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Research Article

The Role of Circular RNAs in Hepatocellular Carcinoma: Mechanisms, Implications, and Therapeutic Potential

Amena Khatun Manica[1*], Md. Robiul Islam[2], Most Farhana Akter[2], Shahadat Hossain[3]

[1]Department of Chemistry, University of New Haven, West Haven, CT, United States.
[2]Department of Pharmacy, University of Development Alternative, Dhaka, Bangladesh.
[3]Department of Microbiology, Galgotias University, UP, India.

Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most common malignancies and a predominant cause of cancer-related death worldwide, featuring high metastasis potential and resistance to chemotherapeutic agents. Both early diagnosis and good treatment options remain major challenges of HCC management. Recent studies have shown that exosomal circRNAs (circular RNAs) can serve as promising diagnostic and therapeutic markers for cancers, given their stability in biological fluids and the involvement of many oncogenic pathways through which they regulate cancer progression. **Methods:** This review focuses specifically on exosomal circRNAs, examining their functions during tumor progression, metastasis, and chemoresistance in HCC. We also describe the ways circRNAs are involved in miRNA-mediator interactions and epigenetic regulation of HCC. We performed a systematic review of the literature, including articles published up to 2015-2025, in the databases of PubMed, Google Scholar, and Web of Science. We selected relevant studies focusing on circRNAs and their involvement in HCC along with miRNA interactions. **Outcomes:** The extensive involvement of exosomal circRNAs in modulating miRNA signaling pathways leads to modulation of processes such as angiogenesis, epithelial-mesenchymal transition (EMT), and metastasis in HCC. They further also promote chemoresistance by modulating the processes of drug resistance and immune evasion. Moreover, circRNA87th53-derived CE-Ang1 is a promising therapy for HCC. **Conclusion:** Exosomal circRNAs present potential as promising biomarkers and therapeutic targets for HCC. More studies should be performed to investigate their clinical implications and to resolve problems with circRNA identification and functional delivery.

Keywords

Exosomal CircRNAs, Hepatocellular Carcinoma (HCC), Biomarkers, miRNA Regulation, Tumor Progression.

1. Introduction

Hepatocellular Carcinoma (HCC) is the most prevalent type of primary liver cancer, and one of the most common causes of cancer mortality globally. Although advances in early diagnosis and treatment have contributed to improving the prognosis of HCC, it is still a clinical challenge with high metastasis, chemoresistance rate and poor prognosis (Amin et al., 2025). There is a clear and urgent clinical need for novel diagnostic biomarkers and efficacious treatment strategies,

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[*]Corresponding author: Amena Khatun Manica

Email addresses: Amena Khatun Manica (monica.95amena@gmail.com)

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especially among patients diagnosed with advanced Stage disease. Herein, circRNAs (circular RNAs) have been identified as potential regulators in HCC progression and metastasis providing new insights into cancer biology. Among these, exosomal circRNAs have particularly attracted interest due to their stability in body fluid and their roles in regulating key biological processes involved in the progression of HCC (M. Wang et al., 2018; Wu et al., 2020).

As non-coding RNAs with a covalently closed loop structure, CirRNAs are resistant to exonuclease degradation and thus more stable in body fluids like blood and urine. This unique stability makes them potential biomarkers for early cancer detection and therapeutic targets. Recent studies have demonstrated that via exosomes, small extracellular vesicles involved in intercellular communication, circRNAs can be secreted into circulation as exosomal circRNAs. These exosomes deliver circRNAs to distant cells, where they adjust gene expression and affect numerous cell activities including proliferation, invasion and metastasis which are essential elements of tumor progression (Andrade et al., 2024; Shafaghat et al., 2025).

With regards to HCC, much of the research concerning exosomal circRNAs has focused on their role in the regulation of miRNA expression and epigenetic mechanisms that are critical for the induction of drug resistance and metastasis in various malignancies. As one example, circRNAs serve as miRNA sponges, sequestering miRNAs from their target mRNA(s) to modulate expression of master oncogenes and tumor suppressors (Seo et al., 2023). miRNAs, including miR-21, miR-155, and miR-210, have also been demonstrated to regulate important signaling pathways such as Wnt/β-catenin or PI3K/AKT, controlling proliferation, survival, and invasion of HCC cells. Moreover, circRNAs also play roles in epigenetic regulation, which impacts the processes of DNA methylation, histone modification, and chromatin remodeling that are accordingly modified during tumor pathogenesis, resulting in dysregulated gene expression in HCC (Deldar Abad Paskeh et al., 2021; Zou et al., 2016).

Exosomal release of circRNAs also allows crosstalk between cancer cells and the tumor microenvironment, wherein exosomal circRNAs promote immune evasion as well as establish the metastasis niche. Exosomal circRNAs induce immune escape, an important characteristic of cancer metastasis, by regulating the functions of immune cells and changing the immune response (Shao & Lu, 2020). In addition, circRNAs have been shown to participate in HCC drug resistance via regulation of drug efflux pumps or apoptosis resistance pathways. Given the dual primacy of exosomal circRNAs as both pro-tumorigenic signals and responsible mediators of chemoresistance, they present ideal databanks for therapeutic targeting (Andrade et al., 2024).

Nevertheless, much work remains to be done before exosomal circRNAs can be understood fully biologically and clinically in HCC. Firstly, further studies that provide additional tissue-specific circRNA profiles in HCC may be useful to determine if any of these candidates can be used as diagnostic biomarkers (Jia et al., 2022). In addition, circRNA-targeted therapies that include RNA interference and small molecule inhibitors need to be validated by preclinical and clinical trials to evaluate their efficacy and safety. The interplay of circRNAs with the tumor microenvironment and their cross talk with other types of non-coding RNAs also remain poorly characterized, which limits our understanding of their potential roles in cancer progression and treatment response.

2. Methods

2.1 Literature Search Strategy

To explore the role of exosomal circRNAs in hepatocellular carcinoma (HCC), a systematic literature search was performed on several databases, namely PubMed, Google Scholar, and Web of Science. The studies were focused on articles up to the date in [2015-2025] with key search terms "exosomal circRNAs", “Hepatocellular Carcinoma"," miRNA regulation"," tumor progression" and "epigenetic regulation". The review also included reviews, clinical studies and experimental findings that were contributive to our understanding of the role of circRNAs in HCC development, but also their use as biomarkers or therapeutic targets.

2.2 Inclusion and Exclusion Criteria

The studies included in this review were required to meet the following criteria. In the above studies, exosomal circRNAs were associated with HCC and other cancers, and their functions in cancer proliferation into metastasis were discussed. Critically, these studies gave experimental insight or biological mechanisms linking circRNAs to miRNA regulation in HCC. Articles investigating non-HCC cancers without specific comparisons or those providing insufficient information on mechanisms of exosomal circRNAs and their interactions with miRNAs were excluded.

2.3 Data Extraction and Analysis

Data extraction was done in an organized way and key factors from each selected study were reviewed. Overview of the types of exosomal circRNAs identified in hepatocellular carcinoma (HCC), their expression levels in HCC tissues and serum exosomes, and functional roles promoting or suppressing tumorigenesis. Moreover, several studies also examined the interactions of miRNA and target as well as the mechanisms of circRNA-induced regulation in HCC. In this review, we also described the clinical significance of circRNAs for diagnosis and treatment of HCC in detail.

3. CircRNAs and their Biogenesis

Circular RNAs (circRNAs) are a special type of non-coding ribonucleic acids possessing a closed-loop structure with internal splicing inside cells (Figure 1). They are also highly optimized and exhibit high resistance to degradation by RNAs, giving them long shelf life. The two primary subtypes of circRNA, ecircRNAs (exonic circRNAs) and EIcircRNAs (exon-intron circRNAs), arise via diverse biogenesis pathways including intron pairing-induced circularization, RBP-based circularization, and exon skipping models (Chen et al., 2015; MSS Khan & Tufael, 2024). These components keep gene expression in check and are involved in many cellular processes.

CircRNAs highly associated with Cancer Progression, Migration, and Drug Resistance Have an Adverse Impact on HCC CircRNA act as regulators of gene expression by interacting with miRNAs and RBPs, and which are shown to influence different stages in cancer (Upadhye & Saif, 2025). Moreover, elucidating these biogenesis mechanisms may provide valuable information regarding the potential use of circRNAs as biomarkers and therapeutic targets in HCC, leading to novel targeted treatment strategies and diagnostic applications (Meng et al., 2022).

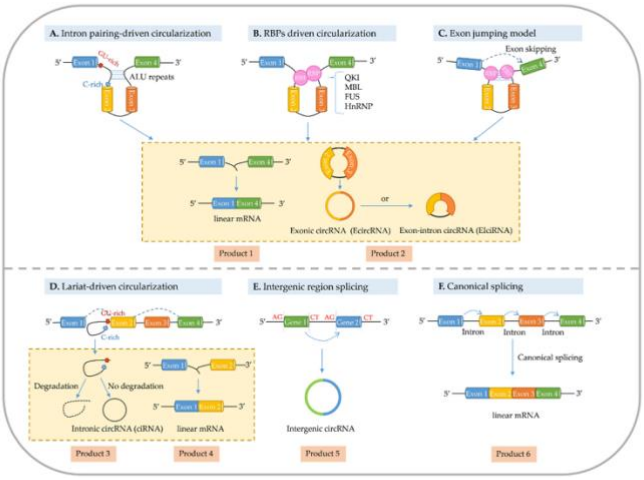

Figure 1. *The following figure displays two cyclic RNA biogenesis models: intron pairing-driven circularization, RBP-driven circularization, and also the exon skipping model.The pathways are exonic circRNAs (EcircRNAs) and exon-intron circRNAs (EIcicrnas), which generate corresponding routes to the formation of different types of circRNAs. Understanding the Molecular Mechanisms of circRNA Biogenesis and Function: Theoretical Background in HCC," which is of pivotal importance given that these processes are also central to regulating gene expression, with implications for diseases such as hepatocellular carcinoma (HCC) in which circRNAs are crucial to stimulating tumor development, metastasis, and drug resistance (Zhang et al., 2024).*

4. Functional Roles of CircRNAs

CircRNAs are implicated in various biological processes. CircRNAs employ miRNA sponging by directly associating with miRNAs and preventing them from interacting with target mRNAs, thus modulating gene expression (Figure 2). In addition, circRNAs are involved in protein sponging and scaffolding function by either preventing proteins or enhancing interactions among them. They are critical in monitoring cellular paths responsible for numerous processes such as signaling, cell-cycle regulation and tumorigenesis; activities that keep cells' homeostasis and functions in check (Meng et al., 2022; MR Islam et al., 2023).

CircRNAs also regulate transcription and epigenetic changes, participating in regulating gene expression at the transcriptional level as well as at the epigenetic level. However, several circRNAs are translated to proteins or small peptides too, which increases functional complexity. This leads to regulation of several beneficial processes like cellular division, gene expression, tumorigenesis, which in turn indicate towards new therapeutic approaches against various diseases including cancer resulting from these mechanisms (Y. Wang & Deng, 2023).

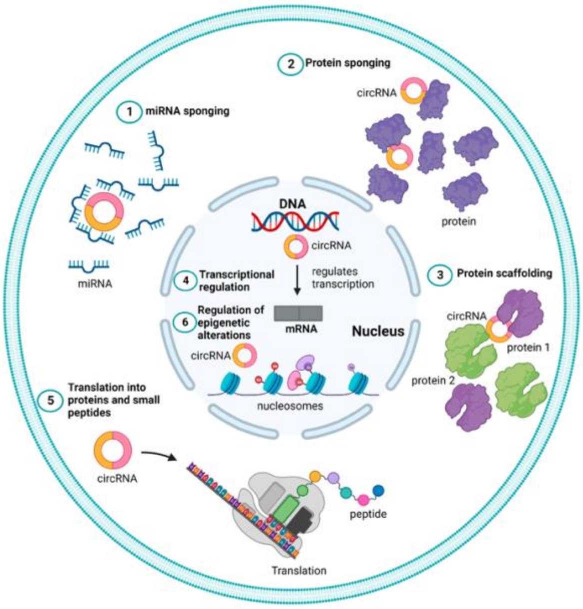

Figure 2. Functional roles of circRNAs in cancer, figure illustrates the diverse functions of circRNAs, including miRNA sponging, protein sponging, protein scaffolding, transcriptional regulation, and epigenetic modifications, all of which contribute to cancer progression, metastasis, and chemoresistance (Abaza et al., 2023).

5. CircRNAs and Cancer Pathology

CircRNAs have been implicated in multiple cancer pathologies, indicating that they have a role as integral players in the cancer process. These can modulate gene expression, are implicated in miRNA sponging and interact with RNA-binding proteins (RBPs), which drive cancer progression. Various circRNAs, such as hsa_circ_0003288, circSETD3, circCRIM1 and hsa_circ_0056836 also regulate signaling pathways that participate in cell proliferation, apoptosis, angiogenesis, tumor invasion and metastasis (Figure3). Publications open new avenues for investigation into the role of the many circRNAs that both are enriched in and hold potential to activate pathways such as Wnt/β-catenin, MAPK, PI3K/Akt and ERK (which have been implicated in tumor progression and growth) in harvesting energy from non-productive carcinogenic settings (AK Manica, MAB Siddique, et al., 2024; Deldar Abad Paskeh et al., 2021).

Additionally, circRNAs modulate the activity of miRNAs against their target genes. Such as circSETD3 and circ-ZEB1.33 interacts with miR-421 and miR-200a-3p, affecting the EMT (Epithelial-Mesenchymal Transition) process and tumor growth (Tang & Hann, 2020). The knowledge of circRNA's structure and function could lead to the new paths in anti-cancer, especially because of circRNA-based detection biomarkers and therapeutic targets. CircRNAs have been significant players in the progression and treatment of cancers like Hepatocellular Carcinoma (HCC) and help with targeted therapy and precision medicine including circCRIM1, circ_0001955, circ_0004913(Meng et al., 2022; Tufael, Kar, et al., 2024).

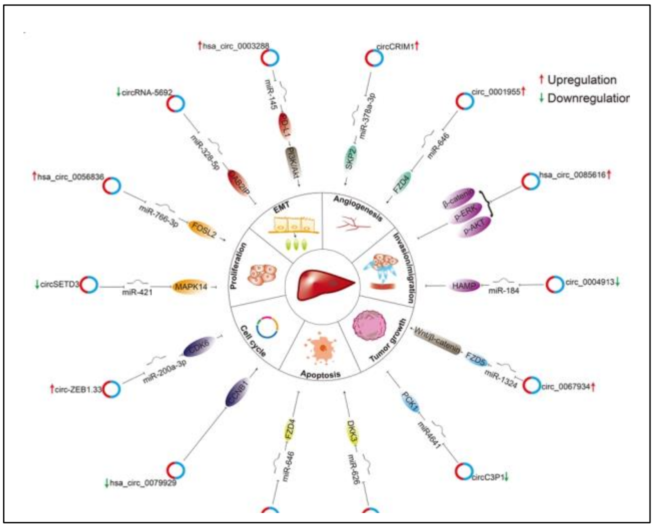

Figure 3. *CircRNAs and cancer pathology is used in this figure among various circRNAs that interact with miRNA and Wnt/β-catenin, PI3K/Akt and MAPK signalling pathways. CircRNAs regulate key processes in cancer including cell proliferation, apoptosis, angiogenesis and metastasis and thus serve as potential biomarkers or may be used as therapeutic targets for various cancers especially Hepatocellular Carcinoma (HCC) (P. Wang et al., 2022).*

6. CircRNAs as Theranostic Agents for HCC

In Table 1, a new paradigm is a circular RNAs (circRNAs) that have become powerful players in the theragnostic toolkit for Hepatocellular Carcinoma (HCC). The presence of these highly stable non-coding RNAs in blood and urine in the form of exosomal circRNAs suggests that they may be good candidates for early diagnostic biomarkers (Tufael, Kar, et al., 2024; Zhang et al., 2024). But showed no evidence for the role of circRNAs in early-stage HCC detection. hsa_circ_0074837 and hsa_circ_0003056 were reported to be associated with HCC progression and tumorigenesis; therefore, they are promising candidates for use as diagnostic biomarkers for early-stage HCC. These circRNAs mediate activation of the Wnt/β-catenin or PI3K/Akt pathways by a number of mechanisms, including miRNA sponging, which is vital for tumor development. In conclusion, the expression patterns of circRNAs might be identified as biomarkers for HCC diagnosis and staging and novel methodology in precision diagnostics (Deldar Abad Paskeh et al., 2021; Seo et al., 2023).

Besides diagnostic implications, circRNAs are also significantly involved in chemoresistance and therapeutic targeting. In the case of HCC, circSORE has been found to modulate Sorafenib resistance via miR-103a-2-5p and miR-660-3p through Wnt/β-catenin pathway (Xu et al., 2020). This indicates circRNAs can be targeted in a therapeutic approach, such as including RNA interference or small molecule inhibitors. Additionally, several circRNAs (e.g., circFBXW4 and circYTHDF3) are capable of controlling tumor progression and mitophagy thereby also leading to drug resistance. These findings identify circRNAs as potential therapeutic targets for the development of tailored treatment strategies in HCC and thus offer a promising avenue to follow-up advance precision medicine (Shen et al., 2021; Tufael & Begum, 2024).

Table 1. *CircRNAs and Their Roles in Hepatocellular Carcinoma (HCC) Progression, Mechanisms, and Therapeutic Potential.*

CircRNAs	Expression Change	Function	Possible Mechanism	References
hsa_circ_0074837	Up	HSC activation(+); proliferation(+)	miR-203/miR-223/FSTL1/TLR4	(Shen et al., 2021)

circFBXW4	Down	HSC activation(-); proliferation(-); apoptosis(+); Anti-inflammation	miR-18b-3p/FBXW7	(Xu et al., 2020)
mmu_circ_34116	Down	HSC activation(-)	BMP7	(P. Wang et al., 2022)
hsa_circ_0071410	Up	HSC activation(+)	miR-9-5p/MRP1/ABCC1	(Tang & Hann, 2020)
hsa_circ_0007874/cMTO1	Down	HSC activation(-); proliferation(-)	miR-181b-5p/PTEN	(Abaza et al., 2023)
circ608	Down	HSC mitophagy (+)	miR222/PINK1	(Y. Wang & Deng, 2023)
hsa_circ_0070963	Down	HSC activation(-); proliferation(-); cell cycle(-)	miR-223-3p/LEMD3	(Meng et al., 2022)
hsa_circ_0004018	Down	HSC activation(-); proliferation(-)	miR-660-3p/TEP1	(Li et al., 2020)
hsa_circ_0003056	Up	Liver cancer promotion	miR-490-3p	(Youness et al., 2024)
hsa_circ_0067127	Up	Carcinoma progression	miR-146b	
circFBLIM1	Up	Hepatoblastoma progression, cell viability, proliferation	miR-346-ceRNA to regulate FBLIM1 expression	(Youness et al., 2024)
circHMGCS1	Up	Hepatoblastoma: Regulates proliferation, apoptosis, glutaminolysis	miR-503-5p/IGF/PI3K/AKT	(Youness et al., 2024)
circSORE	Up	Sorafenib resistance	miR-103a-2-5p/miR-660-3p, Wnt/β-catenin pathway	(Xu et al., 2020)
circYTHDF3	Up	Liver carcinogenesis	miR-136-5p/CBX4/VEGF	(Xu et al., 2020)

7. Exosomal CircRNAs in HCC-Functions and Mechanisms

Exosomal circRNAs regulate HCC progression and act as potential diagnostic and therapeutic biomarkers. Cancer-suppressive circRNAs such as miR-638, miR-335, miR-125b and miR-320d are downregulated in both the exosome-as well as HCC tissue (Table 2). These circRNAs suppress proliferation and invasion of HCC cells, possibly through mechanisms such as miRNA sponging or the modulation of specific signaling pathways, but the precise mechanisms are not clearly defined (MF Akter et al., 2022; Shen et al., 2021). Additionally, these circRNAs provide novel markers for early-stage HCC diagnosis and tracking tumor activity.

Conversely, miR-93, miR-106a and miR-224 upregulated both in extracellular exosomes and HCC tissue suggesting pro-oncogenic activities. The activities of these circRNAs in HCC are related to processes that support malignance such as angiogenesis, epithelial-mesenchymal transition (EMT), and other tumor-promoting properties (Tufael, A Kar, et al., 2024; Xu et al., 2020). Intriguingly, miR-518d is overexpressed within exosomes but it is downregulated in HCC tissues, indicating that its role as a cancer suppressor through preventing the growth and invasion of HCC cells. The dynamic regulation of exosomal circRNAs reveals their dualistic role as cancer suppressor vs. promoter in HCC and uncovers propitious approaches for information-based therapeutic interventions and individualized biomarkers development (A Debnath et al., 2023; P. Wang et al., 2022).

Table 2. Exosomal circRNAs in Hepatocellular Carcinoma (HCC), expression changes, functions, mechanisms, and their role in cancer progression.

Exosomal CircRNAs	Expression Change in Exosomes	Expression Change in HCC	Function	Mechanism	References
miRNA-638	Down	Down	Cancer suppression	Inhibit the proliferation and invasion of HCC	(Chen et al., 2015)
miR-335	Down	Down	Cancer suppression	Inhibit the proliferation and invasion of HCC	(Y. Wang & Deng, 2023)
miR-125b	Down	Down	Cancer suppression	Inhibit the proliferation and invasion of HCC	(Abaza et al., 2023)
miR-320d	Down	Down	Cancer suppression	Inhibit the proliferation and invasion of HCC	(Tang & Hann, 2020)
miR-93	Up	Up	Cancer promotion	Promote the proliferation and invasion of HCC	(Xu et al., 2020)
miR-106a	Up	Up	Cancer promotion	Promote the proliferation and invasion of HCC	(Shen et al., 2021)
miR-224	Up	Up	Cancer promotion	Promote the proliferation and invasion of HCC	(Li et al., 2020)
miR-518d	Up	Down	Cancer suppression	Inhibit the proliferation and invasion of HCC	(Younes et al., 2024)

8. CircRNAs in Epigenetic Regulation in HCC

Differential expression of circRNAs acts as a major regulator of epigenetics in HCC. They modulate gene expression via DNA methylation, histone deacetylation, and chromatin remodeling. miRNAs and RBPs interact with circRNAs to modulate genomic stability and chromatin dynamics, subsequently regulating tumor-related signaling pathways (M. M. H Shabuj & Tufael, 2019; Zhang et al., 2024). These characteristics render circRNAs significant epigenetic regulators, hence the potential of circRNAs in HCC alongside the importance of cancer progression and treatment are to be provided (Figure 4).

These processes imply that circRNAs regulate epigenetic modifications in HCC via molecular mechanisms, including modification of histones or coordination of DNA methylation, that are associated with malignancy occurrence, metastasis and chemoresistance. The epigenetic regulatory roles of circRNA have opened the door to potential applications with respect to precision medicine and targeted therapies, where these molecules can be utilized as biomarkers and therapeutic targets for HCC treatment (A Debnath et al., 2023; M. Guo et al., 2021).

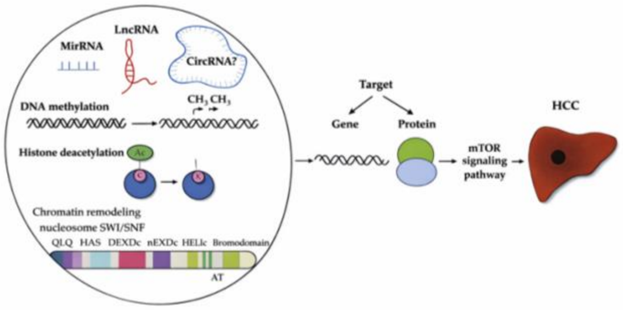

Figure 4. *CircRNAs in Epigenetic Regulation in HCC. This figure shows how circRNAs regulate epigenetic modifications like DNA methylation and histone modification, influencing gene expression and HCC progression. They act as potential biomarkers and therapeutic targets in HCC treatment (M. Guo et al., 2021).*

9. Exosomal miRNAs in HCC and Role in Tumor Promotion

In HCC, tumor exosomes contain specific miRNA signatures and upregulate a number of miRNAs (miR-21, miR-155, miR-210, and so on), which are also upregulated at the plasma and tissue levels in HCC to promote cancer development/metastasis (Table 3). Later, the miRNAs are involved in the regulation of tumor progression, metastasis and angiogenesis by targeting major regulatory proteins (P. Wang et al., 2022). MiR-21 and miR-155, for example, target PTEN in oncogenic signaling pathways. Likewise, even miR-210 aims SMAD4 and STAT6, which promote angiogenesis. Conversely, miR-221 regulates AdipoR1, while miR-10b modulates CADMs and miR-103 affects VE-cadherin and p120-catenin, both modulators of vascular permeability and metastatic spread. All these processes cumulatively lead to the pro-tumorigenic phenome in HCC (AK Manica, MAB Siddique, et al., 2024; Y. Wang & Deng, 2023).

The upregulated expression of exosomal miRNAs in HCC establishes an intricate regulatory network that modulates essential step processes such as epithelial-mesenchymal transition (EMT), angiogenesis, and vascular permeability within the tumor microenvironment. These miRNAs drive HCC development by augmenting tumor invasion, immune evasion and metastatic dissemination (AK Manica et al., 2023; Meng et al., 2022). Consequently, they are potential biomarkers for early diagnosis as well as therapeutic targets. miRNA-Mediated signaling pathways in facing tumor growth and immune modulation/ chemoresistance, novel therapeutic strategies are needed silencing exosomal miRNAs that play a role in HCC could serve as a promising therapeutic target due to their association with multiple processes involved in cancer progression and metastasis (Jia et al., 2022; MAR Biswash et al., 2024).

Table 3. *Exosomal CircRNAs in HCC - miRNA interaction and cancer regulation.*

Exosomal CircRNAs	**Target miRNA**	**Up or Down in HCC**	**Cancer Promotion or Suppression**	**Function**	**Mechanism**	**References**
miR-21	PTEN	Up	Cancer promotion	Promote proliferation, invasion, metastasis of HCC	Angiogenesis	(Tufael & Moyen PK, 2025)
miR-155	PTEN	Up	Cancer promotion	Promote proliferation, invasion, metastasis of HCC	Angiogenesis	(Niu et al., 2022)
miR-210	SMAD4 and STAT6	Up	Cancer promotion	Promote proliferation, invasion, metastasis of HCC	Angiogenesis	(Lin et al., 2018)
miR-221	AdipoR1	Up	Cancer promotion	Promote proliferation, invasion, metastasis of HCC	EMT	(Li et al., 2020)
miR-10b	Cell adhesion molecules (CADMs)	Up	Cancer promotion	Promote metastasis of HCC	EMT	(F. Guo et al., 2024)
miR-103	VE-Cadherin, p120-catenin	Up	Cancer promotion	Promote metastasis of HC	Vascular permeability	(Y. Wang & Deng, 2023)

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10. Future Directions and Challenges

The functions of exosomal circRNAs and their influence on HCC are being gradually understood while still with a lot unknown field. Thus, further studies are needed to elucidate the association of circRNAs with miRNA interactions, in particular involving their mechanisms during epigenetic regulation as well as within the tumor microenvironment (Abaza et al., 2023). Moreover, further studies are needed to investigate the potential exosomal circRNAs as biomarkers and targets of targeted therapy. Application of high throughput sequencing and bioinformatics tools is open to further insights into the roles of circRNAs and miRNAs, which in turn might provide opportunities for novel therapeutic strategies (MF Akter et al., 2022; Zhang et al., 2024).

Moreover, there are a number of challenges in circRNA and exosomal pathway studies. Insights into the tissue-specific expression, mechanistic complexity of circRNAs are limited, making it difficult to determine precise functions and therapeutic resilience (Jia et al., 2022). Second, exosomal circRNAs require extensive studies regarding their stability and bioavailability. These findings pave the way for further development of circRNA-based therapeutics; however, long-term clinical trials and preclinical models are necessary to demonstrate their safety and efficacy prior to broader utilization (AK Manica, MR Islam, et al., 2024; Meng et al., 2022).

11. Conclusion

In summary, exosomal circRNAs are crucial regulatory agents in HCC progression and metastasis. First, miRNAs can serve as biomarkers and therapeutic targets due to their ability to act as epigenetic modifiers. Although the functions of those factors have been largely clarified, we still face many challenges about their stability, bioavailability and tissue specific expression. These compress accuracy and recall performance, indicating the necessity of optimizing these parameters in future studies for circRNA-based treatments as well as HCC diagnosis more broadly. On a larger scale, exosomal circRNAs might contribute to personalized treatment strategies for HCC management.

Author Contributions

A.K.M. conceptualized the study, supervised the project, and drafted the manuscript. M.R.I. contributed to literature review, data collection, and manuscript writing. M.F.A. assisted with literature analysis, figure preparation, and manuscript editing. S.H. contributed to critical revision, validation of scientific content, and final proofreading of the manuscript. All authors reviewed and approved the final version of the manuscript.

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