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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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REVIEW

Unraveling the relationship between histone methylation and nonalcoholic fatty liver disease

Li Xu, Yu-Hong Fan, Xiao-Jing Zhang, Lan Bai

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Abstract

Non-alcoholic fatty liver disease (NAFLD) poses a significant health challenge in modern societies due to shifts in lifestyle and dietary habits. Its complexity stems from genetic predisposition, environmental influences, and metabolic factors. Epigenetic processes govern various cellular functions such as transcription, chromatin structure, and cell division. In NAFLD, these epigenetic tendencies, especially the process of histone methylation, are intricately intertwined with fat accumulation in the liver. Histone methylation is regulated by different enzymes like methyltransferases and demethylases and influences the expression of genes related to adipogenesis. While early-stage NAFLD is reversible, its progression to severe stages becomes almost irreversible. Therefore, early detection and intervention in NAFLD are crucial, and understanding the precise role of histone methylation in the early stages of NAFLD could be vital in halting or potentially reversing the progression of this disease.

Key Words: Non-alcoholic fatty liver disease; Mechanism; Histone methylation; Methyltransferases; Demethytrasferases; Epigenetic modification; Adipogenesis

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a global health concern accounting for a significant proportion of liver-related deaths. However, there are no Food and Drug Administration-approved drugs for NAFLD treatment. Epigenetic mechanisms play multiple roles in the pathogenesis of diseases and hold promise as potential therapeutic targets. Here, we review the impact of histone methylation on the alterations in metabolic homeostasis, inflammatory injury, fibrosis, and carcinogenesis during the progression of NAFLD, providing a theoretical foundation for target discovery and clinical treatment.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent hepatic disorder characterized by the intracellular accumulation of lipid droplets in liver cells, leading to hepatic steatosis. The pathogenesis of NAFLD primarily involves dysregulation of lipid homeostasis, with an aberrant increase in de novo lipogenesis and/or fatty acid uptake, coupled with impaired lipid processing. NAFLD encompasses a spectrum of liver diseases, ranging from simple steatosis non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC)[1]. However, the precise underlying mechanisms driving NAFLD remain incompletely understood, prompting ongoing research efforts to elucidate the intricate molecular pathways governing hepatic lipid accumulation.

There is a growing body of evidence supporting the pivotal role of epigenetic mechanisms in the pathogenesis of NAFLD[2], influencing adipocyte differentiation, fat metabolism and transport, insulin resistance, and the release of inflammatory factors[2,3]. Epigenetic modification is a critical physiological process that deals with altered gene expression or cellular pathways through adaptive mechanisms unrelated to changes in the DNA sequence, including epigenetic modifications of DNA, post-translational modifications of histone proteins, and miRNA and chromatin modifications. DNA methylation modification is a well-recognized genetic epigenetic trait that typically suppresses transcription. When external or intrinsic stimuli lead to abnormally elevated intracellular reactive oxygen species (ROS) levels, they not only trigger oxidative stress to damage DNA structure but may also cause global or gene-specific changes in DNA methylation status by modulating DNA methyltransferase activity[4,5]. These epigenetic adjustments can silence the expression of genes that would otherwise inhibit inflammatory lipid deposition and fibrosis, while promoting the overexpression of genes related to inflammatory factors and fibrosis, thereby exacerbating the progression of NAFLD from pure steatosis to a more severe inflammatory and fibrotic stage[6,7]. In addition, histone methylation is another important epigenetic modification that is crucial in regulating biological development and cellular responses. 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 [8-11]. In recent years, the role of histone methylation in NAFLD has attracted increasing attention. This review aims to explore the relationship between histone methylation and NAFLD, enhancing our understanding of its potential clinical significance and providing a theoretical foundation for identifying promising therapeutic targets for NAFLD.

ELUCIDATING THE MOLECULAR MECHANISMS OF HISTONE METHYLATION MODIFICATION

Histones are indispensable constituents responsible for maintaining the integrity of chromatin structure and playing a pivotal role in the dynamic and long-term regulation of genes. The core region of the nucleosome is composed of two histone octamers, consisting of H2A, H2B, H3, and H4 subunits, which intricately associate with DNA double strands [12]. The terminal amino acid residues of histones are susceptible to covalent modifications, including lysine and arginine methylation, acetylation, ubiquitination, phosphorylation, and adenosine diphosphate ribosylation. Among these, methylation represents a major form of histone modification[13]. The methylation status of histones profoundly affects the occurrence and development of various diseases, notably metabolic disorders, tumors, and immune dysfunctions. Correcting these aberrant modifications holds promise for reversing the associated phenotypes and treating the underlying diseases.

Effector proteins perform a pivotal function in modulating diverse biological processes by interacting with histones that are methylated differently. These processes encompass gene transcription, preservation of genome integrity, regulation of X-chromosome activity, formation of heterochromatin, and cell development[14]. The degree of methylation on specific residues within the histone octamer can influence the recruitment of effector proteins. This recruitment subsequently leads to chromatin structure changes, ultimately affecting downstream genes' transcriptional levels. Histone methylation primarily occurs at lysine (K) or arginine (R) residues in the N-terminal domain of H3 and H4 histones. Lysine residues can undergo mono-, di-, or tri-methylation modifications, while arginine residues undergo only mono- and di-methylation modifications. Lysine methylation is the most prevalent form of post-translational modification on histones. Common types of lysine methylation include H3K4, H3K9, H3K27, and H3K36 methylation. Unlike histone

acetylation, the biological effects of lysine methylation can either activate or inhibit gene transcription, depending on the specific site and degree of methylation. For example, H3K4me2/3, H3K36me1/3, H3K79me1/2, and H4K20me1 are associated with transcriptional activation, while H3K9me2/3, H3K27me2/3, H3K79me3, and H4K20me3 are linked to transcriptional repression[15]. The methylation state of histones is primarily regulated by histone methyltransferases (HMT) and histone demethylases (HDM) synergistically[16]. Methyltransferases are enzymes that add methyl groups to specific lysines or arginines on histones. Different families of methyltransferases are involved in this process, including protein lysine methyltransferases and protein arginine methyltransferases. Examples of methyltransferase families include the SET domain family [such as su(var), enhancer of zest(E(z)), and trithorax] and the non-SET domain family. On the other hand, HDM are enzymes that remove methyl groups from lysines or arginines on histones. There are two families of HDM: The lysine-specific demethylase (LSD) family, which specifically removes mono- and di-methylation marks from histones H3K4 and H3K9, and the JMJD (JmjC domain-containing) family, which can remove various lysine methylation marks[17,18]. These enzymes play a crucial role in dynamically regulating histones' methylation status, thereby influencing gene expression.

HISTONE METHYLATION IN METABOLIC HOMEOSTASIS

NAFL is a complex and heterogeneous disease that results from the accumulation of lipotoxic substances in the liver. However, not all cases of NAFL progress to NASH[19], which is a more severe form of the disease that can lead to liver fibrosis, cirrhosis, and even liver cancer. Recent research has shown that histone methylation modifications can play a critical role in regulating the transcription of genes involved in glycolipid metabolism, a key pathway involved in the pathogenesis of NAFL (Table 1). Therefore, understanding the impact of histone methylation on the onset and progression of NAFL is crucial for developing effective strategies to manage the low conversion rate of NAFL to NASH and prevent the development of liver disease.

The role of H3K4 in regulating glycolipid metabolism

H3K4me3 is induced in the gene promoter region through the enzymatic activity of the histone methyltransferase MLL2/KMT2B, thereby playing a crucial role in the preservation of glucose homeostasis[20]. The cofactor of the pax trans-activating structural domain-interacted protein (PTIP) associates with the methyltransferases MLL3/KMT2C and MLL4/KMT2D, leading to the H3K4me3 in the promoter regions of *PPARγ* and *C/EBPα* genes, which accelerates hepatic lipid synthesis[21,22]. Moreover, methyltransferases MLL3/KMT2C and MLL4/KMT2D induce an increase in H3K4me3 within the promoter region of lipogenic genes (*LPL, SREBF2, SCD1, etc.*), thereby promoting the enrichment of E2F transcription factor 1 (E2F1) and facilitating the stimulation of lipid synthesis[23]. The demethylase LSD1 interacts with the transcription coregulatory factor PRDM16, leading to a reduction in the methylation levels of H3K4me1/2 within its promoter region. This decrease in methylation inhibits the glucocorticoid-activating enzyme HSD11B1, thereby exerting regulatory control over glycolipid metabolism[24,25]. The pivotal involvement of LSD1 in lipid metabolism has also been demonstrated in bats[24,26].

Methylation of H3K9 in adipogenesis, glycolipid, and insulin metabolism

HMT SUV39H1/KMT1A and EHMT1/KMT1D play a crucial role in enriching the H3K9me2/3 in the gene promoter region. This modification inhibits the transcriptional activity of AP-2α on C/EBPα, thereby suppressing adipogenesis[27]. Additionally, EHMT1/KMT1D is an essential methyltransferase involved in the transcriptional regulation of PRDM16 in lipid metabolism[28,29]. Furthermore, the G9a/KMT1C/EHMT2 methyltransferase plays a regulatory role in upregulating the H3K9me marks specifically within the gene promoter regions. This modification effectively inhibits the interaction between the early oncogenic transcription factor C/EBPβ and PPARγ, suppressing *PPARγ* expression and consequent inhibition of adipogenesis[30]. In addition to its role in lipid metabolism regulation, the methylation of H3K9, mediated by G9a/KMT1C/EHMT2, also significantly influences glucose metabolism. This is achieved by modulating the transcriptional level of HMGA1, a key regulator of the insulin receptor (INSR). As a result, this epigenetic modification contributes to the amelioration of impaired hepatic insulin sensitivity, thereby improving overall glucose metabolism[31].

On the contrary, a cluster of H3K9 demethylases featuring the Jumonji structural domain, such as JMJD2B, JMJD1C, JHDM2a, and JHDM1D, has been observed to diminish the levels of H3K9me3, thereby promoting the progression of hepatic steatosis. JMJD2B not only functions to enhance the expression of PPARγ similar to the H3K4 methyltransferase MLL4 but also interacts with the hepatic receptor LXRα, thereby facilitating the deposition of aberrant lipid content[32,33]. JMJD1C collaborates with USF1 to activate the transcription of genes associated with adipogenesis, leading to elevated expression of adipogenic genes[34]. Moreover, JHDM2a diminishes the levels of H3K9me2 on the PPAR response element (PPRE) of UCP1 following β-adrenergic activation, thereby facilitating the recruitment of PPARγ, RXRα, and their coactivators (Pgc1aα, CBP/p300, and Src1) to the PPRE, consequently repressing the expression of genes associated with adipogenesis[35,36]. Hence, the knockout of *JHDM2* in mice manifests obesity, hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia, and hyperleptinemia. Additionally, these mice display increased adipose tissue deposition and elevated lipid levels[36]. Furthermore, a study by Kim *et al*[37] demonstrated that JHDM1D induces hepatic steatosis by causing a diminished enrichment of H3K9me2 in the promoter region of DGAT2, a key enzyme involved in triglyceride synthesis. Moreover, LSD1 has emerged as a significant regulator of H3K9me1/2/3 methylation in the context of lipid metabolism[26,38]. Specifically, it has been reported that HDM containing a plant homologous structural domain finger 2 (Phf2) component play a crucial role in modulating glucose metabolism through their impact on the methylation status of H3K9me2 within the promoter region of ChREBP[39,40]. Furthermore, dysregulations in

Table 1 Effect of histone methylation on glycolipid metabolism

Histone methylation	HMTs/HDMs	Mechanisms	Effects on glycolipid metabolism	Ref.
H3K4me3↑	MLL2/KMT2B	-	Regulation of glucose homeostasis	[20]
H3K4me3↑	MLL3/KMT2C MLL4/KMT2D	(+) KMT2C (2D) + PTIP→promoter (PPARγ) ←Transcript (C/EBPα); (+) KMT2C (2D) + PTIP→promoters (LPL, SREBF2, SCD1) ←Transcript (E2F1)	Lipid synthesis↑	[21,23,68]
H3K9me2/3↑	SUV39H1/KMT1A EHMT1/KMT1D	(-) KMT1A (1D) →Transcript (C/EBPα) ←Enhancer (AP-2α); (-) KMT1D + PRDM16→promoter (HSD11B1)	Lipid synthesis↓ Blood glucose↑	[27,28]
H3K9me2/3↑	EHMT2/KMT1C	(-) KMT1C→promoter (PPARγ) ←Transcript (C/EBPα); (+) KMT1C→Expression of HMGA1	Lipid synthesis↓ Impaired insulin signal↓	[30,31]
H3K27me3↑	EZH2/KMT6A	(-) KMT6A→promoter (Mogat1) →MAG→DAG	Lipid synthesis↑	[42,45]
H3K79me1/2/↑	DOT1L	(+) DOT1L→Pathways of SREBP (+) DOT1L→Brown and beige fat production and thermogenesis	Lipid synthesis↑	[49]
H3K4me1/2↓	LSD1/KDM1A	(-) KDM1A + PRDM16→promoter (HSD11B1)	Lipid synthesis↑ Blood glucose↓	[24,25]
H3K9me2/me3↓	JMJD2B/KDM4B	(+) KDM4B + PTIP→promoter (PPARγ) ←Transcript (C/EBPα) (+) KDM4B + LXRα	Lipid synthesis↑	[32,33]
H3k9me3↓	JMJD1C/KDM3C	(+) KDM3C + USF1→promoter; (Lipogenesis genes)	Lipid synthesis↑	[34]
H3K9me1/2↓	JHDM2a/KDM3A	(+) KDM3A (β-adrenaline) →PPRE←promoter (PPARγ + RXRα)	Lipid synthesis↓	[35,36]
H3K9me2↓ H3K27me2↓	JHDM1D/KDM7A	(+) KDM7A→promoter (DGAT2)	Lipid synthesis↑	[37]
H3K27me3↓	JMJD3/KDM6B	(+) KDM6B + islet1→promoter (SNAI1)	Lipid synthesis↓	[46]
H3K27me3↓	-	(+) promoter (LepRb) →slug-Epigenetic reediting-Leptin resistance axis	Leptin resistance↑	[48]
H3K36me2↑ H3K27me3↓	NSD2	(-) NSD2→promoter (PPARγ)	Lipid synthesis↓	[47]
H3K9me2/3↓	Phf2	(+) Phf2→ChREBP→promoter (FASN)	Lipid synthesis↑ Fructose decomposition↑	[39,40]
H4K20me1↓	KDM7B	(-) promoter (RNA Pol II) →H4K20me1→Expression of glycolytic genes	Lipid synthesis↑	[55]
H4K20me3↓	-	(+) ChREBP→ChoRE + promoter (FASN) →H4K20me3→Expression of FASN	Lipid synthesis↑	[53]

HMTs: Histone methyltransferases; HDMs: Histone demethylases; Mogat1: Monoacylglycerol O-acyltransferase 1; DAG: Diacylglycerol; FASN: Fatty acid synthase; E2F1: E2F transcription factor 1; PTIP: Pax trans-activating structural domain-interacted protein; PPRE: The PPAR response element; Phf2: Plant homologous structural domain finger 2.

H3K9 methylation have been implicated in the induction of endoplasmic reticulum stress[41].

Methylation of H3K27 in hepatic steatosis and lipolysis

The elevation of tri-methylation of H3K27 has been observed to enhance the expression of genes involved in lipid synthesis[42]. EZH2/KMT6A, identified as the specific methyltransferase responsible for H3K27 methylation, plays a significant role in modulating diverse phenotypes of NAFLD and operates through distinct gene targets at different stages of the disease progression[42-44]. EZH2/KMT6A acts to upregulate H3K27me2/3 Levels within the promoter region, thereby impeding the enzymatic conversion of monoacylglycerol to diacylglycerol (DAG) mediated by Monoacylglycerol O-acyltransferase 1 (Mogat1), consequently leading to the induction of hepatic steatosis[42,45]. On the contrary, JHDM1D has been shown to downregulate H3K27me2 within the promoter region of DGAT2, consequently inducing hepatic steatosis[37]. Additionally, JMJD3 diminishes the level of H3K27me3 within the promoter region of SNAI1,

leading to the inhibition of angiogenesis and exacerbation of lipolysis[46]. It is worth noting that NSD2 plays a dual role as a methyltransferase with specificity for H3K27 and H3K36. Alongside its regulatory influence on H3K27me3 within the promoter region to modulate glycolipid metabolism, NSD2 also perturbs lipid synthesis by regulating the level of H3K36me2 in the promoter region of PPARγ[47]. In addition to the intricate regulatory roles played by methyltransferases and demethylases in histone methylation, aberrations in transcription factors can also impact the levels of histone methylation within promoter regions. For instance, the dysfunction of the transcription factor Slug has been shown to diminish the extent of H3K27me3 methylation within the promoter region of the hypothalamic leptin action factor LepRb. This reduction subsequently culminates in the upregulation of LepRb transcription and the potentiation of the slug-epigenetic re-editing-leptin resistance axis in hypothalamic neurons, ultimately disrupting lipid metabolism[48].

Methylation of H3K79 in cholesterol synthesis and adipocyte differentiation

The direct impact of H3K79 methylation is evident in influencing gene programs responsible for controlling lipid biosynthesis and regulating macrophage function. This includes crucial lipid regulators like sterol regulatory element binding proteins SREBP1 and SREBP2, which are known to profoundly influence the lipid metabolism and inflammatory response of macrophages[49]. DOT1L, as the sole methyltransferase, assumes the critical responsibility of facilitating the mono- and dimethylation modification of H3K79. This enzymatic activity subsequently exerts a profound influence on the expression of genes associated with crucial biological processes, including cholesterol synthesis pathways[50], lymphatic system development[51], and thermogenic adipocyte differentiation[52].

The inhibition of H4K20me3 within the promoter region of fatty acid synthase (FASN) has been shown to facilitate the de novo synthesis of FASN, which can consequently lead to hepatic steatosis[53]. Through modulating the levels of H4K20 methylation, the methyltransferase KMT5A plays a pivotal role in promoting the expression of key regulators involved in lipid metabolism, namely *SREBP1*, *SCD*, *FASN*, and *ACC*[54]. In contrast, the demethylase KDM7B, functioning as a counterregulatory enzyme to KMT5A, impedes the dissociation of RNA Pol II from the proximal region of the promoter and diminishes the H4K20me1[55]. As a result, this enzymatic activity influences the expression of genes involved in hepatic glucose and fatty acid metabolism[55].

HISTONE METHYLATION IN INFLAMMATORY INJURY

NASH represents an advanced stage of NAFLD, exhibiting features such as hepatic steatosis, inflammation, hepatocyte injury, and fibrosis, which can progress over time[56]. The C57BL/6J and DBA/2J mouse models, induced by an adipose-derived methyl-deficiency diet, manifest specific phenotypic changes characteristic of NASH. These changes are concomitant with variations in the levels of H3K9, H3K27, and H4K20 methylation[57], underscoring the pivotal role of histone methylation in the initiation and advancement of NASH. In a broader context, histone methylation exerts influence not only on the acute physiological alterations that underlie the transition from NAFL to NASH, but also directly modulates factors implicated in liver inflammation (Table 2), including hepatocyte lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and other related mechanisms[56].

The methyltransferase SET7/9 is responsible for upregulating the levels of H3K4me3 within the promoter region of inflammatory genes induced by tumor necrosis factor-α. This process further facilitates the recruitment of the p65 factor to the promoter region, thereby amplifying the NF-κB-mediated inflammatory cascade response[58]. Consequently, these mechanisms contribute to the exacerbation of NASH[58]. Furthermore, the enzymatic activity of the methyltransferase EZH2/KMT6A, which catalyzes the elevation of H3K27me2/3, has been recognized as a pivotal determinant in liver inflammation[44]. Additionally, the methylation of H3K79, facilitated by the methyltransferase DOT1L, has emerged as highly pertinent to macrophage inflammatory response[49].

The demethylase JHDM1D has been observed to attenuate the levels of H3K9me2 and H3K27me2 within the promoter region of DGAT2. This mechanism effectively alleviates the inhibitory impact imposed by these methylations, consequently activating the NF-κB-mediated inflammatory cascade responses in NASH[37]. Considering the frequent comorbidity between NAFLD and diabetes, it is postulated that the heightened inflammatory response associated with diabetes may play a contributory role in the progression from NAFLD to NASH. Additionally, the demethylation of H3K27me by JMJD3 induces chromatin accessibility in macrophages, thereby facilitating the recruitment of transcription factors to the promoter region of STING. This subsequently triggers the activation of the TBK1/IRF3/IFN-α pathway or NF-κB pathway, ultimately leading to the initiation of chronic inflammation[59-63].

While the pathogenesis of NASH is primarily regulated by lysine methylation of histones, there is a growing recognition of the crucial contributions made by arginine methylation. Specifically, the arginine methyltransferase PRMT5/MEP50 enhances the levels of H3R2me3 within the promoter region of OXR1A, subsequently promoting the transcription of growth hormone within the pituitary gland, inducing oxidative stress in hepatocytes, and ultimately accelerating the progression from NAFLD to NASH[64,65]. Meanwhile, recent research advances indicate that inhibition of PRMT5 induces an increase in hepatic triglyceride levels, leading to severe adverse liver consequences, *i.e.* inducing NAFLD[66].

HISTONE METHYLATION IN LIVER FIBROSIS

In the scenario of persistent exposure to deleterious environmental factors or repetitive injury, the hepatic tissue

Table 2 Effect of histone methylation on inflammatory injury

Histone methylation	HMTs/HDMs	Mechanisms	Effects on Inflammatory Injury	Ref.
H3K4me3↑	SET7/9/KMT7	(+) SET7/9→promoter (TNF-α→Pro-inflammatory genes) ←NF-κB p65	Inflammatory reaction↑	[58]
H3K79me1/2/3↑	DOT1L	(+) DOT1L→Pathways of SREBP→ (-) Inflammatory expression of macrophages	Inflammatory reaction↓	[49]
H3R2me3↑	PRMT5	(+) PRMT5→promoter (OXR1A) →Growth Hormone	Oxidation stress↑	[64, 65]
H3K27me3↓	JMJD3/KDM6B	In case of non-diabetic injury: (+) IFN-β→JAK1/3-STAT3→JMJD3→STING-TBK1/IRF3/IFN-α	In case of non-diabetic injury:Wound Recovery	[59-63]
		In case of diabetic injury: (-) IL-6→JAK1/3-STAT3→JMJD3→IFN-α; (+) IL-6→JAK1/3-STAT3→JMJD3→NF-κB	In case of diabetic injury:Inflammatory reaction↑	

HMTs: Histone methyltransferases; HDMs: Histone demethylases; TNF-α: Tumor necrosis factor-α.

undergoes a cascade of pathological alterations, encompassing diffuse injury, progressive fibrosis, the formation of regenerative nodules, and ultimately culminating in the transition from NASH to the fibrotic stage. The fibrotic stage epitomizes the final phase of NASH, typified by permanent liver damage, heightened mortality rates, and increased susceptibility to cirrhosis and liver cancer. The progression of liver fibrosis largely depends on the differentiation of hepatic stellate cells (HSCs), which entails the suppression of PPARγ activation and the acquisition of a fibroblast-like phenotype[67]. Numerous investigations have underscored the involvement of various histone methylation patterns in orchestrating this process (Table 3). These include the enhancement of H3K4me3 mediated by methyltransferases MLL3/4[68], modification of H3K27me3 orchestrated by EZH2/KMT6A[44], alterations in H3K36me2 regulated by G9a/KMT1C/EHMT2 and NSD2[30,47], as well as the demethylation of H3K9me2 facilitated by demethylase JMJD1A/JHDM2a/KDM3A[36]. These regulations necessitate the presence of methylated CpG-binding protein-2 within the promoter region of PPARγ, which in turn activates the upstream or downstream methyltransferases to modulate H3K9 methylation, thereby repressing transcription initiation. Additionally, it alters H3K27 methylation to impede transcription elongation, consequently governing the activation of diverse fibrogenic genes such as *TGF-β1*, *TIMP-1*, *αSMA*, and *type I collagen*[67,69,70].

HISTONE METHYLATION IN FATTY LIVER CARCINOGENESIS

HCC emerges due to hepatocyte cycle aberrations or disturbances in the interplay between progenitor cells and oncogenes, often precipitated by inadequate treatment and a compromised microenvironment. This malignancy is characterized by a high mortality rate and restricted therapeutic interventions[71]. To ameliorate the five-year survival rate of patients and effectively manage HCC linked with fatty liver disease, comprehending the function of histone methylation in modulating proliferation, differentiation, and invasive potential is essential (Table 4).

The augmentation of H3K4 methylation is frequently correlated with the activation of oncogenes and cell cycle regulators, consequently leading to an unfavorable prognosis in HCC patients with an elevated risk of metastasis and recurrence. The accumulation of a substantial quantity of H3K4me2, catalyzed by the methyltransferase KMT7/SETD7, promotes the progression from the G1 to the S phase of the HCC cell cycle, thereby facilitating the proliferation and differentiation of HCC cells[72,73]. The attenuation of gene transcription *via* the reduction of H3K4 methylation predominantly impacts the expression of tumor suppressor genes as opposed to oncogenes, culminating in the emergence of liver cancer characterized by susceptibility to metastasis, recurrence, and an unfavorable prognosis[74]. As an illustration, the KDM5B/JARID1B demethylase curtails the transcriptional expression of E2F1, P15, and P27 factors by diminishing the levels of H3K4me1/2/3[75], thereby instigating uncontrolled proliferation of HCC cells[76]. The demethylases LSD1/2 have been noted to diminish the levels of H3K4me1/2 and H3K9me1/2, consequently engendering proliferation, differentiation, invasion, and migration of HCC cells through modulation of the cell cycle. Furthermore, they activate β-linked protein signaling by directly inhibiting the expression of several repressors in this pathway[77-80]. This activation culminates in the translocation of β-linked proteins to the nucleus, forming complexes with the nuclear transcriptional complex TCF/LEF. Subsequently, these complexes upregulate the expression of downstream target genes, thereby facilitating the process of hepatocarcinogenesis[81-84].

In contradistinction to the stimulatory impact of heightened H3K4 methylation, the augmentation of H3K9 methylation typically functions as a transcriptional repressor, impeding the expression of oncogenic factors. For instance, the enrichment of H3K9me1/2 brought about by the action of G9a/KMT1C impedes the expression of the oncogene *RARRES3* and the pro-apoptotic gene *Bcl-G*[85,86]. The methyltransferase SUV39H1/KMT1A triggers the establishment of H3K9me3, thereby expediting the progression of HCC[87,88]. Nonetheless, the attenuation of H3K9 methylation actively engages in gene transcription and facilitates the progression of HCC. The diminishment of H3K9me1/2 induced by the demethylase KDM3A/JMJD1A activates the PI3K/AP-1 and JAK2-STAT3 signaling pathways, thereby promoting

Table 3 Effect of histone methylation on hepatic fibrosis

Histone methylation	Functions	Effects on fibrosis	Ref.
H3K9me1/2/3↑	(Upstream) (-) Transcription initiation	Expression of PPARγ↓	[67,69,70]
		Hepatic Fibrosis↑	
H3K27me1/2/3↑	(Downstream) (-) Transcriptional extensions	Expression of PPARγ↓	[67,69,70]
		Hepatic Fibrosis↑	
H3K4me2/3↑	(The whole process) (+) Genes for fibrosis (TGF-β1, TIMP-1, α-SMA and Collagen type I)	Hepatic Fibrosis↑	[67,69,70]
H3K36me3↑			

Table 4 Effect of histone methylation on carcinogenesis of fatty liver

Histone methylation	HMTs/HDMs	Functions	Effects on HCC	Ref.
H3K4me2↑	SETD7/KMT7	(+) Cell cycle G1 phase → S phase	↑	[72,73]
H3K9me1/2↑	G9a/KMT1C	(-) Expression of oncogenic factor RARRES3 and pro-apoptotic gene Bcl-G	↑	[85,86]
H3K9me3↑	SUV39H1/KMT1A	(+) Cell cycle G1 phase → S phase	↑	[87,88]
H3K27me3↑	EZH2/KMT6A	(+) Wnt/β-linked protein signaling pathways	↑	[91,92]
H4K20me1↑	SET8/KMT5A	(+) Cell cycle G1 phase → S phase	↑	[94,95]
H3K4me1/2/3↓	JARID1B/KDM5B	(+) Cell cycle G1 phase → S phase	↑	[75]
		(-) Oncogenic expression ← transcription factors (E2F1, P15 and P27)		
H3K4me1/2↓	LSD1/LSD2/KDM1A	(+) Cell cycle G1 phase → S phase	↑	[77-79,90]
H3K9 me1/2↓		(-) H3K4me1/2↓→Inhibitor expression (β-linked protein signaling)		
		(+) β-linked protein +TCF/LEF→Target gene expression (Oncogenic)		
H3K9me1/2↓	JMJD1A/KDM3A	(+) PI3K/AP-1 pathway	↑	[89,90]
		(+) JAK2-STAT3 signaling pathways		
		(+) Wnt/β-linked protein signaling pathways		

HMTs: Histone methyltransferases; HDMs: Histone demethylases.

the initiation of HCC[89]. Moreover, KDM3A/JMJD1A regulates the expression or activity of the β-linked protein and the C-Myc gene, thereby expediting the malignant transformation of HCC[90].

Like H3K9 methylation, hypermethylation of H3K27 also serves as a universal repressor in gene transcription. The accrual of H3K27me3, facilitated by the methyltransferase EZH2, inhibits the transcription of Wnt signaling antagonists, consequently activating Wnt/β-catenin protein signaling and fostering tumor aggressiveness[91-93]. On the contrary, the methylation of H4K20 induced by the methyltransferase KMT5A is involved in the activation of gene transcription, regulation of DNA replication, repair of DNA damage, and control of the cell cycle[94,95], ultimately resulting in a negative prognosis and adverse outcomes in HCC. Unfortunately, the association between H3K27 and H4K20 methylation and HCC remains poorly studied. This knowledge gap hinders our understanding of the detrimental outcomes associated with a poor prognosis for this disease.

In addition, recent studies have found that abnormal accumulation of lipids leads to disruption of ROS homeostasis in the body, resulting in an enhanced state of oxidative stress *in vivo* and that oxidative stress affects the development of NAFLD by altering epigenetic programs through the regulation of histone demethylase activity[96]. Under oxidative stress, H2O2-induced ROS decreased PRMT5 (arginine methyltransferase 5) protein levels, increased RORα protein levels in HepG2 cells, and inhibited HCC progression[97]. Under oxidative overstimulation, H2O2-induced ROS increased the formation of H4K20me3 in HCC cells and induced HCC formation[98]. To further complicate matters, when ROS alters histone methylation levels alters histone methylation levels, they can give feedback to alter the oxidative stress state, further affecting the development of NAFLD. For example, an aberrant increase in ROS in macrophages induces a decrease in the H3K27me3 demethylase, KDM6A, which leads to an increase in H3K27me3 in the NOX2 promoter, which promotes macrophage M1 polarization and leads to inflammation[99]. H3K4-specific histone methyltransferase WD repeat sequence-containing protein 5 and histone H3K79 methyltransferase (DOT1L) enhance the activation of the STING-NLRP3-GSDMD axis, promote hepatic ROS generation, and cause hepatocyte apoptosis and liver inflammation in liver fibrosis[100].

POTENTIAL CLINICAL APPLICATION OF HISTONE METHYLATION

The increasing severity of NAFLD underscores the urgent need for effective preventive and management strategies. Delving into the realm of epigenetics provides a fresh perspective for identifying potential therapeutic targets for NAFLD. Given the pivotal involvement of histone methylation in the pathogenesis of NAFLD, the exploration of targeting histone methylation has emerged as a prominent and noteworthy area of investigation within the realm of NAFLD therapeutics. Kim's study provided significant insights into the essential contribution of histone methyltransferase MLL4 in the progression of hepatic steatosis mediated by ABL1 and PPARγ in murine models. The findings suggest that the ABL1-PPARγ2-MLL4 axis represents a critical regulatory pathway in steatosis development under conditions of nutrient overload, thereby offering potential avenues for targeting this axis in developing anti-steatosis drugs[101]. Moreover, the growing body of evidence strongly indicates that pharmacological inhibition of the methyltransferase EZH2 presents a highly promising therapeutic approach for effectively managing NAFLD. As a result, a diverse range of small molecule inhibitors explicitly targeting EZH2, along with several naturally occurring compounds exhibiting inhibitory effects on EZH2 activity, have been successfully developed[102,103]. Significantly, it has been demonstrated that treatment with DZNep effectively inhibits the proliferation of HSC-derived fibroblasts by modulating multiple histone methylation pathways[104,105]. Additionally, Xu *et al*[106] have provided evidence suggesting that pharmacological intervention targeting the methyltransferase Dot1L may represent a promising therapeutic approach for addressing diverse tissue fibrosis disorders in human subjects. Furthermore, emerging evidence suggests that the targeted intervention of the methyltransferase KMT5A in HCC therapies exerts a significant inhibitory effect on HCC cell proliferation and invasion. Additionally, this therapeutic approach enhances the cells' responsiveness to chemotherapy. These compelling findings hold substantial implications for the clinical management of HCC, paving the way for promising advancements in HCC therapy in the future[107].

Numerous experimental studies have demonstrated the potential of demethylases G9a/EHMT2, JMJD1C/KDM3C, JMJD2B/KDM4B, and Phf2/JHDM1E/KDM7C to serve as targetable epigenetic loci for preventing the progression of NAFLD[31,32,34,39,40,108-110]. Bricambert *et al*[39] have elucidated a novel epigenetic regulatory mechanism involving Phf2/JHDM1E/KDM7C in both murine and human models. This mechanism entails the facilitation of demethylation of H3K9me2 within the promoter region of ChREBP. Consequently, it acts as a protective checkpoint by attenuating the excessive accumulation of lipids and ROS in the liver, thereby mitigating the pathogenesis of NAFLD[39]. In this context, the development of small molecules tailored to selectively activate JMJC-containing HDM has shed light on the potential of Phf2/JHDM1E/KDM7C as a promising epigenetic target for NAFLD prevention[111-113]. Moreover, emerging evidence indicates that targeting the JMJD2B-PPARγ signaling pathway may represent a viable therapeutic strategy for managing NAFLD[32].

Regrettably, there is a scarcity of clinically significant small molecule inhibitors focusing on histone methylation. Among the small molecule inhibitors presently undergoing clinical trials, Tazemetostat, an EZH2-selective inhibitor of H3K27me3 hypermethylation, has exhibited promising efficacy in addressing relapsed or refractory B-cell non-Hodgkin's lymphoma and advanced solid tumors[106,114,115]. Notably, Tazemetostat has demonstrated its effectiveness both as a monotherapy (NCT01897571) and in combination with R-CHOP (NCT02889523) for newly diagnosed cases[106,115]; TAK-418, a new LSD1 inhibitor that hinders the demethylation of H3K4me1/2, shows potential in treating central nervous system disorders like Kabuki syndrome (NCT03228433, NCT03501069)[116]. Pinometostat, a small molecule inhibitor targeting DOT1L, effectively reduces methylation of H3K79 and holds promise for managing acute leukemia in adults (NCT01684150)[117]. In contrast, the PRMT5 small molecule inhibitor GSK3326595 is undergoing clinical trials in patients with solid tumors and non-Hodgkin's lymphoma (Meteor 1) (NCT0278330), and it is important to be alert to the fact that prolonged low-dose use of GSK3326595 induces NAFLD. The clinical trial stage has revealed the heightened effectiveness of small molecule inhibitors targeting histone methylation in disease treatment. While their impact on NAFLD/NASH remains unexplored, these findings provide valuable insights for researchers aiming to develop histone methylation-targeted drugs for treating NAFLD/NASH.

CONCLUSION

As a complex disease with genetic, environmental, and metabolic stresses, the pathogenesis of NAFLD involves variables, including genetic, environmental, immunological, and nutritional factors. Despite ongoing research, the relevant mechanisms remain elusive. However, the exploration of epigenetic mechanisms offers a novel approach to investigating NAFLD-related mechanisms and identifying therapeutic targets, particularly for the reversal of NAFLD. Numerous studies have demonstrated that histone covalent modification plays a crucial role in the signaling pathway network that can either activate or silence genes in response to specific signals. Among these signals, histone methylation modification is a significant determinant in the development of NAFLD and is intimately associated with the progression of NAFLD, the development of fibrosis, and carcinogenesis. Based on existing research, it is evident that lifestyle modifications have the potential to modulate the epigenome, leading to improved outcomes in NAFLD. Moreover, the advent of inhibitors targeting histone-modifying enzymes holds great promise as a groundbreaking advancement in the therapeutic management of NAFLD. Furthermore, non-invasive diagnostic modalities, including serum biochemical markers, liquid biopsies, and advanced imaging techniques, are poised to enhance the detection and characterization of NAFLD progression. Additionally, improved diagnosis and treatment strategies for patients with NASH-related HCC have the potential to effectively impede the progression of the disease.

FOOTNOTES

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