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Post-translational modifications in the pathophysiological process of metabolic dysfunction-associated steatotic liver disease

Yiyang Min[1†], Yiqiao Zhang[1†], Yu Ji[1†], Shanshan Liu[1], Chengjian Guan[1], Luyang Wei[1*], Huajing Yu[1*] and Zhongtao Zhang[1*]

Abstract

In recent years, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), which was called non-alcoholic fatty liver disease (NAFLD), has been progressively increasing in populations. The progression of MASLD encompasses a spectrum from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), and ultimately to cirrhosis or even hepatocellular carcinoma. During the early stages of the disease, lipid accumulation and endoplasmic reticulum stress may lead to abnormalities in hepatic DNA expression, protein synthesis, and post-translational modifications (PTMs). PTMs play a crucial role in the progression of MASLD and include histone and non-histone modifications, with major types including methylation, acetylation, ubiquitination, and phosphorylation. Numerous studies indicate that within MASLD-related signaling pathways, PTMs can modulate protein activity, localization, folding, and interactions by altering their physicochemical properties. This review summarizes various significant PTMs involved in MASLD progression to elucidate the regulatory mechanisms and pathogenesis associated with the disease.

Keywords Metabolic dysfunction-associated steatotic liver disease (MASLD), Post-translational modifications (PTMs), Histone protein, Non-histone protein

Introduction

Epidemiological characteristics and pathophysiological process of MASLD

The prevalence of MASLD is increasing annually among obese populations. With the accumulation of intrahepatic triglycerides, hepatic cells can progress from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and may eventually lead to more severe conditions such as liver fibrosis and cirrhosis [1, 2]. Patients with MASLD often present with comorbid metabolic disorders, including hypertension, cardiovascular disease, insulin resistance, and even type 2 diabetes [3]. In the pathophysiological progression of MASLD, lipid accumulation is closely associated with insulin resistance. Macrophages of the M1 phenotype in increased

†Yiyang Min, Yiqiao Zhang, Yu Ji these authors contribute equally to this work.

*Correspondence:
Luyang Wei
lywei@mail.ccmu.edu.cn
Huajing Yu
huajingyu@pku.edu.cn
Zhongtao Zhang
zhangzht@ccmu.edu.cn
[1]Department of General Surgery, Beijing Friendship Hospital, State Key Lab of Digestive Health & National Clinical Research Center for Digestive Diseases, Capital Medical University, Beijing 100050, China

adipose tissue secrete various inflammatory chemokines and cytokines [4], including monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), as well as interleukins IL-6, IL-2 and IL-8. TNF-α induces phosphorylation of insulin receptor substrate 1 (IRS-1) through serine/threonine pathways, thereby impairing IRS-1-mediated insulin signaling and leading to insulin resistance [5]. In addition, some researchers have pointed out that high levels of eotaxin, interleukin-2 (IL-2), macrophage migration inhibitory factor (MIF), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and stem cell factor (SCF), which are regulated by the expression and potential secretion of normal T cells after activation (RANTES), are associated with an increased risk of MASLD [6].Additionally, oxidative stress is a critical component of the MASLD disease process. Free fatty acids (FFAs) generated from lipid accumulation are oxidized in hepatic mitochondria and the endoplasmic reticulum (ER), producing reactive oxygen species (ROS). The generated ROS can severely damage cellular tissues, leading not only to mitochondrial dysfunction but also to DNA and protein damage, as well as depletion of glutathione, which induces oxidative stress and apoptosis [7]. Moreover, cytokines such as TNF-α produced by increased adipocytes can directly induce oxidative stress and apoptosis in hepatic cells, playing a significant role in the development and progression of MASLD or MASH [8]. Furthermore, research indicates that hyperinsulinemia and hyperglycemia resulting from insulin resistance can also directly induce oxidative stress [9]. Hyperinsulinemia and hyperglycemia may activate hepatic stellate cell (HSC) proliferation either directly through the release of Indian hedgehog (IHH) or indirectly through oxidative stress-induced hepatic cell damage or inflammation, leading to the secretion of extracellular matrix components associated with fibrosis progression, thereby promoting MASLD and MASH [10].

The role of PTMs in the MASLD progression

Post-translational modifications (PTMs) are primarily mediated through specific "writer" enzymes that add modification groups to substrates, followed by recognition of these modified sites by "reader" proteins that initiate downstream signaling cascades. Conversely, "eraser" enzymes can remove these modification groups. These regulatory proteins are considered PTM modulators [11]. Figure 1 shows the roles of some enzymes in histone modification.

PTMs can be categorized into histone modifications and non-histone modifications. The histone octamer (comprising two copies each of H2A, H2B, H3, and H4) forms the fundamental unit of the nucleosome, which constitutes the basic unit of chromatin [12]. Histone PTMs typically serve as an epigenetic code, primarily affecting lysine and arginine residues with modifications such as methylation, acetylation, and phosphorylation. Each modification site can transmit signals [13]. Table 1 mainly shows the processes of various modifications in histone proteins. Non-histone PTMs involve various amino acid residues, including lysine, arginine, and glutamic acid, and occur mainly on protein side chains, influencing protein structure, stability, and function. Additionally, enzymes responsible for non-histone PTMs are diverse, including methyltransferases, acetyltransferases, and phosphotransferases. Table 2 mainly shows the processes of various modifications in non-histone proteins.

Different PTM types serve distinct functions. For example, ubiquitination primarily regulates protein stability and does not directly affect modification sites but modulates them through other proximal PTMs [14]. Ubiquitination occurs through a three-step ATP-dependent process where ubiquitin is first activated by E1, then conjugated to ubiquitin carrier E2, and finally transferred to the lysine residues of target proteins by the E3 ubiquitin ligase complex [15]. Methylation and demethylation are closely related to gene expression, either activating or repressing it; for instance, H3K9me2 is found at repressive heterochromatin, while H3K4me1 and H3K4me3 are associated with enhancers and promoters, respectively [16]. Acetylation and deacetylation, controlled by acetyltransferases and deacetylases, broadly influence processes such as glycolysis, lipid synthesis, and DNA damage repair by modulating target stability, interactions with binding partners, enzyme activity, or subcellular localization [17]. Phosphorylation and dephosphorylation mainly regulate cellular functions such as growth, differentiation, apoptosis, and signaling, with dysregulation of these pathways potentially contributing to tumorigenesis [18].

Both histone and non-histone PTMs can disrupt various physiological processes, including hepatic lipid accumulation, endoplasmic reticulum stress, oxidative stress, mitochondrial damage, and inflammation—factors that promote MASLD development [19]. While histone PTMs epigenetically regulate transcription of MASLD-associated genes, non-histone PTMs directly modulate enzymatic activity or protein stability. This separation highlights the dual transcriptional and post-translational regulatory axes on which the MASLD pathway converges. This review focuses on summarizing key protein modifications involved in the progression of MASLD to further understand the impact of PTMs on this disease.

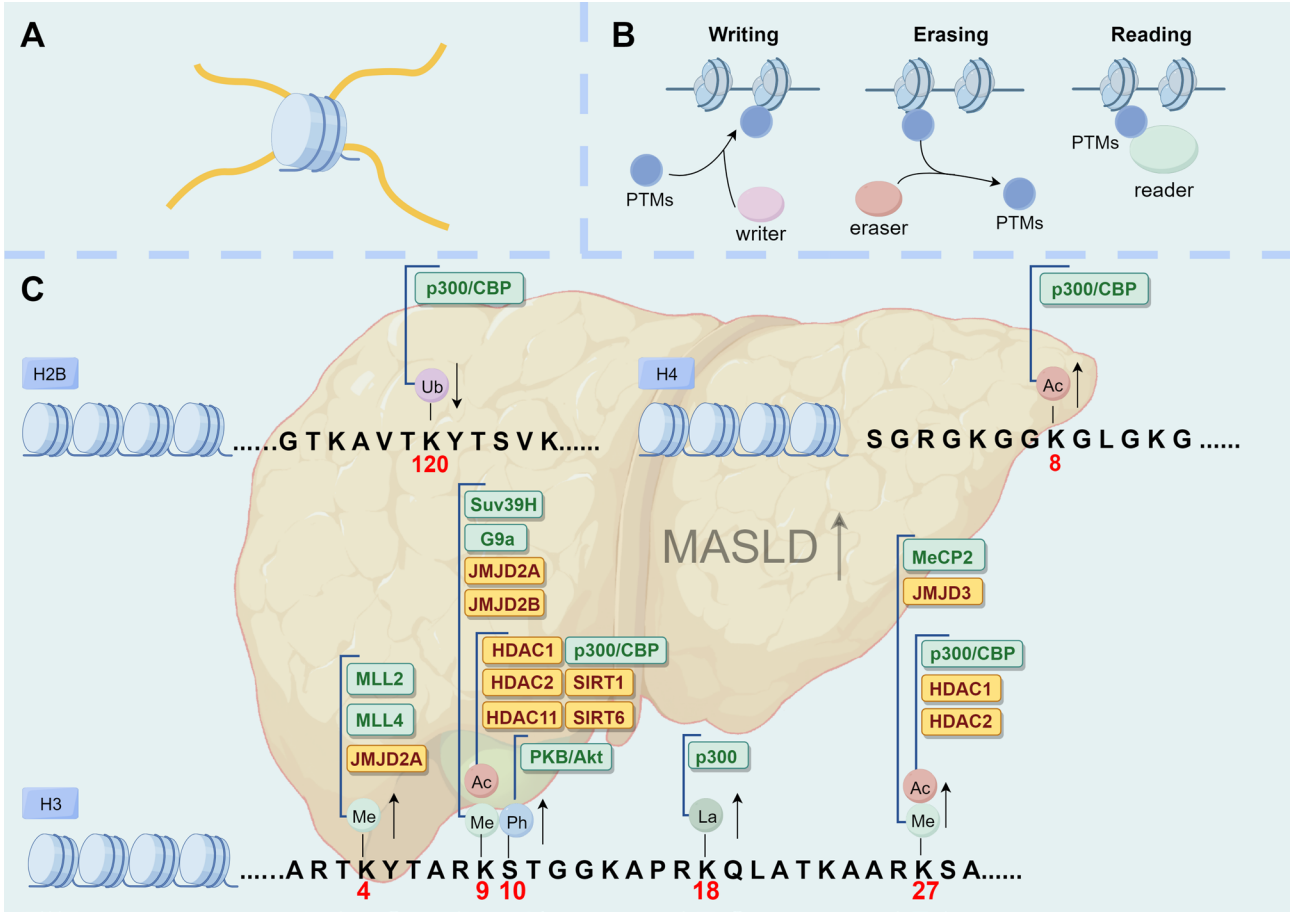

Fig. 1 Schematic diagram of post-translational modifications at different histone sites **A**. Octameric structure of the histone nucleosomes; **B**. Modulators of histones; **C**. The major histones regulate the development of MASLD through writer and eraser at site-specific PTMs, as detailed in Table 1. Ub, Ubiquitination; Ac, Acetylation; Me, Methylation; Ph, Phosphorylation; La, Lactylation

Table 1 Histone post-translational modifications in MASLD

PTM type	Site	Enzyme	Target	Major role	References
Methylation	H3K4	MLL4	PPARγ	Lipid synthesis	[34]
Methylation	H3K9	KMT1B(Suv39H2)	SIRT1–NF-κB	Oxidative stress & Inflammatory factors	[35, 36]
Methylation	H3K9	KMT1C(EHMT2/G9a)	LDLR/ HMGCR	Lipid metabolism	[37]
Methylation	H3K27	MeCP2	PPARγ(FASN), HSC	Lipid synthesis&Fibrosis	[38]
Acetylation	H3K9/H4K8	p300/CBP	ChREBP(FASN)	Lipid synthesis	[50]
Acetylation	H3K27	p300/CBP	NR4A1/ LncRNA-NEAT1/ SCD	Steatosis&Lipid synthesis	[51, 52]
Phosphorylation	H3S10	PKB/Akt	ChREBP(FASN)	Lipid synthesis	[72]
Ubiquitin	H2BK120	RNF20	HSC(LX-2)	Inhibit fibrosis	[98]
Lactylation	H3K18	p300	HSC	Fibrosis	[111]
Demethylation	H3K9	JMJD2A/2B	LXRα/ PPARγ2	Lipid synthesis	[42, 43]
Demethylation	H3K27	JMJD3(KDM6B)	FGF21 signaling	Liver autophagy & Lipid degradation	[47]
Deacetylation	H3K9	HDAC1/2	Snail1- FASN	Inhibit lipid synthesis	[55]
Deacetylation	H3K27	HDAC1/2	Snail1- FASN	Inhibit lipid synthesis	[55]
Deacetylation	H3	HDAC2	MCP-1/ GLP-1R	Reduce inflammatory infiltration	[57, 58]
Deacetylation	H3/FoxO1	HDAC6	FOXO1- FASN	Inhibit lipid synthesis	[59]
Deacetylation	H3K9	HDAC11	Adiponectin-AdipoR-AMPK	Reduce lipid degradation	[60]
Deacetylation	H3K9	SIRT1	PNPLA3	Oxidative stress	[61, 62]
Deacetylation	H3K9	SIRT6	Smad3	Reduce fibrosis & lipid accumulation	[63]

Table 2 Non-histone post-translational modifications in MASLD

PTM type	Substrates	Enzyme	Target	Major role	References
Deacetylation	CPT1A	SIRT2	Lipogenic pathways	Reduce lipid accumulation	[65]
Phosphorylation	SMPD3	-	FXR-AMPK pathway	Inhibit lipid metabolism/oxidative stress	[74]
Phosphorylation	IP3R1(Tyr353)	PA	Ca- AMPK pathway	Oxidative stress	[75]
Phosphorylation	AMPK	-	AMPK-LXR pathway	Inhibit lipid synthesis	[79]
Phosphorylation	PI3K	-	PI3K-AKT pathway	Insulin resistance&apoptosis&oxidative stress	[80–87]
Phosphorylation	NF-κB	-	PI3K-AKT- NF-κB pathway	Apoptosis&oxidative stress	[88–90]
Phosphorylation	JNK/p38/MAPK	-	JNK-p38-MAPK pathway	Apoptosis&oxidative stress	[93, 94]
Phosphorylation	Acc1/2	AMPKα	Lipogenic pathways	Lipid accumulation	[77, 78]
Phosphorylation	AMPKα	LKB1	AMPK pathway	Apoptosis	[73]
Ubiquitin	NF-κB	SCF(β-TrCP)	NF-κB pathway	Apoptosis&oxidative stress	[89]
Ubiquitin	JAK2	NEDD4	JAK2-STAT5-PPARγ	Inhibit lipid synthesis	[99, 100]
Ubiquitin	ATGL(k48)	COP1	Lipolysis pathways	Lipid accumulation	[101]
Ubiquitin	ACLY	Hrd1	Lipogenic pathways	Inhibit lipid synthesis	[102]
Ubiquitin	AMPKα1/α2	MKRN1	AMPK pathway	Inhibit lipid metabolism	[105]
Ubiquitin	HNF4α(lys470)	TRIB3- TRIM8	HNF4α-Lipid metabolism pathway	Lipid accumulation	[103]
Ubiquitin	FASN	TRIM56	Lipogenic pathways	Lipid accumulation	[104]
Lactylation	FASN	-	Lipogenic pathways	Lipid accumulation	[112]
Malonylation	ACC1(lys1523)	-	Lipogenic pathways	Lipid accumulation	[110]
Palmitoylation	CD36	zDHHC6/ 7	Lipogenic pathways	Lipid accumulation	[115]
Palmitoylation	AKT	zDHHC17/24	Lipogenic pathways	Lipid synthesis	[117]
Palmitoylation	MYD88	zDHHC6	TLR4- MyD88-NF-κB	Inflammatory response	[118]
Palmitoylation	IRHOM2(C476)	zDHHC3	JNK-p38-MAPK pathway	Apoptosis&oxidative stress	[119]
Dephosphorylation	ASK1	GSTM2	ASK-p38-MAPK pathway	Anti apoptosis&oxidative stress	[95]
Deacetylation	HNF4α(lys458)	SIRT2	HNF4α-Lipid metabolism pathway	Reduce lipid accumulation	[68]
Deacetylation	ACSL5	SIRT6	Lipogenic pathways	Lipid metabolism	[69]
Deacetylation	TAK1	TRIM16/SWAP70	JNK-P38-MAPK pathway	Reduce lipid accumulation &inflammatory response	[91, 92]
Deacetylation	JNK	SP600125	JNK-p38-MAPK pathway	Reduce lipid accumulation &inflammatory response	[96]
Deubiquitination	ATF4	USP7	Lipogenic pathways	Lipid accumulation	[106]
Deubiquitination	PA	USP2/14	-	Palmitic acid synthesis	[107, 108]
Deubiquitination	LC3B	USP4/10/18	Autophagy pathway	Reduce lipid synthesis &inflammatory response	[109]

Functions and mechanisms of PTMs in MASLD

Methylation modifications

Methylation is a critical modification of proteins and nucleic acids that can regulate gene expression, gene silencing, and post-translational protein functions, and is closely associated with various diseases, including MASLD [20, 21]. Protein methylation can occur on both histone and non-histone proteins. Histone methylation and demethylation are mediated by histone methyltransferases (HMTs) and histone demethylases (HDMs), respectively, and primarily involve lysine and arginine residues on H3 and H4 histones [22]. Arginine methylation is catalyzed by the protein arginine methyltransferase (PRMT) family, while lysine methylation is mediated by histone lysine methyltransferases (KMTs) that contain the evolutionarily conserved SET domain. Additionally, histone lysine demethylases (KDMs)--the Jumonji C (JmjC) domain-containing family members and lysine-specific demethylase 1 (LSD1) are key demethylases for lysine, with some JmjC family members, such as KDM3A, KDM4E, and KDM5C, also catalyzing arginine demethylation [23–25].

Generally, methylation at different sites on histones H3 and H4 and the extent of methylation significantly impact transcriptional regulation. For instance, H3K9me3, H3K27me3, and H4K20me2/3 are associated with transcriptional repression [26–28], whereas H3K4me1/2/3, H3K9me1, H3K27me1, H3K36me1/2/3, and H3K79me1/2/3 are linked to transcriptional activation [29–33].

MLL family proteins (including MLL1/2/3/4) are specific histone H3 lysine 4 methyltransferases, and their normal biological function depends on a conserved SET domain at their C-terminus. According to research by

Kim et al., nutritional excess activates ABL1 kinase, promoting the binding of H3K4 methyltransferase MLL4 (also known as KMT2D) and peroxisome proliferator-activated receptor gamma 2 (PPARγ2), leading to the induction of PPARγ2 fatty degeneration target genes and resulting in steatosis [34]. Additionally, studies using N-ethyl-N-nitrosourea (ENU)-induced MASLD mouse models have identified histone H3K4 methylation catalyzed by methyltransferases, with H3K4 methylation typically associated with transcriptional activity [16].

Histone methyltransferase KMT1B, also known as Suv39H2, can catalyze the trimethylation of H3K9 and is associated with the pathogenesis of MASH. Research by Fan et al. indicated that stimuli promoting MASH, such as a high-fat diet, can increase the expression levels of KMT1B in the liver. In contrast, liver fibrosis induced by a high-fat diet (HFD) is attenuated in KMT1B-deficient mice, and certain pro-fibrotic genes are also reduced. The deficiency of KMT1B allows for normal expression of Sirtuin 1 (SIRT1), which subsequently inhibits the transcription of nuclear factor kappa B (NF-kB) dependent pro-inflammatory mediators [35]. Conversely, another study suggested that H3K9 trimethylation by KMT1B suppresses SIRT-1 expression in the liver, whereas its absence increases SIRT-1 expression [36]. Thus, histone methyltransferase KMT1B plays a crucial role in controlling diet-induced liver inflammation through the regulation of SIRT1 and NF-kB expression, significantly contributing to the pathogenesis of MASH and MASLD.

Another histone methyltransferase, KMT1C, also known as EHMT2 or G9a, is primarily responsible for adding mono- and dimethyl groups to H3K9, thereby regulating the expression of cytochrome P450 enzymes and silencing genes related to cholesterol metabolism, such as the low-density lipoprotein receptor (LDLR) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). These genes play a crucial role in cholesterol synthesis and clearance; hence, the methylation activity of KMT1C on H3K9 may influence cholesterol metabolism [37].

The enhancer of zeste homolog 2 (EZH2), a KMT, catalyzes the methylation of H3K27 and plays an important role in MASLD progression. Methyl-CpG-binding protein 2 (MeCP2), an enhancer of EZH2, stimulates EZH2 expression, leading to the formation of a repressive chromatin structure at the 3′ exon of PPARγ following H3K27 methylation, which results in downregulation of PPARγ [38]. This, in turn, antagonizes the differentiation of HSCs into myofibroblasts [39], ultimately promoting the progression of MASLD towards fibrosis.

Histone demethylases are primarily categorized into two classes: flavin adenine dinucleotide (FAD)-dependent amine oxidases (LSD demethylases) and iron (II)- and α-ketoglutarate-dependent Jumonji domain-containing demethylases (JMJD demethylases). LSD demethylases, including LSD1 and LSD2, remove mono- and dimethylation from H3K4 and H3K9. JmjC domain-containing histone demethylases are further subdivided into numerous subfamilies based on their substrate specificity for H3K4, H3K9, H3K27, or H3K36 [40]. The JMJD2 or KDM4 family consists of JMJD2A (KDM4A), JMJD2B (KDM4B), and JMJD2C (KDM4C), which demethylate di- and trimethylated H3K9 and H3K36 (H3K9me2/me3 and H3K36me2/me3). Specifically, JMJD2B catalyzes the removal of di- and trimethylation from H3K9 (H3K9me2/me3), converting these histones to a monomethylated state [41].

Jumonji C domain-containing histone demethylases JMJD2A and JMJD2B are H3K9 demethylases. JMJD2B promotes lipogenesis mediated by liver X receptor α (LXRα) by removing the repressive dimethylation and trimethylation of H3K9 at the LXRE (LXR response element) in the LXRα target gene promoters, potentially contributing to liver steatosis [42]. JMJD2B expression also enhances lipogenesis and steatosis through increased PPARγ2 expression, hepatic lipid uptake, and intracellular triglyceride accumulation. Kim et al. demonstrated that overexpression of JMJD2B in HepG2 cells, via adenoviral vectors, removes dimethylation and trimethylation from H3K9 at the PPARγ2 promoter, stimulating the expression of PPARγ2 and its associated fatty acid uptake and lipid droplet formation target genes, resulting in increased intracellular triglyceride (TG) accumulation. Knockout of JMJD2B reversed the effects mediated by JMJD2B in HepG2 cells [43]. Inagaki et al. also discovered that H3K9 demethylase JHDM2a is a key regulatory factor in genes involved in energy expenditure and fat storage [44]. Additionally, JMJD2A knockout mice exhibit obesity, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and elevated leptin levels, with increased fat deposition and elevated blood lipid levels unaffected by age or dietary intake [45, 46].

Furthermore, JMJD3 (also known as KDM6B) is considered a regulatory factor in MASLD and may function as a demethylase for histone H3K27. JMJD3 participates in metabolic processes such as lipolysis, glucose homeostasis, and insulin sensitivity. Its liver-specific downregulation results in intrinsic mitochondrial β-oxidation defects and autophagy deficiencies, leading to abnormal liver TG accumulation, liver steatosis, and insulin and glucose intolerance, which are key factors in MASLD progression [47].

In summary, histone methylation and demethylation modification sites relevant to MASLD progression are primarily focused on H3K4, K9, and K27. Then respectively affect the PPARγ-related lipid synthesis [34, 43], the NF-κB-related inflammatory cytokine pathway [37], and the HSC-related fibrogenesis process, cellular autophagy and lipid degradation related to fibroblast growth factor

21 (FGF21) signaling pathway [47], ultimately leading to the occurrence and progression of MASLD. However, the complex effects of gene expression and modification mediated by methyltransferases and demethylases in MASLD require further investigation.

Acetylation modifications

Acetylation, one of the most common PTMs, involves the addition of an acetyl group from acetyl-CoA to proteins, facilitated by histone acetyltransferases (HATs). HATs primarily promote acetylation of histones H3 and H4 by adding acetyl groups to the positively charged lysine residues on the histone tails, thereby reducing their positive charge. This reduction in positive charge decreases the affinity of histones for DNA and facilitates gene expression. Conversely, histone deacetylases (HDACs) remove acetyl groups from lysine residues through hydrolysis, leading to histone deacetylation. This process restricts the accessibility of DNA to transcription factors and reverses acetylation, thereby inhibiting gene expression [48]. Both acetylation and deacetylation mechanisms are essential for the regulation of gene expression. With the discovery of non-histone acetylation, HATs and HDACs are also referred to as histone lysine acetyltransferases (KATs) and histone lysine deacetylases (KDACs).

Histone acetyltransferase (HAT) is an enzyme that promotes histone acetylation modification. HATs in the human body can be classified into two major types, A and B, based on their subcellular localization. Type A can be further divided into five families according to their catalytic domains, playing a role in chromatin and transcription-related histone acetylation, including the GCN5-related N-acetyltransferases (GNAT) family, MYST (MOZ, Ybf2/Sas3, Sas2 and Tip60) family, and transcription factor-related families TATA-box binding protein associated factor 1 (TAF1) and transcription initiation factor III C 90 kDa (TIFIIIC90). The main members of the GNAT family are p300/CBP-associated factor (PCAF), general control non-derepressible 5 (GCN5), and elongator complex protein 3 (ELP3). The MYST family includes MOZ, MORF, HBO1, HMOF, Ybf2/Sas3, Sas2, and TIP60 [49]. Among these HATs, the role of p300/CBP-associated factor (PCAF) has been extensively studied in the progression of MASLD [50].

As a member of the GNAT family, p300 is a crucial upstream regulator of carbohydrate response element-binding protein (ChREBP) activity and is associated with the NF-κB-mediated inflammatory pathway. Hyperglycemia-induced activation of p300 leads to increased acetylation of ChREBP, enhancing its transcriptional activity, ultimately resulting in the activation of lipogenic genes and the development of MASLD. Another upstream regulator of ChREBP, serine/threonine kinase salt-inducible kinase 2 (SIK2), can inhibit p300 HATs activity through phosphorylation of ser89 [50]. Liang et al. found that in MASLD induced by hyperhomocysteinemia (HHcy), Hcy can enhance p300 and reduce the recruitment of deacetylase HDAC7 to the promoter of nuclear receptor subfamily 4 group A member 1 (NR4A1), leading to increased acetylation at the histone H3K27 site of this promoter and upregulation of gene expression, thereby blocking the effect of Hcy on steatosis. However, when NR4A1 is depleted, the progression of MASLD accelerates [51].

Additionally, some researchers believe that in MASLD hepatocytes, FFA upregulates the acetylation of H3K27 in the promoter region of LncRNA-NEAT1, promoting the transcription of LncRNA NEAT1 and inhibiting the expression of miR-212-5p. miR-212-5p directly targets GRIA3(glutamate ionotropic receptor AMPA type subunit 3). The reduction of miR-212-5p can lead to upregulation of GRIA3 and ultimately promote lipid accumulation [52]. Although the liver cell inflammatory response is reduced in mice lacking lipopolysaccharide-binding protein (LBP) when fed a high-fat diet, it significantly exacerbates the progression of MASLD in rats and leads to notable changes in liver histone acetylation and transcriptome characteristics. These changes are mainly manifested as significant H3K27 hyperacetylation, which promotes the binding of C/EBPβ to the promoter region, leading to the activation of stearoyl-CoA desaturase (SCD), the rate-limiting enzyme for synthesizing monounsaturated fatty acids, and triggering lipid accumulation [53].

Histone deacetylases (HDACs) are mainly classified into the histone deacetylase family and the SIRT2 regulator family, including Class I Rpd3-like proteins (HDAC1, HDAC2, HDAC3, and HDAC8); Class II Hda1-like proteins (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10); Class III SIRT2-like proteins (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7); and Class IV proteins (HDAC11) [54]. For example, HDAC1/2 are recruited after Snail1 binds to insulin to induce deacetylation of H3K9 and H3K27, thereby inhibiting the expression of lipogenic genes. Liu et al. found that the insulin/Snail1 pathway is impaired in obese mouse models, leading to steatosis [55]. In mice lacking CD36, the expression of HDAC2 is reduced, resulting in excessive acetylation of histone H3 bound to the MCP-1 promoter, which subsequently leads to increased expression of MCP-1. The upregulation of MCP-1 increases macrophage infiltration, inflammation, hepatic steatosis, and fibrosis, contributing to the progression of MASLD [56, 57]. Zhou et al. discovered that certain short-chain fatty acids, such as Sodium butyrate (NaB), can reverse HDAC2-mediated deacetylation in HepG2 cells of mice fed a high-fat diet, upregulating glucagon-like peptide-1 receptor (GLP-1R) expression and subsequently mitigating the progression of MASLD [58]. Zhang et al. used a tree shrew model of

MASLD, found that overexpression of S100A11 activates autophagy and lipogenesis through the upregulation and acetylation of the transcription factor forkhead box protein O1 (FoxO1), promoting lipid production and accumulation both in vitro and in vivo, while HDAC6 (the deacetylase of FoxO1) remains inhibited [59]. Sun et al. demonstrated in animal experiments that the deletion of HDAC11 can improve insulin resistance and glucose tolerance, thereby alleviating HFD-induced obesity. They suggested that inhibiting the function of HDAC11 or its deletion activates the adiponectin-AdipoR-AMPK pathway in the liver, which may help reverse hepatic steatosis [60].

The activation of Patatin-like phospholipase domain 3 (PNPLA3) predisposes individuals to MASLD. Xu et al. observed that in cells from a mouse model of MASLD induced by a high-sugar diet, overexpression of SIRT1 inhibited high acetylation of H3K9 at the PNPLA3 promoter induced by high glucose, while silenced expression of SIRT1 suppressed low acetylation of H3K9 induced by fasting. In summary, overexpression of SIRT1 prevents SREBP-1c-driven PNPLA3 gene expression and also blocks the endogenous binding of SREBP-1c to PNPLA3, thereby inhibiting the progression of MASLD, whereas its absence promotes it [61]. Yin et al. found in mice with SIRT1 gene knockout that the absence of SIRT1 may lead to the accumulation of inflammatory factors in the liver of mice, promoting oxidative damage [62]. Furthermore, Zhong et al. confirmed in mice with SIRT6 and HSCs knockout that Sirt6 maintains triglyceride (TG) stability in adipose tissue and inhibits neogenesis of fat by participating in the deacetylation of histone H3 [63].

In conclusion, the acetylation and deacetylation modifications at the sites of histone H3K9, H3K27, and H4K8 are mainly related to the expression and silencing of some proteins. Acetylation can promote the progression of MASLD through lipogenesis mediated by ChREBP [50] and fat accumulation associated with NR4A1, LncRNA-NEAT1, and SCD [51, 52]. On the other hand, Sirt1 and Sirt6 can inhibit the progression of MASLD by suppressing oxidative stress associated with PNPLA3 [61, 62] and fat accumulation related to Smad3 [63].Non-histone acetylation and deacetylation enzymes share similarities with histone modifications. In addition to the effects on histone acetylation and deacetylation, the role of non-histone acetylation and deacetylation in the progression of MASLD has also garnered attention from researchers. This primarily involves key cellular processes related to physiology and disease, such as gene transcription, DNA damage repair, cell division, signal transduction, protein folding, autophagy, and metabolism [64].

Helsley et al. discovered that the increase in ketohexokinase-C (KHK-C), an enzyme catalyzing the first step of fructose catabolism, correlates with an increase in lipogenic proteins like ATP citrate lyase (ACLY). The elevation of KHK-C promotes the acetylation of carnitine palmitoyltransferase 1 A (CPT1A), a key rate-limiting enzyme for the transfer of long-chain fatty acids from the cytoplasm to mitochondria for oxidation, resulting in reduced CPT1A levels. Moreover, KHK-C overexpression in vitro decreases CPT1A and increases triglyceride accumulation [65].

The Sirtuin family of deacetylases, members of the Silent Information Regulator-2 family, function as nicotinamide adenine dinucleotide (NAD^+)-dependent histone/protein deacetylases. Among them, SIRT1 serves as a pivotal metabolic sensor that regulates various cellular processes, including energy metabolism and stress responses, by directly linking cellular metabolic status to chromatin structure and gene expression control [66]. In MASLD cells, the activity of SIRT1 may be influenced by multiple factors. On one hand, metabolic disturbances such as high-fat diets and insulin resistance can decrease SIRT1 activity; on the other hand, certain endogenous molecules, like allosteric activators (e.g., NAD^+), and drugs (e.g., sibutramine) may enhance its activity. Geng et al. found that overexpression of Mammalian Ste20-like kinase 1 (Mst1) may increase SIRT1 expression by inhibiting its ubiquitination, thereby promoting lipid metabolism [67]. Meanwhile, SIRT2 plays a significant role in regulating adipocyte differentiation, lipolysis, lipid synthesis, and fatty acid oxidation. Ren et al. suggested that SIRT2 stabilizes hepatocyte nuclear factor 4α (HNF4α) protein by binding to lysine 458 on HNF4α and deacetylating it. Deficiency of HNF4α in the liver leads to lipid accumulation and elevates serum total cholesterol levels. Studies have shown that upregulation of SIRT2 expression in obese mice alleviates insulin resistance, steatosis, and inflammation, whereas specific knockdown of SIRT2 in high-fat diet-induced C57BL/6J mice exacerbates metabolic disorders [68]. Furthermore, Hou et al, discovered that SIRT6 binds to saturated fatty acids, particularly palmitic acid, leading to the deacetylation of long-chain acyl-CoA synthetase 5 (ACSL5), which promotes fatty acid oxidation and impedes MASLD progression. This finding is supported by the significant reduction of cytoplasmic SIRT6 levels and increased ACSL5 acetylation observed in hepatocytes from MASLD or MASH patients and mouse models [69].

It is evident that p300/CBP-associated factor-mediated acetylation and Sirtuin family-mediated deacetylation primarily occur in enzymes related to lipid metabolism processes. As metabolic research delves deeper, additional modifications of non-histone enzymes are expected to be uncovered.

Overall, the Sirt family affects non-histone proteases in the lipid synthesis pathway, such as CPT1A [65], HNF4α

[68], ACSL5 [69], which inhibit fat accumulation and slow down the progression of fat related liver disease.

Phosphorylation modification

Protein phosphorylation modification primarily involves the transfer of phosphate groups onto serine, threonine, and tyrosine residues, serving as a "switch" that regulates molecular or signaling pathway functions [70]. Relatively few studies have examined the regulation of histones through phosphorylation in steatotic liver disease (SLD), particularly MASLD. These studies mainly focus on the addition or removal of phosphate groups from key proteins upstream and downstream of pathways such as AMPK, AKT, and NF-κB, achieving regulatory purposes [71]. Figure 2 illustrates this process.

The phosphorylation modification of histones frequently interacts with other histone modifications and may regulate chromatin states in response to DNA damage and other stresses. The carbohydrate-responsive element-binding protein (ChREBP) serves as a pivotal regulator of glucolipid metabolism. By directly binding to the carbohydrate-responsive element (ChoRE) within promoters, ChREBP induces acetylation of H3 and H4, trimethylation of H3K4, and phosphorylation of H3S10, thereby enhancing the expression of fatty acid synthase (FASN) and subsequently promoting hepatic steatosis [72].

The primary roles of non-histone phosphorylation-related modifications in the progression of MASLD encompass various signaling pathways, with current research predominantly focusing on the AMP-activated protein kinase (AMPK), protein kinase B (AKT), NF-κB-related, and c-Jun N-terminal kinase (JNK) signaling pathways, among others, investigating MASLD-associated phosphorylation modifications [71].

Qiu et al. found that in male mice fed a MASH-inducing diet, hepatic deletion of mitogen-activated protein kinase phosphatase 1 (MKP1) leads to the release of nuclear liver kinase B1 (LKB1) into the cytoplasm to activate AMPKα, thereby preventing hepatocyte death, inflammation, and the progression of MASH. Consequently, nuclear-localized MKP1-p38 MAPK-LKB1 signaling is required to restrain AMPKα, which otherwise triggers hepatocyte death and the development of MASH [73]. The addition of phosphate groups to non-histone proteins at various nodes of signaling pathways can enhance the stability of molecules or metabolic products. For instance, sphingomyelin phosphodiesterase 3 (SMPD3) undergoes degradation upon ubiquitination, but when phosphorylated by upstream AMPK, the phosphate group on SMPD3 inhibits ubiquitination, leading to its recovery from phosphorylation and ultimately contributing to MASLD progression [74]. Additionally, palmitic acid (PA)-induced Tyr353 phosphorylation enhances protein stability in the type 1 inositol 1,4,5-trisphosphate

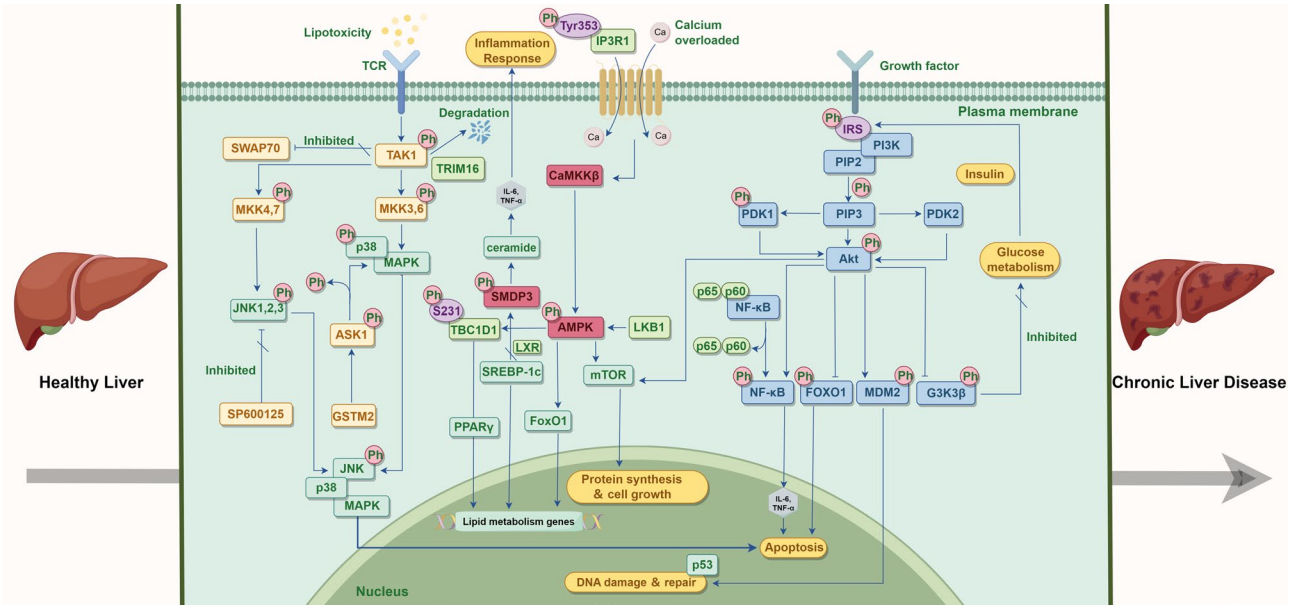

Fig. 2 Non-histone phosphorylation modifications play pivotal roles in MASLD progression through spatiotemporal regulation of key signaling pathways. JNK/MAPK hyperphosphorylation and p38 activation promote lipotoxic apoptosis via ER stress, while TAK1-ASK1 signaling drives fibrosis. AMPK activation reducing malonyl-CoA synthesis and promoting fatty acid oxidation, while stabilizing SMPD3 to modulate sphingolipid metabolism. Dysregulation of the AMPK-TBC1D1 axis exacerbating lipid accumulation via PPARγ stabilization. PI3K/AKT pathway drives insulin resistance through mTOR/FOX family activation and cyclic IRS reactivation under hyperinsulinemia, further aggravating hepatocyte apoptosis. The NF-κB pathway amplifies inflammation by triggering TNF-α and IL-6 production, serving as a hub for PI3K/AKT and JNK crosstalk. Ph, Phosphorylation

receptor (IP3R1), which in turn leads to Ca^{2+} overload, ultimately disrupting hepatocyte mitochondrial function in MASLD [75]. This phenomenon is not limited to the molecules acquiring phosphate groups but can also extend to their downstream regulatory targets. For example, nutrient excess attenuates the phosphorylation level of the AMPK-TBC1D1 signal, enhancing GTP-bound Rab2A activity, which promotes hepatic steatosis by increasing PPARγ protein stability and the expression of PPARγ target genes [76]. AMPK phosphorylates acetyl-CoA carboxylase 1 (ACC1) at Ser79 and ACC2 at Ser212, inhibiting the conversion of acetyl-CoA to malonyl-CoA. Malonyl-CoA serves as a precursor for fatty acid synthesis and an allosteric inhibitor of fatty acid transport into mitochondria for oxidation, potentially leading to the accumulation of fatty acids [77]. Fullerton et al. discovered that mice harboring alanine knock-in mutations at ACC1 (Ser79) and ACC2 (Ser212) exhibited increased lipogenesis and decreased fatty acid oxidation compared to wild-type mice, contributing to the progression of insulin resistance, glucose intolerance, and MASLD. In summary, inhibitory phosphorylation of ACC by AMPK is crucial for controlling lipid metabolism [78].

Sterol regulatory element-binding protein 1 (SREBP-1), a key transcription factor for de novo lipogenesis, is inhibited by AMPK phosphorylation through suppression of LXR or directly. Given that SREBP-1 activation is associated with MASLD development, its regulation by AMPK phosphorylation plays a crucial role in preventing or modulating this condition [79].

Phosphatidylinositol 3-kinase 3 (PI3K) is a dimer consisting of a regulatory subunit p85 and a catalytic subunit p110. Its primary function lies in modifying the protein structure of AKT, thereby activating or inhibiting downstream substrates through phosphorylation. The PI3K/AKT signaling pathway plays a pivotal role in regulating cellular processes such as proliferation, differentiation, apoptosis, and migration. Upon receiving phosphorylation groups from activated PI3K, AKT typically facilitates the regulation of downstream signaling pathways. In the context of insulin resistance in skeletal muscle, AKT has been shown to primarily act on mammalian targets of rapamycin (mTOR) [80, 81]and the FOX family [82, 83], contributing to insulin resistance. Meanwhile, excessive insulin release under insulin resistance conditions restores the phosphorylation activity of IRS, subsequently triggering AKT phosphorylation, forming a cyclic process [84–86]. Additionally, AKT phosphorylation can induce irregularities in cyclins, leading to apoptosis and impacting fatty liver disease [87]. Thus, AKT phosphorylation is primarily associated with insulin resistance and apoptosis in fatty liver disease.

The NF-kB protein typically forms a heterodimeric complex with p65 and p50, remaining inactive due to its binding with the NF-κB inhibitor ε (IκB). Upon activation by upstream signaling factors, IκB is phosphorylated by IκB kinases, leading to its dissociation from the trimer [88]. Phosphorylated NF-κB exposes its nuclear localization sequence (NLS), enabling its translocation from the cytoplasm to the nucleus, where it binds to specific DNA sequences to promote the expression of downstream molecules, including inflammatory factors. These inflammatory factors, such as TNFα, transforming growth factor β (TGFβ), and interleukin family members, can further promote NF-κB activation. Consequently, the phosphorylation and activation of NF-κB can initiate inflammation and immune dysregulation, inducing inflammatory responses and immune abnormalities [89, 90]. In the context of MASLD pathogenesis, the phosphorylation and activation of NF-κB primarily serve as the final step in pathways such as PI3K/AKT and JNK/STAT3.

Wang et al. discovered that overexpression of E3 ligase tripartite motif-containing protein 16 (TRIM16) mitigated lipid accumulation and inflammation in mouse models of MASH, whereas its depletion exacerbated these conditions. Multiomics analysis revealed that TRIM16 inhibited MASH progression by attenuating the activation of the mitogen-activated protein kinase (MAPK) signaling pathway, particularly through preferential interaction with phospho-TAK1 to promote its degradation [91]. Switch-associated protein 70 (SWAP70), a guanine nucleotide exchange factor, was shown by Qian et al. to suppress the progression of MASH by inhibiting lipid accumulation, inflammatory response, and fibrosis. RNA sequencing and immunoprecipitation analyses demonstrated that SWAP70 inhibited the interaction between TGF-β-activated kinase 1 (TAK1) binding protein 1 and TAK1, subsequently suppressing TAK1 phosphorylation and downstream c-Jun N-terminal kinase/P38 signaling, ultimately inhibiting hepatic lipid deposition and inflammation [92].

The unfolded protein response (UPR) in the endoplasmic reticulum (ER) is initially characterized by translational attenuation of protein synthesis, increased degradation of ER-associated proteins via the proteasome pathway, and the activation of genes to adapt cells to triggers of ER dysfunction. If cells fail to adapt, alarm pathways are activated, including the JNK pathway, leading to apoptosis and inflammation. The UPR plays a pivotal role in the progression of MASLD [93]. Alarm signaling in the UPR is mediated by JNK and p38 MAPK. The status of the alarm/death pathway is assessed by measuring total and phosphorylated JNK and p38 MAPK proteins, as well as apoptotic activity, which can be measured using the terminal dUTP nick-end labeling (TUNEL) assay. Puri et al. found that phosphorylation of p38 MAPK protein was significantly increased in both MASLD and MASH

patients, while JNK phosphorylation differed significantly only in MASH patients compared to healthy individuals, as determined by quantitative real-time PCR and Western blot for messenger RNA (mRNA) and protein expression, respectively [94]. Lan et al. found that glutathione S-transferase Mu 2 (GSTM2), a Phase II detoxification enzyme, is significantly downregulated during the progression of MASH. GSTM2 maintains MAPK pathway signaling through direct interaction with apoptosis signal-regulating kinase 1 (ASK1). GSTM2 binds directly to the N-terminal region of ASK1 and inhibits the N-terminal dimerization of ASK1, thereby suppressing ASK1 phosphorylation and the activation of its downstream JNK/p38 signaling pathways under conditions of metabolic dysfunction. Notably, deficiency of GSTM2 in hepatocytes significantly exacerbates insulin resistance, hepatic steatosis, inflammation, and fibrosis induced by high-fat diets and high-fat/high-cholesterol diets [95].

Rinella et al. demonstrated in a methionine-choline-deficient diet (MCD)-fed db/db diabetic mouse model that while the JNK inhibitor SP600125 did not prevent the development of MCD-induced steatohepatitis, it did attenuate UPR and downstream inflammatory signaling. This finding, in turn, corroborated the correlation between JNK phosphorylation and MASH development [96].

In the process of phosphorylation modification, ChREBP induces the phosphorylation of H3S10, enhances the expression of FASN, and further promotes hepatic steatosis [72]. The phosphorylation modification of non-histones mainly activates inflammatory responses and oxidative stress through the activation of several classical signaling pathways, such as the AMPK pathway [73–75, 77, 78], the PI3K-AKT-NF-κB pathway [80–90], and the JNK-p38-MAPK pathway [93, 94], thereby promoting the progression of MASLD.

Ubiquitination modification

Ubiquitination of proteins represents a prevalent form of PTM, capable of regulating a diverse array of protein substrates across various cellular pathways. This modification culminates in the ligation of ubiquitin to proteins through a three-step enzymatic cascade (E1-E2-E3), with the final catalysis facilitated by E3 ubiquitin ligases, which are represented by the cullin-RING complex superfamily [97]. In the context of MASLD and MASH progression, there is a relative scarcity of research on histone ubiquitination, which plays a pivotal role in altering chromatin conformation, recruiting, and activating downstream readers or chromatin regulatory proteins. For instance, overexpression of RNF20 effectively inhibits IL-6, TNFα, and vascular endothelial growth factor A (VEGFA) through ubiquitination of H2BK120 (H2BK120ub), thereby reversing TGF-β-induced activation of hepatic stellate cells LX-2 and preventing liver fibrosis [98].Ubiquitination and deubiquitination of non-histone proteins have been extensively studied in lipid metabolism and inflammation-related processes. As previously mentioned, key transcription factors involved in inflammatory responses, such as NF-κB, undergo phosphorylation of the IκB domain through IKK and ubiquitin-mediated proteasomal degradation upon external stimuli like proinflammatory cytokines. This process enables the translocation of NF-κB to the nucleus, leading to the induction of subsequent proinflammatory genes, thereby triggering hepatocyte apoptosis, M1 polarization of Kupffer cells (KCs), and HSC activation [89]. The ubiquitination of non-histone proteins is also mediated by a diverse array of E3 ubiquitin ligases.

The chromatin remodeling complex SWItch/Sucrose non-fermentable complex (SWI/SNF) reshapes nucleosomes and binds to specific DNA regions, modulating gene expression through epigenetic modifications. AT-rich interaction domain 2 (ARID2), a subunit of SWI/SNF, participates in numerous biological processes. Cao et al. discovered that the ARID2 gene activates the transcription of a novel JAK2 E3 ubiquitin ligase, neural precursor cell expressed developmentally down-regulated protein 4-like (NEDD4L), by enhancing H3R17me2a levels, thereby reducing fat accumulation. Furthermore, a negative correlation exists between ARID2 and JAK2 genes. JAK2 deubiquitination, or JAK2 overexpression, activates the JAK2-STAT5-PPARγ signaling pathway, promoting fat accumulation through the elimination of NEDD4L. Additionally, clinical sample analysis suggests that ARID2 and JAK2 may play pivotal roles in human MASLD [99].

PPARγ is a crucial transcription factor regulating lipid and lipoprotein metabolism. Predominantly expressed in adipose tissue, PPARγ oversees lipid storage and adipocyte differentiation. It also induces M2 polarization of macrophages and inhibits the NF-κB signaling pathway, highlighting the significance of modulating lipid metabolism and inflammation as therapeutic targets in MASLD pathogenesis. PPARγ undergoes ubiquitin-mediated proteasomal degradation through the C-terminus of HSC70-interacting protein (CHIP). Moreover, the E3 ubiquitin ligase NEDD4 promotes PPARγ stability by inhibiting proteasomal degradation [100].

Cytoplasmic coat protein complex I (COP I), an evolutionarily conserved E3 ubiquitin ligase, interacts directly with Adipose triglyceride lipase (ATGL), the first rate-limiting enzyme in cellular triglyceride breakdown, through the VP motif and K48-linked polyubiquitination primarily at lysine 100, thereby participating in the regulation of hepatic triglyceride metabolism. Research by Ghosh et al. demonstrated that knockdown of COP1 in mouse livers increases ATGL levels and prevents TG

accumulation in diet-induced hepatic steatosis [101]. ACLY, a crucial cytosolic enzyme, converts mitochondrial citrate into acetyl-CoA for fatty acid and cholesterol synthesis. Aberrant upregulation of ACLY during MASLD progression is associated with disrupted hepatic lipid metabolism. Hrd1, an E3 ubiquitin ligase, promotes protein ubiquitination leading to proteasomal degradation of target proteins. In db/db mice, Hrd1 expression is significantly downregulated. Hrd1-mediated ubiquitination of ACLY reduces ACLY protein levels, thereby decreasing fatty acid and cholesterol synthesis to alleviate MASLD symptoms. Further, studies revealed physical interaction between Hrd1 and ACLY, with Hrd1 regulating ACLY protein stability through ubiquitination. This research by Li et al. uncovered the role of the Hrd1-ACLY interaction in MASLD, offering novel targets for MASLD therapeutic strategies [102]. The study by Xiao et al. revealed that TRIB3 recruits TRIM8 to form an E3 ligase complex, which catalyzes K48-linked polyubiquitination of HNF4α at lysine 470. The ubiquitin-mediated degradation of HNF4α is closely associated with the progression of MASLD. Furthermore, the gain-of-function variant p.Q84R in tribbles homolog 3 (TRIB3) is linked to MASLD progression in patients and induces decreased levels of HNF4α and more severe hepatic steatosis in mice [103]. The study by Xu et al. discovered that FASN, a lipogenic factor, is a direct binding partner of TRIM56. TRIM56 interacts directly with FASN, triggering its K48-linked ubiquitination-dependent degradation. Hepatocyte-specific knockout of TRIM56 exacerbates the progression of MASLD, whereas overexpression of TRIM56 in the liver inhibits the development of MASLD [104].

Makorin ring finger protein 1 (MKRN1), a novel E3 ligase for AMPKα1 and α2, mediates AMPK ubiquitination inhibition. Han et al. found that MKRN1 knockout mice exhibit strong resistance to metabolic disorders induced by high-fat diets, confirming that MKRN1 mediates AMPK ubiquitination to inhibit fat metabolism [105].

Deubiquitination, primarily mediated by ubiquitin-specific proteases (USPs), the largest subfamily of deubiquitinating enzymes (DUBs), plays a pivotal role in MASLD pathophysiology. Some USPs promote MASLD progression, such as USP7, which participates in activating transcription factor 4 (ATF4)-induced SREBP1c accumulation and subsequent adipocyte differentiation [106]. Deubiquitination by USP2 and USP14 enhances palmitate synthesis [107], a source of lipid droplets in hepatocytes that can lead to decreased insulin sensitivity and hepatocyte apoptosis [108]. Conversely, USPs like USP4, USP10, and USP18 may mitigate lipotoxicity and protect against MASLD progression by altering the expression of proinflammatory cytokines and lipid metabolic enzymes through autophagy pathways [109].

The ubiquitination modification at the histone H2BK120 site can reverse the activation of hepatic stellate cells LX-2 induced by TGF-β and prevent liver fibrosis [98]. Moreover, the ubiquitination and deubiquitination of non-histones also play roles in the inhibition and progression of MASLD through some classical signaling pathways such as JAK2-STAT5-PPARγ, as well as lipid synthesis-related proteins, such as ACLY [102].

Malonylation

In recent years, researchers have also revealed that in MASLD, the lysine malonylation of ACC1 can be attenuated by a ketogenic diet and plays a significant role in promoting hepatic steatosis. Moreover, they have suggested that targeting the anti-malonylation of ACC1 represents a potential therapeutic strategy for MASLD [110].

Lactylation

Rho et al. discovered that the induced expression of hexokinase 2 (HK2) in activated HSCs is essential for the expression of histone lactylation genes. Their research further found that inhibiting histone H3K18 lactylation through HK2 deficiency or drug-mediated suppression of lactate production reduces HSC activation and inhibits liver fibrosis in vivo, while supplementation with exogenous lactylated H3K18 promotes HSC activation. Moreover, histone acetylation and lactylation compete with each other, explaining why Class I HDAC inhibitors hinder HSC activation. Based on the findings of Rho and colleagues, HK2 is suggested to be a potentially effective therapeutic target for liver fibrosis [111].

Among non-histone proteins, lactylation modification is associated with FASN. Studies have identified a potential relationship between mitochondrial pyruvate carrier 1 (MPC1) and inflammation, fibrosis, and insulin sensitivity in mouse models of obesity or MASH. Gao et al. suggested that MPC1 expression is positively correlated with hepatic lipid deposition in MASLD patients. MPC1 knockout affects several proteins, particularly the propionylation of fatty acid synthase, by regulating lactate levels in hepatocytes. Lactylation at the K673 site of fatty acid synthase inhibits the activity of fatty acid synthase, which mediates the downregulation of liver lipid accumulation by MPC1. Furthermore, despite lactate accumulation resulting from MPC1 knockout, inflammation levels are controlled due to mitochondrial protection and macrophage polarization [112].

Palmitoylation

FFA, particularly PA and its derivatives, generated from lipid accumulation in the livers of patients with MASLD serve as crucial substrates for palmitoylation

modifications, which are indispensable in the progression of MASLD and primarily involve non-histone modifications [113]. Palmitoylation, catalyzed by palmitoyltransferases, involves the attachment of PA, containing 16 carbon atoms, to target proteins. Based on the modified residue, palmitoylation can be broadly classified into three types: S-palmitoylation, N-palmitoylation, and O-palmitoylation, with the latter two being irreversible. The protein acyltransferases (PATs) family primarily encompasses the DHHC family (for S-palmitoylation), porcupine (PORCN) from the membrane-bound O-acyltransferase (MOBAT) family (for O-palmitoylation), and hedgehog acyltransferase (HHAT) (for N-palmitoylation) [114].

CD36, a fatty acid translocase, facilitates the entry of lipids into the cytoplasm, and its palmitoylation plays a pivotal role in lipid accumulation, inflammatory signaling, and oxidative stress in MASLD. Yang et al. observed that increased expression of Krüppel-like factor 10 (KLF10) in the livers of MASH mice upregulated zDHHC7 transcription, thereby promoting CD36 palmitoylation, ultimately leading to hepatic lipid accumulation and inflammation [115]. Selenoprotein K (SelK), an ER protein upregulated in NASH mouse livers, interacts with zDHHC6 via its Src homology 3 (SH3) domain to enhance its catalytic efficiency. Furthermore, SelK accelerates the integration of palmitoylated CD36 into cytoplasmic coat protein complex II (COPII) vesicles, facilitating CD36 transport from the ER to the Golgi apparatus and accelerating disease progression [116].

Aberrant activation of the PI3K-AKT signaling pathway in MASLD upregulates the expression of FASN, SREBPs, and ACC, among other lipid synthesis-related genes, promoting intrahepatic lipid production. Protein kinase B (PKB), a key signaling molecule in this pathway, has been shown by Bu et al. to undergo palmitoylation induced by palmitic acid, enhancing hepatic lipid overproduction and steatosis while inhibiting fatty acid oxidation. Overexpression of AKT in the liver induces MASH in mice [117]. Additionally, endogenous fatty acids synthesized by FASN and exogenous fatty acids taken up by CD36 in hepatocytes synergistically promote MyD88 palmitoylation [118], activating the Toll-like receptor 4 (TLR4)-myeloid differentiation primary response 88 (MyD88)-NF-κB pathway and exacerbating inflammatory responses.

Additionally, Xu et al. found that S-palmitoylation at the C476 site of inactive rhomboid protein 2 (IRHOM2), mediated by zDHHC3, maintains its accumulation by blocking ubiquitination of IRHOM2, thereby inhibiting its ubiquitin-proteasome-associated degradation mediated by TRIM31. Higher levels of zDHHC3 found in patient samples were associated with increased palmitoylation of IRHOM2 and inhibition of ubiquitin-mediated degradation, significantly accelerating the progression of NASH [119].

Currently, protein palmitoylation in MASLD primarily targets membrane proteins such as CD36 and certain pathway proteins, with acyl groups primarily derived from FFAs. However, palmitoylation modifications of histones remain largely understudied.

Conclusions

MASLD and NASH are obesity-related diseases that are experiencing growing prevalence and attracting widespread attention, with PTMs of both histones and non-histones playing pivotal roles in their disease progression. While histone methylation and acetylation have been extensively studied for their close association with the promotion and repression of gene transcription, acylation modifications of non-histones encompass a wide range of structural proteins (such as CD36) as well as protein factors within the AMPK and AKT signaling pathways. Non-histone PTMs regulate lipid metabolism through mechanisms such as phosphorylation-mediated activation and ubiquitination-mediated inhibition, thereby influencing the progression of fat-related liver diseases. Additionally, they can target histone-modifying enzymes; for instance, ubiquitination of the deacetylase Sir1 may lead to reduced Sir1 expression and modulate lipid metabolism [67]. In-depth studies of acylation-modifying enzymes and their substrate complexes may offer promising avenues for developing therapeutic strategies for MASLD [120]. Figure 3 mainly illustrates the role of some special modification types in MASLD.

The intricate regulation of diverse acylation modifications of histones and non-histones during the onset and progression of MASLD is evident from previous research, indicating that these modifications do not operate in isolation. For example, the absence of the histone methyltransferase Suv39h2 enables normal expression of the deacetylase Sirtuin 1 (SIRT1), leading to hypoacetylation of nuclear factor κB/p65, which inhibits the transcription of NF-κB-dependent pro-inflammatory mediators, ultimately suppressing inflammatory cytokine production and maintaining immune homeostasis [35]. Another example involves hyperglycemia activating the p300/CBP-associated factor within histone acetyltransferases (HATs), resulting in hyperacetylation of ChREBP and enhanced transcriptional activity, ultimately activating lipogenic genes and promoting MASLD development. Conversely, the serine/threonine kinase SIK2 inhibits p300 HAT activity through phosphorylation of Ser89, reducing ChREBP acetylation and its transcriptional activity [50]. Furthermore, the E3 ubiquitin ligase NEDD4 promotes PPARγ stability by inhibiting its proteasomal degradation, while PPARγ undergoes ubiquitin-mediated proteasomal degradation via the CHIP, leading

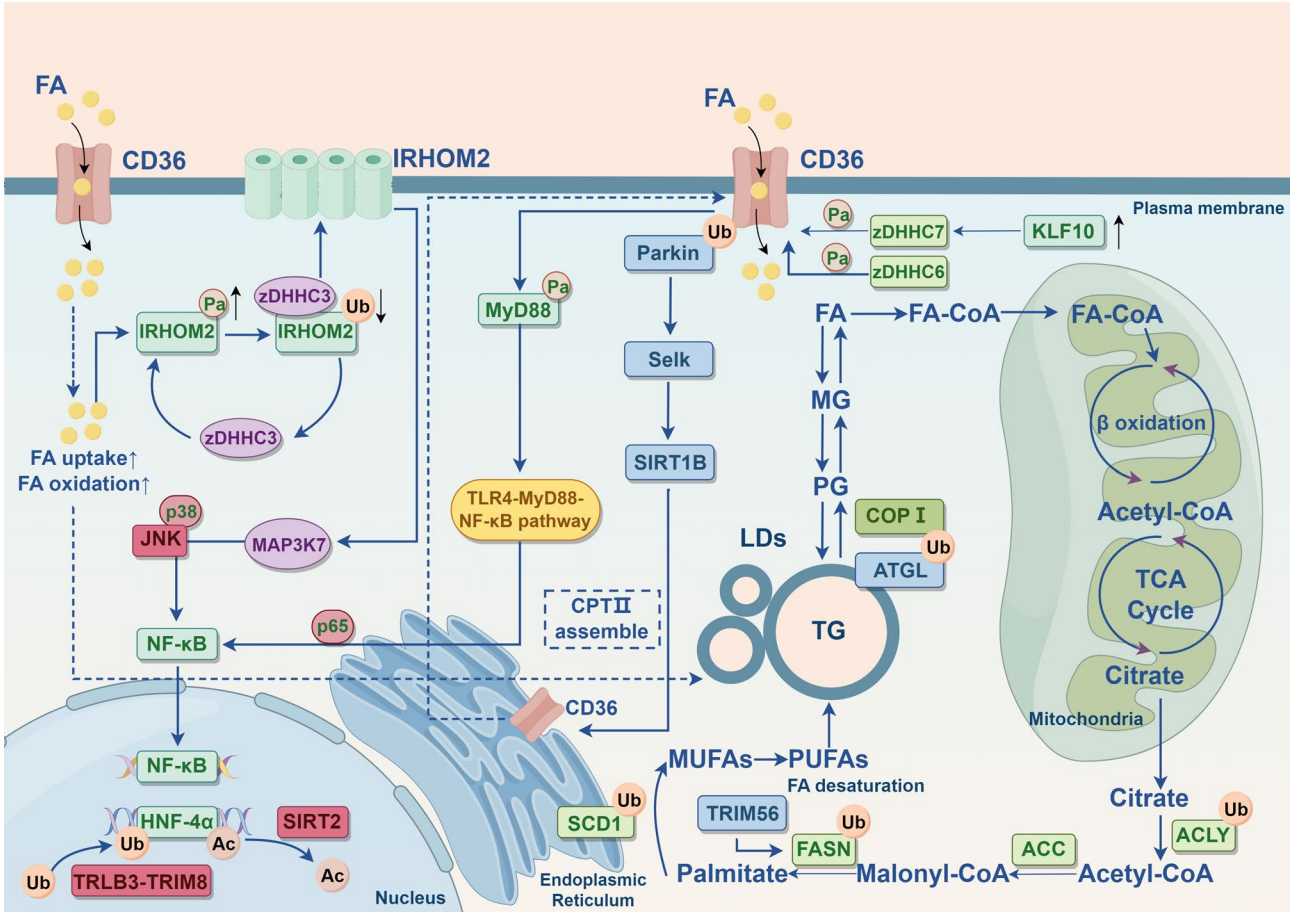

Fig. 3 Schematic diagram of the role of novel non-histone post-translational modifications in MASLD zDHHC3-mediated palmitoylation of IRHOM2 significantly accelerates the progression of MASH by blocking ubiquitination of IRHOM2 to maintain its accumulation, finally leads to the phosphorylation and activation of NF-kB in MASLD. TRIB3 recruits TRIM8 to form an E3 ligase complex degrades HNF4α to exacerbate steatosis. Endogenous and exogenous fatty acids in hepatocytes synergistically promote MyD88 palmitoylation, activating the TLR4-myeloid differentiation primary response 88 (MyD88)-NF-κB pathway and exacerbating inflammatory responses. Increased expression of KLF10 upregulated zDHHC7 transcription, thereby promoting CD36 palmitoylation, and SelK interacts with zDHHC6 accelerates the integration of palmitoylated CD36 into COPII vesicles, facilitating CD36 transport from the ER to the Golgi apparatus leading to hepatic lipid accumulation and inflammation. COP1 targets ATGL to modulate triglyceride breakdown, Hrd1-mediated ubiquitination destabilizes ACLY to reduce lipid synthesis and TRIM56 promotes FASN degradation to suppress lipogenesis. PA, Palmitoylation; Ub, Ubiquitination; Ac, Acetylation

to IκB domain phosphorylation, NF-κB activation, and a cascade of inflammatory responses that drive MASLD onset and progression [89]. However, these studies have certain limitations. These dual mechanisms underscore the complexity of PTM regulation in NAFLD, with therapeutic strategies requiring context-specific targeting. Research on acylation modifications predominantly focuses on single pathways, leaving unclear how these modifications regulate and influence each other or which is dominant in the pathological process of MASLD. Additionally, current research on MASLD-related acylation modifications primarily focuses on histones, leaving significant opportunities for exploration at the non-histone level. Furthermore, research on modifications such as crotonylation, palmitoylation, and malonylation remains limited. Most identified "writers," "erasers," and "readers" are derived from studies on acetylation modifications. Identifying additional regulatory enzymes will enhance our understanding of the roles of novel acylation modifications in MASLD.

In summary, protein acylation modifications play a vital role in the formation and progression of MASLD, with interactions between various modifications both facilitating and inhibiting processes. In-depth study of the regulatory mechanisms underlying these acylation modifications is essential for advancing our understanding of MASLD pathogenesis and identifying stable, safe, and effective therapeutic targets.

Supplementary Information

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Supplementary Material 1

Author contributions
Y.M., Y.Z., and Y.J. collected the related papers and drafted the manuscript. Y.M., Y.Z., and S.L. drew the figures. C.G., L.W., H.Y., and Z.Z. revised and commented on the paper. All authors read and approved the final version of the manuscript.

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Declarations

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Consent for publication
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Conflict of interest
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