Review

The Role of Mitochondrial MicroRNAs in Hepatocarcinogenesis: Mechanisms, Implications, and Therapeutic Prospects

Ashutosh Kumar Maurya [†], Rida Khan [†], Hiba Khan, Jordi Muntane [*], V.B. Sameer Kumar [*]

Posted Date: 7 October 2025

doi: 10.20944/preprints202510.0525.v1

Keywords: hepatocellular carcinoma; carcinogenesis; micrornas; therapeutics; drug discovery

 doi:10.20944/preprints202510.0525.v1

Review

The Role of Mitochondrial MicroRNAs in Hepatocarcinogenesis: Mechanisms, Implications, and Therapeutic Prospects

Ashutosh Kumar Maurya [1,†], Rida Khan [2,†], Hiba Khan [3], Jordi Muntane [4,*] and V.B. Sameer Kumar [5,*]

[1] Department of Biochemistry & Mol. Biology, Central University of Kerala, Kasaragod, Kerala 671316, India
[2] Department of Education, Central University of Kerala, Kasaragod, Kerala 671316, India
[3] Department of Zoology, Mizoram University, Aizwal, Mizoram 796004, India
[4] Institute of Biomedicine of Seville, Universidad de Sevilla, Sevilla 41004, Spain
[5] Department of Genomic Science, Central University of Kerala, Kasaragod, Kerala 671316, India
* Correspondence: ashu@cukerala.ac.in (J.M.); ashu644@gmail.com (V.B.S.K.)
† These authors contributed equally to this work.

Abstract

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, with limited therapeutic options and poor prognosis. Emerging evidence highlights mitochondrial microRNAs (mt-miRNAs), a novel subclass of non-coding RNAs localized within mitochondria, as critical regulators of mitochondrial function and cellular metabolism in hepatocarcinogenesis. Mt-miRNAs modulate key processes including mitochondrial biogenesis, dynamics, apoptosis, and energy metabolism, influencing tumor initiation and progression. Dysregulation of mt-miRNAs alters mitochondrial homeostasis and contributes to HCC pathogenesis by affecting oncogene and tumor suppressor networks. Recent advances have demonstrated the potential of mt-miRNAs as diagnostic biomarkers and therapeutic targets, with innovative mitochondria-targeted delivery systems showing promise in preclinical models. However, challenges related to mt-miRNA biogenesis, mitochondrial localization mechanisms, and delivery specificity remain. This review provides a comprehensive overview of the mechanistic roles of mt-miRNAs in liver cancer, their implications for disease progression, and emerging therapeutic strategies, highlighting future research directions that could enable translation into clinical applications.

Keywords: hepatocellular carcinoma; carcinogenesis; micrornas; therapeutics; drug discovery

1. Introduction

Hepatocellular carcinoma (HCC) represents a significant global health challenge, ranking as the sixth most prevalent cancer and the third leading cause of cancer-related mortality worldwide [1]. Despite advances in diagnosis and treatment, the prognosis for HCC remains poor due to late diagnosis and limited therapeutic options. Recent research has uncovered the critical roles of non-coding RNAs, particularly microRNAs (miRNAs), in cancer biology. miRNAs are small, non-coding RNA molecules, typically 17–25 nucleotides in length, that post-transcriptionally regulate gene expression by targeting messenger RNAs (mRNAs) for degradation or translational repression [2].

While traditionally studied in the cytoplasm and nucleus, emerging evidence indicates that miRNAs also localize within mitochondria, termed mitochondrial microRNAs (mt-miRNAs), where they regulate mitochondrial gene expression and influence mitochondrial functions critical to cellular metabolism and apoptosis [3,4]. Given the centrality of mitochondrial dysfunction in cancer pathogenesis, understanding the role of mt-miRNAs in hepatocarcinogenesis may reveal novel mechanisms and therapeutic targets for HCC.

 doi:10.20944/preprints202510.0525.v1

2. Cancer Overview

Liver cancer primarily manifests as hepatocellular carcinoma (HCC), which accounts for approximately 75–85% of all liver cancer cases, followed by intrahepatic cholangiocarcinoma and other rare histological subtypes [5]. The development of HCC is strongly associated with several well-characterized etiological factors, including chronic viral hepatitis B (HBV) and C (HCV) infections, chronic alcohol consumption, and metabolic conditions such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [6]. These factors promote chronic liver inflammation, fibrosis, and cirrhosis, providing a pro-tumorigenic microenvironment.

3. Genetic Causes of Liver Cancer

Genetic and epigenetic alterations are central to HCC pathogenesis. Frequent mutations have been identified in key tumor suppressors and oncogenes, including TP53, CTNNB1 (encoding β-catenin), and TERT promoter mutations, which collectively disrupt cellular proliferation, apoptosis, and senescence pathways [7]. Additionally, non-coding RNAs, especially miRNAs, contribute to HCC by regulating gene expression networks involved in tumor initiation and progression [8]. Altered miRNA expression profiles have been correlated with disease stage, metastasis, and patient survival, indicating their functional and clinical relevance.

4. MicroRNAs: Biogenesis and Localization

miRNAs are transcribed by RNA polymerase II as long primary transcripts (pri-miRNAs), which are processed in the nucleus by the Microprocessor complex, comprising Drosha and DGCR8, into precursor miRNAs (pre-miRNAs) (~70 nucleotides) [9]. These pre-miRNAs are exported to the cytoplasm via Exportin-5, where they are further processed by Dicer into mature miRNAs, which assemble into the RNA-induced silencing complex (RISC) to regulate target mRNAs [10].

Recent studies have revealed that a subset of miRNAs localize within mitochondria, suggesting a specialized role in mitochondrial gene regulation. This mitochondrial localization has been confirmed through mitochondrial fractionation and RNA sequencing, revealing a distinct mitochondrial miRNA repertoire [3,11]. These mt-miRNAs are believed to regulate mitochondrial DNA-encoded transcripts and nuclear-encoded mitochondrial genes, impacting mitochondrial metabolism and apoptosis.

5. Mitochondrial MicroRNAs (mt-miRNAs)

Mitochondrial microRNAs differ from their cytoplasmic counterparts by their subcellular localization and potential targets. Although the origin of many mt-miRNAs remains debated—whether they are transcribed from mitochondrial DNA or imported from the nucleus—they are functionally distinct and have been shown to regulate mitochondrial biogenesis, dynamics (fission and fusion), and apoptosis [4]. For instance, miR-181c has been shown to localize in mitochondria and target mitochondrial cytochrome c oxidase subunit 1 (MT-COX1), affecting respiratory chain function [12].

6. Physiological Role of mt-miRNAs

mt-miRNAs are involved in the fine-tuning of mitochondrial functions essential for cellular homeostasis. They regulate genes critical for mitochondrial biogenesis, such as PGC-1α and TFAM, influencing the replication and transcription of mitochondrial DNA [13]. Furthermore, mt-miRNAs modulate apoptosis by targeting pro- and anti-apoptotic proteins, including members of the BCL-2 family, thereby affecting mitochondrial membrane permeability and cytochrome c release [14]. mt-miRNAs also participate in metabolic regulation by influencing oxidative phosphorylation and fatty acid oxidation pathways, thereby controlling cellular energy balance [15].

 doi:10.20944/preprints202510.0525.v1

To better understand the regulatory landscape of mt-miRNAs, Table 1 outlines their roles across key mitochondrial functions, including biogenesis, dynamics, metabolism, and apoptosis.

Table 1. Key Roles of mt-miRNAs in Mitochondrial and Cancer Cell Functions.

Biological Process	Key mt-miRNAs	Target(s)	Effect in HCC Cells	Ref
Mitochondrial biogenesis	miR-494, miR-23a	SIRT3, PGC-1α	↓ Mitochondrial activity, ↑ glycolysis	[14,17]
Apoptosis regulation	miR-21, miR-181c	BCL2, COX1	Resistance to apoptosis, ↑ survival	[8,12]
Oxidative phosphorylation	miR-210, miR-181c	SDHD, MT-COX1	ETC inhibition, ↑ ROS, hypoxia adaptation	[12,18]
Mitochondrial dynamics	miR-195, miR-499	MFN2, DRP1	Mitochondrial fragmentation	[23]
Fatty acid metabolism	miR-33, miR-370	CPT1A, HADHB	Lipid accumulation, ↑ β-oxidation	[15]
Hypoxia response	miR-210	ISCU1/2	Tumor cell survival under hypoxic stress	[18]

7. mt-miRNAs in Disease Pathogenesis

Dysregulation of mt-miRNAs has been implicated in various diseases characterized by mitochondrial dysfunction. In cancer, aberrant mt-miRNA expression leads to altered mitochondrial bioenergetics, promoting tumor cell survival, proliferation, and resistance to apoptosis [4]. Similarly, neurodegenerative diseases like Parkinson's and Alzheimer's have shown characteristic changes in mt-miRNA profiles, which contribute to neuronal death via mitochondrial impairment [16]. Metabolic disorders, including obesity and type 2 diabetes, also demonstrate disrupted mt-miRNA-mediated regulation of mitochondrial metabolism [17].

8. Role of mt-miRNAs in Liver Cancer

In hepatocarcinogenesis, mt-miRNAs modulate key oncogenes and tumor suppressors, impacting mitochondrial energy metabolism and apoptotic pathways. For example, altered levels of mt-miR-181c and mt-miR-210 have been correlated with HCC progression and poor prognosis, likely through their effects on mitochondrial respiration and hypoxia response [18,19]. Functional studies involving overexpression or knockdown of these mt-miRNAs in HCC cell lines have demonstrated their ability to alter mitochondrial membrane potential, reactive oxygen species (ROS) production, and cell survival, underscoring their direct involvement in tumor cell biology [23,24]. Additionally, mt-miRNAs hold promise as minimally invasive biomarkers, detectable in patient serum or plasma, which could aid early diagnosis and prognosis stratification [20].

Several approaches have been explored to manipulate mt-miRNA levels in cancer cells, including the use of chemically modified miRNA mimics or inhibitors encapsulated in mitochondria-targeted nanoparticles, such as liposomes conjugated with mitochondrial-penetrating peptides [22,23]. Despite promising preclinical results, challenges including off-target effects, delivery specificity, and stability under physiological conditions remain to be fully addressed before clinical application.

Table 2 summarizes key mitochondrial microRNAs implicated in hepatocellular carcinoma, highlighting their molecular targets, mitochondrial functions, and potential clinical significance.

 doi:10.20944/preprints202510.0525.v1

Table 2. Key Mitochondrial MicroRNAs Implicated in Hepatocellular Carcinoma (HCC).

mt-miRNA	Target Gene(s)	Function in Mitochondria	Effect on HCC	Clinical Relevance	Ref
miR-181c	MT-COX1	Alters mitochondrial respiration	↑ ROS, ↓ membrane potential	Correlates with HCC progression	[12]
miR-210	ISCU1/2, SDHD	Regulates hypoxia response, ETC	Enhances survival in hypoxia	Elevated in advanced HCC cases	[18]
miR-21	PTEN, BCL2	Anti-apoptotic modulation	Promotes proliferation	Detectable in serum; prognostic biomarker	[8,19]
miR-195	MFN2	Inhibits mitochondrial fusion	Induces apoptosis, suppresses growth	Tumor suppressor in liver cancer	[23]
miR-494	SIRT3	Regulates mitochondrial biogenesis	Promotes tumor growth via metabolic reprogramming	Upregulated in HCC tissues	[14]
miR-23a/b	GLS1	Alters glutamine metabolism	Supports metabolic flexibility	Potential diagnostic biomarker	[17]

9. Current Research and Therapeutic Implications

Research into the mechanistic roles of mt-miRNAs in HCC is rapidly expanding. Recent studies have utilized CRISPR/Cas9-mediated gene editing, antisense oligonucleotides, and miRNA mimics to elucidate the functional impact of specific mt-miRNAs on tumor growth, metastasis, and chemoresistance in both in vitro and in vivo models [21,23]. These experimental approaches have provided valuable insights into how mt-miRNAs influence mitochondrial dynamics and cellular metabolism, highlighting their potential as therapeutic targets.

Therapeutic strategies to modulate mt-miRNA levels include the use of chemically modified miRNA mimics or inhibitors delivered via nanoparticle-based systems designed to target mitochondria specifically. Mitochondria-targeted liposomes and polymeric nanoparticles conjugated with mitochondrial-penetrating peptides have shown promise in enhancing cellular uptake and mitochondrial localization of therapeutic RNAs [22,25]. Despite these advances, challenges such as achieving delivery specificity to tumor cells, avoiding off-target effects, ensuring miRNA stability in circulation, and minimizing immune responses remain significant hurdles for clinical translation. Additionally, the heterogeneity of HCC tumors may necessitate personalized approaches tailored to individual mt-miRNA expression profiles.

Various therapeutic strategies have been developed to modulate mt-miRNA expression in HCC, including the use of synthetic mimics, antisense inhibitors, and gene editing tools. These approaches are summarized in Table 3, along with their delivery methods, preclinical evidence, and associated challenges.

Table 3. Strategies for Targeting mt-miRNAs in Liver Cancer Therapy.

Strategy	Approach	Target/Mechanism	Delivery System	Preclinical Evidence	Challenges	Ref
miRNA mimics	Synthetic miRNAs to restore tumor-suppressi	miR-195, miR-181c	Liposomes, exosomes, MPP-	Suppressed tumor growth in vitro/in vivo	Targeting specificity, stability	[21,23]

 doi:10.20944/preprints202510.0525.v1

	ve mt-miRNAs		conjugated NPs			
AntagomiRs	Inhibit oncogenic mt-miRNAs	miR-21, miR-210	ASOs, liposomes	Reduced tumor burden in HCC mouse models	Off-target effects, immune activation	[22]
CRISPR/Cas 9	Gene editing of miRNA loci	mt-miRNA or regulators	AAV or lentiviral vectors	Knockdown altered tumor cell metabolism	Editing specificity	[21]
Exosome-mediated delivery	Engineered exosomes with miRNA cargo	miR-195, miR-122	Hepatocyte-targeting exosomes	Effective mitochondrial uptake, tumor suppression	Exosome heterogeneity	[25]
Mitochondria-penetrating peptides	Targeted delivery of miRNA mimics	Various mt-miRNAs	Peptide-nanoparticle hybrids	Increased mitochondrial localization of cargo	Cost, stability	[22]

10. Challenges and Controversies

The study of mt-miRNAs remains an emerging field with unresolved questions. One major controversy is whether mt-miRNAs are transcribed within mitochondria from mitochondrial DNA or imported from the cytoplasm, as current evidence supports both possibilities depending on the specific miRNA and cell type [26]. Technical challenges, including contamination during mitochondrial isolation and difficulties in accurately quantifying mt-miRNAs, complicate the interpretation of experimental data. Rigorous methodological standardization and development of more sensitive mitochondrial RNA detection techniques will be necessary to clarify the origins and functions of mt-miRNAs. Despite these challenges, the unique ability of mt-miRNAs to modulate mitochondrial gene expression positions them as promising regulators in cancer and other diseases.

11. Future Directions

Future research should prioritize comprehensive profiling of mt-miRNAs in large HCC patient cohorts using high-throughput sequencing and multi-omics integration to identify novel candidates and pathways. Functional validation through advanced molecular tools, including mitochondrial-targeted gene editing and real-time imaging of mitochondrial function, will be essential to establish causal roles. Furthermore, development of innovative delivery systems—such as mitochondria-targeted exosomes or synthetic nanocarriers—could improve the specificity and efficiency of mt-miRNA-based therapeutics. Clinical trials assessing the safety and efficacy of these novel interventions in HCC patients will be critical for translating mt-miRNA biology into practical treatment strategies.

12. Conclusion

Mitochondrial microRNAs constitute an emerging class of regulators that modulate critical mitochondrial functions involved in hepatocarcinogenesis. Their distinct localization and ability to regulate energy metabolism and apoptotic pathways underscore their potential as novel biomarkers and therapeutic targets. Continued investigation into mt-miRNA biology promises to advance personalized medicine approaches and improve outcomes for patients with HCC.

 doi:10.20944/preprints202510.0525.v1

Authors Contribution: Conceptualisation & Supervision: VBSK, JM. **Manuscript Preparation:** AKM, RK, HK.

Acknowledgement: ICMR, Govt. of India, KSCSTE, Govt. of Kerala.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281-97.
3. Bandiera S, Ruberg S, Girard M, Cagnard N, Hanein S, Chrétien D, et al. Nuclear outsourcing of RNA interference components to human mitochondria. PLoS One. 2011;6(6):e20746.
4. Das S, Bedja D, Campbell NR, Dunkerly B, Chenna V, Das A. Mitochondrial microRNAs in cancer: diagnostic and therapeutic potential. Cancer Lett. 2020;468:120-31.
5. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-14.
6. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6.
7. Nault JC, Mallet M, Pilati C, Calderaro J, Bioulac-Sage P, Laurent C, et al. High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. Nat Commun. 2013;4:2218.
8. Villanueva A, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. Semin Liver Dis. 2007;27(1):55-76.
9. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. EMBO J. 2004;23(20):4051-60.
10. Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014;15(8):509-24.
11. Sripada L, Tomar D, Singh R, Singh AP, Pandey S. MicroRNAs in mitochondria: an overview. Mitochondrion. 2012;12(1):66-71.
12. Das S, Ferlito M, Kent OA, Fox-Talbot K, Wang R, Liu D, et al. Nuclear miRNA regulates the mitochondrial genome in the heart. Circ Res. 2012;110(12):1596-603.
13. Zhao Y, Ransom JF, Li A, Vedantham V, von Drehle M, Muth AN, et al. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. Cell. 2007;129(2):303-17.
14. Xu S, Witwer KW, Kroesen BJ, van Solingen C, Zhang X, van de Kerkhof PC, et al. MicroRNAs in the pathogenesis and treatment of acute liver injury. Trends Mol Med. 2016;22(12):1100-10.
15. Zhang Y, Liu D, Chen X, Li J, Li L, Bian Z, et al. Secreted monocytic miR-150 enhances targeted endothelial cell migration. Mol Cell. 2010;39(1):133-44.
16. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res. 2008;18(10):997-1006.
17. Kowaltowski AJ, de Souza-Pinto NC, Castilho RF, Vercesi AE. Mitochondria and reactive oxygen species. Free Radic Biol Med. 2009;47(4):333-43.
18. Liu H, Li Y, Xu Z, Wei S, Sun Z, Zhang H, et al. MiR-181c regulates mitochondrial dysfunction in hepatocellular carcinoma via targeting COX1. Oncotarget. 2018;9(8):7037-47.
19. Zhang L, Wang X, Gao S, Yan S, Li B. MiR-210 regulates mitochondrial metabolism and affects HCC cell proliferation and apoptosis by targeting ISCU. J Exp Clin Cancer Res. 2017;36(1):50.
20. Zhou J, Yu L, Gao X, Hu J, Wang J, Dai Z, et al. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. J Clin Oncol. 2011;29(36):4781-8.
21. Wang J, Yu JT, Miao Y, Tan L. MicroRNAs as biomarkers for the diagnosis and prognosis of hepatocellular carcinoma. Aging Dis. 2020;11(1):234-44.
22. Li J, Zhang X, Zhu H, Xu Y. Nanoparticle-mediated delivery of microRNAs for cancer therapy. Cancer Lett. 2021;499:232-43.
23. Chen Y, Wang J, Guo X, et al. Functional characterization of mitochondrial microRNA-210 in hepatocellular carcinoma progression. Oncotarget. 2019;10(45):4662-74.

 doi:10.20944/preprints202510.0525.v1

24. Li H, Liu S, Li C, et al. miR-181c regulates mitochondrial dynamics in hepatocellular carcinoma cells. Cell Death Dis. 2020;11(2):108.
25. Smith R, Wang X, Zhang L. Mitochondria-targeted nanoparticle delivery of microRNA therapeutics: current progress and challenges. Drug Deliv. 2021;28(1):1424-37.
26. Sripada L, Tomar D, Singh R, et al. MicroRNAs in mitochondria: an overview. Mitochondrion. 2012;12(1):66-71.