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Review

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Interplay between gut microbiota and intestinal lipid metabolism: mechanisms and implications

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Abstract: The gut microbiota is an indispensable symbiotic entity within the human holobiont, serving as a critical regulator of host lipid metabolism homeostasis. Therefore, it has emerged as a central subject of research in the pathophysiology of metabolic disorders. This microbial consortium orchestrates key aspects of host lipid dynamics—including absorption, metabolism, and storage—through multifaceted mechanisms such as the enzymatic processing of dietary polysaccharides, the facilitation of long-chain fatty acid uptake by intestinal epithelial cells (IECs), and the bidirectional modulation of adipose tissue functionality. Mounting evidence underscores that gut microbiota-derived metabolites not only directly mediate canonical lipid metabolic pathways but also interface with host immune pathways, epigenetic machinery, and circadian regulatory systems, thereby establishing an intricate crosstalk that coordinates systemic metabolic outputs. Perturbations in microbial composition (dysbiosis) drive pathological disruptions to lipid homeostasis, serving as a pathogenic driver for conditions such as obesity, hyperlipidemia, and non-alcoholic fatty liver disease (NAFLD). This review systematically examines the emerging mechanistic insights into the gut microbiota-mediated regulation of intestinal lipid metabolism, while it elucidates its translational implications for understanding metabolic disease pathogenesis and developing targeted therapies.

Key words: Gut microbiota; Lipid absorption; Metabolic disease

1 Introduction

Lipid metabolism disorders, encompassing obesity, hyperlipidemia, and non-alcoholic fatty liver disease (NAFLD), represent a growing global health burden, exacerbated by modern dietary patterns, sedentary lifestyles, and environmental stressors (Fan and Pedersen, 2021). These pathologies arise from dysregulated lipid absorption, storage, and utilization, driven by multifactorial inputs such as chronic exposure to hypercaloric diets (Abumrad et al., 2021; Korbelius et al., 2023), circadian misalignment, endocrine dysregulation, and pharmacological interventions (Thingholm et al., 2019; Jin et al., 2023). While traditional paradigms have targeted host-centric determinants, recent advances in multi-omics technologies, including microbiomics and metabolomics, have unveiled the gut microbiota as a pivotal orchestrator of lipid homeostasis.

At present, compelling clinical and preclinical evidence positions gut microbial dysbiosis as a key etiological factor in lipid metabolism disorders (Schoeler and Caesar, 2019; Brown et al., 2023; Xu et al., 2023). The gut microbiota interconnects with host physiology through pleiotropic mechanisms: metabolizing indigestible dietary substrates, modulating intestinal lipid uptake via epithelial transporters, and secreting bioactive metabolites (e.g., short-chain fatty acids (SCFAs), bile acids, and lipopolysaccharides) that systemically influence hepatic lipogenesis, adipocyte differentiation, and energy expenditure (Qin et al., 2014; Korem et al., 2015; Min et al., 2024). Furthermore, emerging research underscores the crosstalk between gut microbiota and host immune responses, epigenetic regulators, and circadian clocks, forming an integrated axis that fine-tunes metabolic flux (Younossi et al., 2016;

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Rothschild et al., 2018). Despite these advances, the molecular pathways linking microbial composition and function to lipid absorption and storage remain incompletely understood. Elucidating these mechanisms is critical for translating microbiota–host interactions into therapeutic modalities, whether through dietary interventions, probiotics, or targeted pharmacological strategies. This review synthesizes the current knowledge on the role of gut microbiota in intestinal lipid metabolism, with a focus on mechanistic insights that bridge microbial ecology to host pathophysiology.

2 Overview of the influence of gut microbiota on lipid metabolism

The gut microbiota, a dynamic ecosystem comprising bacteria, archaea, fungi, and viruses, is increasingly recognized as a functional "second genome" integral to human physiology (Zhu et al., 2010; Guo et al., 2025; Vieujean et al., 2025). This microbial consortium engages in symbiotic interactions with the host, mediating critical processes such as the catabolism of indigestible dietary substrates, the biosynthesis of vitamins (e.g., vitamins K and B12), the maturation of the immune system, and the competitive exclusion of enteric pathogens (Hooper et al., 2002, 2012; Wang et al., 2017; Kuang et al., 2019). Besides, it regulates intestinal epithelial cell proliferation (Duan et al., 2023; Wu et al., 2024a, 2024b), fortifies mucosal barrier integrity, and modulates systemic neuroendocrine signaling, thereby influencing both metabolic and neuropsychiatric health (Wang and Hooper, 2019; Wang YH et al., 2023).

The role of microbiota in lipid metabolism emerged as a significant research frontier in the early 21st century. Initial studies focused on dietary modulation of microbial composition, while subsequent advances in gnotobiotic models and multi-omics technologies elucidated the presence of a bidirectional crosstalk between microbial metabolites and host lipid regulatory pathways (Bäckhed et al., 2004; Turnbaugh et al., 2006). Seminal work by Gordon and colleagues demonstrated that germ-free mice exhibited reduced adiposity and resistance to diet-induced obesity despite hyperphagia, underscoring the role of microbiota in energy harvesting and storage (Hooper and Gordon, 2001; Bäckhed et al., 2004). The colonization of germ-free mice with a conventional specific pathogen-free (SPF) microbiota restored adiposity within 14 d, concomitant with increased monosaccharide uptake and de novo lipogenesis in the liver (Wang et al., 2017; Yadav et al., 2023; Gray et al., 2024). Strikingly, germ-free mice colonized with microbiota from obese donors developed excess adiposity even under normocaloric conditions, confirming the microbial regulation of host energy partitioning (Turnbaugh et al., 2006; Everard et al., 2013). These findings position the gut microbiota as a central node in the host's lipid metabolic network, integrating dietary, immune, and circadian inputs to modulate energy balance.

3 Gut microbiota reprograms gene expression involved in intestinal lipid metabolism

The intestinal epithelium serves as the primary pathway for lipids from food to enter the human body. In the small intestine, bile acids and pancreatic lipases, along with other digestive enzymes, break down dietary lipids into monoglycerides and fatty acids. These processed lipids are then packaged into chylomicrons within intestinal epithelial cells (IECs) for further transport. The resulting fatty acids and monoglycerides are absorbed by cells through the brush border membrane of the small IECs (Wang YH et al., 2023). This process involves several transport proteins, such as the transmembrane fatty acid transporter cluster of differentiation 36 (CD36) and the fatty acid-binding protein 4 (FABP4), which facilitate lipid crossing of the cell membrane before entering the circulatory system, where they are subsequently captured and utilized by the liver and adipose tissues (Wang YH et al., 2023). Therefore, the efficiency of lipid absorption by IECs is a key determinant of lipid metabolism in the body, and the gut microbiota plays a crucial role in regulating this process. Using germ-free mice as the primary animal model, at least four distinct pathways of intestinal lipid absorption regulation mediated by the gut microbiota have been identified (Fig. 1).

3.1 NFIL3 pathway

The association between the transcription factor nuclear factor interleukin-3-regulated (NFIL3) and intestinal lipid absorption was first identified through the transcriptomic analysis of IECs from germ-free

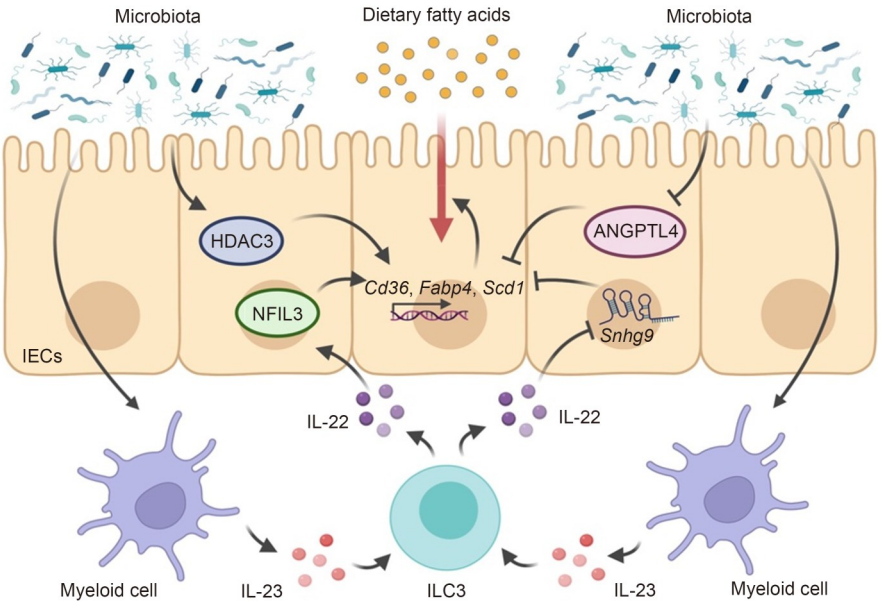

Fig. 1 Gut microbiota reprograms gene expression involved in intestinal lipid metabolism. ANGPTL4: angiopoietin-like 4; *Cd36*: cluster of differentiation 36; *Fabp4*: fatty acid-binding protein 4; HDAC3: histone deacetylase 3; IECs: intestinal epithelial cells; IL: interleukin; ILC3: type 3 innate lymphoid cell; NFIL3: nuclear factor interleukin-3-regulated; *Scd1*: stearoyl-CoA desaturase-1; *Snhg9*: small nucleolar RNA host gene 9. Created with BioRender.com.

mice (Wang et al., 2017), wherein *Nfil3* gene expression was significantly reduced. Studies using *Nfil3* IEC-specific knockout mice ($Nfil3^{\Delta IEC}$) revealed that the loss of *Nfil3* impairs lipid absorption in IECs, leading to decreased metabolic levels and resistance to high-fat diet-induced obesity, with a phenotype resembling germ-free mice. Mechanistic studies demonstrated that NFIL3 regulates lipid absorption by activating proteins involved in lipid transport, processing, and packaging, including CD36, FABP4, lipoprotein lipase (LPL), and stearoyl-CoA desaturase-1 (SCD1), all critical for IEC lipid metabolism (Wang et al., 2017). Interestingly, *Nfil3* expression is regulated by both the gut microbiota and the circadian rhythm: in the mouse intestine, it decreases during the day and increases at night. While microbiota depletion significantly reduces *Nfil3* expression, its circadian rhythm persists (Wang et al., 2017; Kuang et al., 2019). The regulation of *Nfil3* involves the core clock component nuclear receptor subfamily 1 group D member 1 (NR1D1, also known as REV-ERBα), which governs rhythmic expression and mediates amplitude regulation by the gut microbiota. Under germ-free conditions, REV-ERBα rhythmically suppresses *Nfil3* transcription (Wang et al., 2017). Microbial colonization activates dendritic cells (DCs) via lipopolysaccharide (LPS) or flagellin, triggering Toll-like receptor (TLR)-myeloid differentiation primary response 88 (MyD88) signaling that induces interleukin-23 (IL-23) secretion, which stimulates type 3 innate lymphoid cell (ILC3) to release IL-22. IL-22 signaling phosphorylates signal transducer and activator of transcription 3 (STAT3), promoting its nuclear translocation to inhibit *Rev-Erba* transcription, thereby reducing *Nfil3* expression and lipid absorption efficiency (Wang et al., 2017). This multi-level regulatory network, termed the "microbiota-immune-clock-metabolism" axis, reveals how microbiota metabolites fine-tune the epithelial biological clock via the ILC3-STAT3 module, while REV-ERBα and NFIL3 form a reverse regulatory axis, determining the spatiotemporal expression of lipid metabolism pathways. Thus, NFIL3 is a central link between the gut microbiota, circadian rhythm, and lipid metabolism, playing a pivotal role in lipid absorption regulation.

3.2 HDAC3 pathway

The expression and activation of histone deacetylase 3 (HDAC3) are bidirectionally regulated by the biological clock and intestinal microbiota (Kuang et al., 2019), with HDAC3 mediating the rhythmic expression

of genes involved in lipid transport and metabolism. The specific knockout of *Hdac3* in the mouse intestinal epithelium (*Hdac3*$^{\Delta IEC}$) significantly reduced lipid absorption efficiency (Dávalos-Salas et al., 2019). Mechanistically, HDAC3 regulates lipid metabolism via two pathways: (1) as a histone deacetylase, it represses genes like carnitine palmitoyltransferase 1A (*Cpt1a*), *Cpt1b*, apolipoprotein B (*Apob*), and peroxisome proliferator-activated receptor α (*Ppara*) by deacetylating associated histones (Li XX et al., 2020; Wu et al., 2020), and (2) it activates estrogen-related receptor α (ERRα) by deacetylating peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1-α), inducing *Cd36* expression to enhance lipid uptake (Wu et al., 2020; Ng et al., 2023; Eshleman et al., 2024). The gut microbiota is essential for HDAC3 expression and rhythmic activation. In germ-free mice, HDAC3 levels and activity were significantly lower and lacked rhythmicity, whereas SPF mice exhibited higher HDAC3 expression and clear rhythmic activity, aligning with their nocturnal foraging behavior (Kuang et al., 2019). Research suggests that certain *Bacteroides* species may induce HDAC3 via inositol trisphosphate (IP3) secretion. While NFIL3 links circadian and immune pathways to lipid uptake and gut microbiota rhythms influence HDAC3 activity, the precise mechanism of microbiota–clock synergy in HDAC3 regulation remains unclear. The above findings highlight the central role of microbiota in synchronizing HDAC3 activity with host metabolic functions.

3.3 *Snhg9* pathway

Long non-coding RNA (lncRNA) small nucleolar RNA host gene 9 (*Snhg9*), initially investigated for its role in tumorigenesis, has recently emerged as a key regulator of host lipid metabolism. *Snhg9* expression is significantly elevated in the IECs of germ-free mice compared to conventionally raised mice, indicating that the intestinal microbiota suppresses *Snhg9* transcription (Wang YH et al., 2023). Intestinal epithelial-specific *Snhg9*-knockin mice exhibited reduced obesity rates, improved glucose tolerance, decreased insulin resistance, and lower lipid accumulation under a high-fat diet, highlighting the protective role of *Snhg9* against metabolic dysfunction. Mechanistically, *Snhg9* binds to the cell cycle and apoptosis regulatory protein 2 (CCAR2), displacing it from the deacetylase Sirtuin 1 (SIRT1). This releases SIRT1, which deacetylates and represses the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), a transcriptional activator of lipid uptake genes such as *Cd36*, *Fabp4*, and *Scd1*, thereby reducing intestinal lipid absorption (Wang YH et al., 2023). The suppression of *Snhg9* by the intestinal microbiota is mediated by an immune signaling cascade. Specifically, microbial ligands first activate myeloid cells via TLR-MyD88 signaling, inducing the secretion of IL-23. IL-23 then stimulates ILC3 to produce IL-22, which engages STAT3 signaling in IECs to inhibit *Snhg9* expression (Wang YH et al., 2023). This microbiota-ILC3-STAT3-*Snhg9* axis establishes a critical link between microbial signals and host lipid metabolism, offering a potential therapeutic avenue for obesity involving probiotic strategies aimed at activating *Snhg9*.

3.4 ANGPTL4 pathway

Angiopoietin-like 4 (*Angptl4*) was among the first genes identified to be significantly upregulated in IECs of germ-free mice. Studies using *Angptl4*-knockout mice (*Angptl4*$^{-/-}$) revealed that, despite unchanged food intake, these mice exhibited increased body weight, body fat percentage, and intestinal lipid absorption efficiency compared to wild-type mice (Bäckhed et al., 2007a, 2007b). When maintained under sterile conditions and fed a high-fat diet, *Angptl4*$^{-/-}$ mice rapidly developed obesity, fatty liver, and insulin resistance, underscoring the role of ANGPTL4 as an endogenous lipase inhibitor that regulates lipid catabolism and repackaging (Bäckhed et al., 2007a, 2007b). Further research demonstrated that specific gut microbes, such as *Lactobacillus* and *Bacteroides*, enhance ANGPTL4 expression in IECs through metabolites like butyrate, which activates PPARγ (Carey and Montag, 2021). The colonization of germ-free mice with butyrate-producing bacteria, such as *Clostridium tyrobutyricum*, significantly increased ileal and colonic ANGPTL4 levels (Carey and Montag, 2021). Clinically, probiotics like *Lactobacillus paracasei* F19 activate the PPARα/γ pathway, inducing ANGPTL4 transcription, while acetate produced by *Bacteroides thetaiotaomicron* suppresses its expression (Aronsson et al., 2010). These findings highlight the intricate interplay between ANGPTL4, gut microbiota, and their metabolites, involving mechanisms such as SCFA regulation, bacterial influences, and bile acid metabolism. This exemplifies

the complexity of the gut microbial–host regulatory network involved in lipid metabolism.

4 Effects of metabolites produced by gut microbiota on intestinal lipid metabolism

Gut microbial metabolites are bioactive compounds produced by the intestinal microbiota during metabolism, which primarily include SCFAs, secondary bile acids, aromatic compounds, and tryptophan metabolites. These metabolites exert diverse effects on host metabolic health (Fig. 2) (Agus et al., 2021; Ahmed et al., 2022; Su et al., 2022; Wang JJ et al., 2023).

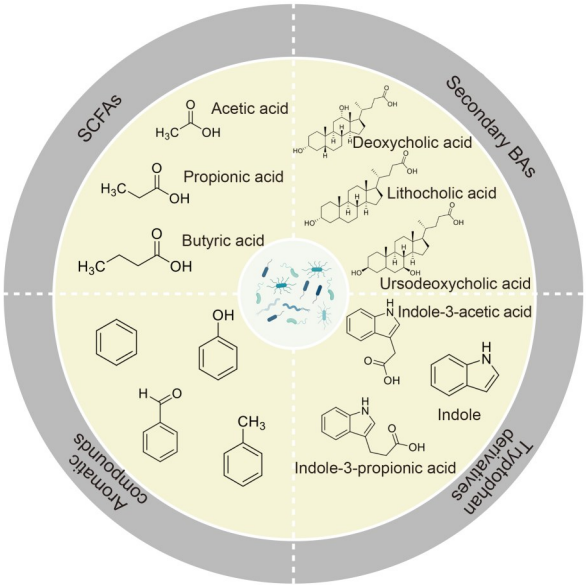

Fig. 2 Major types of microbial metabolites regulating host lipid metabolism. SCFAs: short-chain fatty acids; BAs: bile acids.

SCFAs, such as acetic acid, propionic acid, and butyric acid, are the major metabolites generated by gut microbes through the fermentation of dietary fibers and undigested carbohydrates (Frampton et al., 2020; Nogal et al., 2021; Wang ZN et al., 2023; Yin et al., 2023; Zhang et al., 2023). SCFAs have been widely studied since their discovery in the gut, with the recent finding of being an important link in the metabolic connection between the gut flora and the host. SCFAs are found at high concentrations in the cecum and proximal colon, where they not only are used as energy sources in colonocytes (especially butyrate) but can also be transported to the peripheral circulation via the portal vein to act on the liver and peripheral tissues (Makki et al., 2018). SCFAs can promote fatty acid synthesis and lipid storage by activating signaling pathways, including adenosine monophosphate-activated protein kinase (AMPK), PPARα, and sterol regulatory element-binding protein-1 (SREBP-1), via the activation of G protein-coupled receptor 41 (GPR41) and GPR43 receptors (Agus et al., 2021). SCFAs also influence lipid absorption indirectly by regulating intestinal barrier function and improving the intestinal environment. Some studies have also suggested that SCFAs can modulate energy intake in the brain, thereby affecting appetite via the activation of specific receptors (Ahmed et al., 2022). In this way, SCFAs not only influence lipid metabolism through GPR41 and GPR43 receptors but also modulate the gut barrier function, enhancing the integrity of the intestinal epithelium and thus playing a crucial role in overall metabolic health.

In addition to SCFAs, other dietary fiber fermentation products, such as lactate and succinate, which were traditionally viewed as metabolic intermediates, are now recognized as important signaling molecules influencing host physiology. Lactate acts as an active signaling molecule in the gut, regulating adipocyte function and metabolism while reducing pro-inflammatory responses in adipose tissue and immune cells through both GPR81-dependent and -independent mechanisms (Li et al., 2022; Deehan et al., 2024). This suggests that enhancing lactate production via dietary fiber could offer novel therapeutic strategies for obesity and metabolic disorders. Similarly, succinate, beyond its role in the tricarboxylic acid (TCA) cycle, binds to succinate receptor 1 (SUCNR1, also known as GPR91) on adipocytes and immune cells, exerting anti-lipolytic effects and promoting thermogenesis (Depommier et al., 2021; Li et al., 2022; Deehan et al., 2024). Dietary modulation can selectively boost these metabolites: fructooligosaccharide (FOS) and galactose enrich *Lacrobacillus* and *Bifidobacterium*, increasing lactate and acetate, while resistant starch, xylan, and inulin support acetate and propionate production via cross-feeding by bacteria like *Bacteroides* and *Veillonella*. Furthermore, fiber supplementation promotes next-generation probiotics such as *Akkermansia muciniphila* and *Anaerobutyricum soehngenii*, showing promise in improving metabolic health in individuals with obesity

and metabolic syndrome (Gilijamse et al., 2020; Depommier et al., 2021; Deehan et al., 2024). These findings underscore the therapeutic potential of targeting gut-derived metabolites via precision dietary interventions.

Beyond SCFAs and related intermediates, secondary bile acids, the second major class of microbial metabolites, are synthesized from cholesterol in the liver and are involved in lipid digestion and absorption in the intestine. Gut microorganisms regulate lipid uptake by altering bile acid composition and metabolic pathways. Many intestinal bacteria, particularly *Bifidobacterium* and *Lactobacillus*, can modify bile acid structures by dehydroxylation reactions, producing secondary bile acids such as deoxycholic acid (Honda et al., 2020; Zhao et al., 2023; Fuchs et al., 2025). Secondary bile acids exhibit distinct biological activities that may either enhance or inhibit host lipid metabolism. They act through the activation of farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5 (TGR5), and small heterodimer partner (SHP). FXR regulates bile acid synthesis and inhibits the conversion of cholesterol into bile acids via a negative feedback mechanism. TGR5, expressed in IECs and immune cells (Huang et al., 2019; Jia et al., 2021), primarily promotes intestinal fatty acid oxidation and metabolism via the activation of the AMPK and cyclic adenosine monophosphate (cAMP) signaling pathways. TGR5 is also involved in adipocyte differentiation and fat storage. SHP proteins, through their interactions with FXR (Li et al., 2025), collectively influence bile acid synthesis and cholesterol metabolism, thereby regulating intestinal lipid synthesis and storage.

Aromatic compounds, derived primarily from dietary polyphenols, are metabolized by gut microbes into phenolic acids and flavonoids. These compounds possess potent antioxidant properties and can mitigate oxidative stress induced by fat accumulation during lipid metabolism. Mechanistically, aromatic compounds regulate fatty acid metabolism, adipocyte differentiation, and fat storage by activating transcription factors such as PPARγ and SIRT1 (Dodd et al., 2017; Arnoriaga-Rodríguez et al., 2020). Their antioxidant effects are mediated through the activation of nuclear factor E2-related factor 2 (*Nrf2*), an important transcription factor that regulates the expression of antioxidant genes and alleviates oxidative stress by enhancing the activity of antioxidant enzymes. Furthermore, certain aromatic compounds, such as ellagic acid, can indirectly influence lipid absorption by modulating the diversity of intestinal microbiota, promoting the growth of beneficial bacteria like *Bifidobacteria* and *Lactobacillus*, as well as improving intestinal barrier function (Liu et al., 2020; Li et al., 2023; Stähli et al., 2023).

Recent research has increasingly focused on tryptophan and its metabolites, which are produced primarily by *Bacteroidetes* and *Bifidobacteria* in the gut. These microbes convert tryptophan into metabolites such as indole, indole-3-acetic acid (IAA), and indole-3-propionic acid (Zhao et al., 2018; Agus et al., 2021; Lu et al., 2023). Unlike SCFAs, indoles primarily regulate immune responses and maintain intestinal microbiota homeostasis. Meanwhile, some studies have suggested that indole compounds can influence host lipid metabolism by reducing fatty acid synthesis through the regulation of fatty acid synthase (FASN) and SCD1 expression via aryl hydrocarbon receptor (AHR).

Although gut microbial metabolites have profound effects on host lipid metabolism, the interaction between gut microbiota and the host is bidirectional; gut microbes not only influence host lipid metabolism via metabolites but are also shaped by the host's metabolic state and immune status. Besides, the composition of the gut microbiota varies significantly among individuals, which may result in differential roles for the same metabolites in different individuals. Several metabolites have pleiotropic biological effects, extending beyond lipid metabolism to include roles in immune regulation, intestinal barrier function, and other physiological processes. Controlling the multifaceted roles of gut-derived microbial metabolites presents a significant challenge for the future development of novel metabolic therapies based on these metabolites.

5 Effects of gut microbiota on intestinal lipid metabolism via immune pathways

Gut microbes also influence lipid metabolism through immune pathways, particularly involving helper T 17 (Th17) and regulatory T (Treg) cells in the gut lamina propria (Zhang et al., 2021). Th17 cells, fueled primarily by glycolysis, secrete pro-inflammatory cytokines like IL-17, IL-21, and IL-22, contributing to inflammation and autoimmune diseases. In contrast, Treg cells rely on fatty acid oxidation and

maintain immune tolerance through inhibitory factors such as IL-10 and transforming growth factor-β (TGF-β) (Kawano et al., 2022). High-fat and high-sugar diets reduce Th17 cell numbers and IL-17 secretion, alongside a decreased abundance of segmented filamentous bacteria that promote Th17 differentiation. This decline in Th17 cells inhibits the expression of the fatty acid transporter CD36 in IECs, reducing lipid uptake (Duscha et al., 2020; Wagner et al., 2021; Wen et al., 2021; Jia et al., 2024). Conversely, gut microbiota promotes Treg differentiation through SCFAs, which enhance histone acetylation at the forkhead box protein p3 (Foxp3) promoter and activate the AMPK and STAT3 signaling pathways (Arpaia et al., 2013). In addition, microbiota-activated DCs secrete IL-6 and IL-23, promoting Th17 differentiation, while mature DCs support Treg cell generation (Maiuolo et al., 2022). Thus, the Th17/Treg balance, regulated by gut microbiota, modulates lipid metabolism, with Th17 cells exacerbating lipid abnormalities and Tregs maintaining metabolic homeostasis.

Beyond immune pathways, the gut microbiota indirectly regulates lipid metabolism through various mechanisms. Beneficial bacteria like *A. muciniphila* inhibit histone deacetylase and activate G protein-coupled receptors (GPCRs) via SCFAs, influencing host metabolic pathways (Chambers et al., 2018). The microbiota also interacts with host circadian rhythms, where core clock genes (e.g., basic helix-loop-helix ARNT-like protein 1 (*Bmal1*) and circadian locomotor output cycles protein kaput (*Clock*)) regulate lipid uptake genes like *Cd36*. Dysregulation of these genes, such as in *Clock*$^{-/-}$ mice, leads to hypertriglyceridemia via the inositol-requiring enzyme 1α (IRE1α)/SREBP pathway (Li YY et al., 2020; Frazier et al., 2023; He et al., 2023). Furthermore, the microbiota modulates intestinal permeability by regulating tight-junction proteins, impacts systemic metabolism through trimethylamine *N*-oxide (TMAO) synthesis, and influences lipid metabolism via plasma inflammatory factors like IL-2 and interferon-γ (IFN-γ) (Plovier et al., 2017; Wu et al., 2017; Agus et al., 2021; Jang et al., 2024).

6 Summary and outlook

Research increasingly points to the gut microbiota as a central regulator of host lipid metabolism, orchestrating a complex interplay of immune signaling, circadian rhythms, and metabolic pathways. Clinical studies revealed distinct microbial signatures in obesity, characterized by shifts in the Firmicutes/Bacteroidetes ratio, a reduced abundance of beneficial taxa (e.g., *A. muciniphila*), and alterations in key genera (e.g., *Prevotella* and *Blautia*). These dysbiotic patterns underscore the potential of the microbiota as a therapeutic target for metabolic disorders. Fecal microbiota transplantation (FMT) from lean donors has shown promise in improving insulin sensitivity and attenuating chronic inflammation, although its limited impact on body weight and variability across individuals highlights the complexity of host–microbiota interactions.

The mechanistic insights from this review elucidate how microbiota abundance and microbial metabolites modulate host genes/pathways involved in lipid metabolism, including epithelial metabolic genes, circadian gene regulation, immune cell balance, and lipid transport proteins. These findings reveal that microbiota-driven immune signaling and epigenetic modifications fine-tune lipid absorption, lipid storage, and systemic homeostasis. However, translating these discoveries into clinical applications requires addressing significant gaps. Many studies remain correlative, and the dynamic interplay between microbiota, host genetics, and environmental factors (e.g., diet and antibiotics) complicates the intervention strategies.

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Author contributions

Yuhao WANG and Bingqing HANG conceptualized the review topic and scope. Bingqing HANG performed the systematic literature search, collected the data, and wrote the first draft of the manuscript. Yuhao WANG reviewed and edited the manuscript. Both authors have read and approved the final manuscript.

Compliance with ethics guidelines

Bingqing HANG and Yuhao WANG declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by either of the authors.

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