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REVIEW

Post-Translational Modifications of Histones and Non-Histones in Liver Disease and Traditional Chinese Medicine Treatment: A Narrative Review

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Abstract: Post-translational modifications (PTMs) of histones and non-histones are significant epigenetic modifications in humans, including acetylation, methylation, phosphorylation, glycosylation, and ubiquitination. These modifications regulate chromatin structure and gene expression, enabling proteins to perform their normal biological functions within cells and maintain stable expression. It is also closely related to the development process of liver diseases and plays an important role in the pathological processes of liver cancer, liver fibrosis, alcoholic fatty liver disease and non-alcoholic fatty liver disease. This article reviews the roles and pathway mechanisms mediated by post-translational modifications of histones and non-histones in these liver diseases, and briefly outlines how traditional Chinese medicine (TCM) can intervene in liver diseases by modulating protein post-translational modifications, providing new strategies for future prevention and treatment of liver diseases.

Keywords: post-translational modifications, liver disease, traditional Chinese medicine

Introduction

The precise regulation of protein functions is essential for biological tissues, achieved through post-translational modifications (PTMs), a highly efficient and precise regulatory mechanism. A significant advantage of PTMs is that they can dynamically regulate protein function at a faster rate and with lower energy costs than protein turnover. There are hundreds of different forms of PTMs present in eukaryotic proteins, but only some types of[1] such as acetylation, phosphorylation, glycosylation, methylation, and ubiquitination have been extensively studied. It is believed that these PTMs occur in different subcellular components (including the nucleus) as well as in many tissues, including the liver and brain, as well as in normal physiological and related pathological states of.[2]

The modification process of PTMs is often complex and is mediated by specific enzymes, involving the involvement of multiple enzymes and the presence of multiple modification types. Each type of PTM is catalyzed by its specific enzyme or family of enzymes that specifically recognize specific amino acid residues or domains on substrate proteins, thereby ensuring the accuracy and specificity of the modification.[3] Moreover lysine, as the only side chain in the protein, contains ε -amino group and is a multifunctional protein widely present in organisms and plays crucial roles in various biological processes, including transcriptional regulation, signal transduction, protein degradation and cellular metabolism.[4]

That PTMs occur in both histone and non-histone proteins. In eukaryotes, Chromosomes are formed by condensed chromatin of countless nucleosomes. Each nucleosome consists of double-stranded DNA wrapped around the histone octamer, Core histone pairs containing dimerization (H2A, H2B, H3, H4), with histone H1 linked on a short stretch of linker DNA. All of these histones are structurally composed of a globular domain and extended C-and N-terminal tails, which are subject to a variety of PTMs to modify DNA regulatory processes, chromatin remodeling and gene expression.[5,6] In addition to the basic

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components of the octameric histones, non-histone chromatin proteins similarly play a crucial role in the organization of functional chromatin domains.[7] Histone chromatin proteins mainly regulate protein activity, localization, stability and interaction, which depend on a variety of independent enzyme systems and directly change the function of target proteins, including phosphorylation signaling and ubiquitination-mediated proteasome degradation.[8,9]

In recent years, the role of PTMs in liver diseases has gradually attracted attention. By changing the structure and function of proteins, participating in liver cell metabolism, signal transduction and other processes, and exerting important effects on the occurrence and development of liver diseases.[10] According to statistics global liver disease leads to 2 million deaths a year, accounting for 4% of all deaths. Death is mainly attributed to cirrhosis and hepatocellular carcinoma complications. However, the global cirrhosis of the most common cause of alcoholic fatty liver and alcoholic fatty liver.[11,12] PTMs are involved in the repair and regeneration of hepatocytes, affect inflammatory pathway signaling and regulate immune function during the development of liver disease, and involve histones and a variety of non-histones.[13] Therefore, this review summarizes the effects of common post-translational modifications of histones and non-histones on liver diseases and the mechanism by which traditional Chinese medicine regulates protein modification to treat liver diseases.

PTMs and Liver Cancer

Hepatocellular carcinoma (HCC) is a common malignancy with high morbidity and mortality worldwide, with high malignancy and poor prognosis.[14] Emerging evidence suggests a critical role of epigenetics in tumorigenesis. The development of HCC also depends on epigenetically related disorders of various signal transduction pathways. Many studies have shown that PTMs are associated with the occurrence and development of cancer, and the discovery of related proteins provides new therapeutic targets for cancer, among which protein acetylation, phosphorylation, glycosylation and ubiquitination are the most studied protein modifications involved in the development and development of liver cancer, as shown in Table 1.

Acetylation and Liver Cancer

Acetylation plays a crucial role in the regulation of tumor development, histone acetylation status by Histone acetyltransferases (HATs) and Histone deacetylase enzymes (HDACs), the balance between the two, once the balance is broken, will appear imbalance of gene transcription, which may lead to the tumor or abnormal proliferation of cells. [50] As an important regulator in liver cancer, HDAC can remove acetyl groups from the lysine residues of histones and non-histone proteins. It can be divided into two families according to the conserved deacetylase domain and its dependence on specific cofactors: Zn^{2+} -dependent deacetylase family, and with NAD^{+} -dependent Sirtuin protein family (SIRTs).[51,52]

In the HDAC3-Signal transducer and activator of transcription 3 (STAT3) pathway study, HDAC3 silencing impairs the transition from ac-STAT3 to p-STAT3 in the cytoplasm, resulting in a subsequent collapse of STAT3 signaling, indicating that reducing HDAC3 expression reduced HCC cell growth and inhibited xenograft tumor growth.[15] Moreover, another study reported that loss of HDAC3 also disrupted H3K9me3 deacetylation and subsequent trimethylation, which leads to the accumulation of damaged DNA, while hyperacetylated H3K9ac acts as a transcriptional activator and enhances multiple signaling pathways to promote tumorigenesis.[53] HDAC5 can interact with the newly discovered marker CD13 in HCC stem cells, and has an effect on Lysine-specific demethylase 1 (LSD1) through its mediated deacetylation process, resulting in reduced methylation activity of LSD1 on NF-κB p65, thus enhancing p65 protein stability. This change is one of the driving forces of HCC progression.[16] Likewise, HDAC6 is also important in the development of HCC. It ultimately promotes the development of liver cancer by inhibiting the transcriptional activity of the tumor suppressor gene p53 and deacetylating it at specific sites (K120 and K373/382).[17,18] And HDAC7significantly improved the oncogenic and stemness of hepatocellular carcinoma stem cells by promoting histone H3 deacetylation and inhibiting the expression of the gene of phosphate and Phosphatase and tensin homolog (PTEN).[19] Notably, HDAC11 induces deacetylation of the early growth response gene 1(Egr1). Studies have shown that it inhibits the expression of HDAC11 in human hepatocellular carcinoma cells, prevents the transcription of p53 gene, and thus promotes apoptosis of hepatoma cells.[20]

Table 1 The PTMs and HCC

PTM	Target Protein/Key PTM Moderating Enzyme	Mechanism	Outcome	Reference Number
Acetylation Phosphorylation	HDAC3	Silencing of HDAC3 inhibits STAT3 signaling	Reduced HCC cell growth and inhibited xenograft tumor growth	[15]
	HDAC5,CD13	HDAC5 and CD13 interact with each other to cause HDAC5-mediated deacetylation of LSD1 and protein stabilization, preventing p65 degradation and activating the NF-kB signaling pathway	Promote HCC proliferation, invasion, cell cycle progression as well as sorafenib resistance	[16]
	HDAC6	HDAC6 inhibited the deacetylation of p53 (K120, K373/382)	Promote the proliferation of HCC cells	[17,18]
	HDAC7	HDAC7 promotes histone H3 deacetylation and inhibits PTEN	Improve the carcinogenicity of HCC cells	[19]
	HDAC11	HDAC11 Ines deacetylation of Egr 1, a transcription factor of p53, preventing transcription of the p53 gene	Promoting the apoptosis of HCC cells	[20]
	SIRT1	SIRT1 activates AKT/HIF-1 α to upregulate CCL5 expression	Promote macrophage recruitment and synergistically drive hepatocarcinogenesis	[21]
	SIRT1	SIRT 1 deacetylates p62 (k295) and interferes with Keap 1-mediated polbiquitination of p62	Maintain p62 protein stability and advance hepatocarcinogenesis	[22]
	pSMAD3C	Up-regulated terminal COOH phosphorylation of SMAD3 (pSMAD3C)	Inhibition of liver cancer progression	[23]
	pSMAD3L	Phosphorylation of SMAD3 (pSMAD3L)	Promote liver cancer progression	[23]
	P-Rex1	Downregulation of P-Rex1 results in reduced phosphorylation of the tyrosine kinase receptor c-Met, as well as the phosphorylation of AKT and Erk1 / 2	Inhibiting the migration of hepatoma cells	[24]
	mTORC1	mTORC1 Stimulated AR S96 phosphorylation	Improve AR stability, nuclear localization, and transcriptional activity to promote liver steatosis and hepatocarcinogenesis	[25]
	STAT3	Phosphorylates STAT 3 at Ser727 and passes through the MAPK / ERK 1 / 2 pathway	Improve HCC cell survival	[26]
	ASGR1	Promote the binding of NeMo-like kinase to STAT 3 and inhibit STAT 3 phosphorylation	To inhibit the progression of liver cancer	[27]
	ZNF498	Attenuated p53 Ser46 phosphorylation and inhibited p53-mediated apoptosis and iron death	Promote the occurrence of liver cancer	[28]
Glycosylation	PCK1	Downregulation of PCK 1 expression increased the overall O-GlcNAc level in HCC	Promote the occurrence of liver cancer	[29]
	CAV1	CAV 1 induced cellular O-GlcNAc	Driving HCC cell invasion and potential HCC metastasis	[30]
	PHB2	The O-glycosylation of PHB2 Ser161	Promote the growth and migration of liver cancer cells	[31]
	MerTK	N-glycosylation at the key sites (N294 and N454) of MerTK	Drive the carcinogenic transformation of the cells	[32]
	GnT-IVa	GnT-IVa enhanced the interaction of integrin β 1 with Vimentin through N-glycosylation	Promote the metastasis of HCC	[33]

(*Continued*)

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Table 1 (Continued).

PTM	Target Protein/Key PTM Moderating Enzyme	Mechanism	Outcome	Reference Number
Ubiquitination	PRIM1,UBE2C, UBE2D1	PRIM 1 upregulates the ubiquitin-binding enzyme UBE 2 C as well as UBE2D1, triggering the ubiquitination of P53	Accelerate the progression of liver cancer	[34,35]
	UBE2S,TRIM28	UBE 2 S interacts with TRIM28 in the nucleus and together enhances the ubiquitination of p27 to promote its degradation	Drive the progression of liver cancer	[36]
	UBE2T	UBE 2 T activates the MAPK-ERK pathway and enhances the nuclear translocation and EMT of β -catenin	Cathe state transition of HCC cells	[37,38]
	UBE2T	UBE 2 T promotes the ubiquitination of AKT K63, Increase in the metabolism of the pyrimidines	Drive the progression of liver cancer	[39]
	TRIM7(E3s)	TRIM 7 directly regulates negative regulation of Src protein and regulation of the Src-mTORC1-S6K1 axis	To inhibit the progression of liver cancer	[40]
	PJA1(E3s)	Overexpression of PJA 1 causes a dysregulation of TGF- β signaling	Activate the oncogene of liver cancer and promote the progression of liver cancer	[41,42]
	RNF146(E3s), PTEN	RNF146 Activate the AKT / mTOR pathway by promoting ubiquitin proteolysis of PTEN	Drive the progression of liver cancer	[43]
	PHF19, β-TrCP (E3s)	PHF 19 interacts with β -TrCP to activate the Hedgehog pathway	Promote the growth and proliferation of liver cancer cells	[44]
	RNF128(E3s)	Activation of the EGFR / MEK / ERK pathway	Drive the progression of liver cancer	[45]
	WWP1(E3s)	Ubiquitination of WWP 1 degrades KLF 14	Accelerate HCC cell invasion and migration	[46]
	USP35	Inpressed USP 35 expression and increased the ubiquitination level of PKM 2	Malignant properties of damaged HCC cells	[47]
	TRIM2	Promoting the K63-linked ubiquitination of RIPK 1	To inhibit the progression of liver cancer	[48]
	SERPINE2,c-Cbl (E3s)	SERPINE2 Prevent EGFR degradation by c-Cbl-mediated ubiquitination	Promote metastasis of liver cancer	[49]

The SIRTs are also an important part of the regulation of HCC progression. According to studies, SIRT1 upregulates the expression of CC motif chemokine ligand 5 (CCL 5) by activating protein kinase B / hypoxia-inducing factor-1α signaling axis (AKT / HIF-1α) in mesenchymal stem cells, while promoting macrophage recruitment and hepatocarcinogenesis.[21] Moreover, a team confirmed that SIRT 1 deacetylates p62 (k295), which interferes with Keap 1 polyubiquitination mediated by E3 ligase, upregulates the expression of p62 protein, and promotes the development of liver carcinogenesis.[22]

The central metabolite acetyl-Coenzyme A (acetyl-CoA) is a substrate of acetyltransferase, which catalyzes protein acetylation and plays an important role in metabolism, gene expression, signal transduction and its cellular processes.[54] Some studies through mouse models and HCC patient samples have found that the synthesis of acetyl-CoA is inhibited and the level of acetyl-CoA is reduced, which leads to hypoacetylation of non-histone proteins and ultimately promotes the development of tumors.[55] The malignant progression of HCC progenitors is closely associated with increased K28 acetylation, and this rise in acetylation levels promotes the response of HCC progenitors to the oncogenic and proinflammatory cytokine IL-6, which subsequently drives the full development of premalignant HcPC to HCC.[56] In summary, histone acetylation modification plays a pivotal role, particularly in the malignant progression of HCC. Studies

have demonstrated that histone deacetylase inhibitors can induce apoptosis in HepG2 liver cancer cells, further highlighting the critical function of histone acetylation in HCC regulatory pathways.[57]

Phosphorylation and Liver Cancer

In the complex regulatory network of HCC, the multiple signal pathways and the phosphorylation status of key proteins play a crucial role. Upregulation of SMAD2 in SMAD signaling could promote HCC cell proliferation,[58] revealing a positive regulatory role of SMAD2 in HCC progression. In addition, different phosphorylated forms of SMAD3 regulate the progression of HCC. The phosphorylation of SMAD3 (pSMAD3C) COOH terminal can transmit signals to inhibit HCC, while the phosphorylation of the SMAD3 (pSMAD3L) junction region promotes the signal of HCC.[23] Metabolic reprogramming is a marker of many cancer types, including liver cancer, it involves various metabolic or nutrient sensing pathways in liver cells to promote rapid tumor growth. Recent studies through diethyl nitrosamine detected phosphorylation signal transducers and transcription activator 3 (p-STAT3), phosphorylated nuclear factor kappa B (p-NFκβ) and Alpha-FetoProtein (AFP) expression, STAT3-NFκβsignaling axis regulates the metabolic profile of hepatocellular carcinoma.[24,25] STAT3 phosphorylation is associated with HCC progression, and phosphorylation at Ser727 activates STAT 3 and enhances HCC cell survival[59] through the Mitogen-activated protein kinase (MAPK) /Extracellular signal-regulated kinase 1/2 (ERK1/2) pathway. Furthermore, Asialogolototin receptor 1 (ASGR1) inhibits the progression of liver cancer[60] by promoting the binding of NeMo-like kinase (NLK) to STAT3 and inhibiting STAT3 phosphorylation. All the above studies have shown the key activation of STAT3 phosphorylation in the progression of liver cancer.

Cellular proteins can be regulated by phosphorylation and dephosphorylation reversible cycle of protein kinases and phosphatases. P-Rex1, as a family member of guanine-nucleotide exchange factor (GEF) for GTP enzyme, is involved in the regulation of cancer cell migration. Downregulation of P-Rex1 inhibits cancer cell migration[26] by reducing phosphorylation of tyrosine kinase receptor c-Met, and phosphorylation of AKT and Erk 1/2. MTOR complex 1 (mTORC1) was used to phosphorylate liver androgen receptor (AR) S96, promote the stability, nuclear localization and transcriptional activity of AR, and then promote the lipogenesis and proliferation of hepatocytes. This effect is associated with in inducing liver steatosis and liver carcinogenesis in mice.[27] Furthermore, dysfunctional p53 signaling is one of the main reasons for the development and development of HCC. Recent results strongly suggest that Krüppel-associated box (KRAB) type zinc-finger protein ZNF498 promotes[28] by attenuated p53 Ser46 phosphorylation and inhibiting p53-mediated apoptosis and iron death.

Glycosylation and Liver Cancer

Protein O-linked N-acetylglucosamine (O-GlcNAc) is a type of glycosylation modification, predominantly present in the cell nucleus. There are two main enzymes involved in the regulation of protein O-GlcNAc modification: O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA). Elevated O-GlcNAc and abnormal glucose metabolism are the hallmarks of HCC,[61–63] and elevated O-GlcNAc contributes to rapid tumor growth. Studies have found that the downregulation of the enzyme Phosphoenolpyruvate carboxykinase 1 (PCK1) in gluconeogenesis can improve the overall O-GlcNAc level of liver cancer and promote the development of liver cancer.[29] Aberrant glycosylation is usually associated with aberrant glycosyltransferase expression in cancer, and HCC pathology contains multiple glycosyltransferases, in which OGT may provide a completely new angle for HCC therapy.[64] Glycosylation-related features can be effectively used for prognostic identification, immune efficacy assessment and substance metabolism in HCC, providing new insights into therapeutic target prediction and clinical decision making.[65]

OGT is a unique glycosyltransferase that previous studies identified by transcriptome sequencing as upregulated in hepatocellular carcinoma tissues associated with nonalcoholic fatty liver disease, and found that OGT plays a role in cancer by promoting tumor growth and metastasis in cell and animal models.[66] Moreover, the membrane protein Caveolin-1 (CAV 1), which regulates the expression of glycosyltransferases and cell glycosylation, was also found that CAV 1 induced cell O-GlcNAc and Liver cancer invasion. Related studies have provided evidence of CAV 1-mediated increase in OGT expression and O-GlcNAc increase, raising a view on a new mechanism of potential HCC metastasis.[30] A further point to highlight that the O-glycosylation of Prohibitin2 (PHB2) Ser161 mediated by related genes promotes the growth and migration of hepatoma cells.[31] O-GlcNAc is crucial for HCC treatment. Some

studies show that O-GlcNAc is a key regulator of hepatic differentiation, and the loss of O-GlcNAc leads to the development of HCC.[67,68]

N-glycosylation refers to the glycan chain playing a crucial role in normal physiological processes through the free-NH 2 base connection with the specific asparagine NXS/T (X=P) in the nascent peptide chain, while abnormal N-glycan modification is closely related to liver cancer progression and malignant transformation.[69,70] The glycosylation level of proteins in cancer cells is closely related to the invasion and migration of cancer. CD44 is a transmembrane glycoprotein, which is significantly overexpressed in liver cancer cells. Studies have shown that N-glycosylation modification of three glycosylation sites (N57, N100 and N110) on CD44 can affect the function of CD44 protein in tumors, including its localization and stability.[71] Crucially, another study data also revealed the N-glycosylation of key sites (N294 and N454) of Mer Tyrosine Kinase (MerTK) in HCC cells, which can stabilize MerTK and drive oncogenic transformation of cells.[32] Also in another study, N-Acetylglucosaminyltransferase IVa (GnT-IVa) enhanced the interaction of integrin β1 with vimentin and promoted the transfer of HCC.[33] The above findings further highlight the importance of glycosylation, especially N-glycosylation, in HCC invasion and metastasis.

Ubiquitination and Liver Cancer

Protein ubiquitination is a process of protein degradation that is involved in the development and development of liver cancer. In the complex process of protein degradation, ubiquitination can be divided into three steps, each of which requires specific functional proteins: ubiquitin-activating enzyme (E1s), ubiquitin-binding enzyme (E2s), and ubiquitin ligase (E3s), which each play unique roles in the disease progression of liver cancer.[72,73] As an important tumor suppressor in vivo, P53 activity is strictly regulated. Recent studies found that DNA primase subunit 1 (PRIM 1) can trigger the ubiquitination and subsequent degradation of P53 by upregulating the ubiquitin-binding enzymes UBE2C and UBE2D1, and then accelerating the progression of liver cancer.[34,35] Moreover, E2s can also act on the atypical tumor suppressor p27, UBE2S interacts with TRIM28 in the nucleus, which together enhance the ubiquitination of p27 to promote its degradation and accelerate the development of liver cancer.[36] Another study found that UBE2O interacts with mitochondrialβ-oxidation enzyme HADHA and mediate its ubiquitination and degradation. And HADHA, as a tumor suppressor, has reduced expression levels in HCC and negatively correlated with UBE2O expression level.[74] Furthermore, another study found that UBE2T overexpression enhanced the oncogenic properties in HCC cell lines through the activation of MAPK/ERK, AKT/mTOR, and Wnt /β-catenin pathways. UBE2T Activating the MAPK-ERK pathway, promoting the nuclear translocation ofβ-catenin and the subsequent epithelial-to -stromal transition (EMT), causing the state conversion of hepatCC cells.[37,38] Further studies revealed that UBE2T also increases pyrimidine metabolism by promoting ubiquitination of AKT K63 junctions, thus promoting the development of HCC.[39] Similarly, the upregulation of UBE2Q1 was also found to promote HCC development of through theβ-catenin-EGFR-PI3K-AKT-mTOR signaling pathway.[75]

The negative regulation of Src protein directly by the E3 ubiquitin ligase TRIM7 and the Src-E3 mTORC1-S6K1 axis inhibited HCC progression.[40] PJA1 is a novel E3 ubiquitin ligase that is a key negative regulator in TGF-βsignaling, and overexpression of PJA1 leads to dysregulation of TGF-βsignaling, activating oncogenes in human HCC and promoting HCC proliferation.[41,42] Furthermore, ubiquitin E3 ligase Ring Finger Protein 146 (RNF146) can activate the AKT/mTOR pathway[43] by promoting ubiquitin proteolysis of PTEN, and more importantly, it can promote the progression of liver cancer, as revealed in Figure 1. And in another study found that the short isoform of PHD Finger Protein 19 (PHF19) interacts with the E3 ligase β-TrCP of the Glioma-associated homologue-1, which activates the Hedgehog signaling pathway to promote the growth of HCC.[44] As an E3 ubiquitin ligase, RNF128 has been shown to be critical in oncogenesis, promoting HCC progression to through activation of the EGFR/MEK/ERK signaling pathway.[45] Similarly, WW Domain Containing E3 Ubiquitin Protein Ligase 1(WWP1) degrades the transcription factor KLF14 through ubiquitination, which then accelerates the proliferation, invasion and migration of Homa cells.[46] RNF20 can regulate NOD-like receptor thermal protein domain associated protein 3 (NLRP3) expression and increase NLRP3 ubiquitination to slow down cancer progression in liver cancer.[76] The latest study found that ubiquitin-specific protease 35 (USP35) is highly expressed in HCC. High expression of USP35 is significantly correlated with the poor prognosis of HCC patients. And it is also proved that inhibition of USP35 expression can damage the malignant properties of HCC tumor cells by increasing the ubiquitination level of Pyruvate Kinase M2 (PKM2).[47] In the NF-κB signaling pathway,

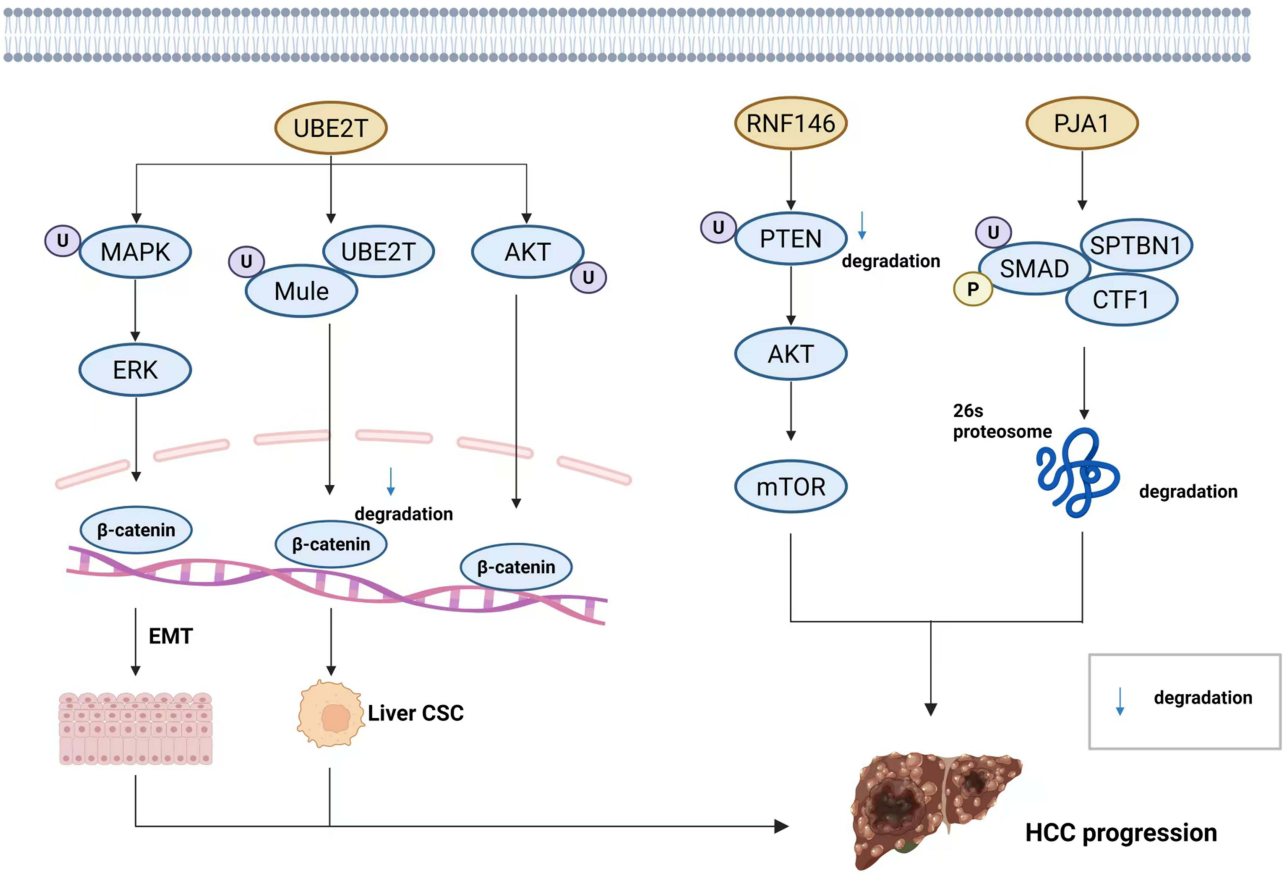

Figure 1 Molecular regulation between the ubiquitin-proteasome system and pathways associated to HCC progression.

Pancreatic progenitor cell differentiation and proliferation factor(PPDPF) and the Receptor Interacting Protein Kinase-1 (RIPK1) interact and promote K63-linked ubiquitination of RIPK1 through recruitment of the E3 ligase TRIM2, inhibiting the development of HCC.[48] Moreover, Serine protease inhibitor E2 (SERPINE2) plays a key role in the metastasis of many tumors. The occurrence of ubiquitination also occurs in the SERPINE2-EGFR axis. SERPINE2 prevents EGFR degradation through E3 ubiquitin ligase c-Cbl-mediated ubiquitination, further promoting liver cancer metastasis.[49]

Other PTMs Were Associated with HCC

In recent years, histone lactfication plays an important role in the regulation of liver cancer progression, the increase of H3 histone lactfication effectively speed up the progress of HCC, such as H3K9la and H3K56la site.[77] Furthermore, H3K56 Lactylation is associated with the up-regulation of Lys 488 acetylation of Pyruvate dehydrogenase complex component X (PDHX), which is common in HCC. It is more helpful for the study of protein post-translational modification in liver cancer.[78] And lactoylation of histones has also become a hot topic in recent liver cancer research. A team found that Pyrroline-5-carboxylate reductase-1 (PYCR1) affects one of the mechanisms of liver cancer progression, which is to reduce the H3K18 lactoylation of Insulin receptor substrate 1 (IRS1) histone, inhibiting the expression of IRS1.[79] Moreover, Zhang et al[80] found that HAT 1, which regulates histone and non-histone proteins, can also participate in succinylation of various proteins, such as histone H3 on succinylation K122, which contributes to epigenetic regulation and gene expression of cancer cells and promotes the progression of liver cancer.

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PTMs with Liver Fibrosis

As a necessary stage for the development of chronic liver disease to cirrhosis and liver cancer, the degree of fibrosis directly affects the disease prognosis. PTMs play a vital role in the changes of liver cells and extracellular matrix (ECM). By finely regulating the key molecular events of liver fibrosis, such as the activation of hepatic stellate cells (HSCs), ECM metabolic imbalance and signaling pathway conduction, they have become the core entry point to reveal the mechanism of liver fibrosis disease, as shown in Table 2.

Acetylation and Liver Fibrosis

Acetylated lysine residues act as epigenetic key sites, modulation of acetylation levels was associated with hepatic stellate cell activation, hepatocyte pyroptosis and activation of inflammatory pathways.[99] Elevated histone acetylation was found in liver fibrosis and cirrhosis, such as H3K9 and H2BK5, but the signaling pathway between gene expression of histone acetylation and HSC activation is unclear.[100] Recent studies have found that hepatocyte specific elimination of

Table 2 PTMS and Liver Fibrosis

PTM	Target Protein/ Key PTM Moderating Enzyme	Mechanism	Outcome	Reference Number
Acetylation	MCRS1	Deletion of the putative SANT domain of MCRS 1 removes HDAC 1 from its histone H3 anchor site, increases histone acetylation of BA transporter genes, and activates FXR in HSCs	Activate HSC and cause liver fibrosis	[81]
	SIRT3	SIRT 3 regulates the acetylation of PINK 1 and NNIPSNAP1 to initiate the mitochondrial autophagy pathway in liver fibrosis, and SIRT 3 overexpression reduces α -SMA and COL1a1 levels	Inhibition of the HSC reactivation	[82]
	TGF-β	KAT 2 A or H3K9ac-associated RNA knockdown, decreased TGF β -mediated FN 1 and SERPINE1	Inhibition of the HSC reactivation	[83]
	Daxx	Daxx binds to the MH1 domain of SMAD 2 and interferes with SMAD 2 acetylation, reducing the transcriptional activity of SMAD2	Inpressed HSC activation and reduced liver fibrosis	[84]
Methylation	Hif-1,NLRP3	Enhanced H3K4 methylation promotes nuclear transport, autophagosome formation and HSC activation, and upregulated NLRP 3 inflammasome-mediated pyroptosis signaling by the inflammasome	Causing the activation of HSCs	[85,86]
	PRMT6	Methylated non-histone proteins, and methylated the R464 residue of ITGA 4	Reduce profibrotic signals in hepatic macrophages and slow liver fibrosis	[87]
Phosphorylation	EGFR/ERK	Hyperphosphorylation of EGFR / ERK	HSC cell activation, aggravating the degree of liver fibrosis	[88]
	SMAD2/3	The phosphorylation cascade of the transcription factor SMAD 2 / 3, the phosphorylated SMAD 2 / 3 accumulated in the nucleus, directly regulates the transcription of profibrotic genes	Both COL and FN 1 were elevated	[89]
	JAK2/STAT3	And JAK 2 and STAT 3 phosphorylation	Transformation of HSC to myofibroblasts	[90]
	p300	C3 transferase inhibitors activate AKT signaling to induce phosphorylation of p300 at serine 1834, and subsequent p300 transfer to the nucleus	Up-regulated transcription of genes that promote HSC activation and transfer	[91]

(*Continued*)

Table 2 (Continued).

PTM	Target Protein/ Key PTM Moderating Enzyme	Mechanism	Outcome	Reference Number
Glycosylation	OGT,RIPK3	OGT inhibits the expression of RIPK 3, a negative regulator of necrotizing apoptosis	Protect the liver from necrotizing apoptosis and inhibit liver fibrosis	[92]
	GLT25D1	GLT25D1 glycosylation	Activating HSCs activation, affecting collagen stability and aggravating liver fibrosis	[93]
Ubiquitination	RNF20	Upregulation of RNF 20 prompted the ubiquitination of H2B	Reduce the symptoms of liver fibrosis in the body	[94]
	TRIM23	Upregulation of TRIM23 expression enhances p53 ubiquitination and attenuates iron death	Promote HSC activation, leading to liver fibrosis	[95]
	SIRT1	Accelerate the degradation and ubiquitination of SIRT 1 and induce apoptosis in hepatocytes	Accelerate liver fibrosis	[96]
	FBXO31	FBXO31 Enhanced the ubiquitination of SMAD 7	The activation of HSC, which accelerated liver fibrosis	[97]
	USP9X	USP 9 X mediates NRP 1 to undergo deubiquitination, and NRP 1 acts through the cytokine TGF- β 1 pathway	Promote HSC activation and liver fibrosis	[98]

Microspherule Protein 1(MCRS1) as an important regulator of histone acetylation, the deletion of the putative SANT domain of MCRS1 removes HDAC1 from its histone H3 anchor site. Increasing histone acetylation of bile acid (BA) transporter gene, disordered BA flox, and activated the Farnesoid X receptor (FXR) of HSCs, causing the occurrence of liver fibrosis.[81]

Deacetylation also inhibits the progression of liver fibrosis. SIRT3, as a mitochondrial deacetylase, specifically regulates the acetylation of PTEN induced putative kinase 1(PINK1) and Nonneuronal SNAP25-like protein 1 (NNIPSNAP1) to initiate the mitochondrial autophagy pathway in liver fibrosis. SIRT3 overexpression reduces α -smooth muscle actin (α -SMA) and Collagen1a1 levels, and suppresses activated in hepatic stellate cells.[82] Conversely, in the SIRT 2-deficient high-fat diet mouse model, the fibrotic phenotype of no fat-accumulating liver tissue and increased expression of genes involved in liver fibrosis, implicated SIRT2 in hepatocyte and hepatic stellate cell activation.[101] Additional studies have shown that senescence exacerbates liver fibrosis through downregulation of SIRT1-induced endothelial cell dysfunction in the sinusoidal liver cells.[102]

TGF-β is identified as an inducer of epithelial stromal transformation in hepatocytes, associated with activation of HSC and apoptosis pathways, thereby initiating liver fibrosis. Aseem et al[83] found that KAT2A or H3K9ac-associated RNA knockdown reduced the TGFβ-mediated increase in Fibronectin 1 (FN1) and SERPINE1. Other studies show that Death-related protein 6 (Daxx) is involved in the TGF-β-induced apoptosis pathway, and Daxx binds to the MH1 domain of SMAD2 and interferes with SMAD2 acetylation, and reduces the transcriptional activity of SMAD2 to reduce liver fibrosis.[84]

Methylation and Liver Fibrosis

Methylation is the addition of uncharged methyl groups to the lysine and arginine residues of histones and other nuclear proteins. Lysine residues can be mono-, di-, or tri-methylated on their ε-amino groups. Previous studies showed that H3K4 methylation is important for the transformation of HSCs to myofibroblasts during HSC transdifferentiation. In general, multiple sites of histone methylation are co-modified to regulate gene expression, including methylation of histone H3, H3K4me2, and H3K4me3.[103] Mechanistically this enhanced H3K4 methylation could promote Hif-1 nuclear transport, autophagosome formation, and HSC activation, and plays a key upregulated role in the NLRP3 inflammasome-mediated cellular pyroptosis signaling pathway.[85,86]

Protein arginine methyltransferase 6 (PRMT 6) is an enzyme that catalyzes the formation of monomethylic and asymmetric dimethyl arginine. It has been reported that PRMT6 can methylate histone H3, enable histone H3 to form H3R2me2a, and act as a repressive marker by blocking the methylation of H3K4, and histones H2A and H4 form H2AR3me and H4R3me, leading to transcriptional activation. In addition, PRMT 6 can methylate non-histone proteins and reduce the profibrotic signaling[87,104] in hepatic macrophages by methyating the R464 residue of the Integrin Alpha-4 (Integrin Alpha-4, ITGA 4), thus slowing the development of liver fibrosis.

Phosphorylation and Liver Fibrosis

In the study of disease progression, classical signaling pathways such as MARK and TGF signaling pathways are often phosphorylated to affect the activation of hepatic stellate cells, such as the upstream signaling pathway of MAPK signaling pathway, EGFR / ERK. In arsenic exposure-induced cell models and rat models, EGFR / ERK can lead to HSC cell activation, and aggravate the degree of liver fibrosis in rats, so liver fibrosis can be alleviated by inhibiting the hyperphosphorylation of EGFR / ERK.[88,105] Moreover, TGF-β ligands bind to heterotetrameric receptor complexes, leading to a phosphorylation cascade of the transcription factor SMAD2/3, and phosphorylated SMAD2/3 accumulated in the nucleus, directly regulate the transcription of important profibrotic genes, such as collagen and fibronectin.[89] Similarly, activation of the JAK2/STAT3 signaling pathway, and phosphorylation of JAK2 and STAT3, prompted conversion from HSC to myofibroblasts,[90] as revealed in Figure 2. The severity of liver fibrosis is usually associated with the PI3K/AKT pathway and with the phosphorylation of key proteins involved. For example, sorting human HSC with high α-SMA showing hyperphosphorylated for AKT / mTOR and Protein kinase C (PKC).[91] The crosstalk of PTM is also noteworthy. E1A binding protein p300 is a histone acetyltransferase that regulates transcription. In HSCs, by

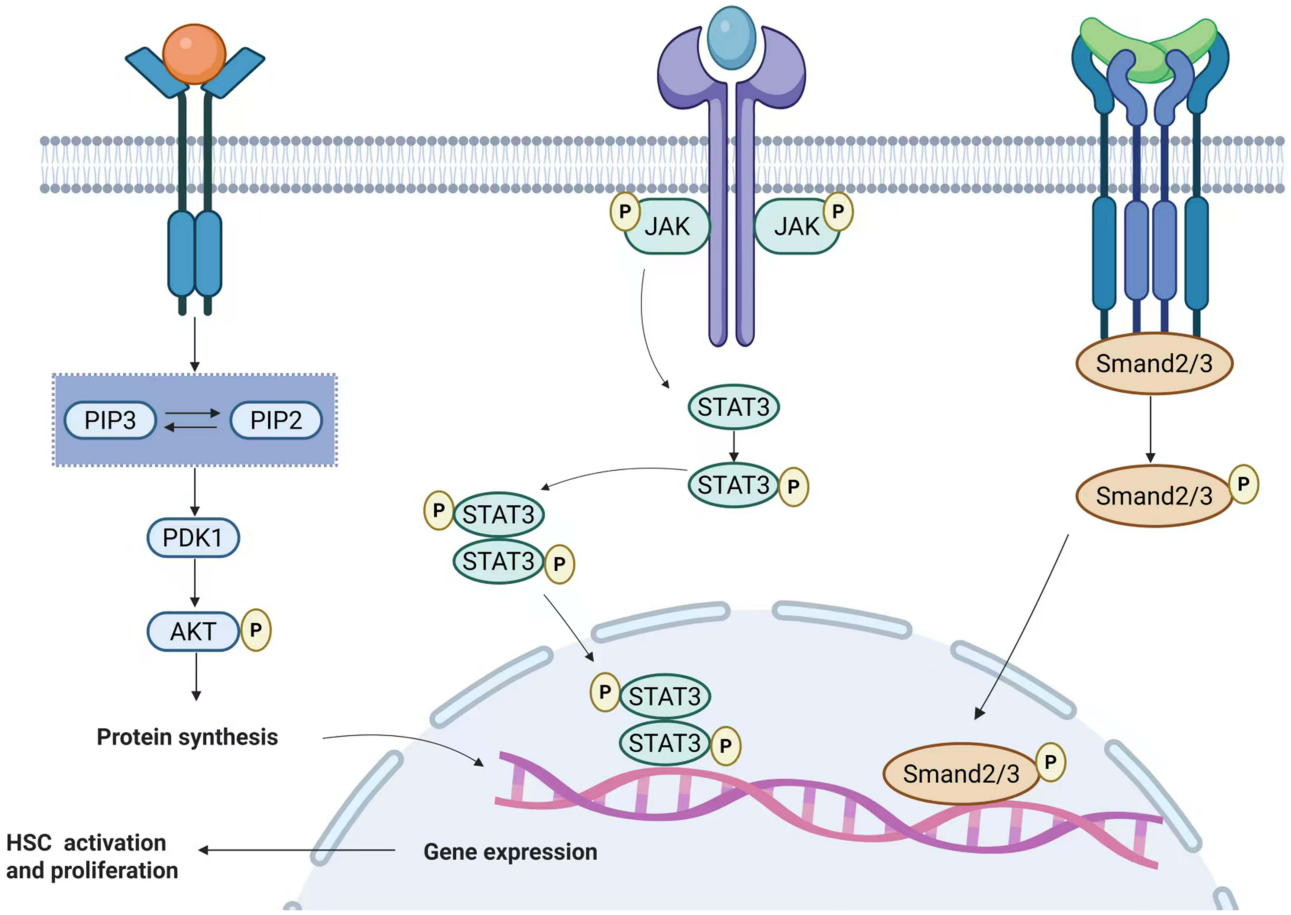

Figure 2 Molecular regulation between phosphorylation of common pathways and HSC activation.

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increasing substrate stiffness, C3 transferase inhibitors were found to activate AKT signaling and induce phosphorylation of p300 at serine 1834, and then p300 to the nucleus, upregulating the transcription of genes promoting HSC activation and transfer.[91]

Glycosylation and Liver Fibrosis

Few studies on glycosylation in liver fibrosis, but some studies have reported that O-GlcNAc modification prevents hepatocyte necrosis and liver fibrosis, and OGT acts as a negative regulator of necrotizing apoptosis by inhibiting RIPK 3 expression.[92] These findings reveal that hepatocyte OGT protects the liver from necrotizing apoptosis, thereby preventing liver fibrosis.

The changes in collagen related to fibrosis and fibrinolysis are mainly changes in the extracellular matrix, and many post-translational modifications occur during procollagen biosynthesis in the rough endoplasmic reticulum to facilitate proper collagen folding, secretion and biological function.[107] In these modifications, glycosylation has not been widely studied. Recently, it has been shown that the upregulation of collagen-β Galactosyltransferase 25 domain 1 (GLT25D1) in HSCs affects the activation of HSCs and collagen stability, promoting the progression of liver fibrosis.[93] Another study found through the C57BL/6 mouse model that loss of O-GlcNAcylation disrupts lipid metabolism, accelerated lipolysis, slowed lipid synthesis, caused liver edema and fibrosis, and altered mitochondrial apoptosis.[108]

Ubiquitination and Liver Fibrosis

The ubiquitination (H2BK120ub) of lysine residue at H2B120 is an important post-translational modification of histone, mainly located in actively transcribed genes. Studies have reported that ring finger protein 20 (RNF 20) is the E3 ligase of ubiquitinated histone H2B120 lysine. The upregulation of RNF 20 significantly inhibits the progression of liver fibrosis through H2B ubiquitination, and reduces the symptoms of liver fibrosis in vivo.[94] Moreover, there is a Tripartite Motif Containing 23 (TRIM23) as an E3 ubiquitin ligase involved in signaling. TRIM23 expression is positively correlated with the severity of liver fibrosis. Upregulation of TRIM23 expression enhances p53 ubiquitination, weakens iron death and promotes the activation of HSC, leading to liver fibrosis.[95] As an anti-fibrotic protein, the downregulation of SIRT1 induces apoptosis in hepatocytes, implying that the accelerated degradation and ubiquitination of SIRT1 can make hepatocyte apoptosis and promote the progression of liver fibrosis.[96]

F-box protein 31 (FBXO31) is a member of the F-box family involved in the ubiquitin-proteasome system. Briefly, FBXO31 enhances the ubiquitination of SMAD 7, which in turn promotes HSC activation and liver fibrosis.[97] Furthermore, Ubiquitin-specific peptidase 9X (USP9X) is a key deubiquitination enzyme with high stability and high activity of Neuropilin 1(NRP1). NRP1 is mainly expressed in activated HSCs. It was found that USP9X mediates deubiquitination of NRP 1, and NRP1can promote HSC activation and liver fibrosis through the cytokine TGF- β1 pathway.[98]

Other Protein Modifications are Associated with Liver Fibrosis

Recent studies have found that some emerging protein modifications are involved in liver fibrosis. Fructose intake can cause nitsylation of intestinal tight junction proteins and adherens junction proteins, in part in a CYP2E1-dependent manner, leading to increased intestinal permeability and the formation of steatohepatitis with hepatic fibrosis.[109] Through RNA-seq and CUT & Tag chromatin analysis, a research team found that lactoylation is involved in the activation of HSC, and that HSC-specific or systemic Hexokinase2 (HK2) deletion can inhibit HSC activation and liver fibrosis in vivo.[110]

PTMs and Alcoholic Liver Disease

Alcoholic Liver Disease (ALD) is caused by the liver damage caused by excessive drinking, early manifestations of simple steatosis, liver cell fat accumulation, and then progress to liver steatosis and alcoholic hepatitis, liver fibrosis, cirrhosis, and even progress to hepatocellular carcinoma, which progress with the cell protein PTMs, as shown in Table 3.

Acetylation and Alcoholic Liver Disease

Ethanol-induced histone acetylation occurs primarily in the H3 sequence, with acetylated histone H3K9 enrichment observed in a mouse alcohol-fed model, and ethanol metabolism supporting lipogenic through histone H3K9 acetylation.[112] In another

Table 3 PTMs and Alcoholic Liver Disease

PTM	Target Protein/Key PTM Moderating Enzyme	Mechanism	Outcome	Reference Number
Acetylation	SIRT1	SIRT 1 suppresses the increase in acetylation	Reduce the damage caused by ethanol	[111]
	SIRT1	Up-regulation of acetylation, nuclear translocation, and release of HMGB 1 was reversed by agonistic SIRT 1	Improve ALD	[111]
	SIRT2	Deacetylation of SIRT 2 decreases C / EBP β ubiquitination, resulting in enhanced protein stability and subsequently increased transcription of LCN 2 from C / EBP β target genes	Improve ALD	[113]
	p53	Inhibition of ethanol oxidation, decreased intracellular acetyl-CoA and histone acetylation levels,	To of hepatic steatosis induced by ethanol	[114]
	NFATc4	Inhibition of acetylation of NFATc4 in RIPK 3-dependent hepatocyte necrotizing apoptotic alcoholic liver disease	Mitigating steatosis in alcoholic liver disease	[115]
Methylation	SAM,SAH	3-Deoxyadenosine inhibited the hydrolysis of SAH, resulting in elevated SAH concentrations, increased lipolysis, and an accompanying abundance of pro-inflammatory cytokines	Fat accumulation and the progression of the disease in fatty liver disease	[116,117]
	MATα1	Alcohol activation of creatine kinase 2 phosphorylates Ser114 of MAT 1 α, promoting interaction with PIN 1 isomerase, causing blockage of its mitochondrial localization, increased MAT 1 α and SAM levels, and increased protein-Lys methylation levels	Upregulation of key mitochondrial proteins involved in the TCA cycle, fatty acid β -oxidation, and oxidative phosphorylation pathways, slowing down ALD disease	[118]
Phosphorylation	PDPK1	Inhibit the phosphorylation of PDPK 1 (ser241)	Improve ALD	[119]
	PPARα	Inflammatory factor-activated NIK recruits MEK 1 / 2 and ERK 1 / 2 to form complexes and downregulates PPAR α phosphorylation	Disdestroy fatty acid oxidation in liver and improved ALD	[120]
	EGFR,ERK1/2, P2Y2	Both phosphorylation upregulation of EGFR and ERK 1 / 2 are inhibited by P2Y2 receptors	Reduce hepatocyte apoptosis and slow down the progression of alcoholic liver disease	[121]

study, it was found that ethanol induced an increase in H3K9 acetylation, and some of the butanol extract inhibited the increase in acetylation by SIRT1, reducing the damage caused by ethanol.[111] The study reported that High mobility group protein 1 (HMGB 1) mRNA levels were increased in patients with clinical Alcoholic liver injury (ALI), While the decreased SIRT1 expression. HMGB1 acetylation and translocation in a model establishing ALI cells and mice, agriting SIRT1 reversed the upregulation of HMGB 1 acetylation, nuclear translocation and release. Briefly, SIRT1 inhibits the acetylation of HMGB1, improving the ALD.[112] Moreover, SIRT2- mediated deacetylation at lysines 102 and 211 reduces C/EBPβ ubiquitination, resulting in an enhanced protein stability. Subsequently increased transcription of Lipid carrier protein 2 (LCN2) in the target gene of CCAAT/enhancer binding protein β (C/EBPβ). Hepatic deacetylation of C/EBPβ and LCN2 compensation reversed the SIRT2 deletion-induced deterioration of ALD in mice. Meanwhile, the clinical samples suggested a positive correlation between C/EBPβ protein expression and SIRT2 and LCN2 expression in the liver of ALD patients, and negatively correlated with the development of ALD.[113] Activation of SIRT 1 and SIRT 2 contributes to ALD prevention. It has been demonstrated that ethanol consumption leads to microtubule hyperacetylation, which could explain the ethanol-induced protein transport

defects. Because almost all steps of the lipid droplet life cycle are dependent on microtubules, and because microtubule acetylation leads to lipogenic.[123]

On the other hand, the tumor suppressor p53 alleviated hepatic steatosis induced by ethanol by inhibiting ethanol oxidation and decreased intracellular acetyl-CoA and histone acetylation levels.[114] In alcoholic liver disease with RIPK 3-dependent hepatocyte necrotic apoptosis, steatosis in ALD is also slowed by inhibiting acetylation of Nuclear Factor Of Activated T Cells 4 (NFATc4).[115] In conclusion, the acetylation of histones and nuclear proteins promotes the aggravation of fat accumulation and eventually leads to ALD.

Methylation and Alcoholic Liver Disease

Methylation of lysine and arginine is a reversible, dynamic process, mediated by Protein lysine methyltransferase (PKMTs) and Protein arginine methyltransferase (PRMTs), with S-adenosylmethionine (SAM) as the methyl donor,[124] and the recipient is usually the ε -amino group of lysine and the guanidine group of arginine. Protein methylation levels were significantly reduced in ethanol-exposed experimental rodents, cells, and alcohol disorders due to increased fatty S-adenosine high cysteine (SAH), a strong inhibitor of transmethylation response. Changes in methylation were found in chronic ethanol-induced in rat adipocytes,[125] associated with elevated SAH levels. This was also observed in cultured adipocytes treated with 3-deoxyadenosine, which inhibited SAH hydrolysis, resulting in increased SAH concentrations and increased lipolysis. These changes thus lead to decreased levels of adipocyte differentiation factors accompanied by large amounts of pro-inflammatory cytokines. Thus, reduced methylation of dysfunctional adipocytes and adipose tissue contributes to fat accumulation and disease progression of fatty liver disease. Alcohol-mediated changes or decreases in the methylation of proteins, including histones, can be reversed by administration of SAM or betaine[116,117](trimethylglycine) to restore methionine homeostasis.

Another recent study mentioned mitochondrial Methionine adenosyl transferase α1 (MATα1), which catalyzes the synthesis of the biological methyl donor S-adenosylmethionine, reduced MATα1 activity and mitochondrial dysfunction occur in alcohol-related liver disease. Mechanistically, alcohol activation of creatine kinase 2 phosphorylates by the Ser114 of MAT1α and promotes its interaction with PIN1 isomerase,[118] causing its blocked mitochondrial localization. These changes lead to increased MAT1α and SAM levels, and increased protein-Lys methylation, up-regulation of several key mitochondrial proteins involved in the TCA cycle, fatty acid β-oxidation and oxidative phosphorylation pathways, ultimately achieving the goal of slowing the disease progression of ALD. Collectively, the methylation of non-histone arginine residues is also important in the regulation of mitochondrial fat metabolism.

Phosphorylation and Alcoholic Liver Disease

3-Phosphoinositide-dependent protein kinase 1 (PDPK1) is a phospho-regulated kinase that plays a central role in the activation of various signaling pathways and cellular processes. Studies have shown that ALD can be alleviated by inhibiting the phosphorylation of PDPK1 (ser241).[119] Downregulating the phosphorylation of inflammatory pathways can achieve the effect of treating ALD. Mechanistically, inflammatory factors activate the inflammatory pathway component NIK recruits MEK1/2 and ERK1/2 to form a complex, and downregulate the phosphorylation of peroxisome proliferator-activated receptor α (PPARα), and destroy hepatic fatty acid oxidation.[120] Through an alcohol-fed mouse model, a team found that the phosphorylation of EGFR and ERK1/2 was effectively inhibited by P2Y2 purinergic receptors, thus playing a role in reducing hepatocyte apoptosis and slowing the progression of alcoholic liver disease.[121]

PTMs and Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a kind of metabolic stress liver injury that is closely related to insulin resistance and genetic predisposition. The disease spectrum mainly includes Non-alcoholic steatohepatitis (NASH), cirrhosis, etc., and the in vivo pathways of disease conversion are closely related to PTMs such as acetylation, phosphorylation and glycosylation, as shown in Table 4.

Table 4 PTMs and Non-Alcoholic Liver Diseases

PTM	Target Protein/Key PTM Moderating Enzyme	Mechanism	Outcome	Reference Number
Acetylation	H3K27	H3K27 activates lncRNA NEAT1 transcription and modulates miR-212-5p / GRIA 3	Promote fat accumulation in NAFLD	[126]
	LBP	LBP activates through C/ EBP β -SCD mediated by H3K27ac acetylation	Leading to a disturbed lipid metabolism	[127]
	NR2F6	NR2F6 Is able to bind directly bound to the CD36 promoter region in hepatocytes and increase enrichment of SRC-1 and histone acetylation of its promoter	Adipose degeneration	[128]
	Srit1	QKI 5 is deacetylated by Srit 1	Lighten NAFLD	[129]
	Srit2	Srit 2 stabilizes the HNF 4 α protein by binding to and deacetylation with the HNF 4α protein on lysine 458	Prevention of hepatic steatosis and metabolic disorders	[130]
	SIRT3	SIRT 3 mediates ACSF3 for deacetylation	Protection against the hepatic fatty acid metabolism disorders induced by a high-fat diet	[131]
	MRG15	A large amount of MRG 15 interacts with TUFM and deacetylates TUFM, accelerating the degradation of deacetylated TUFM in the mitochondria and reducing TUFM in the liver	Impaired mitophagy, increased oxidative stress and activation of the NLRP 3 inflambody pathway drive progression of NASH	[132]
Phosphorylation	RPS6	Reduced phosphorylation of hepatic RPS 6	Control of lipid synthesis and improve NAFLD	[133]
	VEGFR1	Inhibiting the phosphorylation of the JNK / p38 MAPK pathway	Reduce oxidative stress and inflammatory responses and improve liver structure and liver function	[134]
	GSTM2	Blocking the phosphorylation at the ASK1 N terminus	Improve NASH	[135]
Glycosylation	IP6K1	IP6K1 Deficiency in Mouse Liver Significantly Reduces O-GlcNAc Glycosylation Levels	A protective effect on the development of NAFLD/NASH.	[136]
	And the SGLT 2 inhibitors	SGLT2 inhibition inhibits glucose uptake in hepatocytes	Reduce steatosis	[137]

Acetylation and Non-Alcoholic Liver Disease

Acetylated histones are not only involved in protein activity, but also affect lipid accumulation as well as metabolic disorders, such as acetylation of H3K9ac in high fat diet-induced gene expression.[138] Mechanistically, it has been shown that histone H3K27 activates lncRNA NEAT1 transcription and regulates miR-212-5p / GRIA3 to promote fat accumulation in NAFLD.[126]

In Oleic palmitic acid (OPA), non-histone acetylation increased after OPA treatment, and the acetylation of histones H3K9, H4K8 and H4K16 was found to accelerate, and acetylated histones affected through a mediated pathway.[139] Furthermore, Lipopolysaccharide-binding protein (LBP) triggers lipid metabolism disorder through C/EBP β-SCD activation.[127] In addition to the nuclear receptor family, nuclear receptor subfamily 2F group member 6 (NR2F6) is significantly upregulated in obese mice and the liver of NAFLD patients. NR2F6 is able to directly bind to the CD36 promoter region in hepatocytes and increase the enrichment of Steroid receptor coactivator-1 (SRC-1) and histone acetylation of its promoter, leading to steatosis.[128]

In addition to direct effects of histones, nonalcoholic liver disease has been associated with partial deacetylases. Numerous studies have found that aerobic exercise alleviates NAFLD[140] by activating Srit 1 and inhibiting Drp 1

acetylation and apparently altered mitochondrial dysfunction. Moreover, Srit1 was also found to reduce the acetylation level of QKI 5 in the mouse model of NAFLD. QKI 5 is deacetylated at by Srit 1, which helps to slow the progression of NAFLD in mice.[129] And through obese mice and cells, it was found that Srit2 binds and deacetylates protein of Hepatic nuclear factor 4α (HNF4α) on lysine 458, and then stabilizes HNF4α, thus achieving the purpose of preventing hepatic steatosis and metabolic disorders.[130] Hepatic fatty acid metabolism disorder is a key pathogenic mechanism of non-alcoholic fatty liver disease and is associated with hyperacetylation of mitochondrial enzymes. In the Srit3/ACSF3 pathway, Srit 3 mediates ACSF 3 for deacetylation and protects against the hepatic fatty acid metabolism disorder induced by a high-fat diet.[131] Further studies on mitochondria showed that acetylation of Mortality factor 4-like protein 1 in mitochondria (MRG15) -mitochondrial Tu translation elongation factor (TUFM) pathway was closely associated with NASH, elevated MRG15 levels were found in liver of humans and mice with NASH. Briefly, inflammatory cytokines in NASH liver stabilized MRG15 by increasing their acetylation. In the outer mitochondrial membrane, a large amount of MRG 15 interacts with TUFM and deacetylates TUFM, deacetylated TUFM accelerates degradation in mitochondria, and eventually reduced TUFM in the liver causes impaired mitophagy, increased oxidative stress and NLRP3 inflambody pathway activation, prompting NASH progression.[132] Furthermore, lactate accumulates in the liver of patients during NAFLD progression, and studies show that acetylation of enzymes involved in lactate metabolism leads to impaired lactate clearance and exacerbates NAFLD progression.[141]

Phosphorylation and Non-Alcoholic Liver Disease

Phosphorylation is also critical in improving the mechanism of NAFLD. Some studies say that inhibiting mitochondrial oxidation phosphorylation by downregulating TNF6 and further downregulating inflammatory cytokines to reduce inflammation and improve lipid disorder.[142] Moreover, it is also found in the AMPK classical pathway that liver ribosomal protein S6 is the downstream target of AMPK and mTORC1.[133] Aerobic exercise can reduce the phosphorylation of liver ribosomal protein S6, control the synthesis of lipids, and play a role in improving NAFLD. AKT is also one of the core mechanisms of phosphorylation, which mainly affects NAFLD through the regulation of insulin resistance.[143] Conversely, loss of phosphorylation can also promote the development of non-alcoholic liver disease. It has been proposed that bile acids and intestinal bacteria are greatly altered in transgenic mice lacking FGF15/19-SHP phosphorylation and accelerate the development of non-alcoholic liver disease.[144]

After the activation of vascular endothelial growth factor receptor 1 (VEGFR1) in the liver of NAFLD rats, the phosphorylation of the JNK/p38 MAPK pathway is inhibited, thus alleviating oxidative stress and inflammation and improving liver structure and liver function.[134] The apparent downregulation of protein phosphorylation in the liver of high-fat-fed mice suggests a molecular link between protein phosphorylation and reduced lipolysis.[145] Another study found that the phosphorylation downregulates PKM 2 by PKM 2-ARG-246, thus regulating the M1 polarization of rat primary Kupffer cells (KCs) and inhibiting the inflammatory response of liver tissue to treat NAFLD.[146] Hepatocyte glutathione S-transferase Mu2 (GSTM2) is an endogenous repressor that prevents NASH progression to by blocking ASK1 N-terminal phosphorylation.[135]

Glycosylation and Non-Alcoholic Liver Disease

O-GlcNAc glycosylation modification is an important regulation of non-alcoholic liver disease protein post-translational modification, elevated O-GlcNAcylation is not only associated with diabetes diseases such as state and cancer.[147] O-GlcNAc signaling in transduction nutrition regulation of lipid metabolism plays a key role. High fat diet usually lead to excessive fat deposition, adverse effects on the body. Recently, it has been suggested that high fat may activate O-GlcNAcylation and regulate lipid synthesis by affecting the AMPK/ACC pathway.[148]

Furthermore, studies have demonstrated that inositol 6-phosphate kinase 1 (IP6K1) is upregulated in the liver tissues of patients with non-alcoholic steatohepatitis (NASH). IP6K1 has been shown to interact with O-GlcNAc transferase (OGA), an enzyme responsible for reducing protein O-GlcNAc glycosylation levels, suggesting that IP6K1 may regulate this modification's homeostasis. Further in vivo studies confirmed that in mice with systemic IP6K1 deficiency, protein O-GlcNAc glycosylation levels were significantly reduced. This metabolic alteration was accompanied by enhanced systemic metabolism and decreased body fat accumulation, ultimately exerting a protective effect on the development of

non-alcoholic fatty liver disease (NAFLD) and NASH.[136] While OGT regulation by translational control feedback maintains intracellular O-GlcNAc homeostasis. O-GlcNAc acylation is up-regulated in the liver with steatohepatitis and animal models, and finding that downregulation of OGT in NAFLD hepatocytes ameliorates diet-induced liver injury in both in vivo and in vitro models. Meanwhile, proteomic studies show that mitochondrial proteins undergo excessive O-GlcNA acylation in the liver of mice with steatohepatitis. Using in vitro and in vivo models of NAFLD, the researchers realized that OGT inhibition restored mitochondrial oxidation and reduced liver lipid content.[149] Furthermore, Sodium-glucose cotransporter 2 (SGLT 2) inhibitors reduce steatosis in NASH. Studies have demonstrated increased expression of SGLT 2 in NASH and shown that SGLT2 inhibitors inhibit glucose uptake of[137] in hepatocytes and regulate metabolism.

TCM Regulates Protein Posttranslational Modification to Prevent and Treat Liver Diseases

In recent years, traditional Chinese medicine in the clinical treatment of liver disease play a unique curative effect. Traditional Chinese medicine treatment has multi-target, multi-component, multi-level advantages. Herbal extract hydroxygenkwanin can inhibit class I HDAC expression, to induce the expression of tumor suppressor p21, and promote the acetylation of p53 and p65, inhibit the migration and invasion of liver cancer cells and promote liver cancer cell apoptosis.[150] A recent study established a hepatoma cell model, which showed that mulberry polyphenol extract (Mulberry polyphenol extracts, MPE) caused autophagy in Hep3B cells and inhibited the growth of Hep3B cells.[151]

Moreover, the effect of regulating liver fibrosis process through acetylation is also reflected in TCM treatment. Curcumin can activate SIRT1, promote deacetylation of Atg 5, and enhance its protein-protein interaction function, thus inducing autophagy in hepatic stellate cells and reducing liver fibrosis.[152] The STAT3 signaling pathway is associated with the activation of HSC. Briefly, Chrysophanol 8-O-Glucoside from rhubarb significantly inhibited the expression of MMP2, the downstream genes of p-STAT3 and STAT3 in the nucleus, and decreased the mRNA and protein expression of HSC activation markers α-SMA and collagen, reaching liver-preserving.[153]

Liuwei Wuling (LWWL) tablet mainly contains six Chinese medicine formula, which is often used to nourish liver and kidney and remove toxic substances. Some studies have shown that LWWL regulates the expression of SMAD 2/3 and phosphorylation of SMAD3 and up-regulates the expression of SMAD7, which significantly prevents the activation of TGF-β/ SMAD signaling pathway. Meanwhile, LWWL regulates the expression of inflammatory factors and suppresses the activation of NF- κB p65 activation and I κ B α phosphorylation, and reduces rat liver fibrosis[154] after bile duct ligation. The Chinese herbal medicine, Gan Shen Fu Fang (GSFF) consists of danphenolic acid B and diammonium glycyrrhizate. GSGF reduced inflammation and inhibited HSC-T6 cell activation and liver fibrosis progression by downregulating ERK and downregulating NF- κB expression.[155]

A large part of the advantage of TCM lies in that it contains various active ingredients. Studies found that the active ingredient Kinsenoside increased the phosphorylation of UNC51-like kinase-1 (ULK1), which increased the level of the autophagy marker LC3A/B, thus activating AMPK-dependent autophagy to reduce alcoholic liver injury.[156] The active ingredient anthocyanins in honeysuckle, inhibited the expression of SREBP1 and enhanced the phosphorylation of AMPK, and improved the ethanol-induced histological changes and lipid droplet.[157] Furthermore, PLR flavonoids (PLF) and puerarin reduce alcohol-induced hepatic steatosis in juvenile zebrafish by increasing the phosphorylation of AMPKα and reducing the total protein level of ACC1.[158] Magnolol suppresses oxidative stress, reduces inflammation, and prevents alcohol-induced liver injury[159] by upregulating the phosphorylation of PI3K and AKT. Another experiment found that the yellow pigment monascin (MS) and ankaflavin (AK) of Aspergillus fermented rice inhibited the phosphorylation of MAPK family and prevented the damage of alcohol to the liver.[160]

In NASH, some Chinese medicines reduce inflammation and reduce fat accumulation and degeneration by down-regulating glycation in signaling pathways. Curcumin attenuates the severity of hepatic steatosis by reducing the dependence of O-GlcNAcylation on nuclear factor-κB (NF-κB) in inflammatory signaling.[161] Another natural polyphenolic flavonoids, Silibinin reduced inflammation was also due to the inhibition of the O-GlcNAcylation-dependent NF-κB signaling to achieve the treatment of NASH.[162]

Pterostilbene (PTS) has good liver-sparing activity and attenuated RIPK 3-dependent hepatocyte necrotic apoptosis[115] after ethanol exposure by SIRT 2-mediated deacetylation of NFATc4. Kaempferol and nicotiflorin[163] inversely enhanced SIRT1 levels, then reduced the acetylation of FXR, and significantly alleviated oxidative stress and lipid accumulation in the liver. Notably, The researchers found that some flavonoids compounds promote SIRT1 expression makes related protein site deacetylation, so as to achieve the purpose of alleviating nonalcoholic liver disease. For example, Berberine (BBR) has been widely used in the treatment of NAFLD. BBR can increase the expression of SIRT 1, make CPT 1 A at Lys675 deacetylation, thus inhibiting its ubiquitin-dependent degradation, and reduce nonalcoholic hepatic steatosis.[164] Oxyberberine(OBB), a metabolite of BBR, inhibited the abnormal phosphorylation of Insulin receptor substrate-1, (IRS-1) and upregulated the expression and phosphorylation of downstream proteins such as PI3K and p-AKT/AKT, and showed excellent characteristics of AMPK activator, which significantly attenuated hepatic insulin signaling to improve metabolism and maintain lipid homeostasis.[165] Esculin improved methionine and choline deficientdiet-induced NASH, and further studies showed that Esculin increased SIRT 1 expression levels, decreased NF-κB acetylation levels, and downregulated SIRT1 / ac-NF- κ B signaling pathway to activate.[166] C-phycocyanin increased the phosphorylation of AMPK and ACC in hepatocytes to improve hepatic lipid accumulation and inflammatory[167] in mice. Similarly, elevations in AMPK and ACC phosphorylation were also found in the mechanisms that alleviate non-alcoholic steatosis and insulin resistance of Polygonum multiflorum extract by regulating protein expression in hepatic lipid metabolism and glucose transport.[168] In high fatty liver cells, proteins not only undergo a decrease in phosphorylation, Some proteins will also have elevated phosphorylation, For example, by constructing a co-culture system of hepatocytes and BMDMs, studies have found that metabolic load upregulates the phosphorylation of TBK1, leading to the activation of NF- κ B signaling pathway, and elevated the expression of monocyte chemotactic protein-1 (MCP 1), thus inducing macrophage recruitment and accelerating the inflammatory. Gentiana scabra can inhibit TBK1 phosphorylation and MCP 1 expression, and inhibit the recruitment of proinflammatory macrophages, thus generating efficacy for metabolic dysfunction and inflammation.[169]

In summary, traditional Chinese medicine (TCM) demonstrates unique value in the clinical prevention and treatment of liver diseases, with its multi-component, multi-target, and multi-level integrated regulatory advantages becoming increasingly prominent. Various active components of Chinese medicine and compound preparations can regulate key signal pathways to achieve post-translational modification of proteins, and then intervene in liver cancer, liver fibrosis, alcoholic liver disease and NASH. Specifically, hydroxycoronoidin and MPE inhibit liver cancer progression by suppressing HDAC expression, AKT/mTOR phosphorylation, and regulating p21, p53, or autophagy-related mechanisms. Curcumin, rhubarb-derived components, and Liuweiwuling tablets intervene in SIRT1, STAT3, TGF-β/SMAD, and NF-κB pathways to regulate acetylation and phosphorylation processes, thereby alleviating liver fibrosis. In metabolic-related liver injury, ingredients like Kinsenoside, anthocyanins in honeysuckle, and puerarin activate AMPK, regulate lipid metabolism proteins such as SREBP1 and ACC1 to improve fatty degeneration and inflammatory responses. Additionally, components like Esculin and BBR regulate SIRT1/NF-κB and AMPK pathways to alleviate inflammation and insulin signaling abnormalities, thus delaying NASH progression. This systematic elucidation of mechanisms not only reveals the molecular basis of TCM's multi-pathway and multi-level regulation through protein modifications in liver diseases, but also provides new scientific insights and evidence for personalized drug therapy targeting different pathological stages and molecular phenotypes. The mechanisms of the above TCM extracts and TCM compound for the improvement of liver disease through protein post-translational modification are detailed in Table 5.

Conclusion and Outlook

This paper outlines the roles and pathway mechanisms mediated by PTMs in liver diseases, especially for TCM that can interfere in liver diseases by regulating protein post-translational modification. It indicates that PTMs function in regulating protein function, maintaining cell homeostasis, regulating signaling and regulating gene expression in normal cellular molecular mechanisms. PTMs themselves and their crosstalk play an important role in the progression of liver disease. For example, studies conducted a thorough comprehensive analysis of HCC by driving PTMs, proposed PTPN 2-STAT 1-AOX1 for HCC development, and provided multiple databases of PTMs in HCC.[170] Increasing evidence

Table 5 Protein Posttranslational Modification and TCM Treatment

Herbal Extracts/ Medicine Compounds	Liver Disease Management	Target Protein/Key PTM Moderating Enzyme Targets	Mechanism	Outcome	Reference Number
Hydroxygenkwanin	HCC	HDAC	Inhibiting class I HDAC expression, inducing the expression of the tumor suppressor p21, and promoting the acetylation of p53 and p65	Inhibit migration and invasion of and promote apoptosis of HCC cells	[150]
MPE		AKT,mTOR	Inhibition of both AKT and mTOR phosphorylation	Cause autophagy in HCC cells and inhibit the growth of HCC cells	[151]
Curcumin	Liver fibrosis	SIRT1	Activating SIRT 1, promoting Atg 5 deacetylation, and enhancing the protein -protein interaction function	Induce autophagy in hepatic stellate cells and reduced hepatic fibrosis	[152]
Chrysophanol 8-O-Glucoside		STAT3	Suppressed the expression of MMP 2, a downstream gene of p-STAT 3 and STAT3 in the nucleus	Reduce the mRNA and protein expression of α -SMA and collagen to achieve the liver preservation effect	[153]
LWWL		TGF-β/SMAD	Inhibition of SMAD 2 / 3 expression and phosphorylation of SMAD 3, and downregulation of activation of NF-κB p65 and phosphorylation of I κ B α	Regulate the expression of inflammatory factors, inhibit HSC activation and alleviate liver fibrosis	[154]
GSFF		ERK	Downregulation of ERK phosphorylation and the expression of NF-κB	Reducthe inflammatory response, inhibited HSC activation and reduce liver fibrosis	[155]
Kinsenoside	ALD	ULK1 (Ser555), AMPK	Increasing the phosphorylation level of AMPK and promoting the phosphorylation of ULK 1 (Ser555)	Increasing the levels of the autophagy marker LC3A / B further activated AMPK-dependent autophagy and alleviated alcohol-induced liver injury	[156]
Anthocyanin		SREBP1, AMPK	Inhibition of SREBP1 expression and enhanced phosphorylation of AMPK	Improve ethanol-induced histological changes and lipid droplets, and reduce alcoholic fat accumulation	[157]
PLF and puerarin		AMPKα	Increase in the phosphorylation of AMPK α	To of alcohol-induced hepatic steatosis	[158]
Magnolol		PI3K,AKT	Up-regulated the phosphorylation of PI3K and AKT	Inhibit oxidative stress, reduce the inflammatory response, and prevent alcoholic liver injury	[159]
MS and AK		MAPK	Inhibiting the phosphorylation of the MAPK family	Prevention of liver damage by alcohol	[160]
Silibinin		NF-κB	O-GlcNAcylation inhibition of NF-κB	Reduce inflammation	[162]
PTS		SIRT2, NFATc4	And SIRT 2 mediates the deacetylation of NFATc4	Attenuated RIPK 3-dependent hepatocyte necroptotic apoptosis	[115]

(*Continued*)

Table 5 (Continued).

Herbal Extracts/ Medicine Compounds	Liver Disease Management	Target Protein/Key PTM Moderating Enzyme Targets	Mechanism	Outcome	Reference Number
Kaempferol and nicotiflorin	NAFLD	SIRT1,FXR	Enhancing SIRT 1 levels and decreasing FXR acetylation	Relief oxidative stress and lipid accumulation in the liver	[163]
Berberine		SIRT1,CPT1A	Increasing the expression of SIRT 1 deacetylates CPT 1 A and further suppresses the ubiquitin-dependent degradation of CPT 1 A	Reduction of non-alcoholic hepatic steatosis	[164]
Oxygen berberine		IRS-1	Inhibiting the aberrant phosphorylation of IRS-1 And upregulated the expression and phosphorylation of downstream proteins such as PI3K and p-AKT / AKT	Improve hepatic insulin signaling and improve NASH	[165]
Esculin		SIRT1 /ac-NF -κB	Increasing SIRT 1 expression levels and decreasing NF- κB acetylation levels	Relief of non-alcoholic liver disease	[166]
C-phycocyanin		AMPK	Improve the phosphorylation of AMPK and ACC in hepatocytes and activate the AMPK pathway	Improved hepatic lipid accumulation and inflammation	[167]
Gentiana scabra		TBK1	Inhibition of TBK 1 phosphorylation and MCP 1 expression	Inhibit the recruitment of proinflammatory macrophages	

suggests that PTMs targets are important for studying the pathological process of nonalcoholic liver disease, alcoholic liver disease, liver fibrosis, and liver cancer.

TCM has great advantages in the treatment of chronic liver disease, containing rich bioactive ingredients has the function of protecting the liver and gallbladder. In the study of the molecular mechanism of TCM treatment of liver diseases, it plays a role through multi-components, multi-targets and multi-pathway ways. Crucially, PTMs as the key mechanism of regulating protein function, may be one of the important molecular basis of traditional Chinese medicine. For instance, with the clinical application of *Salvia miltiorrhiza* Bunge-*Reynoutria japonica* Houtt. drug pair in the treatment of chronic liver disease, its core metabolite, Luteolin, can relieve NAFLD by inhibiting the phosphorylation of PI3K-AKT-mTOR signaling pathway and inducing autophagy.[171] Danphenolic acid B (Salvianolic acid B, SalB) of Salvia miltiorrhiza inhibited the activation of HSCs and alleviated liver fibrosis by mediating TGF-β/ SMAD and MAPK pathway ways and phosphorylation of SMAD2/3 and SMAD2 at the C end (P-SMAD2C), while increasing the phosphorylation of SMAD 3 at the C end (P-SMAD3C).[172]

PTMs combined with TCM has important scientific significance and clinical application value. By regulating PTMs, TCM can intervene in the pathological process of liver diseases through multiple targets and multiple ways, providing new ideas and methods for the treatment of liver diseases. Future studies should further reveal the molecular mechanisms and drive the development of novel targeted drugs or natural drugs.

Abbreviations

ACC, Acetyl-CoA Carboxylase; ACC1, Acetyl-CoA Carboxylase 1; ACSF3, Acyl-CoA Synthetase Family Member 3; AFP, Alpha-FetoProtein; ALD, Alcoholic Liver Disease; ALI, Alcoholic Liver Injury; AMPK, AMP-activated Protein

Kinase; AR, Androgen Receptor; ASGR1, Asialoglycoprotein Receptor 1; ASK1, Apoptosis Signal-regulating Kinase 1; Atg5, Autophagy-related protein 5; BA, Bile Acid; BBR, Berberine; CAV1, Caveolin-1; CCL5, CC motif Chemokine Ligand 5; C/EBPβ, CCAAT/Enhancer Binding Protein Beta; COL1a1, Collagen Type I Alpha 1 Chain; CPT1A, Carnitine Palmitoyltransferase 1A; CYP2E1, Cytochrome P450 2E1; Daxx, Death-associated protein 6; Drp1, Dynamin-related protein 1; ECM, Extracellular Matrix; Egr1, Early Growth Response 1; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-to-Mesenchymal Transition; ERK, Extracellular Signal-regulated Kinase; FBXO31, F-box Protein 31; FN1, Fibronectin 1; FXR, Farnesoid X Receptor; GLT25D1, Collagen Beta(1-O)Galactosyltransferase 1; GnT-Iva, N-Acetylglucosaminyltransferase IVa; GRIA3, Glutamate Ionotropic Receptor AMPA Type Subunit 3; GSFF, Gan Shen Fu Fang; GSTM2, Glutathione S-transferase Mu 2; HADHA, Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex Subunit Alpha; HAT, Histone Acetyltransferase; HAT1, Histone Acetyltransferase 1; HCC, Hepatocellular Carcinoma; HDAC, Histone Deacetylase; HGF, Hepatocyte Growth Factor; HIF-1α, Hypoxia-Inducible Factor 1 Alpha; HK2, Hexokinase 2; HMGB1, High Mobility Group Box 1; HNF4α, Hepatocyte Nuclear Factor 4 Alpha; HSCs, Hepatic Stellate Cells; IP6K1, Inositol Hexakisphosphate Kinase 1; IRS1, Insulin Receptor Substrate 1; ITGA4, Integrin Alpha-4; JAK2, Janus Kinase 2; KAT2A, Lysine Acetyltransferase 2A; KCs, Kupffer Cells; Keap1, Kelch-like ECH-associated Protein 1; KLF14, Krüppel-like Factor 14; LBP, Lipopolysaccharide-binding Protein; LCN2, Lipocalin 2; LSD1, Lysine-specific Demethylase 1; LWWL, Liuwei Wuling Tablet; MAPK, Mitogen-activated Protein Kinase; MATα1, Methionine Adenosyltransferase Alpha 1; MCP1, Monocyte Chemotactic Protein-1; MCRS1, Microspherule Protein 1; MEK, MAPK/ERK Kinase; MerTK, Mer Tyrosine Kinase; MMP2, Matrix Metallopeptidase 2; MPE, Mulberry Polyphenol Extract; mTOR, Mechanistic Target of Rapamycin; mTORC1, mTOR Complex 1; NAFLD, Non-alcoholic Fatty Liver Disease; NASH, Non-alcoholic Steatohepatitis; NF-κB, Nuclear Factor Kappa B; NFATc4, Nuclear Factor Of Activated T Cells 4; NIK, NF-kappaB-Inducing Kinase; NLRP3, NOD-like Receptor Thermal Protein Domain Associated Protein 3; NIPSNAP1, Nonneuronal SNAP25-like Protein 1; NRP1, Neuropilin 1; NR2F6, Nuclear Receptor Subfamily 2 Group F Member 6; OBB, Oxyberberine; OGA, O-GlcNAcase; OGT, O-GlcNAc Transferase; OPA, Oleic Palmitic Acid; PCK1, Phosphoenolpyruvate Carboxykinase 1; PDPF, Pancreatic Progenitor Cell Differentiation and Proliferation Factor; PDHX, Pyruvate Dehydrogenase Complex Component X; PDPK1, 3-Phosphoinositide-dependent Protein Kinase 1; PHB2, Prohibitin 2; PI3K, Phosphatidylinositol 3-Kinase; PINK1, PTEN Induced Putative Kinase 1; PKB, Protein Kinase B; PKC, Protein Kinase C; PKM2, Pyruvate Kinase M2; PLF, Pueraria Lobatae Radix Flavonoids; PPARα, Peroxisome Proliferator-activated Receptor Alpha; PRIM1, DNA Primase Subunit 1; PRMT6, Protein Arginine Methyltransferase 6; PTEN, Phosphatase and Tensin Homolog; PTMs, Post-translational Modifications; PTS, Pterostilbene; PYCR1, Pyrroline-5-carboxylate Reductase-1; RNF146, Ring Finger Protein 146; RNF20, Ring Finger Protein 20; RPS6, Ribosomal Protein S6; RIPK1/3, Receptor Interacting Serine/Threonine Kinase 1/3; SAH, S-Adenosylhomocysteine; SAM, S-Adenosylmethionine; SalB, Salvianolic Acid B; SCD, Stearoyl-CoA Desaturase; SGLT2, Sodium-Glucose Cotransporter 2; SERPINE1/2, Serpin Family E Member 1/2; SHP, Small Heterodimer Partner; SIRTs, Sirtuin Protein Family; SIRT1/2/3, Sirtuin 1/2/3; SMAD, Mothers Against Decapentaplegic Homolog; SRC-1, Steroid Receptor Coactivator-1; STAT3, Signal Transducer and Activator of Transcription 3; TBK1, TANK-Binding Kinase 1; TGF-β, Transforming Growth Factor Beta; TUFM, Mitochondrial Tu Translation Elongation Factor; ULK1, UNC51-like Kinase-1; USP9X/35, Ubiquitin-specific Peptidase 9X/35; VEGFR1, Vascular Endothelial Growth Factor Receptor 1; WWP1, WW Domain Containing E3 Ubiquitin Protein Ligase 1; ZNF498, Zinc Finger Protein 498.

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Disclosure

The authors report no conflicts of interest in this work.

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