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Review

Tracing the Scientific Evolution of Exosomal microRNA Research in Liver Cancer: A Comprehensive Review

Ashutosh Kumar Maurya ^{1,†}, Rida Khan ^{2,†}, Ashish Kumar Maurya ³, Hiba Khan ⁴, Swetha E ⁶, Jordi Muntane ^{5,*} and V.B. Sameer Kumar ^{6,*}

¹ Department of Biochemistry & Mol. Biology, Central University of Kerala, Kasaragod, Kerala, India, 671316

² Department of Education, Central University of Kerala, Kasaragod, Kerala, India, 671316

³ Institute of Engineering & Technology, Bundelkhand University, Jhansi, Uttar Pradesh, India, 284128

⁴ Department of Zoology, Mizoram University, Aizawl, Mizoram, India, 796004

⁵ Instituto de Biomedicina de Sevilla, Universidad de Sevilla, Sevilla, Spain, 41004

⁶ Department of Genomic Science, Central University of Kerala, Kasaragod, Kerala, India, 671316

* Correspondence: ridakhanjsp@gmail.com (J.M.); mauryaashutoshk@gmail.com (V.B.S.K.)

† These authors contributed equally to this work.

Abstract

Exosomal microRNAs (miRNAs) have emerged as critical mediators of intercellular communication, influencing numerous physiological and pathological processes. In the context of liver cancer, particularly hepatocellular carcinoma (HCC), exosomal miRNAs contribute to tumor initiation, progression, metastasis, and therapy resistance by modulating the tumor microenvironment and signaling pathways. This review comprehensively summarizes the biogenesis, functions, and physiological roles of miRNAs and their exosomal forms, highlighting their involvement in various diseases with a focus on liver cancer. We discuss the current landscape of exosomal miRNA research in HCC, examining their potential as diagnostic and prognostic biomarkers, as well as therapeutic targets. Additionally, we critically evaluate past and ongoing drug development efforts targeting exosomal miRNA pathways and emphasize existing challenges and future directions in this rapidly evolving field. Understanding the intricate roles of exosomal miRNAs in liver cancer will advance biomarker discovery and foster novel therapeutic strategies, ultimately improving patient outcomes.

Keywords: MicroRNA; Exosome; Biomarker discovery; HCC; Biogenesis

1. Introduction

Liver cancer remains one of the most prevalent and deadly malignancies worldwide, ranking as the eighth most common cancer and the fourth leading cause of cancer-related deaths globally [1]. Hepatocellular carcinoma (HCC) accounts for approximately 75–85% of primary liver cancer cases, with high morbidity and poor prognosis due to late diagnosis, high recurrence, and resistance to current therapies [2,3]. Despite advances in imaging and serological biomarkers such as alpha-fetoprotein (AFP), early detection and reliable prognostication remain elusive, limiting treatment success [4].

MicroRNAs (miRNAs) have emerged as pivotal regulators of gene expression, orchestrating diverse cellular processes including proliferation, differentiation, apoptosis, and metabolism. These small (~19–25 nucleotides), non-coding RNAs regulate gene expression post-transcriptionally by binding to complementary sequences in target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression [5,6]. Dysregulation of miRNAs contributes to oncogenesis and tumor progression across multiple cancers, including liver cancer [7].

Exosomes, nanoscale extracellular vesicles secreted by most cell types, carry various molecular cargos, including proteins, lipids, DNAs, and RNAs. Of particular interest are exosomal microRNAs (exo-miRNAs), which serve as mediators of intercellular communication by transferring genetic information between cells [8]. Exo-miRNAs in bodily fluids offer remarkable stability and reflect the physiological or pathological status of their cells of origin, positioning them as promising non-invasive biomarkers and potential therapeutic targets in liver cancer [9,10].

This review comprehensively examines the scientific evolution of exosomal microRNA research in liver cancer. We explore miRNA biogenesis, exosome biology, physiological and pathological roles of exosomal miRNAs, their implications in liver cancer diagnosis, progression, and therapy, and highlight current challenges and future directions in this burgeoning field.

2. Biogenesis and Functional Mechanisms of microRNAs

MicroRNAs originate from endogenous genes transcribed primarily by RNA polymerase II, yielding primary miRNAs (pri-miRNAs) that fold into hairpin structures [11]. In the nucleus, the microprocessor complex comprising Drosha and DGCR8 cleaves pri-miRNAs into precursor miRNAs (pre-miRNAs), approximately 70 nucleotides long [12]. Exportin-5 mediates their transport into the cytoplasm, where Dicer processes them into ~22 nucleotide double-stranded miRNA duplexes [13]. One strand (the guide) incorporates into the RNA-induced silencing complex (RISC), while the passenger strand is typically degraded [14].

Within RISC, miRNAs guide the complex to complementary sequences mainly in the 3' untranslated regions (UTRs) of target mRNAs, inhibiting their translation or promoting degradation [15]. Because individual miRNAs can target multiple mRNAs, and conversely, single mRNAs may be regulated by multiple miRNAs, these molecules act as critical regulators of gene expression networks [16].

MiRNAs influence key biological processes, including development, metabolism, immune responses, and apoptosis. Their dysregulation is implicated in various diseases, particularly cancers, where they may function as oncogenes (oncomiRs) or tumor suppressors depending on their targets and context [7,17].

3. Exosomes and Exosomal microRNAs: Biogenesis and Selective Packaging

Exosomes are extracellular vesicles approximately 30–150 nm in diameter, formed within multivesicular bodies (MVBs) of the endosomal system [18]. Upon fusion of MVBs with the plasma membrane, exosomes are secreted into the extracellular milieu, facilitating communication between cells [19].

Exosome biogenesis involves the endosomal sorting complex required for transport (ESCRT) machinery, tetraspanins, and ceramide-dependent pathways, orchestrating cargo sorting into intraluminal vesicles [20]. Selective packaging of miRNAs into exosomes is a tightly regulated process, influenced by sequence motifs, RNA-binding proteins such as hnRNPA2B1 and YBX1, and cellular context [21,22]. This selectivity enables exosomes to carry specific miRNA cargos reflective of the physiological or pathological status of the donor cells [23].

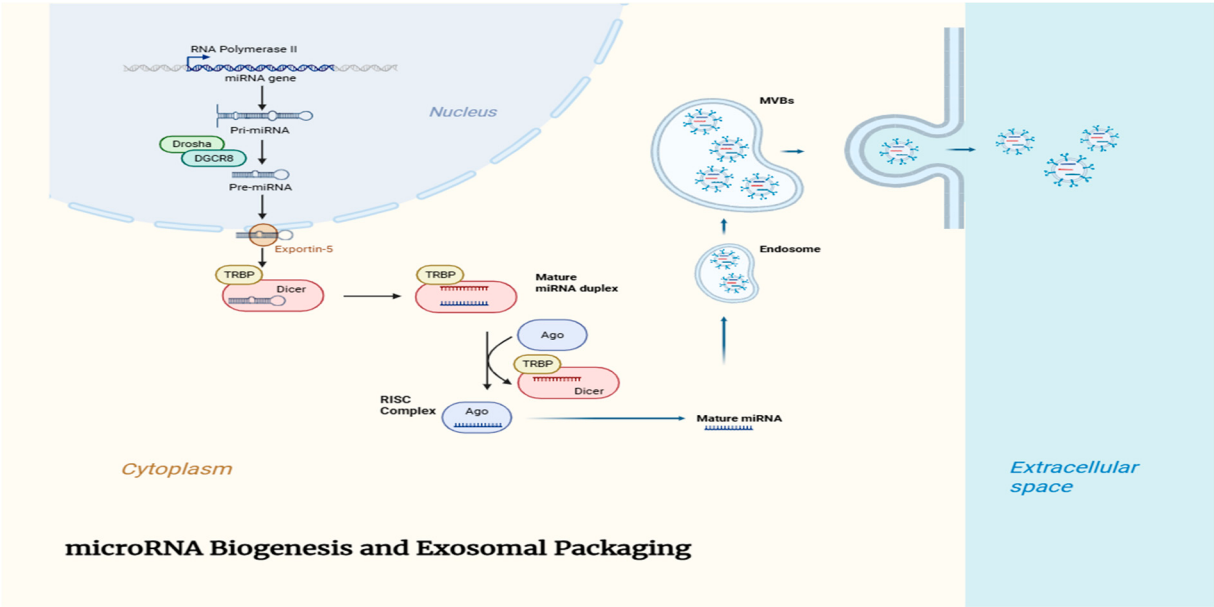


Figure 1. Schematic Diagram of microRNA Biogenesis and Exosomal Packaging: Schematic representation of microRNA biogenesis and selective packaging into exosomes. MicroRNAs are transcribed and processed through nuclear and cytoplasmic steps, followed by selective incorporation into exosomes which mediate intercellular communication.

Exosomal miRNAs are remarkably stable in circulation, protected from RNase degradation by the lipid bilayer of exosomes [24]. They can be taken up by recipient cells through endocytosis, phagocytosis, or membrane fusion, modulating gene expression and cellular phenotypes in target cells [25]. This intercellular transfer plays crucial roles in maintaining homeostasis and in disease pathogenesis. The biogenesis of microRNAs involves a tightly regulated multistep process, including nuclear and cytoplasmic events that ultimately lead to the generation of mature miRNAs. The selective sorting of these miRNAs into exosomes further adds complexity to their regulatory roles. Table 1 outlines the key molecules and steps involved in the biogenesis and exosomal packaging of microRNAs.

Table 1. Biogenesis Pathway Components of microRNAs and Exosomal miRNAs.

Step	Key Molecules/Proteins	Description	Relevance to Exosomal Packaging	Reference(s)
Transcription	RNA Polymerase II	Primary miRNA (pri-miRNA) synthesis	Initial step; source of all miRNAs	[5,11]
Nuclear processing	Drosha, DGCR8	Processing pri-miRNA to precursor miRNA (pre-miRNA)	Generates pre-miRNA for export	[12]
Nuclear export	Exportin-5	Transports pre-miRNA to cytoplasm	Enables cytoplasmic processing	[13]
Cytoplasmic processing	Dicer	Converts pre-miRNA into mature miRNA duplex	Produces mature miRNAs, ready for function	[14]
RISC loading	Argonaute proteins (Ago2)	Assembly into RNA-induced silencing complex (RISC)	Guides miRNA targeting; selective exosomal sorting	[15,24]
Exosomal sorting	hnRNPA2B1, YBX1	RNA-binding proteins mediate selective packaging	Determines miRNA export via exosomes	[21,22]

4. Physiological Roles of Exosomal miRNAs

Under physiological conditions, exosomal miRNAs participate in diverse biological processes. They contribute to tissue development, regeneration, and immune modulation by mediating crosstalk between different cell types [26]. For example, mesenchymal stem cell-derived exosomes enriched with miRNAs support tissue repair and modulate inflammation [27].

In the liver, exosomal miRNAs regulate hepatocyte function, liver regeneration, and responses to injury [28]. They facilitate communication between hepatocytes, hepatic stellate cells (HSCs), Kupffer cells, and immune cells, orchestrating liver homeostasis and repair [29]. Exosomal miRNAs also modulate lipid metabolism and insulin sensitivity, highlighting their role in metabolic regulation [30]. Exosomal microRNAs have shown great promise as minimally invasive biomarkers for early diagnosis and prognosis in liver cancer. Table 2 summarizes the most studied exosomal miRNAs with diagnostic and prognostic potential, along with their performance metrics in clinical samples.

Table 2. Exosomal microRNAs as Diagnostic and Prognostic Biomarkers in Liver Cancer.

miRNA	Sample Type	Diagnostic/Prognostic Utility	Sensitivity/Specificity (if available)	Reference(s)
miR-21	Serum exosomes	Early diagnosis, poor prognosis marker	Sensitivity ~85%, Specificity ~80%	[28,36]
miR-122	Plasma exosomes	Early detection biomarker	Sensitivity ~90%, Specificity ~85%	[9,42]
miR-148a	Serum exosomes	Predicts recurrence after treatment	Data limited	[42,43]
miR-221	Serum exosomes	Associated with aggressive tumor behavior	Data limited	[7]
miR-199a-3p	Serum exosomes	Predicts resistance to sorafenib therapy	Data limited	[47]

5. Pathological Roles of Exosomal miRNAs in Diseases

Aberrant exosomal miRNA expression and signaling are implicated in various diseases, including inflammatory disorders, fibrosis, metabolic diseases, and cancer [31]. In inflammatory and fibrotic diseases, exosomal miRNAs modulate immune responses and fibroblast activation, influencing disease progression [32].

In cancer, tumor-derived exosomal miRNAs facilitate tumor growth and metastasis by remodeling the tumor microenvironment (TME), promoting angiogenesis, immune evasion, and metastasis [33,34]. For instance, exosomal miRNAs can suppress immune cell activity, induce epithelial-mesenchymal transition (EMT), and support metastatic niche formation [35]. The transfer of miRNAs via exosomes can also contribute to drug resistance by altering drug metabolism or apoptotic pathways in recipient cells [36].

Given their stability and accessibility in biofluids, exosomal miRNAs have emerged as promising biomarkers for disease diagnosis, prognosis, and therapeutic monitoring [37].

6. Liver Cancer: Pathogenesis and Clinical Challenges

Hepatocellular carcinoma (HCC) arises primarily in the context of chronic liver disease, including viral hepatitis B and C, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD) [38]. The multistep pathogenesis involves chronic inflammation, fibrosis, cirrhosis, and genetic and epigenetic alterations that dysregulate key signaling pathways such as Wnt/ β -catenin, PI3K/Akt, and TGF- β [39].

Despite advances in treatment modalities including surgical resection, liver transplantation, ablation therapies, and systemic agents like sorafenib and lenvatinib, HCC prognosis remains poor due to late diagnosis, high recurrence rates, and therapeutic resistance [40].

Current serum biomarkers, particularly AFP, lack sufficient sensitivity and specificity, especially for early-stage disease [4]. This highlights an urgent need for novel biomarkers and therapeutic targets to improve HCC management.

7. Roles of Exosomal microRNAs in Liver Cancer

Recent studies have revealed critical roles for exosomal miRNAs in HCC pathogenesis and clinical management. Circulating exosomal miRNAs such as miR-21, miR-122, miR-148a, and miR-192 have been identified as potential diagnostic and prognostic biomarkers [41,42]. Panels of exosomal miRNAs often outperform single markers, improving sensitivity and specificity for early detection and monitoring [43].

Mechanistically, tumor-derived exosomal miRNAs promote tumor progression by modulating the TME, inducing angiogenesis, facilitating EMT, and evading immune surveillance [44,45]. For example, exosomal miR-21 can activate hepatic stellate cells into cancer-associated fibroblasts, promoting fibrosis and tumor progression [46]. Exosomal miR-93 and miR-199a modulate drug resistance pathways, influencing therapeutic response [47,48].

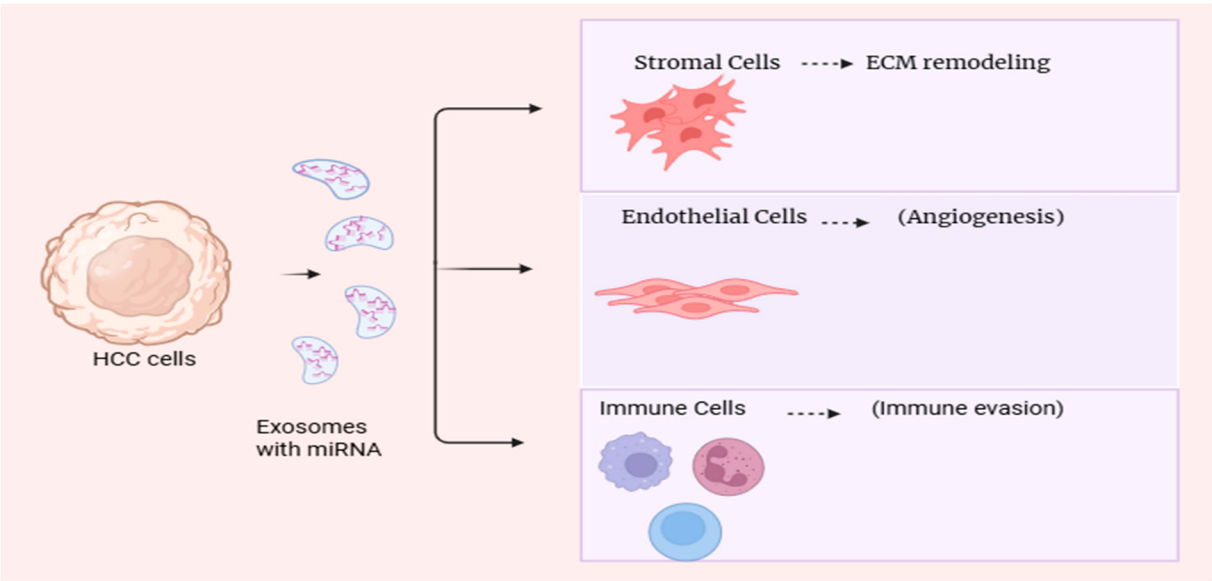


Figure 2. Role of Exosomal miRNAs in Liver Cancer Progression: *Role of exosomal microRNAs in modulating the liver cancer microenvironment. Tumor-derived exosomal miRNAs facilitate communication with stromal and immune cells to promote tumor progression and metastasis.*

Furthermore, exosomal miRNAs contribute to liver fibrosis and cirrhosis, key precursors of HCC, by regulating HSC activation and inflammatory pathways [49]. Several microRNAs have been identified as critical regulators of liver cancer progression, influencing tumor cell proliferation, invasion, and metastasis.

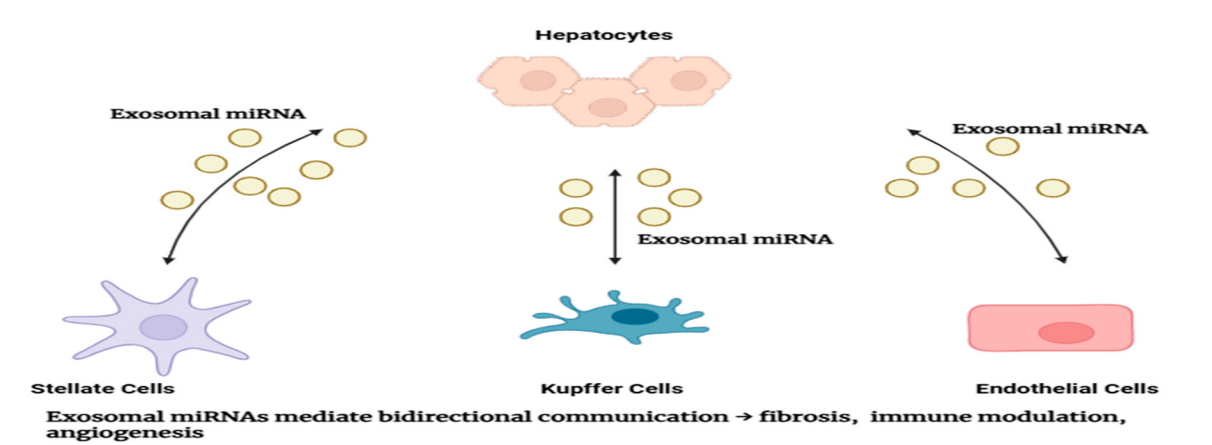


Figure 3. Exosomal miRNA-mediated Communication in Liver Cancer Microenvironment: *Intercellular communication within the liver cancer microenvironment mediated by exosomal microRNAs. Multiple cell types exchange exosomal miRNAs, influencing disease progression and therapeutic response.*

A summary of the key microRNAs implicated in hepatocellular carcinoma, along with their expression patterns and target pathways, is provided in Table 3.

Table 3. Overview of Key microRNAs Implicated in Liver Cancer.

miRNA	Expression Pattern	Target Genes/Pathways	Functional Role in HCC	Reference(s)
miR-21	Upregulated	PTEN, PDCD4	Promotes proliferation, invasion	[28,46]
miR-122	Downregulated	Cyclin G1, ADAM17	Tumor suppressor, regulates metabolism	[9,42]
miR-199a	Downregulated	mTOR, c-Met	Suppresses tumor growth	[47]
miR-221	Upregulated	CDKN1B, PTEN	Enhances proliferation and survival	[7]
miR-25-3p	Upregulated	Notch signaling pathway	Promotes metastasis	[34]
miR-148a	Downregulated	DNMT1	Tumor suppressor	[42,43]
miR-103a	Upregulated	SFRP4, Wnt/ β -catenin	Promotes metastasis and EMT	[45]

8. Therapeutic Implications and Potential

The therapeutic potential of exosomal miRNAs in HCC is multifaceted. Strategies include using exosomes as natural carriers for delivering tumor-suppressive miRNAs or miRNA inhibitors to modulate oncogenic pathways [50]. Engineering exosomes derived from mesenchymal stem cells or other sources allows targeted delivery with minimal immunogenicity [51].

Additionally, inhibiting exosome biogenesis or release may disrupt pathological intercellular communication in tumors, offering novel treatment avenues [52]. However, clinical translation faces challenges including ensuring targeted delivery, understanding biodistribution and pharmacokinetics, avoiding off-target effects, and scalable manufacturing [53].

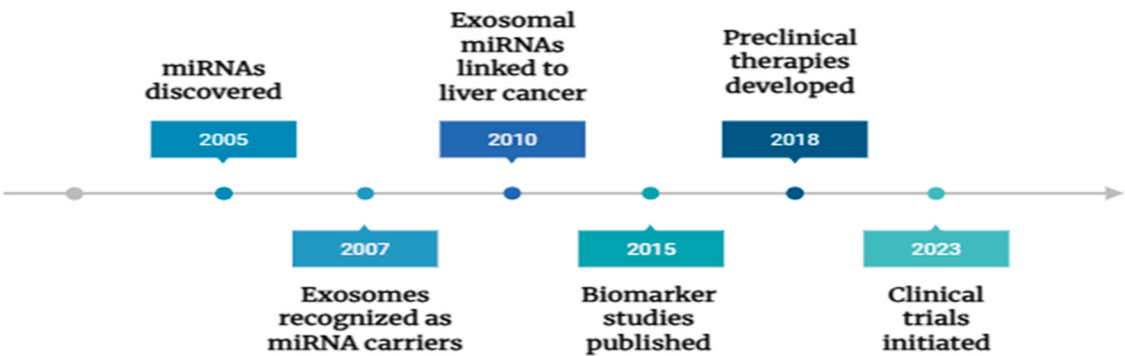


Figure 4. Timeline of Key Discoveries and Therapeutic Developments in Exosomal miRNA Research for Liver Cancer: *Timeline depicting significant advances in exosomal microRNA research related to liver cancer, highlighting major discoveries and therapeutic developments over the past two decades.*

Ongoing clinical trials are exploring exosome-based diagnostics and therapeutics, although large-scale validation is required before routine clinical application [54]. Targeting exosomal microRNAs offers a novel therapeutic strategy for liver cancer, with several approaches currently under investigation. Table 4 provides an overview of existing therapeutic modalities focusing on miRNA mimics, inhibitors, and exosome-based delivery systems.

Table 4. Current Therapeutic Approaches Targeting Exosomal miRNAs in Liver Cancer.

Therapeutic Strategy	Target miRNA(s)	Mode of Delivery	Preclinical/Clinical Status	Outcomes/Notes	Reference(s)
miRNA mimics	miR-122, miR-199a	Lipid nanoparticles, exosomes	Preclinical	Suppression of tumor growth in vivo	[44,45]
Anti-miRNA oligonucleotides	miR-21, miR-221	Systemic administration	Preclinical	Reduced tumor proliferation and metastasis	[28,46]
Exosome-based drug delivery	Various miRNAs	Engineered exosomes	Early clinical/preclinical	Improved targeting, reduced off-target effects	[51,52,53]
Combination therapies	miRNAs + Sorafenib	Co-delivery via nanoparticles	Preclinical	Overcomes drug resistance	[47,48]

9. Emerging Technologies and Future Directions

Advances in high-throughput sequencing, single-vesicle analysis, and multi-omics integration are revolutionizing exosomal miRNA research, enabling comprehensive molecular profiling and biomarker discovery [55]. Novel isolation methods and characterization technologies enhance the specificity and sensitivity of exosomal miRNA detection [56].

Integration of artificial intelligence and bioinformatics facilitates pattern recognition and predictive modeling, accelerating translational research [57]. Future work should focus on standardizing methodologies, validating biomarkers in large cohorts, elucidating mechanistic pathways, and optimizing therapeutic delivery systems. Regulatory frameworks and manufacturing standards must evolve to support clinical translation of exosome-based products [58].

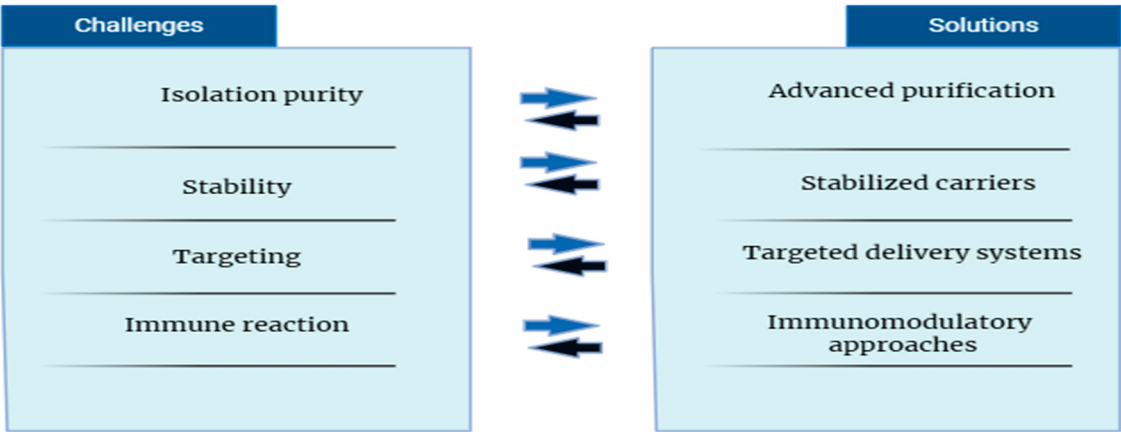


Figure 5. Future Perspectives and Challenges in Exosomal miRNA-based Therapies: Overview of current challenges and future directions in the development of exosomal microRNA-based therapeutics for liver cancer.

10. Conclusions

Exosomal microRNAs represent a rapidly evolving field with significant implications for understanding liver cancer biology, improving diagnostics, and developing novel therapies. Their unique capacity for intercellular communication and biomarker potential positions them at the forefront of precision oncology for HCC.

Continued multidisciplinary research integrating molecular biology, clinical investigation, and technological innovation will be essential to overcome current challenges and translate exosomal miRNA research into impactful clinical applications.

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