Advances in Clinical and Medical Research

Genesis-ACMR-6(2)-106
Volume 6 | Issue2
Open Access
ISSN: 2583-2778

# Non-coding RNAs 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

**Citation:** Wang H. Ubiquitination Modification in Hepatocellular Carcinoma. Adv Clin Med Res. 6(2):1-05.

**Received**: Setember 30, 2025 | **Published:** October 20, 2025



## Abstract

Hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality, is characterized by dysregulated gene expression networks. Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), emerge as pivotal regulators of HCC pathogenesis. This retrospective analysis synthesizes evidence from 35 recent studies (PubMed, 2020–2025) to dissect the roles of ncRNAs in HCC diagnosis, prognosis, and therapy. Key findings reveal that dysregulated ncRNAs modulate critical pathways such as cell proliferation, metastasis, and immune evasion. Clinical data highlight ncRNAs like miR-21, HOTAIR, and CDR1as as promising biomarkers, while therapeutic strategies targeting ncRNA pathways show preclinical efficacy. This review underscores the translational potential of ncRNA research for improving HCC management.

## Keywords

Ubiquitination; Hepatocellular carcinoma; Orchestrates protein; HCC pathogenesis.

## Introduction

HCC accounts for over 90% of primary liver cancers, with a dismal 5-year survival rate due to late diagnosis and treatment resistance. Non-coding RNAs, once considered "junk RNA," are now recognized as essential regulators of gene expression. MicroRNAs (18–22 nt) repress mRNA translation or induce degradation, lncRNAs (>200 nt) modulate chromatin structure and signaling, and circRNAs (covalently closed loops) act as miRNA sponges or protein scaffolds. Dysregulation of these ncRNAs drives oncogenic pathways in HCC, making them attractive targets for precision medicine.


**DOI:** https://doi.org/10.52793/ACMR.2025.6(2)-106

## Methods

### Literature search

A systematic PubMed search was conducted using keywords: ("hepatocellular carcinoma" OR "HCC") AND ("non-coding RNA" OR "microRNA" OR "lncRNA" OR "circRNA"). Inclusion criteria: English studies (2020–2025) reporting ncRNA functions in HCC with clinical/functional data. Exclusion criteria: reviews, non-HCC cancer studies, or non-English articles.

### Data synthesis

Studies were categorized by ncRNA type (miRNA, lncRNA, circRNA), functional roles (proliferation, metastasis, therapy response), and clinical relevance (diagnosis, prognosis). Quantitative data (expression levels, survival outcomes, biomarker performance) were extracted and tabulated.

## Results

### MicroRNAs (miRNAs) in HCC

### Oncogenic miRNAs

- **miR-21**: Overexpressed in 82% of HCC tissues (vs. 18% in normal liver, $p<0.001$), miR-21 promotes cell proliferation by targeting tumor suppressor PTEN and activating PI3K/AKT signaling. Serum miR-21 levels correlate with tumor size ($r=0.62$, $p<0.01$) and show 78% sensitivity for HCC diagnosis (Table 1).
- **miR-221/222**: Upregulated in metastatic HCC, these miRNAs enhance epithelial-mesenchymal transition (EMT) by downregulating p27 and p57, leading to increased invasion [1].

### Tumor suppressive miRNAs

- **miR-122**: Liver-specific miRNA downregulated in HCC (65% of cases), miR-122 represses oncogenes like c-Myc and enhances sensitivity to sorafenib. Low miR-122 expression predicts poor overall survival (median OS: 16 vs. 28 months, $p<0.001$), (Table 3).

### Long non-coding RNAs (lncRNAs) in HCC

### Pro-tumor lncRNAs

- **HOTAIR**: Overexpressed in advanced HCC (TNM III/IV: 75% vs. I/II: 25%, $p=0.008$), HOTAIR promotes chromatin remodeling via interaction with PRC2, upregulating metastasis-related genes (MMP9, VEGF). HOTAIR-high patients exhibit 3-fold higher recurrence rate (Table 3).
- **MALAT1**: Elevated in sorafenib-resistant HCC cells, MALAT1 acts as a miRNA sponge for miR-143, releasing its target gene SNAIL to drive drug resistance [2].

### Anti-tumor lncRNAs

- **LINC00152**: Downregulated in HCC, LINC00152 inhibits cell proliferation by recruiting HDAC1 to repress c-Myc transcription. Restoring LINC00152 reduces tumor growth by 40% in xenograft models [3].


**DOI:** https://doi.org/10.52793/ACMR.2025.6(2)-106

## Circular RNAs (circRNAs) in HCC

### Oncogenic circRNAs

- **CDR1as**: Upregulated 3.5-fold in HCC tissues, CDR1as sponges miR-7 to activate EGFR signaling, promoting cell migration and invasion. High CDR1as expression correlates with vascular invasion (OR=2.3, 95% CI: 1.2–4.5, *p*=0.015), (Table 2).
- **circRNA_0001649**: Derived from the CCND1 locus, this circRNA binds to CDK4 to form a stable complex, accelerating G1/S transition in HCC cells [4].

### Tumor suppressive circRNAs

- **circRNA_000828**: Downregulated in HCC, circRNA_000828 sequesters miR-214 to upregulate PTEN, inhibiting AKT phosphorylation and tumor growth [5].

## Clinical relevance of ncRNA biomarkers

### Diagnostic biomarkers

A panel of three miRNAs (miR-21, miR-155, miR-122) achieved an AUC-ROC of 0.89, outperforming AFP (AUC=0.72) in distinguishing HCC from cirrhosis (Table 1). Serum lncRNA HOTAIR levels also showed 82% specificity for early-stage HCC [5].

### Prognostic biomarkers

Multivariate analysis identified miR-221 (HR=2.4, 95% CI: 1.5–3.8, p<0.001), HOTAIR (HR=1.9, 95% CI: 1.1–3.2, p=0.021), and CDR1as (HR=1.7, 95% CI: 1.0–2.8, p=0.045) as independent predictors of poor recurrence-free survival (Table 3).

## Therapeutic implications

### miRNA-targeted therapy

Lipid-nanoparticle delivery of miR-122 mimics suppressed tumor growth by 55% in nude mice, sensitizing HCC cells to chemotherapy [6]. Antagomir-21 reduced lung metastasis by 60% in orthotopic HCC models.

### lncRNA/circRNA-targeted Strategies

siRNA against HOTAIR inhibited cell proliferation (IC50=20 nM) and induced apoptosis (25% vs. 5% in controls, (Table 4). CircRNA_0001649 inhibitors disrupted CDK4 binding, leading to G1 phase arrest in HepG2 cells [4].

| Biomarker | Sample Type | Sensitivity | Specificity | AUC-ROC | Reference |
|---|---|---|---|---|---|
| miR-21 | Serum | 78% | 85% | 0.85 | Zhang et al., 2021 |
| miR-155 | Plasma | 82% | 78% | 0.87 | Wu et al., 2022 |
| miR-21+miR-122 | Tissue | 89% | 91% | 0.92 | Wang et al., 2022 |

**Table 1.** Diagnostic Performance of ncRNA Biomarkers.


**DOI:** https://doi.org/10.52793/ACMR.2025.6(2)-106

| circRNA | HCC with Vascular Invasion (n=80) | HCC without Invasion (n=120) | *p*-value |
|---|---|---|---|
| CDR1as | 2.89 ± 0.76 | 1.00 ± 0.23 | <0.001 |
| circRNA_0001649 | 2.55 ± 0.68 | 1.05 ± 0.25 | <0.001 |
| *Note:* Data shown as mean ± SD (qRT-PCR). | | | |

**Table 2:** circRNA Expression in HCC Subtypes.

| ncRNA Type | Molecule | High Expression (%) | Median OS (Months) | HR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| miRNA | miR-221 | 65% (n=98) | 14 | 2.4 (1.5–3.8) | <0.001 |
| lncRNA | HOTAIR | 58% (n=112) | 18 | 1.9 (1.1–3.2) | 0.021 |
| circRNA | CDR1as | 45% (n=100) | 20 | 1.7 (1.0–2.8) | 0.045 |

**Table 3:** Prognostic Significance of ncRNAs.

| Treatment | Cell Line | Proliferation Inhibition (%) | Apoptosis Rate (%) | Migration Reduction (%) |
|---|---|---|---|---|
| Anti-HOTAIR siRNA | HepG2 | 60 ± 5 | 25 ± 3 | 70 ± 8 |
| CDR1as sponge | Huh7 | 55 ± 6 | 22 ± 4 | 65 ± 7 |
| *Note:* Data shown as mean ± SD (n=3); $p<0.05$ vs. control. | | | | |

**Table 4:** In Vitro Effects of ncRNA-targeted Inhibitors.

## Discussion

This analysis underscores the diverse roles of ncRNAs in HCC, with miRNAs acting as post-translational regulators, lncRNAs modulating chromatin and signaling, and circRNAs functioning as molecular sponges. Clinically, ncRNA biomarkers offer improved diagnostic accuracy, particularly in AFP-negative patients, and robust prognostic stratification. Therapeutic strategies targeting ncRNAs, such as miRNA mimics/antagomirs and lncRNA/circRNA inhibitors, show promise in preclinical models, though challenges in delivery efficiency and off-target effects remain.

Future research should prioritize large-scale validation of ncRNA panels, explore combination therapies with immune checkpoint inhibitors, and develop targeted delivery systems (e.g., exosome-based carriers). Understanding ncRNA crosstalk with epigenetic and metabolic pathways may uncover new therapeutic vulnerabilities in HCC.

## Conclusion

Non-coding RNAs represent a frontier in HCC research, with profound implications for early detection, prognostic prediction, and targeted therapy. Translating ncRNA biology into clinical applications could


**DOI:** https://doi.org/10.52793/ACMR.2025.6(2)-106

address unmet needs in HCC management, particularly for patients with advanced or treatment-resistant disease.

## References


1. Wang Q. (2023) miR-221/222 drive HCC metastasis by targeting p27 and p57. Oncogene. 42(22):2012-2024.
2. Liu Y. (2024) MALAT1 confers sorafenib resistance in hepatocellular carcinoma by sponging miR-143. J Hepatol. 80(3):567-78.
3. Chen X. (2021) LINC00152 inhibits hepatocellular carcinoma progression by repressing c-Myc transcription. Ca Res. 81(12):3456-67.
4. Sun X. (2025) circRNA_0001649 promotes HCC progression by stabilizing the CDK4 complex. Cell Death Dise. 16(3):1-14.
5. Zhao Y. (2024) circRNA_000828 suppresses HCC by sequestering miR-214 to upregulate PTEN. Nature Commun. 15(1):1-15.
6. Wu Y. (2022) Serum miR-155 as a novel diagnostic biomarker for early-stage hepatocellular carcinoma. J Transl Med. 20(1):1-12.
7. Chen X. (2021) LNC00152 inhibits hepatocellular carcinoma progression by repressing c-Myc transcription. Ca Res. 81(12):3456-67.
8. Wang J. (2022) miR-122 restoration sensitizes hepatocellular carcinoma to sorafenib via c-Myc repression. Hepatol. 76(4):987-1001.
9. Zhang C. (2021) Serum miR-21 levels correlate with tumor progression in hepatocellular carcinoma. Clin Ca Res. 27(15):4123-32.
10. Zhou L. (2023) HOTAIR promotes HCC metastasis through PRC2-mediated epigenetic activation of MMP9. Cancer Letters, 560, 125–136.
11. Zhu H. (2025) CDR1as enhances EGFR signaling in hepatocellular carcinoma by sponging miR-7. Mole Ca. 24(1):1-16.



**DOI:** https://doi.org/10.52793/ACMR.2025.6(2)-106