Histone deacetylase-2: A potential regulator and therapeutic target in liver disease (Review)

YA-RU LIU[1-3*], JIE-QUAN WANG[4,5*], ZHAO-GANG HUANG[1,2], RUO-NAN CHEN[1,2], XI CAO[1,2], DONG-CHUN ZHU[1,2], HAI-XIA YU[1,2], XIU-RONG WANG[1,2], HAI-YUN ZHOU[1,2], QUAN XIA[1,2] and JUN LI[3]

[1]Department of Pharmacy, The First Affiliated Hospital of Anhui Medical University; [2]Department of Pharmacy, The Grade 3 Pharmaceutical Chemistry Laboratory of State Administration of Traditional Chinese Medicine, Hefei, Anhui 230022; [3]The Key Laboratory of Anti-inflammatory Immune Medicines, School of Pharmacy, Anhui Medical University, Ministry of Education, Hefei, Anhui 230032; [4]Department of Pharmacy, Affiliated Psychological Hospital of Anhui Medical University; [5]Department of Pharmacy, Hefei Fourth People's Hospital, Hefei, Anhui 230000, P.R. China

Abstract. Histone acetyltransferases are responsible for histone acetylation, while histone deacetylases (HDACs) counteract histone acetylation. An unbalanced dynamic between histone acetylation and deacetylation may lead to aberrant chromatin landscape and chromosomal function. HDAC2, a member of class I HDAC family, serves a crucial role in the modulation of cell signaling, immune response and gene expression. HDAC2 has emerged as a promising therapeutic target for liver disease by regulating gene transcription, chromatin remodeling, signal transduction and nuclear reprogramming, thus receiving attention from researchers and clinicians. The present review introduces biological information of HDAC2 and its physiological and biochemical functions. Secondly, the functional roles of HDAC2 in liver disease are discussed in terms of hepatocyte apoptosis and proliferation, liver regeneration, hepatocellular carcinoma, liver fibrosis and non-alcoholic steatohepatitis. Moreover, abnormal expression of HDAC2 may be involved in the pathogenesis of liver disease, and its expression levels and pharmacological activity may represent potential biomarkers of liver disease. Finally, research on selective HDAC2 inhibitors and non-coding RNAs relevant to HDAC2 expression in liver disease is also reviewed. The aim of the present review was to improve understanding of the multifunctional role and potential regulatory mechanism of HDAC2 in liver disease.

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1. Introduction

The level of histone acetylation is of importance for nuclear stability, chromatin structure, gene expression and physiological functions in hepatocytes (1,2). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are antagonistic proteases that serve regulatory roles in the balance of histone acetylation and deacetylation in nucleosomes (3). HATs, which favor of histone acetylation, transfer acetyl groups from acetyl-CoA to the ε-NH$_2$ group of lysine residue side chains and neutralize the positive charge of histone tails, thus making chromatin structure more loose and conducive to active transcription (4-6). HDACs, which facilitate histone deacetylation, remove the acetyl group from the ε-amino group of lysine residue side chains, reconstitute positive charge on the surface of lysine and increase binding affinity with the negatively charged surface of DNA (5,6). Furthermore, interactions between histone and DNA result in the formation of compacted and inactive chromatin that restrains gene transcription (7-10).

The dysfunction of histone deacetylation is associated with the occurrence and development of liver disease (11). HDACs

Correspondence to: Professor Quan Xia, Department of Pharmacy, The First Affiliated Hospital of Anhui Medical University, 218 Jixi Road, Hefei, Anhui 230022, P.R. China
E-mail: xiaquan2010@163.com

Professor Jun Li, The Key Laboratory of Anti-inflammatory Immune Medicines, School of Pharmacy, Anhui Medical University, Ministry of Education, 81 Meishan Road, Hefei, Anhui 230032, P.R. China
E-mail: lijunahmu@163.com

*Contributed equally

are emerging as next-generation drug targets, thus gaining increasing attention and recognition (12-15). HDAC2 is responsible for the deacetylation of the N-terminal of histone H3 and H4, leading to a more compacted chromatin structure and transcriptional gene silencing (16,17). HDAC2 participates in the genesis and development of renal, cardiovascular, neurological and lung disease (18-23). Furthermore, small molecular compounds, peptides and other biological agents that inhibit HDAC2 show potential in the treatment of cancer (24-26), as well as degenerative and inflammatory immune disease (27-29). In particular, evidence has also highlighted the key role of HDAC2 in the pathological process of liver disease (30-32).

The present review introduces gene localization, structural information and biological functions of HDAC2, as well as the pharmacological role of HDAC2, its expression level in a variety of liver diseases and effects on hepatocyte apoptosis and proliferation, liver regeneration, hepatocellular carcinoma (HCC), liver fibrosis and non-alcoholic steatohepatitis (NASH). Finally, a number of selective HDAC2 inhibitors and non-coding (nc)RNAs relevant for HDAC2 expression in liver disease are reviewed (Fig. 1).

2. HDAC2

Characterization and classification of HDACs. Histone proteins serve structural and functional roles almost in all nuclear processes (33,34). Histones, DNA and a number of different protein complexes form chromatin to facilitate dynamic changes that occur during DNA replication, cell-cycle progression, transcription process and post-transcription events (35). Changes in chromatin that do not involve a change in DNA sequence are defined as epigenetic modification. One of the earliest known types of chromatin epigenetic modifications is histone acetylation, although its potential role in cell fate determination has not been fully elucidated (36). Acetylation has been widely studied and its potential roles and regulatory mechanisms have been revealed (37,38).

Like HATs, HDACs are rich in structural diversity and serve multiple functions (39), making them potential targets for pharmacological intervention and drug development (40). HDACs are part of a multiprotein family in which each member of HDAC has its own specialized function. In mammals, the HDAC family can be divided into four distinct subfamilies according to their structure, enzyme function, subcellular localization, expression pattern and homology with a typical HDAC in yeast (Table I): Class I (HDACs 1-3 and 8), II (HDACs 4-7, 9 and 10), III [Sirtuins (Sirs/SIRTs)] and IV (HDAC11) (41-44). The class I HDAC family consists of HDAC1-3 and 8, which have a relatively high similarity to HDAC2. They are ~50 kDa in size, are ubiquitously expressed and have homology with yeast reduced potassium dependency 3 (37,45,46). Class II HDACs comprise HDAC4-7, 9 and 10, which have a high degree of homology to yeast HDA-1 (47-49). They are ~120-150 kDa in size and are widely expressed in a tissue-specific manner (50,51). Class II HDACs can be separated into class IIa (HDACs 4, 5, 7 and 9) and IIb (HDACs 6 and 10), depending on the presence of tandem deacetylase domains (41,52). The class III HDACs, also known as Sir2 family, are named for their homology to the yeast Sir2 gene. Sir2 family is a highly conservative gene family, including Sirt1-7 (53-55). Among these, Sirt1, 2, 3 and

5 have a common NAD-dependent deacetylase domain, which can catalyze the deacetylation of histone as well as non-histone proteins. By contrast, Sirt4 and 6 have a NAD$^+$-dependent ADP ribosylation domain, which is key for protein ribosylation (54,55). Class III HDACs share little homology with class I and II HDACs, and their enzyme activity is not inhibited by broad-spectrum HDAC inhibitors [such as butyrate, valproic acid, trichostatin A (TSA) or suberoyl anilide hydroxamic acid] (56). The class IV family HDAC11 shares some, but not sufficient, homology with class I and II HDACs (57,58). HDAC11 is enriched in the brain, heart, muscle, kidney and testis in a cell type-specific manner (48,59). Furthermore, class I, II and IV HDACs have a zinc-dependent active site that can be specifically targeted by(compounds containing hydroxamates), such as TSA. As many drugs targeting HDAC isotypes have shown positive effects, HDAC enzymes may represent a novel therapeutic target for liver disease (2,11).

Structure and subcellular location of HDAC2. HDAC2 belongs to class I HDAC family, which is primarily located in the nucleus. HDAC2 is a specific enzyme with high activity and enantioselectivity to histone substrates (60). HDAC2 shares high structural homology and a common catalytic mechanism with other class I HDACs, particularly HDAC1. Similar to other class I HDACs, HDAC2 comprises a conserved deacetylase domain with short amino- and carboxy-terminal extensions, which are key for localization and maintaining their stability and function (48). HDAC1 and HDAC2 have notable amino acid homology. In large-scale gene expression analysis of brain and heart tissue, they affect different target gene sets by forming the same compressor complex (61). The crystal structure of human HDAC2 protein in the presence of hydroxamates has been revealed. The HDAC2 catalytic site is made up of a 'foot pocket', a lipophilic 'tube' and a catalytic Zn^{2+} 8 Å deep. More specifically, the 'foot pocket', tightly adjacent to the zinc binding site, is primarily formed by Tyr29, Met35, Phe114 and Leu144. The lipophilic tube, leading from the surface to the zinc binding site, is surrounded by Gly154, Phe155, His183, Phe210 and Leu276 (62,63). Furthermore, the zinc ion is accompanied by Asp181, His183, and Asp269 (62-64). HDAC2 inhibitors typically have a pharmacophore comprising three sectors: A zinc-binding group, a linker portion and a hydrophobic cap group (65-67). Based on molecular docking and virtual screening techniques, a series of compounds with novel skeletal structures have been identified as HDAC inhibitors, and their inhibitory activities and clinical therapeutic effects have been investigated (68,69). HDAC2 is the most thoroughly studied member of the HDAC family, which can be modulated by post-translational modifications, such as phosphorylation (70,71), acetylation (72), ubiquitination (73) and sumoylation (74). In particular, post-translational phosphorylation of HDAC2 negatively regulates its deacetylase activity and serves an active role in chronic inflammation (75). Furthermore, HDAC2 possesses several phosphorylation sites at the C-terminal, which are concentrated on serine residue (76).

3. Role of HDAC2 in hepatocyte apoptosis and proliferation

HDAC2 inhibits hepatocyte apoptosis. Due to its anatomical location and complex intersection, the liver is vulnerable to

Table I. Classification of classic HDACs.

Class	Co-factors	Sequence homology	Protein	Size (AA)	Chromosomal location	Sub-cellular localization	Tissue expression
I	Zn$^+$	Yeast RPD3	HDAC1	482	1p34	Nucleus	Ubiquitous
			HDAC2	488	6q21	Nucleus	Ubiquitous
			HDAC3	428	5q31	Nucleus/cytoplasm	Ubiquitous
			HDAC8	377	Xq13	Nucleus	Ubiquitous
IIa	Zn$^+$	Yeast HDA1	HDAC4	1084	2q37	Nucleus/cytoplasm	Heart, smooth muscle, brain
			HDAC5	1122	17q21	Nucleus/cytoplasm	Heart, smooth muscle, brain
			HDAC7	952	12q13	Nucleus/cytoplasm	Heart, placenta, pancreas, smooth muscle
			HDAC9	1011/879/590	7p15-p21	Nucleus/cytoplasm	Smooth muscle, brain
IIb	Zn$^+$	Yeast HDA1	HDAC6	1215	Xp11	Nucleus/cytoplasm	Kidney, liver, heart, pancreas
			HDAC10	669	22q13	Nucleus/cytoplasm	Spleen, kidney, liver
III	NAD$^+$/NAD	Yeast Sir2	SIRT1	564	No data	Euchromatin	Unknown
			SIRT2	377		Cytoplasm	
			SIRT3	396		Mitochondrial	
			SIRT4	320		Mitochondrial	
			SIRT 5	308		Mitochondrial	
			SIRT6	356		Heterochromatin	
			SIRT7	407		Nucleolus	
IV	Zn$^+$	Yeast RPD3/HDA1	HDAC11	347	3p25	Nucleus	Heart, smooth muscle, kidney, brain

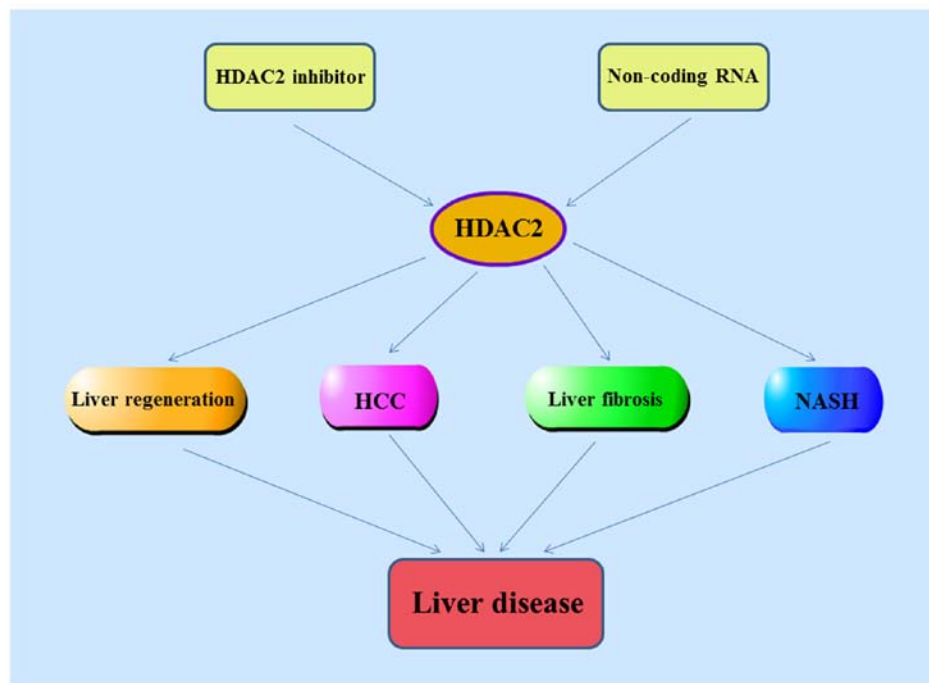HDAC/HDA, histone deacetylase; RPD3, reduced potassium dependency 3; Sir/SIRT, sirtuin.

Figure 1. HDAC2 inhibitor and non-coding RNA relevant to HDAC2 expression in liver disease. HDAC2, histone deacetylase 2; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

a variety of toxic, metabolic, inflammatory and necrotic stimuli (77,78). Hepatocytes are highly sensitive to death receptor-mediated apoptosis due to ubiquitous expression of death receptors in the liver (79). It has been demonstrated

that the abnormal death of hepatocytes is a key trigger factor for the occurrence and development of both acute and chronic liver disease (77). It is therefore necessary to investigate the underlying pathogenesis and therapeutic targets of liver disease and the expression levels and pharmacological activity of HDAC2. There is increasing evidence that HDAC2 is involved in the regulation of hepatocyte death, thereby implying that HDAC2 serves a key role in the pathogenesis of liver disease (80,81). Here, experimental evidence for the effects of HDAC2 on hepatocyte apoptosis will be discussed.

TGF-β, a pleiotropic growth factor, has been shown to induce apoptosis in primary rat and AML-12 murine hepatocytes, consequently leading to liver injury and regeneration termination (80,81). Through transfection of HDAC2 RNA interference (RNAi) plasmid, Lei *et al* (80) found that HDAC2 serves as a significant anti-apoptotic factor in TGF-β1-induced apoptosis of AML-12. Lei *et al* further found that downregulation of HDAC2 significantly induces spontaneous cell apoptosis and increases the apoptotic response following TGF-β1 treatment. Moreover, ERK1/2 has been shown to be significantly inhibited in cells transfected with HDAC2i. In HDAC2i-transfected cells, low baseline levels of phosphorylated ERK1/2 were concomitant with decreased TGF-β1-induced apoptosis, suggesting that negative regulation of ERK1/2 is associated with the role of HDAC2 in apoptosis. In sum, these findings highlighted that silencing HDAC2 may induce spontaneous apoptosis of AML12 hepatocytes by promoting ERK1/2 expression and pharmacological activity. Taken together, this supports the important physiological role of HDAC2 in hepatocyte apoptosis. The anti-apoptotic effect of HDAC2 overexpression may be a promising therapeutic strategy for treatment of liver disease.

HDAC2 promotes proliferation of hepatocytes. Impaired proliferation of hepatocytes is associated with the occurrence and progression of liver disease (82). However, little is known about the underlying mechanisms that lead to defective hepatocyte proliferation. HDAC2 serves critical roles in cell proliferation and tissues regeneration (83). HDAC2 knockout inhibits proliferation and induces senescence of MCF7 cells by enhancing the binding activity and interaction of p53-DNA (84). HDAC2 deficiency usually results in different cellular phenotypes, suggesting that HDAC2 has a cell-type-specific role that may be relevant to the cell proliferative status (30). Turgeon *et al* (85) demonstrated that defects in tissue structure and perturbation of microenvironment homeostasis are accompanied by inhibition of cell proliferation when HDAC1/2 is knocked out. There is increasing evidence that HDAC2 promote the proliferation of liver cancer cell lines, although there is no indication of HDAC2 involvement in the proliferation of normal liver cells (86-88). Ler *et al* (86) found that the combined knock out of HDAC2 and HDAC1 decreases cell proliferation and improves survival of patients with HCC. HDAC2 overexpression is routinely detected in cancer cells, and HDAC2 deficiency and inhibition lead to HCC cell apoptosis (87). The role of HDAC2 in cell proliferation was previously observed in the development of cardiac and B cells; HDAC2 and HDAC1 jointly inhibit cell cycle protein-dependent kinase p21 (WAF1/CIP1) and

p57KIP2 transcription and promote progression from G_1 to S phase (88). By contrast, HDAC2 suppresses transcription of p21WAF1/CIP1 via binding to Sp1-binding site enriched proximal region of the p21WAF1/CIP1 promoter (89).

4. HDAC2 in liver disease

HDAC2 promotes liver regeneration. Liver regeneration is of clinical significance in various types of liver disease (90,91). In the event of massive hepatocyte loss or damage, the intrinsic regenerative capacity of hepatocytes is activated by endogenous molecule-mediated signaling pathways (92). Rapid synchronous compensatory regeneration occurs following 2/3 partial hepatectomy (PH), and regenerated hepatocytes immediately enter the cell cycle and proliferate rapidly, restoring their original quality and function (93). Studies on the deficiency of HDAC2 in mouse liver regeneration have confirmed the key role of HDAC2 in liver regeneration (94,95). Following PH, the liver/body weight ratio is significantly lower in hepatocyte-selective HDAC2$^{-/-}$ mice compared with wild-type mice; HDAC2$^{-/-}$ mice also show more severe liver damage. Additionally, the expression of HDAC2 gradually increases within 0.5 to 3.0 days in mouse post-hepatectomy livers at an early stage of regeneration. Ki67, a mitotic marker, is decreased by ~30-70% in HDAC2 knockout mice, subsequently leading to defective mitosis. Decreased cyclinD1 and CDK2 in HDAC2-deficient hepatocytes suggests that HDAC2 liver-specific knockout triggers downregulation of cell cycle proteins and blocks cell cycle progression. Studies have shown that HDAC2 is expressed differently in male and female mice, and HDAC2 can directly bind to the promoter of B-myc (93,95). The expression of B-myc in the female liver is higher than in the male liver, which may be potential mechanism for the significantly slower rate of replication and quality reconstruction of individual female hepatocytes following PH. In conclusion, the altered metabolic pattern in HDAC2 knockout mice is consistent with the well-known regenerative characteristic of hepatocytes. This evidence also confirms a key role for HDAC2 in the metabolic response following PH (Fig. 2).

HDAC2 in liver fibrosis. Liver fibrosis, primarily characterized by excessive accumulation of extracellular matrix proteins, is a worldwide medical problem with increasing annual morbidity (96,97). The majority cases of liver fibrosis arise in the context of various etiology of liver damage, such as chronic viral infections (98), excessive alcohol consumption (99), metabolic disorder (100) or autoimmune disease (101). The regression and improvement of liver fibrosis are primarily attributed to inactivation and apoptosis of activated hepatic stellate cells (HSCs) (102). Notably, emerging evidence has revealed the potential features and roles of HDACs in the progression of liver fibrosis (103,104). It was also reported that several HDACs are involved in the activation of HSCs and the progression of hepatic fibrosis (105,106). In addition, accumulating evidence has highlighted the key role of HDAC2 in the development of renal fibrosis and pulmonary fibrosis (18,107,108). In this regard, it is worth verifying the functional role of HDAC2 in the occurrence and reversal of liver fibrosis.
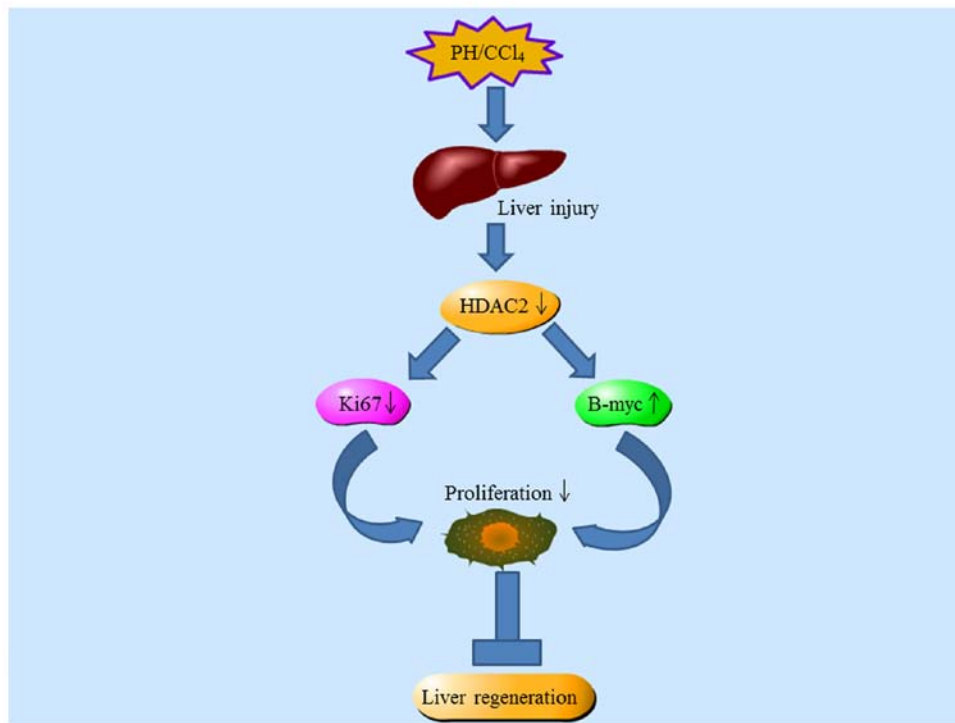
Figure 2. Schematic representation of the role of HDAC2 in liver regeneration. Following PH or CCl_4 exposure, the expression of HDAC2 decreases. The loss of HDAC2 inhibits expression of Ki67 and induces expression of B-myc, which results in hepatocyte mitosis defects and impaired liver regeneration. PH, partial hepatectomy; HDAC2, histone deacetylase 2.

In order to reveal the possible association between HDAC2 and liver fibrosis, a CCl_4-induced mouse liver fibrosis and its spontaneous reversal model have been successively established (119); this supported the view that aberrant HDAC expression and activity participate in the occurrence and development of liver fibrosis. Expression of HDAC2 is increased during CCl_4-induced liver fibrosis and significantly decreased during its reversal. Similarly, the expression of HDAC2 is also significantly increased in human hepatic fibrosis. Exposure of HSC-T6 cells to TGF-β1 results in increased HDAC2 expression in a dose- and time-dependent manner. Loss-of-function analyses have confirmed that loss of HDAC2 induces cell cycle arrest and inhibits the expression of collagen 1α1 and α-smooth muscle actin protein in HSC-T6 cells activated by TGF-β1 (110-112). Mechanistically, it has been widely reported that HDAC2-small interfering (si)RNA leads to increased expression of SMAD7 compared with scramble siRNA-transfected groups (111,112). Collectively, these results suggest that HDAC2 activates HSCs and promotes the occurrence of liver fibrosis by suppressing SMAD7 expression. In conclusion, these findings may demonstrate the role of HDAC2 in the progression and reversal of liver fibrosis, and therefore have significant implications for the development of novel treatment strategies for liver fibrosis (Fig. 3).

HDAC2 in NASH. NASH, a more aggressive form of non-alcoholic fatty liver disease, is pathologically characterized by cell damage, inflammatory cell infiltration and hepatocyte ballooning (113,115). Sustained accumulation of reactive oxygen species (ROS) and resultant oxidative stress, mitochondrial dysfunction and accumulation of triglyceride and lipotoxic metabolites have been identified as contributing

factors to NASH (115). To date, there are no current Food and Drug Administration (USA)-approved effective therapies to manage NASH (116). The inhibitory modulation of HDAC2 may contribute to the prevention of NASH (117).

Zhong *et al* (117) found that CD36 deficiency specifically upregulates monocyte chemotactic protein-1 (MCP-1) expression, thereby aggravating macrophage infiltration and hepatic inflammation. In addition, they also indicated that CD36 deficiency effectively suppresses nuclear HDAC2 expression by decreasing intracellular ROS and increasing the binding of acetyl histone 3 to MCP-1 promoter, which subsequently enhances expression of MCP-1, increases hepatic macrophage infiltration and promotes NASH development. Screening of 11 classic HDACs in $CD36^{-/-}$ mouse liver and CD36-deficient hepatocytes also revealed that CD36 deletion significantly inhibits nuclear expression of HDAC2 in hepatocytes, but not that of other HDACs. Taken together, this indicates that CD36 deficiency in hepatocytes promotes MCP-1 expression by inhibiting nuclear expression of HDAC2. Thus, the loss of CD36 results in decreased ROS levels, which lead to the development of NASH in mice by inhibiting the expression of HDAC2 and promoting that of MCP-1. Overall, maintaining a good balance between nuclear HDAC2 expression and hepatic ROS levels may be a potential novel therapeutic strategy for the prevention of NASH (Fig. 4).

HDAC2 promotes HCC. HCC is one of the most common types of solid malignancy and is driven by different molecular mechanisms (118,119). Researchers have linked gene expression signatures with the occurrence and prognosis of HCC and investigated gene expression patterns and potential therapeutic targets (120). Evidence suggests that HDAC2 is
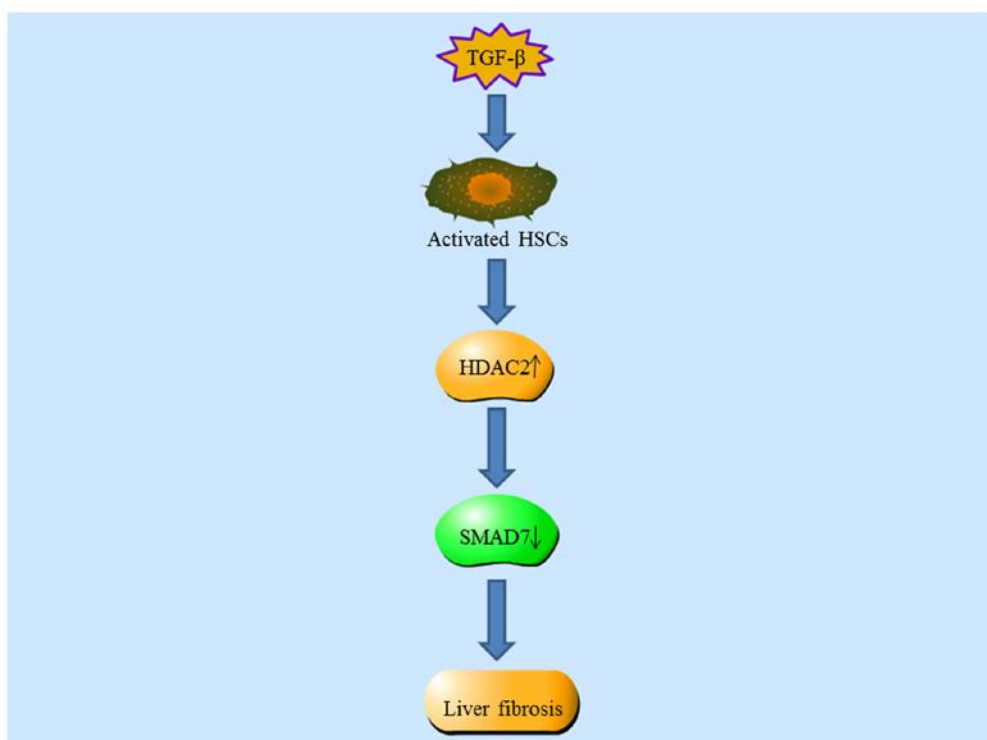
Figure 3. Potential regulatory mechanisms of HDAC2 in liver fibrosis. The expression of HDAC2 protein increases in mice exposed to CCl_4 and HSC-T6 cells treated with TGF-β. Furthermore, HDAC2 exerts its key role in HSC activation and liver fibrosis by suppressing the expression of SMAD7, which is a negative modulator in of HSC activation and liver fibrosis. HDAC2, histone deacetylase 2; HSCs, hepatic stellate cells.
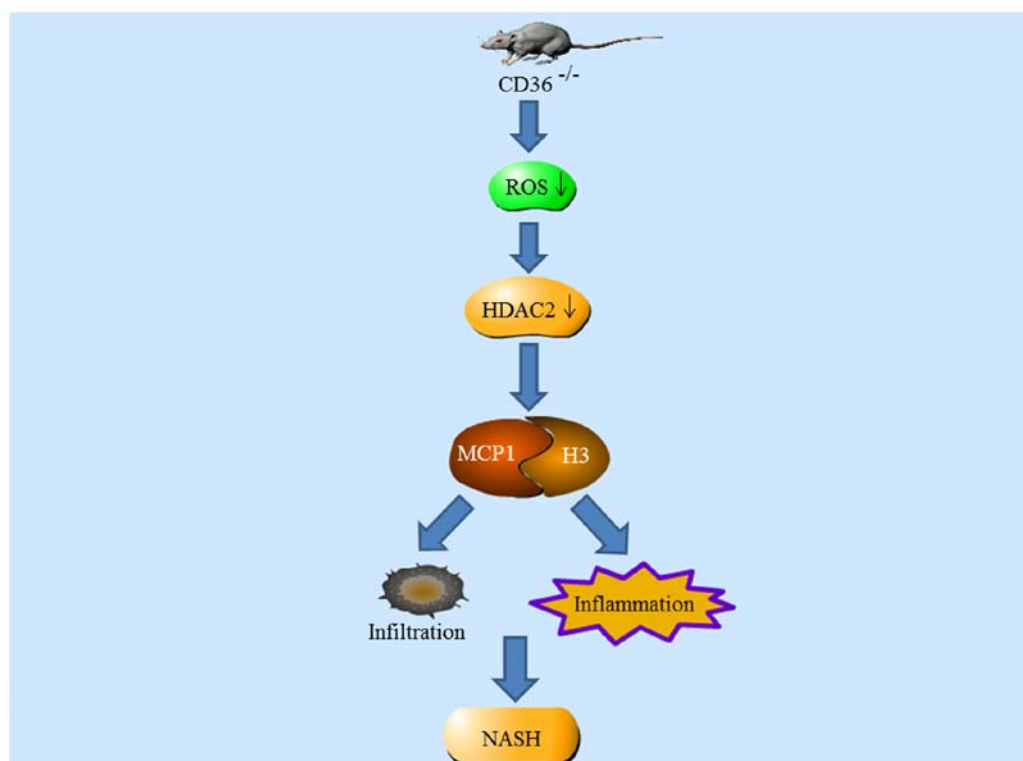

Figure 4. Key roles of HDAC2 in the progression of NASH. In CD36^{-/-} mice, CD36 deficiency blocks hepatic HDAC2 by decreasing ROS levels, and increases acetyl histone3 binding to MCP-1, thus enhancing expression of MCP-1, increasing hepatic macrophage infiltration and promoting NASH development. HDAC2, histone deacetylase 2; NASH, non-alcoholic steatohepatitis; ROS, reactive oxygen species; MCP-1, monocyte chemotactic protein-1.

overexpressed in tumors, and HDAC2 downregulation leads to high expression levels of cell cycle circuit elements, including p21WAF1/Cip1, which is a well-characterized regulatory factor that serves a key role in cell senescence (121,122). With
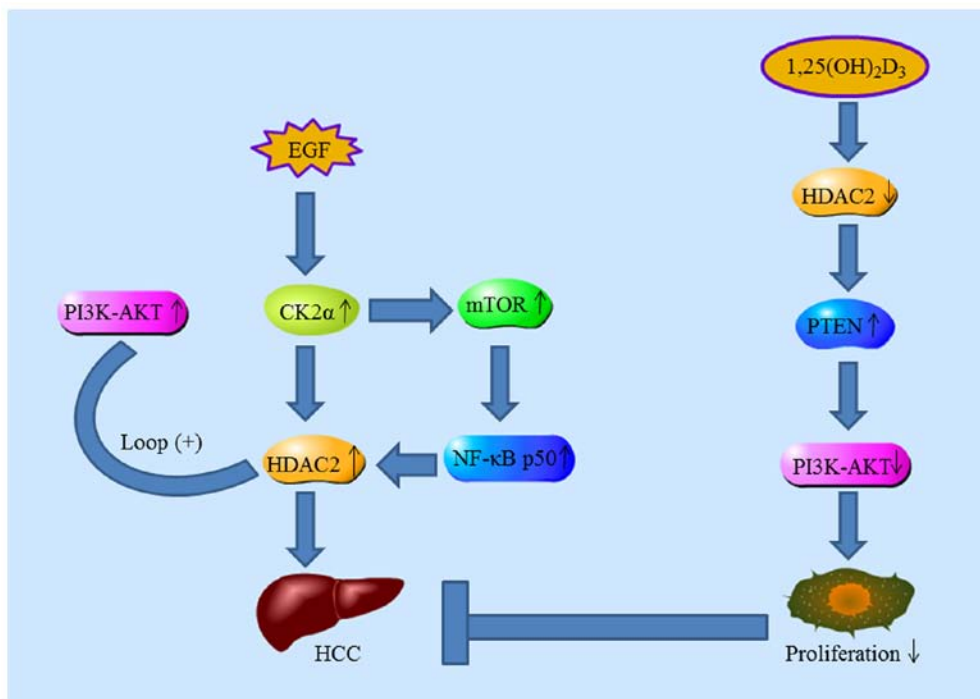
Figure 5. Schematic representation of the role of HDAC2 in HCC. Treatment with EGF increases CK2α expression and phosphorylation of mTOR and AKT, inducing expression of HDAC2 in HCC. In addition, elevated expression of HDAC2 triggers a positive feedback loop of AKT phosphorylation via transcriptional modulation of phosphoinositide signaling molecules. Furthermore, $1,25(OH)_2D_3$ inhibits the growth of HCC cells via downregulating HDAC2-mediated PTEN upregulation, and upregulating p21 (WAFI/CIP1), AKT deactivation and inhibition of the PI3K/AKT signaling pathway. HDAC2, histone deacetylase 2; CK2α, casein kinase II; HCC, hepatocellular carcinoma.

regard to liver cancer, HDAC2 promotes proliferation, and its aberrant expression may be a prognostic indicator of HCC (86).

A study found that HDAC2 overexpression is associated with poor survival of patients with low-grade and early-stage tumors, suggesting that HDAC2 is an independent and reliable predictor of survival of patients with HCC (123). Noh *et al* (89) assessed the tumorigenic potential of HDAC2, evaluated abnormal HDAC2 expression and investigated its regulatory mechanism in HCC; abnormal regulation of HDAC2 served a key role in HCC progression by regulating cell cycle regulatory components at the transcriptional level. Their data also showed that HDAC2 overexpression was not associated with Wnt and c-myc signaling pathways, which play an important role in malignant cell proliferation. Kim *et al* (124) investigated the underlying mechanism of HDAC2 in tumorigenesis; increased expression of casein kinase II (CK2α) was positively correlated with HDAC2. They proposed a regulatory mechanism whereby increased HDAC2 expression in HCC is primarily caused by the activation of CK2α/AKT pathways mediated by EGF. Lee *et al* (108) indicated that systemic delivery of HDAC2 siRNA encapsulated in lipid nanoparticles is sufficient to inhibit HCC progression. In addition, mTORC1 activation and NF-κB p50 nuclear translocation are essential for the transcriptional activation of oncogenic HDAC2 in HCC (125). Furthermore, $1,25(OH)_2D_3$ inhibits the progression of HCC by downregulating HDAC2 (126,127). Consistently, Wang *et al* (128) also found that high levels of HDAC2 expression are negatively correlated with PTEN expression in HCC patients with poor prognosis (Fig. 5).

Merck60 selectively inhibits HDAC1 and HDAC2, thereby increasing histone acetylation and disrupting core gene regulatory architecture in rhabdomyosarcoma (129). Methot *et al* (130) investigated novel selective HDAC1/HDAC2 inhibitors (SHI-1:2), which incorporate a biaryl zinc-binding motif into a nicotinyl scaffold; the optimized SHI-1:2 structure exhibited notable inhibitory activity against HDAC1 and HDAC2, and its specific selectivity for HDAC1/HDAC2 was 100 times higher than that for other HDACs (131). N-(2-amino-5-substituted phenyl) benzamide significantly induced HCT116 cell death by specifically targeting HDAC2 (62). In addition, the effects of C15 urushiol and its triazole derivatives on the apoptosis of liver cancer cells have been qualitatively and quantitatively verified (132). Venturelli *et al* (133) reported that 6- and 8-prenylnaringenin enter into the 'foot pocket' of HDAC2 and combine with zinc ion of their catalytic center, subsequently inhibiting excessive proliferation of melanoma cells. N-[4-(Hydrazinecarbonyl)phenyl]-3,5,6-trimethylpyrazine-2-carboxamide exhibits notable anticancer activity *in vivo* (IC_{50}=1.60 μM) (134) Among squaramide-based derivatives, the lead compound 42 exhibits good druggability by specifically inhibiting HDAC2 (67). Isopropyl derivative 5 and tert-butyl derivative 6, is which derived from the lead compound NSC746457, exhibit a significantly inhibitory effect on HDAC2 (63). Novel indazole and pyrazolo(3,4-b) pyridine derivatives have been designed and synthesized via fragment-based virtual screening; biological evaluation showed that compounds 15k and 15m possess distinctly inhibitory effect towards HDAC2 (66). Rosmarinic acid has been demonstrated to downregulate HDAC2 expression, subsequently leading to cell cycle arrest and apoptosis (135). N-(2-aminophenyl)-4-[(4-fluorophenoxy)methyl] benzamide

Table II. Lead compounds of potential histone deacetylase 2 inhibitors.

Inhibitor	Function	IC_{50}, nM	Analysis method	(Refs.)
Compound 12	Anticancer	44.0	SAR	(136)
Compound 5/8	Anticancer	27.0/39.0	SAR	(59)
K560	Neuroprotection	520.0	VS	(138)
Compound 4b	ND	40.6	SAR	(87)
RH01652	Prevent AD	ND	MDs-QC	(139)
BRD8430	Neuroblastoma differentiation	ND	HTS	(140)
Eight hits urushiol derivatives	ND	ND	PM-VS	(141)
C15 Triene	ND	ND	MD-MDs-VS	(61)
Triazole	Anticancer	ND	SAR-MD	(143)
ST088357	ND	16870.0	Scaffold-Merging HQ	(148)
6-PN/8-PN	Anticancer	ND	SAR	(145)
Compound 4g/6c/6g	ND	130.0/160.0/580.0	MD	(146)
LAQ824	ND	3.0	MD	(147)
Compound 7a	Anticancer	53.7	QSAR	(148)
Squaramide-based hydroxamic acids	Anticancer	ND	SAR	(64)
ID5/TD6	Anticancer	22.0/18.0	Click-chemistry/MD	(60)
Compound 15k/15m	Anticancer	4.2/3.6	VS-MD	(63)
Rosmarinic acid	Anticancer	ND	Activity screening	(149)
Compound 12a	Anticancer	ND	MD-SAR	(62)
Compounds12g/12h	Anticancer	205.0/144.0	SAR	(65)

ND, no description available; SAR, structure-activity relationship; VS, virtual screening; MDs, molecular dynamics; QC, quantum chemistry; HTS, high-throughput screening; PM, pharmacophore modeling; MD, molecular docking; HQ, hybrid query; QSAR, quantitative SAR.

exhibits antitumor activity by inhibiting HDAC2 at an IC_{50} of 3.84 μM (65). In addition, a series of 2-aminobenzamide-based compounds exhibit highly inhibitory effects on solid cancer cell lines and low cytotoxicity against normal cells (Table II) (68).

ncRNAs mediate HDAC2 expression at the posttranscriptional level (136,137). A meta-analysis of 1,258 HCC samples showed that downregulation of microRNA (miRNA or miR)-100-5p contributes to the progression and prognosis of HCC by negatively regulating HDAC2 expression (138). Noh *et al* (87) found that miR-145 functions as a tumor suppressor by directly targeting HDAC2 in liver cancer. In addition, another study demonstrated that miR-31 significantly decreases HDAC2 expression by suppressing mRNA translation in HCC cells (139). In sum, these results suggest that promotion or suppression of certain miRNAs cause aberrant expression of HDAC2, which be involved in HCC tumorigenesis. Dai *et al* (140) found that long ncRNA SNHG15 upregulates HDAC2 expression by sponging miR-490-3p, which further promotes HCC progression.

In summary, these results demonstrate that HDAC2 possesses carcinogenic properties. These studies also suggest that the development of novel compounds or ncRNAs may be a promising therapeutic modality for liver cancer by selectively targeting HDAC2.

5. Conclusion

Epigenetic modifications serve prime regulatory roles in genetic events, such as transcriptional activation and silencing (141). The effects of epigenetic modifications have been recognized, although their specific roles may still be controversial. Histone acetylation contributes to gene expression, while histone deacetylation leads to suppression of gene transcription (142). Studies have shown that relative levels of histone acetylation and deacetylation are of significance for the regulation of pathophysiological processes, including proliferation, cell-cycle progression, differentiation, immune evasion, inflammatory lesion, apoptosis and death (143-145). Pharmacological inhibition of HDAC activity or expression alters chromatin acetylation levels, subsequently confusing boundaries between transcriptionally active and quiescent chromatin (146-148).

The increasing incidence of liver disease requires novel effective therapeutic interventions. HDAC2 exhibits attractive pharmacological effects in hepatocyte loss or injury, HCC and NASH by modulating hepatocyte death and regulating cell cycle components. In the past decades, researchers have characterized HDAC classification, structure and subcellular localization (47-50,52,54). The malignant or beneficial role of HDAC2 in liver fibrosis, non-alcoholic fatty liver disease and

liver cancer has been revealed. Nonetheless, the mechanism of HDAC2 in the development of liver disease has not been elucidated and more investigations are needed in future. In summary, these properties of HDAC2 make it an appealing therapeutic target by regulating expression of HDAC2 and HDAC2-dependent signaling pathways.

HDAC2 presents favorable characteristics as a potential drug target. Consequently, pharmacological agents that inhibit HDAC2 may be a prospective treatment for liver ailments. However, the few known HDAC2 inhibitors are broad spectrum inhibitors that simultaneously inhibit several members of HDACs family and thus may have more potential adverse side effects. Therefore, it is necessary to develop novel HDAC2 inhibitors with higher targeting selectivity. High homology and cellular co-localization of multiple HDACs makes development and use of HDAC2 inhibitors difficult. The expression and pharmacological activity of HDAC2 is important for the prediction, diagnosis and prognosis of liver disease. NF-κB, c-Myc, Sp1 and Sp3 can bind to the HDAC2 promoter, thereby augmenting HDAC2 transcription (149-151). These findings suggest that the HDAC2 promoter may also be a potential target for pharmacological intervention.

The present study reviewed the specific roles of HDAC2 and the potential application of HDAC2 inhibitors in liver disease. Increasing evidence has highlighted the key role of HDAC2 in the occurrence and development of liver disease and demonstrated that HDAC2 inhibitor therapy may be a therapeutic approach. Better understanding of the potential roles and regulatory mechanisms of HDAC2 in liver disease may improve the ability to predict the pace of liver disease progression and exploit specific targeted therapeutic strategies.

Availability of data and materials

Not applicable.

Authors' contributions

YRL, JL and JQW conceived and designed the study and wrote the manuscript. ZGH, RNC and XC prepared the figures. DCZ and HXY prepared the tables. QX, XRW and HYZ revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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