A tale of dual role: HECT-type E3 ubiquitin ligase mechanisms in liver diseases (Review)

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Abstract. HECT-type E3 ubiquitin ligases play crucial and complex roles in liver diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, viral hepatitis and hepatocellular carcinoma (HCC). In MASLD/MASH, these enzymes regulate lipid homeostasis and inflammatory signaling through bidirectional modulation of key metabolic pathways, including PPARα-SREBP, JAK-STAT and MAPK cascades. During liver fibrosis, specific HECT members simultaneously promote TGF-β/Smad signaling by ubiquitinating Smad7 while limiting extracellular matrix deposition through the degradation of TGF-β receptors. In viral hepatitis, they restrict viral replication via direct ubiquitination and proteasomal degradation of viral proteins yet concurrently facilitate viral release by hijacking the host ESCRT machinery. In HCC, these ligases critically influence tumor progression through opposing mechanisms: Acting as oncogenic drivers by destabilizing tumor suppressors such as PTEN, while functioning as tumor suppressors by degrading oncoproteins including c-Myc and β-catenin to attenuate proliferative signaling. Collectively, the 'dual-role' behavior of HECT-type E3 ligases is governed by disease-specific contexts, substrate selection, ubiquitin linkage type (K48 vs. K63), and integration of microenvironmental cues. Although this functional duality presents significant translational challenges, understanding these dual regulatory networks provides critical insights into the pathogenesis of liver diseases and reveals potential avenues for targeted interventions.

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1. Introduction

Ubiquitination is a key mechanism of post-translational modification, accomplished through a cascade reaction involving E1, E2 and E3 enzymes. E1 activates ubiquitin and transfers it to E2, while E3 determines substrate specificity and catalyzes ubiquitin chain formation (1). This process marks target proteins for degradation by the proteasome, constituting the ubiquitin-proteasome system (UPS) (2). The UPS regulates physiological processes such as the cell cycle, inflammation and DNA repair, and its dysregulation is closely associated with various diseases, including cancer and neurodegenerative disorders (3,4). Among the enzymes involved, E3 ubiquitin ligases act as direct 'molecular switches' that interact with target proteins and have thus emerged as important therapeutic targets (2,5). E3 ligases can be classified into four major families, including RING, HECT, RBR and CRL complexes (6-8). HECT-type E3 ligases possess a unique C-terminal HECT domain that mediates ubiquitin transfer via a cysteine-dependent thioester intermediate, conferring broader substrate selectivity (9,10). Consequently, HECT-type E3s are likely to participate in ubiquitination across a wide spectrum of diseases. Several studies have highlighted the critical functions of HECT-type E3 ubiquitin ligases in regulating the molecular networks underlying disease pathogenesis and progression (6,11,12).

By regulating protein ubiquitination, HECT-type E3 ligases play pivotal roles in protein stability, signal transduction and quality control within the protein synthesis pathway. These regulatory functions include the following: i) direct

regulation of structural/functional protein synthesis, whereby certain HECT family members directly bind and ubiquitinate target proteins that affect liver function (for example, SMURF2 promotes the degradation of TGF-β receptor I via ubiquitination, thereby inhibiting the TGF-β/Smad signaling pathway and influencing fibrosis and tumor progression) (13,14); ii) regulation of ribosomal protein homeostasis and synthesis efficiency, whereby HECT-type E3s indirectly modulate protein synthesis by maintaining ribosomal protein stability (for example, HUWE1 ubiquitinates the ribosomal protein RPL7 as part of the ribosomal quality control program, impacting ribosome pool integrity and consequently affecting protein translation) (15); and iii) synthetic reprogramming under stress conditions, whereby, under pathological conditions, such as endoplasmic reticulum stress (ERS), the unfolded protein response promotes the degradation of misfolded proteins: HECT-type E3s are involved in this adaptive regulation of protein synthesis, with examples including the interaction of E6AP with HSP70 and the roles of SMURF1 with IRAK2 and WFS1 in these processes (16-18). The liver, as a central metabolic organ, synthesizes key functional proteins such as albumin, coagulation factors (for example, fibrinogen, Factors II, VII, IX, X), and apolipoproteins, all of which are essential for substance metabolism, bile secretion, coagulation and immune regulation. These functions rely on the precise regulation of protein homeostasis.

HECT-type E3 ubiquitin ligases are key regulators involved in multiple hepatic functions and disease processes, where they are involved in mediating the homeostatic balance between protein synthesis and degradation. In the field of liver diseases, although the mechanisms of an increasing number of HECT-type E3 ligases are being elucidated, only those associated with lipid droplet formation have been systematically summarized to date (19). Through comprehensive literature review, it was identified that HECT-type E3 ubiquitin ligases exhibit a remarkable 'dual role' across the spectrum of liver pathologies, wherein identical enzymes can exert diametrically opposite functions depending on the disease stage, cellular context, and prevailing signaling environment. This functional versatility arises from several interconnected mechanisms: Substrate selection shifts as the disease progresses, with distinct target proteins becoming available or prioritized at different pathological phases; the cellular context dictates both the expression of potential substrates and the availability of accessory proteins that direct ligase activity; and dynamic signaling cues, including post-translational modifications, metabolic pressures, and fine-tuned ligase-substrate interactions. Consequently, the same ligase may suppress pathological initiation, promote disease progression, or exert protective effects in one cell type while driving pathogenesis in another. This context-dependent functional duality reflects the complexity and spatiotemporal specificity of HECT family regulatory networks. Therefore, in the present review, the current knowledge of the roles of HECT-type E3 ubiquitin ligases in liver pathology was summarized, with particular emphasis on how identical enzymes orchestrate opposing effects across different disease stages, cellular contexts, and signaling environments. This perspective provides crucial insights into liver disease pathogenesis and reveals both challenges and opportunities for therapeutic intervention.

2. Structure and classification of HECT-type E3 ubiquitin ligases

The HECT-type E3 family comprises 28 members, characterized by a core HECT domain consisting of an N-lobe that binds to the E2 enzyme and a C-lobe containing the catalytic cysteine (Cys) residue (9,20,21). The E2 transfers ubiquitin to the catalytic cysteine within the C-lobe, forming a thioester intermediate; subsequent conformational changes facilitate the transfer of ubiquitin to lysine residues or non-canonical sites on the substrate (22,23). Accessory domains (for example, WW, C2 and RCC1) are responsible for substrate recognition and subcellular localization, leading to the classification of HECT-type E3s into NEDD4, HERC and other subfamilies (Fig. 1) (24,25).

NEDD4 subfamily. The NEDD4 subfamily, also referred to as C2-WW-HECT-type E3s, typically contains an N-terminal C2 domain (mediating Ca^{2+}-dependent membrane targeting), two to four WW domains (recognizing PPxY motifs or phosphorylated sequences), and a C-terminal HECT domain (4,26,27). The C2 domain is a Ca^{2+}-dependent phospholipid-binding motif that mediates membrane association and recognition of membrane-associated substrates (4,26). WW domains mediate protein-protein interactions by recognizing PPxY, LPxY, or related sequences, as well as phosphorylated Ser/Thr-Pro motifs (4,27). Essentially, the C2 and WW domains determine the specificity of target protein binding for NEDD4 family members. Known NEDD4 subfamily E3s include NEDD4, NEDD4L, ITCH, SMURF1, SMURF2, WWP1, WWP2, HECW1 and HECW2 (28). The NEDD4 family represents the most extensively studied group of HECT-type E3s, which regulate processes such as plasma membrane protein stability and misfolded protein degradation, and are widely implicated in the mechanisms of liver diseases (29).

HERC subfamily. HERC subfamily members contain an N-terminal RCC1-like domain (involved in regulating GTPases) and a C-terminal HECT domain. They are subdivided into members such as HERC1-6 based on variations in their intermediate domains. The conserved RCC1 domain mediates GTPase regulation, contributing to pleiotropic roles in cellular homeostasis (30). Their diverse intermediate domains (for example, zinc fingers, ISG15-binding domains) confer distinct functions to individual members, including roles in DNA repair, antiviral immunity and metabolic regulation, potentially exerting protective or repair functions in pathological processes such as liver injury and hepatitis (30,31).

Other HECT members. The other group of HECT members includes 13 HECT-type E3s (for example, HECTD1-4, E6AP/UBE3A, HUWE1, TRIP12, UBR5, UBE3B, UBE3C, HACE1, G2E3 and AREL1), all of which possess a C-terminal HECT domain but often contain N-terminal or intermediate domains that are unstructured or lack defining features, precluding their classification into the aforementioned subfamilies (32,33). These E3s have been reported to participate in various disease processes by regulating energy metabolism, ERS, oxidative stress and cell death (34,35).

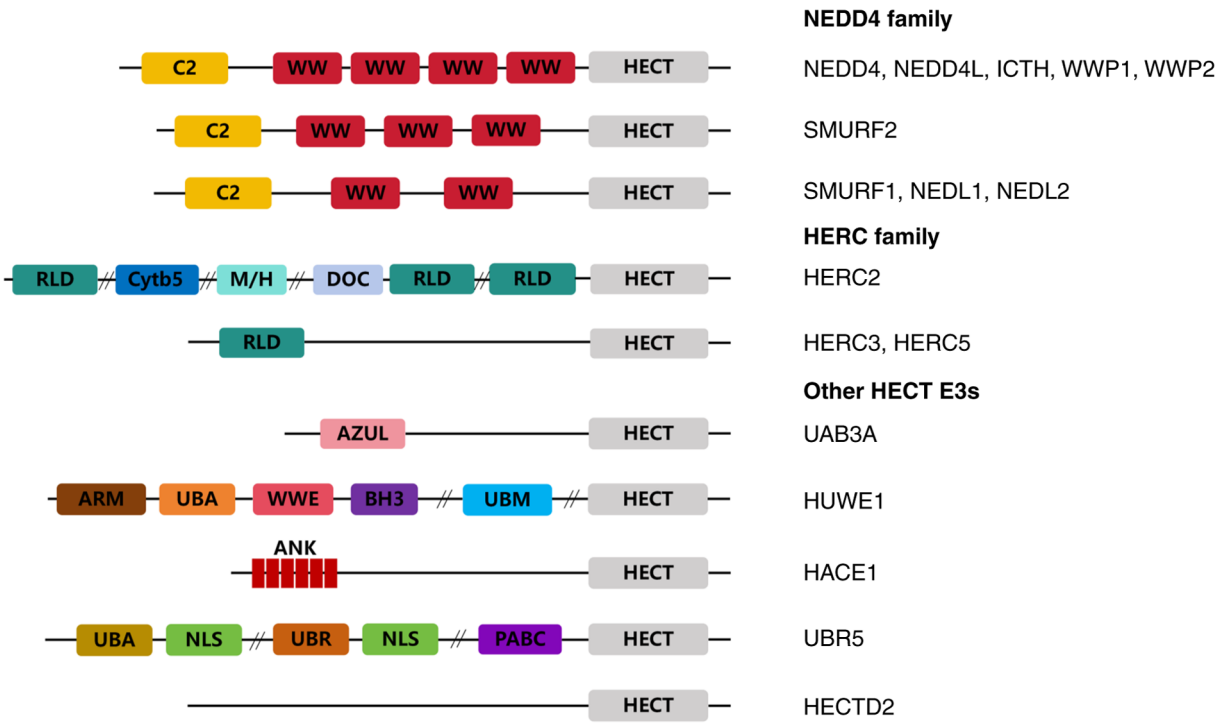

Figure 1. Structural characterization of HECT-type E3 ubiquitin ligases. The prevalent structure of the NEDD4 family of HECTs is a C2 structural domain at the N-terminus with 2-4 tryptophan-within-tryptophan (WW) structural domains in the middle, whereas the HECT structural domains are at the C-terminus. The HERC-type subfamily contains at least one RCC1 structural domain at its N-terminus, whereas the HECT structural domain is at the C-terminus, with the intervening structural domains The intermediate domains vary. The other HECT-type E3 enzymes all have a HECT structure at the C-terminus, but the N-terminal and intermediate domains are often disordered and cannot be categorized.

3. Role of HECT-type E3 ubiquitin ligases in metabolic dysfunction-associated steatotic liver disease (MASLD)/ metabolic dysfunction-associated steatohepatitis (MASH)

MASLD, formerly known as non-alcoholic fatty liver disease, is associated with systemic metabolic dysregulation and has a global prevalence of up to 38%. The MASLD nomenclature accurately reflects the pathophysiology and systemic metabolic implications of this common liver condition (36-39). The core mechanisms of MASLD involve multiple factors, including lipotoxicity, insulin resistance, pro-inflammatory diets and gut dysbiosis, leading to hepatic steatosis combined with cardiovascular risks associated with metabolic abnormalities. These processes can drive hepatic inflammation and the development of systemic low-grade inflammation, with its inflammatory subtype termed MASH (36). Undoubtedly, the intrinsic functions of HECT-type E3 ligases play significant roles in regulating the molecular networks underlying these pathogenic mechanisms.

Role of HECT-type E3 in mediating lipid metabolism in MASLD/MASH. Dysregulation of lipid homeostasis is a central pathological event in patients with MASLD. Several HECT-type E3 ligases directly modulate key transcriptional regulators and enzymes within lipid metabolic pathways.

The roles of proteins from the NEDD4 subfamily in the pathogenesis of MASLD/MASH have been extensively reported. Research on NEDD4 within this subfamily in MASLD remains relatively limited; current evidence indicates that it is upregulated under conditions of elevated hepatic free fatty acids, where it regulates high-density lipoprotein metabolism by ubiquitinating the scavenger receptor SR-BI (40). Conversely, a study in geese reported opposing findings, showing increased NEDD4 expression in fatty liver that appeared to suppress hepatic steatosis-related injury via ubiquitination of PTEN and IGF-1R (41), suggesting potential species-specific functional differences. NEDD4L has been more extensively studied, revealing a dual role: Wherein reduced AT-rich interactive domain 2 expression in MASLD livers leads to NEDD4L transcriptional downregulation, impairing JAK2 ubiquitination and subsequent degradation, which results in hyperactivation of the JAK-STAT pathway and ultimately exacerbates hepatic steatosis (42), indicating that the normal function of NEDD4L suppresses lipid accumulation. However, the markedly elevated NEDD4L levels observed in MASH serve to promote the K48-linked ubiquitination and degradation of lysosomal-associated protein transmembrane 5 (LAPTM5), activating the cell division cycle 42 (CDC42)-MAPK axis and paradoxically worsening lipid accumulation (43), while NEDD4L-mediated degradation of TMBIM1 has also been confirmed to aggravate steatosis (44). The role of ITCH in lipid metabolism is similarly complex. ITCH knockout mice fed a high-fat diet exhibit reduced hepatic lipid accumulation and inhibited atherosclerosis formation, suggesting that ITCH promotes lipid accumulation, Previous studies indicated that ITCH knockout mice fed a high-fat diet exhibit reduced hepatic lipid accumulation and suppressed atherosclerosis formation. This is associated with ITCH enhancing LDL uptake by mediating the ubiquitination of proteins such as sirtuin 6 (SIRT 6), Sterol regulatory element

binding protein 2 (SREBP 2) and liver kinase B1, thereby influencing lipid accumulation. Clinical samples similarly reveal a negative correlation between human ITCH protein abundance and hepatic steatosis severity (45-48). Additionally, ITCH binds to the PPAY motif in Spartin through its WW domain; this interaction recruits ITCH from the cytoplasm to the surface of lipid droplets, leading to the ubiquitination of surface proteins. This process may impair lipid droplet degradation in hepatocytes (49), thereby promoting or exacerbating the onset and progression of MASLD. The regulatory mechanism of SMURF1 in lipid metabolism is particularly unique. Although considered a protective factor that is upregulated in human and mouse MASLD, SMURF1 deficiency alleviates hepatic steatosis. This occurs because SMURF1 interacts with SREBP-1c not to ubiquitinate and degrade it, but to occupy the binding site for its primary E3 ligase, FBW7A, thereby inhibiting SREBP-1c ubiquitination and degradation, which markedly exacerbates hepatic steatosis (50,51). However, another study observed that SMURF1 knockout leads to spontaneous hepatic steatosis and increased susceptibility to HFD-induced MASLD, associated with a sharp increase in PPARγ expression. Research on alcoholic steatohepatitis also suggests that SMURF1 deficiency restricts lipid degradation, thereby exacerbating hepatic lipotoxicity (52,53). These findings indicate that SMURF1 exerts multiple regulatory effects on lipid metabolism, though it is generally considered a protective E3 ligase in MASLD. SMURF2 participates in lipid metabolism by regulating C/EBPβ stability; under high-fat conditions, PRMT1 suppresses SMURF2 expression, thereby inhibiting the ubiquitination and degradation of C/EBPβ, which promotes preadipocyte proliferation and enhances lipid droplet formation induced by PPARγ pathway activation (54). Furthermore, WWP1 knockout mitigates hepatic lipid accumulation by reducing AKT phosphorylation levels (55).

A limited number of studies have reported that other HECT-type E3 ligases outside the NEDD4 subfamily are associated with lipid accumulation in MASLD/MASH. HUWE1, a prominent member of the other HECT family members, promotes lipid accumulation through multiple pathways: it directly binds and ubiquitinates PPARα for degradation, suppressing the fatty acid metabolism-related LXR/RXR/PPARα axis, a process modulated by PAQR3 and PAQR9 through competitive binding and significantly influenced by MCT1 via lactate metabolism (56-59); additionally, HUWE1 is linked to mTORC1 regulation, mediating WIPI2 ubiquitination and degradation (60), with both mechanisms collectively exacerbating hepatic steatosis. Meanwhile, UBE3A overexpression significantly exacerbates hepatic steatosis in MASLD by mediating ubiquitination of PDHA1 and ACAT1, reprogramming hepatic energy metabolism to promote cholesterol and triglyceride accumulation in the liver (61). These findings demonstrate that HECT-type E3 ubiquitin ligases exert precise and complex regulatory effects on lipid accumulation in MASLD by targeting multiple key lipid metabolism pathways, including SREBP, PPAR, JAK-STAT and mTOR.

HECT-type E3 in mediating inflammation in MASLD/MASH. The inflammatory response is a key driver of the progression from MASLD to MASH, and HECT-type E3 ubiquitin ligases play an important role in shaping the hepatic inflammatory microenvironment by regulating various inflammation-related signaling pathways. Members of the NEDD4 subfamily are involved in the regulation of inflammation. NEDD4 is upregulated under conditions of elevated hepatic free fatty acids and exacerbates liver inflammation and promotes atherosclerosis by ubiquitinating SR-BI and affecting high-density lipoprotein metabolism (40). NEDD4L exhibits significant dual effects in inflammatory regulation: Downregulated NEDD4L expression in MASH leads to impaired ubiquitination of thioredoxin interacting protein (Txnip), consequently enhancing ERS and promoting hepatocyte apoptosis (62); however, another study found markedly elevated NEDD4L levels in MASH that worsen inflammatory responses through LAPTM5 degradation and activation of the CDC42-MAPK axis (43). The association of ITCH with inflammation is equally complex. ITCH knockout mice fed a high-fat diet exhibit suppressed macrophage polarization and show protection against body weight gain and insulin resistance (45); however, further investigation revealed that ITCH knockout leads to elevated branched-chain amino acid (BCAA) levels, which promote inflammatory responses (48). This contradiction between macroscopic protective effects and microscopic pro-inflammatory effects highlights the complexity of ITCH within the global metabolic-immune network. SMURF1 indirectly participates in MASLD-related inflammation and fibrosis by regulating the TGF-β pathway (50-52,63). Notably, SMURF1 and SMURF2 also play a role in hepatic stellate cell (HSC) activation during liver fibrosis by interacting with talin1 (TLN1) and mediating its ubiquitination and degradation, thereby regulating the TLN1/FAK signaling axis and subsequently influencing HSC activation status and downstream inflammatory responses in models of hepatic ischemia-reperfusion injury associated with liver transplantation (64). SMURF2-mediated ubiquitination of AXIN1 attenuates AXIN1-induced Smad7 phosphorylation, inhibiting TGF-β-mTORC1 pathway activation and delaying MASLD-hepatocellular carcinoma (HCC) progression (63). TRIP12, an important member of the other HECT family members, exerts pro-inflammatory effects indirectly through the gut-liver axis: TRIP12 expression is upregulated in the intestines of MASLD and MASH mice, where it promotes K48-linked ubiquitination and degradation of nuclear transcription factor EB, leading to intestinal barrier disruption, increased permeability and worsened MASH severity (65). Additionally, in a proteomic analysis of alcohol-induced hepatic steatosis, TRIP12 was identified as the most significantly altered protein (66), suggesting that it may also participate in local hepatic pathological processes. Although direct studies of HERC subfamily members in MASLD/MASH are limited, their RCC1-like domain-mediated GTPase regulation and known functions in DNA repair, antiviral immunity and metabolic regulation suggest that they may exert protective or reparative functions in pathological processes such as liver injury and hepatitis (30,31). While other HECT members, including HECTD1-4, UBR5 and HACE1, have not been extensively studied in MASLD/MASH, their roles in regulating energy metabolism, ERS, oxidative stress, and cell death in other disease models provide important clues for future exploration of these E3 ligases in the context of MASLD inflammation (34,35).

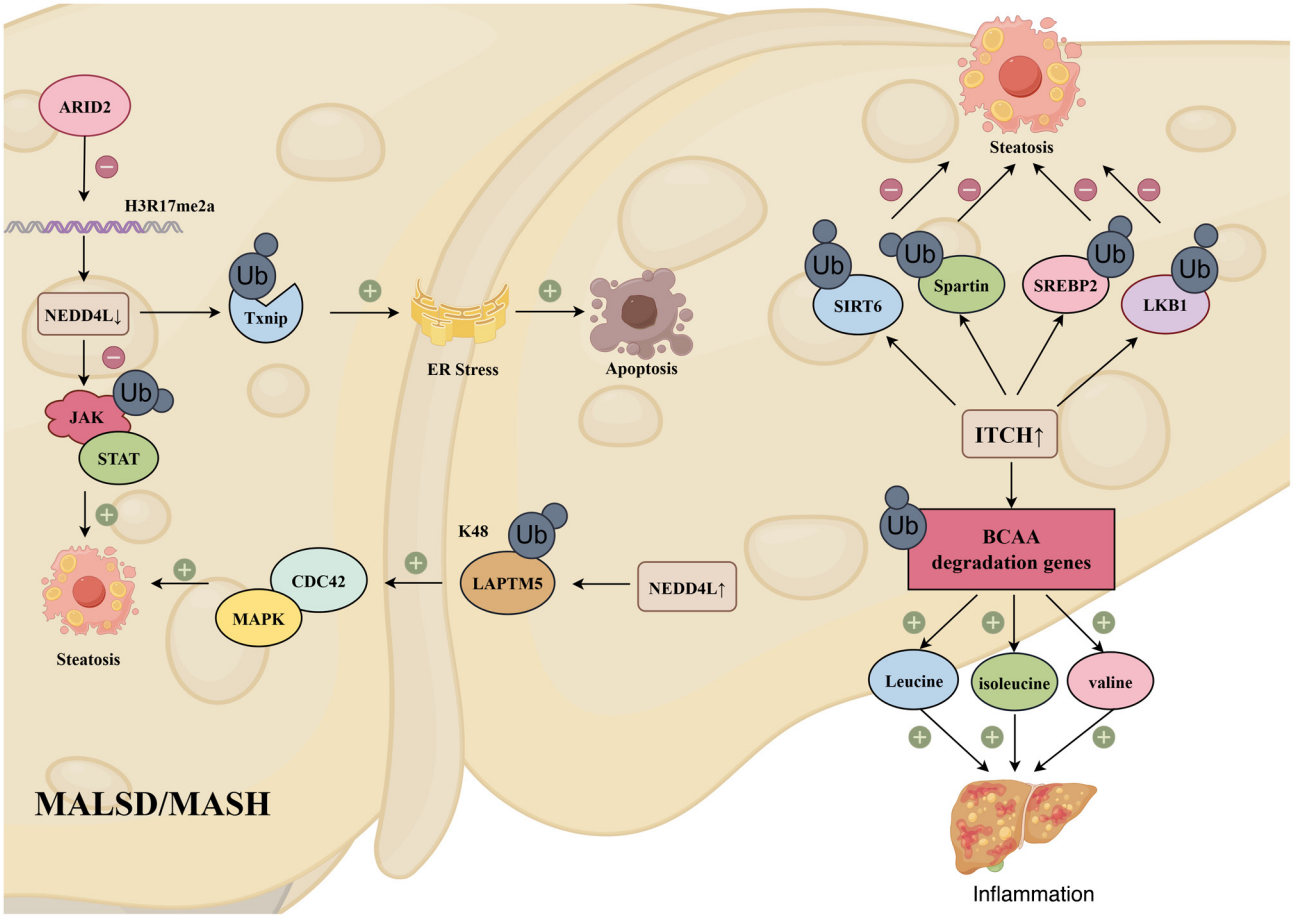

Figure 2. Role of HECT-type E3 ubiquitin ligases involved in MASLD/MASH. NEDD4L and ITCH exhibit a classic dual-role effect in the course of MASLD/MASH. NEDD4L may mediate steatosis through specific pathways regardless of whether it is up- or downregulated. Meanwhile, the inherent ITCH upregulation in MASLD/MASH simultaneously exerts both steatosis-suppressing and inflammation-promoting effects. ARID2, AT-rich interactive domain 2; TxNIP, thioredoxin interacting protein; LAPTM5, lysosomal-associated protein transmembrane domain 5; CDC42, cell division cycle 42 protein; SIRT 6, sirtuin 6; SREBP2, sterol regulatory element-binding protein 2; LKB1, liver kinase B1; BCAA, branched-chain amino acid. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

Mechanistic synthesis. Synthesizing the aforementioned findings, HECT-type E3 ubiquitin ligases exhibit a distinct dual role in the pathogenesis of MASLD/MASH, wherein the same E3 ligase can both promote and inhibit disease progression. This functional duality reflects the complexity and spatiotemporal specificity of the regulatory networks involving HECT family members. First, members of the same NEDD4 subfamily target different substrates in distinct cellular environments or disease stages, producing diametrically opposite effects. NEDD4L serves as a paradigmatic example: In MASH, NEDD4L downregulation impairs degradation of Txnip and JAK2, activating ERS and the JAK-STAT pathway respectively, thereby promoting apoptosis and steatosis (42,62); however, in advanced MASH, upregulated NEDD4L recognizes the PY motif of LAPTM5 through its WW domain, leading to the ubiquitination and degradation of LAPTM5, and subsequently activates the CDC42-MAPK axis, exacerbating lipid accumulation and inflammation (Fig. 2) (43). Such substrate-switching mechanisms may be determined by cell type, subcellular localization, post-translational modifications, or interactions with accessory proteins, enabling NEDD4L to play both disease-promoting and disease-suppressing roles at different disease stages.

This E3 ligase can exert functions contrary to its classical enzymatic activity through non-canonical mechanisms. The regulatory mechanisms of SMURF1 provide multiple illustrations. Although considered a protective E3 ligase, SMURF1 stabilizes SREBP-1c by occupying the binding site for its primary E3 ligase FBW7A, rather than through classical ubiquitin-mediated degradation, a 'steric hindrance' mechanism that paradoxically promotes steatosis (50,51); simultaneously, SMURF1 exerts protective effects by suppressing PPARγ, while in HSCs, SMURF1 performs protective functions by inhibiting HSC activation and inflammatory responses through ubiquitination and degradation of TLN1. These findings indicate that the effect of SMURF1 ultimately depends on the dynamic balance of different substrates in specific cell types and under specific metabolic stresses (52,64).

ITCH also plays a 'dual role' in MASLD/MASH, revealing the holistic and complex nature of HECT-type E3 ligase function. This is demonstrated by the marked hepatoprotective effect observed in systemic ITCH knockout mice (45), while human clinical samples show a negative correlation between ITCH protein abundance and hepatic steatosis severity (46). Paradoxically, ITCH knockout-induced alterations in BCAA profiles promote inflammation (Fig. 2) (48). This suggests

that ITCH simultaneously suppresses lipid accumulation and exerts pro-inflammatory effects within the MASLD/MASH environment, making it difficult to determine whether ITCH possesses therapeutic potential in MASLD/MASH.

These findings suggest that a single E3 ligase may exert opposing effects across the disease spectrum. Specific E3s, notably NEDD4, NEDD4L, and ITCH, engage diverse substrates across different cell types, simultaneously influencing pro-disease and protective outcomes. Their ultimate functional output is determined by the integration of dominant microenvironmental cues, cellular metabolic status and tissue-specific stress responses. This pervasive duality indicates that HECT-type E3 ligases are not mere linear promoters or suppressors of disease but function as dynamic, environmentally responsive molecular hubs. Their activity is precisely calibrated by a confluence of factors, including disease stage, cellular origin, metabolic pressure and local tissue microenvironment. In conclusion, HECT-type E3 ubiquitin ligases act as complex regulators of MASLD/MASH, with functional duality arising from substrate diversity, spatiotemporal expression, non-canonical catalytic activities and trans-organ regulatory networks. Defining a single ligase simply as protective or pathogenic is incomplete.

4. Role of HECT-type E3 ubiquitin ligases in liver fibrosis

Liver fibrosis is a wound-healing response to chronic liver injury, characterized by excessive deposition of extracellular matrix (ECM), which represents a common pathological outcome of chronic liver diseases. The central events driving fibrosis include HSC activation and disruption of ECM metabolism triggered by inflammation and oxidative stress. Current research has confirmed the involvement of HECT-type E3 ubiquitin ligases in the pathogenesis of liver fibrosis (67). However, unlike MASLD/MASH, the role of most HECT-type E3 ubiquitin ligases in liver fibrosis lacks bidirectional effects, which may be attributed to the limited number of studies conducted.

A carbon tetrachloride (CCl_4)-induced liver fibrosis model established by Song *et al* (68) revealed that NEDD4-2 in HSC promoted the ubiquitination and degradation of the hepatoprotective factor tyrosine kinase receptor B. This enhanced TGF-β-mediated Smad2/3 phosphorylation, thereby exacerbating fibrotic injury (68). Furthermore, phosphorylated (p-) NEDD4L levels were increased in liver fibrosis, and p-NEDD4L promoted HSC activation, contributing to fibrosis aggravation (69). Thus, NEDD4/NEDD4L appear to promote liver fibrosis, although further research is needed to confirm these roles and elucidate the underlying molecular mechanisms. In contrast to NEDD4/NEDD4L, WWP2, which belongs to the same NEDD4 subfamily, has been demonstrated to be a distinct antifibrotic gene. Research on WWP2 emerged from a pharmacological study that demonstrated that costunolide inhibits cholestatic and CCl_4-induced fibrosis. This effect is based on costunolide promoting the interaction between WWP2 and Notch3, leading to UPS-mediated degradation of Notch3 (70). A few studies exist regarding the HERC subfamily's role in fibrosis. Because of its unique ISG15-binding domain, HERC5 mediates ISGylation, a ubiquitin-like modification. HERC5 was shown to mediate P53 ISGylation, inhibit HSC activation, and alleviate fibrosis, a process regulated by upstream miR-145 and zinc-finger proteins (71). Another study in a murine fibrosis model using single-cell RNA-sequencing revealed that HERC6 was predominantly enriched in inflammatory neutrophils and promoted liver injury. This effect was suppressed by the CCR2/CCR5 dual antagonist cenicriviroc (72), suggesting that CCR family proteins act as upstream regulators of HERC6 and provide initial insights into its cell-specific localization. Among other HECT members, Kim *et al* (73) reported that E6AP expression is upregulated in fibrosis, where it ubiquitinates MAPK pathway proteins, inhibiting HSC activation and exerting an antifibrotic effect. It is worth noting that the HECT-type E3 ubiquitin ligase identified in the aforementioned study has not been demonstrated to simultaneously promote and inhibit the progression of liver fibrosis during its disease course. Therefore, it may be a therapeutic target for the treatment of liver fibrosis.

Unlike the aforementioned genes, the SMURF proteins are distinguished by their specificity in regulating Smad family proteins. Numerous studies have focused on the role of SMURF1 and SMURF2 in liver fibrosis. One study indicated that SMURF1 ubiquitinates Smad1/5 (74), but its relevance in liver fibrosis has not been explored. However, SMURF2, a member of the NEDD4 family, simultaneously exhibits both a promoting effect on liver fibrosis and resistance to fibrosis. Two separate studies reported that SMURF2 binds to and ubiquitinates Smad7, promoting Smad2/3 phosphorylation and ultimately worsening fibrosis (75,76). However, Cai *et al* (77) found that SMURF2 was upregulated in both cholestatic and CCl_4-induced cirrhosis models and exerted antifibrotic effects through both ubiquitination-dependent and miRNA-mediated mechanisms. Although the role of SMURF2 in fibrosis remains controversial, two pharmacological studies targeting antifibrotic therapy have identified potential SMURF2 activators. Jiang *et al* (78) synthesized an isothiazole derivative, J-1155, which exhibited high selectivity for SMURF2, upregulating its expression and inhibiting fibrosis. A similar effect was observed with curcumin in treating fibrosis (79). These studies provide valuable agonist tools for future SMURF2 research. In summary, current research on HECT-type E3s in fibrosis primarily focuses on SMURF2. However, whether this upregulation during fibrosis is protective or detrimental remains debatable and warrants further investigation.

Mechanistic synthesis. The involvement of HECT-type E3 ligases in liver fibrosis demonstrates their functional diversity and context-dependent activities. First, distinct family members can exert opposing effects within the same pathological process. It remains challenging to develop targeted therapies by focusing on a specific domain of NEDD4 or a particular HERC subfamily member. For instance, SMURF1/2 exhibits potentially opposing effects on fibrosis compared with NEDD4/4L and WWP2. HERC5/HERC6 also show opposing actions. Second, a single E3 ligase can exhibit functional contradictions, as exemplified by SMURF2, which has been reported to be both profibrotic and antifibrotic, depending on the experimental model and mechanistic context. Collectively, these factors contribute to failure of domain-targeted therapies.

5. Role of HECT-type E3 ubiquitin ligases in viral hepatitis

Viral hepatitis poses a significant public health threat and is a leading cause of mortality worldwide (80). The five main types are hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and E (HEV) viruses. HECT-type E3 ligases play dual roles in viral hepatitis by regulating both host antiviral immunity and the viral life cycle (81). However, these studies have primarily focused on the more common HBV and HCV, with only a few studies on HAV. Thus, strategies targeting specific HECT-type E3s may offer novel avenues for antiviral therapy. The following sections detail these cutting-edge findings, organized by virus type.

HECT-type E3 ubiquitin ligases in HBV. Multiple HECT-type E3 ligases have been implicated in HBV infection and exhibit complex and often opposing functions via distinct mechanisms. Several HECT-type E3 ligases promote HBV replication and release through various strategies. ITCH expression is decreased in HBV-positive human cells, leading to suppressed ubiquitination of Notch1 and subsequent aberrant activation of the Notch pathway, which promotes transcription of covalently closed circular DNA (cccDNA) and enhances HBV replication (82). HERC5 is hijacked by the HBV X protein (HBx), which directly binds HERC5 for ISGylation modification, conferring enhanced replication capability and interferon-α resistance to HBV (83). UBR5 mediates K29-linked ubiquitination of the HBV core protein, which may be involved in regulating HBV transcription, RNA encapsidation, reverse transcription and viral release, although the functional consequences require further elucidation (84).

Conversely, other HECT-type E3 proteins exert protective effects by targeting viral proteins for degradation. NEDD4 directly induces proteasomal degradation of HBx via K48-linked ubiquitination, suggesting an antitumor role in HBV-associated HCC (85). However, NEDD4 exhibits functional duality as it also interacts with and ubiquitinates γ2-Adaptin, promoting HBV nucleocapsid assembly and disrupting the multivesicular body (MVB) pathway, with NEDD4 knockdown significantly reducing HBV release (86-88). Thus, NEDD4 simultaneously facilitates viral production while suppressing viral oncoprotein stability. E6AP forms a p53/E6AP/HBx ternary complex that leads to HBx ubiquitination and degradation, and all-trans retinoic acid activates this pathway to suppress HBV replication (89,90).

HECT-type E3 ubiquitin ligases in HCV. HCV infection involves multiple HECT-type E3 ligases acting via diverse mechanisms that collectively influence viral replication, particle release and disease progression. Several HECT-type E3s promote HCV propagation. ITCH plays a proviral role where increased reactive oxygen species (ROS) induce ITCH phosphorylation, leading to ubiquitination of the ATPase VPS4A, a protein necessary for MVB formation, thereby promoting HCV particle release (91). HERC5's role remains controversial, with some studies reporting that HERC5 specifically promotes NS5A ISGylation, thereby enhancing HCV replication (92), while others demonstrate that the inhibitory effect of ISG15 on HCV RNA replication does not require HERC5 binding (93).

By contrast, other HECT-type E3s exert anti-HCV effects. E6AP represents the most extensively studied protective factor, initially characterized as promoting HCV pathogenesis through nonstructural protein 5B (NS5B)-recruited ubiquitination of retinoblastoma tumor suppressor protein (pRb) leading to chromosomal instability (94), but subsequently established as an anti-HCV replication factor through direct binding and ubiquitination of the viral nucleocapsid core protein (95,96). The HCV core protein suppresses E6AP expression via DNA promoter methylation to evade ubiquitin-proteasome system-mediated degradation, while p53 upregulation enhances E6AP expression and recruits E6AP to form a ternary complex with the HCV core, promoting its ubiquitination and degradation (97-99). All-trans retinoic acid activates E6AP by inhibiting its methylation, thereby suppressing HCV replication (100).

SMURF2 has dual functions in HCV infection. It enhances ubiquitination and degradation of the viral protease NS3-4A, inhibiting TGF-β-induced Smad2/3 phosphorylation and alleviating HCV-associated fibrosis (101). However, the SMURF2/NS3-4A complex also interacts with quinolinate phosphoribosyl-transferase (QPRT), leading to QPRT degradation, which lowers the NAD^+/NADH ratio, potentially shifting lipid metabolism to favor HCV replication (102).

HECT-type E3 ubiquitin ligases in HAV. Current evidence for HECT-type E3 involvement in HAV infection primarily focuses on a single mechanism. ITCH facilitates HAV release, and its catalytic activity is essential for the efficient release of quasi-enveloped virions (eHAV). During acute infection, eHAV is released into the blood via the MVB pathway, which involves an interaction between the pX domain and the ESCRT complex and the HECT domain of ITCH, resulting in inhibition of viral activity and release (103).

Mechanistic synthesis. Synthesizing the findings across different hepatitis viruses reveals that HECT-type E3 ubiquitin ligases exhibit a striking dual role in viral hepatitis, wherein the same E3 ligase can both promote and inhibit viral replication, host pathogenesis, or antiviral responses, depending on the viral context, cellular environment, and target substrate specificity. This functional duality profoundly reflects the evolutionary arms race between host antiviral defense and viral evasion strategies.

The same HECT-type E3 ligases can exert opposing effects on the same virus by targeting different viral or host proteins. NEDD4 in HBV infection provides a paradigmatic example: While NEDD4 promotes HBV nucleocapsid assembly and viral release through γ2-Adaptin ubiquitination and HBc modification (86-88), it simultaneously induces proteasomal degradation of HBx via K48-linked ubiquitination, potentially suppressing HBV-associated hepatocarcinogenesis (85). This substrate-specific duality positions NEDD4 as both a facilitator of viral production and a suppressor of viral oncoprotein stability, suggesting that its net effect may depend on the relative abundance and accessibility of different substrates during different stages of infection.

The same E3 ligase plays different roles in distinct hepatitis viruses, reflecting virus-specific coevolutionary adaptations. ITCH exemplifies this virus-dependent

functional diversity: In HAV infection, ITCH facilitates eHAV release through ESCRT pathway interactions (103); in HCV infection, ROS-induced ITCH phosphorylation promotes VPS4A ubiquitination and viral particle release (91); whereas in HBV infection, decreased ITCH expression leads to Notch1 stabilization and enhanced cccDNA transcription (82). This virus-specific engagement suggests that therapeutic targeting of ITCH would require careful consideration of viral context.

E6AP demonstrates how the same E3 ligase can be reinterpreted from pathogenic to protective as mechanistic understanding deepens. Initially characterized as a pro-HCV factor through NS5B-mediated pRb ubiquitination, promoting chromosomal instability (94), E6AP was subsequently identified as an anti-HCV factor through direct HCV core ubiquitination and degradation (95,96). The discovery of the p53/E6AP/viral core axis operating in both HCV and HBV infections unified these observations, establishing E6AP as a host restriction factor whose activity is subverted by viral proteins through epigenetic suppression (97-99).

HERC5 exemplifies the controversy arising from the context-dependent mechanisms. Conflicting studies on HERC5's role in HCV replication and whether it inhibits or promotes viral RNA synthesis through NS5A ISGylation (92,93) may reflect differences in experimental systems, viral strains, or the balance between the direct antiviral effects and proviral consequences of ISGylation.

In conclusion, HECT-type E3 ubiquitin ligases function as critical nodes at the host-virus interface during viral hepatitis, with their dual roles arising from substrate diversity, virus-specific adaptations and the complex interplay between viral life cycle requirements and host antiviral defenses. However, owing to the presence of the aforementioned factors, therapeutic approaches that simply target a specific enzyme or HECT domain cannot be developed. This limitation has constrained the advancement of viral hepatitis treatments.

6. Role of HECT-type E3 ubiquitin ligases in HCC

HCC is a highly prevalent malignancy with a high mortality rate worldwide. Its development stems from the accumulation of genetic and epigenetic alterations caused by chronic liver injury, which involves the dysregulation of complex signaling pathways. The diverse roles of HECT-type E3 ligases in HCC have been partially summarized. For instance, NEDD4 and SMURF1 can promote tumor proliferation, invasion and metastasis by degrading tumor suppressors (for example, PTEN) or stabilizing oncoproteins (for example, c-Myc) via ubiquitination. Conversely, specific HECT enzymes (for example, HACE1) exert tumor-suppressive functions, such as inhibition of the Rac1 signaling pathway, and their loss or mutation is associated with HCC progression (104). Furthermore, the HECT family participates in regulating DNA damage repair, inflammatory microenvironment and metabolic reprogramming, potentially driving HCC malignant transformation indirectly by affecting genomic stability or immune evasion (Fig. 3) (105). Based on these findings, this section provides a detailed and updated description of the dual roles of HECT-type E3 ligases in HCC pathogenesis.

HECT-type E3 ubiquitin ligases in proliferation. In studies investigating the function of HECT-type E3 ligases in HCC, multiple studies have confirmed NEDD4 as an oncogene that mediates the ubiquitination and degradation of the classical tumor suppressor PTEN, accelerating HCC progression (106-110). Two clinical studies found that patients with HCC and high NEDD4 expression had shorter survival times, and subsequent experimental validation indicated that NEDD4 upregulation suppresses PTEN expression, thereby promoting PI3K-AKT phosphorylation (106,107). This finding was corroborated by Zhou *et al* (108), who also suggested that the NEDD4/PTEN/PI3K/AKT axis is modulated by the interaction between craniofacial development protein 1 and NEDD4 (108). Beyond PTEN, some research shows that NEDD4 also promotes HCC invasion and metastasis by ubiquitinating large tumor suppressor kinase 1 (LATS1) in the HIPPO pathway, and TGF-β type I receptor (TGFBR1) in the TGF-β pathway (109,110). Therefore, NEDD4 is currently the most promising HECT-type E3 enzyme to serve as a novel therapeutic target for HCC.

In studies of other HECT-type E3 ligases, HECTD1/2 appear to promote HCC proliferation, although they have been reported to do so through distinct mechanisms. HECTD1 targets growth factor receptor-bound protein 2 (GRB2), and its degradation inhibits MAPK pathway-mediated angiogenesis, although this ubiquitination is competitively inhibited by elevated Golgi protein 73 levels in HCC (111). HECTD2 is highly expressed in HCC and promotes proliferation through KEAP1 ubiquitination and subsequent antioxidant response activation (112). Liu *et al* (113) suggested that E6AP interacts with G protein-coupled receptor 26 (GPR26) through its HECT domain. By altering the conformation of this domain, E6AP induces ubiquitination at the K286 site of GPR26, thereby promoting tumor proliferation (113). UBR5 interacts with the tumor suppressor esophageal cancer-related gene 4 (ECRG4). ECRG4 overexpression conversely downregulates UBR5 expression, leading to increased p21 levels and anti-proliferative effects (114). Wang *et al* (115) found that targeting and inhibiting UBR5 with Echinacoside promoted apoptosis and inhibited glycolysis in HepG2 cells (115). Leboeuf *et al* (116) demonstrated that simultaneous small interfering RNA silencing of UBR1, UBR2, UBR4 and UBR5 inhibited the Arg/N-degron pathway, reducing HCC cell proliferation while increasing spontaneous apoptosis (116). HACE1 was initially found to be downregulated in HCC tissues, and patients with low HACE1 expression had lower overall survival rates (117). Mechanistic studies revealed that HACE1 mediates the ubiquitination of SREBP cleavage-activating protein (SCAP), thereby inhibiting SREBP2-mediated cholesterol biosynthesis, which is crucial for membrane synthesis during rapid proliferation. However, this process is antagonized by the ZDHHC3-mediated S-acylation of SCAP at Cys264 (118). Additionally, LINC00161 recruits EZH2, leading to HACE1 methylation and promotion of HCC progression (119). Therefore, HACE1 is currently recognized as a tumor suppressor that inhibits HCC proliferation. These HECT-type E3 ligases have been extensively studied for their roles in regulating HCC proliferation; however, no significant bidirectional effects have been observed. Consequently, they represent promising novel therapeutic targets for HCC

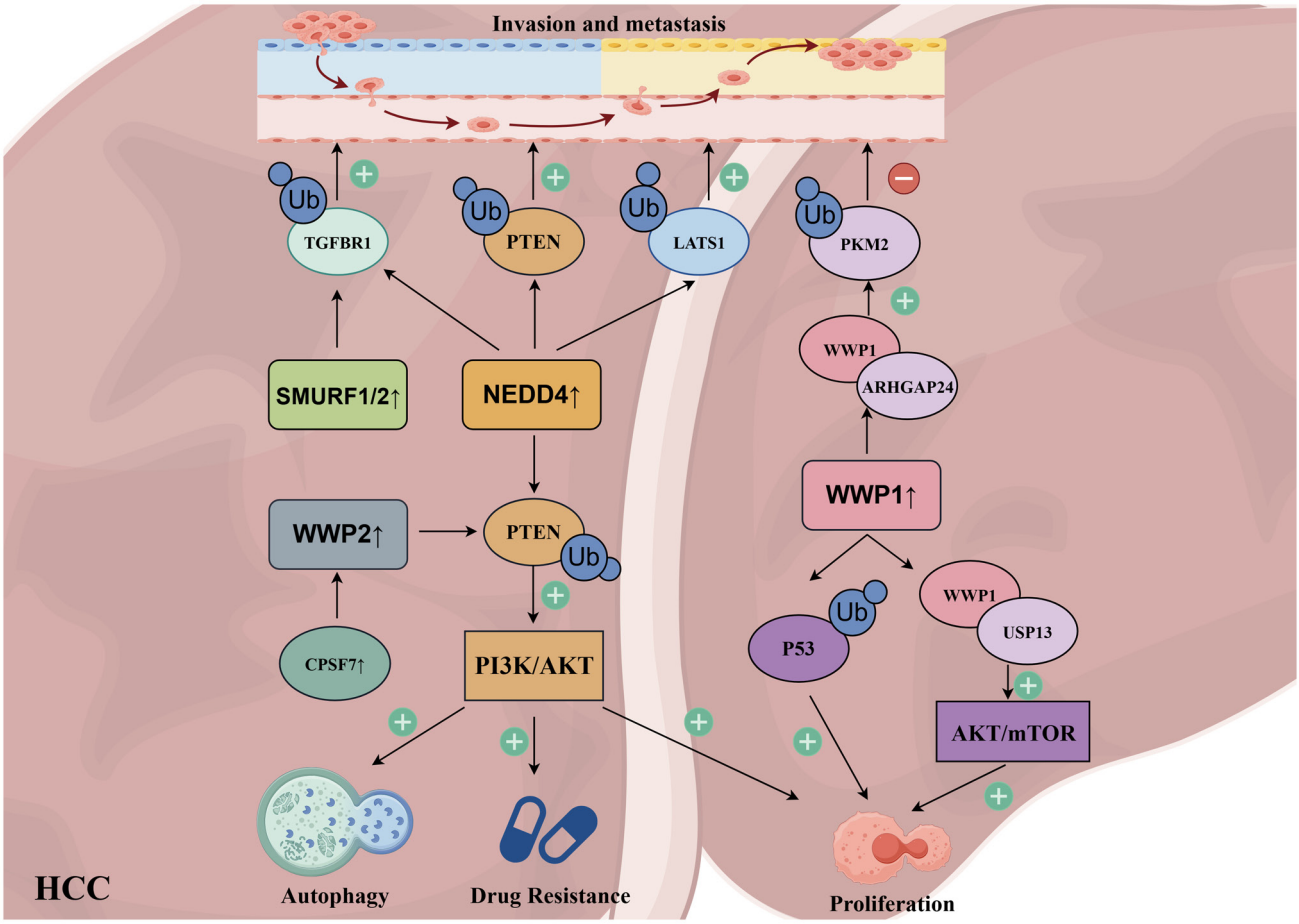

Figure 3. Role of HECT-type E3 ubiquitin ligases involved in HCC. In HCC, PTEN, as a classic tumor suppressor gene, can undergo ubiquitination and degradation by multiple HECT-type E3 ubiquitin ligases. Among these, NEDD4 holds the greatest translational potential as a HECT-type E3 ubiquitin ligase target due to its ability to simultaneously activate multiple signaling pathways and exert oncogenic effects. WWP1, however, exhibits a classic 'dual role' effect in HCC. It can both suppress tumor growth and potentially promote tumor invasion and metastasis. HCC, hepatocellular carcinoma; TGFBR1, TGF-β type I receptor; LATS1, large tumor suppressor kinase 1; PKM2, pyruvate kinase M2; ARHGAP24, RhoGAP 24; CPSF7, cleavage and polyadenylation specificity factor 7; USP13, ubiquitin specific peptidase 13.

diagnosis and treatment, although they currently lack the level of recognition attained by NEDD4.

The HECT-type E3 ligases described below have demonstrated dual functionality in current research, representing a significantly controversial aspect of HCC proliferation studies, with findings potentially exhibiting both promoting and inhibitory effects. Focus was first addressed on studies of other HECT-type E3 ubiquitin ligases within the NEDD4 subfamily, excluding NEDD4 itself, that regulates HCC proliferation. The role of NEDD4L in HCC proliferation remains controversial. Lee *et al* (120) demonstrated that NEDD4L expression is significantly upregulated upon activation of the canonical cancer-related Wnt/β-catenin pathway. Conversely, Zhao *et al* (121) reported that downregulation of NEDD4L in HCC tissues correlates with poor prognosis. The authors proposed that NEDD4L binds to ERK1/2 not to ubiquitinate it but rather to promote its phosphorylation and activation, thereby inducing apoptosis and inhibiting HCC cell proliferation (121). Another study also characterized NEDD4L as a tumor suppressor, attributing this role to its ability to ubiquitinate cyclin-dependent kinase 5 (CDK5). The same study indicated that ubiquitin-specific peptidase 1 (USP1) acts as a deubiquitinating enzyme, counteracting NEDD4L's effect on CDK5 (122). Research on ITCH in HCC proliferation is relatively limited but suggests tumor-suppressive functions. Ge *et al* (123) found that ITCH ubiquitinates transforming growth factor β-activated kinase 1 (TAK1). TAK1 degradation leads to inhibition of the MAPK and NF-κB pathways, which are critical for cell proliferation and survival. The glycosyltransferase Rab-like GTPase activating protein and GRAM domain-containing protein 4 (GRAMD4) recruits ITCH, thereby promoting TAK1 degradation and inhibiting HCC progression (123). Additionally, ITCH has been linked to programmed cell death ligand 1 (PD-L1) regulation through GLI1 ubiquitination, although this primarily affects immune evasion rather than direct proliferation control (124). Conflicting reports exist regarding the role of WWP1 in HCC proliferation. Cheng *et al* (125) identified WWP1 as an oncogenic factor and found that its expression was elevated in tissues of patients with HCC and positively correlated with alpha-fetoprotein levels. WWP1 knockout led to HCC cell apoptosis and inhibited proliferation via the upregulation of caspase-3 and P53, although the involvement of ubiquitination was not clarified (125). By contrast, another study reported a tumor-suppressive role for WWP1, associated with its binding to and degradation of pyruvate kinase M2 (PKM2), inhibiting

HCC cell proliferation. However, this interaction requires RhoGAP 24 (ARHGAP24) as a scaffolding protein (126). Furthermore, in HCC, WWP1 can be influenced by the deubiquitinating enzyme USP13, leading to activation of AKT and mTOR phosphorylation and accelerated HCC proliferation (127). Similar to NEDD4, WWP2 is also a key regulator of PTEN, cleavage and polyadenylation specificity factor 7 is upregulated, inducing the upregulation of WWP2 and promoting the ubiquitination and degradation of PTEN (128). However, the current body of research on WWP2 remains insufficient, and its potential as a therapeutic target warrants further investigation.

Research on the role of the HERC subfamily in HCC proliferation, although limited, suggests pro-tumorigenic functions. HERC2 is significantly upregulated in primary hepatocytes under inflammatory stimulation, promoting STAT3 activation during the inflammation-to-cancer transition and enhancing cancer stemness (129). HERC4 is elevated in HCC tissues, enhancing cell proliferation through the suppression of Salvador 1 (SAV1) (130,131). HERC5 is also upregulated in HCC, promoting cancer cell proliferation and influencing apoptosis. Wang *et al* (132) synthesized a disubstituted quinazoline derivative, HZ-6d, which binds to HERC5, inhibits its expression, and activates P53, effectively delaying HCC growth *in vivo* (132). Interestingly, integrated omics and clinical data analyses identified HERC5 as a prognostic marker for post-liver transplant recurrence in patients with HCC, with low expression associated with poor prognosis because of immune escape mechanisms (133).

HUWE1, TRIP12 and UBE3B/C regulate HCC proliferation. HUWE1 mediates p53 degradation and participates in the regulation of HCC cell apoptosis, which is modulated by the deubiquitinating enzyme USP7 (134). Similar to HUWE1, TRIP12 is also regulated by USP7-mediated de-ubiquitination. Overexpression of USP7 blocks TRIP12-mediated ubiquitination and degradation of p14ARF, promoting HCC proliferation (135). A large-scale population sequencing study found that UBE3C overexpression in HCC tissues was significantly associated with reduced survival, and that UBE3C promoted HCC progression by regulating epithelial-mesenchymal transition (EMT), which indirectly affects proliferation (136). Tao *et al* (137) also described UBE3C upregulation in HCC and its regulation by the upstream miR-542-3p. Although these genes have also been shown to potentially regulate HCC proliferation, the current body of research remains insufficient. Therefore, it remains unclear whether they exhibit bidirectional effects.

HECT-type E3 ubiquitin ligases in invasion and metastasis. HECT-type E3 ubiquitin ligases play critical roles in HCC invasion and metastasis by regulating cell migration, adhesion, EMT and ECM remodeling. NEDD4 promotes HCC cell invasion and metastasis via multiple mechanisms. Beyond its role in proliferation, research shows that NEDD4 ubiquitinates LATS1 in the HIPPO pathway and TGFBR1 in the TGF-β pathway, thereby relieving the tumor-suppressive effects of these pathways and enhancing the migratory and invasive capacity of HCC cells (109,110). The HIPPO pathway is a key regulator of organ size and metastasis, and its inactivation by NEDD4-mediated LATS1 degradation promotes nuclear translocation of YAP/TAZ, driving EMT and metastasis. Similarly, TGFBR1 ubiquitination by NEDD4 modulates TGF-β signaling, which has dual roles in HCC but often promotes metastasis in advanced stages.

SMURF1 and SMURF2 predominantly exert inhibitory effects on invasion and metastasis in HCC, particularly through negative regulation of the TGF-β signaling pathway, which is a major driver of EMT and metastasis. Liu *et al* (138) demonstrated that in HCC, SMURF1/2 binds to TGFBR1, inducing its ubiquitination and degradation, which suppresses the TGF-β pathway and its pro-metastatic effects. TGF-β Receptor associated protein 1 (TGFBRAP1) competes with SMURF1/2 for the TGFBR1 binding site, thereby enhancing cancer stemness and metastatic potential. Similarly, Niemann-Pick disease, type C1 protein exerts an effect analogous to TGFBRAP1 (138,139). SMURF1 can also suppress TGF-β pathway activation by binding to and ubiquitinating TGFBR2 (140). Beyond TGF-β signaling, SMURF1 ubiquitinates ultra-violet radiation resistance associated, which inhibits HCC proliferation and metastasis by promoting autophagosome maturation and lysosomal degradation of EGFR, a key driver of metastatic signaling (141). Signal transducer and activator of transcription 1, which can have tumor-suppressive functions in HCC, is also targeted for degradation by SMURF1, but this process depends on the presence of SIRT 7. In addition, hsa_circ_0000235 participates in SMURF1's regulation of HSP60 in a manner similar to that of SIRT 7 (142,143). These findings collectively support the metastasis-suppressive role of SMURF1 in HCC. Therefore, the aforementioned studies conclusively demonstrate the roles of NEDD4 and SMURF1/2 in the regulation of HCC invasion and metastasis. Notably, NEDD4 has emerged as a well-defined target that promotes proliferation, invasion and metastasis and has significant translational potential.

The functions of HECT-type E3 enzymes remain controversial because of limited studies and their bidirectional activity. ITCH indirectly inhibits HCC invasion and metastasis through TAK1 ubiquitination and degradation, which leads to inhibition of the MAPK and NF-κB pathways, both of which can promote EMT and metastasis. GRAMD4 recruits ITCH to promote this process, thereby suppressing HCC progression (123). Additionally, the ITCH/GLI1 axis may indirectly influence HCC metastatic potential by regulating PD-L1 expression and subsequent immune evasion; however, its direct effects on cell migration remain to be explored (124). The role of WWP1 in HCC invasion and metastasis is unclear. One study reported that WWP1, through binding to and degradation of PKM2, inhibits HCC cell migration and invasion, requiring ARHGAP24 as a scaffolding protein (126). However, the oncogenic functions of WWP1 described in other studies suggest context-dependent effects on metastasis, which require further investigation. HERC4, through suppression of SAV1, may influence HCC metastasis, as SAV1 is a core component of the HIPPO pathway that regulates YAP/TAZ activity and subsequent EMT (130,131). UBE3C overexpression promotes HCC progression by regulating EMT in HCC cells, directly implicating it in metastatic spread (136). UBR5 influences HCC cell migration through the regulation of the Arg/N-degron

pathway, as simultaneous silencing of UBR1, UBR2, UBR4 and UBR5 reduces HCC cell migration (116).

HECT-type E3 ubiquitin ligases in drug resistance. HECT-type E3 ubiquitin ligases significantly contribute to therapeutic resistance in HCC by affecting the responses to multiple classes of anticancer drugs, including targeted therapies and chemotherapy. NEDD4 plays an important role in drug resistance by regulating the PTEN/PI3K/AKT axis. Inhibition of NEDD4/PTEN axis-mediated autophagy can enhance the sensitivity of HCC animal models and cell lines to sorafenib, a first-line multi-kinase inhibitor used in advanced HCC (107,108,144). Autophagy is a cellular survival mechanism that promotes resistance to therapy, and NEDD4-mediated PTEN degradation activates AKT, which in turn promotes autophagy and survival under stress conditions. In the context of the FOLFOX (5-fluorouracil, oxaliplatin and leucovorin) chemotherapy regimen, glycolysis-enhanced histone lactylation forms an H3K14la/NEDD4/PTEN axis regulating multidrug resistance in HCC (145). This epigenetic mechanism links metabolic reprogramming to drug resistance through NEDD4 upregulation. Notably, this study indicated that NEDD4L is not involved in PTEN regulation in this context (146).

The following enzymes may be underrepresented because of the limited number of studies on drug resistance. SMURF1/2 may indirectly influence drug resistance through their regulation of TGF-β signaling. TGFBRAP1 competes with SMURF1/2 for TGFBR1 binding, thereby enhancing cancer stemness and HCC resistance to regorafenib, another multi-kinase inhibitor used in second-line treatment for HCC (138). HECTD2 is highly expressed in lenvatinib-resistant HCC cell lines, patient tissues, patient-derived organoids and xenografts. Lenvatinib is another multi-kinase inhibitor used as a first-line treatment for advanced HCC. HECTD2 promotes ubiquitination of KEAP1, a negative regulator of antioxidant response. KEAP1 degradation leads to the activation of NRF2 and the subsequent antioxidant response, which reduces oxidative stress-induced cell death and decreases sensitivity to lenvatinib in HCC cells (112). WWP2 contributes to doxorubicin resistance in HCC through its regulation of PTEN. METTL3-mediated m6A modification of WWP2 increases its stability, leading to enhanced PTEN ubiquitination and AKT activation, which counteracts the antitumor effects of doxorubicin, an anthracycline antibiotic used in HCC chemotherapy (147). UBE3B is associated with lenvatinib resistance in HCC. Lobeline, an m6A antagonist, downregulates UBE3B expression, partially reversing lenvatinib resistance. This suggests that UBE3B expression, which is potentially regulated by m6A modifications, contributes to the resistant phenotype (148).

Mechanistic synthesis. Synthesizing the aforementioned findings, HECT-type E3 ubiquitin ligases exhibit a dual-role effect in the pathogenesis of HCC across all aspects of tumor biology, including proliferation, invasion, metastasis and drug resistance. Different members of the same subfamily, and even the same E3 ligase in different cellular contexts or targeting different substrates, can either promote or suppress HCC progression. This functional duality profoundly reflects the intricate regulation of complex signaling networks in HCC and the functional diversity of the HECT family members.

NEDD4 acts as a definitive oncogene by degrading PTEN to activate PI3K-AKT signaling and promote proliferation (107,108). It also enhances invasion and metastasis by ubiquitinating LATS1 and TGFBR1 (109,110) and contributes to drug resistance through autophagy regulation and epigenetic mechanisms (107,108,144). Although it is now widely recognized that inhibiting NEDD4 significantly suppresses tumor proliferation, invasion and metastasis while improving drug resistance, no studies have described its dual role in HCC treatment, demonstrating its immense translational potential. Unfortunately, no clinical trials have confirmed whether this effect can be effectively applied to HCC therapy.

Unlike NEDD4, the following genes fully demonstrate the complexity of HECT-type E3 ubiquitin ligases in HCC progression. WWP1 illustrates how the same E3 ligase may exhibit contradictory roles owing to context-dependent interactions and substrate availability. WWP1 has been reported both as an oncogene promoting proliferation through caspase-3 and P53 regulation (125), and as a tumor suppressor that inhibits migration and invasion through PKM2 degradation in an ARHGAP24-dependent manner (126). This functional switch may depend on the presence of scaffolding proteins such as ARHGAP24, which direct WWP1 to specific substrates, and on the cellular context that determines which substrates are available or relevant. The involvement of USP13 in the regulation of WWP1 stability and subsequent AKT/mTOR activation further complicates its functional characterization (127). Other HECT members exhibit specialized roles in specific aspects of HCC biology. HECTD1 regulates angiogenesis through GRB2 modulation (111). HECTD2 promotes proliferation and lenvatinib resistance through KEAP1 ubiquitination and NRF2 activation (112). E6AP enhances tumor activity through GPR26 degradation (113). UBR5 affects proliferation, apoptosis, glycolysis and migration through multiple mechanisms (115,116). HACE1 acts as a tumor suppressor by regulating cholesterol metabolism and immune evasion through SCAP ubiquitination, with its activity antagonized by S-acylation (118). HUWE1 and TRIP12 regulate apoptosis through the p53/p14ARF axis and are modulated by USP7 (134,135). UBE3C promotes EMT and metastasis (136), while UBE3B contributes to lenvatinib resistance (148). This functional specialization reflects the diverse roles of different HECT members within the complex signaling network of HCC.

From structural and functional perspectives, the domain architecture of HECT-type E3 ligases determines their substrate recognition specificity and functional outcomes in HCC. The WW domains of NEDD4 and WWP1/2 mediate the recognition of substrates containing PPxY motifs, such as PTEN, enabling these ligases to regulate the PI3K-AKT pathway. The C2 and WW domains of SMURF1/2 enable interaction with membrane-associated proteins such as TGF-β receptors, allowing precise regulation of TGF-β signaling. The RCC1-like domains of the HERC family confer the ability to regulate GTPase-related signaling and respond to inflammatory stimuli. Through their diverse N-terminal domains, other HECT members participate in the regulation of fundamental biological processes including metabolism (HACE1), stress

responses (HECTD2) and cell death (HUWE1 and TRIP12). This structure-function relationship explains the molecular basis of the protective or pathogenic roles of different HECT members in HCC. In conclusion, HECT-type E3 ubiquitin ligases function as critical regulatory nodes in HCC, influencing tumor proliferation, invasion, metastasis, and drug resistance through diverse mechanisms. Their functional duality arises from substrate diversity, context-dependent interactions, scaffolding protein involvement, post-translational modifications and tumor microenvironment.

7. Limitations and conclusion

Although numerous studies have highlighted the potential of HECT-type E3 ubiquitin ligases as therapeutic targets in liver diseases, significant limitations remain. First, research coverage is uneven. The majority of evidence focuses on the NEDD4 subfamily (for example, NEDD4 and SMURF1/2) and HUWE1, whereas functional studies on the HERC subfamily (for example, HERC5/6) and unclassified members (for example, HECTD2/3 and UBE3C) are scarce, potentially leading to the oversight of critical regulatory nodes. Second, our mechanistic understanding is often incomplete. The precise characterization of ubiquitination sites and linkage types (for example, K48 vs. K63) is frequently lacking, and some conclusions rely heavily on single animal models without validation in human tissues. However, further comparative analyses were impeded by several limitations. Third, the majority of studies on MASLD lack clear definitions of disease staging, thereby precluding a stratified comparison between early- and late-stage disease. Moreover, liver fibrosis and cirrhosis are frequently conflated in the literature, obscuring distinctions critical for mechanistic interpretation. Forth, numerous studies fail to specify the precise cell types in which HECT-type E3 ubiquitin ligases exert their functions; for example, whether their actions are localized to hepatocytes or HSC. Collectively, these gaps constrain a more nuanced understanding of the potentially divergent roles of different HECT-type E3 ligases across the continuum of disease progression.

Most critically, the evidence supporting clinical translation remains limited. While NEDD4 has emerged as a promising oncogenic target in HCC, with multiple clinical correlation studies supporting its prognostic value, most HECT-type E3 ligases lack validation in human patient cohorts. Even for NEDD4, therapeutic translation remains hindered by the absence of selective small-molecule inhibitors that have advanced to clinical trials. For other family members such as SMURF1/2, ITCH and NEDD4L, the current findings are predominantly derived from preclinical models, with human data limited to correlative expression analyses that cannot establish causality. Although SMURF2 agonists (for example, J-1155) and E6AP activators (for example, all-trans retinoic acid) show promise in preclinical models, their selectivity, safety and cross-species efficacy require further validation. Furthermore, targeted therapies may cause off-target effects because of the dual role nature of these enzymes (for example, profibrotic yet anti-carcinogenic actions). Furthermore, evidence supporting its clinical translation is weak. Finally, functional contradictions are evident: For instance, NEDD4L can suppress ER stress but also activate pro-inflammatory pathways in MASLD; SMURF2 may promote TGF-β/Smad signaling in fibrosis while exerting protective effects via miRNA mechanisms. These paradoxes suggest highly context-dependent regulation, potentially fine-tuned by microenvironmental metabolic pressure, immune status, or epigenetic modifications. However, most current studies have focused on single disease models or isolated molecular mechanisms, lacking systematic analysis across disease stages and multi-organ interactions, which hampers a comprehensive understanding of their functional duality.

Future investigations should integrate multi-omics technologies (for example, single-cell sequencing and spatial transcriptomics) to delineate the dynamic expression and substrate profiles of HECT-type E3s across different liver disease stages and cellular subpopulations. Structurally, techniques such as cryo-electron microscopy and AI-based prediction can elucidate structure-function relationships, facilitating the design of allosteric modulators to circumvent functional contradictions. For clinical translation, patient-derived organoids or humanized mouse models are essential for validating the conservation of regulatory networks, along with the exploration of biomarkers for prognostic stratification. Greater attention should also be directed towards understudied members that may influence disease progression by modulating the immune microenvironment or metabolic reprogramming.

HECT-type E3 ubiquitin ligases function as critical molecular hubs in the pathogenesis of diverse liver diseases and exhibit a remarkable dual role that profoundly influences disease initiation, progression and therapeutic responses. This functional duality manifests across the entire spectrum of hepatic pathologies, wherein the same ligase can both promote and inhibit disease progression through context-dependent substrate selection, spatiotemporally specific expression patterns, and the integration of diverse microenvironmental cues. Upon analyzing the underlying reasons for this trend, it is considered that the 'dual-role' nature of HECT-type E3 ubiquitin ligases may offer a plausible explanation. Most of these genes do not consistently exhibit uniform effects across multiple pathological features throughout disease progression, which may lead to suboptimal outcomes in clinical studies and subsequent stagnation in translational development. As a result, advancing from fundamental research to clinical application remains particularly challenging. In metabolic dysfunction-associated liver disease, these enzymes simultaneously modulate lipid homeostasis and inflammatory responses through opposing actions on key metabolic regulators and signaling networks. During fibrogenesis, individual family members demonstrate both profibrotic and antifibrotic activities depending on the cellular context and experimental models. In viral hepatitis, HECT-type E3 ligases occupy a central position at the host-virus interface, either restricting replication through direct viral protein degradation or facilitating propagation by hijacking the host cellular machinery. Within HCC, these ligases exert pleiotropic effects, including proliferation, invasion, metastasis and drug resistance, and function as either oncogenic drivers or tumor suppressors through diverse substrate interactions.

Although the specific mechanisms underlying this 'dual role' effect cannot be fully elucidated due to variations in the depth of previous studies, it is proposed that analyzing

differences in disease stage, tissue specificity and heterogeneity among experimental models can partially explain the conflicting findings regarding HECT-type E3 ubiquitin ligases in liver diseases. Stage-specific substrate switching accounts for numerous contradictory observations, as exemplified by NEDD4L in MASLD/MASH: Its downregulation in early stages impairs Txnip and JAK2 degradation, thereby exacerbating hepatic steatosis; conversely, its upregulation in late stages targets LAPTM5, activating the pro-inflammatory CDC42-MAPK signaling pathway. Cellular specificity within the liver microenvironment further reinforces functional duality: SMURF1 protects hepatocytes from steatosis via PPARγ regulation yet promotes HSC activation through TLN1 ubiquitination; similarly, ITCH knockout confers systemic metabolic protection while simultaneously elevating pro-inflammatory BCAA levels in specific cellular compartments. Heterogeneity in experimental models, including interspecies differences, disease induction methods (for example, CCl_4 vs. cholestatic models), and temporal analysis points, has generated conflicting reports regarding the roles of SMURF2 in fibrosis and HERC5 in HCV replication. The innovative contribution of the present review lies in integrating these disparate observations into a unified framework that positions HECT-type E3s as dynamic, context-dependent molecular hubs rather than linear disease-promoting factors. Unlike previous reviews that merely catalog individual ligase functions in isolation, paradigm-shifting connections were establish by elucidating how substrate switching across disease stages generates functional duality, revealing how scaffold proteins (for example, ARHGAP24 directing WWP1 activity) dictate context-specific outcomes, and integrating microenvironmental signals, such as metabolic stress, inflammatory cues and viral hijacking, as critical determinants of ligase behavior. This framework transforms apparent contradictions from obstacles into opportunities, providing a mechanistic roadmap for developing stage-specific and cell-type-selective therapeutic strategies. By targeting auxiliary domains rather than conserved catalytic sites, this approach holds promise for inhibiting pathological activity while preserving beneficial functions.

Given the highly context-dependent nature of HECT-type E3 ligase activity, current therapeutic strategies aimed at directly targeting the conserved HECT domain to treat common chronic liver diseases remain inadvisable. The structural similarity of catalytic domains across family members raises significant concerns regarding off-target effects, whereas the dual roles of individual ligases across different disease stages and cell types complicate predictable therapeutic outcomes. Future efforts should focus on elucidating upstream regulatory mechanisms, developing strategies to modulate specific protein-protein interactions involving accessory domains, and identifying context-specific biomarkers that can predict functional directionality. Only through such refined approaches can the tremendous therapeutic potential of HECT-type E3 ligases be safely and effectively harnessed.

Future efforts should therefore prioritize the following: i) Expanding clinical correlation studies with functional validation in patient-derived models; ii) elucidating upstream regulatory mechanisms that govern context-specific activities; iii) developing strategies to modulate specific protein-protein interactions involving accessory domains rather than the conserved HECT domain; and iv) identifying context-specific biomarkers that can predict functional directionality. Only through such refined approaches can the tremendous therapeutic potential of HECT-type E3 ligases be safely and effectively harnessed, moving beyond correlative observations toward mechanism-based interventions. The path to clinical translation requires patience and rigor; however, the central position of these enzymes in liver disease networks offers unprecedented opportunities for eventual therapeutic innovation.

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Authors' contributions

TXL and HC read and analyzed the references and wrote the manuscript. PZ and CZY performed literature review. ZFS conceptualized the study and provided written ideas and financial support. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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