

REVIEW ESSAY

Involvement of microRNAs and their potential diagnostic, therapeutic, and prognostic role in hepatocellular carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) accounts for 85%–90% of primary liver cancer. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by targeting the 3'UTR of mRNA. Abnormal expression and regulation of miRNAs are involved in the occurrence and progression of HCC, and miRNAs can also play a role in the diagnosis and treatment of HCC as oncogenes or tumor suppressors.

Methods: In the past decades, a large number of studies have shown that miRNAs play an essential regulatory role in HCC and have potential as biomarkers for HCC. We reviewed the literature to summarize these studies.

Results: By reviewing the literature, we retrospectively examined the roles of miRNAs in the development, diagnosis, treatment, and prognosis of HCC, and put forward prospects for the further research on miRNAs in the precision treatment of HCC.

Conclusion: MicroRNAs are important regulators and biomarkers in the occurrence, progression, outcome, and treatment of HCC, and can provide new targets and strategies for improving the therapeutic effect of HCC.

KEYWORDS

biological process, hepatocellular carcinoma, liver regeneration, microRNAs, tumor microenvironment

1 | INTRODUCTION

In the treatment of hepatocellular carcinoma (HCC), although surgical resection, interventional therapy, radiotherapy/chemotherapy, targeted therapy, immunotherapy, and liver transplantation are effective, the 5-year survival rate is still meager. The main reason is that HCC is more prone to recurrence and metastasis. Furthermore, HCC has an insidious onset and progresses slowly,

and patients often miss the optimal time for treatment.¹ MicroRNAs (miRNAs) are non-coding single-stranded RNAs first discovered in *Caenorhabditis elegans* in 1993. They are highly conserved and widely exist in animals, plants, and some viruses.² miRNAs promote the degradation of target genes or inhibit the translation of target genes through complementary base pairing, thus achieving the post-transcriptional regulation of target genes.³ The pathological processes of many diseases, including cancer, metabolic diseases,

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inflammatory diseases, and cardiovascular, are highly dependent on the regulation of miRNA.⁴⁻⁶

Over the past decades, there has been increasing research on the role of miRNAs in cancer.⁷ A large number of abnormally expressed miRNAs exist in HCC. MiRNAs expression profiles have potential as biomarkers for the diagnosis and prognosis of HCC.⁸ In-depth research of the expression of miRNAs and their regulatory mechanism in HCC is of great importance to guide early diagnosis, treatment, and prognosis of HCC. In this review, the regulatory role of miRNAs in the occurrence and development, diagnosis, treatment, and prognostic assessment of HCC will be elaborated, with emphasis on the regulation and related mechanisms of miRNAs on the occurrence and development of HCC.

2 | REGULATION OF HCC OCCURRENCE AND DEVELOPMENT BY MIRNAS

2.1 | MiRNAs and cellular biological processes in HCC

In HCC, miRNAs can act as promoters or suppressors to regulate multiple cellular biological processes such as proliferation, migration, invasion, and apoptosis.⁹ For example, miR-182-5p directly targeted the 3' UTR of FoxO3a in surgically treated HCC patients, activating the Akt/FoxO3a pathway and promoting proliferation and migration of HCC cells.^{10,11} MiR-1225-5p level was decreased in HCC patients. Transfection with miR-1225-5p mimics inhibited the viability, proliferation, migration, and invasion of HCC cells and reduced the expression of matrix metalloproteinase 9 (MMP-9).¹² MiR-199b-5p inhibited the proliferation of HCC cells through regulating CDC24A to induce cell cycle arrest.¹³ The level of miR-222 in HCC patients with tumors larger than 5 cm was significantly higher than that of patients with tumors smaller than 5 cm. Inhibition of miR-222 suppressed the proliferation and promoted the apoptosis of HCC cells.¹⁴ Other miRNAs, such as miR-217, miR-340, miR-206, miR-302a, and miR-30a-5p could regulate the biological processes of HCC cells by targeting different genes.¹⁵⁻¹⁹

Some miRNAs can regulate hepatocyte apoptosis through intrinsic and extrinsic pathways.²⁰ In HBV-related HCC, miR-15a/miR-16-1 regulated anillin, which was essential for tumor growth, thereby affecting apoptosis of HCC cells.²¹ MiR-125b promoted HCC cells apoptosis and attenuated human HCC malignancy by targeting SIRT6.²² MiR-221/222 promoted HCC development by targeting apoptosis-related factor p53, signal transducers and activators of transcription 3 (STAT3), and nuclear factor κ B (NF- κ B).²³ MiR-221/222 induced TNF-related apoptosis and ligand (TRAIL) resistance by modulating tumor suppressors phosphatase, tensin homomorphs located on chromosome 10 (PTEN), and tissue metalloproteinase inhibitor 3 during hepatocellular carcinogenesis. Moreover, the activation of Akt pathway and matrix metalloproteinase activity by miR-221/222 could promote the migration of HCC cells.²⁴

2.2 | MiRNAs and angiogenesis in HCC

Some angiogenesis-related miRNAs were significantly reduced in HCC, such as miR-15b, miR-125b, miR-423-3p, miR-424, miR-494, miR-497, miR-612, miR-637, and miR-1255b.²⁵ MiR-130b-3p directly targeted HOXA5 to upregulate the expression of endothelial markers CD31 and CD34, thereby promoting HCC angiogenesis and ultimately leading to larger tumor size and shorter overall survival time.²⁶ MiR-3064-5p induced the expression of anti-angiogenic endostatin via inhibiting the vascular endothelial growth factor A (VEGFA).²⁷ MiR-20b regulated hypoxia-inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) to promote HCC cell adaptation to different environments.²⁸

Precise identification of signaling molecules that play a vital role in angiogenesis is helpful for targeted therapy of HCC. Overexpression of miR-126 in HCC cells was found to reduce tumor volume, serum alanine aminotransferase and alpha-fetoprotein (AFP), and VEGF levels, suggesting that miR-126 can inhibit HCC angiogenesis.²⁹ MiR-126 in combination with novel angiogenesis inhibitors may be developed into new targeted therapies.³⁰ Vasculogenic mimicry (VM) is a mode of angiogenesis, which tumor tissues nourish themselves.³¹ MiR-138-5p inhibited VM by targeting the HIF-1 α /VEGFA pathway in HCC.³² A complex miRNAs-target RNAs interaction network inhibited VM formation in HCC by downregulating the circRNA7/miR7-5p/VE-Cadherin/Notch4 signaling pathway.³³

2.3 | MiRNAs and cell tolerance in HCC

MiRNAs-target RNAs interaction network also mediates the therapeutic sensitivity of HCC cells.³⁴ MiR-20a induced HCC cells radio-resistance via the PTEN/phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway.³⁵ MiR-193a-3p improved the viability and proliferation of HCC cells after radiotherapy and chemotherapy.³⁶ MiR-26b enhanced the radio-sensitivity of HCC cells by targeting erythropoietin-producing HCC A2.³⁷ In addition, miR-320b, miR-203, miR-146a-5p, miR-1271-5p, and miR-621 could increase the radio-sensitivity of HCC cells.³⁸⁻⁴² Fer-1 like family member 4 promoted E2F1-dependent NF- κ B activation by inhibiting miR-106a-5p/miR-372-5p, thus leading to cisplatin resistance in HCC cells.⁴³

As a multiple tyrosine protein kinase inhibitor, sorafenib is considered as a first-line treatment for advanced HCC. However, drug resistance limits the clinical efficacy of sorafenib. MiR-25 enhanced sorafenib resistance of HCC cells via inducing FBXW7-mediated autophagy, which might provide a therapeutic target for the treatment of HCC.⁴⁴ The level of liver-specific miR-122 in sorafenib-resistant cells was significantly reduced. MiR-122 could radiosensitize HCC cells by suppressing cyclin G1.⁴⁵ Overexpression of miR-122 restored the sensitivity of HCC cells to sorafenib and induced apoptosis. In contrast, knockdown of miR-122 upregulated the expression of insulin-like growth factor 1 receptor and activated Ras/Raf/ERK signaling pathway, thereby mediating drug resistance in HCC cells.⁴⁶

Sorafenib upregulated miR-375 level in HCC cells through the transcription factor ASH1, thereby inhibiting platelet-derived growth factor C (PDGFC) and exerting its anti-angiogenic effect. MiR-375 level was reduced in sorafenib-resistant HCC cells. The restoration of miR-375 partially sensitized drug-resistant cells to sorafenib through degradation of astrocyte elevated gene 1, suggesting that miR-375 was crucial for sorafenib tolerance and HCC angiogenesis.⁴⁷

MiR-221 was also over-expressed in sorafenib-resistant HCC cells. Sorafenib can drive the anti-apoptotic activity of miR-221; however, miR-221 can also participate in sorafenib-resistance by regulating caspase-3. The level of serum miR-221 reflected the reactivity of HCC cells to sorafenib. MiR-221 level was also elevated in that with high reactivity. Therefore, miR-221 may be a biomarker of sorafenib-reactivity in HCC patients.⁴⁸

2.4 | MiRNAs and tumor microenvironment in HCC

In addition to tumor cells, tumor microenvironment contains a large number of mesenchymal cells, including macrophages, cancer-associated fibroblasts (CAFs), endothelial cells, neutrophils, and so on. Macrophages are highly heterogeneous that can be polarized into different phenotypes by stimulating factors in the microenvironment. Classically activated M1-type macrophages are pro-inflammatory and anti-tumor, while alternatively activated M2-type macrophages are anti-inflammatory and pro-tumor. Tumor-associated macrophages (TAMs) usually present M2 phenotype and are associated with poor prognosis.^{49,50} Tumor-derived exosomes can regulate the polarization of TAMs through transporting miRNAs.^{51,52}

The regulation of TAMs by miRNAs mainly includes three aspects: differentiation, functional polarization, and cellular crosstalk.⁵² Macrophage-derived microvesicles carrying miR-223 mediated monocyte differentiation.⁵³ In the presence of a granulocyte-macrophage colony-stimulating factor, miR-148a-3p promoted monocytes differentiate into macrophages through Notch signaling pathway.⁵⁴ MiR-148b downregulation induced TAM infiltration and promoted HCC metastasis through colony-stimulating factor-1.⁵⁵ MiR-28-5p was significantly downregulated in HCC and affected the metastasis of HCC through IL-34-mediated TAMs infiltration, suggesting that metastasis of HCC was regulated by the feedback loop of miR-28-5p-IL-34-macrophage.⁵⁶ Clusters of miR-144/miR-451a promoted M1 polarization by targeting hepatocyte growth factor, predicting a better prognosis in HCC patients.⁵⁷

MiRNAs contained in CAFs-derived exosomes also regulate the tumor microenvironment. The content of miR-150-3p was significantly decreased in CAFs-derived exosomes. Using exosomes to transfer miR-150-3p from CAFs to HCC cells could inhibit HCC migration and invasion.⁵⁸ HCC cells-derived miR-21 directly targeted PTEN to activate the PDK1/AKT signaling pathway in hematopoietic stem cells, thereby activating CAFs. The latter further promoted the progression of HCC through secreting angiogenic cytokines such as VEGF, bFGF, and transforming growth factor- β (TGF- β).⁵⁹

2.5 | MiRNAs and hepatocyte regeneration

The liver has a very high regenerative capacity. Liver regeneration is precisely regulated by a variety of molecular mechanisms. MiRNAs also play an essential role in the proliferation of regenerating hepatocytes. About 40% of miRNAs were upregulated 3h after partial hepatectomy as initiation signals for cell proliferation, including miRNAs that target miRNA synthesis such as Drosha, DGCR8, Dicer, and TRBP. At 24h after partial hepatectomy, about 70% of miRNAs were downregulated, providing negative feedback and promoting cell proliferation.⁶⁰ Most miRNAs levels decreased within 3 days after partial hepatectomy. The cell cycle and cell proliferation-related genes expression increased correspondingly.⁶¹ MiR-21 is critical in liver regeneration. MiR-21 upregulation promoted hepatocyte proliferation via targeting PTEN and Ras homolog family member B, while Dicer1 deletion inhibited liver regeneration by downregulating miR-21.^{62,63} MiR-23b was highly expressed within 24h after partial hepatectomy. This could promote hepatocyte proliferation. However, a continued decline was observed at 3–7 days after surgery.⁶⁴ Sustained overexpression of miR-34a, a tumor suppressor, was found 24h after partial hepatectomy.⁶⁵ Thus, targeting miRNA and its related pathways may provide a new strategy to promote liver regeneration.

The list of miRNAs and their roles in HCC mentioned in this section is as follows (Table 1).

3 | MOLECULAR MECHANISMS OF MIRNAS IN REGULATING THE DEVELOPMENT OF HCC

MiRNAs have stable expression in vivo and can regulate key molecules closely related to the development of HCC through a variety of signaling pathways. Several key molecules and pathways regulated by miRNAs are summarized here.

3.1 | Transforming growth factor- β

Transforming growth factor- β is a critical enforcer for immune homeostasis and tolerance. The interference of TGF- β signaling is the basis of inflammatory diseases, which promotes the emergence of tumors. TGF- β expresses in almost all tumor cells and plays a vital role in tumor immune evasion and adverse reactions to immunotherapy.^{66,67} In HCC, TGF- β evades the tumor suppression by inducing specific miRNAs. MiR-23a was significantly upregulated and played anti-apoptotic and pro-proliferative effects in human HCC. TGF- β induced changes in the expression of miR-23a in HCC cells, which depended on the Smad2/3/4 signaling pathway.^{68,69} MiR-140-5p inhibited the proliferation and metastasis of HCC cells by targeting TGF- β receptor 1 (TGFBR1). However, the miR-140-5p level was significantly decreased in HCC tissues, which was closely related to HCC cell differentiation, disease-free survival, and overall survival.^{70,71} MiRNAs can interact with long non-coding RNAs

TABLE 1 MiRNAs and their roles in HCC

miRNAs	Roles	References
miR-182-5p, miR-1225-5p, miR-199a-5p, miR-222, miR-217, miR-340, miR-206, miR-302a, miR-30a-5p, miR-1271-5p, miR-106a-5p, miR-372-5p, miR-150-3p	To regulate the biological processes, including proliferation, migration, and invasion of hepatocytes	[10–18, 41, 43, 58]
miR-222, miR-217, miR-340, miR-206, miR-302a, miR-30a-5p, miR-15a, miR-16-1, miR-125b, miR-221	To regulate apoptosis of hepatocytes	[14–18, 20, 23, 24]
miR-15b, miR-125b, miR-423-3p, miR-424, miR-494, miR-497, miR-612, miR-637, miR-1255b, miR-20b	To regulate angiogenesis in HCC	[25, 28]
miR-130b-3p	To promote tumor angiogenesis and progression of HCC	[26]
miR-3064-5p, miR-126, miR-138-5p, miR-7-5p, miR-375	To suppress angiogenesis in HCC	[27, 29, 30, 32, 33, 47]
miR-20a, miR-193a-3p	To enhance the radio-resistance of hepatocellular carcinoma cells	[35, 36]
miR-193a-3p	To enhance the chemotherapeutic tolerance of hepatocellular carcinoma cells	[36]
miR-26b, miR-320b, miR-203, miR-146a-5p, miR-1271-5p, miR-621, miR-122	To enhance the radio-sensitivity of hepatocellular carcinoma cells	[37–42, 45]
miR-106a-5p, miR-372-5p	To enhance the chemotherapy sensitivity of hepatocellular carcinoma cells	[43]
miR-25, miR-122	To confer sorafenib resistance to hepatocellular carcinoma cells	[44, 46]
miR-375	To reverse sorafenib resistance to hepatocellular carcinoma cells	[47]
miR-221	To regulate sorafenib resistance to hepatocellular carcinoma cells	[48]
miR-223, miR-148a-3p, miR-148b, miR-28-5p, miR-144/miR-451a	To regulate tumor-associated macrophages	[53–57]
miR-150-3p, miR-21	To regulate the tumor microenvironment	[58, 59]
miR-21, Dicer1, miR-34a	To regulate liver regeneration	[61, 63, 65]
miR-23b	To promote hepatocyte proliferation	[64]

(lncRNAs) to regulate downstream target genes. In HCC, lncRNA AK002107 directly inhibited miR-140-5p to upregulate TGFBR1, thereby inducing epithelial-mesenchymal transition (EMT).⁷² LncRNA SBF2-AS1 also regulated the miR-140-5p-TGFB1 pathway to promote HCC progression.⁷³

3.2 | Receptor tyrosine kinases

Receptor tyrosine kinases (RTKs) are enzyme-linked receptors that also act as kinases, phosphorylating tyrosine residues of target proteins. The insulin receptor family, epidermal growth factor receptor family, vascular endothelial growth factor receptor family, platelet-derived growth factor receptor family, Eph receptor family, and neurotrophic factor receptor family all belong to RTKs. RTKs maintain a balance between cell proliferation and cell death under normal physiological conditions. Abnormal activation of RTKs leads to balance disruption and triggers RTKs-induced tumorigenesis.^{74,75}

MiRNAs can regulate the expression of RTKs directly.⁷⁶ For example, miR-10a promoted HCC metastasis by directly targeting Eph tyrosine kinase receptor A4-mediated EMT.⁷⁷ The miR-296-5p level was decreased in HCC tissues. MiR-296-5p overexpression

suppressed the EMT, migration, and invasion of HCC cells by inhibiting the NRG1/ERBB2/ERBB3/RAS/MAPK/fra2 signaling pathway.⁷⁸ LncRNA MYLK-AS1 activated the EGFR/HER2-ERK1/2 signaling pathway via targeting miR-424-5p, thereby promoting HCC growth and invasion.⁷⁹

MiRNAs can also regulate the expansion of liver cancer stem cells (CSCs) by targeting certain RTKs, are thus participate in the regulation of occurrence, development, drug resistance, and recurrence of HCC. For example, miR-206 directly inhibiting the EGFR to suppress CSCs proliferation in HCC.⁸⁰ MiR-486-3p targeted FGFR4 and EGFR to control the sorafenib resistance.⁸¹

3.3 | Wnt- β -catenin pathway

The typical Wnt- β -catenin pathway strictly controls hepatobiliary development, maturation, and zoning. In mature healthy livers, the Wnt- β -catenin pathway is primarily inactive but can be reactivated during cell renewal, regeneration, and in certain pathological conditions or malignancy conditions.⁸² The Wnt- β -catenin signaling pathway is frequently over-activated in HCC, and this over-activation is closely related to core events of EMT, angiogenesis, and

chemotherapy or radiotherapy resistance.^{83,84} MiRNAs can regulate genes encoding key components of the Wnt- β -catenin signaling pathway in HCC. For example, miR-182-5p inhibited β -catenin degradation by targeting FoxO3 and enhanced the interaction between β -catenin and TCF4, thereby activating the Wnt/ β -catenin signaling pathway.^{10,11} MiR-370a inhibited the activity of Wnt- β -catenin pathway by downregulating ubiquitin-4, thus reducing the proliferation and invasion of HCC cells.⁸⁵ Mir-129-5p exerted a Wnt-dependent inhibitory role by directly targeting hepatoma-derived growth factor (HDGF).⁸⁶

3.4 | Notch signaling pathway

The Notch signaling pathway plays an essential role in the regulation of HCC cell injury/stress response and EMT.⁸⁷ MiRNAs can regulate the expression of Notch signaling components and their interactions with other signaling pathways.⁸⁸ MiR-3163 downregulated ADAM-17 to inhibit Notch cleavage and activation, thus increasing HCC cells sensitivity to sorafenib.⁸⁷ MiR-449a directly targeted Notch1 to inhibit its translation, thereby regulating EMT and inhibiting HCC cells invasion.⁸⁹

3.5 | PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway

The PI3K/Akt/mTOR pathway regulates cell proliferation and metabolism.⁹⁰ Abnormal activation of the PI3K/Akt/mTOR pathway is closely related to pathological features of HCC. MiRNAs can regulate the proliferation, differentiation, apoptosis, and metabolism of HCC by targeting the PI3K/Akt/mTOR axis.⁹¹ A miRNAs-regulated proteins interaction network analysis revealed that miRNA-149 exerted tumor-suppressive effect by inhibiting the Akt/mTOR pathway in HCC.⁹² MiR-1914 suppressed HCC progression by inhibiting the GPR39-mediated PI3K/Akt/mTOR pathway.⁹³ MiR-379-5p inhibited Akt by directly targeting focal adhesion kinase (FAK), thereby regulating EMT and metastasis of HCC.⁹⁴

4 | MIRNAS IN THE DIAGNOSIS OF HCC

The co-existence of hepatitis and cirrhosis often complicates the early diagnosis of liver cancer. The main blood markers for screening of liver cancer include AFP, abnormal prothrombin, and AFP-L3 variants.⁹⁵ Advances in omics and analytical techniques have led to new biomarkers for the diagnosis of liver cancer, including osteopontin, Glypican-3, Golgi Protein-73, and miRNAs.⁹⁶⁻⁹⁹ They not only contribute to the early diagnosis but also contribute to the understanding of the pathogenesis of liver tumors.

The stable expression and diverse functions of miRNAs in the human genome make them candidates as diagnostic biomarkers for early cancer.¹⁰⁰ Serum miR-130b and miR-15b were both

upregulated in HCC. MiR-130b had a sensitivity of 87.7% and a specificity of 81.4% for detecting HCC, while miR-15b had an extremely high sensitivity of 98.3% but a low specificity of only 15.3%. Their combination as HCC biomarkers may be beneficial, especially for HCC patients with low AFP levels at an early stage.¹⁰¹ MiR-16-2 and miR-21-5p had high sensitivity and specificity in distinguishing HCC patients from healthy volunteers and patients with chronic hepatitis C.¹⁰² The expression of miR-16 and miR-122 was significantly increased in patients with early-stage HCC, which can be used as biomarkers for the diagnosis of early HCC.¹⁰³ Plasma miR-224 level not only indicated liver tumors smaller than 18 mm but also might be a sensitive biomarker for monitoring tumor dynamics.¹⁰⁴

In addition to the expression patterns, several other characteristics of miRNAs render them biomarkers for HCC. First, miRNAs have good stability in circulating body fluids. Even abnormally expressed miRNAs remain highly stability and easily detected in the serum or plasma of HCC patients.¹⁰⁵ Second, miRNAs are readily available and can also be extracted from saliva and urine.^{106,107} It has been reported that five miRNAs (miR-516-5P, miR-532, miR-618, miR-625, and miR-650) detected in urine can be used to screen patients at high risk of HCC.¹⁰⁸ Mir-122, miR-483, and miR-335 can be used as biomarkers for early diagnosis of HCC without invasion. Studies in Egyptian patients showed that miR-122 and miR-483 were upregulated while miR-335 was downregulated in HCC patients compared with normal controls and HCV-infected patients.¹⁰⁹

5 | MIRNAS IN THE TREATMENT OF HCC

MiRNAs are non-immunogenic in human and can be used in the treatment of liver cancer. Aiming at the role of miRNAs in the molecular pathological mechanism of liver cancer, the use of miRNAs mimics or inhibitors may improve the therapeutic effect.

Activation of NF- κ B is crucial in mediating inflammation-induced tumor progression. A series of miRNAs targeting the NF- κ B signaling pathway were screened. Among them, miR-127-5p was found to inhibit the NF- κ B activity and its downstream signaling molecules by suppressing the nuclear translocation of p65. MiR-127-5p mimics suppressed NF- κ B activity by targeting biliverdin reductase B (BLVRB), thus hindering the growth and colony formation of HCC cells and improving the therapeutic efficacy.¹¹⁰

Vessels that encapsulated tumor cluster (VETC) is a typical vascular pattern in HCC that promotes the invasion of the entire tumor cell population into the bloodstream independently. Angiopoietin 2 is essential for VETC formation. Overexpression of miR-125b or miR-100 in HCC cells could reduce VETC formation in xenografts and inhibit the metastasis of xenografts in vivo.¹¹¹

MiRNA-based therapeutic strategies may alter the expression networks of HCC, thereby significantly affecting cell behavior and making it possible to cure HCC. Virus-based delivery system or non-viral systems including nanoparticles, lipid-based vesicles, exosomes, and liposomes can deliver miRNAs.¹¹²⁻¹¹⁵ Delivery of miR-26a using an exosomes-based nanosystem inhibited proliferation

of HCC.¹¹³ Targeted delivery of miR-199a-3p using self-assembled dipeptide nanoparticles or exosomes reduced HCC efficiently.^{115,116}

MiR-34a was a potent tumor suppressor and identified as a p 53 target.¹¹⁷ A clinical study (Clinical Trial Registration: NCT01829971) using a miR-34a mimics (MRX34) in the treatment of solid tumors predominantly hepatocellular carcinoma was prematurely terminated due to severe immune-mediated adverse events that resulted in the death of 4 patients, but the results still showed dose-dependence of relevant target genes, providing a proof-of-concept for miRNA-based HCC treatment.¹¹⁸

6 | MIRNAS IN THE PROGNOSTIC ASSESSMENT OF HCC

Clinically, the commonly used indicators of prognosis for HCC include portal hypertension, liver function status, tumor status, and physical status. Still, in fact, these indicators cannot accurately determine the prognosis of patients. More accurate and reliable molecular indicators are necessary for assessing prognosis. Some miRNAs can precisely predict the prognosis of HCC.¹¹⁹

A miRNA microarray analyses of serum samples from HCC patients before and after treatment validated four candidate miRNAs. Among them, the combination of miR-4443, miR-4530, and miR-4454 can predict the treatment response, the combination of miR-4530 and miR-4454 can predict the overall survival, and miR-4492 can distinguish patients' complete response from partial response.¹²⁰

A miRNAs database containing clinical data for HCC prognostic assessment was established using TCGA (RNA-seq) database, GEO (Microarray) database, and PubMed. There were 55 miRNAs associated with overall survival in the TCGA database, among which miR-139, miR-149, and miR-3677 were the most significant. There were 84 miRNAs correlated with the overall survival in the GEO database, among which miR-31, miR-146B-3p, and miR-584 were the most significant. The establishment of this database provided rich guidance information for evaluating the prognosis of HCC patients.¹²¹

MiRNAs that are abnormally expressed in chronic liver disease may also act as prognostic indicators for HCC. Serum miR-21 and miR-885-5p levels were significantly elevated in HCV-infected patients with cirrhosis. Serum miR-21 was a marker of HCV infection and may serve as a potential diagnostic marker for HCC, while serum miR-885-5p was an important marker of cirrhosis and a potential diagnostic marker of advanced liver injury in HCV-related chronic liver disease.¹²²

MiRNAs are also closely related to tumor recurrence after orthotopic liver transplantation (OLT). A miRNA microarray analysis confirmed that miRNA expression patterns were different in patients with HCC recurrent and patients without recurrent after OLT. Six miRNAs with high sensitivity and specificity for predicting HCC recurrence were screened, including miR-19a, miR-24, miR-126, miR-147, miR-223, and miR-886-5p, which were independent predictors of overall survival and relapse-free survival after OLT.¹²³

The occurrence, progression, metastasis, and recurrence of HCC are inseparable from the precise regulation of miRNAs, and the role of some liver-specific miRNAs cannot be ignored. MiR-122 is a completely conserved liver-specific miRNA in vertebrates, which is essential for maintaining liver homeostasis.¹²⁴ Circulating MiR-122 is a sensitive biomarker of liver injury.^{125,126} MiR-122 level was significantly decreased in HCC patients, while patients with higher miR-122 level had a lower postoperative recurrence rate. Codelivery of miR-122 and 5-fluorouracil (5-FU) using a macromolecular prodrug approach was a highly promising strategy toward HCC synergistic therapy.¹²⁷ Ultrasound-targeted microbubble destruction-mediated delivery of miR-122 and anti-miR-21 modulated the immune microenvironment of HCC at the level of cytokine expressions.¹²⁸

7 | PROSPECT

According to epidemiological statistics, the number of primary liver cancer cases and deaths in China is expected to reach 591,000 and 572,000, respectively, by 2040. The number of people over the age of 70 will also rise, and the direct medical expenses will also increase year by year.^{129,130} The development of new strategies for diagnosis, treatment, and prognosis assessment of liver cancer by utilizing the characteristics of miRNAs will help improve the treatment status of this disease.

Further research on miRNAs also brings many new challenges. The number of miRNAs is relatively large, and one miRNA may have multiple target genes. Up to now, the in-depth study of the role of miRNAs in the molecular pathological mechanism of different stages of liver cancer is not sufficient. In addition, there are differences among the genomes of different geographical populations. Therefore, more in-depth research, development, and utilization of miRNAs are needed for the precision medicine strategies for HCC.

AUTHOR CONTRIBUTIONS

Yilong Zhou, Fan Liu, Chunyang Ma, and Qiong Cheng contributed to the writing of the manuscript. Qiong Cheng conceived and finalized the content of the manuscript. All authors reviewed, contributed to the revisions, and finalized the drafts.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available.

CONSENT FOR PUBLICATION

All authors agree to publish this article.

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