geography, Nature 486 (7402) (2012) 222–227.
[47] Y. Vandenplas, V.P. Carnielli, J. Ksiazyk, M.S. Luna, N. Migacheva, J. M. Mosselmans, J.C. Picaud, M. Possner, A. Singhal, M. Wabitsch, Factors affecting early-life intestinal microbiota development, Nutrition 78 (2020), 110812.
[48] J. Xu, B. Lawley, G. Wong, A. Otal, L. Chen, T.J. Ying, X. Lin, W.W. Pang, F. Yap, Y.S. Chong, P.D. Gluckman, Y.S. Lee, M.F. Chong, G.W. Tannock, N. Karnani, Ethnic diversity in infant gut microbiota is apparent before the introduction of complementary diets, Gut Microbes 11 (5) (2020) 1362–1373.
[49] M.B. Azad, T. Konya, H. Maughan, D.S. Guttman, C.J. Field, R.S. Chari, M. R. Sears, A.B. Becker, J.A. Scott, A.L. Kozyrskyj, I. CHILD Study, Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months, CMAJ: Can. Med. Assoc. J. = J. l'Assoc. Med. Can. 185 (5) (2013) 385–394.
[50] C.C. Cioffi, H.F. Tavalire, J.M. Neiderhiser, B. Bohannan, L.D. Leve, History of breastfeeding but not mode of delivery shapes the gut microbiome in childhood, PLoS One 15 (7) (2020), e0235223.
[51] M. Francino, Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances, Front. Microbiol. 6 (2015) 1543.
[52] S. Zeissig, R. Blumberg, Life at the beginning: perturbation of the microbiota by antibiotics in early life and its role in health and disease, Nat. Immunol. 15 (4) (2014) 307–310.
[53] D.A. Medina, F. Pinto, V. Ortuzar, D. Garrido, Simulation and modeling of dietary changes in the infant gut microbiome, FEMS Microbiol. Ecol. 94 (9) (2018).
[54] M.J. Claesson, I.B. Jeffery, S. Conde, S.E. Power, E.M. O'Connor, S. Cusack, H. M. Harris, M. Coakley, B. Lakshminarayanan, O. O'Sullivan, G.F. Fitzgerald, J. Deane, M. O'Connor, N. Harnedy, K. O'Connor, D. O'Mahony, D. van Sinderen, M. Wallace, L. Brennan, C. Stanton, J.R. Marchesi, A.P. Fitzgerald, F. Shanahan, C. Hill, R.P. Ross, P.W. O'Toole, Gut microbiota composition correlates with diet and health in the elderly, Nature 488 (7410) (2012) 178–184.
[55] T. He, X. Cheng, C. Xing, The gut microbial diversity of colon cancer patients and the clinical significance, Bioengineered 12 (1) (2021) 7046–7060.
[56] A. Reyes, M. Haynes, N. Hanson, F.E. Angly, A.C. Heath, F. Rohwer, J.I. Gordon, Viruses in the faecal microbiota of monozygotic twins and their mothers, Nature 466 (7304) (2010) 334–338.
[57] J. Qin, R. Li, J. Raes, M. Arumugam, K.S. Burgdorf, C. Manichanh, T. Nielsen, N. Pons, F. Levenez, T. Yamada, D.R. Mende, J. Li, J. Xu, S. Li, D. Li, J. Cao, B. Wang, H. Liang, H. Zheng, Y. Xie, J. Tap, P. Lepage, M. Bertalan, J.M. Batto, T. Hansen, D. Le Paslier, A. Linneberg, H.B. Nielsen, E. Pelletier, P. Renault, T. Sicheritz-Ponten, K. Turner, H. Zhu, C. Yu, S. Li, M. Jian, Y. Zhou, Y. Li, X. Zhang, S. Li, N. Qin, H. Yang, J. Wang, S. Brunak, J. Doré, F. Guarner, K. Kristiansen, O. Pedersen, J. Parkhill, J. Weissenbach, C. MetaHIT, P. Bork, S. D. Ehrlich, J. Wang, A human gut microbial gene catalogue established by metagenomic sequencing, Nature 464 (7285) (2010) 59–65.
[58] The Human Microbiome Project Consortium, Structure, function and diversity of the healthy human microbiome, Nature 486 (7402) (2012) 207–214.
[59] S. Lynch, O. Pedersen, The human intestinal microbiome in health and disease, N. Engl. J. Med. 375 (24) (2016) 2369–2379.
[60] S.F. Clarke, E.F. Murphy, K. Nilaweera, P.R. Ross, F. Shanahan, P.W. O'Toole, P. D. Cotter, The gut microbiota and its relationship to diet and obesity: new insights, Gut Microbes 3 (3) (2012) 186–202.
[61] I. Cho, S. Yamanishi, L. Cox, B.A. Methé, J. Zavadil, K. Li, Z. Gao, D. Mahana, K. Raju, I. Teitler, H. Li, A.V. Alekseyenko, M.J. Blaser, Antibiotics in early life alter the murine colonic microbiome and adiposity, Nature 488 (7413) (2012) 621–626.
[62] C. Maurice, H. Haiser, P. Turnbaugh, Xenobiotics shape the physiology and gene expression of the active human gut microbiome, Cell 152 (2013) 39–50.
[63] L. Dethlefsen, D. Relman, Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation, Proc. Natl. Acad. Sci. USA 108 (2011) 4554–4561.
[64] C. Jernberg, S. Löfmark, C. Edlund, J.K. Jansson, Long-term impacts of antibiotic exposure on the human intestinal microbiota, Microbiology 156 (2010) 3216–3223.
[65] S. Iacob, D. Iacob, L. Luminos, Intestinal microbiota as a host defense mechanism to infectious threats, Front. Microbiol. 9 (2018) 3328.
[66] A. Hsiao, A.M. Ahmed, S. Subramanian, N.W. Griffin, L.L. Drewry, W.A. Petri Jr., R. Haque, T. Ahmed, J.I. Gordon, Members of the human gut microbiota involved in recovery from Vibrio cholerae infection, Nature 515 (7527) (2014) 423–426.
[67] B.A. Matenchuk, P.J. Mandhane, A.L. Kozyrskyj, Sleep, circadian rhythm, and gut microbiota, Sleep Med. Rev. 53 (2020), 101340.
[68] C.A. Thaiss, D. Zeevi, M. Levy, G. Zilberman-Schapira, J. Suez, A.C. Tengeler, L. Abramson, M.N. Katz, T. Korem, N. Zmora, Y. Kuperman, I. Biton, S. Gilad, A. Harmelin, H. Shapiro, Z. Halpern, E. Segal, E. Elinav, Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis, Cell 159 (3) (2014) 514–529.
[69] T. Ondee, K. Pongpirul, P. Visitchanakun, W. Saisorn, S. Kanacharoen, L. Wongsaroj, C. Kullapanich, N. Ngamwongsatit, S. Settachaimongkon, N. Somboonna, A. Leelahavanichkul, Lactobacillus acidophilus LA5 improves saturated fat-induced obesity mouse model through the enhanced intestinal Akkermansia muciniphila, Sci. Rep. 11 (1) (2021) 6367.
[70] R.E. Ley, P.J. Turnbaugh, S. Klein, J.I. Gordon, Microbial ecology: human gut microbes associated with obesity, Nature 444 (7122) (2006) 1022–1023.
[71] C. Indiani, K.F. Rizzardi, P.M. Castelo, L. Ferraz, M. Darrieux, T.M. Parisotto, Childhood obesity and firmicutes/bacteroidetes ratio in the gut microbiota: a systematic review, Child Obes. 14 (8) (2018) 501–509.
[72] C. Human Microbiome Project, Structure, function and diversity of the healthy human microbiome, Nature 486 (7402) (2012) 207–214.

[73] J. Li, H. Jia, X. Cai, H. Zhong, Q. Feng, S. Sunagawa, M. Arumugam, J.R. Kultima, E. Prifti, T. Nielsen, A.S. Juncker, C. Manichanh, B. Chen, W. Zhang, F. Levenez, J. Wang, X. Xu, L. Xiao, S. Liang, D. Zhang, Z. Zhang, W. Chen, H. Zhao, J.Y. Al-Aama, S. Edris, H. Yang, J. Wang, T. Hansen, H.B. Nielsen, S. Brunak, K. Kristiansen, F. Guarner, O. Pedersen, J. Doré, S.D. Ehrlich, C. MetaHIT, P. Bork, J. Wang, C. MetaHIT, An integrated catalog of reference genes in the human gut microbiome, Nat. Biotechnol. 32 (8) (2014) 834–841.
[74] J. Qin, R. Li, J. Raes, M. Arumugam, K.S. Burgdorf, C. Manichanh, T. Nielsen, N. Pons, F. Levenez, T. Yamada, D.R. Mende, J. Li, J. Xu, S. Li, D. Li, J. Cao, B. Wang, H. Liang, H. Zheng, Y. Xie, J. Tap, P. Lepage, M. Bertalan, J.M. Batto, T. Hansen, D. Le Paslier, A. Linneberg, H.B. Nielsen, E. Pelletier, P. Renault, T. Sicheritz-Ponten, K. Turner, H. Zhu, C. Yu, S. Li, M. Jian, Y. Zhou, Y. Li, X. Zhang, S. Li, N. Qin, H. Yang, J. Wang, S. Brunak, J. Doré, F. Guarner, K. Kristiansen, O. Pedersen, J. Parkhill, J. Weissenbach, C. MetaHIT, P. Bork, S. D. Ehrlich, J. Wang, A human gut microbial gene catalogue established by metagenomic sequencing, Nature 464 (7285) (2010) 59–65.
[75] B.A. Peters, J.A. Shapiro, T.R. Church, G. Miller, C. Trinh-Shevrin, E. Yuen, C. Friedlander, R.B. Hayes, J. Ahn, A taxonomic signature of obesity in a large study of American adults, Sci. Rep. 8 (1) (2018) 9749.
[76] C.L. Boulangé, A.L. Neves, J. Chilloux, J.K. Nicholson, M.E. Dumas, Impact of the gut microbiota on inflammation, obesity, and metabolic disease, Genome Med. 8 (1) (2016) 42.
[77] L.B. Thingholm, M.C. Rühlemann, M. Koch, B. Fuqua, G. Laucke, R. Boehm, C. Bang, E.A. Franzosa, M. Hübenthal, A. Rahnavard, F. Frost, J. Lloyd-Price, M. Schirmer, A.J. Lusis, C.D. Vulpe, M.M. Lerch, G. Homuth, T. Kacprowski, C. O. Schmidt, U. Nöthlings, T.H. Karlsen, W. Lieb, M. Laudes, A. Franke, C. Huttenhower, Obese individuals with and without type 2 diabetes show different gut microbial functional capacity and composition, Cell Host Microbe 26 (2) (2019) 252–264, e10.
[78] M. Million, M. Maraninchi, M. Henry, F. Armougom, H. Richet, P. Carrieri, R. Valero, D. Raccah, B. Vialettes, D. Raoult, Obesity-associated gut microbiota is enriched in Lactobacillus reuteri and depleted in Bifidobacterium animalis and Methanobrevibacter smithii, Int. J. Obes. 36 (6) (2012) 817–825.
[79] B. Wei, Y. Wang, S. Xiang, Y. Jiang, R. Chen, N. Hu, Alterations of gut microbiome in patients with type 2 diabetes mellitus who had undergone cholecystectomy, Am. J. Physiol. Endocrinol. Metab. 320 (1) (2021) E113–E121.
[80] K.M. Utzschneider, et al., Mechanisms linking the gut microbiome and glucose metabolism (vol. 101, pg 1445, 2016), J. Clin. Endocrinol. Metab. 101 (6) (2016) (p. 2622-2622).
[81] L. Brunkwall, M. Orho-Melander, The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities, Diabetologia 60 (6) (2017) 943–951.
[82] R. Lin, D. Li, Y. Xu, M. Wei, Q. Chen, Y. Deng, J. Wen, Chronic cereulide exposure causes intestinal inflammation and gut microbiota dysbiosis in mice, Environ. Pollut. 288 (2021), 117814.
[83] G. Li, C. Xie, S. Lu, R.G. Nichols, Y. Tian, L. Li, D. Patel, Y. Ma, C.N. Brocker, T. Yan, K.W. Krausz, R. Xiang, O. Gavrilova, A.D. Patterson, F.J. Gonzalez, Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota, Cell Metab. 26 (5) (2017) 801.
[84] D. Li, T. Gwag, S. Wang, Absence of CD47 maintains brown fat thermogenic capacity and protects mice from aging-related obesity and metabolic disorder, Biochem. Biophys. Res. Commun. 575 (2021) 14–19.
[85] G.B. Lim, Improved gut microbiota profile in individuals with obesity taking statins, Nat. Rev. Cardiol. 17 (7) (2020) 385.
[86] A. Cotillard, S.P. Kennedy, L.C. Kong, E. Prifti, N. Pons, E. Le Chatelier, M. Almeida, B. Quinquis, F. Levenez, N. Galleron, S. Gougis, S. Rizkalla, J. M. Batto, P. Renault, c. ANR MicroObes, J. Doré, J.D. Zucker, K. Clément, S. D. Ehrlich, Dietary intervention impact on gut microbial gene richness, Nature 500 (7464) (2013) 585–588.
[87] M.C. Collado, E. Isolauri, K. Laitinen, S. Salminen, Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women, Am. J. Clin. Nutr. 88 (4) (2008) 894–899.
[88] A. Santacruz, M.C. Collado, L. García-Valdés, M.T. Segura, J.A. Martín-Lagos, T. Anjos, M. Martí-Romero, R.M. Lopez, J. Florido, C. Campoy, Y. Sanz, Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women, Br. J. Nutr. 104 (1) (2010) 83–92.
[89] H. Zhang, J.K. DiBaise, A. Zuccolo, D. Kudrna, M. Braidotti, Y. Yu, P. Parameswaran, M.D. Crowell, R. Wing, B.E. Rittmann, R. Krajmalnik-Brown, Human gut microbiota in obesity and after gastric bypass, Proc. Natl. Acad. Sci. USA 106 (7) (2009) 2365–2370.
[90] F. Armougom, M. Henry, B. Vialettes, D. Raccah, D. Raoult, Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients, PLoS One 4 (9) (2009), e7125.
[91] M. Million, F. Thuny, E. Angelakis, J.P. Casalta, R. Giorgi, G. Habib, D. Raoult, Lactobacillus reuteri and Escherichia coli in the human gut microbiota may predict weight gain associated with vancomycin treatment, Nutr. Diabetes 3 (2013), e87.
[92] L. Bervoets, K. Van Hoorenbeeck, I. Kortleven, C. Van Noten, N. Hens, C. Vael, H. Goossens, K.N. Desager, V. Vankerckhoven, Differences in gut microbiota composition between obese and lean children: a cross-sectional study, Gut Pathog. 5 (1) (2013) 10.
[93] M.C. Collado, E. Isolauri, K. Laitinen, S. Salminen, Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy, Am. J. Clin. Nutr. 92 (5) (2010) 1023–1030.
[94] E. Munukka, P. Wiklund, S. Pekkala, E. Völgyi, L. Xu, S. Cheng, A. Lyytikäinen, V. Marjomäki, M. Alen, J. Vaahtovuo, S. Keinänen-Kiukaanniemi, S. Cheng, Women with and without metabolic disorder differ in their gut microbiota composition, Obesity 20 (5) (2012) 1082–1087.
[95] V. Martins dos Santos, M. Müller, W. de Vos, Systems biology of the gut: the interplay of food, microbiota and host at the mucosal interface, Curr. Opin. Biotechnol. 21 (4) (2010) 539–550.
[96] H. Tilg, A.R. Moschen, Microbiota and diabetes: an evolving relationship, Gut 63 (9) (2014) 1513–1521.
[97] P.V. Nerurkar, D. Orias, N. Soares, M. Kumar, V.R. Nerurkar, Momordica charantia (bitter melon) modulates adipose tissue inflammasome gene expression and adipose-gut inflammatory cross talk in high-fat diet (HFD)-fed mice, J. Nutr. Biochem. 68 (2019) 16–32.
[98] C. Graham, A. Mullen, K. Whelan, Obesity and the gastrointestinal microbiota: a review of associations and mechanisms, Nutr. Rev. 73 (6) (2015) 376–385.
[99] C. Rajani, W. Jia, Disruptions in gut microbial-host co-metabolism and the development of metabolic disorders, Clin. Sci. 132 (7) (2018) 791–811.
[100] A. Agus, K. Clement, H. Sokol, Gut microbiota-derived metabolites as central regulators in metabolic disorders, Gut 70 (6) (2021) 1174–1182.
[101] G. den Besten, K. van Eunen, A.K. Groen, K. Venema, D.J. Reijngoud, B.M. Bakker, The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism, J. Lipid Res. 54 (9) (2013) 2325–2340.
[102] V. Tremaroli, F. Bäckhed, Functional interactions between the gut microbiota and host metabolism, Nature 489 (7415) (2012) 242–249.
[103] D.J. Morrison, T. Preston, Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism, Gut Microbes 7 (3) (2016) 189–200.
[104] S. Rahat-Rozenbloom, J. Fernandes, G.B. Gloor, T.M.S. Wolever, Evidence for greater production of colonic short-chain fatty acids in overweight than lean humans, Int. J. Obes. 38 (12) (2014) 1525–1531.
[105] S. Murugesan, M. Ulloa-Martínez, H. Martínez-Rojano, F.M. Galván-Rodríguez, C. Miranda-Brito, M.C. Romano, A. Piña-Escobedo, M.L. Pizano-Zárate, C. Hoyo-Vadillo, J. García-Mena, Study of the diversity and short-chain fatty acids production by the bacterial community in overweight and obese Mexican children, Eur. J. Clin. Microbiol. Infect. Dis. 34 (7) (2015) 1337–1346.
[106] M.J. Khan, K. Gerasimidis, C.A. Edwards, M.G. Shaikh, Role of gut microbiota in the aetiology of obesity: proposed mechanisms and review of the literature, J. Obes. 2016 (2016), 7353642.
[107] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Bäckhed, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites, Cell 165 (6) (2016) 1332–1345.
[108] A. Adak, M.R. Khan, An insight into gut microbiota and its functionalities, Cell Mol. Life Sci. 76 (3) (2019) 473–493.
[109] A.W.C. Man, Y. Zhou, N. Xia, H. Li, Involvement of gut microbiota, microbial metabolites and interaction with polyphenol in host immunometabolism, Nutrients 12 (10) (2020) 3054.
[110] G. Tolhurst, H. Heffron, Y.S. Lam, H.E. Parker, A.M. Habib, E. Diakogiannaki, J. Cameron, J. Grosse, F. Reimann, F.M. Gribble, Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2, Diabetes 61 (2) (2012) 364–371.
[111] M. Priyadarshini, K.U. Kotlo, P.K. Dudeja, B.T. Layden, Role of short chain fatty acid receptors in intestinal physiology and pathophysiology, Compr. Physiol. 8 (3) (2018) 1091–1115.
[112] F. De Vadder, P. Kovatcheva-Datchary, D. Goncalves, J. Vinera, C. Zitoun, A. Duchampt, F. Bäckhed, G. Mithieux, Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits, Cell 156 (1–2) (2014) 84–96.
[113] S. Zhao, C. Jang, J. Liu, K. Uehara, M. Gilbert, L. Izzo, X. Zeng, S. Trefely, S. Fernandez, A. Carrer, K.D. Miller, Z.T. Schug, N.W. Snyder, T.P. Gade, P. M. Titchenell, J.D. Rabinowitz, K.E. Wellen, Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate, Nature 579 (7800) (2020) 586–591.
[114] T. Jensen, M.F. Abdelmalek, S. Sullivan, K.J. Nadeau, M. Green, C. Roncal, T. Nakagawa, M. Kuwabara, Y. Sato, D.H. Kang, D.R. Tolan, L.G. Sanchez-Lozada, H.R. Rosen, M.A. Lanaspa, A.M. Diehl, R.J. Johnson, Fructose and sugar: a major mediator of non-alcoholic fatty liver disease, J. Hepatol. 68 (5) (2018) 1063–1075.
[115] S.A. Hannou, D.E. Haslam, N.M. McKeown, M.A. Herman, Fructose metabolism and metabolic disease, J. Clin. Invest. 128 (2) (2018) 545–555.
[116] S. Softic, D.E. Cohen, C.R. Kahn, Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease, Dig. Dis. Sci. 61 (5) (2016) 1282–1293.
[117] J. Zou, B. Chassaing, V. Singh, M. Pellizzon, M. Ricci, M.D. Fythe, M.V. Kumar, A. T. Gewirtz, Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health, Cell Host Microbe 23 (1) (2018) 41–53, e4.
[118] D.N. Chagwedera, Q.Y. Ang, J.E. Bisanz, Y.A. Leong, K. Ganeshan, J. Cai, A. D. Patterson, P.J. Turnbaugh, A. Chawla, Nutrient sensing in CD11c cells alters the gut microbiota to regulate food intake and body mass, Cell Metab. 30 (2) (2019) 364–373, e7.
[119] B. Wang, X. Jiang, M. Cao, J. Ge, Q. Bao, L. Tang, Y. Chen, L. Li, Altered fecal microbiota correlates with liver biochemistry in nonobese patients with non-alcoholic fatty liver disease, Sci. Rep. 6 (2016) 32002.
[120] H.E. Da Silva, A. Teterina, E.M. Comelli, A. Taibi, B.M. Arendt, S.E. Fischer, W. Lou, J.P. Allard, Nonalcoholic fatty liver disease is associated with dysbiosis independent of body mass index and insulin resistance, Sci. Rep. 8 (2018) 1466.
[121] R. Sonowal, A. Swimm, A. Sahoo, L. Luo, Y. Matsunaga, Z. Wu, J.A. Bhingarde, E. A. Ejzak, A. Ranawade, H. Qadota, D.N. Powell, C.T. Capaldo, J.M. Flacker, R.

M. Jones, G.M. Benian, D. Kalman, Indoles from commensal bacteria extend healthspan, Proc. Natl. Acad. Sci. USA 114 (36) (2017) E7506–E7515.
[122] A. Lavelle, H. Sokol, Gut microbiota-derived metabolites as key actors in inflammatory bowel disease, Nat. Rev. Gastroenterol. Hepatol. 17 (4) (2020) 223–237.
[123] D. Weber, P.J. Oefner, A. Hiergeist, J. Koestler, A. Gessner, M. Weber, J. Hahn, D. Wolff, F. Stämmler, R. Spang, W. Herr, K. Dettmer, E. Holler, Low urinary indoxyl sulfate levels early after transplantation reflect a disrupted microbiome and are associated with poor outcome, Blood 126 (14) (2015) 1723–1728.
[124] J.R. Liu, H. Miao, D.Q. Deng, N.D. Vaziri, P. Li, Y.Y. Zhao, Gut microbiota-derived tryptophan metabolism mediates renal fibrosis by aryl hydrocarbon receptor signaling activation, Cell. Mol. Life Sci. 78 (3) (2021) 909–922.
[125] A. Lavelle, H. Sokol, Gut microbiota-derived metabolites as key actors in inflammatory bowel disease, Nat. Rev. Gastroenterol. Hepatol. 17 (4) (2020) 223–237.
[126] A. Agus, J. Planchais, H. Sokol, Gut microbiota regulation of tryptophan metabolism in health and disease, Cell Host Microbe 23 (6) (2018) 716–724.
[127] J.M. Natividad, A. Agus, J. Planchais, B. Lamas, A.C. Jarry, R. Martin, M. L. Michel, C. Chong-Nguyen, R. Roussel, M. Straube, S. Jegou, C. McQuitty, M. Le Gall, G. da Costa, E. Lecornet, C. Michaudel, M. Modoux, J. Glodt, C. Bridonneau, B. Sovran, L. Dupraz, A. Bado, M.L. Richard, P. Langella, B. Hansel, J.M. Launay, R.J. Xavier, H. Duboc, H. Sokol, Impaired Aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome, Cell Metab. 28 (5) (2018) 737–749 (e4).
[128] S. Taleb, Tryptophan dietary impacts gut barrier and metabolic diseases, Front. Immunol. 10 (2019) 2113.
[129] M. Beaumont, A.M. Neyrinck, M. Olivares, J. Rodriguez, A. de Rocca Serra, M. Roumain, L.B. Bindels, P.D. Cani, P. Evenepoel, G.G. Muccioli, J.B. Demoulin, N.M. Delzenne, The gut microbiota metabolite indole alleviates liver inflammation in mice, FASEB J. (2018), 201800544 p. fj201800544.
[130] N.H. Mallmann, E.S. Lima, P. Lalwani, Dysregulation of tryptophan catabolism in metabolic syndrome, Metab. Syndr. Relat. Disord. 16 (3) (2018) 135–142.
[131] B.J. Moyer, I.Y. Rojas, J.S. Kerley-Hamilton, H.F. Hazlett, K.V. Nemani, H. W. Trask, R.J. West, L.E. Lupien, A.J. Collins, C.S. Ringelberg, B. Gimi, W. B. Kinlaw, C.R. Tomlinson, Inhibition of the aryl hydrocarbon receptor prevents Western diet-induced obesity. Model for AHR activation by kynurenine via oxidized-LDL, TLR2/4, TGFbeta, and IDO1, Toxicol. Appl. Pharmacol. 300 (2016) 13–24.
[132] L. Laurans, N. Venteclef, Y. Haddad, M. Chajadine, F. Alzaid, S. Metghalchi, B. Sovran, R.G.P. Denis, J. Dairou, M. Cardellini, J.M. Moreno-Navarrete, M. Straub, S. Jegou, C. McQuitty, T. Viel, B. Esposito, B. Tavitian, J. Callebert, S. H. Luquet, M. Federici, J.M. Fernandez-Real, R. Burcelin, J.M. Launay, A. Tedgui, Z. Mallat, H. Sokol, S. Taleb, Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health, Nat. Med. 24 (8) (2018) 1113–1120.
[133] J.J. Liu, J. Movassat, B. Portha, Emerging role for kynurenines in metabolic pathologies, Curr. Opin. Clin. Nutr. Metab. Care 22 (1) (2019) 82–90.
[134] R.L. Young, A.L. Lumsden, D.J. Keating, Gut serotonin is a regulator of obesity and metabolism, Gastroenterology 149 (1) (2015) 253–255.
[135] J.D. Crane, R. Palanivel, E.P. Mottillo, A.L. Bujak, H. Wang, R.J. Ford, A. Collins, R.M. Blümer, M.D. Fullerton, J.M. Yabut, J.J. Kim, J.E. Ghia, S.M. Hamza, K. M. Morrison, J.D. Schertzer, J.R. Dyck, W.I. Khan, G.R. Steinberg, Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis, Nat. Med. 21 (2) (2015) 166–172.
[136] M. Fukui, M. Tanaka, H. Toda, M. Asano, M. Yamazaki, G. Hasegawa, S. Imai, N. Nakamura, High plasma 5-hydroxyindole-3-acetic acid concentrations in subjects with metabolic syndrome, Diabetes Care 35 (1) (2012) 163–167.
[137] T. Matsubara, F. Li, F.J. Gonzalez, FXR signaling in the enterohepatic system, Mol. Cell. Endocrinol. 368 (1–2) (2013) 17–29.
[138] E.R. McGlone, S.R. Bloom, Bile acids and the metabolic syndrome, Ann. Clin. Biochem. 56 (3) (2019) 326–337.
[139] C. Xie, W. Huang, R.L. Young, K.L. Jones, M. Horowitz, C.K. Rayner, T. Wu, Role of bile acids in the regulation of food intake, and their dysregulation in metabolic disease, Nutrients 13 (4) (2021).
[140] S. Lazarević, M. Đanić, S. Goločorbin-Kon, H. Al-Salami, M. Mikov, Semisynthetic bile acids: a new therapeutic option for metabolic syndrome, Pharmacol. Res. 146 (2019), 104333.
[141] S. Fiorucci, E. Distrutti, Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders, Trends Mol. Med. 21 (11) (2015) 702–714.
[142] S.A. Joyce, C.G. Gahan, Disease-associated changes in bile acid profiles and links to altered gut microbiota, Dig. Dis. 35 (3) (2017) 169–177.
[143] B.A. Neuschwander-Tetri, R. Loomba, A.J. Sanyal, J.E. Lavine, M.L. Van Natta, M. F. Abdelmalek, N. Chalasani, S. Dasarathy, A.M. Diehl, B. Hameed, K.V. Kowdley, A. McCullough, N. Terrault, J.M. Clark, J. Tonascia, E.M. Brunt, D.E. Kleiner, E. Doo, N. NASH Clinical Research, Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial, Lancet 385 (9972) (2015) 956–965.
[144] S.A. Harrison, M.E. Rinella, M.F. Abdelmalek, J.F. Trotter, A.H. Paredes, H. L. Arnold, M. Kugelmas, M.R. Bashir, M.J. Jaros, L. Ling, S.J. Rossi, A.M. DePaoli, R. Loomba, NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial, Lancet 391 (10126) (2018) 1174–1185.
[145] H. Duboc, Y. Tache, A.F. Hofmann, The bile acid TGR5 membrane receptor: from basic research to clinical application, Dig. Liver Dis. 46 (4) (2014) 302–312.
[146] T. Fu, S. Coulter, E. Yoshihara, T.G. Oh, S. Fang, F. Cayabyab, Q. Zhu, T. Zhang, M. Leblanc, S. Liu, M. He, W. Waizenegger, E. Gasser, B. Schnabl, A.R. Atkins, R. T. Yu, R. Knight, C. Liddle, M. Downes, R.M. Evans, FXR regulates intestinal cancer stem cell proliferation, Cell 176 (5) (2019) 1098–1112, e18.
[147] L. Sun, Y. Pang, X. Wang, Q. Wu, H. Liu, B. Liu, G. Liu, M. Ye, W. Kong, C. Jiang, Ablation of gut microbiota alleviates obesity-induced hepatic steatosis and glucose intolerance by modulating bile acid metabolism in hamsters, Acta Pharm. Sin. B 9 (4) (2019) 702–710.
[148] M.S. Trabelsi, M. Daoudi, J. Prawitt, S. Ducastel, V. Touche, S.I. Sayin, A. Perino, C.A. Brighton, Y. Sebti, J. Kluza, O. Briand, H. Dehondt, E. Vallez, E. Dorchies, G. Baud, V. Spinelli, N. Hennuyer, S. Caron, K. Bantubungi, R. Caiazzo, F. Reimann, P. Marchetti, P. Lefebvre, F. Bäckhed, F.M. Gribble, K. Schoonjans, F. Pattou, A. Tailleux, B. Staels, S. Lestavel, Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells, Nat. Commun. 6 (2015) 7629.
[149] Y. Pi, C. Mu, K. Gao, Z. Liu, Y. Peng, W. Zhu, Increasing the hindgut carbohydrate/protein ratio by cecal infusion of corn starch or casein hydrolysate drives gut microbiota-related bile acid metabolism to stimulate colonic barrier function, mSystems 5 (3) (2020).
[150] L. Wang, B. Ren, Q. Zhang, C. Chu, Z. Zhao, J. Wu, W. Zhao, Z. Liu, X. Liu, Methionine restriction alleviates high-fat diet-induced obesity: involvement of diurnal metabolism of lipids and bile acids, Biochim. Biophys. Acta Mol. Basis Dis. 1866 (11) (2020), 165908.
[151] L.A. Rubio, I. Aranda-Olmedo, M. Martin-Pedrosa, Inclusion of limited amounts of extruded legumes plus cereal mixes in normocaloric or obesogenic diets for rats: effects on lipid profile, Foods 9 (6) (2020).
[152] Z.R. Huang, J.C. Deng, Q.Y. Li, Y.J. Cao, Y.C. Lin, W.D. Bai, B. Liu, P.F. Rao, L. Ni, X.C. Lv, Protective mechanism of common buckwheat (Fagopyrum esculentum Moench.) against nonalcoholic fatty liver disease associated with dyslipidemia in mice fed a high-fat and high-cholesterol diet, J. Agric. Food Chem. 68 (24) (2020) 6530–6543.
[153] Z.R. Huang, J.C. Deng, Q.Y. Li, Y.J. Cao, Y.C. Lin, W.D. Bai, B. Liu, P.F. Rao, L. Ni, X.C. Lv, Protective mechanism of common buckwheat (Fagopyrum esculentum Moench.) against nonalcoholic fatty liver disease associated with dyslipidemia in mice fed a high-fat and high-cholesterol diet, J. Agric. Food Chem. 68 (24) (2020) 6530–6543.
[154] P.A. Godoy, O. Ramirez-Molina, J. Fuentealba, Exploring the role of P2X receptors in Alzheimer's disease, Front. Pharmacol. 10 (2019) 1330.
[155] L. Antonioli, M. Fornai, C. Blandizzi, P. Pacher, G. Haskó, Adenosine signaling and the immune system: when a lot could be too much, Immunol. Lett. 205 (2019) 9–15.
[156] H. Yu, Z. Guo, S. Shen, W. Shan, Effects of taurine on gut microbiota and metabolism in mice, Amino Acids 48 (7) (2016) 1601–1617.
[157] H. Fang, F. Meng, F. Piao, B. Jin, M. Li, W. Li, Effect of taurine on intestinal microbiota and immune cells in Peyer's patches of immunosuppressive mice, Adv. Exp. Med. Biol. 1155 (2019) 13–24.
[158] J.R. Yaron, S. Gangaraju, M.Y. Rao, X. Kong, L. Zhang, F. Su, Y. Tian, H.L. Glenn, D.R. Meldrum, K(+) regulates Ca(2+) to drive inflammasome signaling: dynamic visualization of ion flux in live cells, Cell Death Dis. 6 (2015), e1954.
[159] !!! INVALID CITATION !!!
[160] J.L. Round, S.M. Lee, J. Li, G. Tran, B. Jabri, T.A. Chatila, S.K. Mazmanian, The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota, Science 332 (6032) (2011) 974–977.
[161] A. Beam, E. Clinger, L. Hao, Effect of diet and dietary components on the composition of the gut microbiota, Nutrients 13 (8) (2021) 2795.
[162] K.E. Bouter, D.H. van Raalte, A.K. Groen, M. Nieuwdorp, Role of the gut microbiome in the pathogenesis of obesity and obesity-related metabolic dysfunction, Gastroenterology 152 (7) (2017) 1671–1678.
[163] L.H.S. Lau, S.H. Wong, Microbiota, obesity and NAFLD, Adv. Exp. Med. Biol. 1061 (2018) 111–125.
[164] A. Pascale, N. Marchesi, C. Marelli, A. Coppola, L. Luzi, S. Govoni, A. Giustina, C. Gazzaruso, Microbiota and metabolic diseases, Endocrine 61 (3) (2018) 357–371.
[165] L. Crovesy, M. Ostrowski, D.M.T.P. Ferreira, E.L. Rosado, M. Soares-Mota, Effect of Lactobacillus on body weight and body fat in overweight subjects: a systematic review of randomized controlled clinical trials, Int. J. Obes. 41 (11) (2017) 1607–1614.
[166] X. Gao, Y. Zhu, Y. Wen, G. Liu, C. Wan, Efficacy of probiotics in non-alcoholic fatty liver disease in adult and children: a meta-analysis of randomized controlled trials, Hepatol. Res. 46 (12) (2016) 1226–1233.
[167] Y. Fan, O. Pedersen, Gut microbiota in human metabolic health and disease, Nat. Rev. Microbiol. 19 (1) (2021) 55–71.
[168] C. Bressa, M. Bailén-Andrino, J. Pérez-Santiago, R. González-Soltero, M. Pérez, M. G. Montalvo-Lominchar, J.L. Maté-Muñoz, R. Domínguez, D. Moreno, M. Larrosa, Differences in gut microbiota profile between women with active lifestyle and sedentary women, PLoS One 12 (2) (2017), e0171352.
[169] P. de Groot, T. Scheithauer, G.J. Bakker, A. Prodan, E. Levin, M.T. Khan, H. Herrema, M. Ackermans, M.J.M. Serlie, M. de Brauw, J.H.M. Levels, A. Sales, V.E. Gerdes, M. Ståhlman, A.W.M. Schimmel, G. Dallinga-Thie, J.J. Bergman, F. Holleman, J.B.L. Hoekstra, A. Groen, F. Bäckhed, M. Nieuwdorp, Donor metabolic characteristics drive effects of faecal microbiota transplantation on recipient insulin sensitivity, energy expenditure and intestinal transit time, Gut 69 (3) (2020) 502–512 (502-+).
[170] H.Y. Li, D.D. Zhou, R.Y. Gan, S.Y. Huang, C.N. Zhao, A. Shang, X.Y. Xu, H.B. Li, Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on

metabolic diseases targeting gut microbiota: a narrative review, Nutrients 13 (9) (2021) 3211.
[171] S. Khanna, S. Walia, K.K. Kondepudi, G. Shukla, Administration of indigenous probiotics modulate high-fat diet-induced metabolic syndrome in Sprague Dawley rats, Antonie Van Leeuwenhoek 113 (9) (2020) 1345–1359.
[172] T. Cerdó, J.A. García-Santos, M. G Bermúdez, C. Campoy, The role of probiotics and prebiotics in the prevention and treatment of obesity, Nutrients 11 (3) (2019).
[173] R. Luoto, M. Kalliomäki, K. Laitinen, E. Isolauri, The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years, Int. J. Obes. 34 (10) (2010) 1531–1537.
[174] P. Gerard, Gut microbiota and obesity, Cell. Mol. Life Sci. 73 (1) (2016) 147–162.
[175] Y. Kadooka, M. Sato, K. Imaizumi, A. Ogawa, K. Ikuyama, Y. Akai, M. Okano, M. Kagoshima, T. Tsuchida, Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial, Eur. J. Clin. Nutr. 64 (6) (2010) 636–643.
[176] S.P. Jung, K.M. Lee, J.H. Kang, S.I. Yun, H.O. Park, Y. Moon, J.Y. Kim, Effect of Lactobacillus gasseri BNR17 on overweight and obese adults: a randomized, double-blind clinical trial, Korean J. Fam. Med. 34 (2) (2013) 80–89.
[177] J. Sanchis-Chordà, E. Del Pulgar, J. Carrasco-Luna, A. Benítez-Páez, Y. Sanz, P. Codoñer-Franch, Bifidobacterium pseudocatenulatum CECT 7765 supplementation improves inflammatory status in insulin-resistant obese children, Eur. J. Nutr. 58 (7) (2019) 2789–2800.
[178] L. Abenavoli, E. Scarpellini, C. Colica, L. Boccuto, B. Salehi, J. Sharifi-Rad, V. Aiello, B. Romano, A. De Lorenzo, A.A. Izzo, R. Capasso, Gut microbiota and obesity: a role for probiotics, Nutrients 11 (11) (2019).
[179] H.S. Ejtahed, J. Mohtadi-Nia, A. Homayouni-Rad, M. Niafar, M. Asghari-Jafarabadi, V. Mofid, Probiotic yogurt improves antioxidant status in type 2 diabetic patients, Nutrition 28 (5) (2012) 539–543.
[180] E.F. Murphy, P.D. Cotter, A. Hogan, O. O'Sullivan, A. Joyce, F. Fouhy, S.F. Clarke, T.M. Marques, P.W. O'Toole, C. Stanton, E.M. Quigley, C. Daly, P.R. Ross, R. M. O'Doherty, F. Shanahan, Divergent metabolic outcomes arising from targeted manipulation of the gut microbiota in diet-induced obesity, Gut 62 (2) (2013) 220–226.
[181] A. Vrieze, C. Out, S. Fuentes, L. Jonker, I. Reuling, R.S. Kootte, E. van Nood, F. Holleman, M. Knaapen, J.A. Romijn, M.R. Soeters, E.E. Blaak, G.M. Dallinga-Thie, D. Reijnders, M.T. Ackermans, M.J. Serlie, F.K. Knop, J.J. Holst, C. van der Ley, I.P. Kema, E.G. Zoetendal, W.M. de Vos, J.B. Hoekstra, E.S. Stroes, A. K. Groen, M. Nieuwdorp, Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity, J. Hepatol. 60 (4) (2014) 824–831.
[182] A. Everard, V. Lazarevic, M. Derrien, M. Girard, G.G. Muccioli, A.M. Neyrinck, S. Possemiers, A. Van Holle, P. François, W.M. de Vos, N.M. Delzenne, J. Schrenzel, P.D. Cani, Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice, Diabetes 60 (11) (2011) 2775–2786.
[183] C.P. Moran, F. Shanahan, Gut microbiota and obesity: Role in aetiology and potential therapeutic target, Best Pract. Res. Clin. Gastroenterol. 28 (4) (2014) 585–597.
[184] J. Jansma, F. Brinkman, S. van Hemert, S. El Aidy, Targeting the endocannabinoid system with microbial interventions to improve gut integrity, Prog. Neuropsychopharmacol. Biol. Psychiatry 106 (2021), 110169.
[185] J.A. Parnell, R.A. Reimer, Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults, Am. J. Clin. Nutr. 89 (6) (2009) 1751–1759.
[186] P.J. Turnbaugh, R.E. Ley, M.A. Mahowald, V. Magrini, E.R. Mardis, J.I. Gordon, An obesity-associated gut microbiome with increased capacity for energy harvest, Nature 444 (7122) (2006) 1027–1031.
[187] A. Vrieze, E. Van Nood, F. Holleman, Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome (vol. 143, pg 913, 2012), Gastroenterology 144 (1) (2013) (p. 250-250).