REVIEW

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The Influence of Epigenetic Mechanisms on the Development of Metabolic Dysfunction Associated Steatotic Liver Disease: A Review

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) occupies a leading place in the structure of modern hepatology. A growing body of literature identifies MASLD as a global epidemic. Accumulated data from studies in the field of hepatology support the idea that MASLD is a hepatic manifestation of a systemic metabolic disease. MASLD is a multifactorial metabolic disease associated with the presence of insulin resistance, abdominal obesity, oxidative stress, endothelial dysfunction and a systemic inflammatory response. Current scientific data demonstrate the existence of a relationship between MASLD and an increased risk of developing cardiovascular disease, regardless of traditional risk factors such as diabetes mellitus, dyslipidemia, obesity and hypertension. The pathogenesis of MASLD includes the development of hepatic steatosis with subsequent progression to metabolic dysfunction-associated steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Epigenetics, a new field of biology that studies the influence of external factors on gene activity without changing in deoxyribonucleic acid (DNA) sequences, offers a new perspective on the pathogenesis of MASLD. This review summarizes current knowledge on the epigenetic determinants of MASLD, such as DNA methylation, histone modifications, noncoding ribonucleic acids (RNAs) and N6-methyladenosine in patients with MASLD which may also contribute to the development of preventive or therapeutic strategies for MASLD-associated complications.

Key words: epigenetics – metabolic dysfunction-associated steatotic liver disease – metabolic dysfunction – associated steatohepatitis – DNA methylation – histone modifications – noncoding RNAs – N6-methyladenosine.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; circRNAs: circular RNAs; DNA: deoxyribonucleic acid; DNMT: DNA methyltransferase; H3K27: 27th amino acid in histone H3; H3K9; 9th amino acid in Histone H3; HCC: hepatocellular carcinoma: HDAC: histone deacetylases; LF: liver fibrosis; lncRNAs: long noncoding ribonucleic acids; MASLD: metabolic dysfunction-associated steatotic liver disease; miRNAs: micro ribonucleic acids; mRNA: messenger ribonucleic acids; MASH: metabolic dysfunction-associated steatohepatitis; ncRNAs: noncoding ribonucleic acids; RNAs: ribonucleic acids; TC: total cholesterol; TG: triglycerides.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a progressive spectrum of liver diseases that begins with benign fat accumulation in hepatocytes (steatosis), followed by inflammation and hepatocellular injury – metabolic dysfunction-associated steatohepatitis (MASH) and progresses to liver fibrosis (LF) [1]. Although MASLD is typically asymptomatic, 25% of patients with MASH may progress to liver cirrhosis, and 10% may develop decompensated liver disease [2]. MASLD is currently considered the most common liver disease in developed countries [3]. Its global prevalence in the general population is variable: in the Eastern countries it is 20–30% and in Asia 5–18% [4]. Currently, liver-related mortality constitutes the third leading cause of death in MASLD individuals [5]. The development of MASLD is closely related to the characteristics of the metabolic syndrome, such as central obesity, insulin resistance, type 2 diabetes mellitus, arterial hypertension and dyslipidemia [6]. The underlying mechanisms of metabolic diseases are multifaceted and involve

both genetic and non-genetic (epigenetic) factors. Epigenetics, first described by Conrad Hal Waddington in 1942, refers to heritable yet reversible changes in gene expression. It influences the phenotype by regulating gene transcription without altering the primary deoxyribonucleic acid (DNA) sequence. Epigenetic changes modulated by environmental influences such as diet, physical activity, or lifestyle shape gene expression by switching genes on and off [7]. Epigenetic modifications may alter the expression of genes involved in lipid metabolism, inflammation, and oxidative stress, all of which contribute to the development of MASLD [8]. Despite the undeniable role of genetic factors in the pathogenesis of MASLD, the rising prevalence of the disease cannot be explained solely by environmental and genetic influences. Epigenetics, involving reversible and heritable changes in gene expression without altering the underlying nucleotide sequence, serves as an important mechanistic link in this phenomenon. A growing body of evidence identifies epigenetics as a crucial factor contributing to the pathogenesis and progression of MASLD [9].

According to the current understanding of MASLD pathogenesis, epigenetic changes such as DNA methylation and histone modifications may activate genes that promote lipid synthesis in hepatocytes, thereby contributing to the development of hepatic steatosis. At later stages, alterations in histone proteins promote the release of inflammatory cytokines, the development of oxidative stress, and the progression to MASH [10]. A growing body of evidence also suggests that hepatic DNA methylation in patients with MASLD is a key factor in the transition from steatosis to severe LF with the development of MASH [11]. Moreover, alterations in histone proteins trigger the development of hepatocellular carcinoma (HCC) in patients with MASLD [12]. Elucidation of the epigenetic factors that predispose individuals to MASLD may lead to the development of non-invasive biomarkers for early diagnosis and may enable preventive and therapeutic strategies for high-risk populations [13].

This review discusses current epigenetic variations associated with the development and progression of MASLD and possible therapeutic strategies aimed at correcting these variations.

EPIGENETIC FACTORS IN THE DEVELOPMENT OF MASLD

In 1942, the English biologist Conrad Hal Waddington proposed the new term 'epigenetics' to describe the processes by which the genotype brings the phenotype into being [14]. Epigenetics involves heritable modifications to the structure and biochemistry of chromatin, without altering the DNA sequence [15]. The epigenetic mechanisms modulate diverse physiological and pathological processes via the regulation of gene expression through alterations in epigenetic code accessibility within the chromatin [16]. Epigenetic changes can be inherited and modified by environmental factors, are considered reversible, and may offer novel personalized approaches to the prevention and treatment of a variety of diseases [17]. Cytosine and histone modifications, as well as alterations in the localization of nucleosomes occurring at the molecular level, are potential drivers of epigenetic regulatory mechanisms [18]. Growing evidence suggests that MASLD progression is substantially influenced by multiple epigenetic mechanisms. Although some studies reported that one of the DNA methylation variants was associated with a threefold increased risk of lean MASLD compared with non-lean MASLD, the epigenetic pathogenesis of lean MASLD remains poorly understood despite extensive basic and clinical research on MASLD [19]. Epigenetic factors – including DNA methylation, histone post-translational modifications, noncoding RNAs, and N6-methyladenosine – have been associated with fatty liver disease and its severity [20].

The Role of DNA Methylation

DNA methylation (Fig. 1) is a universal chemical modification by which methyl groups are added to the DNA molecule [21]. DNA methylation most often happens on the cytosine phosphate guanine islands, a site in which a cytosine is located next to a guanidine [22]. Mainly noted within telomeres, centromeres, repeat sequences, and inactive X-chromosomes, DNA methylation is involved in several biological processes, such as genomic imprinting, regulation of epigenetic gene expression, genome stability and transposon silencing [23].

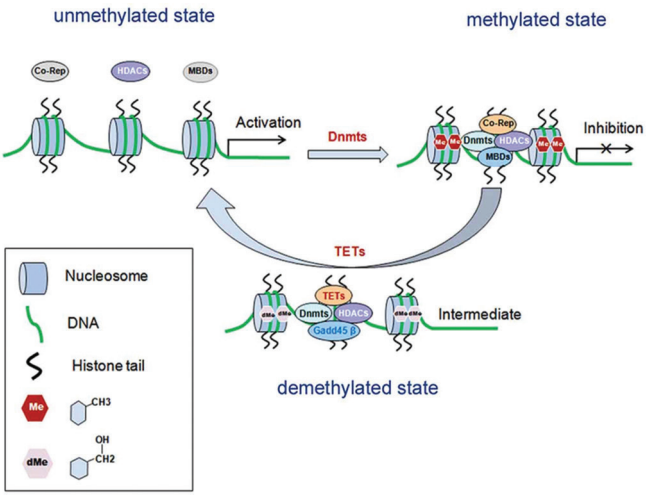

Fig. 1. Schematic diagram of DNA methylation in the regulation of gene transcription. DNA methylation is mediated by DNA methytransferases (Dnmts), which is recruited by methyl-binding domain proteins (MBDs) and form transcription repressor complexes together with co-repressors (Co-Rep) and HDACs – induces transcriptional inhibition. DNA demethylation is mediated by the ten-eleven translocases (TETs), which can catalyze oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) leads to gene transcriptional activation. Copyright © 2015 Chen, Huang, Michael and Xiao [24]. Available via license: Creative Commons Attribution 4.0 International.

Many DNA methylations take place in the liver, so that hepatic steatosis is commonly seen from the point of view of the deregulation of carbon metabolism, being related to folate deficiency [25].

In a study of liver mitochondrial DNA methylation significantly higher methylation of mitochondrial gene nicotinamide adenine dinucleotide dehydrogenase-6 and lower

messenger RNA (mRNA) levels was reported in MASH patients in comparison to simple steatosis patients. This points towards an association of hepatic methylation and transcriptional downregulation of dinucleotide dehydrogenase-6 with the severity of MASLD [26]. In a study, using genome wide DNA methylation analysis from liver samples of 45 morbidly obese patients in different stages of MASLD, 9 MASLD associated genes were extracted exhibiting the variation in methylation [27].

Also, in a study, using epigenome-wide association studies six differentially methylated 5'-C-phosphate-G-3' sites (regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases along its 5' → 3' direction) in genes such as *ACSL4, CRLS1, CTP1A, SIGIRR, SSBP1* and *ZNF622* were identified which could serve as serum biomarkers to distinguish between those with MASH and simple steatosis [28]. It was demonstrated that the relationship of increased hepatic dipeptidyl peptidase-4 expression levels and corresponding reduction in DNA methylation was observed in human liver biopsies to different hepatosteatosis and MASH stages which suggested a very complex intertwined regulation of fuel metabolism through epigenetic modulation [29]. In a study using epigenome-wide association studies, eight genes were identified associated with markers of liver function, among which altered DNA methylation at Solute carrier family 7 member 11 was linked with the reduced incidence of hepatic steatosis, through a favorable association with a panel of genes involved in lipid metabolism [30]. In an epigenomic analysis, which used data from the Infinium Methylation EPIC array from 325 individuals with MASLD, it was demonstrated that DNA methylation is a mechanism underlying changes in the cellular composition of hepatocytes in the pathogenesis of MASLD, including the development of LF [31].

Recent studies suggest that altered gene expression due to abnormal DNA methylation may also be involved in the progression of MASLD to HCC. In a study investigating liver gene expression along with DNA methylation changes in mice using the stelic animal model of MASH derived hepatocarcinogensis, it was found that aberrantly expressed genes had greater accrual of DNA methylation abnormalities with the majority of atypically methylated genes found in fully developed HCC. One of these genes, tubulin beta 2B class IIB, was found hypomethylated and overexpressed as liver carcinogenesis progressed [32]. Another study, using relevant mice models (diet induced MASLD mice, stelic animal model of MASH derived HCC as well as choline and folate deficient diet mice models exhibiting MASLD to HCC progression that resemble carcinogenesis in humans) characterized a progressive increase in glycine N-methyltransferase promoter methylation and a corresponding reduction of glycine N-methyltransferase expression [33]. In a meta-analysis decreased mRNA levels of *patatin-like phospholipase domain-containing protein 3* while increased expression of *PARVB (a protein that in humans is encoded by the PARVB gene)* was correlated with MASLD succession to HCC [34].

Thus, numerous studies in human and animal models suggest altered DNA methylation patterns at global and locus specific levels leading to hepatic lipid accumulation, steatosis, inflammation, and injury responsible for establishment and progression of MASLD [35]. The study of DNA methylation is a promising field of modern science for understanding the influence of epigenetic factors on the development and progression of MASLD.

The Role of Histone Modification

DNA within cells is packaged as chromatin, a dynamic structure composed of nucleosomes as the fundamental building blocks. Histones are the central component of the nucleosomal subunit, forming an octamer containing the four core histone proteins (H3, H4, H2A, H2B) [36]. As a component of octamer, histone undergoes several different post-translational modifications through different histone-modifying enzymes [37]. There are various types of histone modifications (Fig. 2), such as methylation, acetylation, lactylation, phosphorylation, dopaminylation, and ubiquitination, among others [38, 39].

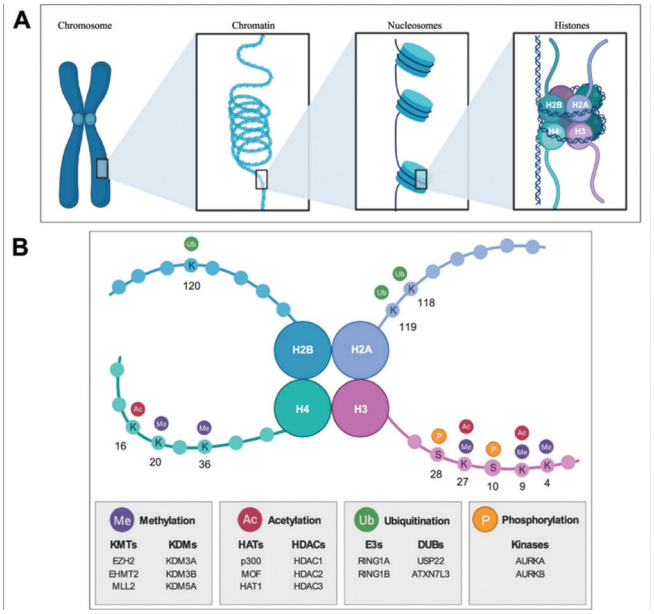

Fig. 2. Schematic diagram of histone modification. A. Schematic representation of DNA-histone protein complexes. B. Schematic representation of a nucleosome. The main histone modifications (methylation, acetylation, ubiquitination and phosphorylation) are localized on the tails of the four main histones (H2B, H2A, H4, H3). Enzymes involved in the mentioned modifications are listed in gray boxes. © The Author(s) 2022 (Braghini M.R., Lo Re O., Romito I., et al.) [40]. Available via license: Creative Commons Attribution 4.0 International.

Dysregulated modifications of histone methylation contribute to functional abnormalities that exacerbate the progression of various diseases, including diabetes, hypertension, atherosclerosis, fatty liver disease, tumors and autoimmune disorders [41, 42]. In recent years, the role of histone methylation in MASLD has attracted increasing attention. In a study it was reported that increased trimethylation of the 27th amino acid in histone H3 (H3K27) affects the increased expression of genes involved in lipid synthesis. Enhancer of zeste 2 polycomb repressive complex 2 subunit, identified as the specific methyltransferase responsible for H3K27 methylation, plays a significant role in modulating diverse phenotypes of MASLD and operates through distinct

gene targets at different stages of the disease progression [43]. In a study the inbred strain of laboratory mouse models (C57BL/6J and DBA/2J), induced by an adipose-derived methyl-deficiency diet, manifest specific phenotypic changes characteristic of MASH. The study reported that these changes were concomitant with variations in the levels of 9th amino acid in Histone H3 (H3K9), H3K27, and 20th amino acid in Histone H4 methylation, underscoring the pivotal role of histone methylation in the initiation and advancement of MASH [44]. Schuster et al. [45] reported that histone methylation exerted an influence not only on the acute physiological alterations that underlie the transition from liver steatosis to MASH, but also directly modulated factors implicated in liver inflammation, including hepatocyte lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and other related mechanisms of the MASLD development. Also in a study it was shown that histone demethylation was involved in the development of MASLD [46]. The study demonstrated that lysine demethylase 7A overexpression could erase the H3K9me2 and H3K27me2 repressive markers on the diacylglycerol O-acyltransferase 2 promoter, thereby increasing the expression of diacylglycerol O-acyltransferase 2 and triglycerides accumulation, which, finally, induced hepatic steatosis. As Stearoyl-CoA desaturase 1 and diacylglycerol O-acyltransferase 2 enzymes are potential targets for the treatment of MASLD and clinical trials are ongoing, PHD Finger Protein 2 and lysine demethylase 7A could provide potential therapeutic targets in treating MASLD [47].

A few studies further suggested that histone acetylation can be a potential target for MASLD. The active phosphorylated form of FTY720/fingolimod, a prodrug treating multiple sclerosis, could reduce fatty acid synthase expression by histone acetylation alteration, inhibit ceramide production and hepatic steatosis in diet-induced MASLD mice [48, 49]. Interestingly, nuclear receptor subfamily 2 group F member 6 expression was increased in the livers of MASLD patients and reduced by metformin treatment in obese mice. Therefore, nuclear receptor subfamily 2 group F member 6 antagonists might offer a therapeutic approach for treating MASLD through histone acetylation [50]. It has also been reported that histone acetylation can be simultaneously involved in the regulation of multiple genes. The homozygous knock-in of a serine-to-alanine mutation at Phospho-Caspase 9 in Liver X receptor alpha could induce liver steatosis but prevent cholesterol accumulation, inflammation and fibrosis, thereby slowing the development from simple hepatic steatosis to MASH [51].

Ubiquitination (the covalent attachment of ubiquitin to acceptor residues in proteins) and sumoylation (the conjugation of any small ubiquitin-like modifiers member to a substrate) are recently demonstrated to be novel forms of histone modification. Studies have reported that post-translational modifications of transcription factors during protein processing play an important role in controlling many biological events [52]. In a study investigating the hepatic gene networks in obese patients with MASLD, hepatic fibrosis signaling was found to be the most significant pathway in the up-regulated MASLD gene cluster, whereas the endoplasmic reticulum stress and protein ubiquitination pathways to be the most significant pathways in the down-regulated MASLD gene cluster [53]. Besides ubiquitination, transcription factors can undergo several types of protein post-translational modifications, including acetylation, phosphorylation, and glycosylation. Currently, little is known about the role of these factors in the development of MASLD [54]. There are also relatively few reports on the role of histone ubiquitination and phosphorylation in the development and progression of MASLD [55].

The Role of Noncoding RNAs

Noncoding RNAs (ncRNAs) constitute a substantial part of the transcriptome and lack discernible protein-coding functions. However, ncRNAs have been involved in a wide range of biological processes, including disease pathogenesis [56]. Advancements in sequencing technology and data analysis have allowed researchers to discover numerous ncRNAs, including long noncoding RNAs (lncRNAs) [57], circular RNAs (circRNAs) [58] and small ncRNAs [59]. One subgroup of small ncRNAs – microRNAs – are endogenous single-stranded RNAs that play a crucial role in the regulation of biological processes and epigenetic mechanisms [60]. Recently, experimental studies have appeared that link aberrant function of lncRNAs with the development and progression of MASLD. In a study alu-mediated p21 transcriptional regulator was first identified in a search for human lncRNAs involved in cell proliferation [61]. The alu-mediated p21 transcriptional regulator was later found to be significantly upregulated in the fibrotic liver that was experimentally induced by repeated exposure to carbon tetrachloride and in mice with bile duct ligation, as well as humans with LF [62]. LF-associated lncRNA-1 was first identified in a microarray analysis to profile lncRNAs in carbon tetrachloride-treated mice, with increased expression occurring in hematopoietic stem cells [63]. In a study LF-associated lncRNA-1 was also found to promote intrahepatic cholangiocarcinoma proliferation and invasion through a similar pathway [64]. Most of the lncRNAs that have been implicated in MASH have been identified using animal models of hepatic fibrosis, largely carbon tetrachloride-induced fibrosis. Carbon tetrachloride is a common method for inducing LF, and like fibrogenesis attributed to MASLD in humans, it causes hematopoietic stem cell activation, dysregulated extracellular matrix production and degradation, and progressive hepatic fibrosis [65]. Several lncRNAs have been recently described to be clinically relevant in HCC [66]. The lncRNA activating regulator of dickkopf-related protein 1 was markedly upregulated in patients with HCC and HCC-derived cell lines. Upregulation of lncRNA activating regulator of dickkopf-related protein 1 was associated with poor patient survival [67]. Xu et al. [68] investigated lncRNAs with potential functions in cell cycle by analyzing RNA-sequencing data of tumor and adjacent healthy tissue from patients with HCC. LncRNA-mRNA coexpression analysis revealed that the DDX11-AS1 (an lncRNA located on chromosome 12p11), was highly upregulated in HCC and its covarying genes were associated with cell cycle progression.

Studies have shown that circRNAs and N6-methyladenosine had a critical role in the development of various diseases including obesity and MASLD [69]. circRNA may also play a role in a non-invasive approach to predict MASLD [70]. A growing body of evidence suggested that aberrant expression

of circRNAs was linked to the occurrence and development of liver diseases, including HCC, liver regeneration, and hepatic steatosis [71-73]. Guo X.Y. conducted a major survey, reporting that circRNA-0046367 expression was downregulated during hepatocellular steatosis in vivo and in vitro and its normalization abolished the inhibitory effects exerted by microRNA 34a on peroxisome proliferator-activated receptor α (PPARα) by blocking the miRNA/mRNA interaction with miRNA response elements [74]. CircRNA-002581 expression was significantly upregulated in MASH cell and mouse models. In a study was demonstrated that circRNA-002581 knockdown markedly attenuated hepatic lipid accumulation, oxidative stress, and inflammation (as evidenced by decreased tumour necrosis factor α (TNFα) and interleukin-6 expression) [75]. In addition, new data suggested a link between circRNA and the development of LF in patients with MASLD. It was reported that changes in the expression profile of circRNAs could promote or suppress hepatic fibrosis by regulating the activation and proliferation of hepatic stellate cells [76]. CircRNAs have become a new research hotspot in the field of MASLD in recent years. Many circRNAs with important physiological and clinical significance have been identified. Given their stability, tissue specificity, and functional activity, circRNAs are promising to as a non-invasive diagnostic tool and therapeutic target for MASLD [77].

Another subtype of ncRNAs that are involved in the fundamental pathological process that regulates the progression of simple steatosis to steatohepatitis, cirrhosis, and ultimately HCC are microRNAs (miRNAs) [78]. The miRNAs are short (19–23 nucleotides) noncoding RNA molecules that confer a crucial layer of regulation of gene expression via mRNA destabilization, translational repression, or activation of transcription/translation [79]. These molecules are receiving increasing attention since they are commonly deregulated in pathological situations, and are currently the most intensely studied epigenetic factors in MASLD [80, 81]. A study was demonstrated that altered expression of miRNAs was associated with liver metabolism dysregulation, liver injury, LF and tumour development, making miRNAs attractive therapeutic strategies for the diagnosis and treatment of liver diseases [82].

The most expressed miRNA in human liver - miR-122 - is inhibited in steatohepatitis, acting as a suppressor of tumors in the liver [83]. A study demonstrated that silencing of miR-122 was an early event during hepatocarcinogenesis from MASH, and miR-122 could be a novel molecular marker for evaluating the risk of HCC in patients with MASH [84]. Also, other miRNAs have been identified to be involved in MASLD progression. Thus, Pirola et al. [85] identified significant fold differences in serum levels of miR-192 (4.4-fold change in MASH vs. controls). Cermelli et al. [86] identified increased serum levels of miRNA-34a and miRNA-16 in MASLD patients compared to controls [86]. Yamada et al. [87] identified in a cohort of MASLD diagnosed patients increased serum abundance of miRNA-21, miRNA-34a and miRNA-451 relative to controls [87]. Tan et al. [88] identified miRNA-1290, miRNA-27b-3p and miRNA-192-5p as a panel of high diagnostic accuracy for MASLD . Guo et al. [89] reported three miRNAs (miRNA-301a-3p, miRNA-34a-5p and miRNA-375) as potential biomarkers to access the severity of MASLD. In addition, several studies have evaluated the contribution of miRNA-34a upregulation to the progression of LF and the development of HCC. In a study using a chemically induced rat model of LF combined with *in vitro* experiments in human hepatocytes and co-cultured hematopoietic stem cells, it was demonstrated that the miRNA-34a/SIRT1/p53 signalling pathway was activated specifically in hepatocytes and contributed to hepatocyte apoptosis and subsequent hematopoietic stem cell activation [90]. Thus, MASLD is associated with changes in hepatic miRNAs expression patterns at early, intermediate and late stages, and specific miRNAs species appear to be involved in steatosis development and steatosis progression to MASH and LF [91]. Further research is required to investigate the impact of ncRNAs on the development and progression of MASLD, as well as to explore the therapeutic potential of their use in the treatment of this cohort of patients.

The Role of N6-methyladenosine RNA Modification

The N6-methyladenosine modification has been increasingly described to have a dense association with the pathological machinery of various diseases [92]. The N6-methyladenosine RNA modification may highly regulate hepatic function and the development of liver diseases, providing some directions to understand the mechanism of malicious activities in the development of liver diseases [93]. A study found that N6-methyladenosine modification might be closely associated with the initiation and/or development of obesity and MASLD, which might progress to end-stage liver disease [94]. Another study demonstrated that N6-methyladenosine modification might play a role in the formation of specific and complexed microenvironments in the liver [95]. Recent studies have shown that N6-methyladenosine modification might be a key player in the pathogenesis of MASLD, which may provide new mechanistic insight into this disease [96]. The roles of N6-methyladenosine RNA methylation in the pathogenesis of liver diseases were also explored, providing new insights for studying the molecular mechanism of liver diseases [97]. However, the exact mechanism and role of N6-methyladenosine-modified RNAs in development and progression of MASLD remains poorly understood.

EMERGING THERAPEUTIC STRATEGIES TARGETING EPIGENETIC MECHANISMS

In recent years, there has been growing interest among researchers in elucidating the role of epigenetic modifications in the treatment of MASLD.

Considering the essential function of epigenetic enzymes in the regulation of inflammation associated with MASH progression, epigenetic inhibitors could hold significant promise for the exploration and development of innovative treatments for this condition [98]. In contrast to traditional therapies, drugs targeting epigenetic-modifying enzymes have been developed with a focus on gene regulation [99]. These drugs are categorized into four main types based on their mechanisms: DNA methyltransferase (DNMT) inhibitors,

histone deacetylases (HDAC) inhibitors, and miRNA inhibitors.

DNMT Inhibitors

In the early 1960s, two nucleoside DNMT inhibitors were discovered. These were 5-azacytidine (azacitidine, AZA, Vidaza) and its derivative, 5-2'-deoxycytidine (decitabine, DAC, Dacogen). Although the majority of DNMT inhibitors therapeutic effects are focused on oncology, numerous studies now explore their role in adipocyte biology. Treatment with decitabine induces significant hepatic DNA hypomethylation in mice fed a high-fat diet, thereby leading to a marked reduction in hepatic lipid accumulation [100, 101].

Pant et al [102] demonstrated that treatment of MASLD mice with DNMT inhibitors (azacitidine and zebularine) ameliorated different metabolic biochemical parameters (decrease the levels of plasma glucose, total cholesterol (TC), serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase) and increased insulin sensitivity, preventing the progression and development of MASLD [102]. This finding lays the groundwork for developing epigenetic-based therapeutics for the prevention and treatment of MASLD and other metabolic disorders. In another study, treatment with the DNA methylation inhibitor 5-Aza-2'-deoxycytidine significantly reversed DNA methylation levels and improved lipid accumulation in MASLD rat models [103].

Recently, some new nucleoside DNMT inhibitors and nonnucleoside DNMT inhibitors, including hydralazine, procaine and MG98, have been identified and are currently being investigated [104]. In a study hydralazine treatment significantly attenuated the progression of LF [this led to moderate alleviation of hepatocyte degeneration, significantly decreased LF, moderately ameliorates insulin resistance, decreased the serum and hepatic triglycerides (TG) levels] in rats with hypertension and steatohepatitis. Research data suggest that hydralazine shows promise as a potential treatment for MASH exacerbated by hypertension [105].

Current evidence suggests that epigenetic therapies demostrate promise as a treatment of the terminal stage of MASLD – HCC. In the study, DNMT inhibitors irreversibly bound to DNMT1 and partially restored hepatocytic differentiation in HCC cells, making them less tumorigenic [106]. Despite numerous studies, administration strategies for DNMT inhibitors as a treatment for MASLD still need to be thoroughly evaluated in carefully designed clinical trials.

HDAC Inhibitors

HDAC inhibitors have received considerable attention in the field of hepatology, probably owing to their antiproliferative properties and ability to induce cell death via deacetylation of multiple HDAC substrates [107]. Increasing evidence suggests that HDAC1 and HDAC2 (members of the HDAC family) are involved in the regulation of hepatocyte death, thereby implying that HDAC1 and HDAC2 serves a key role in the pathogenesis of liver disease. In this study, the roles of HDAC inhibitors (trichostatin A, sodium butyrate, and MS-275) in mouse hepatocyte apoptosis were examined. It was shown that HDAC inhibitors suppressed hepatocyte apoptosis and increase cell viability [108]. Valproate sodium, a broad class I and II HDAC inhibitor, has also been shown to block myofibroblast differentiation and fibrogenesis in mouse models of LF [109]. Another study found that HDAC11, a subtype of the HDAC family, was markedly overexpressed in both in vitro and in vivo models of MASLD. In this study, a novel hydrazide-based HDAC11 inhibitor was found to inhibit de novo lipogenesis and promote fatty acid oxidation, thus mitigating hepatic lipid accumulation and pathological symptoms in MASLD mice [110].

Consequently, although there is considerable interest in developing HDAC inhibitors as therapeutic agents for liver diseases, particularly MASLD, further investigation is required to assess potential side effects, design more target-selective inhibitors, and evaluate their efficacy in patients.

miRNA Inhibitors

Over the last few decades, numerous studies have demonstrated that inhibition of miRNAs can control the development of MASLD. miRNA-34a antagonists significantly restored the transmembrane potential of cellular mitochondria, improved cellular mitochondrial function, and reduced fat accumulation in the construction of MASLD mouse models [111].

In the meta-analysis, in which miR-34a antagonists were used as an intervention, hepatic TG, TC, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were significantly reduced, supporting the hypothesis that endogenous miRNA-34a is detrimental to MASLD and MASH. Inhibition of miRNA-34a activated fatty acid oxidation, and inhibited hepatocyte steatosis. It was also found that inhibition of hepatic miRNA-34a reduced hepatocyte reactive oxygen species levels and decreased gene expression of fibrogenesis [112].

Using complementary animal models of MASH, the study demonstrated that miRNA-21 ablation significantly reduces liver steatosis, inflammation and fibrosis [113]. Wang et al. [114] injected miRNA-21 antagonists into MASLD mice, and the levels of serum lipids (TG, TC, low-density lipoprotein) and transaminases (ALT, AST) were decreased. The expression of lipid synthesis-related genes was inhibited, confirming that fat accumulation and inflammation associated with MASLD progression to MASH can be reduced by inhibition of miRNA-21 [114]. In further animal tests, when MASLD mice were given miRNA-103a-3p inhibitors, this significantly decreased the serum TG, TC, ALT, and AST levels of the mice [115]. The administration of miRNA-103-3p antagonists reduced lipid droplet aggregation and significantly reduced inflammatory responses, abnormal lipid metabolism, and oxidative stress in MASLD mice. Therefore, inhibition of miRNA-103-3p offers a potential therapeutic strategy for treating MASLD [116].

Despite the promising therapeutic effects of miRNA inhibitors, there is still a scarcity of evidence to support the efficacy of individual miRNAs-based treatments for MASLD and MASH. More carefully designed preclinical studies involving miRNAs-inhibitor therapies in MASLD and MASH are essential to advance miRNA-based therapies for patients with these diseases.

CONCLUSIONS AND FUTURE PERSPECTIVES

This review summarizes the current knowledge regarding epigenetic determinants of MASLD. Genetic variation explains only a small fraction of environmental and hereditary disease risks, whereas epigenetic modifications, such as DNA methylation, histone modifications, noncoding RNAs, N6-methyladenosine, affect the majority of MASLD phenotypes. The research into the potential role of epigenetics in MASLD is still in its infancy and needs to be improved. There is currently considerable interest in identifying epigenetics-based therapeutic strategies to prevent the development of MASLD-related conditions. Despite the fact that there is still limited knowledge, current evidence suggests that epigenetic therapies also offer promise as a treatment of MASLD. However, administration strategies for incorporating epigenetic drugs into routine clinical practice still need to be thoroughly evaluated in further clinical studies.

Conflicts of interest: None to declare.

Authors' contributions: N.Z. conceived and designed the study. T.A. analyzed the data and drafted the manuscript. N.Z. and T.A. interpreted the data. N.Z. critically revised the manuscript, approved the final version to be published.

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