

Reprogramming of the hepatic ubiquitin-immune axis: A unifying mechanism in liver disease progression (Review)

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Abstract. The progression of liver disease from steatosis to hepatocellular carcinoma has previously been interpreted as a sequential pathological continuum. In the present review, an integrated paradigm wherein this progression arises fundamentally from systematic reprogramming of the ubiquitin code within the hepatic microenvironment was proposed. Under sustained pathological stress, key E3 ligases and deubiquitinases undergo functional remodeling, transitioning from homeostatic guardians to pathogenic drivers of disease. The mechanism by which this reprogramming forms a central axis governing disease progression was systemically illustrated. During initiation, it disrupts inflammasome regulation and mitophagy; throughout progression, it dismantles immune tolerance and activates cell death pathways; and in advanced stages, it stabilizes oncoproteins, degrades tumor suppressors and facilitates immune evasion. Building upon this mechanistic model, novel therapeutic strategies aimed at achieving a functional reset of the dysregulated ubiquitin system via targeted protein degradation were further explored. This approach offers a transformative

framework for intercepting the malignant progression of liver disease and presents new prospects for clinical intervention.

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Abbreviations: A20, TNF- α -induced protein 3; ALD, alcoholic liver disease; BAFF, B-cell activating factor; BAFFR, BAFF receptor; BRCC3, BRCA1-BRCA2-containing complex subunit 3; β TrCP, β -transducin repeat-containing protein; Cbl-b, casitas B-lineage lymphoma-b; cIAP1, cellular inhibitor of apoptosis protein 1; CSN5, COP9 signalosome subunit 5; CYLD, cylindromatosis; c-Myc, cellular myelocytomatosis oncogene; CD28, cluster of differentiation 28; cGAS, cyclic GMP-AMP synthase; DAMPs, damage-associated molecular patterns; DUBs, deubiquitinating enzymes; E3 ligases, E3 ubiquitin ligases; FBXO38, F-box only protein 38; Fbw7, F-box/WD repeat-containing protein 7; HCC, hepatocellular carcinoma; HECT, homologous to E6-AP carboxyl terminus; IKK α , I κ B kinase α ; IRF3, interferon regulatory factor 3; IL-1 β , interleukin-1 β ; Itch, itchy E3 ubiquitin ligase; K63, lysine 63; LUBAC, linear ubiquitin chain assembly complex; MARCH5, membrane-associated RING-CH 5; Met1, N-terminal methionine 1; MDM2, mouse

double minute 2 homolog; mtDNA, mitochondrial DNA; NAFLD, non-alcoholic fatty liver disease; NEDD4, neural precursor cell expressed developmentally downregulated protein 4; NF- κ B, nuclear factor κ B; NEMO/IKK γ , NF- κ B essential modulator/I κ B kinase γ ; NIK, NF- κ B-inducing kinase; NLRP3, NOD-like receptor family pyrin domain-containing 3; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PARKIN, Parkin RBR E3 ubiquitin ligase; PINK1, PTEN-induced kinase 1; PLC γ 1, phospholipase C γ 1; PKC θ , protein kinase C θ ; PPAR γ , peroxisome proliferator-activated receptor γ ; PROTACs, proteolysis-targeting chimeras; RBR, RING-between-RING; RING, really interesting new gene; RIPK1, receptor-interacting serine/threonine-protein kinase 1; RNF5, ring finger protein 5; ROS, reactive oxygen species; SCF, Skp1-Cullin-F-box; Smad2/3, mothers against decapentaplegic homolog 2/3; SPOP, Speckle-type POZ protein; SREBP1c, sterol regulatory element-binding protein 1c; STING, stimulator of interferon genes; TCR, T-cell receptor; TBK1, TANK-binding kinase 1; TGF β , transforming growth factor β ; Th2, type 2 T-helper cell; TNF α , tumor necrosis factor α ; TRAF2, TNF receptor-associated factor 2; TRIM29, tripartite motif-containing 29; UCHs, ubiquitin C-terminal hydrolases; USP7, ubiquitin-specific protease 7

Key words: ubiquitin system, liver disease progression, immune-metabolic reprogramming, hepatocellular carcinoma

1. Introduction

The progression of liver disease from initial steatosis through chronic hepatitis and fibrosis to hepatocellular carcinoma (HCC) constitutes a major global health burden (1), accounting for ~2 million deaths annually worldwide, with HCC alone responsible for >800,000 deaths each year (2). While traditionally viewed as a linear sequence triggered by diverse etiologies, emerging evidence reveals a shared, deeper molecular foundation, including the systematic disruption and reprogramming of the ubiquitin code, which is a central post-translational regulatory system governing hepatic proteostasis. The ubiquitin system was first discovered in the late 1970s and early 1980s as a pathway responsible for ATP-dependent protein degradation, a finding that was later recognized with the Nobel Prize in Chemistry in 2004 (3). Subsequent studies have revealed that beyond its canonical role in proteolysis, the ubiquitin code governs a wide array of cellular processes, including cell cycle control, DNA repair and immune signaling (4-6). The implication of ubiquitin signaling in tumorigenesis emerged from seminal observations that aberrant expression or mutation of E3 ubiquitin ligases (E3 ligases) and deubiquitinases (DUBs) frequently occurs in human cancers, leading to dysregulation of oncoproteins and tumor suppressors. This historical trajectory underscores the relevance of the ubiquitin system as a critical node in cancer biology (7,8).

In physiological conditions, the ubiquitin system, coordinately executed by E3 ligases and DUBs, functions as a precise molecular operating system. It maintains immune tolerance, metabolic equilibrium and cell survival by decoding ubiquitin signals to determine the fate of key signaling proteins, thereby preserving hepatic homeostasis despite continuous antigen exposure. Under persistent pathological stress, including metabolic lipotoxicity, chronic inflammatory signals and cell death, this regulatory network becomes fundamentally corrupted. Key E3 ligases and DUBs are functionally subverted, transitioning from homeostatic guardians to pathogenic drivers. For instance, the immune-regulatory functions of A20 and casitas B-lineage lymphoma-b (Cbl-b) are compromised, whereas destructive pathways, such as NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation [which has been linked to BRCA1-BRCA2-containing complex subunit 3 (BRCC3) in certain contexts] and cylindromatosis (CYLD)-dependent death, are aberrantly engaged (9,10). This reprogramming converts protective responses into a chronic engine of tissue damage, fibrosis and genomic instability.

Ultimately, during cirrhosis and carcinogenesis, the ubiquitin code is comprehensively hijacked to establish a pro-tumorigenic state. Oncoproteins including β -catenin and c-Myc evade degradation, while tumor suppressors such as p53 are targeted by E3 ligases such as MDM2. Concurrently, immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) are stabilized by specific DUBs, reinforcing an immunosuppressive microenvironment (11).

The present review hypothesized that the spectrum of liver disease progression reflects the systematic corrosion and reprogramming of the hepatic ubiquitin code by a pathological microenvironment. The functional metamorphosis of E3 ligases and DUBs represents a unifying molecular axis linking steatosis, inflammation, fibrosis and carcinogenesis.

In addition, this paradigm was systematically deciphered and novel therapeutic strategies, including targeted inhibitors and proteolysis-targeting chimeras, designed to reset hepatic homeostasis and intercept disease progression were explored.

2. Regulatory mechanisms of the ubiquitin system in hepatic immunity

Composition and function of the ubiquitin system. Ubiquitination is a post-translational modification wherein ubiquitin is covalently attached to substrate proteins. The functional outcome is determined by polyubiquitin chain topology, which can be linked via any of the seven lysine residues of ubiquitin (K6, K11, K27, K29, K33, K48 and K63) or its N-terminal methionine (Met1). K48-linked chains primarily target substrates for proteasomal degradation, whereas K63-linked chains regulate non-proteolytic processes including signal transduction and DNA repair. Linear (Met1-linked) chains play specialized roles in nuclear factor κ B (NF- κ B) signaling and cell death regulation.

Ubiquitination machinery: A tripartite enzymatic cascade. Ubiquitination proceeds via a three-step enzymatic cascade involving E1 (activating), E2 (conjugating) and E3 (ligating) enzymes (12-14). E3 ligases confer substrate specificity, with >600 members encoded in the human genome classified into three families based on catalytic mechanism (15,16). Fig. 1 describes the mechanisms of each family, demonstrating that each family uses a distinct strategy to transfer ubiquitin to the substrate.

Really interesting new gene (RING)-type E3s act as scaffolds that facilitate direct ubiquitin transfer from E2 to the substrate (17-21). Homologous to E6-AP carboxyl terminus (HECT)-type E3s form a catalytic intermediate, accepting ubiquitin from E2 via a thioester bond before transferring to substrate (19-21). RING-between-RING (RBR)-type E3s utilize a hybrid RING-HECT mechanism involving a transient E3 ubiquitin intermediate (16,20).

Deubiquitination: Reversal and regulation. Ubiquitination is reversed by DUBs (22-24), whereby the 100 human DUBs cleave ubiquitin-substrate bonds to terminate signaling, rescue proteins from degradation and recycle ubiquitin monomers to maintain cellular homeostasis (23). As shown in Fig. 1, major DUB families include: i) Ubiquitin-specific proteases (USPs); ii) ovarian tumor proteases (OTUs); and iii) ubiquitin C-terminal hydrolases (24).

Central role of ubiquitination in cellular processes. The ubiquitin system regulates numerous fundamental cellular processes (24). It modulates the intensity and duration of signal transduction by controlling the stability of receptors, adaptors and kinases. In inflammatory responses, ubiquitination exerts precise control over inflammasome components and key molecules within the NF- κ B pathway, thereby orchestrating the initiation and resolution of inflammation. Furthermore, the system directly regulates apoptotic and necroptotic pathways by influencing caspase activity and the stability of critical signaling molecules such as receptor-interacting serine/threonine-protein kinase 1 (RIPK1) (25). During

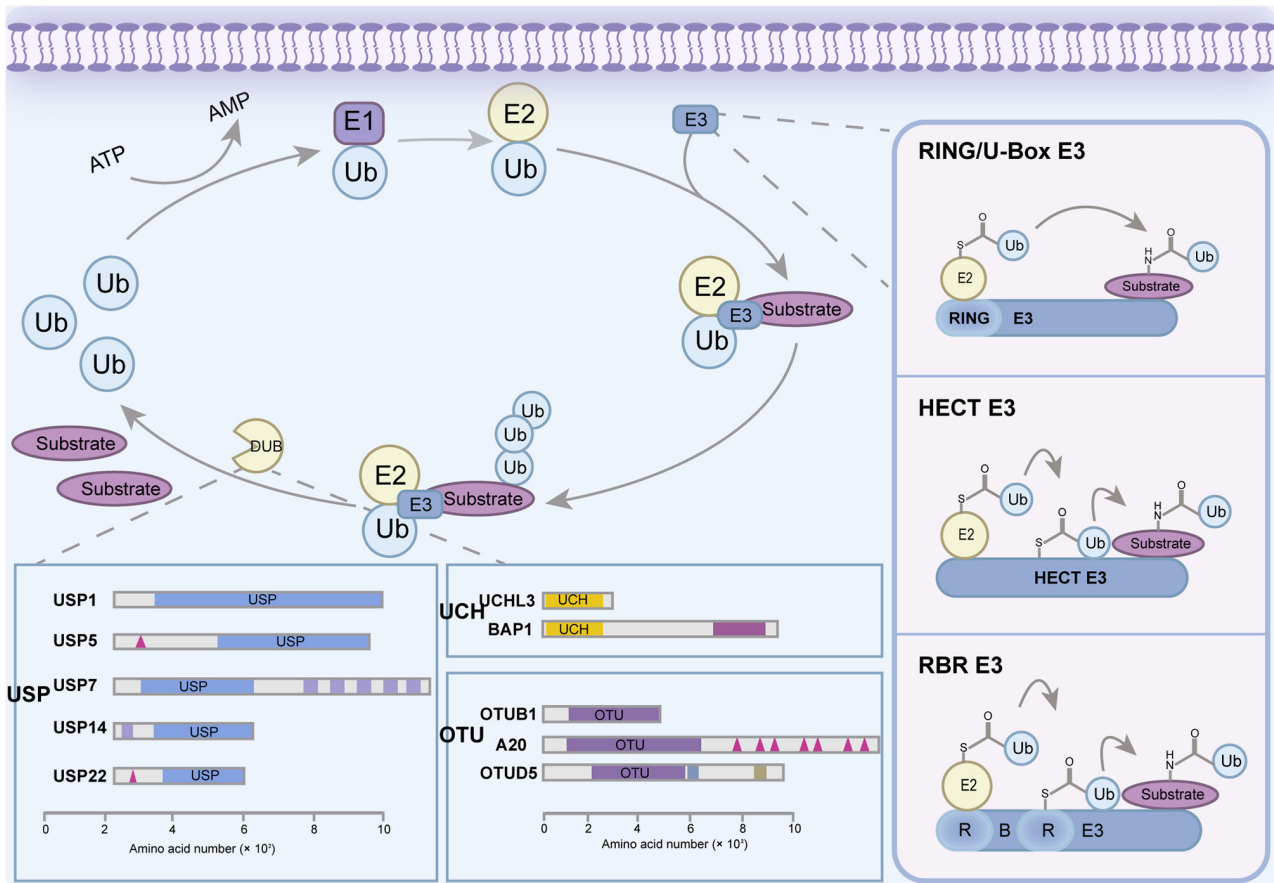


Figure 1. Main families of Ub ligases and DUBs and their core features. E3 Ub ligases (key subtypes) mainly include HECT (with C-terminal HECT domain), RING (with N-terminal zinc-binding RING domain), U-box (with C-terminal U-box domain) and RBR (with RING1/IBR/RING2 domains). DUBs (main families) mainly include USP, UCHL and OTU families, and the domain composition of these families (such as catalytic domains and accessory domains of USP) is described. Ub, ubiquitin; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; RING, really interesting new gene; HECT, homologous to E6-AP C-terminus; RBR, RING-between-RING; DUBs, deubiquitinating enzymes; USP, ubiquitin-specific protease; UCH, ubiquitin C-terminal hydrolase; OTU, ovarian tumor protease; UCHL3, ubiquitin C-terminal hydrolase L3; BAP1, BRCA1-associated protein 1; A20, TNF- α -induced protein 3; OTUB1, OTU domain-containing ubiquitin aldehyde-binding protein 1; OTUD5, OTU deubiquitinase 5.

autophagy, ubiquitin acts as a degradation signal that labels damaged organelles for clearance (26). Within metabolic pathways, ubiquitination controls the stability of metabolic enzymes and transcription factors, including sterol regulatory element-binding proteins, thereby coordinating glucose and lipid homeostasis.

Hepatic immune milieu and the role of ubiquitination. The liver constitutes an immunologically-privileged organ, continuously exposed to gut-derived antigens and metabolites via the portal venous circulation (27). This results in a microenvironment characterized by a high antigenic load (28). To maintain homeostasis under such conditions, the liver has developed robust tolerogenic mechanisms that enable distinction between harmless substances and genuine threats, thereby preventing excessive immune damage.

Within this unique immunological setting, the ubiquitin system serves as a pivotal regulator of hepatic immune homeostasis (29). It establishes and sustains immune tolerance by precisely controlling the initiation and resolution of innate immune signaling, such as the Toll-like receptor (TLR) and NF- κ B pathway, and by setting stringent activation thresholds for adaptive immune cells, such as both T and B lymphocytes.

This regulatory function is exemplified by E3 ligases such as Cbl-b and itchy E3 ubiquitin ligase (Itch) (30,31). Consequently, the stability of the hepatic microenvironment is highly dependent on the precise, dynamic and context-dependent regulation of immune pathways by the ubiquitin system.

3. Central role of the ubiquitin system in maintaining hepatic homeostasis

Ubiquitin-mediated regulation of immune tolerance. The liver is a central organ for systemic metabolism and immune regulation. Due to its unique anatomical location and continuous exposure to gut-derived antigens via the portal circulation, the liver requires sophisticated regulatory mechanisms to distinguish self from non-self, balance immune clearance with tolerance and maintain metabolic stability. The ubiquitin system, comprising E1 activating enzymes, E2 conjugating enzymes, E3 ligases, DUBs and downstream degradation pathways, plays a central regulatory role in this context. Through reversible ubiquitin-chain modifications, this system precisely governs protein activity, subcellular localization, protein-protein interactions and stability (32,33). Under physiological conditions, a coordinated network of E3 ligases and

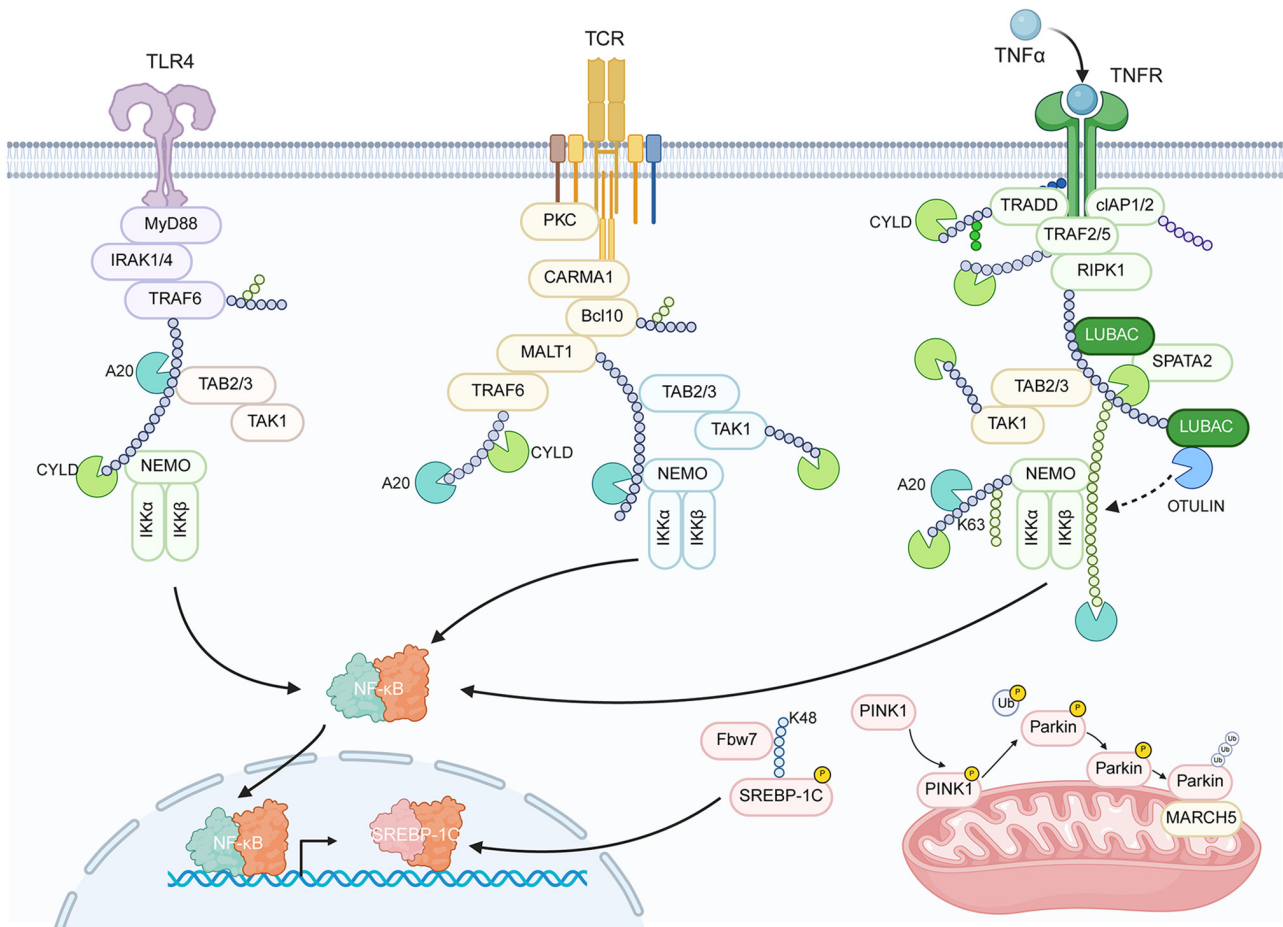


Figure 2. Hepatic ubiquitin system-mediated homeostatic regulatory networks under physiological conditions. Key components (such as A20, CYLD, Fbw7, PINK1-PARKIN and MARCH5) acting across pathways: i) Fine-tuning immune responses downstream of TLR4, TCR and TNFR signaling; ii) governing metabolic pathways via regulators such as Fbw7; and iii) executing protein quality control through the PINK1-PARKIN axis and MARCH5. The coordinated, context-dependent actions of these components underpin hepatic functional homeostasis. TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88; IRAK1/4, interleukin-1 receptor-associated kinase 1/4; TRAF6, TNF receptor-associated factor 6; A20, TNF- α -induced protein 3; TAB2/3, TAK1-binding protein 2/3; TAK1, TGF- β -activated kinase 1; CYLD, cylindromatosis; NEMO, NF- κ B essential modulator; IKK α/β , I κ B kinase α/β ; NF- κ B, nuclear factor κ B; TCR, T-cell receptor; Cbl-b, casitas B-lineage lymphoma-b; Itch, itchy E3 ubiquitin ligase; PKC θ , protein kinase C θ ; PLC γ 1, phospholipase C γ 1; Fbw7, F-box/WD repeat-containing protein 7; SREBP-1c, sterol regulatory element-binding protein 1c; PINK1, PTEN-induced kinase 1; PARKIN, Parkin RBR E3 ubiquitin ligase; MARCH5, membrane-associated RING-CH 5; NLRP3, NOD-like receptor family pyrin domain-containing 3; Ub, ubiquitin; K48, lysine 48; K63, lysine 63.

DUBs sustains hepatic homeostasis by regulating immune responses, metabolic equilibrium and cellular quality control.

Hepatic immune homeostasis depends on the precise negative regulation of innate immune signaling. In the TLR4-NF- κ B pathway, the E3 ligase tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) activates the I κ B kinase (IKK)-NF- κ B axis via K63-linked polyubiquitination, initiating pro-inflammatory gene expression (34). To prevent excessive activation, a built-in negative feedback mechanism operates through the ubiquitin-editing enzyme A20 (TNFAIP3) (35,36). A20 terminates signaling by removing K63-linked chains from TRAF6 and RIPK1 via its OTU domain, while simultaneously targeting these substrates for proteasomal degradation through K48-linked ubiquitination mediated by its zinc-finger domains (Fig. 2) (37). This coordinated activity ensures the self-limiting nature of inflammatory responses.

The ubiquitin system also establishes stringent activation thresholds for adaptive immunity, particularly in T-cell activation. Full T-cell activation requires signaling through both the T-cell receptor (TCR) and the CD28 costimulatory

pathway (38). As illustrated in Fig. 2, this threshold is enforced by a network of E3 ligases, including Cbl-b, Itch and GRAIL, that collectively restrain TCR and costimulatory signaling. The figure visually organizes the mechanism by which the ligases intersect distinct signaling nodes to cooperatively maintain immune tolerance. In the absence of CD28 co-stimulation, activated Cbl-b catalyzes K48-linked ubiquitination and degradation of key TCR-signaling components, including protein kinase C θ , phospholipase C γ 1 and CD28 itself, thereby attenuating signal transduction (39). Cbl-b further impairs immunological-synapse formation by targeting the adaptor protein Crk-L for degradation (40). Additional E3 ligases contribute to this layered control, including Itch, which, in concert with the E2 enzyme ubiquitin-conjugating enzyme H7, mediates degradation of the TCR ζ chain, whereas GRAIL restricts T-cell activation and clonal expansion by promoting the endocytosis and degradation of membrane proteins such as CD154. Collectively, these E3 ligases constitute a multilayered regulatory network that actively maintains the immune-tolerant state of the liver.

Ubiquitin-dependent regulation of metabolic pathways. The metabolic function of the liver is critically regulated by the ubiquitin system, which controls the stability of key metabolic transcription factors. This regulation occurs through targeted ubiquitination and degradation of key metabolic transcription factors, a mechanism that integrates hepatic metabolic control with the broader ubiquitin-mediated regulatory framework (Fig. 2). Lipid homeostasis exemplifies this regulation. The F-box/WD repeat-containing protein 7 (Fbw7), a substrate-recognition component of the Skp1-cullin-F-box E3 ligase complex, targets phosphorylated nuclear sterol regulatory element-binding protein 1c for K48-linked ubiquitination and proteasomal degradation. This process establishes a negative feedback loop that limits excessive hepatic lipid accumulation (41). Furthermore, the typically low expression of peroxisome proliferator-activated receptor γ in hepatocytes is maintained partly through constitutive ubiquitination and degradation mediated by E3 ligases, such as neural precursor cell expressed developmentally downregulated protein 4, thereby suppressing hepatocyte transdifferentiation toward an adipocyte-like phenotype (42).

Ubiquitin-dependent quality control in organelle stress. The ubiquitin system plays a critical role in quality control mechanisms that counteract organelle stress induced by high metabolic activity. For the clearance of damaged mitochondria, the phosphatase and tensin homolog-induced kinase 1 (PINK1) - parkin RBR E3 ubiquitin ligase (PARKIN) pathway serves as a central regulatory axis. As shown in Fig. 2, two key stress-resisting mechanisms mediated by the ubiquitin system, mitochondrial quality control through mitophagy and constrained NLRP3 inflammasome activation, are presented side by side to illustrate their coordinated roles in preserving cellular homeostasis. PINK1 stabilizes on the outer mitochondrial membrane and phosphorylates ubiquitin, leading to recruitment and activation of the cytosolic E3 ligase PARKIN (43). Activated PARKIN deposits ubiquitin chains on mitochondrial surface proteins, thereby tagging damaged organelles for elimination via mitophagy.

Similarly, the activation of the NLRP3 inflammasome is tightly regulated by ubiquitination. Under basal conditions, constitutive ubiquitination of NLRP3 suppresses its oligomerization and activation. This inhibitory state is maintained by the mitochondria-localized E3 ligase membrane-associated RING-CH 5 (MARCH5), which mediates K48-linked ubiquitination and degradation of NLRP3. Additionally, tripartite motif containing 31 (TRIM31) promotes NLRP3 clearance under cellular stress, further highlighting the multilayered ubiquitin-dependent regulation of inflammasome activity (44).

Summary. Under physiological conditions, the hepatic ubiquitin system operates as an integrated and dynamically regulated network that sustains homeostasis. Key components, including A20, Cbl-b and Itch, precisely modulate immune responses; regulators such as Fbw7 govern metabolic pathways; and mediators such as the PINK1-PARKIN axis and MARCH5 execute quality control. The precision and context-dependency of this system, supported by multi-layered feedback, are essential for maintaining hepatic function. However, under sustained metabolic, toxic or immunological stress, core

elements of this network can be subverted or impaired. This functional conversion transforms regulatory components from homeostatic regulators into pathological progression.

4. Mechanisms of hepatic ubiquitin homeostasis disruption by metabolic stress

Metabolic stress as a pathogenic initiator in liver disease. In liver disease pathogenesis, metabolic dysregulation represents a key initiating event (45). Within the shared multiple-hit model of non-alcoholic and alcoholic fatty liver disease, persistent metabolic stressors, such as lipotoxicity and oxidative stress, act as primary inducers (1,46,47). These stressors not only disturb metabolic pathways but also disrupt the hepatic ubiquitin system. This disruption involves the functional conversion of core E3 ligases and DUBs from homeostatic regulators into promoters of pathological efforts (48). The process is characterized by aberrant activation of innate immune and inflammatory pathways alongside impaired cellular quality control.

Aberrant activation of the NLRP3 inflammasome: Dysregulation of ubiquitin-dependent control. Under physiological conditions, the activation of innate immune signaling pathways, such as the NLRP3 inflammasome, is tightly regulated by ubiquitination (49). However, in the pathological contexts of non-alcoholic fatty liver disease (NAFLD) and alcoholic steatohepatitis, metabolic danger signals, including excess saturated fatty acids, free cholesterol and its crystals, and lipid peroxidation products, disrupt this ubiquitin-mediated control, leading to aberrant activation of these pathways (50).

NLRP3 inflammasome activation constitutes a crucial checkpoint for the proteolytic maturation of IL-1 β and IL-18, dependent on caspase-1, thereby orchestrating the transition from simple fatty liver to steatohepatitis (51). Under basal conditions, NLRP3 is tonically inhibited by constitutive ubiquitin modifications (52). A two-step process, involving priming and activation signals, is necessary for its complete engagement (53). Metabolic stress fulfills this dual requirement by acting as a priming stimulus and, through the direct perturbation of NLRP3 ubiquitination, serving as an activation trigger (54,55).

The DUB BRCC3 has been implicated as a key mediator in this pathway (56). Specifically, BRCC3 possesses K63-specific DUB activity and directly binds to NLRP3, removing the K63-linked ubiquitin chains from it. Exposure to saturated fatty acids (such as palmitate) and cholesterol crystals in macrophages and Kupffer cells potentiates this interaction and augments the catalytic function of BRCC3 (57). This deubiquitination is proposed to serve as a molecular prerequisite for the oligomerization of NLRP3 and its subsequent assembly into an active inflammasome. Consistently, attenuating BRCC3 expression blunts the assembly of the NLRP3 inflammasome and the secretion of IL-1 β triggered by metabolic danger signals. Consistent with this, preclinical studies have established that BRCC3-mediated deubiquitination is a critical regulatory step for NLRP3 inflammasome activation (52,58). Given the central role of NLRP3-driven inflammation in NASH pathogenesis, it is plausible that similar dysregulation of the BRCC3-NLRP3 axis may contribute to the hepatic

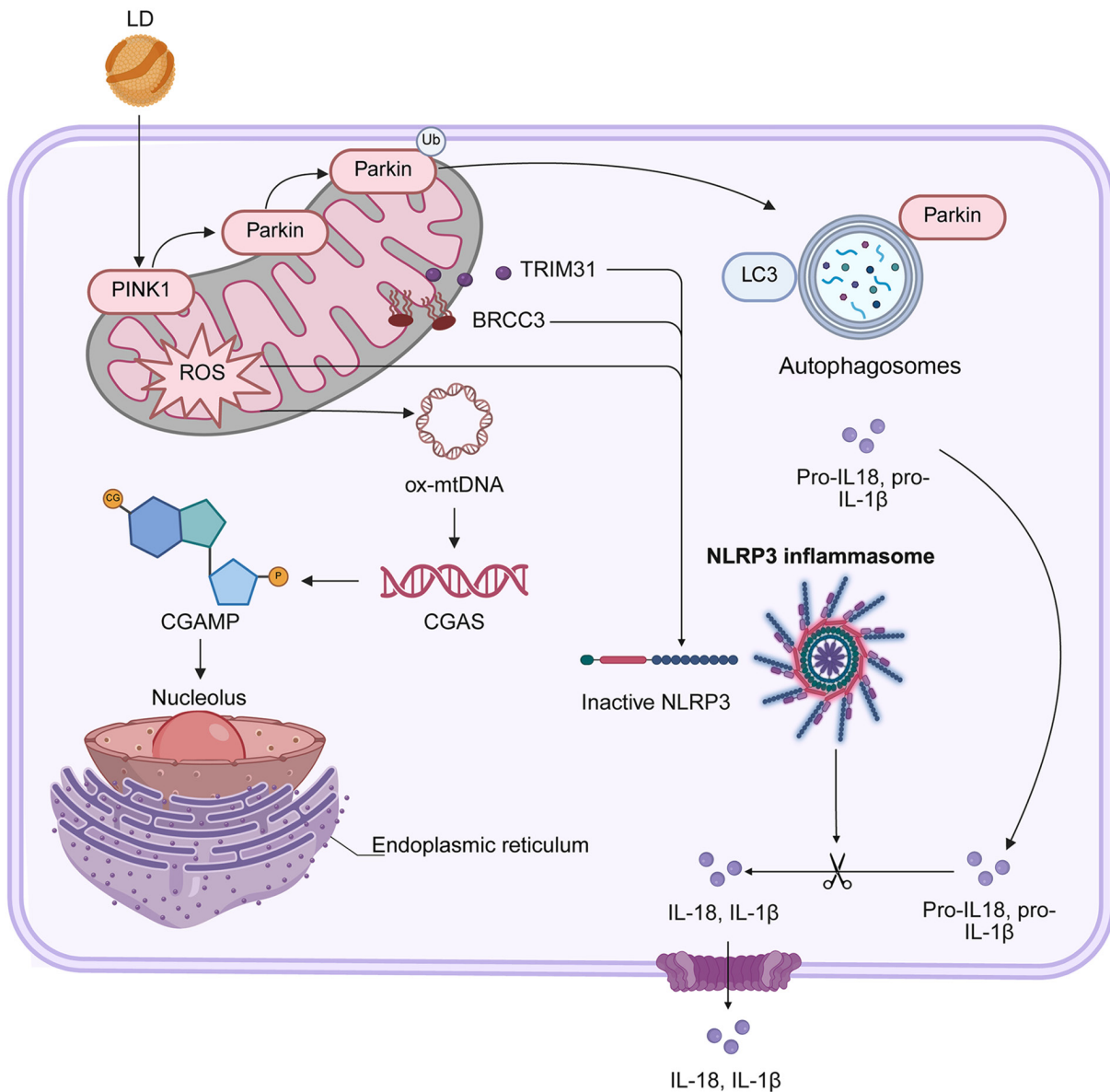


Figure 3. Metabolic stress-driven dysregulation of hepatic ubiquitin system nodes and pathogenic initiation, including impaired PINK1-PARKIN mitochondrial quality control (linked to mitochondrial ROS/oxmtDNA release), BRCC3 (deubiquitinase) activation that relieves NLRP3 inflammasome inhibition and suppressed protective E3 ligase MARCH5. These altered ubiquitin-modifying enzyme nodes are repurposed from homeostatic guardians to drivers of pathogenic events (such as NLRP3-dependent IL-18/1 β secretion) initiating hepatic pathology. PINK1, PTEN-induced kinase 1; PARKIN, Parkin RBR E3 ubiquitin ligase; TRIM31, tripartite motif-containing 31; BRCC3, BRCA1-BRCA2-containing complex subunit 3; NLRP3, NOD-like receptor family pyrin domain-containing 3; IL-1 β , interleukin-1 β ; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes.

inflammatory milieu in NASH, although direct evidence from NASH-specific models remains to be fully elucidated.

However, it is worth noting that the role of DUBs in NLRP3 inflammasome regulation is highly context-dependent. While BRCC3 has been shown to promote NLRP3 activation in myeloid cells under lipotoxic conditions, other DUBs such as USP7 and USP47 have been reported to enhance NLRP3 activation through facilitating ASC oligomerization, and USP50 by removing K48-linked ubiquitin chains to stabilize NLRP3 (59,60). By contrast, the DUB A20 has been shown to suppress NLRP3 inflammasome activation by competitively binding to NIMA-related kinase 7 (61), highlighting that different DUBs can exert opposing effects on NLRP3 depending on the cellular context and specific protein-protein interactions. Furthermore, the current evidence linking

BRCC3 to NLRP3 activation in the liver remains largely correlative. The majority of studies, including those cited in the present review, are derived from macrophage or Kupffer cell models; whether BRCC3 exerts a similar function in other hepatic cell types (such as hepatocytes or hepatic stellate cells) under lipotoxic stress is less well-established. Additionally, direct evidence for BRCC3-mediated NLRP3 deubiquitination *in vivo*, such as from conditional knockout models or *in situ* enzymatic assays, is still limited.

Fig. 3 illustrates the proposed mechanism by which metabolic stress triggers NLRP3 inflammasome assembly through BRCC3-driven deubiquitination. The figure also highlights the counterregulatory role of TRIM31, which promotes K48-linked ubiquitination and proteasomal degradation of NLRP3 (62). Collectively, these findings indicate that

metabolic stress disrupts the normal regulatory constraints on the NLRP3 inflammasome through a dual mechanism, involving coordinately activating DUBs while simultaneously suppressing specific E3 ubiquitin ligases (62-64).

Disruption of mitochondrial quality control: Impairment of the PINK1-PARKIN pathway. While competent mitochondria constitute the hub of cellular energy metabolism, dysfunctional organelles are notable sources of reactive oxygen species (ROS) and mitochondrial DNA (mtDNA) (65). These released molecules serve as potent damage-associated molecular patterns (DAMPs), capable of activating both the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway and the NLRP3 inflammasome (66-68). Therefore, the selective removal of damaged mitochondria via mitophagy is a critical homeostatic mechanism. The canonical PINK1-PARKIN mitophagy pathway, which is crucial for this process, has been reported to be susceptible to disruption under lipotoxic conditions (69), although the precise mechanisms remain incompletely defined and may vary by cell type or experimental context. Fig. 3 captures the proposed consequences of this disruption, including mitochondrial damage accumulation driven by PINK1-PARKIN impairment, and the ensuring of pathological crosstalk with immune signaling cascades, representing a potential vicious cycle that links metabolic stress to sterile inflammation.

Under physiological conditions, the PINK1-PARKIN pathway continuously monitors mitochondrial integrity (70). Following the dissipation of the mitochondrial membrane potential, PINK1 accumulates on the outer mitochondrial membrane and recruits cytosolic PARKIN through the phosphorylation of ubiquitin molecules (71). The activated PARKIN polyubiquitinates the mitochondrial surface, generating ubiquitin chains that serve as recognition signals for the autophagy machinery via specific autophagy receptors (such as p62, optineurin and nuclear dot protein 52 kDa), thereby marking the damaged organelle for sequestration and clearance (72).

In addition to the PINK1-PARKIN pathway, the liver employs alternative mitochondrial quality control mechanisms that contribute to cellular homeostasis. These include receptor-mediated mitophagy, in which mitophagy receptors such as BCL2 interacting protein 3 (BNIP3), NIP3-like protein X (NIX) and FUN14 domain-containing protein 1 (FUNDC1) directly recruit autophagic machinery to damaged mitochondria independently of PARKIN (73). Additionally, mitochondrial-derived vesicles represent an alternative route for selective removal of oxidized mitochondrial proteins or mtDNA without requiring whole-organelle degradation. While the functional relevance of these pathways in NAFLD and alcoholic liver disease (ALD) remains incompletely characterized, they may partially compensate when PINK1-PARKIN function is compromised under lipotoxic stress. Elucidating the interplay between these parallel quality control systems represents an important direction for future investigation.

In hepatocytes affected by NAFLD and ALD, emerging evidence suggests that the PINK1-PARKIN pathway becomes dysfunctional. Severe lipid overload directly impairs mitochondrial function, leading to membrane depolarization and excessive ROS production (74). This creates

a supra-physiological burden of damaged mitochondria, which may overwhelm the PINK1-PARKIN clearance system. Furthermore, elevated levels of free fatty acids have been proposed to interfere with the effective translocation of PARKIN to impaired mitochondria, potentially through post-translational modifications of PARKIN by lipid metabolites or alterations in mitochondrial membrane lipid composition. However, conflicting studies have reported that PARKIN-independent mitophagy pathways (such as those mediated by FUNDC1 or NIX) may partially compensate under lipotoxic conditions (75,76), and it is not clear whether PARKIN dysfunction is a primary driver or a secondary consequence of mitochondrial stress.

These functional defects are considered to contribute to the intracellular accumulation of dysfunctional mitochondria. These organelles are not only bioenergetically inefficient but also perpetually generate ROS, exacerbating oxidative stress and inducing lipid peroxidation and DNA damage. The mtDNA released from these mitochondria acts as a DAMP, which is recognized by cGAS, thereby activating the cGAS-STING pathway and inducing the expression of interferon-stimulated genes, including type I interferons. This response aggravates hepatic inflammation and immune cell infiltration. Simultaneously, mtDNA serves as a potent activator of the NLRP3 inflammasome. Thus, it is hypothesized that by impairing PINK1-PARKIN-mediated mitochondrial quality control, metabolic stress could transform the hepatocyte into a persistent source of oxidative stress and pro-inflammatory signals, potentially providing a sustained driving force for chronic hepatitis and subsequent fibrogenesis. It must be acknowledged that these mechanistic conclusions are largely derived from *in vitro* models using acute lipotoxic stimuli; further studies using chronic *in vivo* models and human tissue are needed to fully validate the causal role of PINK1-PARKIN impairment in NAFLD or ALD pathogenesis.

Summary. This section systematically outlined the mechanisms through which metabolic stress initiates hepatic pathology by disrupting key regulatory nodes within the ubiquitination system. Specifically, metabolic stress disrupts the normal inhibitory constraints on the NLRP3 inflammasome by activating deubiquitinating enzymes such as BRCC3 while concurrently suppressing protective E3 ligases such as MARCH5. In parallel, it disrupts mitochondrial quality control by impairing the function of the PINK1-PARKIN pathway. The defining feature of this initial pathogenic phase is the dysregulation of critical E3 ligases and DUBs within the disease microenvironment, which may repurpose them from regulators of cellular homeostasis to drivers of pathological progression.

Understanding this early stage carries notable therapeutic implications. It suggests that dysregulated ubiquitin-modifying enzymes may represent candidate therapeutic targets, and that intervening during the initial phase of disease could potentially interfere with the progression from simple steatosis to active steatohepatitis. However, given that multiple ubiquitin-modifying enzymes are likely implicated at this early stage, and given the inherent redundancy within the ubiquitin system, it remains uncertain whether targeting any single enzyme or combination would suffice to halt disease progression. Future

studies employing genetic and pharmacological approaches in preclinical models are needed to evaluate the feasibility and efficacy of such strategies. However, once this cascade is initiated, it fosters a more complex and self-sustaining pathological milieu. This culminates in a broader, more pervasive reprogramming of the ubiquitin system. The subsequent stage, characterized by the breakdown of immune tolerance and alterations in cell fate decisions under conditions of persistent inflammation and cell death, will be the primary focus of the following section.

5. Systemic regulatory mechanisms of immune tolerance disruption and altered cell fate

Evolution to a systemic pathological landscape. The progressive and sustained impact of metabolic stress drives fundamental reprogramming of the hepatic ubiquitin system. This reprogramming extends beyond initial, focal disruptions and culminates in a complex, self-perpetuating pathological landscape within the liver. The microenvironment evolves from one defined by metabolic disturbance and localized inflammation to a state characterized by the pervasive accumulation of cellular debris, elevated titers of pro-inflammatory cytokines, sustained infiltration and activation of diverse immune cells and excessive deposition of extracellular matrix components.

At this advanced stage, disease progression becomes increasingly decoupled from the original exogenous metabolic insults. Instead, it is critically driven and amplified by the breakdown of intrinsic homeostatic and regulatory circuits. The hepatic ubiquitin system undergoes systemic and maladaptive reprogramming, with its most consequential manifestations being the comprehensive breakdown of immune tolerance and the loss of precise control over cell fate decisions. These cardinal dysfunctions are molecularly instantiated through the impairment of adaptive immune checkpoint pathways and the pathological rewiring of the regulatory networks that govern hepatocyte survival, death and phenotypic plasticity. This section will delineate the mechanisms through which the reprogrammed ubiquitin system orchestrates this transition to a state of chronic, unresolving inflammation and tissue remodeling.

Disruption of B-cell tolerance via the B-cell activating factor (BAFF)/TRAF3/NF- κ B axis. Under homeostatic conditions, E3 ubiquitin ligases serve pivotal roles in maintaining peripheral immune tolerance by modulating the activation threshold of both T and B lymphocytes. However, this regulatory mechanism becomes dysfunctional within the inflammatory milieu characteristic of NASH or chronic viral hepatitis.

In the context of B-cell homeostasis, the B-cell activating factor (BAFF) signaling pathway is critical for the survival of mature B-cells. Under physiological conditions, an E3 ligase complex composed of cellular inhibitor of apoptosis protein (cIAP)-1, cIAP2, TRAF2 and TRAF3 constitutively suppresses BAFF-receptor (BAFF-R) signaling. Central to this suppression, TRAF3 continuously recruits NF- κ B-inducing kinase (NIK) and targets it for ubiquitin-mediated degradation, thereby maintaining the non-canonical NF- κ B pathway in a quiescent state (77).

Within the inflammatory microenvironment, cytokines such as type I interferon and interleukin-6 upregulate BAFF expression. The ensuing excess BAFF binds to BAFF-R, inducing receptor multimerization (78). This event triggers the recruitment of the TRAF2-cIAP1 and cIAP2 complex, which subsequently targets TRAF3 for proteasomal degradation via K48-linked polyubiquitination (79). The elimination of TRAF3 relieves the constitutive inhibition of NIK (80), and stabilized NIK phosphorylates and activates IKK α , which in turn processes the NF- κ B precursor p100 into its mature form, p52 (81). The p52 subunit forms a heterodimer with reticuloendotheliosis viral oncogene homolog B, and this complex translocates to the nucleus, where it initiates the transcription of genes that promote B-cell survival and maturation.

In autoimmune liver diseases, including primary biliary cholangitis and autoimmune hepatitis, elevated serum BAFF promotes sustained non-canonical NF- κ B2 activation through chronic TRAF3 degradation (82). This process subverts B-cell central tolerance, permitting the survival and maturation of autoreactive B-cells. Their subsequent differentiation into autoantibody-producing plasma cells drives hepatic inflammation through complement activation and immune-complex deposition.

Inflammatory suppression of E3 ligases compromises T-cell tolerance. In T cells, the inflammatory microenvironment disrupts the function of key E3 ubiquitin ligases, notably Cbl-b and Itch, through multiple mechanisms. Cbl-b activity is compromised via transcriptional repression and oxidative inactivation under inflammatory conditions. The consequent loss of Cbl-b function, combined with enhanced co-stimulatory signals, markedly lowers the threshold for T-cell activation. This dysregulation renders T cells prone to excessive responses against self-antigens or persistent viral antigens. This notion is supported by evidence from Cbl-b-deficient models, which develop severe CD8⁺ T-cell-driven hepatitis, suggesting that analogous mechanisms may contribute to immunopathology in human chronic viral hepatitis (83).

Similarly, the activity of Itch is modulated by the inflammatory milieu. Itch function is tightly regulated by its phosphorylation status and conformational dynamics; inflammatory signaling may alter the kinase/phosphatase balance, thereby affecting Itch activation. Deficiency in Itch leads to the accumulation of transcription factor JunB, which drives excessive production of T helper (Th)-2-type cytokines and impairs the negative regulation of TCR signaling. In the hepatic context, downregulation or functional impairment of Itch may disrupt the balance between Th17 cells and regulatory T cells, thereby facilitating the activation of autoreactive T cells and promoting inflammatory liver pathology (84).

Metabolic reprogramming and loss of feedback control in hepatocytes. In the context of hepatocyte fate determination, dysregulation occurs in metabolic control pathways. During the steatotic phase, hepatocytes initiate a compensatory feedback response through the upregulation of E3 ligases, such as Fbw7, which targets the sterol regulatory element-binding protein (SREBP) for degradation, thereby suppressing lipogenesis (85). However, as NASH progresses, upregulation of the DUB USP20, either in expression or activity, antagonizes

Fbw7-mediated degradation and stabilizes the SREBP protein (86). This disruption of regulatory equilibrium leads to persistent activation of the lipogenic program even under lipotoxic conditions, establishing a self-sustaining cycle of metabolic dysregulation. Concurrently, the transcription factor carbohydrate-responsive element-binding protein, which mediates glucose-to-lipid conversion, may accumulate aberrantly, potentially due to insufficient activity of its cognate E3 ligase(s).

Deregulation of cell death pathways: From survival signaling to necroptosis. Simultaneously, regulatory control over cell death pathways becomes compromised. TNF- α serves as a pivotal cytokine within the inflammatory hepatic microenvironment. Under physiological conditions, TNF- α binding to TNF receptor 1 induces the formation of Complex I, leading to recruitment of the linear ubiquitin chain assembly complex (LUBAC) (87). LUBAC catalyzes the synthesis of linear (M1-linked) ubiquitin chains on key signaling molecules, including RIPK1 and NF- κ B essential modulator (also termed $\text{IKK}\gamma$). This specific ubiquitination event is critical for productive NF- κ B pathway activation and subsequent expression of pro-survival genes.

In the context of NASH or drug-induced liver injury, this homeostatic balance is disrupted. Persistent inflammation and oxidative stress can impair NF- κ B transcriptional activity, while concurrently activating the deubiquitinating enzyme CYLD. Under pathological conditions, signaling inputs such as TNF- α , ROS or feedback from necroptotic pathways can activate phosphatases that dephosphorylate and thereby activate CYLD. Activated CYLD is subsequently recruited to the TNF-R1 signaling complex, where it catalyzes the removal of both K63-linked and linear (M1-linked) ubiquitin chains from RIPK1 (88). This deubiquitination promotes the release of RIPK1 kinase activity and facilitates the stabilization of Complex II (also referred to as the death-inducing signaling complex) (89). The resultant signaling outcome shifts toward caspase-8-dependent apoptosis or, if caspase-8 is inhibited, RIPK3/mixed lineage kinase domain-like protein-mediated necroptosis. In contrast to apoptosis, necroptosis elicits a more robust inflammatory response due to the release of intracellular DAMPs. The critical role of CYLD activation as a key driver of extensive hepatocyte death has been substantiated across multiple experimental models of liver injury.

In addition to apoptosis and necroptosis, ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation, has emerged as a key contributor to hepatocyte death in NAFLD and NASH (90). Ferroptosis is characterized by the accumulation of lethal lipid peroxides resulting from glutathione depletion and inactivation of glutathione peroxidase 4, a critical enzyme that neutralizes phospholipid hydroperoxides (91). The lipotoxic environment in steatotic livers, characterized by excess free fatty acids, iron overload and mitochondrial dysfunction, creates a permissive setting for ferroptosis (91). Recent studies have demonstrated that pharmacological inhibition of ferroptosis alleviates hepatic inflammation and fibrosis in preclinical NASH models, highlighting its pathogenic relevance (92,93). Notably, ferroptosis may intersect with the aforementioned CYLD-driven cell death axis, as ROS generated during ferroptosis can further

potentiate necroptotic signaling, and conversely, mitochondrial dysfunction, a hallmark of both pathways, may serve as a common upstream trigger (94). While the precise interplay between ferroptosis, apoptosis and necroptosis in the context of hepatic ubiquitin system dysregulation remains to be fully elucidated, emerging evidence suggests that ferroptosis represents an additional, and potentially parallel, cell death mechanism that warrants consideration in the pathogenesis of steatohepatitis (95).

Summary. Understanding this phase of functional rewiring reveals novel targets for therapeutic intervention. It suggests that during intermediate and advanced disease stages, strategies should aim to directly modulate these critical nodal points. Such approaches may include enhancing Cbl-b activity, promoting targeted degradation of hyperactive CYLD or employing BAFF-neutralizing antibodies. When extensive fibrosis develops and hepatocytes acquire pre-malignant transformative potential, the ubiquitin system is further co-opted by emerging tumor cells, which is a process that will form the central focus of the subsequent section.

6. Functional reprogramming of the ubiquitin system and construction of the tumor microenvironment in HCC

As chronic liver disease progresses to the cirrhotic stage, the hepatic microenvironment undergoes profound alterations. During this phase, the ubiquitin system, which has already undergone functional adaptation in earlier disease stages, is further reprogrammed. Under neoplastic selection pressure, hepatocyte clones with a survival advantage establish a microenvironment conducive to tumor growth, invasion and immune evasion by subverting ubiquitination regulatory networks. The core mechanisms driving this process include the systematic inactivation of tumor suppressor pathways, aberrant stabilization of oncoproteins and effective evasion of antitumor immune responses.

Systematic inactivation of the p53 tumor suppressor pathway. The tumor suppressor p53 is primarily regulated at the protein stability level by the E3 ubiquitin ligase MDM2 (96). Under physiological conditions, p53 and MDM2 form an autoregulatory negative feedback loop, ensuring that p53 is activated only in response to cellular stress (97). In HCC, this balance is disrupted through MDM2 gene amplification or overexpression (98). The resulting excess of MDM2 drives constitutive ubiquitin-mediated degradation of p53, thereby preventing the initiation of p53-dependent programs such as cell cycle arrest, DNA repair and apoptosis (99).

The DUB USP7 further reinforces suppression of the p53 pathway by stabilizing both MDM2 and DNA methyltransferase 1 (DNMT1) (100,101). Through its deubiquitinating activity, USP7 extends the half-life of MDM2 (102). Simultaneously, by stabilizing DNMT1, it promotes hypermethylation of the promoter regions of p53 target genes, adding a layer of transcriptional repression to the existing post-translational inhibition. These actions block p53 at both the protein level and the transcriptional level.

In addition to post-translational regulation, the p53 pathway is frequently inactivated through somatic mutations

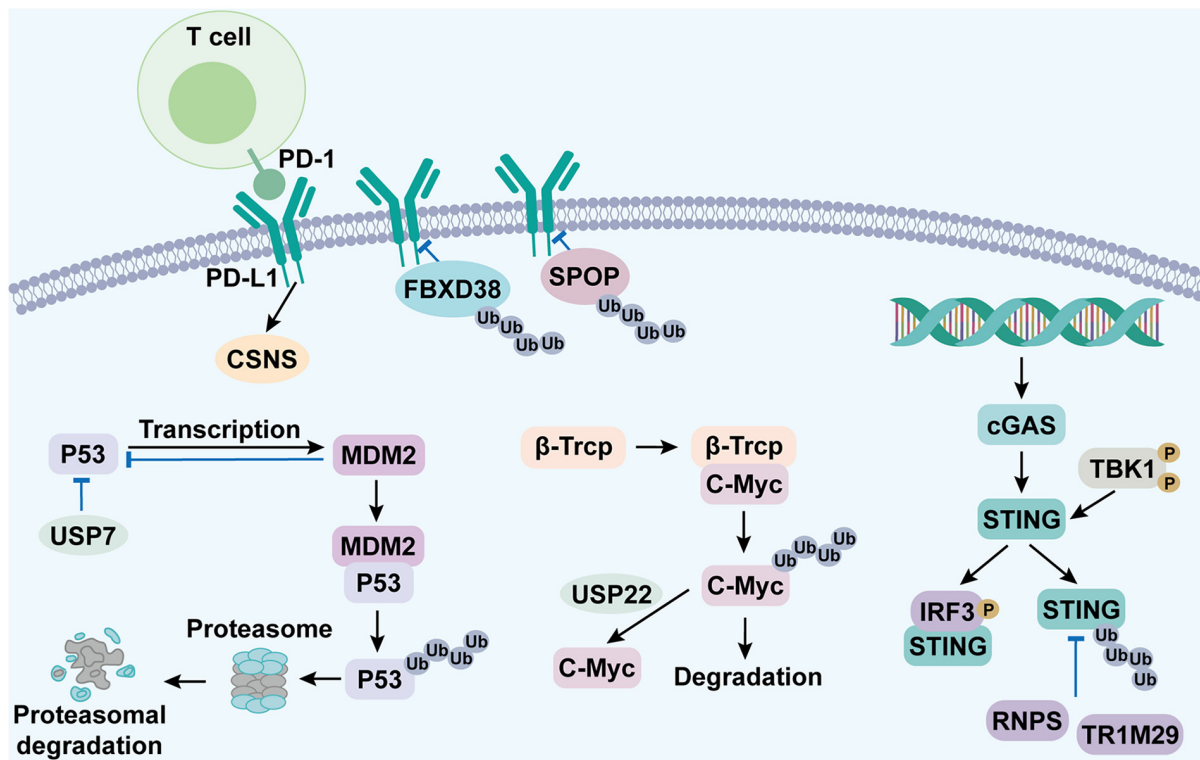


Figure 4. Schematic of ubiquitin system reprogramming in hepatocarcinogenesis and PROTAC therapeutic potential. During hepatocarcinogenesis, ubiquitin system rewiring drives tumorigenesis via four core alterations: i) CSN5-stabilized PD-L1 engages PD-1 on T-cells for immune evasion; ii) MDM2 (p53-induced) + USP7 promote p53 ubiquitination and proteasomal degradation; iii) impaired β -TrCP + enhanced USP22 block c-Myc ubiquitination, causing its accumulation; and iv) TRIM29 mediates STING ubiquitination, inhibiting the cGAS-STING pathway. These changes foster a tumor-promoting microenvironment. PROTAC may selectively degrade key nodes, although delivery/resistance challenges remain. PROTACs (proteolysis-targeting chimeras) offer a potential strategy to selectively degrade key oncogenic nodes within this reprogrammed network. PD-1, programmed death 1; PD-L1, programmed death-ligand 1; FBXD38, F-box only protein 38; SPOP, Speckle-type POZ protein; CSN5, COP9 signalosome subunit 5; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; IRF3, interferon regulatory factor 3; MDM2, mouse double minute 2 homolog; USP7, ubiquitin-specific protease 7; p53, tumor protein p53; β -TrCP, β -transducin repeat-containing protein; c-Myc, cellular myelocytomatosis oncogene; RNF5, ring finger protein 5; TRIM29, tripartite motif-containing 29; PROTAC, proteolysis-targeting chimera; Ub, ubiquitin.

in HCC. Missense mutations in the TP53 gene, particularly at hotspot codons such as R249S, R273H and R175H, occur in 30-50% of human HCCs, with the highest frequency observed in geographic regions associated with aflatoxin B1 exposure (103). These mutations not only abolish the tumor-suppressive functions of wild-type p53, but also confer gain-of-function (GOF) properties that promote proliferation, invasion and chemoresistance (104). Notably, numerous mutant p53 proteins exhibit increased stability due to impaired MDM2-mediated degradation, leading to their accumulation in tumor cells (105). Thus, in a substantial subset of HCCs, p53 inactivation is driven by genetic mutations rather than, or in addition to, MDM2 overexpression. The coexistence of MDM2 amplification and TP53 mutations is typically mutually exclusive, reflecting distinct molecular subtypes of HCC (106). Understanding the mutation status of p53 is therefore critical for accurately assessing the status of the tumor suppressor pathway and for guiding therapeutic strategies that may differentially target wild-type vs. mutant p53.

Fig. 4 depicts the mechanism by which this system operates in HCC, demonstrating that MDM2 drives p53 degradation, while USP7 locks in repression by stabilizing both enzymes.

Impaired degradation and aberrant stabilization of oncogenic drivers. β -Transducin repeat-containing protein (β -TrCP) acts

as the substrate-recognition subunit within the SCF family of E3 ubiquitin ligases, orchestrating the ubiquitin-mediated degradation of numerous critical regulatory proteins (107,108). Within the Wnt signaling pathway, β -TrCP serves as an essential component of the β -catenin destruction complex, specifically targeting phosphorylated β -catenin for proteasomal degradation (109). In HCC, this regulatory axis is frequently subverted, either through inactivating mutations in genes encoding core components of the destruction complex or through activating mutations in the β -catenin gene itself.

The destruction complex is composed of several core proteins, including adenomatous polyposis coli (APC), axin 1 (AXIN1), AXIN2, glycogen synthase kinase 3 β and casein kinase 1. In HCC, inactivating mutations in these genes are observed at varying frequencies, with AXIN1 mutations occurring in ~8% of cases, AXIN2 mutations in ~3% and APC mutations in ~3% (110). Taken together, disruption of the destruction complex through mutations in these core components occurs in 10-15% of HCCs, complementing the 25-30% of cases with activating mutations in the gene encoding β -catenin (CTNNB1) (111,112). These mutations disrupt the assembly or function of the destruction complex, leading to impaired phosphorylation and subsequent ubiquitination of β -catenin, thereby allowing its nuclear accumulation and transcriptional activation of pro-proliferative target genes such as

c-Myc and cyclin D1 (111). In numerous cases, these mutations are mutually exclusive with activating mutations in CTNNB1, reflecting distinct molecular subclasses of HCC with different clinical outcomes (113). Collectively, regardless of whether the initiating event is a destruction complex mutation or a CTNNB1 mutation, the common consequence is the stabilization and nuclear accumulation of β -catenin. Consequently, β -catenin escapes degradation, accumulates aberrantly and translocates to the nucleus, where it drives the transcription of proliferation-associated genes. Fig. 4 schematically outlines the coordinated disruption of ubiquitin-dependent oncoprotein control in HCC, demonstrating the loss of β -TrCP-mediated degradation and gain of USP22-driven stabilization of β -catenin and c-Myc.

The regulatory function of β -TrCP toward the oncoprotein c-Myc is also commonly impaired in HCC. Phosphorylated c-Myc constitutes a physiological substrate for β -TrCP and its degradation represents a crucial mechanism for restraining c-Myc-driven oncogenicity. Tumor cells employ diverse strategies to evade this β -TrCP-mediated degradation, including alteration of c-Myc phosphorylation status or engagement of competitive binding partners (114). Concurrently, the frequent upregulation of the DUB USP22 in HCC further enhances c-Myc stability by catalyzing the removal of its ubiquitin chains. In addition to stabilizing c-Myc, USP22 also promotes the stability of other pro-tumorigenic transcription factors, thereby collectively fostering malignant progression in HCC.

Evasion of innate immune surveillance via STING pathway degradation. In tumor immune evasion, cytosolic DNA released from genomically unstable or damaged tumor cells is recognized by cGAS, leading to activation of the cGAS-STING signaling pathway (115). Following STING activation, TANK-binding kinase 1 and the transcription factor IRF3 are recruited and phosphorylated, thereby driving the production of type I interferons and initiating an antitumor immune response (116).

HCC cells circumvent this innate immune surveillance by upregulating the E3 ubiquitin ligases ring finger protein 5 (RNF5) (117) and TRIM29 (118), which target STING for ubiquitination and subsequent proteasomal degradation, effectively dampening pathway activation. Clinical analyses corroborate that elevated expression of either RNF5 or TRIM29 is associated with suppressed STING signaling, reduced intratumoral infiltration of CD8⁺ T-cells and poorer patient prognosis (117,118). Together, these mechanisms enable tumor cells to evade cell-intrinsic immune detection.

Promotion of adaptive immune evasion through PD-L1 stabilization. PD-L1, a critical immune-regulatory molecule expressed on the surface of tumor cells, functions to suppress T-cell activity (119). The disruption of PD-L1 homeostatic turnover in HCC via COP9 signalosome subunit 5 (CSN5)-dependent deubiquitination, and its implications for antitumor immunity and therapeutic resistance, is illustrated in Fig. 4. The homeostatic turnover of PD-L1 is governed by several E3 ubiquitin ligases, including Speckle-type POZ protein and F-box only protein 38, which mediate its ubiquitin-dependent degradation (120,121). However, in HCC, the frequent overexpression of the DUB CSN5 counteracts

this regulatory process. By catalyzing the removal of ubiquitin chains from PD-L1, CSN5 stabilizes the protein, prolongs its half-life and elevates its surface expression on tumor cells (122).

This stabilization mechanism holds considerable clinical relevance. During treatment with immune checkpoint inhibitors, tumor cells can upregulate CSN5 to maintain PD-L1 stability. Consequently, even under antibody-mediated blockade, the high synthesis rate of PD-L1 coupled with its enhanced stabilization sustains its surface expression, contributing to acquired therapeutic resistance. A promising strategy to overcome such resistance may involve combination therapy that co-administers programmed cell death 1/PD-L1-blocking antibodies with a CSN5 inhibitor, thereby synergistically reducing PD-L1 stability and restoring antitumor immunity.

Summary. During hepatocarcinogenesis, the ubiquitin system is systematically reprogrammed to favor tumorigenesis. This reprogramming is characterized by: i) Coordinated suppression of the p53 pathway via MDM2 overexpression and USP7-mediated stabilization, as well as through TP53 somatic mutations that confer GOF properties and occur in 30-50% of HCCs; ii) aberrant stabilization of oncoproteins such as β -catenin and c-Myc, resulting from inactivating mutations in destruction complex components (such as APC, ANIX1 and ANIX2) in 10-15% of HCCs, activating CTNNB1 mutations in 25-30% of HCCs, impaired β -TrCP-mediated degradation and enhanced USP22 activity; iii) inhibition of innate immune surveillance through RNF5- and TRIM29-dependent degradation of STING; and iv) promotion of adaptive immune evasion via CSN5-stabilized PD-L1. Together, these alterations establish a tumor-promoting microenvironment that fuels the initiation and progression of HCC.

These mechanistic insights provide a rational basis for therapeutic intervention. Conventional single-target inhibitors typically show limited efficacy against the complex, rewired network. By contrast, proteolysis-targeting chimera (PROTAC) technology offers a promising strategy by enabling the selective degradation of key nodal proteins within the ubiquitin-proteasome system, thereby allowing precise intervention in the reprogrammed network. Nevertheless, critical challenges remain, including the development of liver-specific delivery systems and the need to overcome intrinsic and acquired resistance mechanisms. In addition to the asialoglycoprotein receptor (ASGPR)-targeted approach, alternative liver-specific delivery strategies have been actively explored, such as N-acetylgalactosamine (GalNAc)-conjugated PROTACs that leverage ASGPR-mediated endocytosis for hepatocyte-selective targeting (123,124). The successful clinical translation of PROTAC-based therapies for HCC will likely require the integration of such targeted delivery platforms with optimized pharmacokinetic properties.

7. Therapeutic strategies targeting the ubiquitin system: From mechanism to clinic

Paradigm shift: From pathway inhibition to network restoration. Informed by a comprehensive analysis of the functional evolution of the ubiquitin system throughout liver disease progression, contemporary therapeutic strategies must

now pivot from merely inhibiting discrete signaling pathways toward intervening in the dysregulated regulatory networks themselves. This paradigm shift entails moving beyond the suppression of aberrant signals to actively restoring the homeostatic function of the ubiquitination machinery. Within this conceptual framework, targeted protein degradation technologies emerge as a transformative modality, offering novel therapeutic potential for achieving this objective.

Limitations of conventional therapeutic paradigms. Conventional small-molecule inhibitors typically function by occupying the active site of a target protein, thereby blocking its activity (125). However, this approach faces inherent limitations when applied to the complex regulatory networks governed by the ubiquitin system. For targets such as transcription factors and scaffold proteins, which often lack conventional, druggable active sites, developing effective inhibitors remains a notable challenge (126). Furthermore, tumor cells can develop resistance through feedback mechanisms and the activation of compensatory pathways. Early therapeutics targeting the ubiquitin-proteasome system have provided both proof-of-concept and important lessons for the field. The proteasome inhibitors bortezomib and carfilzomib were approved by the US Food and Drug Administration (FDA) in 2003 and 2012, respectively, for the treatment of multiple myeloma and mantle cell lymphoma (127,128). These agents demonstrated that pharmacological manipulation of the UPS is clinically feasible. However, their application in solid tumors such as HCC has been limited by notable off-target toxicity, including peripheral neuropathy and thrombocytopenia, as well as the development of acquired resistance (127,129). These limitations are largely attributable to their broad, systemic impact on global proteostasis, highlighting the need for more selective strategies that target specific E3 ligases or DUBs rather than the proteasome itself (129).

Rise of targeted protein degradation: PROTACs and molecular glues. PROTACs and molecular glues represent a novel class of therapeutics that exploit the endogenous ubiquitin-proteasome system to achieve selective degradation of target proteins (130). A PROTAC molecule is a hetero-bifunctional agent designed to simultaneously bind both a protein of interest and an E3 ubiquitin ligase, thereby inducing ubiquitination and subsequent proteasomal degradation of the target (124). Unlike conventional inhibitors, this strategy operates through a catalytic mechanism, enables the targeting of proteins traditionally considered ‘undruggable’ and offers the potential for enhanced selectivity through rational molecular design.

The clinical translation of targeted protein degradation has advanced notably. The molecular glue degraders lenalidomide and pomalidomide, which recruit the E3 ligase cereblon (CRBN) to induce degradation of Ikaros (IKZF1) and Aiolos (IKZF3), are FDA-approved for multiple myeloma and have provided clinical validation for pharmacologically induced protein degradation (124,131).

PROTAC technology has now entered clinical evaluation. The most advanced PROTAC, vepdegestrant (ARV-471), which targets the estrogen receptor, has completed Phase III trials and is under regulatory review for ER⁺/HER2⁻ advanced

breast cancer (132). Other PROTACs in clinical development include ARV-110 targeting androgen receptor for prostate cancer and KT-474 targeting interleukin-1 receptor-associated kinase 4 for inflammatory diseases (132). These clinical-stage degraders have demonstrated proof-of-mechanism and favorable safety profiles in patients (124,132).

Application prospects in liver diseases. Targeted protein degradation holds considerable therapeutic promise in the context of liver diseases (124,133,134). In metabolic-associated liver diseases, PROTACs designed to target the TGF- β receptor or Smad2/3 proteins could potentially inhibit fibrosis progression by eliminating key signaling molecules responsible for hepatic stellate cell activation (134-138). Similarly, selective degraders targeting the NLRP3 inflammasome may allow precise modulation of the innate immune response. Furthermore, restoring hepatic metabolic homeostasis could be achieved through the degradation of USP20, which would normalize the stability and activity of the transcription factor SREBP.

Potential in HCC therapy. In HCC, targeted protein degradation holds considerable therapeutic promise. PROTAC molecules designed against historically challenging oncoproteins, such as c-Myc and β -catenin, have demonstrated notable efficacy in a preclinical study (138).

The therapeutic application of MDM2-targeted degradation in HCC is critically dependent on p53 mutation status. In p53 wild-type HCC, targeted degradation of MDM2 is expected to restore p53-mediated tumor suppression by preventing MDM2 from ubiquitinating and degrading p53.

However, this strategy is unlikely to be effective in p53-mutated HCC, which accounts for 30-50% of cases (103). In these tumors, the mutant p53 protein lacks wild-type tumor-suppressive function and often acquires oncogenic GOF properties that promote proliferation, invasion and chemoresistance (104). Notably, numerous mutant p53 proteins exhibit increased stability due to impaired MDM2-mediated degradation, leading to their accumulation in tumor cells (105). Therefore, in p53-mutated HCC, MDM2 degradation would not restore functional p53 activity. For these patients, alternative PROTAC-based strategies are being actively explored, including direct degradation of the mutant p53 itself or targeting downstream effectors of mutant p53-driven oncogenic pathways (105).

Beyond target selection, the pharmacokinetic properties of PROTACs, particularly their *in vivo* half-life, represent a critical determinant of therapeutic efficacy. The catalytic mechanism of PROTACs, where one molecule can induce degradation of multiple target proteins, partially compensates for pharmacokinetic limitations, enabling sustained target suppression even after drug clearance (139). Furthermore, the development of liver-specific delivery systems (such as GalNAc-conjugated PROTACs or lipid nanoparticles) has been shown to improve tissue accumulation and prolong effective exposure in the liver, as discussed previously (111,112). Notably, the turnover rates of MDM2 and p53 also influence the duration of the therapeutic effect. p53 is a short-lived protein (half-life, 20-40 min), whereas MDM2 has a longer half-life (2-4 h), suggesting that sustained MDM2 degradation may be required for prolonged p53 stabilization. p53 is a short-lived

protein (half-life, 20-40 min), whereas MDM2 has a longer half-life (2-4 h), suggesting that sustained MDM2 degradation may be required for prolonged p53 stabilization (140).

Furthermore, employing PROTAC technology to degrade immune checkpoint molecules such as PD-L1 represents a novel strategic approach to overcoming resistance mechanisms associated with current immunotherapies.

Challenges in clinical translation. The clinical translation of targeted degradation technologies continues to face notable challenges. Tissue-specific delivery is crucial to ensure both efficacy and safety, as systemic administration may lead to off-target effects, highlighting the need for liver-targeted delivery systems such as those utilizing the ASGPR. Additionally, optimizing targeting specificity remains an ongoing endeavor. A PROTAC molecule must exhibit high selectivity not only for the target protein and the recruited E3 ligase, but must also account for the physiological roles of the hijacked E3 ligase, as prolonged use could disrupt the homeostasis of its endogenous substrates. Finally, the issue of drug resistance cannot be overlooked. Tumor cells may develop resistance through various mechanisms, including down-regulation of the E3 ligase, mutations in the target protein or alterations in proteasome function.

Beyond these well-established obstacles, several additional challenges have emerged from recent clinical experience. First, the suboptimal pharmacokinetic properties of PROTACs, including limited oral bioavailability and short half-lives, pose formulation and dosing hurdles (124). Second, acquired resistance to degraders has been documented clinically. For example, decreased expression of the E3 ligase CRBN underlies resistance to lenalidomide in multiple myeloma (124). Third, on-target off-tumor toxicity remains a concern, as the targeted protein may also play essential roles in normal tissues, necessitating careful evaluation of therapeutic windows. Finally, robust biomarkers for patient selection and pharmacodynamic monitoring are critical for successful clinical deployment (124). Addressing these challenges will require iterative optimization of degrader chemistry, innovative delivery strategies and combination therapies.

8. Conclusion

The progression of liver disease, from steatosis and hepatitis to fibrosis, and ultimately to HCC, cannot be adequately described by a linear, additive model driven by distinct etiologies. The present review advances a central thesis, whereby this deleterious pathological cascade is fundamentally propelled by a systemic functional reprogramming of the ubiquitin system, initiated by persistent insults within the evolving hepatic microenvironment. A pivotal molecular link connecting these pathological stages is the transformation of key E3 ubiquitin ligases and DUBs from guardians of cellular homeostasis under physiological conditions into active drivers of disease pathogenesis.

Functional reprogramming of the ubiquitin system constitutes a core mechanism underlying disease progression. Under physiological conditions, this system ensures precise control of immune tolerance, metabolic equilibrium and quality control via key regulators such as A20, Cbl-b, Fbw7

and the PINK1-PARKIN axis. However, the pathological microenvironment induces a specific rewiring of this regulatory network. For instance, metabolic stress activates effectors such as BRCC3, while suppressing others such as MARCH5, thereby lifting the inhibition of the NLRP3 inflammasome and concurrently impairing mitophagy. Notably, alternative mitophagy pathways mediated by FUNDC1, BNIP3 and NIX may partially compensate when the PINK1-PARKIN axis is compromised under lipotoxic stress. Within the inflammatory milieu, suppression of Cbl-b and Itch activity, coupled with BAFF-mediated persistent degradation of TRAF3, disrupts adaptive immune tolerance. In hepatocytes, USP20 stabilizes SREBP to promote lipogenesis, whereas CYLD activation drives programmed cell death, including apoptosis, necroptosis and ferroptosis, the latter being a newly recognized iron-dependent, lipid peroxidation-driven cell death mechanism critically involved in steatohepatitis.

In HCC, the ubiquitin system is reconfigured to support tumor survival and immune evasion. This is exemplified by MDM2/USP7 axis-mediated functional inactivation of p53, which is further compounded by TP53 somatic mutations (occurring in 30-50% of HCCs) that confer GOF properties and exhibit increased stability due to impaired MDM2-mediated degradation; aberrant accumulation of β -catenin and c-Myc resulting from inactivating mutations in destruction complex components (such as APC, AXIN1 and AXIN2 in 10-15% of HCCs) or activating CTNNB1 mutations (in 25-30% of cases); RNF5/TRIM29-dependent degradation of STING to suppress innate immune sensing; and CSN5-mediated stabilization of PD-L1, which fosters an immunosuppressive microenvironment.

This insight necessitates a paradigm shift in the understanding of liver diseases. Pathological stages previously viewed as discrete entities are unified by a common framework of staged reprogramming within the ubiquitin system. Diverse initiating etiologies ultimately converge on perturbing critical nodal points within this system, thereby accounting for both the heterogeneity in clinical manifestations and the limitations of single-pathway therapeutic interventions.

Consequently, therapeutic strategies must pivot towards interventions that directly correct the dysregulated ubiquitin system. Targeted protein degradation technologies, such as PROTACs, offer a potent means to achieve this by enabling the direct elimination of key pathological driver proteins. This approach holds distinct advantages for addressing traditionally 'undruggable' targets and overcoming acquired treatment resistance. Notably, the therapeutic application of MDM2 degradation is effective primarily in p53 wild-type HCC; for p53-mutated tumors, alternative strategies such as direct degradation of mutant p53 itself are being actively explored. Promising clinical applications may include the degradation of inflammatory mediators (such as NLRP3 or TGF- β signaling components), the elimination of oncoproteins (such as c-Myc, β -catenin or MDM2) and the enhancement of immunotherapies via degradation of immune checkpoint proteins such as PD-L1. The ultimate objective of this strategic paradigm is to achieve a functional reset of the pathological ubiquitinome.

The clinical translation of this therapeutic paradigm faces distinct challenges. Achieving tissue-specific delivery necessitates the development of sophisticated delivery

systems leveraging liver-specific receptors or carriers, including GalNAc-conjugated PROTACs, lipid nanoparticles and antibody-drug conjugates. Optimizing on-target specificity requires careful consideration of the physiological functions of the recruited E3 ligase to avoid unintended consequences on its native substrates. The suboptimal pharmacokinetic properties of PROTACs, such as limited oral bioavailability and short half-lives, pose formulation and dosing hurdles, although their catalytic mechanism partially compensates for these limitations. Furthermore, proactively understanding and addressing potential drug resistance mechanisms is paramount, mandating the exploration of rational combination strategies and the development of backup compounds. Future research should be directed towards three key objectives: i) To systematically map the functional landscape of E3 ligases and DUBs across disease stages; ii) to advance cell-type-specific delivery technologies; and iii) to propel degrader-based combination therapies into clinical validation.

In conclusion, the present review establishes that functional reprogramming of the ubiquitin system is a consistent molecular hallmark throughout the spectrum of liver disease progression. This understanding provides a compelling rationale for developing therapies aimed at correcting these dysregulated core networks. Targeted interventions against specific components of the ubiquitin system signify a strategic shift in the therapeutic paradigm for liver diseases towards approaches informed by system-level biology.

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Authors' contributions

YJ conceptualized the present review, performed the literature search and selection, reviewed the data and wrote the manuscript. WN, YaS and YL provided supervision, contributed to the conceptual framework and critically revised the manuscript for important intellectual content. YJ, YiS and XC reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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