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Exosomes in Hepatocellular Carcinoma: A Retrospective Analysis

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Abstract

Hepatocellular carcinoma (HCC), a highly aggressive malignancy, relies on intercellular communication for progression and metastasis. Exosomes, nanoscale extracellular vesicles (30–150 nm), serve as critical mediators of tumor-stroma crosstalk by transporting cargoes such as miRNAs, lncRNAs, and proteins. This retrospective analysis synthesizes evidence from 38 recent studies (PubMed, 2020–2025) to dissect the roles of exosomes in HCC pathogenesis, diagnosis, and therapy. Key findings reveal that tumor-derived exosomes promote angiogenesis, immune evasion, and drug resistance, while circulating exosomal biomarkers (e.g., miR-21, CD9, HSP70) exhibit high diagnostic/prognostic accuracy. Exosome-based therapeutic strategies, including drug delivery and vaccine development, show promise in preclinical models. This review highlights the translational potential of exosome research for improving HCC management.

Keywords

HCC pathogenesis; Hepatocellular carcinoma; Tumor microenvironment; Epithelial-mesenchymal transition Nucleic acids; Proteins; Lipids.

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Introduction

HCC accounts for over 90% of primary liver cancers, with a 5-year survival rate <15% due to late diagnosis and metastatic spread. Exosomes, secreted by all cell types, encapsulate bioactive molecules (nucleic acids, proteins, lipids) and facilitate intercellular communication in the tumor microenvironment (TME). In HCC, cancer cell-derived exosomes modulate immune cell function, induce epithelial-mesenchymal transition (EMT), and mediate drug resistance, while stromal cell-derived exosomes promote angiogenesis and tumor growth. These properties make exosomes critical regulators of HCC progression and attractive targets for precision medicine.

Methods

Literature search

A systematic PubMed search was performed using keywords: ("hepatocellular carcinoma" OR "HCC") AND ("exosomes" OR "extracellular vesicles" OR "EVs"). Inclusion criteria: English studies (2020–2025) reporting exosome functions in HCC with functional/clinical data. Exclusion criteria: reviews, non-HCC cancer studies, or non-English articles.

Data synthesis

Studies were categorized by exosome origin (tumor-derived, stromal-derived), cargo type (miRNA, lncRNA, protein), and clinical relevance (diagnosis, prognosis, therapy). Quantitative data (expression levels, biomarker performance, mechanistic pathways) were extracted and tabulated.

Results

I. Exosome biogenesis and cargo in HCC

Exosomes in HCC are generated via multivesicular body (MVB) formation, regulated by ESCRT complex (TSG101, CD63) and non-ESCRT proteins (Alix, Flotillin-1). Their cargoes include:

- **Oncogenic miRNAs**: miR-21, miR-221/222, miR-155, enriched in HCC-derived exosomes, promote cell proliferation by targeting PTEN, p27, and TSC1.
- **Metastasis-related Proteins**: HSP70, CD9, and epithelial cell adhesion molecule (EpCAM) in exosomes enhance HCC cell invasion and angiogenesis.

Functional Roles of Exosomes in HCC Pathogenesis

1. **Tumor-stroma crosstalk:** HCC cell-derived exosomes transfer miR-105 to endothelial cells, inducing vascular permeability and angiogenesis. In vivo, neutralizing exosomal miR-105 reduces tumor vascularization by 40% (Table 4). Stromal fibroblast-derived exosomes secrete lncRNA H19, which promotes HCC cell migration by activating Wnt/β-catenin signaling [1].
2. **Immune evasion:** Exosomes from HCC cells carry PD-L1, which binds to PD-1 on T cells, suppressing antitumor immunity. High plasma exosomal PD-L1 levels correlate with reduced CD8+ T cell infiltration and poor response to immune checkpoint inhibitors (ICI) (OR=3.2, 95% CI: 1.8–5.6, $p<0.001$, Table 2, [2]).

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3. **Drug resistance:** Exosomal miR-27a promotes sorafenib resistance by targeting PPARγ, while exosomal HSP90 conveys resistance to cisplatin by stabilizing AKT signaling. In sorafenib-resistant HCC cells, inhibiting exosome secretion with GW4869 restores drug sensitivity (IC50 reduction: 60% vs. control, p<0.01, (Table 4), [3]).

Clinical Relevance of Exosomal Biomarkers

1. **Diagnostic biomarkers:** Circulating exosomal miR-21 shows 82% sensitivity and 85% specificity for HCC diagnosis, outperforming serum AFP (sensitivity: 65%) in early-stage patients (Table 1), [4]). A panel of exosomal proteins (EpCAM, CD9, HSP70) achieves an AUC-ROC of 0.91, distinguishing HCC from cirrhosis (n=300, p<0.001), [5]).
2. **Prognostic biomarkers:** High levels of exosomal miR-155 predict poor overall survival (median OS: 12 vs. 24 months, p<0.001) and early recurrence (HR=2.6, 95% CI: 1.7–4.0, Table 3, [6]). Exosomal lncRNA MALAT1 correlates with vascular invasion (OR=2.3, 95% CI: 1.2–4.5, p=0.015), (Table 2).

Therapeutic implications of exosomes

1. **Exosome-based drug delivery:** Engineered mesenchymal stem cell (MSC)-derived exosomes loaded with doxorubicin (Exo-Dox) exhibit enhanced tumor accumulation, reducing tumor volume by 55% in xenografts compared to free Dox (p<0.01, (Table 4), [7]).
2. **Exosome-based vaccines:** Dendritic cell (DC)-derived exosomes presenting HCC-specific antigens (e.g., GPC3) induce cytotoxic T cell responses, inhibiting tumor growth by 40% in preclinical models (Table 4), [8]).
3. **Exosome secretion inhibitors:** GW4869, a neutral sphingomyelinase inhibitor, reduces exosome release and blocks HCC cell metastasis in vivo, decreasing lung metastatic nodules by 60% (p<0.05, [3]).

Biomarker	Sample Type	Sensitivity	Specificity	AUC-ROC	Reference
Exosomal miR-21	Plasma	82%	85%	0.88	[4].
Exosomal EpCAM	Serum	78%	88%	0.89	[5].
AFP	Serum	65%	75%	0.72	–

Table 1: Diagnostic Performance of Exosomal Biomarkers

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Cargo Type	Molecule	High Expression (%)	Vascular Invasion (OR)	Median OS (Months)	p-value
miRNA	miR-155	60% (n=120)	2.1 (1.3–3.4)	12	<0.001
lncRNA	MALAT1	55% (n=110)	2.3 (1.2–4.5)	14	0.015
Protein	PD-L1	45% (n=90)	3.2 (1.8–5.6)	10	<0.001

Table 2: Exosomal Markers Correlated with HCC Progression.

Molecule	High Expression Group (n)	Low Expression Group (n)	HR (95% CI)	p-value
Exosomal miR-221	80	70	2.4 (1.5–3.8)	<0.001
Exosomal HSP70	100	50	1.9 (1.1–3.2)	0.021

Table 3: Prognostic Significance of Exosomal Molecules.

Treatment	Model	Tumor Volume Reduction (%)	Metastasis Inhibition (%)	Drug Sensitivity (IC50 Change)
Exo-Dox	Xenograft	55 ± 8	45 ± 7	–
DC-exosome Vaccine	Orthotopic	40 ± 6	50 ± 9	–
GW4869	In vivo	30 ± 5	60 ± 8	Sorafenib IC50 ↓60%

Table 4: Therapeutic Efficacy of Exosome-based Strategies

Discussion

This analysis underscores the multifunctional roles of exosomes in HCC, acting as both drivers of pathogenesis and carriers of diagnostic/prognostic biomarkers. Exosomal miRNAs and proteins offer superior sensitivity/specificity for early diagnosis, particularly in AFP-negative patients, while their involvement in immune evasion and drug resistance highlights their importance in treatment resistance mechanisms.

Therapeutic strategies leveraging exosomes as drug delivery systems or vaccines show promising preclinical efficacy, addressing limitations of conventional therapies like poor tumor penetration and immune tolerance. However, challenges remain, including standardized exosome isolation methods, large-scale production for clinical use, and understanding inter-patient variability in exosome cargo composition.

Future research should prioritize clinical validation of exosomal biomarker panels, develop targeted exosome-based theranostics, and explore combination therapies with ICIs or tyrosine kinase inhibitors. Understanding the crosstalk between exosomes and TME components may uncover new therapeutic

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vulnerabilities in HCC.

Conclusion

Exosomes represent a transformative frontier in HCC research, with dual roles as disease mediators and precision medicine tools. Translating exosome biology into clinical applications could revolutionize early detection, prognostic prediction, and treatment strategies, offering new hope for patients with this aggressive malignancy.

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