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Epigenomic Cascades Across Organs in Metabolic Dysfunction–Associated Steatotic Liver Disease: New Therapeutic Horizons

Shurui Yang[1,2,3,4] | Zhongyu Huang[2,3,4] | Sanchun Tan[1] | Fengxia Liang[1,2,3,4] | Li Chen[2,3,4]

[1]Acupuncture and Moxibustion Department, Hubei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Hubei University of Chinese Medicine, Wuhan, China | [2]College of Acupuncture and Orthopedics, Hubei University of Chinese Medicine, Wuhan, China | [3]Hubei Provincial Collaborative Innovation Center of Preventive Treatment by Acupuncture and Moxibustion, Wuhan, China | [4]Hubei Shizhen Laboratory, Wuhan, China

Correspondence: Fengxia Liang (fxliang5@hotmail.com) | Li Chen (3051@hbucm.edu.cn)

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ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disorder worldwide, affecting approximately one-third of the population and increasing the risk of severe hepatic and cardiovascular complications. Growing evidence indicates that MASLD is a systemic disease in which epigenetic changes—including DNA and RNA methylation as well as histone modifications—drive its progression by integrating metabolic and inflammatory signals across organs. This review introduces the concept of "networked epigenome cascades" and highlights how epigenetic alterations in extrahepatic metabolic organs contribute to insulin resistance (IR) and systemic inflammation. MASLD is thereby reframed as a disorder of systemic epigenomic miscommunication rather than a liver-only disease. We further discuss preclinical and emerging interventions, with an emphasis on natural compounds that modulate epigenomic regulation, while noting the uncertainties that remain regarding their translational potential for MASLD. By positioning the epigenome as a central mechanism, this review underscores its promise for biomarker development and mechanistically targeted interventions, although robust validation in humans is still required.

1 | Background

The terminology for fatty liver disease has evolved from nonalcoholic fatty liver disease to metabolic dysfunction–associated fatty liver disease and, most recently, to metabolic dysfunction–associated steatotic liver disease (MASLD) [1, 2]. MASLD spans a continuum that ranges from hepatic steatosis and metabolic dysfunction–associated steatohepatitis (MASH) to fibrosis, cirrhosis, and MASLD-related hepatocellular carcinoma (HCC) [3]. With an estimated global prevalence of approximately 30% and a rising trend, it has become the most common cause of liver disease worldwide and poses a substantial public health and clinical burden [4, 5]. Moreover, MASLD is associated with a markedly increased risk of cardiovascular disease, including myocardial infarction, stroke, heart failure, and cardiovascular mortality [6]. Its progression is shaped by multiple factors, including dietary habits, genetic predisposition, and epigenetic mechanisms [7–11]. Although obesity-related systemic metabolic disorders are strongly associated with MASLD, lean individuals can also develop the disease, underscoring its multifactorial nature [12–14]. Notably, lean patients with MASLD exhibit a lower prevalence of metabolic disorders but higher rates of fibrosis, greater cardiovascular risk, and increased all-cause mortality than non-lean patients [15]. However, no disease-specific drugs have been approved for MASLD, and lifestyle modification remains the mainstay of treatment; nonselective agents such as metformin, thiazolidinediones, ursodeoxycholic acid, and silymarin are commonly used to target associated metabolic pathways [16].

Epigenetics refers to heritable changes in gene function that occur without alterations to the underlying DNA sequence. Such changes encompass DNA methylation, histone modifications, and RNA-mediated processes, which together regulate gene expression, cellular differentiation, and genomic stability [17–21]. Metabolic disturbances can alter the expression and activity of histone methyltransferases and acetyltransferases, thereby producing widespread epigenetic modifications [22, 23]. These modifications, in turn, contribute to IR and hepatic steatosis. Epigenetic studies of metabolism-related diseases have already enabled meaningful clinical progress, with key advances including the development of epigenetic biomarkers, targeted drugs, and gene-editing technologies [24]. Integrating genetic and epigenetic insights into precision-medicine strategies offers considerable potential for refining patient stratification and developing tailored therapeutic interventions [25].

Interorgan communication is itself shaped by metabolic disturbances [26–28]. Within the liver, dysregulated de novo lipogenesis and an imbalance between lipid influx and efflux give rise to lipotoxicity, inducing mitochondrial dysfunction, endoplasmic reticulum stress, and the activation of inflammatory responses [29]. Extrahepatic organs, in turn, influence the liver through multiple pathways [30]. The liver-brain axis regulates hepatic metabolism via neural signals, whereas the liver receives nutrients and bacterial products from the gut through the portal vein [31]. IR in adipose tissue drives an overflow of free fatty acids that activate hepatic macrophages and thereby contribute to MASLD pathogenesis [32]. Muscle-derived follistatin-like 1 modulates hepatic steatosis, inflammation, and fibrosis through distinct receptor-mediated effects across different liver cell populations [33]. Although several studies have documented epigenetic changes in metabolism-related organs, few have examined how these changes are linked to MASLD. Here, we introduce the concept of interorgan epigenomic cascades, framing MASLD as a systemic epigenomic disorder and highlighting new opportunities for early diagnosis, prevention, and therapeutic innovation.

2 | Hepatic Epigenetic Alterations in MASLD

2.1 | DNA Methylation

DNA methylation involves the addition of a methyl group to the fifth carbon of cytosine to form 5-methylcytosine (5mc) [34]. This reaction is catalyzed by DNA methyltransferases (DNMTs), which use S-adenosylmethionine as the methyl donor. Hypermethylation of CpG islands typically silences gene expression, whereas hypomethylation generally promotes gene activation [35]. Patients with MASLD display differential methylation at 65 CpG sites in circulating leukocytes, more than half of which are hypomethylated [36]. Moreover, accelerated DNA methylation age can predict a higher incidence of MASLD [37]. The methylation profile associated with hepatic saturated fatty acids may exert a greater influence on hyperglycemia, whereas the insulin-related methylation profile is more closely linked to MASLD or MASH [38, 39]. The genes involved in methylation and demethylation in MASLD, together with the roles of DNMTs, are summarized in Figure 1 and Table 1.

2.1.1 | Regulatory Roles of Specific Gene Methylation

In hepatocytes, high-fat diet (HFD)–induced demethylation of peroxisome proliferator–activated receptor gamma (*Pparγ*) enhances the expression of lipid-storage genes such as the very low-density lipoprotein receptor (*Vldlr*) and *Cd36*, thereby promoting hepatic lipid accumulation and accelerating the progression of MASLD [40]. Hypomethylation of C-Maf-inducing protein (*Cmip*) activates the *Pparγ-Cd36* signaling pathway via guanylate-binding protein 2 and accelerates the uptake of lipids into hepatocytes [41]. Methylation levels of several hepatic genes—including transforming growth factor beta, Moesin, IQ motif-containing GTPase-activating protein 1, cytochrome b-245 alpha chain, and Fc gamma receptor I—are also reduced, contributing to MASH progression [48]. The expression of L-type pyruvate kinase (L-PK) is decreased in the livers of MASLD rats, consistent with reductions in both DNA hypermethylation and histone deacetylation within its regulatory regions [49]. Elevated fibrosis risk in MASLD promotes active DNA demethylation, as reflected by increased levels of 5-hydroxymethylcytosine (5hmC) and 5-formylcytosine (5fC); this process drives hypomethylation of suppressor of cytokine signaling and upregulates proinflammatory genes, including interleukin-6 (*IL-6*) and monocyte chemoattractant protein-1, as well as the fibrotic gene thioredoxin-interacting protein [50]. Compared with fetal liver, methylation of the fatty acid β-oxidation genes is reduced in adult human liver [51].

Hepatic DNA methylation in other endocrine and metabolic diseases may offer useful clues for future mechanistic studies of MASLD. Methylation of the peroxisome proliferator–activated receptor alpha (*Pparα*) promoter by hepatic adenosine kinase reduces *Pparα* expression, impairs fatty acid oxidation, and increases lipid accumulation in hepatocytes [42]. Demethylation of intronic CpG sites within the dipeptidyl peptidase-4 (*Dpp4*) gene enhances its transcription, a change associated with weight gain, elevated triglyceride levels, and hepatic steatosis [43]. The DNA N6-methyladenine (6mA) level is markedly increased in hepatic steatosis, whereas AlkB homolog 1 expression is markedly downregulated in fatty liver [52]. In addition, genetic variants in fatty acid desaturase 2 may influence the development of MASLD by modulating DNA methylation patterns [53]. These genes are involved primarily in hepatic lipid metabolism.

2.1.2 | Functions of DNMTs

Inhibition of DNA methyltransferase 1 (DNMT1) reduces promoter methylation of autophagy-related genes, thereby enhancing macrophage autophagy and suppressing inflammation to delay MASLD progression [54]. A chronic high-sugar diet promotes MASLD progression through downregulation of DNA methyltransferase 3B (DNMT3B), accompanied by reduced expression of DNMT1, DNA methyltransferase 3A (DNMT3A), and ten-eleven translocation 2 [55]. HFD raises DNMT1 and DNMT3A levels, leading to methylation of the β-klotho (*Klb*) promoter, which impairs fatty acid oxidation and contributes to hepatic steatosis [44]. High glucose-induced elevation of 25-hydroxycholesterol can activate DNMT1 and promote lipid accumulation in hepatocytes [56]. Fibroblast growth factor 1 decreases insulin-like growth factor binding protein 2 (*Igfbp2*)

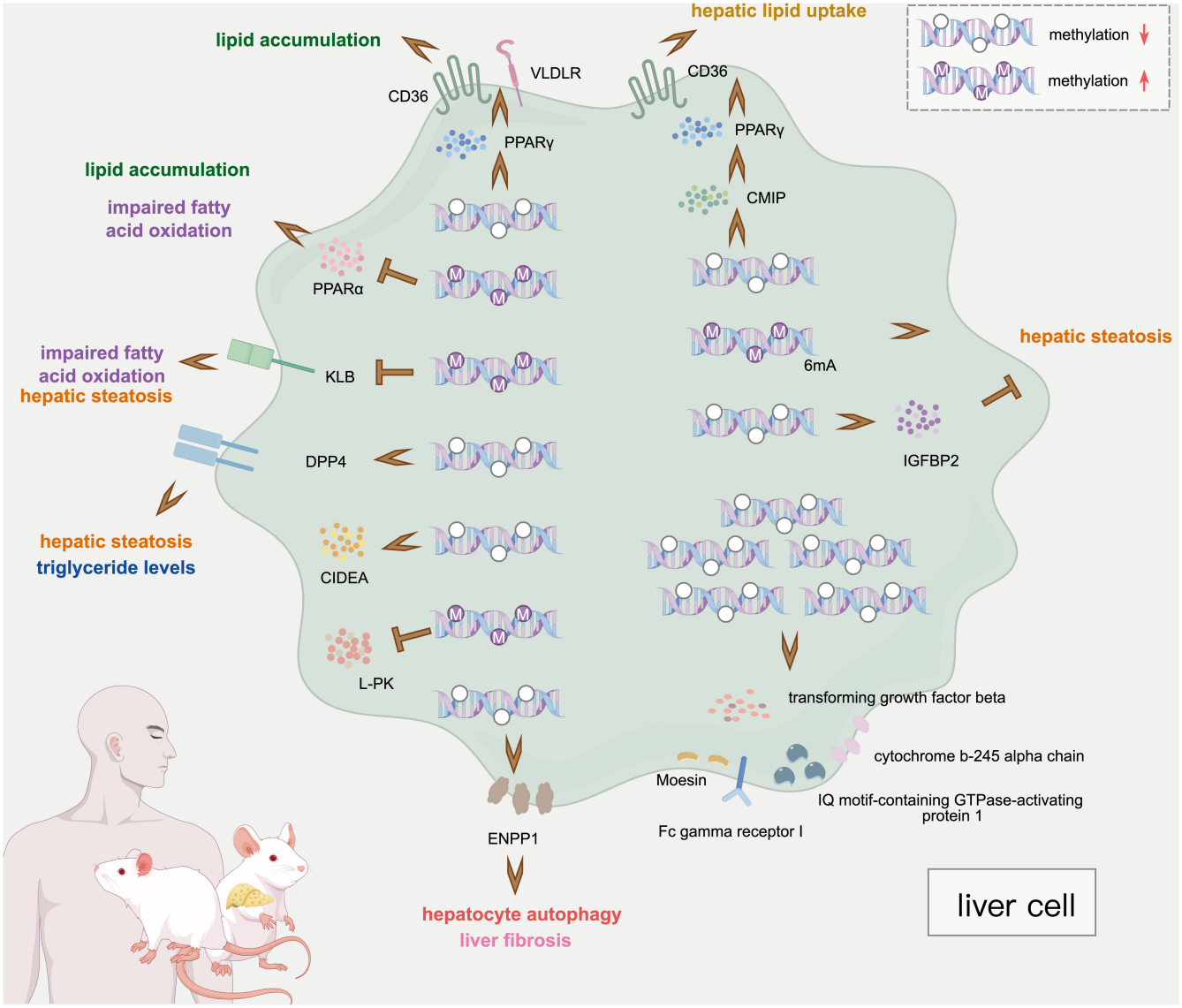

FIGURE 1 | Mechanisms of DNA Methylation in MASLD. It was created by Figdraw (ID: PSYAS7c3f4). VLDLR, very low-density lipoprotein receptor; PPARγ, peroxisome proliferator–activated receptor gamma; PPARα, peroxisome proliferator–activated receptor alpha; KLB, β-klotho; DPP4, dipeptidyl peptidase-4; CIDEA, cell death-inducing DNA fragmentation factor alpha-like effector A; L-PK, L-type pyruvate kinase; ENPP1, ecto-nucleotide pyrophosphatase/phosphodiesterase 1; CMIP, C-Maf-inducing protein; IGFBP2, insulin-like growth factor binding protein 2. Abnormal DNA methylation alters the transcription of lipid metabolism-related genes and their protein expression, thereby promoting lipid storage and triglyceride synthesis while impairing fatty acid oxidation, ultimately driving hepatic steatosis and MASLD.

hypermethylation and increases IGFBP2 expression by inhibiting DNMT3A recruitment, thereby ameliorating hepatic steatosis [45]. Reduced DNMT3B causes hypomethylation of the cell death-inducing DNA fragmentation factor alpha-like effector A (*Cidea*) promoter, enhancing sterol regulatory element-binding protein 1c (SREBP-1c) binding and activating CIDEA expression [46]. Ten-eleven translocation 3 increases ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) expression by demethylating its promoter, thereby boosting hepatocyte autophagy and aggravating liver fibrosis [47].

2.2 | RNA Methylation

The most common form of RNA methylation is N6-methyladenosine (m6A) [57]. It is deposited by methyltransferases such as methyltransferase-like 3 (METTL3) and methyltransferase-like 14 (METTL14), removed by demethylases including fat mass and obesity-associated protein (FTO) and AlkB homolog 5 RNA demethylase, and interpreted by YTH-family proteins that act as readers. Other prevalent forms of RNA methylation include 5-methylcytosine (m5C) and N1-methyladenosine [58, 59]. Their roles in the progression of MASLD are illustrated in Figure 2 and Table 2.

2.2.1 | N6-Methyladenosine (m6A)

Under HFD conditions, METTL3-targeted genes shift toward fatty acid catabolism and the positive regulation of fatty acid oxidation [60]. METTL3 binds Rubicon mRNA to promote its m6A modification, while YTH N6-methyladenosine RNA binding

TABLE 1 | DNA methylation in MASLD.

Epigenetic regulator	Target gene	Methylation level	Functional mechanism	Pathological outcome	References
DNMTs	*Pparγ*	Decrease	Increase expression of *Pparγ* and its target genes *Vldlr* and *Cd36*.	Exacerbate lipid accumulation and the pathogenesis of MASLD.	[40]
DNMT1	*Cmip*	Decrease	Increase expression of *Cmip* and activate the *Pparγ-Cd36* signaling pathway.	Facilitate the entry of hepatic lipids into cells and accelerate MASLD progression.	[41]
Adenosine kinase	*Pparα*	Elevate	Reduce *Pparα* expression.	Reduce fatty acid oxidation, contributing to excessive lipid accumulation.	[42]
Not mentioned	*Dpp4*	Decrease	Facilitate *Dpp4* transcription.	Accompanied by weight gain, increased triglyceride levels, and hepatic steatosis.	[43]
DNMT1 and DNMT3A	*Klb*	Elevate	Reduce *Klb* expression.	Inhibit fatty acid oxidation, leading to the development of hepatic steatosis.	[44]
DNMT3A	*Igfbp2*	Decrease	Increase *Igfbp2* expression.	Ameliorate hepatic steatosis.	[45]
DNMT3B	*Cidea*	Decrease	Promote *Cidea* expression.	Promote hepatic steatosis.	[46]
Ten-eleven translocation methylcytosine dioxygenase 3	*Enpp1*	Decrease	Increase expression of *Enpp1*.	Enhance hepatocyte autophagy and aggravate hepatic fibrosis.	[47]

Abbreviations: *Cidea*, cell death-inducing DNA fragmentation factor alpha-like effector A; *Cmip*, C-Maf-inducing protein; DNMTs, DNA methyltransferases; DNMT1, DNA methyltransferase 1; DNMT3A, DNA methyltransferase 3A; DNMT3B, DNA methyltransferase 3B; *Dpp4*, dipeptidyl peptidase-4; *Enpp1*, ecto-nucleotide pyrophosphatase/phosphodiesterase 1; *Igfbp2*, insulin-like growth factor binding protein 2; *Klb*, β-klotho; MASLD, metabolic dysfunction–associated steatotic liver disease; *Pparα*, peroxisome proliferator–activated receptor alpha; *Pparγ*, peroxisome proliferator–activated receptor gamma; *Vldlr*, very low-density lipoprotein receptor.

protein 1 (YTHDF1) recognizes the m6A-modified Rubicon mRNA and enhances its stability [74]. METTL3 impairs hepatic insulin sensitivity by catalyzing m6A methylation of fatty acid synthase (*Fasn*) and cytochrome P450 family 2 subfamily B member 6 (*Cyp2b6*) mRNAs, thereby enhancing fatty acid metabolism while inhibiting insulin receptor substrate (IRS) phosphorylation and glucose transporter type 2 (GLUT2) membrane translocation [61, 62]. In addition, the METTL3-m6A-YTH N6-methyladenosine RNA binding protein 2 axis disrupts the rhythm of lipid metabolism by degrading *Pparα* mRNA, thereby promoting lipid accumulation [63]. METTL3 further increases ATP citrate lyase (ACLY) and stearoyl-CoA desaturase 1 (SCD1) protein levels through m6A modification, intensifying fatty acid synthesis and lipid accumulation [64]. Conversely, silencing METTL3 attenuates MASLD progression by modulating *Fasn* m6A methylation [65]. However, conflicting evidence also exists. Several studies have shown that METTL3 suppresses *Cd36* and C-C motif chemokine ligand 2 (*Ccl2*) transcription by recruiting histone deacetylase 1/2 to their promoters, thereby preventing MASH development under a methionine- and choline-deficient diet [66]. Likewise, hepatocyte-specific METTL3 deficiency aggravates MASLD progression by impairing the m6A-dependent regulation of lipid-metabolism genes [67]. These discrepant findings indicate that the role of METTL3 in MASLD is context-dependent—varying with diet, disease stage, and target gene—and warrants further mechanistic investigation. METTL14 deficiency downregulates glutaminase 2 (GLS2) via m6A-YTHDF1, inducing oxidative stress and recruiting C-X3-C motif chemokine receptor 1 (Cx3cr1)+ C-C motif chemokine receptor 2 (Ccr2)+ macrophages [68]. These macrophages activate the S100 calcium-binding protein A4 (S100A4)+ subtype through the Cx3cr1/myeloid differentiation primary response 88 (MyD88)/nuclear factor kappa-B (NF-κB) pathway, ultimately driving liver fibrosis [68]. METTL14 also enhances the binding of DiGeorge critical region 8 to pri-miR-34a through m6A modification, thereby promoting miR-34a-5p expression; this microRNA (miRNA) suppresses SID1 transmembrane family member 2 (SIDT2), leading to mitochondrial dysfunction and exacerbating

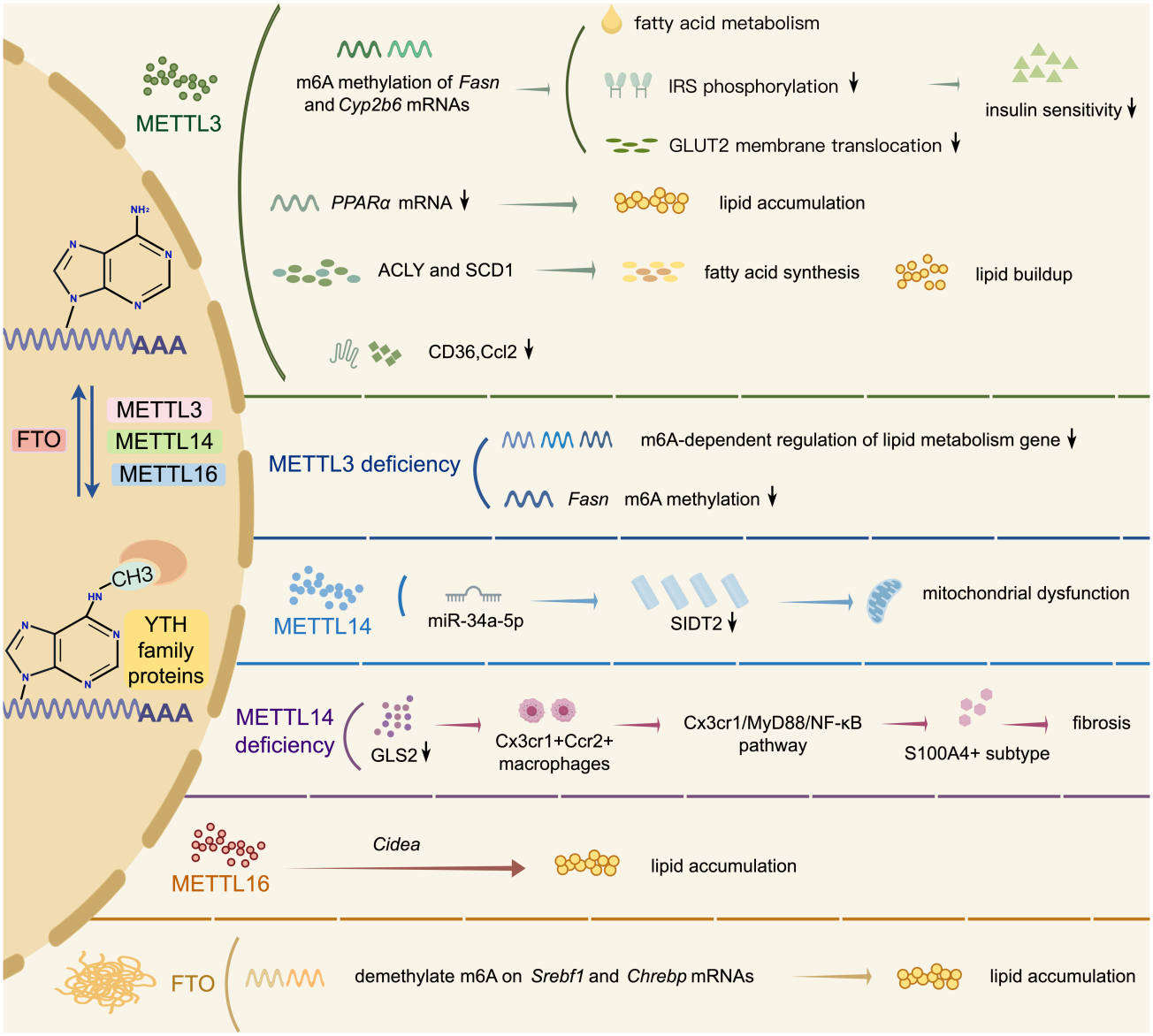

FIGURE 2 | Mechanisms of N6-methyladenosine in MASLD. It was created by Figdraw (ID: WTSUSfa56f). METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; FTO, fat mass and obesity-associated protein; *Fasn*, fatty acid synthase; *Cyp2b6*, cytochrome P450 family 2 subfamily B member 6; IRS, insulin receptor substrate; GLUT2, glucose transporter type 2; PPARα, peroxisome proliferator–activated receptor alpha; ACLY, ATP citrate lyase; SCD1, stearoyl-CoA desaturase 1; *Ccl2*, C-C motif chemokine ligand 2; SIDT2, SID1 transmembrane family member 2; GLS2, glutaminase 2; Cx3cr1, C-X3-C motif chemokine receptor 1; Ccr2, C-C motif chemokine receptor 2; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-B; S100A4, S100 calcium-binding protein A4; *Cidea*, cell death-inducing DNA fragmentation factor alpha-like effector A; *Srebf1*, sterol regulatory element binding transcription factor 1; *Chrebp*, carbohydrate-responsive element-binding protein. m6A modification affects MASLD via METTL3, FTO, METTL14, and METTL16, altering lipid metabolism, adipogenesis, and fatty acid oxidation pathways.

MASLD progression [69]. Methyltransferase-like 16 (METTL16) expression is substantially increased in both in vivo and in vitro MASLD models, and METTL16 has been shown to upregulate the lipogenic gene *Cidea* in HepG2 cells [70].

FTO promotes MASLD by demethylating m6A on lipid-related mRNAs, leading to lipid accumulation and reduced fatty acid oxidation [71, 72]. Specifically, it drives hepatic lipid accumulation by demethylating m6A on sterol regulatory element binding transcription factor 1 (*Srebf1*) and carbohydrate-responsive element-binding protein (*Chrebp*) mRNAs [73]. The *FTO* variants rs1421085-C, rs8050136-A, rs3751812-T, and rs9939609-A—particularly the C-A-T-A haplotype—are significantly associated with increased MASLD risk in the older Chinese Han population, likely through shared genetic linkage and metabolic dysregulation [75]. Moreover, a genome-wide meta-analysis identified genetic variants near glucokinase regulatory protein, tribbles pseudokinase 1, AU2 sister chromatid cohesion factor/transmembrane 6 superfamily member 2, apolipoprotein E, patatin-like phospholipase domain-containing protein 3, and FTO as susceptibility loci for MASLD [76].

TABLE 2 | m6A modification in MASLD.

Classification	Type	Mechanism	References
Methyltransferase (WRITER)	METTL3	METTL3-targeted genes participate in fatty acid catabolism and positively regulate fatty acid oxidation.	[60]
		Enhance m6A methylation of *Fasn* and *Cyp2b6* mRNAs, reducing hepatic insulin sensitivity, promoting fatty acid metabolism, and inhibiting IRS phosphorylation and GLUT2 membrane translocation, ultimately impairing insulin sensitivity.	[61, 62]
		Degrade *Pparα* mRNA via the METTL3-m6A-YTH N6-methyladenosine RNA binding protein 2 axis, promoting lipid accumulation and disrupting the rhythm of lipid metabolism.	[63]
		Promote ACLY and SCD1 expression, thereby boosting fatty acid synthesis and lipid accumulation.	[64]
		Silencing METTL3 ameliorates the disease by regulating *Fasn* m6A methylation.	[65]
		Inhibit *Cd36* and *Ccl2* transcription to prevent MASH development.	[66]
		METTL3 deficiency in hepatocytes disrupts the m6A-dependent regulation of lipid-metabolism genes.	[67]
	METTL14	METTL14 deficiency induces oxidative stress by decreasing GLS2 expression and recruiting Cx3cr1 + Ccr2 + macrophages, which activate the S100A4 + subtype through the Cx3cr1/MyD88/NF-κB pathway, ultimately promoting hepatic fibrosis.	[68]
		Increase miR-34a-5p expression, thereby inhibiting SIDT2 and causing mitochondrial dysfunction.	[69]
	METTL16	Promote expression of the lipogenic gene *Cidea*.	[70]
Demethylase (ERASER)	FTO	Demethylate m6A on lipid-related mRNAs to promote lipid accumulation and reduce fatty acid oxidation.	[71, 72]
		Demethylate m6A on *Srebf1* and *Chrebp* mRNAs, enhancing their stability and promoting hepatic lipid accumulation.	[73]

Abbreviations: ACLY, ATP citrate lyase; *Ccl2*, C-C motif chemokine ligand 2; Ccr2, C-C motif chemokine receptor 2; *Chrebp*, carbohydrate-responsive element-binding protein; *Cidea*, cell death-inducing DNA fragmentation factor alpha-like effector A; Cx3cr1, C-X3-C motif chemokine receptor 1; *Cyp2b6*, cytochrome P450 family 2 subfamily B member 6; *Fasn*, fatty acid synthase; FTO, fat mass and obesity-associated protein; GLS2, glutaminase 2; GLUT2, glucose transporter type 2; IRS, insulin receptor substrate; MASH, metabolic dysfunction–associated steatohepatitis; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-B; PPARα, peroxisome proliferator–activated receptor alpha; SCD1, stearoyl-CoA desaturase 1; SIDT2, SID1 transmembrane family member 2; *Srebf1*, sterol regulatory element-binding transcription factor 1.

2.2.2 | m5C Modification

Research on m5C modification has focused mainly on hepatocellular carcinoma and acute liver injury [77–79]. Nevertheless, several studies have also revealed a role for it in lipid metabolism. LINC00618 enhances the stability of NOP2/Sun RNA methyltransferase 2 (NSUN2), increasing m5C modification and stabilizing sterol regulatory element-binding protein 2 mRNA in a Y-box binding protein 1-dependent manner, thereby promoting cholesterol synthesis in hepatocellular carcinoma cells [80]. Similarly, cyclin-dependent kinase 13 (CDK13) induces phosphorylation of NOP2/Sun RNA methyltransferase 5 at Ser327, increasing m5C modification of acetyl-CoA carboxylase 1 (*ACC1*) mRNA and thereby elevating fatty acid synthesis and lipid deposition in prostate cancer [81]. Because selective ACC1 inhibitors effectively reduce hepatic steatosis and delay MASLD progression [82], m5C modification of *ACC1* may play a comparable role in the liver. In addition, NSUN2-mediated m5C modification of cyclin-dependent kinase inhibitor 1A (*Cdkn1a*) mRNA enhances its expression via the Aly/REF export factor, thereby inhibiting adipogenesis [83]. As CDKN1A is a potential key regulator of MASLD [84], NSUN2-mediated m5C modification may exert a similar effect in this disease. These processes are illustrated in Figure 3.

2.2.3 | Other Methylation Modifications

RNA N1-methyladenosine (m1A) modification regulates immune-cell activity and contributes to the heterogeneity and inflammatory progression of MASLD, with key m1A regulatory genes modulating immune responses and signaling pathways [85]. In the HEK293 cell line, 61 genes were found to harbor frequent 2′-O-methylation (Nm) modifications, which were significantly enriched in pathways such as glycolysis and

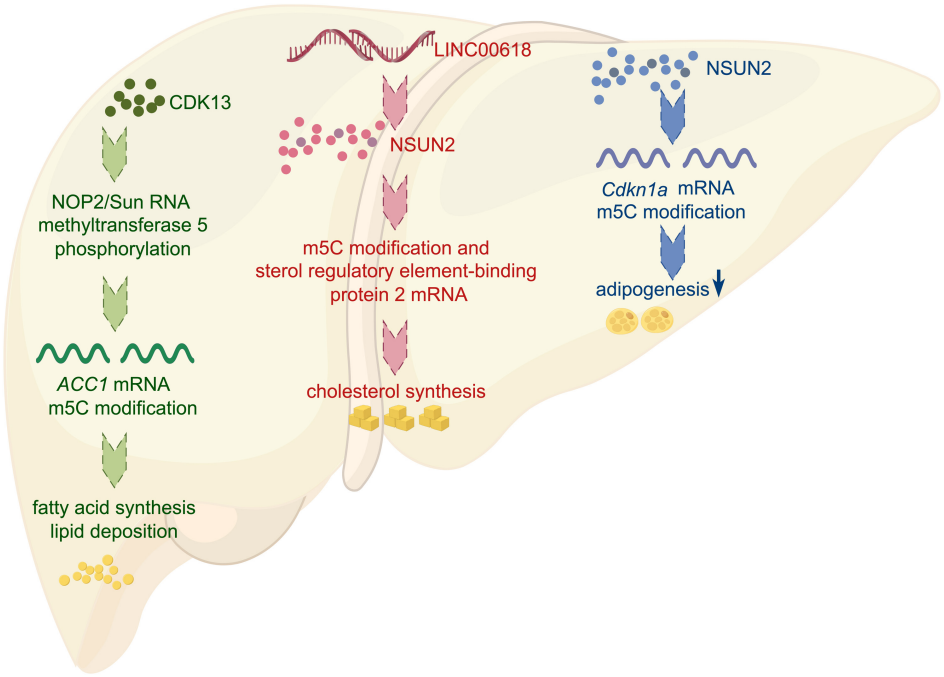

FIGURE 3 | m5C modification associated with MASLD. It was created by Figdraw (ID: UTWSY5ca5a). CDK13, cyclin-dependent kinase 13; *ACC1*, acetyl-CoA carboxylase 1; NSUN2, NOP2/Sun RNA methyltransferase 2; *Cdkn1a*, cyclin-dependent kinase inhibitor 1A. m5C modifications mediated by NSUN2 and CDK13 regulate lipid metabolism by influencing cholesterol synthesis, fatty acid accumulation, and adipogenesis, and may exert similar effects in hepatic tissue.

gluconeogenesis [86]. Furthermore, 7-methylguanosine and Nm are associated primarily with the development of liver cancer, although whether they are involved in MASLD remains unknown.

2.3 | Histone Modification

Histone modifications critically influence the progression of various chronic liver diseases by modulating gene transcription [87]. Genome-wide variation in H3K27ac alters the expression of key metabolic genes—such as cytochrome P450 family 8 subfamily B member 1, phospholipase A2 group XIIB, and cytochrome P450 family 7 subfamily A member 1—thereby driving disease progression [88]. Insulin enhances FASN expression in MASLD by promoting SREBP-1c and ChREBP binding to the *FASN* promoter and by increasing H3K4 trimethylation and H3/H4 acetylation [89]. Similarly, high-fat or high-fructose diets increase global histone acetylation in steatotic livers, accompanied by chromatin relaxation and DNA damage [90].

2.3.1 | Histone-Modifying Enzyme-Mediated Acetylation and Deacetylation

Both acetyltransferases and deacetylases play vital roles in the pathogenesis and progression of MASLD. Acetyltransferases promote lipogenesis and hepatic lipid accumulation by acetylating transcription factors involved in lipid metabolism, and they also amplify NF-κB-mediated inflammatory responses. By contrast, deacetylases such as Sirtuin 1 (SIRT1), Sirtuin 3 (SIRT3), and Sirtuin 6 (SIRT6) exert protective effects by promoting fatty acid oxidation, suppressing lipid synthesis, and mitigating inflammation. Classical histone deacetylases (HDACs)—including histone deacetylase 3 (HDAC3), histone deacetylase 4 (HDAC4), and histone deacetylase 6 (HDAC6)—help regulate hepatic metabolic rhythms, lipid homeostasis, and autophagy, with roles that are context-dependent and sometimes dual. These effects are depicted in Figure 4 and Table 3.

The acetyltransferase p300 enhances hepatic lipogenesis by increasing the transcriptional activity and stability of *Srebp-1c* and by synergizing with CCAAT/enhancer-binding protein alpha (C/EBPα) to drive lipogenic gene expression [91–93]. p300 also promotes lipogenesis through ChREBP activation, whereas its inhibition suppresses lipogenic genes and ameliorates disease [94–96]. General control nonderepressible 5 (GCN5) acetylates peroxisome proliferator–activated receptor gamma coactivator 1-alpha (PGC-1α), diminishing its ability to coactivate transcription factors such as forkhead box O1 (FOXO1) and hepatocyte nuclear factor 4 alpha (HNF4α), thereby suppressing gluconeogenic gene expression [97]. Tip60 forms a complex with regulator of G-protein signaling 7 and activating transcription factor 3 (ATF3) to promote tumor necrosis factor-α (TNF-α) release and oxidative stress, thereby driving hepatocellular injury, inflammation, and fibrosis [98]. Males absent on the first promotes transcriptional activation of the *Cd36* promoter by the circ-solute carrier family 9 member A6 (SLC9A6)-derived peptide SLC9A6-126aa through H4K16 acetylation [113]. Reduced LPS-binding protein (LBP) induces excessive H3K27 acetylation via CCAAT/enhancer-binding protein beta (C/EBPβ), which upregulates the lipid-metabolism gene stearoyl-CoA desaturase (*Scd*) and ultimately results in lipid deposition [99]. Enrichment of H3K27ac at the nuclear paraspeckle assembly transcript 1

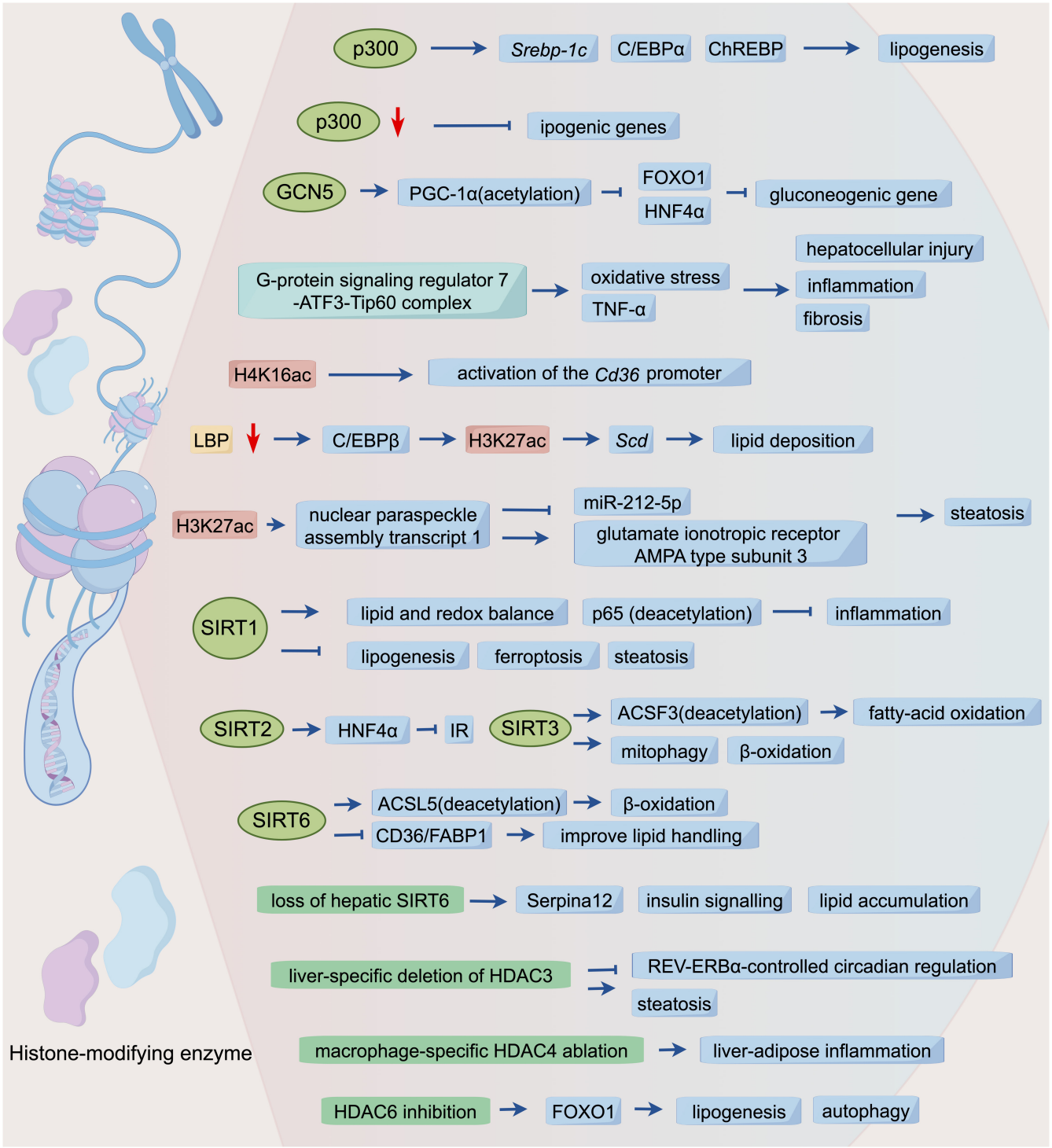

FIGURE 4 | Mechanism of histone acetylation in MASLD. It was created by Figdraw (ID: TOYUP995f5). *Srebp-1c*, sterol regulatory element-binding protein 1c; C/EBPα, CCAAT/enhancer-binding protein alpha; ChREBP, carbohydrate-responsive element-binding protein; GCN5, general control non-derepressible 5; PGC-1α, peroxisome proliferator–activated receptor gamma coactivator 1-alpha; FOXO1, forkhead box O1; HNF4α, hepatocyte nuclear factor 4 alpha; ATF3, activating transcription factor 3; TNF-α, tumor necrosis factor-α; LBP, LPS-binding protein; C/EBPβ, CCAAT/enhancer-binding protein beta; *Scd*, stearoyl-CoA desaturase; SIRT1, Sirtuin 1; SIRT2, Sirtuin 2; IR, insulin resistance; SIRT3, Sirtuin 3; ACSF3, acyl-CoA synthetase family member 3; SIRT6, Sirtuin 6; ACSL5, acyl-CoA synthetase long-chain family member 5; FABP1, fatty acid binding protein 1; HDAC3, histone deacetylase 3; HDAC4, histone deacetylase 4; HDAC6, histone deacetylase 6. Histone acetylation and deacetylation, regulated by enzymes such as p300, SIRTs, and HDACs, modulate lipid metabolism, inflammation, and mitochondrial function, thereby profoundly influencing MASLD progression.

TABLE 3 | Histone acetylation and deacetylation in MASLD.

Classification	Type	Mechanism	References
Acetylation	p300	Promote lipogenesis by enhancing the transcription of *Srebp-1c* and cooperating with C/EBPα.	[91–93]
		Activate ChREBP to promote lipogenesis, whereas inhibiting p300 reduces the expression of lipogenic genes.	[94–96]
	GCN5	Acetylate PGC-1α, reducing its coactivation of FOXO1 and HNF4α and thereby inhibiting the expression of gluconeogenic genes.	[97]
	Tip60	The RGS7-ATF3-Tip60 complex promotes TNF-α release and oxidative stress, leading to hepatocellular injury, inflammation, and fibrosis.	[98]
Deacetylation	LBP	LBP deficiency causes H3K27 hyperacetylation through C/EBPβ, which promotes *Scd* expression and lipid deposition.	[99]
	SIRT1	Deacetylate p65 and maintain lipid and redox homeostasis to reduce inflammation.	[100–102]
		Inhibit lipogenesis, restrict ferroptosis, and reduce hepatic steatosis.	[103]
	SIRT2	Stabilize HNF4α to ease IR.	[104]
	SIRT3	Deacetylate ACSF3 to enhance fatty acid oxidation.	[105]
		Induce mitochondrial autophagy and enhance β-oxidation.	[106]
	SIRT6	Target ACSL5 to promote β-oxidation.	[107]
		Loss of hepatic SIRT6 activates insulin signaling and exacerbates lipid accumulation by upregulating Serpina12.	[108]
		Downregulate CD36/FABP1 to improve lipid handling.	[109]
	HDAC3	Liver-specific deletion of HDAC3 disrupts circadian regulation and induces steatosis.	[110]
	HDAC4	Macrophage-specific HDAC4 ablation exacerbates liver–adipose inflammation in male models.	[111]
	HDAC6	Reducing HDAC6 activity activates FOXO1, promoting lipogenesis and autophagy.	[112]

Abbreviations: ACSF3, acyl-CoA synthetase family member 3; ACSL5, acyl-CoA synthetase long-chain family member 5; ATF3, activating transcription factor 3; C/EBPα, CCAAT/enhancer-binding protein alpha; C/EBPβ, CCAAT/enhancer-binding protein beta; ChREBP, carbohydrate-responsive element-binding protein; FABP1, fatty acid-binding protein 1; FOXO1, forkhead box O1; GCN5, general control nonderepressible 5; HDAC3, histone deacetylase 3; HDAC4, histone deacetylase 4; HDAC6, histone deacetylase 6; HNF4α, hepatocyte nuclear factor 4 alpha; IR, insulin resistance; LBP, LPS-binding protein; PGC-1α, peroxisome proliferator–activated receptor gamma coactivator 1-alpha; *Scd*, stearoyl-CoA desaturase; *Srebp-1c*, sterol regulatory element-binding protein 1c; SIRT1, Sirtuin 1; SIRT2, Sirtuin 2; SIRT3, Sirtuin 3; SIRT6, Sirtuin 6; TNF-α, tumor necrosis factor-α.

promoter enhances its expression, represses miR-212-5p, and upregulates glutamate ionotropic receptor AMPA type subunit 3, thereby exacerbating steatosis [114].

SIRT1 mitigates inflammation by deacetylating p65 while preserving lipid and redox homeostasis [100–102]. Activation of SIRT1 further suppresses lipogenesis, limits ferroptosis, and alleviates hepatic steatosis in HFD-fed mice [103]. Sirtuin 2 (SIRT2) stabilizes HNF4α, thereby easing IR [104]. SIRT3 promotes fatty acid oxidation by deacetylating acyl-CoA synthetase family member 3 (ACSF3) [105]. It also enhances β-oxidation and mitophagy, thereby alleviating MASLD through the forkhead box O3 and BCL2/adenovirus E1B 19-kDa protein-interacting protein 3 pathways [106]. Likewise, SIRT6 promotes β-oxidation by targeting acyl-CoA synthetase long-chain family member 5 (ACSL5) [107]. Loss of hepatic SIRT6 upregulates Serpina12, activates insulin signaling, and worsens lipid accumulation [108], whereas SIRT6 activation downregulates CD36/fatty acid binding protein 1 (FABP1) and improves lipid handling in db/db mice [109]. Among Zn^{2+}-dependent HDACs, liver-specific deletion of HDAC3 disrupts REV-ERBα-controlled circadian regulation and precipitates severe steatosis [110]. Macrophage-specific HDAC4 ablation intensifies liver–adipose inflammation in male MASH models, revealing marked sexual dimorphism [111]. Conversely, HDAC6 inhibition activates FOXO1, thereby promoting lipogenesis and autophagy [112].

2.3.2 | Histone Methylation and Demethylation

Histone methylation and demethylation are important modes of epigenetic regulation, mediated by histone methyltransferases and histone demethylases, respectively. These enzymes act on specific histone residues, such as H3K4, H3K9, H3K27, H3K36, and H4K20. Slug, also known as Snail family transcriptional repressor 2, binds the *Fasn* promoter and recruits lysine-specific demethylase 1A (LSD1) to catalyze H3K9 demethylation, thereby promoting Fasn expression and lipogenesis [115]. Jumonji domain-containing protein 2B (JMJD2B)

contributes to hepatic steatosis by removing the repressive H3K9me2 and H3K9me3 marks at the peroxisome proliferator–activated receptor gamma 2 (*Pparγ2*) and liver X receptor response element (LXRE) promoters, thereby enhancing LXRα-mediated adipogenesis [116]. This effect can be reversed by pirfenidone, which downregulates JMJD2B and restores H3K9me3 marks, thereby reducing inflammation and steatosis in MASH [117]. Lysine demethylase 7A (KDM7A) further promotes hepatic steatosis by decreasing H3K9me2 and H3K27me2 enrichment at the diacylglycerol O-acyltransferase 2 (*Dgat2*) promoter and upregulating DGAT2 expression [118]. By contrast, lysine-specific demethylase 6B (KDM6B) is enriched at the Snail family transcriptional repressor 1 (*Snai1*) promoter and upregulates SNAI1 expression through demethylation, thereby inhibiting adipogenesis and enhancing lipolysis [119]. In addition, the histone methyltransferase Suv39h2 promotes MASH progression by repressing Vanin-1, leading to impaired fatty acid oxidation [120]. These changes are illustrated in Figure 5 and Table 4.

2.4 | Noncoding RNA

2.4.1 | miRNA

miRNA-mediated repression operates in a simple on–off manner [122]. The miRNAs most closely related to MASLD include miR-223, miR-192-5p, miR-33a/b, miR-34a, miR-27a/b, miR-218-5p, and miR-122. miR-223 inhibits lipid deposition and fibrosis by downregulating E2F transcription factor 1 (E2F1) [123]. It also suppresses profibrotic genes such as PDZ-binding motif (*Taz*), NOD-like receptor thermal protein domain associated protein 3 (*Nlrp3*), C-X-C motif chemokine 10 (*Cxcl10*), and insulin-like growth factor 1 receptor (*Igf1r*), thereby protecting against liver fibrosis [124, 125]. In the liver, miR-33a expression correlates positively with PGC-1α and upstream transcription factor 1 (USF1), whereas miR-33b correlates negatively with carnitine palmitoyltransferase 1A (CPT1A) [126]. Lipotoxic hepatocyte–derived exosomal miR-192-5p promotes macrophage polarization toward the proinflammatory M1 phenotype by modulating

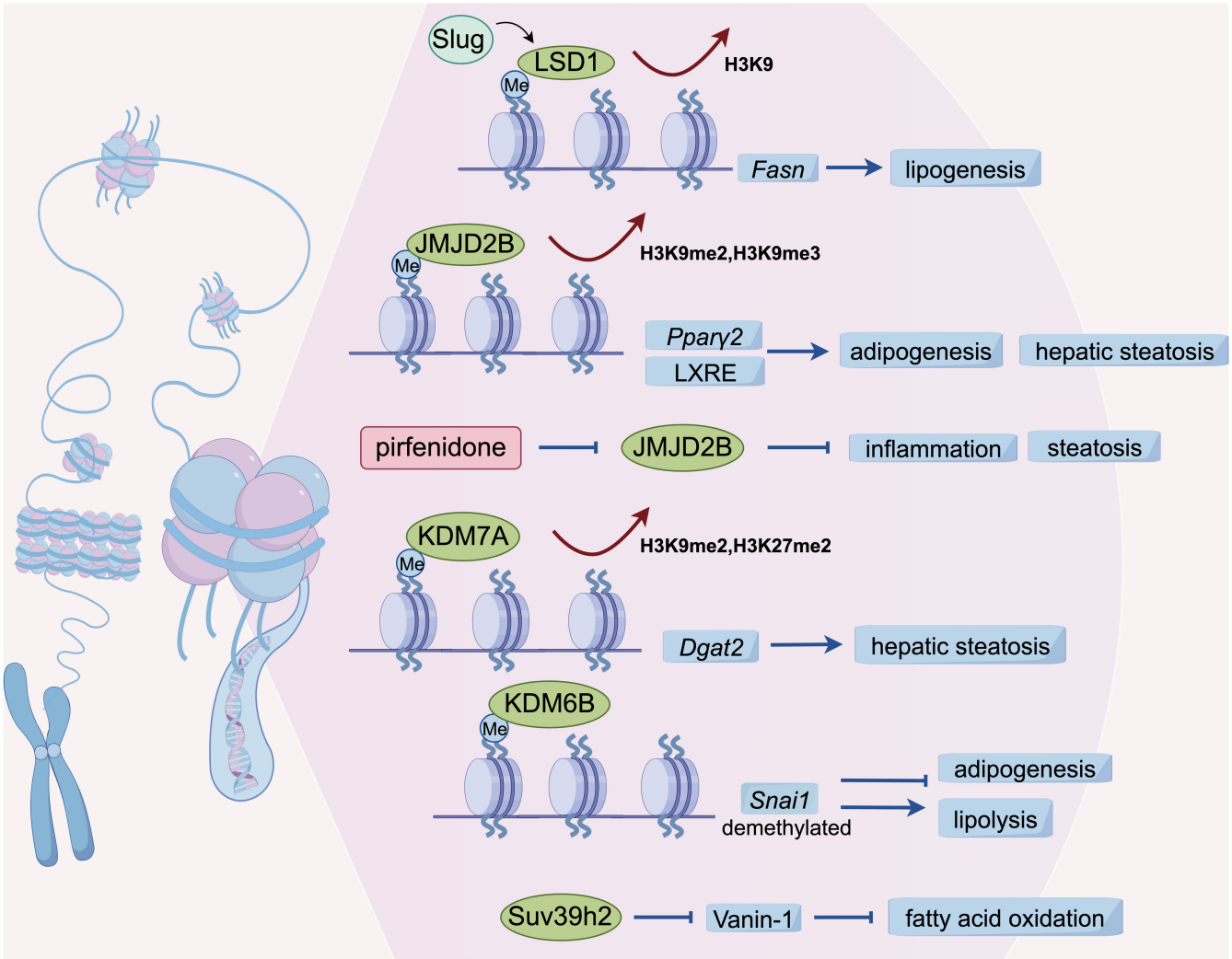

FIGURE 5 | Mechanism of histone methylation in MASLD. It was created by Figdraw (ID: PPzrqaa71a). LSD1, lysine-specific demethylase 1A; *Fasn*, fatty acid synthase; JMJD2B, Jumonji domain-containing protein 2B; *Pparγ2*, peroxisome proliferator–activated receptor gamma 2; LXRE, liver X receptor response element; KDM7A, lysine demethylase 7A; *Dgat2*, diacylglycerol O-acyltransferase 2; KDM6B, lysine-specific demethylase 6B; *Snai1*, Snail family transcriptional repressor 1. Histone methylation regulators such as KDM7A, Suv39h2, and JMJD2B promote hepatic steatosis and inflammation, whereas KDM6B counteracts these effects by enhancing lipolysis.

TABLE 4 | Histone methylation in MASLD.

Classification	Type	Mechanism	References
Methylation	Suv39h2	Downregulate Vanin-1 to disrupt fatty acid oxidation.	[120]
Demethylation	LSD1	Catalyze H3K9 demethylation of the *Fasn* promoter to promote lipogenesis.	[115]
	JMJD2B	Eliminate the repressive marks H3K9me2 and H3K9me3 at the *Pparγ2* and LXRE promoters, thus facilitating adipogenesis and triggering hepatic steatosis.	[116, 121]
		Reducing JMJD2B can ameliorate inflammation and steatosis in MASH.	[117]
	KDM7A	Reduce the enrichment of H3K9me2 and H3K27me2 at the *Dgat2* promoter, thereby increasing DGAT2 expression and ultimately inducing hepatic steatosis.	[118]
	KDM6B	Upregulate SNAI1 expression through demethylation, thereby inhibiting adipogenesis and promoting lipolysis.	[119]

Abbreviations: *Dgat2*, diacylglycerol O-acyltransferase 2; *Fasn*, fatty acid synthase; JMJD2B, Jumonji domain-containing protein 2B; KDM6B, lysine-specific demethylase 6B; KDM7A, lysine demethylase 7A; LSD1, lysine-specific demethylase 1A; LXRE, liver X receptor response element; *Pparγ2*, peroxisome proliferator–activated receptor gamma 2; SNAI1, Snail family transcriptional repressor 1.

the rapamycin-insensitive companion of mammalian target of rapamycin (Rictor)/protein kinase B (Akt)/FOXO1 signaling pathway [127]. However, miR-192-5p also targets SCD-1, thereby suppressing hepatic lipid synthesis and accumulation in MASLD [128]. miR-34a activates hepatic transforming growth factor-β (TGF-β) signaling, which may contribute to hepatocyte apoptosis [129]. miR-27b promotes hepatic lipid accumulation, at least in part, by repressing β-1,4-galactosyltransferase 3 (*B4GALT3*), matrix AAA peptidase interacting protein 1 (*MAIP1*), and PH domain and leucine rich repeat protein phosphatase 2 (*PHLPP2*) [130]. By contrast, miR-27a inhibits *Fasn* and *Scd1* expression and suppresses lipid accumulation in hepatocytes, thereby delaying the development of MASLD [131]. miR-218-5p targets *Elovl5* and directly regulates the SREBP1-mediated fatty acid synthesis pathway in MASLD [132]. miR-122 suppresses the serine/threonine kinase 11 (LKB1)/AMP-activated protein kinase (AMPK) signaling pathway by directly downregulating *Sirt1*, thereby inducing steatosis and lipogenesis in MASLD [133]. Conversely, inhibition of miR-122 suppresses the Toll-like receptor 4 (TLR4)/MyD88/NF-κB p65 signaling pathway and attenuates lipid accumulation and inflammation in oleic acid–induced L02 cells [134]. These regulatory mechanisms are presented in Figure 6 and Table 5.

For the detection of MASLD, liver biopsy remains the diagnostic gold standard but may cause complications, whereas serum miRNA-based diagnosis is noninvasive and promising [135]. Serum levels of miR-122 can aid in the diagnosis of MASH and the prediction of mortality in patients with MASLD [136]. Nevertheless, the predictive value of miRNAs for MASLD remains insufficiently developed, and whether the cross-expression of individual factors is interrelated requires further investigation.

2.4.2 | Long Noncoding RNA (lncRNA)

HFD-fed, insulin-resistant mice exhibit dysregulated hepatic expression of 37 lncRNAs and 254 protein-coding RNAs [137]. The lncRNA growth arrest-specific 5 (GAS5) is markedly upregulated in patients with MASLD, correlating positively with NOTCH2 and negatively with miR-29a-3p, with the highest levels observed in cirrhosis [138]. LncTNF promotes MASLD by activating the NF-κB signaling pathway, thereby causing liver inflammation and lipogenesis [139]. In human liver samples, LINC01468 promotes lipogenesis and HCC progression by enhancing cullin 4A–mediated SHIP2 degradation, thereby relieving SHIP2-dependent inhibition of phosphoinositide 3-kinase (PI3K)/Akt [140]. In MASLD mice, the lncRNA HOX transcript antisense RNA (HOTAIR) regulates the miR-130b-3p/ROCK1 axis to promote hepatic lipid accumulation [141]. The lncRNA AK142643 promotes hepatic lipid accumulation by enhancing insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2)–mediated stabilization and upregulation of CD36 in the livers of ob/ob and HFD mice [142]. LncRNA Gm28382 is significantly elevated in ex vivo and in vivo MASLD models and binds miR-326-3p to promote ChREBP-mediated lipid synthesis [143]. In addition, in patients with MASLD and HFD-fed mice, the lncRNA HLA complex group 18 (HCG18) promotes hepatic lipid accumulation and IR via miR-197-3p [144]. These mechanisms are depicted in Figure 7 and Table 6.

3 | Epigenetic Influences of Metabolic Tissues on the Development and Progression of MASLD

Epigenetic changes in nonhepatic metabolic organs can influence MASLD both by causing organ-specific dysfunction and by transmitting signals that alter liver metabolism. Dysregulation in the brain, skeletal muscle, gut, adipose tissue, and pancreas can affect the liver by modulating insulin sensitivity, substrate flux, inflammation, and fibrogenic signaling. Although definitive causal evidence is still lacking, this framework supports the concept of a "networked epigenome cascade," as illustrated in Figure 8.

3.1 | Brain

Neural pathways—particularly the hypothalamic nuclei and the autonomic nervous system—play a central role in coordinating the bidirectional metabolic crosstalk between the brain and the liver [145]. Oxidation resistance 1 acts as a coactivator of PRMT5 to promote H3R2me2s at the *Gh* promoter, thereby sustaining

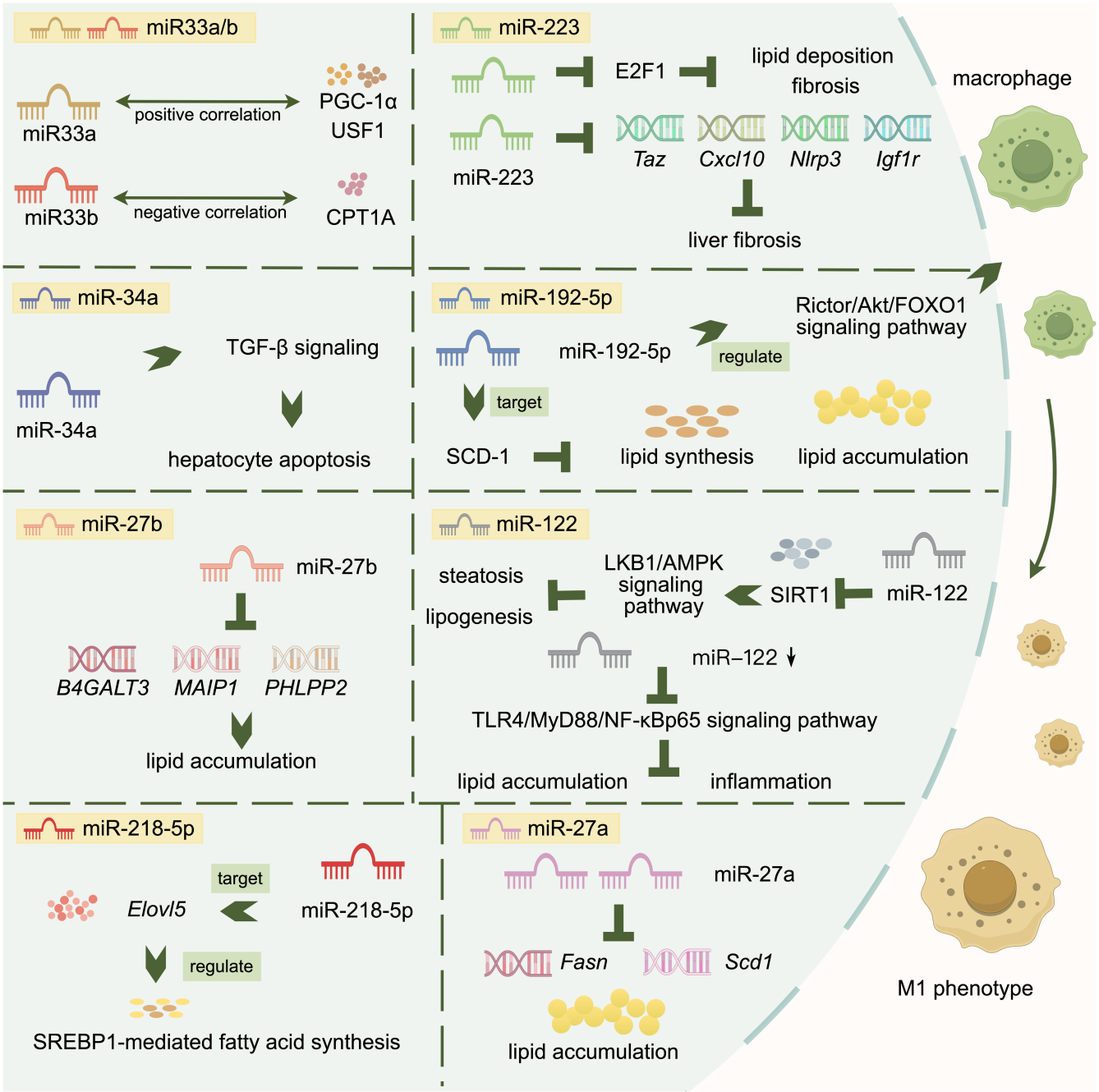

FIGURE 6 | Mechanism of microRNA in MASLD. It was created by Figdraw (ID: IAUOOa2a99). PGC-1α, peroxisome proliferator–activated receptor gamma coactivator 1-alpha; USF1, upstream transcription factor 1; CPT1A, carnitine palmitoyltransferase 1A; E2F1, E2F transcription factor 1; *Taz*, PDZ-binding motif; *Cxcl10*, C-X-C motif chemokine 10; *Nlrp3*, NOD-like receptor thermal protein domain associated protein 3; *Igf1r*, insulin-like growth factor 1 receptor; TGF-β, transforming growth factor-β; Rictor, rapamycin-insensitive companion of mTOR; Akt, protein kinase B; FOXO1, forkhead box O1; *B4GALT3*, β-1,4-galactosyltransferase 3; *MAIP1*, matrix AAA peptidase interacting protein 1; *PHLPP2*, PH domain and leucine rich repeat protein phosphatase 2; SIRT1, Sirtuin 1; LKB1, serine/threonine kinase 11; AMPK, AMP-activated protein kinase; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88; *Fasn*, fatty acid synthase; *Scd1*, stearoyl-CoA desaturase 1. miRNAs closely related to MASLD, such as miR-223, miR-192-5p, miR-33a/b, miR-34a, miR-27a/b, miR-218-5p, and miR-122, participate in disease progression by regulating lipid metabolism, liver inflammation, and fibrosis.

pituitary GH production and protecting against fatty liver in male mice [146]. Neuronal Slug promotes leptin resistance and obesity by binding the *LepRb* promoter and increasing repressive H3K27 methylation, thereby suppressing *LepRb* transcription in the hypothalamus [147]. Leptin resistance and obesity may, in turn, be accompanied by hepatic lipid accumulation. Thus, hypothalamic epigenetic dysregulation may influence hepatic metabolism through both autonomic neural outputs and endocrine signaling, providing a central regulatory route to hepatic steatosis that extends beyond local liver injury.

TABLE 5 | miRNA regulation in MASLD.

Type	Mechanism	References
miR-223	Suppress E2F1 to inhibit lipid deposition and fibrosis.	[123]
	Inhibit the expression of profibrotic genes such as *Taz*, *Nlrp3*, *Cxcl10*, and *Igf1r*, thereby reducing liver fibrosis.	[124, 125]
miR-33a/b	miR-33a expression is positively associated with PGC-1α and USF1, whereas miR-33b expression is negatively associated with CPT1A.	[126]
miR-192-5p	Regulate the Rictor/Akt/FOXO1 pathway to promote M1 polarization of macrophages.	[127]
	Target SCD-1 to reduce lipid synthesis and accumulation.	[128]
miR-34a	Activate TGF-β signaling to promote hepatocyte apoptosis.	[129]
miR-27b	Promote hepatic lipid accumulation, partly by repressing *B4GALT3*, *MAIP1*, and *PHLPP2*.	[130]
miR-27a	Inhibit lipid accumulation by reducing *Fasn* and *Scd1* expression.	[131]
miR-218-5p	Regulate SREBP1-mediated fatty acid synthesis via *Elovl5*.	[132]
miR-122	Suppress *Sirt1* and block the LKB1/AMPK pathway, thereby inducing steatosis and lipogenesis.	[133]
	Inhibition of miR-122 suppresses the TLR4/MyD88/NF-κB p65 signaling pathway, reducing lipid accumulation and inflammation.	[134]

Abbreviations: *B4GALT3*, β-1,4-galactosyltransferase 3; AMPK, AMP-activated protein kinase; Akt, protein kinase B; CPT1A, carnitine palmitoyltransferase 1A; *Cxcl10*, C-X-C motif chemokine 10; E2F1, E2F transcription factor 1; *Fasn*, fatty acid synthase; FOXO1, forkhead box O1; *Igf1r*, insulin-like growth factor 1 receptor; LKB1, serine/threonine kinase 11; *MAIP1*, matrix AAA peptidase interacting protein 1; MyD88, myeloid differentiation primary response 88; *Nlrp3*, NOD-like receptor thermal protein domain associated protein 3; *PHLPP2*, PH domain and leucine-rich repeat protein phosphatase 2; PGC-1α, peroxisome proliferator–activated receptor gamma coactivator 1-alpha; Rictor, rapamycin-insensitive companion of mTOR; *Scd1*, stearoyl-CoA desaturase 1; SIRT1, Sirtuin 1; *Taz*, PDZ-binding motif; TGF-β, transforming growth factor-β; TLR4, Toll-like receptor 4; USF1, upstream transcription factor 1.

3.2 | Skeletal Muscle

Emerging evidence highlights the role of skeletal muscle epigenetics in modulating hepatic lipid metabolism through the muscle–liver axis. In female mice, muscle-specific deficiency of the histone methyltransferase G9a reduces repressive H3K9me2 levels and increases musclin expression, thereby attenuating HFD-induced hepatic steatosis [148]. Notably, HDAC inhibition attenuates age-related sarcopenia by reducing oxidative stress and apoptosis while enhancing mitochondrial biogenesis and metabolic function [149]. By preserving muscle structure and function, these epigenetic interventions may offer promising strategies to modulate the muscle–liver axis and delay MASLD progression.

3.3 | Gut Microbiota and Their Metabolic Products

Gut microbiota-derived factors modulate host DNA methylation and histone acetylation, thereby reprogramming lipid metabolism and immune responses and contributing to the development and progression of MASLD [150]. Patients with MASLD who undergo fecal microbiota transplantation show significant shifts in hepatic DNA methylation profiles [151]. Butyrate may inhibit histone deacetylase 2 (HDAC2) to restore hepatic glucagon-like peptide-1 (GLP-1) expression, thereby improving hepatic GLP-1 sensitivity and preventing MASH [152]. Acetate alleviates diabetes-associated hepatic lipotoxicity by suppressing HDAC activity and improving insulin sensitivity [153]. Butyrate activates the G-protein-coupled receptor 41 (GPR41) and GPR43 (GPR41/43)-CaMKII/histone deacetylase 1 (HDAC1)-cAMP-response element binding protein signaling pathway in both primary hepatocytes and the livers of high-fat, high-fructose diet-fed mice [154].

In addition, nuclear receptor–binding SET domain protein 2 enhances endoplasmic reticulum-to-nucleus signaling 1 (ERN1) transcription by demethylating H3K36me2 and activating the ERN1-JNK pathway, which aggravates intestinal barrier damage and promotes MASH progression [155]. Collectively, these findings indicate that gut epigenetic regulation may influence MASLD progression through microbiota-derived metabolites, alterations in liver chromatin, and gut–liver signaling across the intestinal barrier.

3.4 | Adipose Tissue

Obesity induces epigenetic alterations in adipose tissue that persist after weight loss, forming a so-called "obesity memory" that drives metabolic dysfunction and heightened sensitivity to HFD [156]. Adipose-liver crosstalk has been shown to exacerbate MASLD [157, 158]. In *Mettl14*$^{\Delta fat}$ mice, enhanced systemic fatty acid β-oxidation consumes free fatty acids released from adipose tissue, counteracting hepatic lipid influx and mitigating liver steatosis [159]. Activation of the adipose SIRT1/FOXO1/AMPKα signaling pathway protects the murine liver from ectopic lipid accumulation by suppressing lipolysis in visceral adipocytes [160]. These findings suggest that epigenetic alterations in adipose tissue may influence MASLD progression chiefly by modulating adipose lipolysis and systemic fatty acid handling, thereby altering hepatic lipid influx and ectopic lipid deposition.

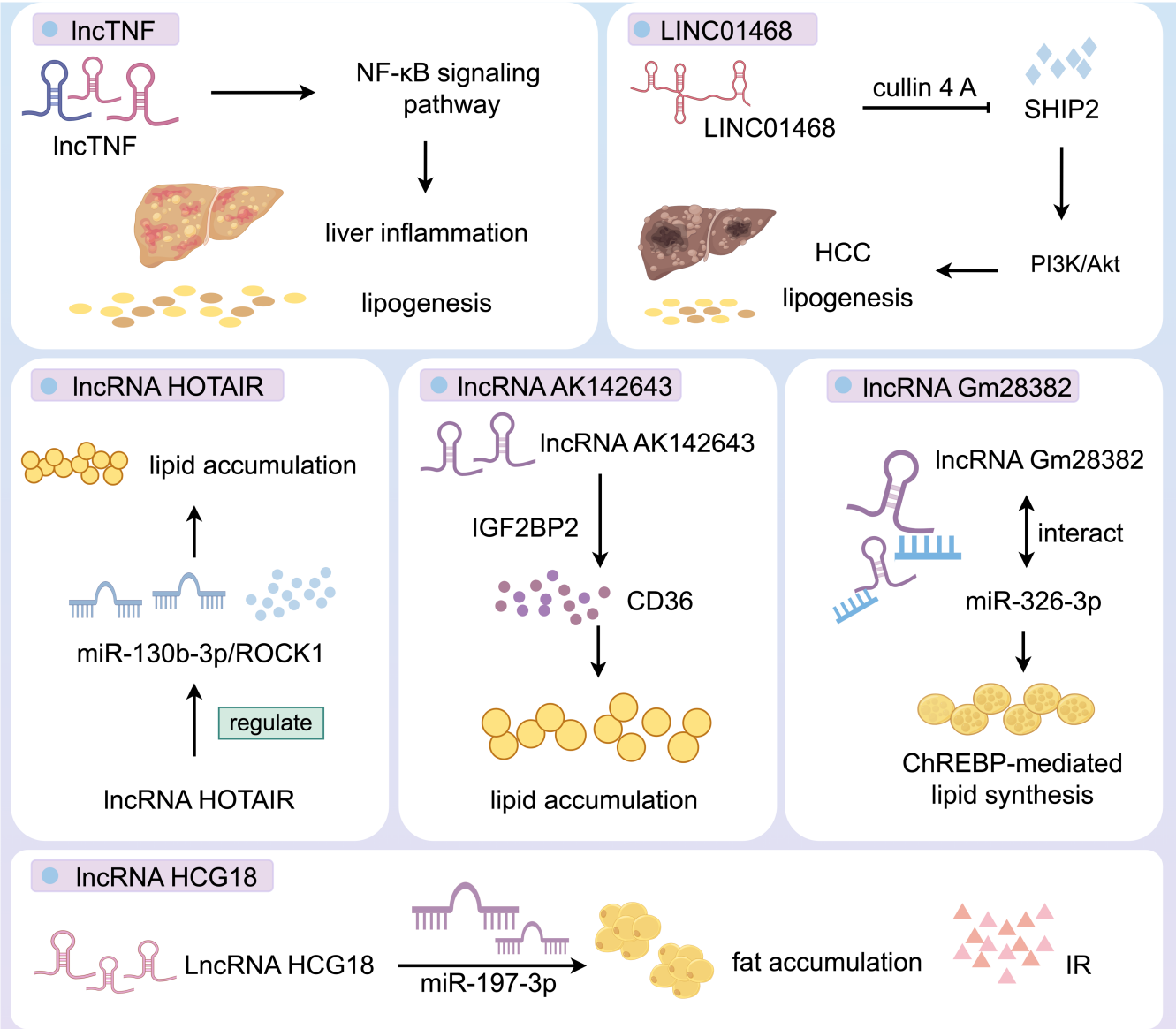

FIGURE 7 | Mechanism of long noncoding RNA in MASLD. It was created by Figdraw (ID: SAIWYfabb5). NF-κB, nuclear factor kappa-B; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; HOTAIR, HOX transcript antisense RNA; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; ChREBP, carbohydrate-responsive element-binding protein; HCG18, HLA complex group 18; IR, insulin resistance. LncRNAs mediate hepatic lipid metabolism and inflammatory processes by interacting with miRNAs and proteins.

TABLE 6 | lncRNA regulation in MASLD.

Type	Mechanism	References
LncTNF	Activate the NF-κB signaling pathway to induce liver inflammation and lipogenesis.	[139]
LINC01468	Enhance SHIP2 degradation, thereby relieving PI3K/Akt inhibition and, in turn, promoting lipogenesis and HCC.	[140]
LncRNA HOTAIR	Promote lipid accumulation by regulating the miR-130b-3p/ROCK1 signaling pathway.	[141]
LncRNA AK142643	Enhance IGF2BP2-mediated upregulation of CD36, thereby promoting lipid accumulation.	[142]
LncRNA Gm28382	Promote lipid synthesis by binding miR-326-3p.	[143]
LncRNA HCG18	Facilitate lipid accumulation and IR through miR-197-3p.	[144]

Abbreviations: Akt, protein kinase B; HCG18, HLA complex group 18; HOTAIR, HOX transcript antisense RNA; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; IR, insulin resistance; NF-κB, nuclear factor kappa-B; PI3K, phosphoinositide 3-kinase.

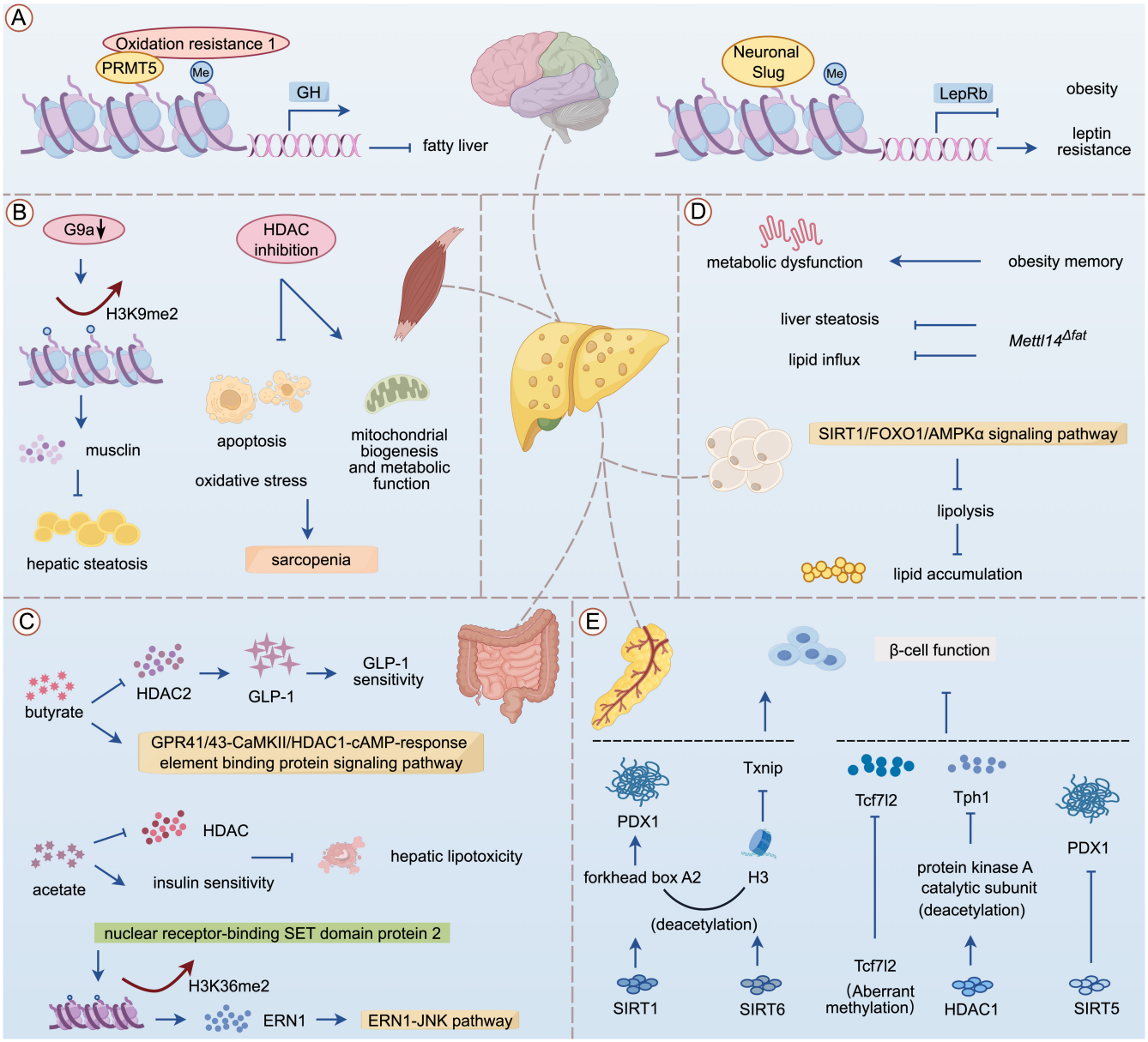

FIGURE 8 | Mechanisms of epigenetic changes in various tissues affecting MASLD. It was created by Figdraw (ID: PRURS34739). HDAC, histone deacetylase; HDAC2, histone deacetylase 2; GLP-1, glucagon-like peptide-1; GPR41, G-protein-coupled receptor 41; GPR43, G-protein-coupled receptor 43; HDAC1, histone deacetylase 1; ERN1, endoplasmic reticulum-to-nucleus signaling 1; METTL14, methyltransferase-like 14; SIRT1, Sirtuin 1; FOXO1, forkhead box O1; AMPK, AMP-activated protein kinase; PDX1, pancreatic and duodenal homeobox 1; SIRT6, Sirtuin 6; SIRT5, Sirtuin 5. Epigenetic changes across organs influence MASLD by modulating fat metabolism, leptin resistance, lipolysis, and pancreatic β-cell function, with key roles in liver–adipose and gut–liver interactions.

3.5 | Pancreas

Impaired compensatory pancreatic β-cell function is associated with MASLD [161]. The regulation of pancreatic β-cell function is influenced by epigenetic mechanisms involving pancreatic and duodenal homeobox 1 (PDX1) [162]. SIRT1 promotes pancreatic β-cell formation and differentiation by deacetylating forkhead box A2 and cooperatively enhancing *Pdx1* transcription, thereby supporting glucose homeostasis [163]. Similarly, SIRT6 suppresses *Txnip* expression by deacetylating histone H3, thereby maintaining β-cell function [164]. SIRT5 contributes to type 2 diabetes (T2D)-associated β-cell dysfunction by repressing *Pdx1* transcription through its deacetylase activity, thereby inhibiting β-cell proliferation and insulin secretion [165]. HDAC1 restrains β-cell adaptation by deacetylating the protein kinase A catalytic subunit to repress Tph1 transcription [166]. DNA methylation is likewise critical for the regulation of β-cell function: aberrant methylation of the transcription factor 7 like 2 (*Tcf7l2*) gene promoter suppresses Tcf7l2 expression and impairs β-cell function [167]. These observations suggest that epigenetic dysregulation in the pancreas may contribute to MASLD by impairing β-cell function and disrupting systemic glucose and lipid homeostasis.

4 | Discussion and Future Directions

4.1 | Interorgan Epigenetic Crosstalk in MASLD

The pathogenesis of MASLD involves complex epigenetic interactions across multiple metabolic organs, forming an interorgan regulatory network in which epigenetic changes in adipose tissue, skeletal muscle, gut, pancreas, and brain influence liver metabolism through secreted factors, neural pathways, and microbial metabolites. Several limitations nonetheless temper these conclusions. Most of the available evidence derives from animal or in vitro studies, and direct causal links in humans have yet to be confirmed. Mechanistic interpretations—such as short-chain fatty acid (SCFA)–mediated HDAC inhibition or the liver-targeted effects of extracellular vesicles—are largely inferential and may not generalize across species, sexes, or metabolic contexts. Moreover, factors such as diet and genetic background can affect reproducibility.

Despite these uncertainties, the concept of a networked epigenome cascade provides a valuable framework for understanding MASLD progression from a perspective that extends beyond the liver. The epigenetic interactions among organs point to promising avenues for experimental and translational research. For example, approaches such as CRISPR-dCas9–based epigenetic editing, small-molecule epigenetic modulators, and lifestyle or nutritional interventions targeting specific epigenetic pathways all warrant exploration. In parallel, longitudinal multiomics profiling—integrated with metabolomics and neural tracing in both human and animal studies—may facilitate the identification of early biomarkers, liquid biopsy panels, and precision therapeutic targets. Rigorous validation in well-controlled human studies will be essential to distinguish mechanisms that are genuinely causal from those that merely reflect secondary metabolic effects.

4.2 | Epigenetics-Based Prevention and Treatment of MASLD in Clinical Practice

Genetic and epigenetic factors can inform risk prediction and guide individualized therapeutic strategies [168]. Several epigenetic-targeted interventions have shown efficacy in preclinical MASLD and MASH models. Givinostat markedly reduces hepatic steatosis, inflammation, and fibrosis in MASH models by preventing histone deacetylation [169]. Arbutin alleviates MASLD by inhibiting FTO, thereby increasing m6A methylation of SLC7A11, enhancing its expression, and suppressing hepatocyte ferroptosis [170]. Silibinin reduces intestinal HDAC2 activity and increases histone acetylation at the farnesoid X receptor promoter, which raises fibroblast growth factor 15/19 levels in the ileum and ultimately enhances hepatic lipid metabolism [171]. Ethanol extract of *Schisandra chinensis* berry lowers hepatic fat by inhibiting histone acetyltransferase, reducing SREBP-1c expression, and decreasing histone H3K9 acetylation [172]. Betaine reduces hepatic lipid accumulation through the BHMT/NADPH/FTO pathway by modulating m6A-dependent PGC1α expression [173]. Overall, although these interventions show promising preclinical efficacy, rigorous human studies are needed to confirm their long-term safety, to clarify whether their effects are mediated directly through epigenetic regulation or indirectly via metabolic improvement, and to determine their true translational potential as precision therapies for MASLD.

5 | Conclusion

MASLD arises from a complex interplay between epigenetic regulation and metabolic processes. DNA methylation, histone modifications, and noncoding RNAs play crucial roles in orchestrating hepatic metabolism and in mediating systemic dysfunction. Importantly, epigenetic changes in extrahepatic metabolic organs—including adipose tissue, skeletal muscle, the gut, pancreas, and brain—can influence hepatic metabolism through interorgan epigenomic interactions and thereby affect overall metabolic homeostasis. Conceptualizing MASLD as a systemic epigenomic disorder shifts attention away from a strictly liver-centric view and creates opportunities for biomarker discovery, the development of mechanistically targeted therapies, and personalized interventions. Future progress will depend on integrating longitudinal multiomics profiling with the identification of novel epigenetic regulators, which will be essential for developing precise, mechanism-based strategies for the prevention, diagnosis, and treatment of MASLD and its associated comorbidities.

Author Contributions

S.Y. and Z.H. contributed equally and are listed as co-first authors. S.Y. and Z.H.: conceptualization. S.Y., Z.H., and S.T.: data collection, writing, and original draft preparation. F.L. and L.C.: design, writing, review, and editing. All authors have read and agreed to the published version of the manuscript and approved the version as submitted.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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