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Review

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Epigenetic and epitranscriptomic regulations of metabolic dysfunction-associated steatotic liver disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by excessive hepatic lipid accumulation and can progress to metabolic dysfunction-associated steatohepatitis (MASH), which is manifested with persistent liver injury, inflammation, and fibrosis, increasing the risk for cirrhosis and hepatocellular carcinoma. Aberrant epigenetic reprogramming and epitranscriptomic remodeling emerge to be a driving force for MASLD and MASH. SNAIL1 and SLUG, two related transcriptional regulators, regulate *de novo* lipogenesis and liver steatosis by opposing epigenetic mechanisms. RNA m^{6}A modification regulates not only liver steatosis but also liver injury and regeneration. MASLD is associated with changes in the expression of m^{6}A writers, erasers, and readers, which significantly influence its progression.

Keywords: SNAIL1, SLUG, m^{6}A, MASLD, MASH

INTRODUCTION

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as

nonalcoholic fatty liver disease (NAFLD), is rising rapidly, paralleling the obesity epidemic worldwide[1,2]. Approximately 90% of people with obesity, 60% of patients with type 2 diabetes, and 50% of patients with dyslipidemia develop MASLD[3]. MASLD could progressively progress to metabolic dysfunction-associated steatohepatitis (MASH), also known as nonalcoholic steatohepatitis (NASH), cirrhosis, and/or liver cancer. Unfortunately, the option of MASH treatment is limited, and there is only one MASH drug approved by the U.S. Food and Drug Administration (FDA) recently. The safety of long-term use of the drug has not yet been assessed[4]. To develop new drugs, it is imperative to elucidate the mechanism of MASH, which may serve as therapeutic targets. The pathogenesis of MASLD and MASH is complex and multifactorial, involving genetic, epigenetic, and environmental factors. Hepatic lipid accumulation (steatosis) is a hallmark of MASLD/MASH and arises from an imbalance of free fatty acid (FFA) uptake and *de novo* lipogenesis over FFA consumption in hepatocytes[5]. FFA β oxidation and very low-density lipoprotein (VLDL) secretion account for hepatic lipid consumption to counteract liver steatosis[6]. Recent research highlights epigenetics and epitranscriptomics in liver health and disease. Epigenetic modifications include DNA methylation and posttranslational modifications of histones, which profoundly influence DNA packaging, chromatin accessibility, gene expression, and cell functions[7]. Various lipogenic transcription factors, such as upstream stimulatory factor-1 (USF1), carbohydrate-responsive element-binding protein (ChREBP), liver X receptor (LXR), can interact with and recruit specific histone modifiers to guide the expression of lipid metabolic enzymes, lipogenesis, and/or β oxidation[8]. The epigenetic regulation of lipogenesis and hepatosteatosis has been extensively discussed elsewhere[8]. Recently, RNA modifications and related RNA-binding proteins have gained attention for their critical roles in regulating liver metabolism and liver homeostasis. An epitranscriptomic concept has been introduced to describe an RNA modification landscape and profile in cells and tissues. N^6-methyladenosine (m^6A) methylation is the predominant modification of mRNA in cells[9,10]. Enzymes that install m^6A on RNA are called m^6A writers; conversely, m^6A demethylases are referred to as m^6A erasers. A m^6A reader refers to proteins that specifically bind to m^6A-modified RNA. The methyltransferase-like 3 (METTL3) and METTL14 complex are the primary m^6A writers[11,12], and fat mass and obesity-associated protein (FTO) and ALKBH5 are the two main m^6A erasers[13,14]. YTH domain family proteins (YTHDF1-3 and YTHDC1-2) are well-characterized m^6A readers that regulate RNA metabolism and fate, including pre-mRNA splicing, mRNA nuclear export, degradation, and/or translational efficiency[15]. Interestingly, m^6A writers, erasers, and readers are emerging as pivotal regulators for metabolism, proliferation, and differentiation[13-15]. In the current review, we attempt to discuss epigenetic reprogramming and epitranscriptomic reprogramming in the pathogenesis of liver disease, particularly MASLD [Figure 1].

EPIGENETIC REGULATION OF LIVER STEATOSIS, LIVER INJURY, AND LIVER REGENERATION

Here, we use SNAIL1 and SLUG as prototype transcription factors to illustrate epigenetic regulation of liver metabolism and homeostasis. SNAIL1 and SLUG (also called SNAI2) are SNAIL family members containing a N-terminal Snail1 and Gfi-1 domain (SNAG) and C-terminal zinc-finger domains that bind to DNA at a consensus E2 box (CAGGTG or CACCTG)[16,17]. The SNAG domain binds to various histone modification enzymes, including HDAC1/2, EZH2, G9a, SUV39H1, and lysine-specific demethylase-1 (LSD1), and these enzymes catalyze histone deacetylation (HDAC1/2), methylation (EZH2, G9a, SUV39H), or demethylation (LSD1), leading to chromatin remodeling and changes in target gene transcription[16]. Functionally, SNAIL1 and SLUG have been well known to promote epithelial-mesenchymal transition (EMT) in development and cancer metastasis[16,18,19]. SNAIL1 and SLUG play pleiotropic functions in addition to stimulating EMT. We report that SLUG represses the expression of leptin receptor LepRb in hypothalamic neurons to induce leptin resistance, resulting in obesity, MASLD, and metabolic disorders[20]. SNAIL1 inhibits the expression of adipose triglyceride lipase (ATGL) in adipocytes by decreasing histone 3

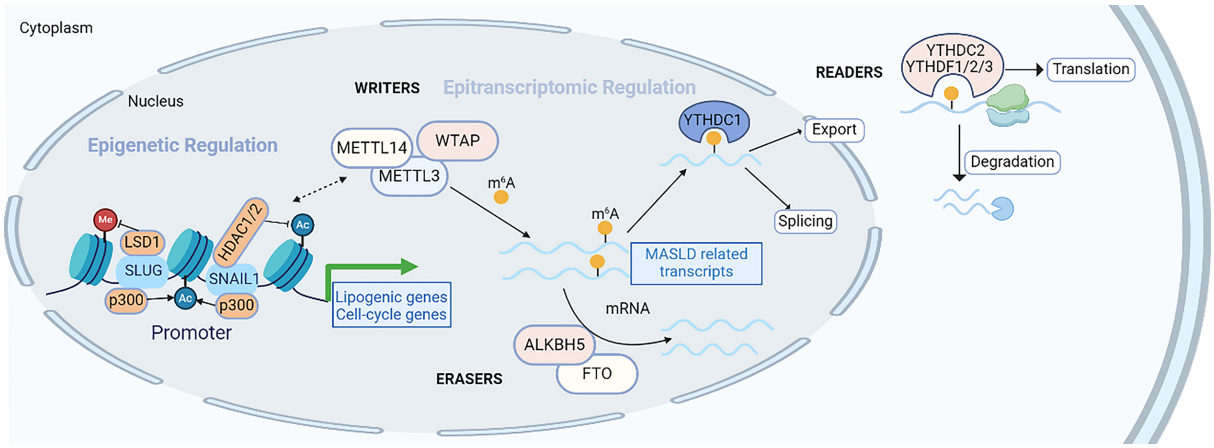

Figure 1. Epigenetic and epitranscriptomic regulation in MASLD pathogenesis. Epigenetic regulators SNAIL1 recruits HDAC1/2 to catalyze repressive deacetylation of H3K9 and H3K27 on the promoter region of lipogenic genes, thereby suppressing lipogenesis, while SLUG interacts with LSD1 that can demethylate H3K9, thus increasing lipogenic gene transcription in an opposite way. Both SNAIL1 and SLUG can recruit P300, which stimulates H3K27 acetylation, promoting cell-cycle gene expression in response to liver injury. Epitranscriptomic regulation, especially m^6A modification, involves writers, erasers, and readers. These m^6A regulators modulate liver metabolism by altering the RNA methylation of genes involved in lipogenesis, fatty acid oxidation, inflammation, and fibrogenic pathways, controlling different stages of MASLD progression by affecting the RNA fate. Epigenetic mechanisms can influence epitranscriptomic modifications, while epitranscriptomic processes can, in turn, modulate epigenetic states, creating a dynamic interplay that mutually shapes each other's regulatory roles in the MASLD liver. This figure is created in BioRender. Zheng Q. (2024) https://BioRender.com/w13h393. Me: Methylation; Ac: acetylation; m^6A: N^6-methyladenosine; FTO: fat mass and obesity-associated protein; METTL3: methyltransferase-like 3; METTL14: methyltransferase-like 14; MASLD: metabolic dysfunction-associated steatotic liver disease; LSD1: lysine-specific demethylase-1; HDAC1/2: histone deacetylase 1/2; H3K9: histone H3 lysine-9; H3K27: histone H3 lysine-27; WTAP: wilms tumor 1-associated protein; YTHDC1/2: YTH domain-containing protein 1/2; YTHDF1/2/3: YTH domain-containing family protein 1/2/3.

lysine-9 acetylation (H3K9ac), and adipocyte-specific deletion of Snail1 increases lipolysis and trafficking of FFAs from white adipose tissue (WAT) to the liver[21]. Likewise, SNAIL1 and SLUG pivotally regulate liver lipid metabolic processes, liver injury, and liver regeneration[22-24].

LIVER STEATOSIS

SNAIL1 was first reported to function as a transcriptional repressor of lipogenic genes, including fatty acid synthase (FASN), acetyl coenzyme A carboxylase 1 (ACC1), and ATP citrate lyase (ACL), thereby exerting a protective effect against excessive lipid accumulation[22]. Mechanistically, SNAIL1 binds to the promoters of lipogenic genes where it recruited HDAC1/2 to catalyze repressive deacetylation of H3K9 and H3K27, thereby suppressing the expression of lipogenic genes[22]. In hepatocytes, interestingly, insulin stimulates Snail1 expression in a PI3-kinase/Akt pathway-dependent manner, raising the possibility that insulin activates two opposing arms of the canonical, sterol regulatory element-binding protein 1c (SREBP1c)-mediated lipogenic pathway and the noncanonical SNAIL1-mediated anti-lipogenic pathway. The noncanonical SNAIL1 arm counterbalances the canonical arm to fine-tune insulin stimulation of lipogenesis. Impairment in the SNAIL1-elicited epigenetic arm is expected to tip the balance toward the lipogenic arm, leading to increased lipogenesis and MASLD[22].

Unexpectedly, SLUG, in contrast to SNAIL1, stimulates *de novo* lipogenesis in hepatocytes[23]. SLUG interacts with LSD1 via its SNAG domain, and the complex binds, via SLUG DNA-binding domain, to the *FASN* promoter where LSD1 demethylates H3K9, thus increasing *FASN* transcription and *de novo* lipogenesis. Hepatocyte-specific ablation of *Slug* suppresses hepatic lipogenesis and protects against diet-induced MASLD, insulin resistance, and glucose intolerance in mice[23]. Conversely, liver-specific

overexpression of SLUG, but not epigenetic-defective SLUG mutants, promotes MASLD. Given that SLUG and SNAIL1 have opposing actions on *de novo* lipogenesis, it is likely that SLUG recruits transcriptionally-stimulating epigenetic modifiers, whereas SNAIL1 recruits repressive epigenetic enzymes, to the promoters of lipogenic genes, resulting in functionally opposite and histone modification-based epigenetic reprogramming. Therefore, a SLUG/SNAIL1 balance influences hepatic lipogenesis and liver lipid levels, and a hepatic SLUG/SNAIL1 imbalance is expected to lead to epigenetic reprogramming of lipogenic pathways and an increase in *de novo* lipogenesis, contributing to MASLD[22,23].

LIVER INJURY AND REGENERATION

Sekiya *et al.* reported that Snail1 represses hepatocyte proliferation after partial hepatectomy (PH)[25]. Snail1 is expressed in quiescent hepatocytes and rapidly degraded post PH-induced liver injury. Glycogen synthase kinase 3β (GSK-3β) phosphorylates SNAIL1 and stimulates ubiquitination and proteasomal degradation of SNAIL1. SNAIL1 degradation is believed to increase the expression of cell cycle-related proteins and DNA synthesis in hepatocytes[25]. It is worth mentioning that Wang *et al.* reported that hepatocyte deletion of either *Snail1* or *Slug* does not influence PH-stimulated liver regeneration[24]. The reason for the discrepancy between the two studies is currently unclear. Interestingly, simultaneous ablation of both *Snail1* and *Slug* in hepatocytes markedly suppresses reparative hepatocyte proliferation and liver regeneration in mice treated with either PH or carbon tetrachloride (CCl_4)[24]. At the molecular level, SNAIL1 and SLUG bind to the promoters of *Cyclin A2* and *D1*, stimulate H3K27 acetylation by recruiting CBP/P300, and increase the expression of *Cyclin A2* and *D1*.

Rowe *et al.* reported that hepatocyte-specific deletion of *Snail1* attenuates CCl_4-induced liver inflammation and fibrosis[26]. In contrast, Wang *et al.* demonstrated that hepatocyte-specific deletion of *Snail1* or *Slug* has no effects on CCl_4-stimulated liver injury and fibrosis in mice[24]. Wang *et al.* further showed that deletion of hepatic *Snail1* and *Slug* together exacerbates CCl_4-stimulated activation of hepatic stellate cells (HSCs) and liver fibrosis, accompanied by increased expression of inflammatory cytokines in the liver[24]. These findings suggest that SNAIL1 and SLUG act redundantly to mitigate fibrosis. In line with this notion, overexpression of SLUG in the liver attenuates CCl_4-induced liver fibrosis[24]. These observations raise the possibility that SNAIL1- and SLUG-elicited epigenetic pathways may serve as potential therapeutic targets to treat liver fibrosis and related chronic liver disease.

EPITRANSCRIPTOMIC REGULATION OF LIVER STEATOSIS AND LIVER INJURY

RNA modifications, particularly m^6A and m^6A-based RNA binding proteins, emerge to profoundly influence liver metabolic processes and liver homeostasis. Aberrant expression and/or activation of m^6A writers, erasers, and/or readers are involved in the pathogenesis of liver disease, including MASLD.

LIVER STEATOSIS

FTO is a m^6A eraser[27,28], and the genome-wide association study (GWAS) has identified *FTO* single nucleotide polymorphisms (SNPs) that are linked to obesity and metabolic syndrome in humans[29-34]. Chen *et al.* found that in hepatocytes, FTO promotes lipid accumulation by enhancing the maturation and nuclear translocation of SREBP1c, which in turn upregulates cell death inducing DFFA like effector C (CIDEC). The FTO/SREBP1c cascade stimulates *de novo* lipogenesis, contributing to hepatic lipid accumulation and MASLD[35]. Additionally, other studies demonstrate that FTO demethylates m^6A on mRNAs of multiple lipogenic genes and stabilizes these transcripts, thereby promoting lipogenesis and MASLD[36,37].

The METTL14/METTL3 complex is the main m^{6}A writer, in which METTL14 is the essential structural subunit while METTL3 is the catalytic subunit[11,12]. Salisbury *et al.* reported that liver-specific deletion of *Mettl14* increases triglyceride content in the liver[38]. Deletion of hepatic *Mettl14* decreases m^{6}A modification of mRNAs encoding lipogenic enzymes such as SREBP1c, diglyceride acyltransferase 2 (DGAT2), and FASN, and these changes increase stability and translation of the mRNAs, thereby enhancing lipogenesis and liver steatosis[38]. Interestingly, loss of hepatic METTL14 differentially affects males and females, highlighting the sex-dimorphic impact of METTL14 on lipid metabolism[38]. Another report found that the downregulation of METTL14 increases lipid accumulation in hepatocytes by multiple mechanisms, including inhibiting fatty acid β oxidation and increasing lipid synthesis and uptake[39]. In line with these findings, Li *et al.* showed that hepatocyte-specific deletion of *Mettl3* also enhances liver steatosis; however, the authors suggest that METTL3 achieves this action by a m^{6}A-independent mechanism[40]. METTL3 recruits HDAC1/2 to the promoter of the *Cd36* gene to suppress *Cd36* transcription by deacetylating H3K9 and H3K27, thereby decreasing CD36-mediated FFA uptake. In addition, METTL3 mediates m^{6}A modification on *Pparα* transcript and reduces *Pparα* mRNA stability, thereby suppressing peroxisome proliferator activated receptor alpha (PPARα) synthesis and PPARα-promoted fatty acid β oxidation[41]. Paradoxically, hepatocyte-specific deletion of *Mettl3* was also reported to decrease diet-induced liver steatosis, insulin resistance, and glucose intolerance in mice[42]. Silencing of liver *Mettl14* can ameliorate diet-induced liver steatosis, inflammation, and injury in C57BL/6 mice[43]. In line with the liver phenotypes, Yang *et al.* reported that METTL14 and METTL3 install m^{6}A modification on mRNAs of *Acly* and *Scd1* and increase expression of the lipogenic enzymes in hepatocellular carcinoma (HCC) cell lines, thereby increasing lipogenesis and lipid droplet accumulation[44]. METTL3 also deposits m^{6}A on *Rubicon* mRNA and increases *Rubicon* stability and RUBICON production, and RUBICON, in turn, inhibits autophagosome-lysosome fusion and lipophagy, leading to the accumulation of lipid droplets in hepatocytes[45]. The reasons for the discrepancy between the above studies remain unclear and warrant further investigations in the future.

The YTH domain-containing family members (YTHDF1-3 and YTHDC1-2) are the first m^{6}A readers discovered[15]. Liver YTHDC2 is downregulated in obesity and MASLD, and silencing of *Ythdc2* in the liver enhances, whereas overexpression of YTHDC2 suppresses, liver steatosis in mice[46]. YTHDC2 suppresses lipogenesis, at least in part, by binding to and decreasing the stability of *Srebp-1c* and *FASN* mRNAs[46]. Zhong *et al.* reported that YTHDF2 binds to m^{6}A-modified *Pparα* mRNA to increase its degradation, and knockdown of *Ythdf2* or *Mettl3* increases the stability and expression of *Pparα* mRNA[41], thereby defining a METTL3/YTHDF2/PPARα/fatty acid β oxidation loop. Peng *et al.* found that YTHDF1 binds and stabilizes *Rubicon* mRNA to increase RUBICON protein production, and a METTL3/YTHDF1/RUBICON/autophagy inhibition axis appears to promote MASLD[45]. METTL3 also deposits m^{6}A on *Gys2* mRNA, and IGF2BP2, a m^{6}A reader, binds to m^{6}A-methylated *Gys2* mRNA to increase its stability, thereby increasing liver glycogen synthesis[47]. Hepatocyte-specific deletion of *Mettl3* lowers liver glycogen levels in mice[47]. Collectively, these observations indicate that m^{6}A writers, erasers, and readers act coordinately to regulate liver metabolism by multiple complex mechanisms, and they may serve as potential drug targets for the treatments of metabolic disease and liver disease.

LIVER INJURY

The functions of epitranscriptomic regulators extend beyond lipid metabolism and influence liver injury and inflammation. A study led by Wang *et al.* finds that METTL14 downregulation plays a role in the progression of liver injury and fibrosis by enhancing the recruitment and activation of S100A4+ macrophages[39]. The activated macrophages promote HSC activation and liver fibrosis. METTL14's influence on glutaminase 2 (GLS2) expression plays a significant role in controlling oxidative stress within

the liver. METTL14 downregulation also decreases GLS2 synthesis to increase liver oxidative stress, thereby exacerbating liver injury[39]. The METTL3/METTL14 complex installs m^{6}A on *Chop* mRNA to decrease its stability and CHOP protein production, and hepatocyte-specific deletion of *Mettl14* increases liver CHOP levels and CHOP-induced apoptosis, thus promoting liver injury[48]. Likewise, hepatocyte-specific deletion of *Mettl3* also causes liver injury, hepatocyte hypertrophy, and growth retardation in mice through increasing toxic ceramide accumulation[49]. Additionally, deficiency of hepatic METTL3 increases C-C motif chemokine ligand 2 (CCL2) expression and CCL2-driven inflammation, further worsening liver injury[40]. Liver FTO, which is downregulated in aging and hepatic ischemia/reperfusion injury, inhibits hepatocyte ferroptosis by increasing *Ascl4* and *Tfrc* mRNA stability dependently on m^{6}A methylation[50]. Aside from liver injury, the m^{6}A system is also involved in liver regeneration. Liver expression of METTL3 and METTL14 are rapidly upregulated in 3-6 h post PH, and deletion of hepatic *Mettl14* impedes liver regeneration while increasing liver necrosis and ER stress after PH[51].

RECONCILING DISCREPANCIES IN THE ROLES OF EPIGENETIC AND EPITRANSCRIPTOMIC REGULATORS

The literature presents conflicting findings regarding the roles of SNAIL1 and SLUG in liver regeneration and fibrosis[24-26]. These discrepancies may be attributed to compensatory mechanisms between SNAIL1 and SLUG, differences in experimental models, or variations in the stages of liver disease being studied. Notably, in one of the reports[25], a large volume of a small interfering RNA (siRNA) solution was rapidly injected into the liver to mediate *Snail1* knockdown, known as a hydrodynamic delivery[25]. Hydrodynamic injection is expected to induce liver injury, which may interfere with the regeneration phenotype. The discrepancy between Wang *et al.*[24] and Rowe *et al.*[26] regarding the functional role of SNAIL1 on liver fibrosis may be due to the different treatment times of CCl4 between the two studies (24 day *vs.* 14 day). It is plausible that SNAIL1 and SLUG have redundant or overlapping functions in certain contexts, which masks the effects when only one is deleted[24]. Further research is needed to elucidate the precise conditions under which SNAIL1 and SLUG exert their effects and to determine whether their functions are context-dependent.

Discrepant findings were also reported as to epitranscriptomic regulators, even when the same modulators, such as METTL14 or METTL3, are involved in regulating lipid metabolism[38-45]. Again, liver phenotypes may be influenced by different knockdown approaches and associated conditions, including sex variables. For example, Salisbury *et al.* revealed that METTL14 mediates sex-dimorphic effects in hepatic lipid metabolism, where the loss of METTL14-mediated m^{6}A modification enhances lipogenic protein production and increases triglyceride accumulation more effectively in males than females under normal chow conditions[38]. One of the underlying mechanisms is that normal males had higher m^{6}A levels than females on lipogenic mRNAs, which may enhance the METTL14-m^{6}A deletion effect on males. Lower m^{6}A levels of lipogenic mRNAs corresponding with higher lipid biogenesis protein production in females also explain why normal female mice have higher fasting liver triglyceride levels than males. These findings reinforce the idea that m^{6}A modifications on lipogenic transcripts may be a factor contributing to sex differences in lipogenic protein levels and triglyceride content[38]. Overall, comprehensive factors should be considered in the future when probing the definitive role of m^{6}A modification in MASLD.

EPIGENETIC AND EPITRANSCRIPTOMIC MODIFICATIONS ACROSS DIFFERENT STAGES OF MASLD

MASLD represents a spectrum of metabolic liver disease ranging from relatively benign hepatic steatosis to steatohepatitis (MASH). The latter is characterized by persistent liver injury, inflammation, and liver fibrosis that collectively increase the risk for end-stage liver disease such as cirrhosis and HCC[1]. As discussed above, epigenetic and epitranscriptomic modifications of DNA and RNA play distinct roles at

various stages of MASLD progression. It is noted that the same regulator may target multiple pathways involved in the different stages of MASLD progression. For example, SNAIL1 or SLUG not only directly regulates lipogenic programs but also targets cell cycle-related proteins in response to liver injury, and can affect liver fibrosis by indirectly modulating stellate cell activation[22-24].

Likewise, m^{6}A writers, erasers, and readers can regulate the stability of lipogenic transcripts and targeted mRNAs involved in oxidative stress and apoptosis, influencing the transition from steatosis to steatohepatitis. In advanced stages, epitranscriptomic reprogramming affects hepatocyte proliferation and liver regeneration, as well as the activation of fibrogenic pathways[38-45]. Moreover, Pan *et al.* demonstrated that METTL3 promotes MASLD-associated HCC by driving cholesterol biosynthesis and impairing antitumor immunity[52]. Thus, understanding these stage-specific epigenetic and epitranscriptomic modifications is crucial for developing targeted interventions that can halt or reverse disease progression.

INTERPLAY BETWEEN EPIGENETIC REGULATION AND M^{6}A MODIFIERS

Emerging evidence suggests a synergistic interplay between epigenetic regulators and epitranscriptomic m^{6}A modulators under physiological and pathological conditions[53,54]. Epigenetic modification, including histone modification and DNA methylation, has been reported to directly regulate the expression level of m^{6}A writer METTL3 and METTL14. For example, Xu *et al.* found that H3K4me3 histone modification enriched at the METTL3 promoter region drives its transcriptional activation in intrahepatic cholangiocarcinoma (ICC)[55]. This modification supports elevated METTL3 expression, which promotes ICC progression[55]. Du *et al.* reported that in cervical cancer, the transcription factor ETS1 recruits both P300 and WDR5 to the METTL3 promoter[56]. P300 mediates H3K27 acetylation, and WDR5 mediates H3K4me3 methylation, collectively enhancing METTL3 transcription and contributing to cancer cell proliferation and metastasis[56]. Similarly, Wang *et al.* demonstrated that P300-driven H3K27 acetylation at the METTL3 promoter increases METTL3 expression in gastric cancer, which promotes tumor growth and metastasis by stabilizing HDGF mRNA through IGF2BP3 recognition[57]. Moreover, Xiong *et al.* revealed that lactate accumulation in the tumor microenvironment induces H3K18 lactylation at the METTL3 promoter, enhancing METTL3 transcription in tumor-infiltrating myeloid cells[58]. In addition, Chen *et al.* identified that KDM5C-mediated demethylation of H3K4me3 at the METTL14 promoter reduces METTL14 transcription in colorectal cancer[59]. This histone modification effectively suppresses METTL14 expression, contributing to cancer's progression by affecting downstream m^{6}A modifications of target mRNAs, such as SOX4[59]. Interestingly, the expression of METTL14 was also reported to be transcriptionally regulated in a sex-dimorphic manner influenced by dietary factors[38]. Under high-fat diet (HFD) or western diet conditions, male mice exhibit reduced METTL14 levels, a pattern not observed in females. This difference is proposed to be controlled by the BCL6-STAT5A axis, which can bind to the METTL14 promoter region and repress METTL14 transcription in male livers but has a limited effect in females[38].

On the other hand, beyond its post-transcriptional regulation role, m^{6}A can be deposited on mRNAs encoding histone modifiers and transcription factors to affect transcription regulation indirectly[60]. For example, METTL14 knockout in neural stem cells increases the stability of transcripts encoding key histone acetyltransferases, such as CREB binding protein (CBP) and P300, resulting in elevated H3K27ac levels[61]. This shift promotes active transcription of differentiation-related genes, which disrupts stem cell maintenance and accelerates premature differentiation[61]. Additionally, METTL3 depletion reduces m^{6}A-modified EZH2 mRNA, leading to decreased EZH2 protein and H3K27me3 levels, which are associated with the repression of neurogenesis pathways[62]. Interestingly, Dou *et al.* revealed that METTL14 can regulate heterochromatin structure independently of m^{6}A by recruiting the demethylase KDM6B to reduce

H3K27me3 levels[63]. This action promotes gene activation essential for stem cell differentiation[63]. Though most of the epigenetic regulatory roles of these m^{6}A writers are tested in stem cells, it is highly likely that they exert similar functions in MASLD conditions. Indeed, as discussed above, METTL3 can recruit HDAC1/2 to the promoter of the *Cd36* or *Ccl2* gene to suppress *Cd36* or *Ccl2* transcription by deacetylating H3K9 and H3K27, thereby decreasing CD36-mediated FFA uptake and CCL2 -driven inflammation, conferring protective role against MASLD pathogenesis[40].

THERAPEUTIC POTENTIAL OF TARGETING EPIGENETIC AND EPITRANSCRIPTOMIC PATHWAYS

Targeting epigenetic and epitranscriptomic pathways offers promising therapeutic avenues for MASLD and MASH. Based on the roles of SNAIL1 and SLUG in regulating lipogenesis through epigenetic mechanisms, therapeutic strategies aimed at enhancing SNAIL1/HDAC-mediated repression of lipogenic genes or inhibiting SLUG/LSD1-mediated activation of lipogenic pathways hold significant potential[22,23].

Given that SNAIL1 recruits HDAC1/2 to repress lipogenic genes, activating HDAC1/2 activity could enhance the repression of lipogenic gene expression, thereby reducing lipogenesis and liver steatosis[22]. However, direct activators of HDAC1/2 are currently limited, as most available HDAC modulators are inhibitors primarily tested for cancer treatment[64,65]. It is important to note that the HDAC family consists of four distinct classes, each containing multiple enzymes with both overlapping and unique functions[64]. Beyond HDAC1/2, other HDAC members have also been studied in the context of MASLD, with various agonists and antagonists tested in mouse models of the disease[64]. Future research could focus on identifying compounds that increase HDAC1/2 expression or activity, or on modulating upstream pathways that stabilize SNAIL1, thereby enhancing HDAC recruitment to target gene promoters.

Inhibition of LSD1, a histone demethylase that interacts with SLUG to activate lipogenic gene transcription, represents a viable therapeutic strategy to decrease lipogenesis and mitigate liver steatosis[23]. LSD1 inhibitors are currently in clinical trials for various forms of cancer[66]. It will be of interest to determine whether such inhibitors are efficacious in preclinical models of MASLD and MASH. Of note, Ramms *et al.* reported that systemic administration of an LSD1 inhibitor (GSK-LSD1) in obese mouse models led to significant improvements in several obesity-related metabolic dysfunctions, including MASLD[67]. Although the authors conclude that the overall beneficial effects of systemic LSD1 inhibition on glucose homeostasis and liver steatosis are not directly due to LSD1 inhibition in hepatocytes, they observed a reduction in hepatic triglyceride levels in hepatocyte-specific *Lsd1* deletion mice, suggesting a hepatocyte-autonomous role for LSD1 in hepatic lipid metabolism regulation[67]. These findings suggest that LSD1 could be a promising therapeutic target for treating liver steatosis and related metabolic disorders.

Beyond HDAC and LSD1 inhibitors, modulators of m^{6}A writers, erasers, and readers are being investigated for their ability to regulate lipid metabolism and inflammation in the liver. FTO as an m^{6}A demethylase has been reported to promote lipid accumulation and MASLD[35-37]. Thus, inhibiting FTO activity has been proposed as a strategy to reduce hepatic steatosis. Entacapone, an FDA-approved drug, was first identified by Peng *et al.* as an effective FTO inhibitor[68]. In diet-induced obese (DIO) mouse models, entacapone administration resulted in decreased body weight and lowered fasting blood glucose levels, demonstrating its potential for treating obesity and type 2 diabetes[68]. Though the author did not evaluate the effect of entacapone on MASLD phenotype, this study found that entacapone treatment could interfere with gluconeogenesis in the liver by directly targeting forkhead box O1 (FOXO1)[68]. It is worth investigating if entacapone also exerts a beneficial effect on liver lipid metabolism. Another study led by Huang *et al.* identified another FTO selective inhibitor, meclofenamic acid (MA)[69], which was later tested by Hu *et al.*,

who found it can prevent the OA/DEX–induced increase in total TG content in primary hepatocytes[37]. These findings position FTO inhibitors as promising candidates for MASLD therapies, pending further research and clinical validation.

In addition, Dang *et al*. demonstrated that Ling-gui-zhu-gan (LGZG) decoction is effective in ameliorating hepatic steatosis in a high-fat diet-induced NAFLD rat model[70]. The treatment significantly reduced hepatic m^{6}A methylation levels and downregulated the expression of SOCS2 at both mRNA and protein levels, suggesting that LGZG may alleviate steatosis by modulating m^{6}A-mediated SOCS2 regulation[70]. Similarly, Wu *et al*. demonstrated that resveratrol improves HFD-induced hepatic lipid imbalance by reducing m^{6}A methylation levels[71]. Resveratrol decreased lipid accumulation and modulated the expression of key m^{6}A regulators, including downregulating YTHDF3 and upregulating METTL3 and YTHDF2, which are critical for lipid metabolism[71].

Despite the great potential of ameliorating MASLD by targeting m^{6}A epitranscriptomic pathways, therapeutic modulation of m^{6}A regulators requires a thorough understanding of their roles in liver metabolism to avoid unintended consequences on other metabolic pathways.

CONCLUSION AND FUTURE DIRECTIONS

This review summarizes recent advances in the roles of epigenetic regulators SNAIL1 and SLUG, as well as epitranscriptomic modifiers METTL3, METTL14, FTO, and YTH family members in MASLD and MASH. SNAIL1 and SLUG regulate lipid metabolism and liver injury by influencing histone modifications and transcriptions of lipogenic and fibrogenic genes. The METTL3/METTL14 complex installs m^{6}A modification on target transcripts and YTH family members act as m^{6}A readers to regulate the metabolism and fate of target mRNAs, thereby controlling intracellular proteostasis. The epigenetic and epitranscriptomic mechanisms act in concern to govern liver function in health and disease.

Despite the promising potential, several challenges remain in translating these findings into clinical therapies. The redundancy and compensatory mechanisms among epigenetic regulators necessitate a comprehensive understanding of their interactions and functions. Additionally, the conflicting effects of m^{6}A modulators contributing to MASLD pathogenesis highlight the need for personalized approaches in therapy design. For instance, sex-dimorphic effects should be considered in treatment design to enhance therapeutic efficacy and minimize adverse effects.

In addition, the current diagnosis of MASLD is highly dependent on liver biopsy, and a reliable biomarker that can accurately diagnose and stage MASLD across the entire disease spectrum does not yet exist[72]. Meanwhile, the rising prevalence of MASLD, particularly among young adults, reflects an increasing need for early screening and preventive strategies[73]. Moreover, effective screening for advanced liver fibrosis in MASLD, especially among overweight and obese patients, remains a critical challenge[74]. Epigenetic and epitranscriptomic markers hold promise as diagnostic and prognostic biomarkers for MASLD and MASH. Notably, studies indicate an increase in m^{6}A regulators, such as METTL3 and METTL14, alongside FTO, while wilms tumor 1-associated protein (WTAP) shows decreased levels in MASLD[72]. Further research is crucial to determine whether these m^{6}A regulators, alone or combined with other markers, could enhance MASLD diagnosis and patient risk stratification.

In the future, it is essential to elucidate the precise molecular mechanisms through which SNAIL1, SLUG, and m^{6}A modifiers regulate their downstream targets in different contexts that affect MASLD and MASH progression. It is also important to develop innovative therapies for liver disease by targeting the epigenetic

and/or epitranscriptomic pathways.

DECLARATIONS

Authors' contributions

Conception or design: Zheng Q, Rui L
Drafting the manuscript and editing: Zheng Q, Rui L

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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