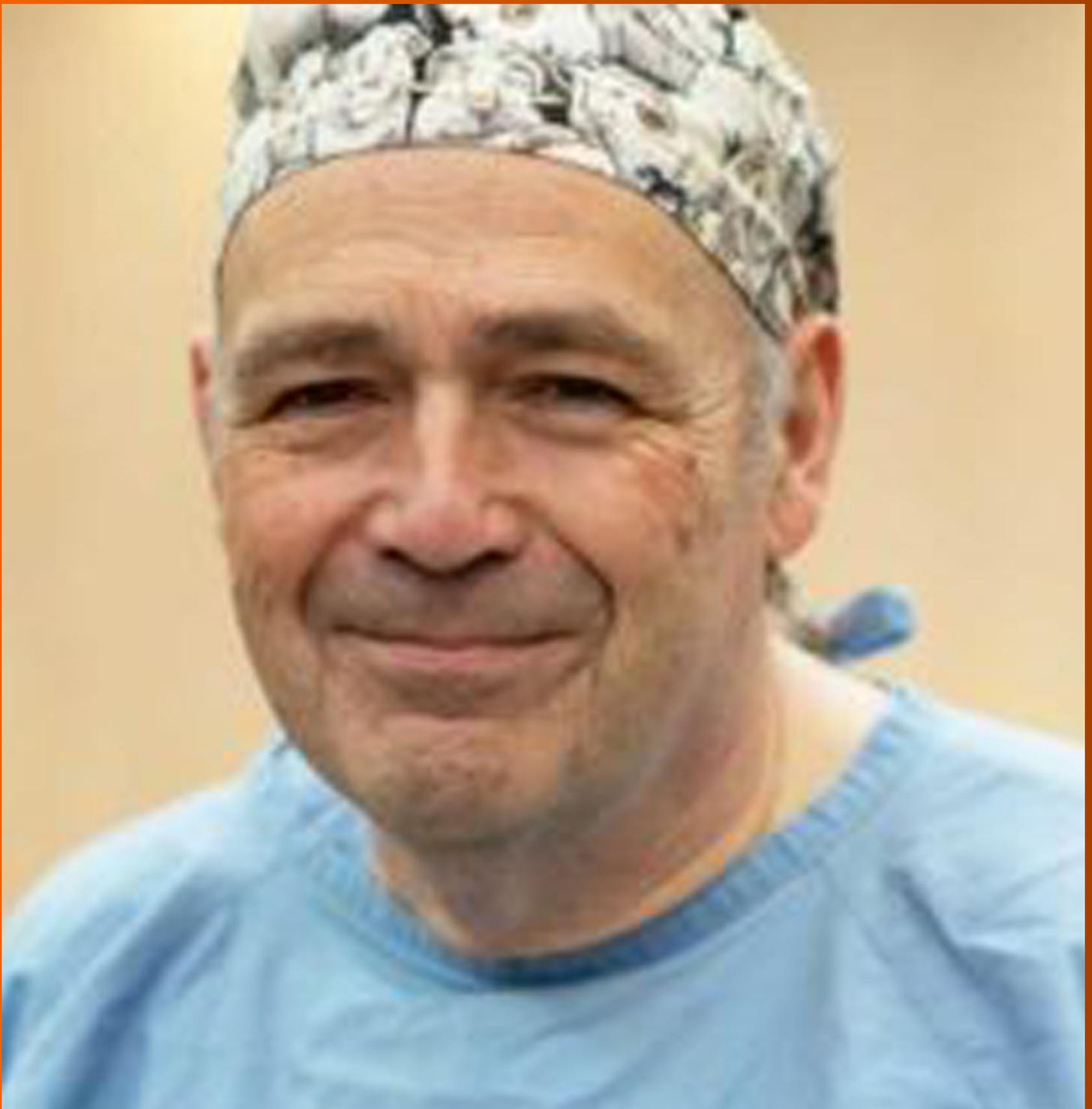


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Editorial Board of *World Journal of Gastroenterology*, David L Morris, MD, FRCS (Ed), Professor, Department of Surgery, University of New South Wales, Sydney 2217, New South Wales, Australia. david.morris@unsw.edu.au

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MicroRNAs in hepatocellular carcinoma treatment: Charting the path forward

Hong T Lin, Antonio F Alvarez Castaneda, Somashekar G Krishna, Khalid Mumtaz

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Hong T Lin, Antonio F Alvarez Castaneda, Somashekar G Krishna, Khalid Mumtaz, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Corresponding author: Khalid Mumtaz, MBBS, Associate Professor, Doctor, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, The Ohio State University Wexner Medical Center, 395 W 12th Ave, Columbus, OH 43210, United States.

khalid.mumtaz@osumc.edu

Abstract

MicroRNAs (miRNAs) are recognized for their involvement in the regulation of gene expression and exhibit significant potential in both the prognostic assessment and treatment of hepatocellular carcinoma (HCC). HCC, like other tumors, seldom occurs in isolation; instead, it evolves within a microenvironment featuring oncogenic and tumor-suppressive elements. When combined with suitable delivery vehicles, miRNA technology provides the capability to directly engage with these elements, thereby hindering tumor formation and progression. Ongoing research in this domain holds the promise of enabling a more efficacious and multi-modal treatment approach for HCC in the near future.

Key Words: Hepatocellular carcinoma; Tumor microenvironment; MicroRNA; Mesenchymal stem cell; Exosome

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Core Tip: MicroRNAs (miRNAs) constitute a family of molecules with dual roles in both the development and prevention of cirrhosis and hepatocellular carcinoma (HCC). Depending on the type of miRNA and the target of interest, they have the potential to promote or inhibit angiogenesis, facilitate or inhibit immune invasion, and enable or halt cell cycle progression amongst other effects. When paired with safe and effective delivery vehicles, specific miRNAs show promise as targeted therapies for treating HCC. Nonetheless, owing to the intricate interactions within *in vivo* systems and limitations of current retrospective studies, further research is imperative to ensure the safety and efficacy of miRNA in HCC therapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) comprises 75% of primary liver cancers and stands as the third most prevalent cause of cancer-related deaths globally[1,2]. Beyond the immeasurable human toll, HCC inflicts a substantial financial burden and costs the United States healthcare system over \$405 million annually[3]. Common triggers for cirrhosis and consequent HCC include excessive alcohol consumption, metabolic syndrome (including metabolic-associated fatty liver disease), hepatitis B virus infection, hepatitis C virus infection, autoimmune liver diseases, and exposure to aflatoxin B1[1].

Until recently, treatment of HCC was rudimentary. Options such as surgical resection, radiofrequency ablation, chemoembolization, systemic therapy, and radiation therapy come with significant potential complications and broad systemic effects. For instance, while procedures such as transcatheter arterial embolization (TAE) and chemoembolization (TACE) have become the treatment of choice for unresectable HCC, they are associated with significant side effects such as hepatic failure and abscess formation, biliary tract disease, and necrotizing pancreatitis[4]. As TAE and TACE trigger hypoxia in embolized regions, they paradoxically stimulate angiogenesis[5] and may potentially worsen the cancer. In the early stages of HCC, surgical resection may be an option. However, this option is limited by recurrence due to inadequate margins and can only be done if a functional liver remnant can be left. Lastly, while liver transplantation offers a cure for cirrhosis and HCC, it is often inaccessible due to delayed diagnoses and graft shortages.

It's now known that factors within tumor macroenvironments and tumor microenvironments (TME) significantly influence the onset, progression, and prognosis of HCC[6]. Cancer, immune, and stromal cells communicate with each other to promote angiogenesis, invasion, and evasion of the body's immune system. This communication takes place through the release of various biologically active molecules (*e.g.*, enzymes, lipoproteins, and nucleic acids) into the TME and the extracellular matrix (ECM). Examples include angiogenesis-promoting factors such as platelet-derived growth factor and vascular endothelial growth factor, as well as various matrix metalloproteinases that remodel the ECM and aid cellular invasion[6].

An intriguing mode of intercellular communication occurs *via* exosomes. These are phospholipid-bound vesicles known for their capacity to transport diverse noncoding RNAs, among other active contents, while shielding them from nucleases and proteases present in the ECM[6,7]. One possible component of exosomes is microRNAs (miRNAs). miRNAs hold particular interest due to their role in selective gene silencing and are capable of either promoting or inhibiting cancer progression depending on the tissue type, specific sequence, and originating cell[7]. They may prove valuable as biomarkers for diagnosing and prognosticating various cancers, such as HCC, and serve as therapeutic targets. However, much is still unknown about the role of miRNAs in the pathogenesis of cancer and how they are targeted to certain cell types in living systems. While theories have been postulated based on *in vitro* observations, little is known about their validity in *in vivo* systems. Furthermore, more studies are also required to identify other possible miRNAs related to HCC.

SIGNIFICANCE OF MIRNAS

The review paper titled "Function and biomedical implications of exosomal microRNAs delivered by parenchymal and nonparenchymal cells in hepatocellular carcinoma", published in *World Journal of Gastroenterology*, provides a comprehensive exploration of how elements within the TME, particularly exosomal miRNAs, are associated with HCC[8]. Through review of recent literature, it summarizes current understanding regarding the role of miRNAs in promoting, preventing, and predicting the prognosis of HCC.

The development of HCC is linked with loss of tumor suppressive miRNAs (Table 1). The authors commented on the association of deficiency of miR-122 and miR-192 with increased rates of HCC and observed that their restoration in *in vitro* systems resulted in the inhibition of HCC growth and activation, respectively. This is of particular interest because miR-122 has previously been shown to sensitize HCC cells to chemotherapy by inhibiting multidrug resistance-associated genes, the anti-apoptotic gene Bcl-w, as well as the cell cycle-related gene cyclin B1. As such, miR-122 has been classified as a tumor suppressor gene. While the exact mechanism remains unclear, it appears to serve as a regulator and correlates with liver-specific transcription factors such as hepatocyte nuclear factor 4 alpha[9].

The review also discusses the tumor-suppressive role of certain miRNAs. miR-223, well known for its immune system-modulating activity, plays a distinct role in the pathogenesis of various liver diseases. Upregulation of miR-223 has been shown to protect against alcoholic liver disease (ALD) and metabolic-dysfunction-associated steatohepatitis (MASH). In ALD, it directly inhibits interleukin-6 (IL-6) expression and its downstream target p47phox. This leads to reduced neutrophil infiltration and reactive oxygen species production-factors that are significant drivers of the disease's pathophysiology[10]. In MASH, miR-223 similarly reduces the inflammatory cascade resulting from insults to the liver parenchyma due to metabolic syndrome. In HCC, miR-223 can induce tumor cell apoptosis, inhibit cancer spread, and reduce multidrug resistance through its effects on mammalian target of rapamycin, integrin αV , and multidrug resistance

Table 1 Current understanding of pro- and anti-tumor microRNAs in hepatocellular carcinoma and brief descriptions of their effects

MicroRNAs of interest in hepatocellular carcinoma		
Prevents HCC	Dual influence	Promotes HCC
miR-122 - inhibits HCC growth and enhances tumor cell susceptibility to chemotherapy	miR-192 - suppresses tumor when acting on the PABPC4 and TRIP13 genes. Promotes tumor when acting on SEMA3A	miR-155 - role in promoting inflammation and tumor growth through unclear mechanisms
miR-223 - anti-inflammatory effects and role in resolution of liver fibrosis		miR-21 - stimulates cancer-associated fibroblasts
miR-335-5p - inhibition of tumor growth and invasion		miR-20a-5p - suppresses expression of tumor suppressors
miR-320a - blocks activation of MAPK pathway		miR-103 - facilitates tumor metastasis by damaging the integrity of endothelial junctions
miR-150-3p - suppresses tumor migration and invasion		miR-210 - derived from HCC cells. Promotes angiogenesis
miR-214 - suppresses angiogenesis		miR-93-5p - facilitates HCC progression <i>via</i> inducing immune evasion
miR-148a-3p - inhibits HCC proliferation and invasiveness		miR-107 - promotes HCC progression by increasing epithelial-to-mesenchymal transition (however, this notably seems to act as a tumor suppressor in head and neck squamous cell carcinoma)
		miR-4739 - associated with poor HCC prognosis. Unclear mechanism

HCC: Hepatocellular carcinoma; PABPC4: Poly-A binding protein cytoplasmic 4; TRIP13: Thyroid receptor-interacting protein 13; SEMA3A: Semaphorin 3A.

protein 1 (MDRP1 or ABCB1)[11].

Oncogenic miRNAs have been discussed in this article as well as in previous literature. They exert their effects through a multitude of routes. Examples include promotion of angiogenesis or loss of epithelial cell polarity (*e.g.*, miR-210 and miR-107), immune evasion (*e.g.*, miR-93-5p), and through unknown mechanisms (*e.g.*, miR-4739)[8,12,13]. As will be discussed later, many of these miRNAs will have relevant interactions with other proteins as well.

Moreover, some miRNAs have been shown to exhibit both tumor suppressor and oncogene roles, with miR-192 serving as a key example. While miR-192 has demonstrated anti-tumor properties through its effect on the poly-A binding protein cytoplasmic 4 (PABPC4) and thyroid receptor-interacting protein 13 (TRIP13) genes, it has also been shown to function as an oncogene by inhibiting semaphorin 3A (SEMA3A), an inhibitor of tumor angiogenesis[14]. Thus, while this review paper proposes the administration of miR-192 as a therapy for HCC, further research is required to selectively target this molecule to the PABPC4 or TRIP13 genes rather than SEMA3A. Moreover, miR-192 has been found to have both beneficial and harmful effects on different organ systems, highlighting the need for careful consideration when selecting an appropriate delivery vehicle and target.

The authors further describe the prognostic role of specific miRNAs in the early detection of HCC. For instance, the deficiency of exosomal miR-122 has been observed in patients with ALD, MASH, and HCC. Conversely, levels of other miRNAs such as miR-155 are elevated in patients with ALD, autoimmune hepatitis, and HCC. Another miRNA, miR-34a, has been associated with cirrhosis and HCC progression[8]. As additional prognostic miRNAs are identified, their use in calculating HCC pre-test probability may be explored.

Several limitations in the cited studies are acknowledged in this article, including the inconsistency in experimental subjects and varied study designs. Also recognized is the low targeting efficacy and durability of exosomal systems when used for treatment. Other limitations of miRNA treatment include the lack of testing in *in vivo* systems, the potential toxicity of certain targeting systems, and the unintended silencing or activation of other genes. Additionally, there are immune-related implications of miRNA therapy. Systemic and poorly targeted miRNA infusion may trigger the release of cytokines and interferons *via* the activation of toll-like receptors[15].

Discussion of the therapeutic possibilities of miRNAs would not be complete without acknowledgment of the importance of delivery vehicles. Mesenchymal stem cells (MSCs) are multipotent stem cells and integral components of the TME. They are present in various locales such as the skin, bone marrow, intestines, adipose tissue, lungs, and liver. While they may serve both oncogenic and tumor-suppressive roles when acting on different pathways, MSCs have been shown to exhibit chemotactic abilities and the capability to migrate with signals such as chemokine ligand 15, tumor growth factor β , macrophage inflammatory protein 1 δ (MIP-1 δ), and MIP-3 α [16]. When loaded with miRNAs like MiR-122, exosomes derived from MSCs offer unique vehicles for targeting HCC cells to inhibit growth and sensitize them to chemotherapy.

Concerns regarding the safety and effectiveness of exosome therapy are valid; the long-term side effects are unclear and there have been reports of infection and contamination with unapproved regenerative therapy in the United States. However, these adverse events were likely secondary to the stem cells carried within the exosomes as well as improper preparation and poor selection of surface targeting ligands. Multiple regulated small-scale studies on exosomal delivery systems have shown positive outcomes with a favorable side effect profile[17,18]. Exosomes are structurally simple and

are relatively inert as they are composed of lipids already present within cells. The imperative will be to determine a way of effectively synthesizing them in large volumes and to identify effective targeting ligands to selectively transport them to the desired location.

CONCLUSION

The field of molecular medicine, coupled with our deepening understanding of miRNAs, holds significant promise for the future of HCC treatment. As discussed above, specific miRNAs are found to have an association with tumor suppression and oncogenesis. Other miRNAs may individually have either tumor suppressive or tumor-promoting effects depending on the target that they are acting on. Future research in multifactorial *in vivo* systems, perhaps with miRNA epitope tagging, would assist in delineating the pathways and targets responsible for these effects. Further knowledge in this area would prove highly applicable to the selection of therapeutic miRNAs as well as an appropriate delivery vehicle. Another avenue of exploration may encompass interactions between miRNAs and other cellular proteins. For example, H19 (a long non-coding RNA) and circGPR37B (a circular RNA) have shown promise in reducing the effects of oncogenic miRNAs such as miR-107 and miR-4739, respectively[12,13].

Additionally, most of the clinical studies cited in the in-press article by Wang *et al*[8] are retrospective in nature, which makes them inherently susceptible to biases in case selection (*e.g.*, subclinical HCC may have differing levels of association with certain miRNAs). They also offer weaker causal relationships (*e.g.*, does increased expression of a miRNA increase the risk for HCC, or does HCC development cause an increase in the miRNA). Future prospective studies in patients with high HCC risk factors may provide a resource-effective avenue for investigating the role of miRNAs.

MiRNAs offer the potential to become valuable tools for HCC prognosis, diagnosis, and clinical risk assessment. By comprehending their multifaceted roles, we can manipulate specific miRNAs to mitigate and combat tumors. When integrated with an enhanced understanding of MSC and exosome systems, miRNA infusions may be used either independently or in conjunction with existing HCC treatment modalities to improve treatment outcomes. For example, manipulation of miRNAs involved in the promotion or inhibition of angiogenesis, such as miR-214 and miR-210, may offer a remedy for the paradoxical angiogenesis associated with embolization procedures as noted above. Similarly, the application of miRNAs involved in tumor growth may allow for neoadjuvant debulking and improve the success rate of surgical resection.

Ongoing research is crucial to address these knowledge gaps and assess the safety of miRNAs within intricate, complex *in vivo* systems. As we continue to unlock the potential of miRNAs and molecular medicine, we stand on the cusp of transforming the landscape of HCC treatment, offering new hope and possibilities for patients facing this deadly disease.

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Country/Territory of origin: United States

ORCID number: Hong T Lin 0000-0002-1888-2860; Somashekar G Krishna 0000-0001-5748-7890; Khalid Mumtaz 0000-0001-7868-6514.

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