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Interplay between gut microbiome, host genetic and epigenetic modifications in MASLD and MASLD-related hepatocellular carcinoma

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a wide spectrum of liver injuries, ranging from hepatic steatosis, metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis to MASLD-associated hepatocellular carcinoma (MASLD-HCC). Recent studies have highlighted the bidirectional impacts between host genetics/epigenetics and the gut microbial community. Host genetics influence the composition of gut microbiome, while the gut microbiota and their derived metabolites can induce host epigenetic modifications to affect the development of MASLD. The exploration of the intricate relationship between the gut microbiome and the genetic/epigenetic makeup of the host is anticipated to yield promising avenues for therapeutic interventions targeting MASLD and its associated conditions. In this review, we summarise the effects of gut microbiome, host genetics and epigenetic alterations in MASLD and MASLD-HCC. We further discuss research findings demonstrating the bidirectional impacts between gut microbiome and host genetics/epigenetics, emphasising the significance of this interconnection in MASLD prevention and treatment.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), encompasses a wide range of liver injuries and remains as one of the leading causes of hepatic disease worldwide, affecting approximately 32.4% of the population.[1] In 2023, a multisociety statement proposed the adoption of the term MASLD to replace NAFLD, which is defined as the presence of hepatic steatosis accompanied by at least one cardiometabolic risk factor, including overweight/obesity, type 2 diabetes mellitus (T2DM) or evidence of metabolic dysregulation.[2] MASLD begins with hepatic steatosis, characterised by accumulation of excess triglyceride in the liver (≥5% hepatocytes). A subset of patients with MASLD progresses to metabolic dysfunction-associated steatohepatitis (MASH), which involves inflammatory responses associated with ballooned hepatocytes and/or fibrosis, encountering a higher risk of liver

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading chronic liver disease and a primary cause of hepatocellular carcinoma (HCC).
⇒ The developmental process of MASLD is intricate and comprises various risk factors, including cardiometabolic risk factors, genetic polymorphisms, epigenetic alterations and the gut microbiome.

WHAT THIS STUDY ADDS

⇒ This review provides a thorough overview of the existing research on the gut microbial profile and heritable components of MASLD and HCC, consolidating the current understanding of this crucial aspect.
⇒ Accumulating evidence highlights the significance of epigenetic modifications, such as DNA methylation, histone modification, chromatin remodeling, and non-coding RNA, and proposes their utilisation as non-invasive biomarkers.
⇒ The findings present compelling evidence role of the gut microbiota and its metabolites as potential epigenetic modifiers in modulating epigenetic patterns associated with MASLD pathogenesis.
⇒ Carriers of MASLD risk alleles exhibit a distinct enrichment of pathogenic bacteria, depletion of beneficial bacteria and alterations in microbial metabolite production. This review highlights the novel perspective on the reciprocal relationship between host genetics and the gut microbiome, which holds great promise for the development of new therapeutic avenues.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review analyses the intricate interplay between the gut microbiome, host genetics, and epigenetic modifications in the development of MASLD and HCC, shedding light on their potential as promising therapeutic targets in personalised medicine.
⇒ This review further underscores the clinical advantages of modulating the gut microbiome and epigentic patterns, to mitigate the effects of genetic variations linked to MASLD.

cirrhosis and MASLD-associated hepatocellular carcinoma (MASLD-HCC), which are end-stage liver diseases.[3]

The factors that associate with the development of MASLD and HCC include not only cardiometabolic risk factors but also genetic polymorphisms, epigenetic alterations and the gut microbiome. Research through familial aggregation studies,[4] twin studies[5] and investigations into interethnic differences susceptibility[6 7] has provided evidence supporting the heritable components of MASLD. The alterations of gut microbiota (dysbiosis) have also gained attention as a risk factor of pathogenesis and progression of MASLD. The gut microbiome maintains a symbiotic relationship with the host via contributing to the immune system homeostasis and energy metabolism.[8] Dysbiosis has been causally linked to multiple liver diseases because the gut and the liver are connected via the portal vein, biliary tract and systemic circulation,[9] and thus, this gut-liver axis takes an important role in MASLD. Furthermore, host genetics and gut microbiome have bidirectional impacts. The influence of host genetics on the composition of human

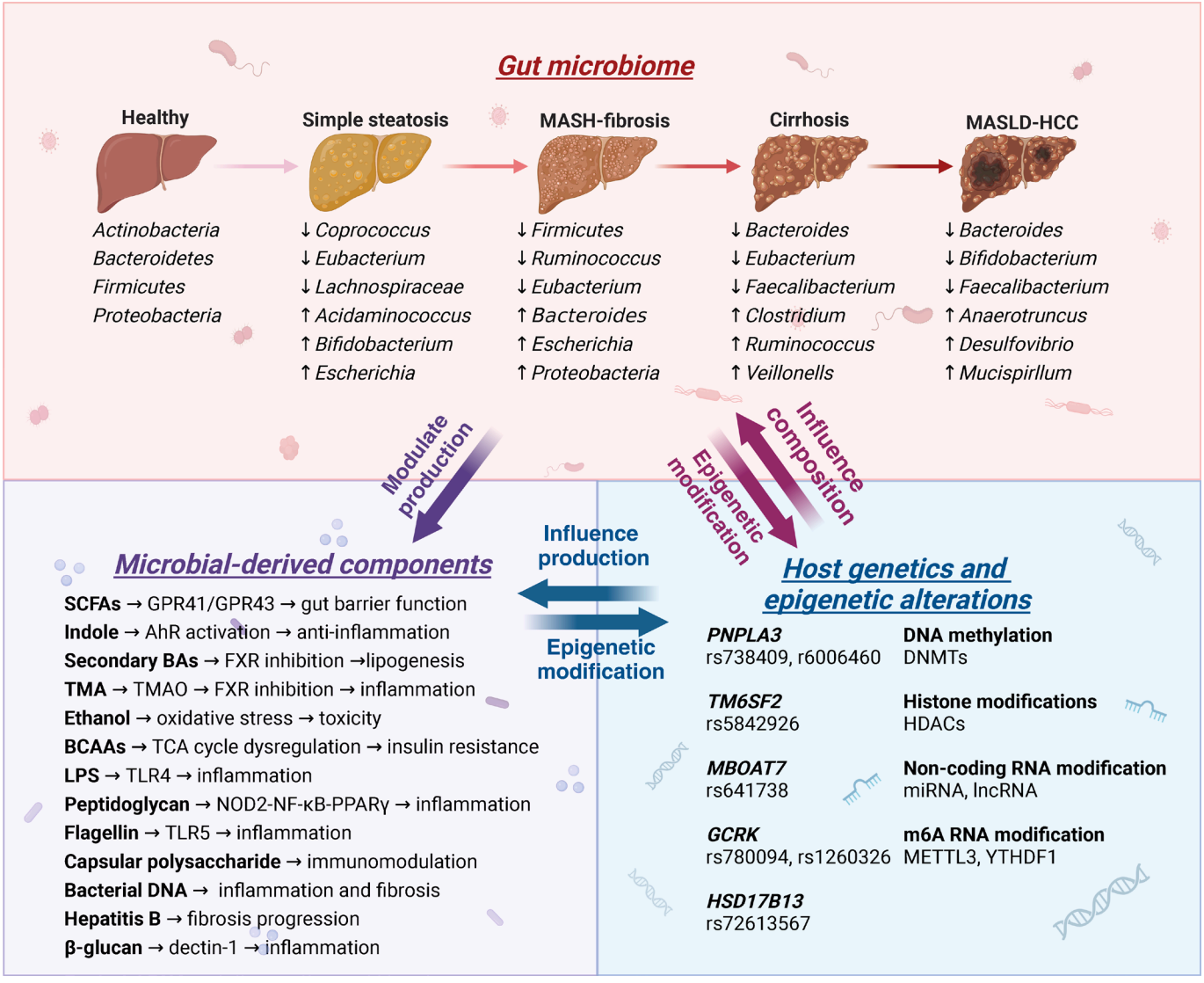

Figure 1 Risk factors in MASLD and the intricate interplay between gut microbiome, microbial metabolites, and host genetics and epigenetics. MASLD is a multifactorial disease which associates with host genetics, epigenetics, gut microbiome and gut-derived metabolites. More importantly, these risk factors may influence one another in the course of MASLD development and progression. The altered gut microbial abundance impacts their metabolite production and thus affecting lipid metabolism, inflammatory response and gut barrier function. The gut microbiome also influences host epigenetics at a transcription level, while host genetics shape the composition and function of the gut microbial community. The results of these various factors eventually lead to hepatic lipid accumulation, persisted inflammation and progression to MASLD-HCC. The microbiota-gene interaction may provide novel therapeutic strategies in MASLD and MASLD-HCC treatments. BAs, bile acids; BCAAs, branched-chain amino acids; DNMT, DNA methyltransferase; GCRK, glucokinase regulatory protein; HDACs, histone deacetylases; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; m6A, n6-methyladenine; MASH, metabolic dysfunction-associated steatohepatitis; MASLD-HCC, metabolic dysfunction-associated steatotic liver disease (MASLD)-associated hepatocellular carcinoma; MBOAT7, membrane-bound O-acyltransferase 7; METTL3, methyltransferase 3; miRNA, microRNA; NF-κB, nuclear factor kappa B; NOD2, nucleotide-binding oligomerization domain 2; PNPLA3, patatin-like phospholipase domain-containing protein 3; PPARγ, peroxisome proliferator-activated receptor gamma; SCFAs, short-chain fatty acids; TCA, tricarboxylic acid; TG, triglyceride; TLR, Toll-like receptor; TM6SF2, transmembrane 6 superfamily member 2; YTHDF1, YTH N6-methyladenosine RNA binding protein F1.

gut microbiome has been confirmed in twin studies, which showed that monozygotic twins tend to have a more similar microbiota than dizygotic twins.[10] While host genetics shape the species richness and abundance of individual taxa,[11] the gut microbiota and their derived metabolites can induce epigenetic modifications,[12] which in turn may influence the progression of MASLD and HCC.[13] This complex crosstalk has potential implications on patients' health status and disease development in MASLD and HCC (figure 1). This review intends to comprehensively evaluate and summarise different aspects of the gut microbial and genetic factors of MASLD, and more importantly, explore the potential of new therapeutic approaches based on elucidating the interplay between host genetics, epigenetics and gut microbiome in MASLD and HCC.

GUT MICROBIOME AND METABOLITES IN MASLD AND ITS RELATED HCC

Gut microbiome and its produced metabolites play crucial roles in the development of MASLD and its related HCC. Patients with MASLD often exhibit an altered ratio of *Firmicutes*/*Bacteroidetes*, which is correlated with hepatic steatosis and obesity, indicating gut dysbiosis.[14] This dysbiosis leads to the production of metabolites that can disrupt the intestinal barrier, also known as 'leaky gut', which causes portal translocation of bacteria and/or their metabolic products to the liver and triggers sustained inflammation.[15] Dysregulation of gut microbial metabolites including short-chain fatty acids (SCFAs), bile acids (BAs), endogenous ethanol, tryptophan metabolites, trimethylamine and branched-chain amino acids have been linked to the development of MASLD and HCC.[16] Our team has reported the supplementation of probiotics and beneficial metabolites protected against MASLD and its related HCC. For instance, *Parabacteroides distasonis* and its produced pentadecanoic acid ameliorates MASH by restoring gut barrier function and preventing bacterial toxin translocation,[17] and *Lactobacillus acidophilus*-derived valeric acid exhibits robust anti-tumourigenic effects in MASLD-HCC by binding to G protein-coupled receptors to inactivate the oncogenic Rho-GTPase signalling pathway.[18] In addition to metabolites, bacterial antigens such as lipopolysaccharide (LPS), peptidoglycan, flagella, polysaccharide A and bacterial DNA also contribute to MASLD. LPS is endotoxin that compromises the integrity of the gut barrier and induces inflammation via Toll-like receptor (TLR) 4, leading to the activation of nuclear factor κB (NF-κB) and tumour cell proliferation.[19] Peptidoglycan induces MASH development through stimulating lipogenesis through nucleotide oligomerization domain 2 (NOD2)-NF-κB-peroxisome proliferator-activated receptor gamma (PPARγ) signalling.[20] Flagellin, the primary structural component of flagella, is associated with an increased risk of MASLD and HCC via stimulating inflammatory responses via TLR5.[21 22] Moreover, polysaccharide A produced by *Bacteroides fragilis* can be recognised by dendritic cells to stimulate the development of Tregs with the ability to attenuate colitis.[23] Bacterial DNA in the liver is closely associated with MASLD severity.[24] *Lachnospiraceae* DNA links to more severe histology, and *Proteobacteria* DNA correlates with higher inflammation scores. Besides, viral and fungal antigens are also associated with MASLD, for instance, the coexistence of hepatic steatosis in patients with chronic viral hepatitis B infection leads to the aggravation of liver fibrosis,[25] while β-glucans from fungi *Candida albicans* are known to induce intestinal inflammation and accelerate obesity, T2DM and MASLD in mice via the dectin-1-dependent pathway.[26] Taken together, these gut microbiota-derived metabolites and antigens play crucial roles in MASLD.

Studies have proposed the idea of gut microbial signature to distinguish different phases of MASLD. A model based on gut microbial changes has demonstrated the ability to discriminate patients with steatosis, achieving an area under curve (AUC) of 0.727, while a multivariate model that integrates metagenomic, transcriptomic and metabolomic information improved the performance to AUC of 0.87.[27] 12 MASH-associated bacteria species could discriminate MASH from healthy control with AUC of 0.75–0.81 in 279 patients with biopsy-proven MASH and 78 healthy controls.[28] 37 bacterial species could distinguish mild/moderate MASLD from advanced fibrosis, yielding an impressive AUC of 0.936. Another study has highlighted that a combination of two bacteria (*Veillonellaceae* and *Ruminococcaceae*) could diagnose significant fibrosis (fibrosis score ≥2) in non-obese MASLD, achieving an AUC of 0.765. The addition of stool metabolites (cholic acid, chenodeoxycholic acid, ursodeoxycholic acid and propionate) further enhanced the performance, resulting in an AUC of 0.939.[29] Additionally, the gut microbiome signature comprising 19 discriminatory species demonstrated an AUC of 0.91 in detecting MASLD-cirrhosis in the proband cohort.[30] In addition to bacteria, viral changes have also been observed in MASLD with a significant reduction in the proportion of bacteriophage compared with other intestinal viruses. The combination of viral diversity (inverse Simpson index), aspartate transaminase (AST) and age showed AUC of 0.95 for predicting MASLD activity score 5–8 or liver cirrhosis. The combination of viral diversity with age, alanine transaminase (ALT) and platelet counts could diagnose advanced fibrosis with AUC of 0.88.[31] However, there is currently no consistent evidence of microbial signature that can be applied universally to determine the stage of simple steatosis, MASH or HCC, since the gut microbial composition differs between populations and ethnicities. Moreover, the potential confounding impact of metabolic variables might influence the detection of microbial signatures. Larger cohorts comprising various population groups detailed information pertaining to diet composition and extensive control groups (eg, patients with the presence of metabolic syndrome, diabetes or T2DM) are essential in developing diagnostic/prognostic markers and new therapeutic targets.

GENETICS AND EPIGENETICS IN MASLD AND HCC

Both genetics and epigenetics have been established as crucial factors in the development of MASLD and HCC. Genetic alterations involve single nucleotide polymorphisms in genes such as patatin-like phospholipase domain-containing 3 (*PNPLA3*), transmembrane 6 superfamily member 2 (*TM6SF2*), membrane bound O-acyltransferase domain containing 7 (*MBOAT7*), glucokinase regulator (*GCKR*) and hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*), which have been identified through genome-wide association studies (GWAS) and exome-wide association studies. The *PNPLA3* gene encodes for a multifunctional enzyme that associates with hepatic lipid regulation via its triglyceride hydrolase and acylglycerol O-acyltransferase activity on the surface of lipid droplets.[32] The G allele of rs738409 (C>G) is associated with higher hepatic fat content and inflammation, as well as MASLD-HCC,[33 34] while r6006460 (G>T) is associated with lower hepatic fat content.[35] The *TM6SF2* gene is predominately expressed in the liver and small intestine and encodes for proteins that participate in lipid metabolism via mediating hepatic triglyceride secretion.[36] The rs5842926 (C>T)

variant leads to lower total cholesterol and low-density lipoproteins levels[37] and confers a significantly greater risk of advanced hepatic fibrosis and progression to MASLD-HCC.[38] *MBOAT7* encodes for an integral membrane protein that serves as a lysophosphatidylinositol acyltransferase to transfer polyunsaturated acyl-CoAs to lysophosphatidylinositol and other lysophospholipids in the Lands cycle. The variant rs641738 (C>T) is associated with MASLD, resulting in more severe liver damage and an increased risk of fibrosis.[39] The *GCKR* gene encodes glucokinase regulatory protein that inhibits glucokinase expressed in the liver and β-cells of Islets.[40] Two common variants in the *GCKR* gene, rs780094 (C>T) and rs1260326 (C>T), have been shown to impact hepatic fat content, triglycerides and lipoprotein levels, and more severe MASH and fibrosis stages.[41] *HSD17B13* gene encodes for lipid droplet enzymes essential for hepatic lipid droplet targeting.[42] The variant rs72613567 (T>TA) is found to be protective against MASLD and mitigate liver injury in patients who are genetically predisposed to liver disease caused by *PNPLA3* 148M polymorphisms via reducing PNPLA3 mRNA expression,[43] suggesting the therapeutic potential of *HSD17B13* rs72613567 in specific group of patients with MASLD. In addition, rs72613567 TA allele associates with a reduced risk of HCC development and greater survival advantages in HCC.[44]

In addition to genetic alterations, epigenetic modifications also play a significant role in MASLD and HCC. Epigenetics is the study of heritable and stable phenotypes that occur through alteration in the chromosome without changes in the DNA sequence.[45] These modifications influence gene expression patterns and cellular phenotypes, thereby impacting the development and progression of MASLD and HCC. The role of epigenetic mechanisms, such as DNA methylation, histone modification, chromatin remodelling and non-coding RNA in metabolic diseases including MASLD, has been extensively investigated and documented.[46] In recent years, epitranscriptomics, which focuses on RNA modifications, has emerged as a critical area of study in post-transcriptional regulation of gene expression, including protein translation, RNA stability and function. Among RNA modifications, n6-methyladenine (m6A) is the most prevalent and well-studied modification. Our recent research demonstrated that the m6A 'writer' protein, methyltransferase 3 (METTL3), plays a significant role in promoting MASLD-HCC progression. Specifically, METTL3 mediates m6A modification on mRNA of sterol regulatory element-binding protein cleavage-activating protein (SCAP), resulting in enhanced translation of SCAP. This process leads to the activation of cholesterol biosynthesis and drives MASLD-HCC progression.[47] Furthermore, another m6A-related protein, the 'reader' YTH N6-methyladenosine RNA binding protein F1 (YTHDF1), was found to be involved in MASLD-HCC tumourigenesis.[48] YTHDF1 promotes tumourigenesis through the enhancer of zeste homolog 2/interleukin 6 (EZH2/IL-6) signalling pathway. This pathway recruits and activates myeloid-derived suppressor cells, which in turn cause dysfunction in cytotoxic CD8 T cells, ultimately contributing to MASLD-HCC development. These studies highlight the intricate involvement of RNA modifications, particularly m6A, in the pathogenesis of MASLD and HCC. The dysregulation of m6A writers, readers and downstream signalling pathways can have profound effects on gene expression, cellular processes and tumour microenvironment, ultimately impacting MASLD-HCC progression and therapeutic interventions.

INTERPLAY BETWEEN GUT MICROBIOME, HOST GENETICS AND EPIGENETICS IN MASLD AND HCC

Genetic susceptibility of MASLD involves gene-gene and gene-environment interactions, which goes beyond mere specific loci identification. Aberrant epigenetic modification alters the expression of genes involved in the pathogenesis of MASLD and MASLD-HCC. In recent findings, studies have concluded that changes in gut microbial and metabolite composition can induce epigenetic modifications in liver diseases (figure 2), while MASLD-associated genetic variants and gene expression can shape the composition and function of gut microbiota and their derived metabolites (table 1). The interplay of this host gene-gut microbiota linkage could provide new therapeutic insights in tackling the onset and progression of MASLD.

GUT MICROBIOTA AND METABOLITES INDUCE HOST EPIGENETIC ALTERATIONS IN MASLD

DNA methylation involves DNA methyltransferases (DNMTs) and plays an important role in maintaining genome stability and transcription factor binding by catalysing the transfer of methyl group from S-adenosyl methionine to cytosine. DNA methylation is the key in governing gene expression by silencing or activating genes through hypermethylation or hypomethylation, respectively.[49] Alteration of gut microbiome is closely associated with DNA methylation of genes involved in lipogenesis. Studies demonstrated that the modulation of gut microbiome via antibiotics protects against diet-induced weight and adipocyte expansion. The depletion of *Firmicutes*, *Lactobacillus* and *Helicobacter*, and enrichment in *Bacteroides, Enterobacter* and *Klebsiella* by antibiotics elevates adipose expression of adiponectin and resistin via DNA hypomethylation in their promoters and downregulation of DNMT1 and DNMT3A.[50] The inhibitive effects on body weight gain are also accompanied by the increased expression of genes associated with fatty acid β-oxidation and thermogenesis, including PPARα, PPARγ coactivator 1-alpha and adipose triglyceride lipase. In addition, the depleted mRNA levels of adiponectin and resistin in obese mice can be rescued by SCFA supplementation through inhibiting the binding of DNMT1, DNMT3A and DNMT3B to their promotors.[51] Regarding PPARα, its activity can be influenced by microbial-derived metabolites. LPS hinders the expression of PPARα by inhibiting hepatocyte nuclear factor 4 (HNF4) activity in PPARα transactivation. The suppressed PPARα activation further inhibits the production of pigment-epithelium-derived factor (PEDF), which is a Wnt inhibitor that restrains intestinal stem cell proliferation and maintains gut homeostasis.[52] Moreover, PPARα also interacts with other epigenetic enzymes, such as sirtuin-1,[53] which opens the door to investigation on how gut metabolites modulate MASLD via PPARα in epigenetics. Faecal microbiota transplantation (FMT) is another emerging therapeutic intervention in gut microbial modulation. FMT from healthy donors to patients with MASLD not only altered gut microbial composition but is also accompanied by changes in liver DNA methylation. The enriched *Eubacterium siraeum* in recipients is found to be negatively correlated with DNA methylation of cg16885113 in zinc finger protein 57 (ZFP57),[54] a key regulator of epigenetic imprinting which has implication in insulin resistance and diabetes.[55 56] More intriguingly, MASLD may induce persistent changes in gut microbial composition and liver DNA methylation pattern even after therapeutic intervention. Persistent hypomethylation of apolipoprotein A4 (APOA4) in MASLD is found to be associated with serum triglyceride levels and sustained gut *Odoribacter* abundance. *Odoribacter* is well known for its ability to produce butyrate which potentially modulates APOA4 methylation and APOA4-mediated hepatic triglyceride export, intestinal lipid absorption and very low-density lipoprotein particle expansion.[57]

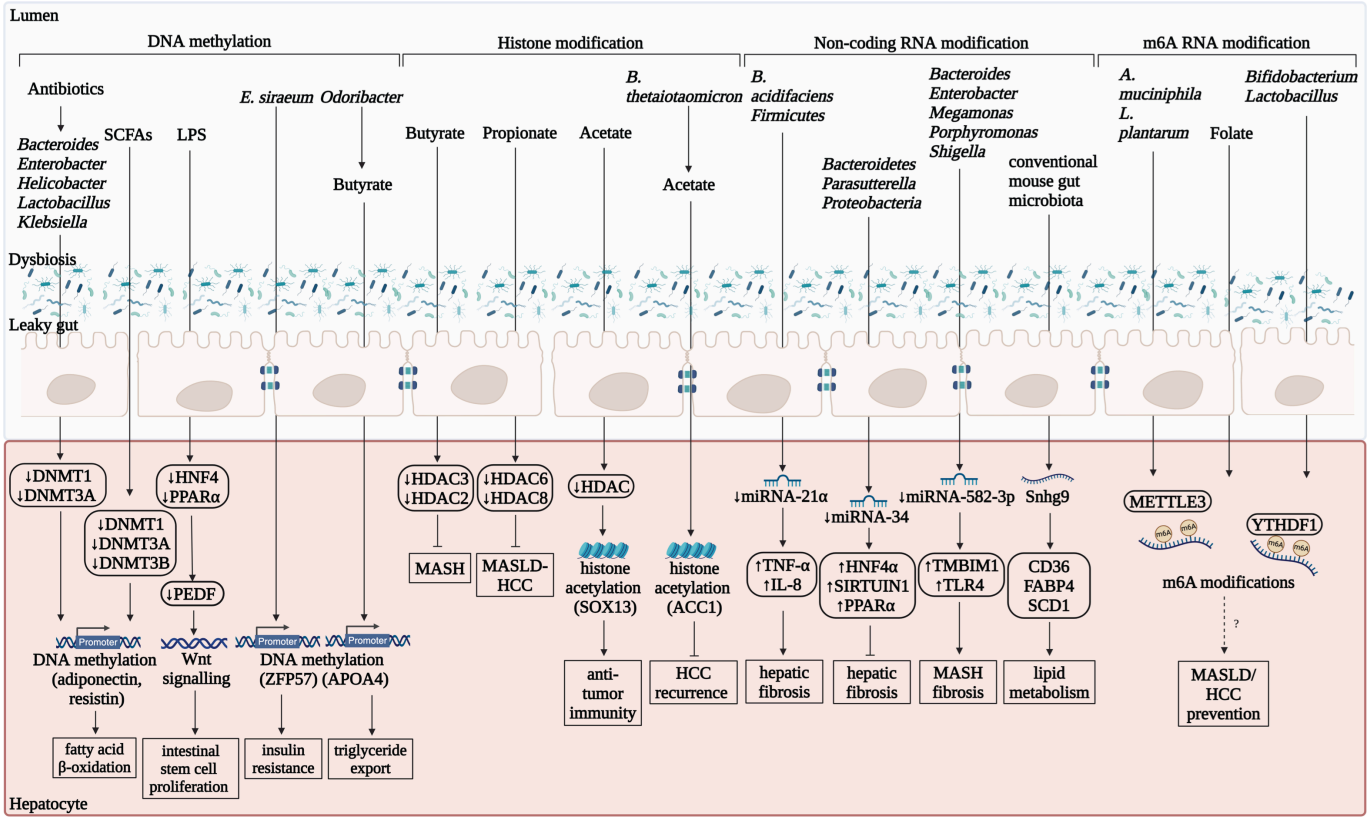

Figure 2 Gut microbiota and microbial metabolites modulate host epigenetics in MASLD. Gut microbiome and their derived metabolites are closely linked with host epigenetic modifications, influencing DNA methylation, histone modification and RNA regulation. Gut dysbiosis may promote DNA methylation and DNMT activity in genes associated with lipid metabolism, insulin resistance and stem cell proliferation. SCFAs are well-known histone deacetylase inhibitors and regulate transcription in anti-inflammatory genes. Dysbiosis also favour specific miRNA activity in promoting MASH and MASLD-HCC. Moreover, gut microbiota and metabolites may regulate m6A modification in MASLD and HCC prevention which require further investigation. ACC1, acetyl-CoA carboxylase 1; APOA4, apolipoprotein A4; DNMT, DNA methyltransferase; FABP4, fatty acid binding protein 4; HNF4, hepatocyte nuclear factor 4; IL-6, interleukin 6; LPS, lipopolysaccharide; MASH, metabolic dysfunction-associated steatohepatitis; MASLD-HCC, metabolic dysfunction-associated steatotic liver disease (MASLD)-associated hepatocellular carcinoma; METTLE3, methyltransferase 3; miRNA, microRNA; m6A, n6-methyladenine; PEDF, pigment-epithelium-derived factor; PPARα, peroxisome proliferator-activated receptor-alpha; SCD1, stearoyl-CoA desaturase 1; SCFAs, short-chain fatty acids; Snhg9, small nucleolar RNA host gene 9; SOX13, Sex-determining Region Y-box transcription factor 13; TNF-α, tumour necrosis factor-alpha; TMBIM1, transmembrane BAX inhibitor motif containing 1; TLR4, Toll-like receptor 4; YTHDF1, YTH N6-methyladenosine RNA binding protein F1; ZFP57, zinc finger protein 57.

Histone modifications are crucial in the epigenetic regulation of gene expression. Histone acetyltransferases and histone deacetylases (HDACs) are responsible for histone acetylation and deacetylation, respectively. Furthermore, their activities are highly sensitive to gut microbiota and their derived molecules.[58] Histone deacetylation regulates transcriptional inactivation, and overexpression of HDACs has been linked to multiple intestinal diseases. Hence, HDAC inhibitors have well-known potential to serve as therapeutic agents. In conventional mice, HDAC3 enriched in adipocytes plays an important role in intestinal homeostasis owing to its high sensitivity to microbial signals in mediating lipid metabolism in liver, muscle and adipose cells. Intestinal-specific deletion of HDAC3 increased the susceptibility to intestinal damage and inflammation caused by the loss of Paneth cells and impairment of intestinal epithelial cell function. However, the effect of HDAC3 knockout was not observed in germ-free mice.[59] Conversely, in diet-induced obesity models, HDAC3 was found to promote weight gain and insulin resistance, while HDAC3 knockout resulted in increased energy expenditure and a decrease in serum triglycerides, body fat and weight gain. SCFAs, including butyrate, propionate and acetate are well-known HDAC inhibitors. Butyrate administration in conventional high-fat diet-fed mice, but not in HDAC3 knockout mice, significantly reduced weight gain, supporting the specific role of butyrate as a HDAC3 inhibitor in diet-induced liver abnormalities.[60] Furthermore, butyrate hinders the progression of hepatic steatosis to MASH via inhibition of HDAC2 and promotion of hepatic glucagon-like peptide-1 receptor (GLP-1R) expression.[61] In MASLD-HCC, the expressions of various HDACs are upregulated in patients, and enhanced expression of HDACs has been found to be a crucial factor in malignant growth and immune escape.[62] The synergistic cytotoxic effect of sodium propionate in combination with chemotherapeutic agent cisplatin enhanced the inhibition of proliferation and induction of apoptosis of cancer cell by reduction of HDAC6 and 8 activities in a GPR41-dependent manner.[63] In addition, acetate has been reported in regulating anti-tumour immunity through inhibition of HDAC activity and induction of sex-determining region Y-box transcription factor 13 (SOX13) acetylation in HCC. The consequential decreased expression of SOX13 reduces the production of IL-17A in type 3 innate lymphoid cells. Moreover, the combination programmed death 1/programmed death ligand 1 blockade with acetate administration enhances anti-tumour immunity in HCC model, suggesting that the therapeutic

Table 1 MASLD-associated host genetics and gene expression in shaping composition of liver and gut microbiome

Host genes	Liver microbial alterations	Associated disease pathways	References
PNPLA3 rs738409	↑*Enterobacter*, *Marivota*	De novo fatty acid biosynthesis	11 120
TM6SF2 rs58542926	↑*Gemella*, *Fusobacterium* ↑*Methylobacterium*, *Prevotelle_9* ↑*Pseudoalteromonas*, *Megamonas*	Tryptophan metabolism	11
MBOAT7 rs641738	↑*Tyzzerella* ↓*Butyricicoccus*, *Streptococcus*	Nucleotide and purine biosynthesis	11
HSD17B13 rs72613567	↑*Methylotenera* ↓*Fusobacterium*, *Parasutterella*	Phosphatidylglycerol and gondoate biosynthesis	11
Host genes	**Gut microbial alterations**	**Associated disease pathways**	**References**
PNPLA3 rs738409	↑*Desulfobacteraceae bacterium* ↑*Bacteroidetes*, *Gemmiger* ↑*Oscillospira*	De novo fatty acid biosynthesis	73
GPR35	↑*Ruminococcus gnavus*	Hepatic fat accumulation	79
FKBP5	↑*Bacteroidales*, *Verrucomicrobiales* ↓*Clostridiales*, *Burkholderiales* ↓*Enterobacteriales*	MASLD-HCC inhibition	87
HIF-2α	↑*Bacteroides vulgatus* ↓*Ruminococcus torques*	Adipose tissue thermogenesis BA metabolism	81
SQLE	↑*Desulfovibrio fairfieldensis* ↑*Brucella abortus*, *Chlamydia muridarum* ↑*Lachnospiraceae* ↓*Ruminococcus*	BA metabolism De novo hepatic lipogenesis Hepatic cholesterol accumulation Gut barrier disruption	83 85

BA, bile acid; FKBP5, FK506-binding protein; Gpr35, G protein-coupled receptor 35; HIF-2α, hypoxia-inducible factor 2α; HSD17B13, 17-beta hydroxysteroid dehydrogenase; MBOAT, membrane bound O-acyltransferase domain containing 7; PNPLA3, patatin-like phospholipase domain-containing protein 3; SQLE, serum squalene epoxidase; TM6SF2, transmembrane 6 superfamily member 2.

effect of acetate in improving immunotherapy efficacy may be mediated via HDAC regulation.[64] In addition, *Bacteroides thetaiotaomicron*-derived acetic acid was found to inhibit HCC recurrence through histone acetylation modification in the acetyl-CoA carboxylase 1 (ACC1), a key enzyme in fatty acid biosynthesis.[65] These findings suggested a complex interplay between gut microbial metabolites and epigenetic regulations in HCC; further research is essential to elucidate the clinical application potentials by targeting gut metabolites in modulating histone modifications.

The miRNAs are involved in the course of MASLD and the severity of hepatic disease can be characterised by specific microRNA (miRNA) signature. In high-fat diet-induced metabolic adaptation, the altered abundances of *Firmicutes* and *Bacteroides acidifaciens* are significantly associated with miRNA-21α activity, thus, influencing hepatocyte apoptosis, insulin signalling, proinflammatory cytokines and liver fibrosis.[66] Gut microbial modulation in *Eubacterium*, *Blautia*, *Clostridium*, *Lactobacillus* and *Parasutterella* mitigates diet-induced hepatic steatosis via regulating miRNA-130α, miR-34α and miR-29α. The abundance of *Bacteroidetes*, *Proteobacteria* and *Parasutterella* reveals robust negative correlations with miRNA-34α and potentially suppresses miRNA-34α to regulate hepatic lipid metabolism via hepatocyte nuclear factor 4α (HNF-4α), SIRTUIN1 and PPARα.[67] Gut dysbiosis in patients with MASH is associated with the upregulation of miRNA-582-3 p in plasma. Dysbiosis in *Shigella*, *Enterobacter*, *Bacteroides*, *Porphyromonas* and *Megamonas* was found to upregulate miRNA-582-3p to promote hepatic stem cell proliferation and myofibroblast markers expression via transmembrane BAX inhibitor motif containing 1 (TMBIM1) and TLR4, leading to MASH and fibrosis.[68] In addition to miRNA, the gut microbiota can reprogramme intestinal lipid metabolism through long non-coding RNAs. Whole-transcriptome sequencing of small intestinal epithelial cells from conventional and germ-free mice identified that the small nucleolar RNA host gene 9 (Snhg9) activity is highly suppressed by gut microbiota through myeloid cells and group 3 innate lymphoid cells. Overexpression of Snhg9 was found to reduce the expression of fatty acid transporter CD36, fatty acid binding protein 4 (FABP4) and lipogenic enzyme stearoyl-CoA desaturase 1 (SCD1) via direct binding to cell cycle and apoptosis regulator 2 (CCAR2), suggesting that the gut microbiota promotes lipid absorption and metabolism by repressing the expression of long non-coding RNAs.[69]

While the contribution of gut microbiota in influencing host m6A profiles in MASLD and HCC is still under investigation, it has been well established that the gut microbiota can indeed impact m6A modifications in intestinal metabolism and disease development. Using m6A-methylated RNA-immunoprecipitation and sequencing of liver tissue from conventional and germ-free mice, variations in gut microbiota were found to be correlated with m6A modification in metabolic pathways associated with lipid, vitamin, amino acids and insulin signalling. The study further showed that *Akkermansia muciniphila* and *Lactobacillus plantarum* impact specific m6A modifications in mono-associated mice.[70] Alteration of m6A level in the liver and small intestine is presented in high-fat diet-fed animal models and is closely associated with gut dysbiosis. FMT has been shown to restore m6A level and abrogate diet-induced obesity in mice potentially via enrichment of *Lactobacilli*.[71] Folic acids, a major donor for DNA synthesis and methylation, synthesised by beneficial *Lactobacillus* and *Bifidobacterium* have also been reported in regulating m6A modification to maintain normal intestinal environment.[72] These studies unravelled the role of gut microbiota in m6A modification, which deserves further exploration in future MASLD-HCC research.

HOST GENETIC VARIANTS AND GENE EXPRESSION PROFILE SHAPING MICROBIAL COMPOSITION IN MASLD AND HCC

The roles of genetics and microbiome in MASLD have been studied extensively. However, the specific mechanisms by which genetics modulates gut microbiota in MASLD are still unclear. The advancements in omics and bioinformatics allow disentangling the complex interplay between host genetics and gut microbiome. Nonetheless, the majority of human studies were conducted in small sample sizes and findings have yet to be widely replicated across larger and more diverse cohorts. A study comparing 44 obese youth with MASLD to 29 obese youth without MASLD showed that the abundance of faecal *Gemmiger*, *Oscillospira* and *PNPLA3* rs738409 variant was predictive of hepatic fat fraction.[73] Another study of 10 patients with simple steatosis and 22 patients with steatohepatitis showed that the faecal *Desulfobacteraceae bacterium* was significantly decreased, while fungi such as *Fusarium*, *Candida*, *Aspergillus* and *Saccharomyces* were higher in patients with the *PNPLA3* rs738409 GG genotype.[74] Microbiome analysis in the liver tissue of 116 patients with MASLD (19 control, 44 patients with MASL and 53 patients with MASH) confirmed the linkage between host genetics and the liver microbiome. *PNPLA3* rs738409 G allele carriers presented enriched liver *Enterobacter* and *Marivota*, while *TM6SF2* rs58542926 T allele carriers had enriched *Pseudoalteromonas* and *Megamonas*. The carriers of *MBOAT7* rs641738 T allele showed depleted *Butyricicoccus* and *Streptococcus,* while carriers of *HSD17B13* rs72613567 TA allele showed decreased abundances of *Fusobacterium* and *Parasutterella*.[11] The strongest associations were between *Enterobacter* and *PNPLA3* rs738409, and *Pseudoalteromonas* and *TM6SF2* rs58542926. These two genera belong to *Gamma proteobacteria* which are associated with more severe forms of MASLD.[24]

Considering the interpatient variations in host genetics and gut microbiome, the lack of high-quality studies hinders establishing conclusive evidence and elucidating underlying mechanisms. Future studies should employ rigorous statistical analysis and ensure biological plausibility. Another limitation of the related studies is their descriptive nature. Despite the remarkable progress in GWAS and metagenomic data, the biological mechanisms underlying the association between host genetics, specific microbial species and metabolite production remain poorly understood, particularly with respect to the role of host genetics in shaping gut microbiome. However, our recent research has shed light on this topic. We have discovered that the genetic deletion of *Tm6sf2* in the intestine alters gut microbiome composition by increasing free fatty acid secretion, leading to MASLD development.[75] Nonetheless, further investigations are needed to elucidate how host genetics influence the gut microbiota in patients with MASLD. While some evidence suggests an association between the microbiome and host genetics in humans, it is important to consider the strength of these findings.

Besides the role of host genetic variants, MASLD-related gene expression profiles also impact composition of gut microbiome. G protein-coupled receptor 35 (GPR35) is an orphan receptor highly expressed in the gut epithelial and myeloid cells. Regulation of hepatic cholesterol homeostasis by GPR35 has been found to mitigate obesity-related MASH.[76] Polymorphisms in *GPR35* are associated with intestinal inflammation, metabolic stress and T2DM.[77 78] Global and intestinal-specific *GPR35* deletions induce gut dysbiosis and increased susceptibility to liver steatosis and metabolic syndrome. Further research has shown that the loss of GPR35 leads to an increase in *Ruminococcus gnavus* in the gut, which, in combination with high-fat diet, disturbs lipid metabolism and causes hepatic fat accumulation through the production of indoxylsulfuric acid, a uraemic toxin. These findings indicate that GPR35 plays a crucial role in gut-liver signalling serving as a chemosensor of microbial metabolites and potentially be a potential target for to mitigating the risk of metabolic diseases.[79] Human studies have reported that the constitutive expression of hypoxia-inducible factor 2α (HIF-2α) contributes to the development of hepatoic steatosis.[80] Therefore, the HIF-2α pathway is becoming recognised as a vital mediator of lipid metabolism in the liver, although its molecular mechanisms in MASLD remain obscure. It is reported that HIF-2α expression increases *Bacteroides vulgatus* and reduces *Ruminococcus torques* abundances by upregulating intestinal lactate; furthermore, both bacteria have the ability to modulate BA metabolism.[81] HIF-2α ablation downregulates intestinal lactate dehydrogenase A expression and the sequential lactate production, thus reducing *Bacteroides vulgatus* and promoting the growth of *Ruminococcus torques*. The altered gut bacterial abundances induced by HIF-2α ablation elevate the conjugated BA levels and the activation of TGR5, promoting white adipose tissue thermogenesis. More importantly, the phenotype of HIF-2α knockout mice can be mirrored by FMT, and the beneficial effects of HIF-2α ablation are diminished when the gut microbiome is eliminated by antibiotics, suggesting the influence of host gene expression profile in gut microbial composition as well as BA metabolism.[81]

In MASLD-HCC, the influence of host genes on the gut microbiome is a developing field of study. By performing RNA sequencing analysis of 17 paired human MASLD-HCC and adjacent normal tissues, *squalene epoxidase* (*SQLE*) was found as an outlier gene which markedly upregulated in MASLD-HCC. SQLE exerts its effect via epigenetic reprogramming by cholesteryl ester and NADP+ and activating the phosphatase and tensin homologue deleted on chromosome ten (PTEN)/phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signalling cascade to drive carcinogenesis in MASLD-HCC.[82] Moreover, our team has also recently proposed that the highly expressed SQLE, together with carbonic anhydrase 3 (CA3), could be used as non-invasive biomarkers to distinguish patients with MASH from steatosis and healthy individuals. SQLE has a profound impact on hepatic cholesterol accumulation and thereby inducing proinflammatory NF-κB signalling and steatohepatitis. The direct binding of SQLE and CA3 also triggers SREBP1C activation and expression of genes involved in de novo hepatic lipogenesis.[83] Downregulation of SQLE expression has been shown to suppress hepatic lipid accumulation, accompanied by the increase of *Lachnospiraceae* and decrease of *Ruminococcaceae* that are responsible for hepatic cholesterol metabolism.[84] Our team has further demonstrated that the SQLE transgenic mice display significant enrichment of pathogenic *Desulfovibrio fairfieldensis*, *Brucella abortus* and *Chlamydia muridarum*. Moreover, SQLE transgenic mice showed altered abundance of BAs. Lithocholic acid (LCA), chenodeoxycholic acid (CDCA), taurodeoxycholic acid and deoxycholic acid (DCA) were significantly enriched in the stools compared with wild-type mice.[85] The enriched LCA and DCA function as FXR antagonists in the presence of CDCA and suppress FXR-mediated lipid metabolism and fatty acid β-oxidation.[86] FMT of SQLE transgenic mice into germ-free mice promoted gut barrier disruption confirmed by downregulation of mucin 2, junctional adhesion molecule C and occludin mRNA level.[85] Another gene, *FK506-binding protein 5* (*FKBP5*), has been proposed to play an essential role in promoting HCC development.[87] FKBP5 is also implicated in the development of

various cancers and cancer cell motility and invasion.[88] FKBP5 has been found highly expressed in human HCC tissue as well as HCC cell lines. Loss of FKBP5 inhibited DEN-induced HCC progression via alterations in gut microbial composition and their production of BAs. The enriched abundance of *Bacteroidales* and *Verrucomicrobiales*, and decreased *Clostridiales*, *Burkholderiales* and *Enterobacteriales* in FKBP5 knockout mice was accompanied by the depletion in BA concentration. The altered gut microbiome and total BAs potentially participate in the effect of FKBP5-mediated reduction of abdomen adipose tissues and the level of serum total cholesterol.[87]

Acknowledgement in host gene-gut microbiome interplay is still a relatively new aspect in MASLD, especially MASLD-HCC. Whether targeting modulation on specific gene expression can override the causative effects of gut dysbiosis, or the mechanisms on how these two factors influence one another is undetermined. Strong associations have been presented in studies, researchers ought to place their attention in the crosstalk between host genetics/gene expression profile and gut microbiome in MASLD and MASLD-HCC.

SEXUAL DIMORPHISM IN GUT MICROBIOME, GENETIC RISK FACTORS AND MASLD DEVELOPMENT

Sex is a crucial biological variable that needs to be taken into account in studies, given the evidence of sexual dimorphism in MASLD.[89] Generally, male are more prone to MASLD,[90] MASH,[91] fibrosis[92] and HCC[93] than female. Studies suggest that female sex hormones, such as oestrogen in the premenopausal state, may confer a protective influence against MASLD. In multiple studies, premenopausal female presented higher abundance of gut bacteria that are inversely associated with metabolic profiles.[94–96] In a Chinese prospective cohort involving 188 male and 233 female patients with MASLD, and 571 male and 567 female healthy controls, it was observed that male patients presented lower microbial α-diversity, higher abundance of *Dialister*, *Streptococcus* and *Bifidobacterium*, and lower abundance of *Phascolarctobacterium*. Conversely, female patients presented a higher α-diversity and reduced abundance of liver cirrhosis-associated *Dialister*.[97] Sexual dimorphism may also contribute to the genetic and epigenetic determinants of MASLD. Despite female being generally protected against MASLD, the carriage of the rs738409 variant conferred an increased risk of MASLD in females than in males.[98 99] In contrast, the *TM6SF2* rs58542926 variant may have a more significant impact on males with impaired glucose tolerance and T2DM,[100] while the TT genotype of *GCKR* rs780094 and rs1260326 potentially involve in hyperuricaemia in female.[101] In addition, sex hormones play roles in epigenetics modification and HCC development.[102 103] Larger and more ethnically diverse studies are necessary to gain a comprehensive understanding of the sex-associated genetic and epigenetic basis of MASLD, considering the inconsistent findings in other studies.[98]

POTENTIAL ADVANCES IN CLINICAL APPLICATIONS

MASLD is currently the most prevalent chronic liver disease on a global scale, becoming a major contributor to adverse liver outcomes including HCC. In the last decade, clinical trials targeting the gut-liver axis underwent intensive investigation in aiming to reduce ALT/AST levels, intestinal inflammation and hepatic fat content in patients with MASLD. Interestingly, the effects of the microbiota-based therapy seem to be influenced by ethnicity,[104] implicating the role of host genetics in shaping the complexity of the gut microbial community. Untargeted modification of gut microbiota by antimicrobials, FMT and

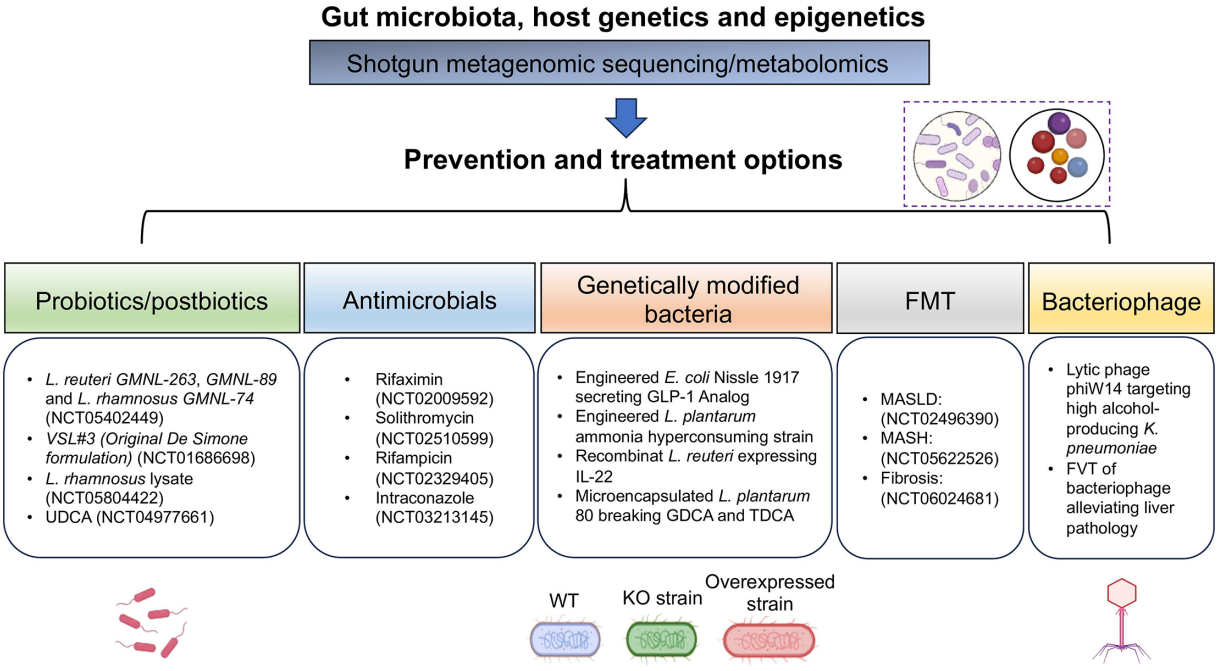

Figure 3 Development of personalised gut microbiota-based therapy targeting host genetics and epigenetics. Recent studies have unravelled the effects of host genetics and epigenetics in shaping the composition and metabolic production of the gut microbiota. Identification of the host genotype-associated gut dysbiosis allows development of personalised gut microbiota-based therapies. Preclinical studies and randomised clinical trials (ClinicalTrials.gov ID labelled in brackets) are currently ongoing in investigating the therapeutic effects of probiotics, postbiotics, antimicrobials, genetically modified bacteria, FMT and bacteriophage in MASLD. FVT, faecal virome transplantation; GDCA, glycodeoxycholic acid; GLP-1, glucagon-like peptide 1; KO, knock out; MASLD, metabolic dysfunction-associated steatotic liver disease; TDCA, taurodeoxycholic acid; WT, wild type; UDCA, ursodeoxycholic acid.

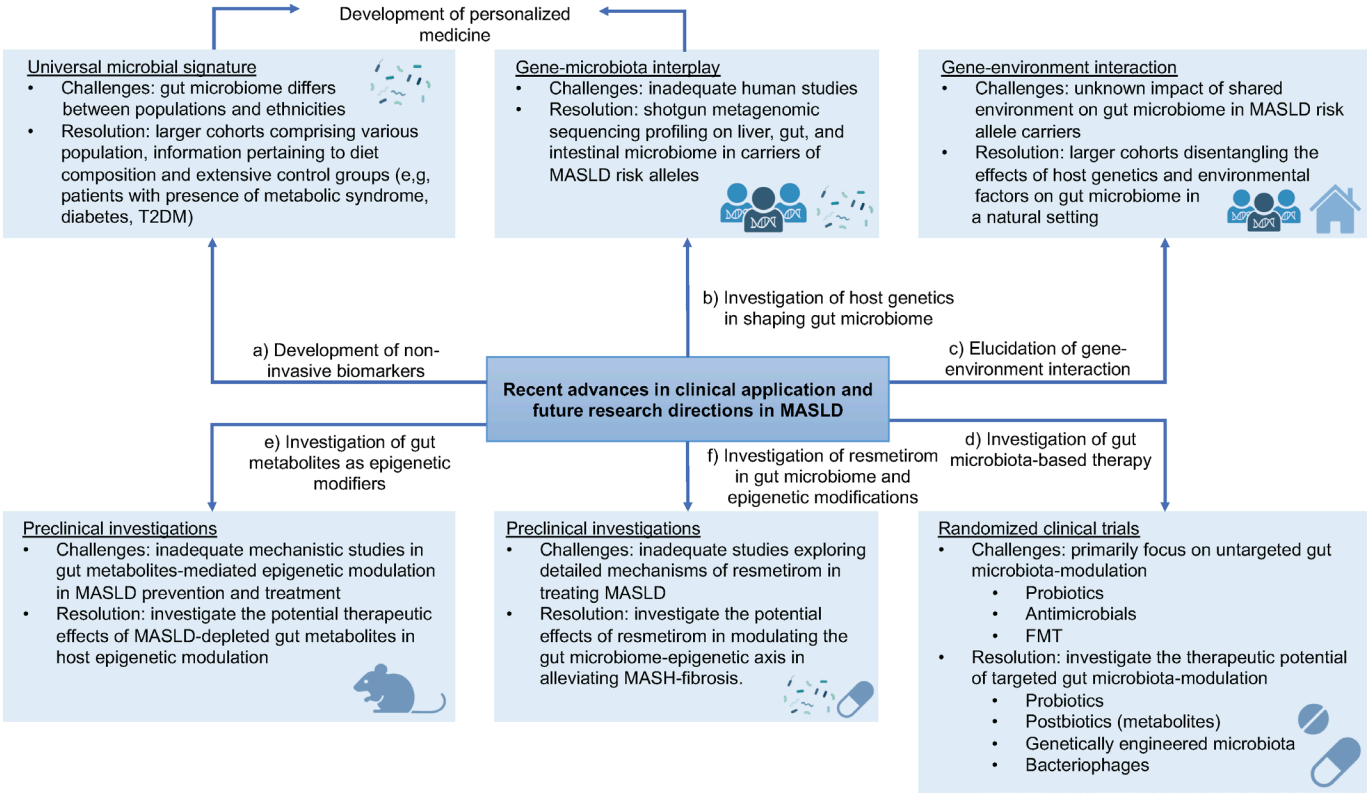

Figure 4 Recent advances in clinical application and future research directions in MASLD in relation to gut microbiome and genes. (a) There is currently no consistent evidence of a single microbial signature that can be applied universally to distinguish or determine the stage of simple steatosis, MASH or HCC. Potential confounding impact of metabolic variables might also influence the detection of microbial signatures. Larger cohorts comprising various population groups, detailed information pertaining to diet composition and extensive control groups are essential in developing diagnostic/prognostic markers and new therapeutic targets. (b) Conducting larger cohorts to explore the effect of the host genome on the liver, gut and intestinal microbiome is important to understand the impact of host genetics on MASLD and HCC gut microbial composition and, more importantly, to aid in the development of personalised medicine. (c) It is crucial to comprehend the gene-environment interaction to understand whether gut microbiome is primarily influenced by host phylogenetics or shared environments, or if both factors have a co-regulatory effect in the development of MASLD. (d) Randomised clinical trials have demonstrated the promising therapeutic effects of untargeted gut microbiota modulation by probiotics, antimicrobials and FMT in patients with MASLD. In the future, there should be more focus on modulating the gut microbiota in a targeted manner via probiotics, postbiotics (metabolites), genetically engineered microbiota and bacteriophages. (e) The collection of preclinical research has revealed the role of gut metabolites in mediating the modification of host epigenetics. A comprehensive understanding of the underlying mechanisms could offer valuable insights into potential clinical applications. (f) While resmetirom is the sole FDA-approved drug for treating MASH-fibrosis, its mechanism remains unclear. As the gut microbiome-epigenetic interplay plays a vital role in MASLD, exploring resmetirom's potential impact on gut microbiome and epigenetic modifications could shed light on its efficacy in mitigating MASLD. FDA, Food and Drug Administration; FMT, faecal microbiota transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

probiotic cocktails serve as an initial approach to improve dysbiosis and disease outcomes. In this review, we emphasise that the host genetic and epigenetic profiles are closely linked to the gut microbiome and appear to be associated with the specific bacteria abundances. These findings prompt the idea of a more targeted approach by precisely targeting specific bacterial strains or their metabolites with the ultimate objective of restoring gut microbial eubiosis and maintaining intestinal homeostasis (figure 3). Our team has demonstrated that the administration of MASLD-depleted and HCC-depleted gut bacteria and metabolites exerted protective effects on disease development and progression.[13 17 18] The innovation in targeted gut microbiota modulation has encouraged the development of genetically modified probiotics.[105 106] Preclinical studies have demonstrated the antiobesity effect of *Escherichia coli* Nissle 1917[107] via genetic manipulation to secret gut hormone glucagon-like peptide 1 (GLP-1),[107] while engineered *Lactobacillus plantarum* exhibited ammonia hyperconsuming ability in protecting against liver failure.[108] More intriguingly, the utilisation of bacteriophage could selectively eradicate specific pathogenic bacteria to attenuate hepatic dysfunction via gut microbiota modulation.[109 110] Furthermore, accumulated evidence indicates the roles of epigenetics as pathological mechanisms and non-invasive biomarkers in MASLD and HCC. The gut microbial metabolites are well-known epigenetic modifiers, which in turn might be used as therapeutic reagents to modify host epigenetics and the sequential expression of genes involved in MASLD and HCC. Random clinical trials are underway in investigating the effects of postbiotics (components derived from probiotics), including probiotic lysate and their metabolites in alleviating MASLD pathology (NCT05804422 and NCT04977661). Further preclinical investigations and clinical trials are needed to determine the potential applications of gut metabolites in modulating host epigenetics.

In the current scenario, the treatment options of MASLD are limited while lifestyle intervention remains the primary course of therapy. Recently in March 2024, resmetirom developed by Madrigal Pharmaceuticals was approved by Food and Drug Administration (FDA) as the first therapeutic drug for

the treatment of MASH with moderate to advanced fibrosis in clinical settings,[111] based on the promising results from phase 3 MAESTRO clinical programme (NCT03900429 and NCT04197479). Resmetirom serves as a liver-targeted thyroid hormone receptor β (THR-β) agonist and has also been demonstrated to reduce hepatic fat content, improve liver histology and mitigate biomarkers associated with liver damage and dyslipidaemia in MASH clinical trial (NCT02912260). Resmetirom may function by binding to THR-β, forming a heterodimer with retinoid X receptor to activate transcription of carnitine palmitoyltransferase I (CPT1) and sterol regulatory element binding transcription factor 1 (SREBF1), which mediate mitochondrial fatty acid oxidation and hepatic de novo lipogenesis, respectively.[112] Emerging research also suggests that thyroid dysfunction can lead to changes in the gut microbiome,[113 114] supplementation of thyroid hormones can alter metabolomics profiling in lipid metabolites,[115] and more crucially, thyroid hormones also participate in the epigenetic modification of histones in the liver to regulate lipogenesis.[116 117] Hence, it might be worth exploring the potential of resmetirom in modulating the gut microbiome-epigenetic axis as a means of addressing the severity of MASH.

Both the microbiome and epigenome represent promising targets for therapeutic interventions in MASLD. However, the intricate interplay between these two factors, as well as their interactions with host genetics, has yet to be fully elucidated in the context of MASLD treatment. Previous research has provided compelling evidence of how host genetics affecting the gut microbiome, which in turn can affect epigenetic modifications that contribute to MASLD pathogenesis. By manipulating the gut microbiome, it may be possible to mitigate the effects of genetic variants implicated in MASLD. For instance, our recent research showed that modulating the gut microbiome could suppress MASLD resulting from intestinal *Tm6sf2* deficiency.[75] This finding highlights the potential therapeutic value of targeting the gut microbiome in individuals with specific genetic risk alleles. Further mechanistic studies are necessary to fully understand the intricate connections of these factors in MASLD treatment. Moreover, human studies are needed to explore the potential for targeted treatments that aim to modulate the gut microbiome and epigenome in patients carrying specific genetic risk alleles.

CONCLUSION

The deleterious effect of MASLD can lead to end-stage liver diseases, particularly HCC. Although much ground-breaking research has been conducted to understand the pathophysiology, genetic predisposition and treatment of MASLD and HCC, many elements are yet to be investigated (figure 4). Studies on the gut microbiome in MASLD have primarily focused on microbial composition, alteration in abundance, functionality and associated pathways, however, less appreciation on the interplay of microbiome/metabolites and host genetics/epigenetics. Studying the effects of host genetics on gut microbiome also poses challenges. While several studies support the notion that host genetics can shape the gut microbial composition, others have suggested that environmental factors may override the impacts of host genetics.[118 119] Environmental factors such as diet, lifestyle and medication can also alter microbial composition even in familial studies. Therefore, the central question in MASLD revolves around whether host phylogenetics or shared environments dominate the shaping of the gut microbiome, or if there is a specific co-regulation of the gut microbiome by both factors in MASLD pathogenesis. To gain a comprehensive understanding of how host genetics contribute to gut microbiome with or without other co-mediating factors in MASLD and HCC, future research should focus on disentangling the effects of host genetics and environmental factors in a natural setting. Investigating the effects of MASLD risk alleles on microbial metabolic pathways contributing to liver diseases, and conducting larger cohorts to explore the influence of the host's entire genome on the liver, gut and intestinal microbiome are necessary steps in understanding the role of host genetics in MASLD and HCC gut microbial signatures and vice versa, more crucially, aiding the development of personalised medicine. Research in the field of the direct regulatory role of host genetics on the gut microbiome is still in its preliminary stages, requiring urgent attention in future studies focusing on the underlying biological mechanisms.

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