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Mini Review

Prevention and Treatment of Hepatocellular Carcinoma Using miRNAs

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Abstract

Hepatocellular carcinoma (HCC) is the second leading cause of death due to cancer. Liver transplantation, surgical liver resection, chemotherapy, and radiotherapy are the main options for the treatment of HCC. However, these methods are unable to limit the growth, survival, and metastasis of HCC cells. Several signaling pathways control propagation, metastasis, and recurrence of HCC. Recent studies have established new approaches for the prevention and treatment of HCC using miRNA technology. MicroRNAs are a class of non-coding RNAs with an average of 22 nucleotides that play critical roles in controlling gene expression in a variety of biological processes. miRNAs can induce or suppress HCC proliferation, migration, metastasis, and tumorigenesis. The anti-cancer effects of molecular agents can be evaluated directly in animal models or indirectly through the injection of HCC cell lines treated with anti-cancer agents. Targeting cancer-specific signaling pathways with miRNAs can be novel therapeutic strategies against HCC. This study provides the latest findings on using miRNAs in the control of HCC in both *in vitro* and *in vivo* models.

Keywords: Cancer, Hepatocellular carcinoma, miRNA, Signaling pathways

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death around the world.[1-4] Non-viral (alcohol consumption and non-alcoholic fatty liver)[5-7] and viral (hepatitis B/C virus) risk factors[8, 9] enhance the risk of HCC.[10-13] There are three main options, including liver transplantation,[14-16] surgical liver resection,[17-19] and non-surgical methods (chemotherapy and radiotherapy) for the treatment of HCC.[20-22] However, these approaches are unable to limit the progression and metastasis of HCC cells and cause side effects on the surrounding healthy cells.[23,24] Several signaling pathways, including Wnt, Notch, EGF, SHH, hippo, and BMPs are associated with cell-division, metastasis, epithelial to mesenchymal transition (EMT), migration, and tumorigenesis of HCC.[25-27] Targeting these signaling pathways may promote the treatment of the disease.[28-30] Recent studies have established new approaches for the prevention and treatment of HCC using miRNA technology.[31-33] microRNAs are a branch of RNA interference (RNAi) technology that contain about 20 nucleotides and target the specific mRNA in the cells.[34,35] Evidence from miRNA expression profiles shows that some miRNAs are upregulated in HCC (oncomiR) and enhance the acquisition of metastatic potential.[36,37] miRNAs can inhibit the expression of specific proteins (ligand or secondary messenger) in tumor-promoting signaling pathways and enhance HCC treatment efficacy.[38,39] Molecularly targeted therapies using miRNAs with a high degree of specificity may be a suitable strategy in cancer treatment.[31,40,41] This study provides the latest findings on using miRNAs in the control of HCC in both *in vitro* and *in vivo* models.

The Canonical miRNA Biogenesis

MicroRNAs are a class of non-coding RNAs with an average of 22 nucleotides that play an important role in controlling gene expression.[42] miRNAs by microRNA-binding sites in the 3′ UTR of the target mRNAs trigger mRNA degradation to control the rate of translation.[43] miRNAs can bind with the 5′ UTR, coding sequences, and gene promoters[42] to regulate the expression of target genes or suppress translation by one of two distinct mechanisms.[44] Pri-miRNAs or primary miRNAs are produced by the RNase II or III (poll III) in the nucleus.[45,46] Subsequently, pri-miRNA with the Drosha/DGCR8 holoenzyme undergoes nuclear cleavage to produce a hairpin structured precursor or the precursor miRNA (pre-miRNA) with ~60- to 70-nt.[47] Exportin-5 (Exp5) and Ran-GTP can transport pre-miRNAs to the cytoplasm.[48] Dicer is an RNase III endonuclease that combined with the transactivating response RNA-binding protein (TRBP) cleaves pre-miRNA hairpin to form a mature microRNA duplex (~22-nt).[49-51] Finally, miRNA binds with the AGO protein (RNA-induced silencing

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complex (RISC)) to target messenger RNA (mRNA) and stimulate mRNA cleavage, degradation, and translation repression.[52,53] (Figure 1).

Targeting Signaling Pathways in HCC with miRNAs

Several previous studies have provided evidence that miRNA can suppress HCC metastasis[54,55] (Table 1). miRNAs have been shown to control several signaling pathways, including Wnt, Notch, FGF, SHH, and hippo, and suppress the tumorigenesis of HCC (Figure 1).

It has been shown that overexpression of miR-34, miR-200, miR-133, and miR-663a inhibits the activation of the TGF-β ligand.[56,57,59] miR-122 and miR-3194-3p have been found to suppress the Wnt/β-catenin pathway in HCC.[61,63]

Table 1. Effects of miRNA on Signaling Pathways Related to HCC

Pathway	miRNA	Target	HCC cell line	Animal model	Result	Ref.
TGF-B	miR-200	Ligand	MHCC-97 H, SMMC 7721, HepG2, Huh7	-	Inhibit HCC proliferation, EMT, and invasion	56
	miR-663	Ligand	SK-Hep1, Huh7 and other HCC line	-	Inhibit the tumor growth and invasion	57
	miR-34	Ligand	Huh7, HepG2, Hep3B	-	Decrease the HCC proliferation	58
	miR-133		SMMC7721, Huh7	1 × 10^7 SMMC7721 d subcutaneously to limb of nude mice	Decrease proliferation, migration, increase apoptosis, decrease tumor growth	59
Wnt	miR-298	B-catenin	MHCC-97 H, HCCLM3	MHCC-97H subcutaneously to flank of nude mice	Decrease the HCC proliferation and metastasis	60
	miR-504	FZD receptor	Huh7, HepG2	-	Decrease the HCC proliferation and metastasis	60
	miR-122	Pathway	SMMC7721, Bel-7402	5×10^6 cells subcutaneously to flank of nude mice	Decrease the HCC proliferation, survival and tumor weight	61
	miR-148b	Wnt1	HepG2	5 × 10^6 HepG2 subcutaneously to flank of nude mice	Induce apoptosis and cell cycle arrest, inhibit tumor growth	62
	miR- 3194-3p	BCL9	MHCC-97H, Hep3B	1×10^6 MHCC-97H or Hep3B to tail veins	Inhibit migration, invasion, and metastasis	63
Shh	miR-138	Smo receptor	HepG2	-	Decrease colony formation and invasion, increase apoptosis	64
	miR-338-3p	Smo receptor	MHCC-97H	1×10^7 MHCC-97H to flank of nude mice then cut and transplant to left liver	Inhibit the EMT	65
Notch	miR-3163	NICD	MHCC97-H, LM-3	MHCC97-H subcutaneous or intraportal of nude mice	Decrease the tumor growth	66
	miR-206	NICD	HepG2	-	Cell cycle arrest, apoptosis, and inhibit the EMT	67
EGF	miR-874	ERK	SK-Hep1	overexpressed miR-874 SK-hep-1 to BALB/c nude mice	Inhibit proliferation and metastasis, decrease the tumor size	68
HGF	miR-181a-5p	c-met	SNU, Mahlavu	-	Inhibit proliferation and metastasis	69
VEGF	miR-195	VEGF/FGF	BEL-7402	-	Inhibit migration and invasion	70
	miR-126	EGF/VEGF	HCCLM3, SMMC-7721, MHCC-97H	subcutaneously to flank of SCID mouse	Inhibit proliferation and tumor growth	71
Stat3	miR-345	Jak	HCCLM3, HepG2	6×10^6 HCCLM3 cells intravenously into nude mice	Inhibit the EMT and metastasis	72
	miR-30e	Jak	HepG2, Huh7	-	Inhibit the proliferation, migration, and invasion of HCC	73
YAP/TAZ	miR-9-3p	TAZ	Huh1, HLF	-	Inhibit proliferation	74
	miR186	YAP	HepG2, Hep3B, SNU398	-	Inhibit the migration and proliferation	75
HIF-1α	miR-592	HIF-1α	SK-hep1, SMMC-7721	1.5 × 10^6 SK-Hep-1 subcutaneously into flank of SCID mice	Inhibit proliferation tumor growth, and glycolysis	76
Cell cycle	miR-144	Cyclin B1	HepG2, SMMC-7721	5×10^6 SMMC-7721 subcutaneously to flanks of nude mice	Decrease proliferation, migration, survival, and the tumor size	77
	miR-214-3p	Serin, theronin kinase	HepG2, Huh7	-	Decrease proliferation, increase the apoptosis	56
	miR-300	B-Catenin	HepG2, Huh7	-	Decrease proliferation	78
Apoptosis	miR-383	Stat3	HepG2, Huh7	DEN	Increase the apoptosis, decrease proliferation	79
	miR-644a	Heat shock factor 1	HepG2, SMMC-7721	2×10^7 SMMC-7221 subcutaneously to nude mice	Increase the apoptosis, decrease proliferation inhibit tumor growth	80
	miR-377	Bcl2	HepG2	-	Inhibit proliferation and apoptosis	81
Autophagy	miR-423-5p	ATG7	Huh7	-	Autophagy and cell cycle arrest	82
	miR100	mTOR	HepG2	5×10^6 HepG2 subcutaneously to flank of BALB/c mice	Autophagy and apoptosis	81
ROS	miR-125b-5p	TXNRD	Huh7, SK-hep1	-	Decrease proliferation and migration	81
	miR-124	SIRT1	Huh7, HepG2	5×10^6 HepG2 subcutaneously to armpit of nude mice	Increase the apoptosis in combination with Cisplatin	83

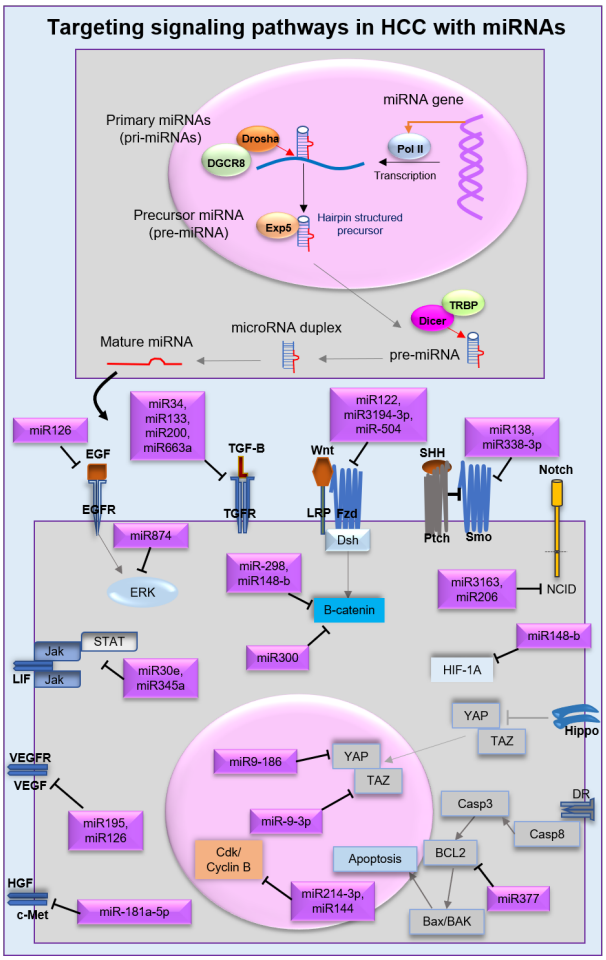

Figure 1. miRNA Biogenesis and Anti-oncogenic Functions on Signaling Pathways Related to Hepatocellular Carcinoma.

Ectopic overexpression of miR-504 in HCC cells leads to blocking the *FZD*, while the overexpression of miR-298 and miR-148-b inhibits the activation of β-catenin.[60,62] Overexpression of miR-138[64] and miR-338-3p was shown to suppress *Smo* in the SHH pathway.[65] Interestingly, SHH inhibitors accompanied by radiotherapy enhanced the radiosensitivity of HCC.[84] miR-3163 and miR-206 have been reported to suppress the notch 1 intracellular domain (NICD) transcriptional activation in the Notch pathway.[66,67] It has been confirmed that miR-874 blocks the EGF/ERK pathway in HCC.[68] miR-181a-5p as a selective c-MET inhibitor in the HGF pathway decreases HCC proliferation, migration, and tumor growth.[69,85-87] miR-195 inhibits angiogenesis by targeting VEGF and FGF,[70] while miR-126 decreases the expression of VEGF and EGF.[71] miR-30e and miR-345 are able to target the Jak/Stat3 pathway.[72,73] miR-186 and miR-9-3p as tumor suppressors repress YAP[75] and TAZ[74] in the hippo pathway. Overexpression of miR-592 leads to disruption of hypoxia-inducible factor-1α (HIF-1α), suppression of glycolysis and lactate production, and reduction of G6PD mRNA levels in HCC.[76]

Anti-proliferative miRNA are significantly downregulated in HCC cell lines.[78] Overexpression of miR-214-3p was reported that reduced HCC progression, by binding to the 3′-UTR of maternal embryonic leucine zipper kinase expression.[88] miR-144 and miR-300 by targeting cyclin B and β-catenin, respectively, couldpromote cell cycle arrest in HCC.[77,78,9] miR-383 by targeting IL-17 can suppress the Stat3 function, miR-644a inhibits heat shock factor 1 (an anti-apoptotic transcription factor), and miR-377 represses Bcl-2, thereby increasing apoptosis and decreasing cellular proliferation in HCC.[79-81] Several studies have shown that miR100 and miR-423-5p induce autophagy.[82,90] miR-124 interacts with sirtuin 1 (SIRT1) protein to enhance the cytotoxic effects of cisplatin in the CSC subpopulation.[83]

Taken together, targeting cancer-specific signaling pathways using miRNAs may be novel therapeutic strategies against HCC.

In conclusion, several important signaling pathways are misregulated in HCC compared to the normal hepatocytes.[91,92] These pathways can trigger EMT, metastasis, migration, and tumorigenesis. Hence, suppression of the critical pathways with miRNAs causes cell cycle arrest, apoptosis, inhibits the tumorigenesis of HCC, and facilitates the sensitivity of HCC cells to drugs. Therefore, miRNAs may be a valuable approach to HCC treatment.[93]

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

Not applicable.

Conflict of Interest Disclosures

The authors declare no conflict of interest.

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