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Ubiquitination Modification in Hepatocellular Carcinoma

Houhong Wang*
Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

***Corresponding author:** Houhong Wang, Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

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Abstract

Hepatocellular carcinoma (HCC), a globally prevalent and lethal malignancy, is characterized by complex post-translational regulatory dysfunctions. Ubiquitination, a key post-translational modification, orchestrates protein stability, localization, and signalling networks critical for HCC pathogenesis. This retrospective analysis synthesizes recent advancements in ubiquitination-related molecules (E3 ubiquitin ligases, deubiquitinating enzymes [DUBs]) and their roles in HCC diagnosis, prognosis, and therapy. Data from 32 eligible studies (PubMed, 2020–2025) were analysed to evaluate associations between ubiquitination dysregulation and clinical outcomes. Key findings include the oncogenic roles of NEDD4, RNF214, and USP14, as well as diagnostic/prognostic potentials of ubiquitination-related biomarkers. Targeting ubiquitination pathways via small-molecule inhibitors or combination therapies shows promise in preclinical models. This review underscores the translational significance of ubiquitination research for improving HCC management.

Keywords

Ubiquitination; Hepatocellular carcinoma; Orchestrates protein; HCC pathogenesis.

Introduction

HCC accounts for 80% of primary liver cancers, with a 5-year survival rate <15% due to late diagnosis and therapeutic resistance. Post-translational modifications (PTMs), particularly ubiquitination, govern proteostasis by tagging proteins for degradation or functional modulation. The ubiquitination cascade involves E1 activators, E2 conjugators, and E3 ligases (substrate-specific), counterbalanced by DUBs that

remove ubiquitin moieties. Dysregulation of these enzymes drives oncogenic pathways in HCC, making ubiquitination a promising target for precision medicine.

Methods

Literature search

A systematic PubMed search was performed using keywords: ("hepatocellular carcinoma" OR "HCC") AND ("ubiquitination" OR "E3 ubiquitin ligase" OR "deubiquitinating enzyme" OR "DUB"). Inclusion criteria: English studies (2020–2025) reporting ubiquitination-related molecules in HCC with clinical/functional data. Exclusion criteria: reviews, non-HCC cancer studies, or non-English articles.

Data synthesis

Studies were categorized by molecular type (E3 ligases, DUBs), functional roles (proliferation, metastasis, therapy response), and clinical relevance (diagnosis, prognosis). Quantitative data (expression levels, survival outcomes, biomarker performance) were extracted and tabulated.

Results

Ubiquitination-related molecules in HCC

E3 Ubiquitin ligases

- **NEDD4**: Overexpressed in 72% of HCC tissues (vs. 28% in adjacent non-tumor tissues, p<0.001), NEDD4 promotes HCC progression by ubiquitinating tumor suppressor PTEN, activating PI3K/AKT signaling. In vivo models show NEDD4 knockdown reduces tumor volume by 40% (Table 1).
- **RNF214**: Upregulated in HCC cell lines (HepG2, Huh7) by 2.3-fold (vs. normal hepatocytes), RNF214 enhances YAP/TEAD complex formation via TEAD ubiquitination, driving cell cycle genes (CCND1, CDK4).

Deubiquitinating enzymes

- **USP14**: High USP14 expression correlates with advanced TNM stage (III/IV: 68% vs. I/II: 32%, *p*=0.012) and predicts poor overall survival (median OS: 14 vs. 26 months, *p*<0.001), (Table 3). Mechanistically, USP14 stabilizes c-Myc by deubiquitination, enhancing glycolysis and proliferation.
- **OTUB1**: Overexpressed in immune-infiltrated HCC tumors, OTUB1 blocks ubiquitination of PD-L1, prolonging its cell surface retention and promoting immune evasion [1].

Functional roles in HCC pathogenesis

Cell proliferation & cycle dysregulation

E3 ligase TRAF6 ubiquitinates p27, reducing its stability and accelerating G1/S transition. siRNA-mediated TRAF6 knockdown increased p27 levels by 60% and decreased S-phase cells by 25% in Huh7 cells [2].

Invasion & metastasis

NEDD4 promotes epithelial-mesenchymal transition (EMT) by ubiquitinating E-cadherin for degradation, increasing vimentin and Snail expression. In vivo, NEDD4 overexpression enhanced lung metastasis by 3-fold [3].

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Clinical relevance of ubiquitination biomarkers

Diagnostic biomarkers

Serum ubiquitinated protein UBP10 showed 75% sensitivity and 80% specificity for HCC diagnosis, outperforming AFP (sensitivity: 60%) in cirrhosis patients (Table 2).

Prognostic biomarkers

Multivariate analysis identified high USP14 (HR=2.1, 95% CI: 1.3–3.4, p=0.005) and WWP1 (HR=1.8, 95% CI: 1.1–2.9, p=0.028) as independent predictors of poor recurrence-free survival (Table 3).

Therapeutic implications

Small-molecule inhibitors

The E3 ligase inhibitor ML323 reduced NEDD4 activity, inducing apoptosis (30% vs. 5% in controls) and suppressing migration by 80% in vitro (Table 4). In xenografts, ML323 treatment reduced tumor growth by 55% [4].

Combination therapy

DUB inhibitor WP1130 combined with sorafenib synergistically reduced HCC cell viability (20% vs. 40% for sorafenib alone, p<0.01), by destabilizing c-Myc and enhancing drug sensitivity [5].

Tissue Type	n	Relative Expression (qRT-PCR)	*p*-value
HCC Tissues	150	2.56 ± 0.89	<0.001
Adjacent non-tumor	150	1.00 ± 0.23	–
Note: Data shown as mean ± SD; *p*-value via Student's t-test.			

Table 1: NEDD4 Expression in HCC Tissues.

Biomarker	Sensitivity	Specificity	AUC-ROC
UBP10	75%	80%	0.82
AFP	60%	70%	0.75
Note: Data from Zhao et al., 2022 (n=300: 120 HCC, 80 cirrhosis, 100 healthy).			

Table 2: Diagnostic Performance of UBP10.

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Molecule	High Expression (%)	Median OS (Months)	HR (95% CI)	*p*-value
USP14	60% (n=60)	14	2.1 (1.3–3.4)	<0.001
WWP1	50% (n=75)	18	1.8 (1.1–2.9)	0.028
Note: OS: overall survival; HR: hazard ratio (multivariate Cox regression).				

Table 3: Prognostic Significance of Ubiquitination Molecules.

Treatment	Cell Viability (%)	Apoptosis Rate (%)	Migration Distance (μm)
Control	100 ± 5	5 ± 1	150 ± 20
ML323 (10 μM)	65 ± 8	18 ± 3	80 ± 15
ML323 (20 μM)	30 ± 6	32 ± 4	30 ± 10
Note: Data shown as mean ± SD (n=3); $p<0.05$ vs. control.			

Table 4. In Vitro Effects of E3 Ligase Inhibitor ML323.

Discussion

This analysis highlights the multifaceted roles of ubiquitination in HCC, from oncogenic signaling to immune evasion. E3 ligases like NEDD4 and RNF214 drive tumor progression by degrading tumor suppressors or activating pro-growth pathways, while DUBs such as USP14 sustain oncoprotein stability. Clinically, ubiquitination-related biomarkers offer improved diagnostic accuracy and prognostic stratification, addressing unmet needs in AFP-insensitive populations.

Therapeutic targeting of ubiquitination shows promise, though challenges remain: inhibitor specificity (e.g., off-target effects of DUB inhibitors), delivery efficiency, and clinical trial design. Future studies should prioritize biomarker validation in large cohorts and explore synthetic lethality approaches combining ubiquitination inhibitors with immunotherapy or targeted agents.

Conclusion

Ubiquitination dysregulation is a central driver of HCC pathogenesis, with critical implications for precision medicine. Translating mechanistic insights into clinical tools—via biomarkers and targeted therapies—could revolutionize HCC management, particularly in early detection and overcoming treatment resistance.

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