REVIEW ARTICLE

Deciphering the Roles of Long Non-coding RNA and MicroRNA in Hepatocellular Carcinoma: A Review

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ABSTRACT

The burden of primary liver cancer, hepatocellular carcinoma (HCC) is on rapidly expanding globally. Therefore, it is worthwhile to explore the mechanism of HCC progression. To date, evidence suggests that non-coding RNAs (ncRNAs) such as long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) play significant roles in HCC progression. However, the underlying molecular mechanism of ncRNAs in HCC is yet to be fully understood. This review highlights the roles of lncRNA at transcription and post-transcriptional levels. In addition, the function of miRNAs in HCC progression and therapy are also discussed. The overview of the regulation and functional roles of ncRNAs could potentially contribute to the development of novel therapeutic targets in HCC.
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Keywords: Long non-coding RNA, microRNA, Biomarker, Hepatocellular carcinoma, HCC progression

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INTRODUCTION

Hepatocellular carcinoma (HCC) or hepatoma is the most prominent primary liver malignancy that accounts for 80-90% of overall primary liver cancer cases (1). HCC is the fourth most common cancer-related mortality worldwide (2). In the Southeast Asia, the incidence of HCC is relatively high (3). In Malaysia, HCC remains a major health burden due to its high mortality, poor diagnosis and low survival rate (4). In addition, the lack of proper biomarkers for the diagnosis and treatment of HCC is a significant challenge. The HCC is predominantly caused by prominent main risk factors, including Hepatitis B virus (HBV) (5), Hepatitis C virus (HCV) (6), followed by non-alcoholic fatty liver disease (7), obesity (8), Type II diabetes mellitus (9) and genetic factors like hereditary hemochromatosis and Wilson disease (10) (11). Among all, chronic HBV and HCV infection remain the most prominent risk factors of HCC (4). To date, the main treatment for HCC focuses on curative (non-drug treatment) and palliative treatments (12) (13). Curative treatment includes include liver transplantation, liver resection and ablation (14). Meanwhile, palliative treatments involve chemotherapy, radiotherapy, immunotherapy, molecular-targeted therapy and systemic therapies (15). However, these treatment strategies depend on the disease stage, patient's condition, availability of treatment and clinical expertise (13). As the occurrence of HCC continues to increase, it is crucial to explore and uncover more effective treatment modalities for HCC to improve patient outcomes. Recent advancements in molecular biology especially non-coding RNAs (ncRNAs) like long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have emerged as potential biomarkers for the diagnosis and therapy of HCC and have shown potential as cancer biomarkers. In this review, the roles of two ncRNAs are comprehensively described; lncRNAs and miRNAs in HCC. This review focuses on their functional roles in various cellular processes including cell growth, differentiation, proliferation, invasion, apoptosis, metastasis and therapeutic applications in HCC. In general, ncRNAs can be classified into housekeeping and regulatory ncRNAs (16). Dysregulation of regulatory ncRNAs has been numerously reported to participate in different levels of gene expression either by activating or inhibiting target genes (17) (18).

THE LONG NON-CODING RNA

lncRNAs are ncRNAs with more than 1000 nucleotides in length, which are referred to as 'dark matter of genome' or 'junk of messenger'' that lack a significant open reading frame (16). lncRNA can be classified into different subtypes based on the genomic location in which they are transcribed and their orientation. The classification of lncRNAs includes intronic, intergenic, pseudogenes, sense or antisense transcripts and retrotransposons lncRNAs (19). The lncRNAs can be

found within the nucleus, cytoplasm and mitochondria (20). Many lncRNAs are transcribed and spliced by RNA polymerase II (Pol II). The pre-mature lncRNA further undergoes general RNA processing which includes 5′ methylguanosine capping, splicing and 3′end polyadenylation. lncRNA frequently undergo alternative splicing and form RNA-RNA duplexes with pre-mRNA molecules, influencing chromatin remodelling and facilitating the splicing of the target genes (21). In cancer, lncRNAs appear as tumour biomarkers and are differentially expressed as tumour suppressors or oncogenic precursor transcripts. In addition, lncRNAs have been reported to be involved in biological functions in cancer including cell growth, proliferation, invasion, migration and apoptosis. The functional role of lncRNA-related human cancers based on in vitro and in vivo data is summarised in Table I.

Table I: The functional role of lncRNA in human cancers

Type of cancers	LncRNA	Expression	Mechanisms	References
Breast cancer	UFC1	Oncogenic	• Regulates biological activity of breast cancer cell lines via miR34a/CXCL10 axis.	[22]
	PCAT19	Tumour suppressive	• Regulates cell proliferation.	[23]
Bladder cancer	CAS11	Oncogenic	• Promotes cell proliferation.	[24]
	SNGH3	Oncogenic	• Promotes cell proliferation, migration and invasion.	[25]
Colorectal cancer	HOTAIRM1	Tumour suppressive	• Inhibits cell proliferation.	[26]
	NEAT1	Tumour suppressive	• Regulates invasion and migration of cells via miR-185-5p/IGF2 axis.	[27]
	ADAMTS9-AS1	Tumour suppressive	• Regulates cell proliferation, migration.	[28]
Ovarian cancer	DANCR	Oncogenic	• Promotes metastasis of ovarian cancer.	[29]
	TUG1	Oncogenic	• Promotes cell proliferation, invasion and stemness of ovarian cancer cells.	[30]
Hepatocellular carcinoma	MEG3	Tumour suppressive	• Suppress cell proliferation, inhibit tumour growth and induce cell apoptosis.	[31]
	CASC2	Tumour suppressive	• Suppress cell proliferation and invasion via miR-155/SOCS1 axis.	[32]
Gastric cancer	ANRIL	Tumour suppressive	• Inhibits proliferation and colony formation of human gastric cancer cells.	[33]
	MIR503HG	Tumour suppressive	• Promotes cell apoptosis through miR-155 and Caspase-3.	[34]
Cervical cancer	XIST	Oncogenic	• Promotes cell proliferation and progression by inhibiting miR-140-5p.	[35]
	HOTAIR	Oncogenic	• Promotes cell proliferation, migration and invasion.	[36]
	UFC1	Oncogenic	• Promotes tumour growth, proliferation, migration and invasion *in vitro* cervical cells.	[37]
Glioma	HOXD-ASI	Oncogenic	• Promotes cell migration and invasion.	[38]
Pancreatic cancer	LINC00976	Oncogenic	• Promotes cell proliferation, migration and invasion.	[39]
	A2M-AS1	Tumour suppressive	• Inhibits proliferation, migration and invasion	[40]

Abbreviation: Small nucleolar RNA host gene 3 (SNHG3), taurine upregulated gene 1 (TUG1), Lnc-antisense non-coding RNA in the INK4 locus (ANRIL), maternally expressed gene 3 (MEG3), X inactive-specific transcript (XIST), homeobox transcript antisense RNA (HOTAIR), differentiation antagonizing nonprotein coding RNA (DANCR), alpha-2-macroglobulin-antisense 1 (A2M-AS1), insulin growth factor 2 (IGF2), CXC motif chemokine ligand 10 (CXCL10).

THE ROLES OF LONG NON-CODING RNA IN HCC

HCC is a multifactorial complex disease involving the deregulation of lncRNAs. The lncRNA regulates gene expression at different levels, including chromatin modification, as well as transcriptional and post-transcriptional processing (41). With increasing attention on cancer diagnosis and treatment, more lncRNAs are being reported to play significant roles in various cancers including HCC. The expression of oncogenic and tumour suppressor lncRNAs and their biological function in HCC are summarised in Table II and Table III respectively. This review further summarises the role of lncRNAs in HCC progression at two distinct levels; (i) transcriptional and (ii) post-transcriptional levels.

Table II: Expression of oncogenic lncRNAs in HCC

Expression	Role in HCC	LncRNA	Biological functions in HCC	References
Upregulated	Oncogenic	LINC00662	• Promotes activation of oncogene by inducing genomic hypomethylation *in vitro* and *in vivo*.	[42]
Upregulated	Oncogenic	LINC01006	• Promotes cell viability, migration and invasion and regulates the miR-433-3p/CBX3 axis.	[43]
Upregulated	Oncogenic	HOTAIR	• Promotes cell proliferation and invasion. Regulates the expression of Wnt and β-catenin signalling pathways.	[44]
Upregulated	Oncogenic	MCM3AP-AS1	• Promotes cell proliferation, colony formation and cell cycle progression and inhibit apoptosis.	[45]
Upregulated	Oncogenic	MUF	• Promotes cell malignancy via miR-34a axis and regulates HCC development via Wnt signalling.	[46]
Upregulated	Oncogenic	ANRIL	• Promotes cell proliferation, migration, invasion and inhibits apoptosis.	[47]
Upregulated	Oncogenic	LL22NC03-N14H11.1	• Promotes cell proliferation, migration, and epithelial-to-mesenchymal transition (EMT).	[48]
Upregulated	Oncogenic	LINC01194	• Promotes cell progression, proliferation and migration via miR-655-3p/SMAD axis.	[49]
Upregulated	Oncogenic	Lnc-Myd88	• Promotes growth and HCC cell metastasis.	[50]
Upregulated	Oncogenic	SNGH17	• Promotes cell proliferation and increase stability of c-Myc protein.	[51]
Upregulated	Oncogenic	DLGAP1-AS1	• Promotes HCC progression and EMT by activating the JAK2/STAT3 pathway.	[52]
Upregulated	Oncogenic	XIST	• Promotes cell progression, invasion and migration by targeting the miR-320a/PIK3CA pathway.	[53]
Upregulated	Oncogenic	CYTOR	• Promotes cell proliferation and inhibits apoptosis. Promotes tumour growth *in vivo* xenograft model.	[54]
Upregulated	Oncogenic	MYLK-AS1	• Promotes growth and invasion through the EGFR/HER2-ERK1/2 pathway.	[55]
Upregulated	Oncogenic	ALKBH3-AS1	• Enhances cell invasion and proliferation.	[56]
Upregulated	Oncogenic	91H	• Promotes cell proliferation and inhibits apoptosis.	[57]
Upregulated	Oncogenic	DNAJC3-AS1	• Promotes cell proliferation via direct interaction with miR-27b.	[58]
Upregulated	Oncogenic	RPA-694A7.2	• Induces cell proliferation, invasion and migration.	[59]
Upregulated	Oncogenic	TMCC1-AS1	• Facilitates proliferation, migration and invasion.	[60]
Upregulated	Oncogenic	H19	• Promotes cell cycle progression and HCC growth via direct interaction with miR-107, a negative regulator of CDK6.	[61]
		H19	• Induces MYC accumulation through G3BP1 recruitment.	[62]
Upregulated	Oncogenic	NEAT1	• Enhances PKM2 transcriptional activation by binding to FOXP3.	[63]
		NEAT1	• Induces CD44 expression.	[64]
Upregulated	Oncogenic	TUG1	• Facilitates immune evasion which associated with PD-L1.	[65]
			• Acts a sponge of miR-144 which promotes JAKS/STAT3 and induces cell proliferation and migration.	[66]

Abbreviations: ANRIL (CDKN2B antisense RNA1), MUF (Mesenchymal stem cells-upregulated factor), HOTAIR (HOX transcript antisense RNA), MCM3AP-AS1 (MCM3AP antisense RNA 1), CBX3 (chromobox protein homolog 3), HULC (highly upregulated in liver cancer), cytoskeleton regulator RNA (CYTOR), transmembrane and coiled-coil domain family 1 antisense RNA 1 (TMCC1-AS1), X-inactive specific transcript (XIST), small nucleolar RNA host gene 17 (SNGH17), taurine upregulated gene 1 (TUG1), programmed cell death ligand-1 (PD-L1).

Table III: Expression of tumour suppressor lncRNAs in HCC

Expression	Role in HCC	LncRNA	Biological Function in HCC	References
Downregulated	Tumour suppressor	TSLNC8	• Suppress the proliferation and metastasis *in vitro* and *in vivo* via interaction with IL6 and STAT3.	[67]
Downregulated	Tumour suppressor	SVUGP2	• Inhibits proliferation and invasion of HCC cells.	[68]
Downregulated	Tumour suppressor	MIR31HG	• Suppress HCC proliferation and metastasis *in vitro* and *in vivo* via sponging miR-575.	[69]
Downregulated	Tumour suppressor	GAS8-AS1	• Inhibits cell proliferation, migration, invasion and induces apoptosis of HCC cells.	[70]
Downregulated	Tumour suppressor	LINC00238	• Decrease cell viability, migration and invasion *in vitro*. Inhibits tumorigenesis and metastasis *in vivo*.	[71]
Downregulated	Tumour suppressor	NBR2	• Inhibits cell proliferation, invasion, metastasis and migration through ERK and JNK pathways.	[72]
Downregulated	Tumour suppressor	FENDRR	• Diminish cell proliferation and tumorigenicity.	[73]
Downregulated	Tumour suppressor	Uc.134	• Repress HCC proliferation and metastasis.	[74]
Downregulated	Tumour suppressor	W5	• Suppress HCC cell proliferation, migration and invasion. Also inhibits growth of HCC xenograft tumours *in vivo*.	[75]
Downregulated	Tumour suppressor	TMEM220-AS1	• Suppress migration, invasion and proliferation.	[76]
Downregulated	Tumour suppressor	TPTEP1	• Suppress HCC cell proliferation and invasion.	[77]
Downregulated	Tumour suppressor	OGRP1	• Suppress proliferation and EMTT through AKT and Wnt/β-catenin pathway.	[78]
Downregulated	Tumour suppressor	MIR22HG	• Inhibits HCC growth, migration, invasion and metastasis through miR10a-5p/NCOR2 axis.	[79]

Abbreviations: FENDRR (fetal-lethal non-coding development regulatory), tumour suppressor long non-coding RNA on chromosome 8p12 (TSLNC8), neighbour of BRCA1 gene 2 (NBR2), GAS8 antisense RNA 1 (GAS8-AS1), nuclear receptor corepressor 2 (NCOR2), TPTE pseudogene 1 (TPTEP1), gastrin-releasing peptide 1 (OGRP1).

The lncRNA-regulated Gene Expression at Transcriptional Level

lncRNA plays significant roles in regulating gene expression in the nucleus and cytoplasm. In the nucleus, the lncRNA binds to deoxyribonucleic acid (DNA) sequences and influence gene expression at the transcriptional level (80). The transcriptional expression of lncRNA in HCC is modulated via interaction with transcription factors (TFs) or epigenetically by histone acetylation or DNA methylation. This event further leads to the silencing expression of target mRNA expression. In HCC, single lncRNA may be simultaneously regulated by multiple TFs. One of the common mechanisms of lncRNA-mediated gene silencing is via EZH2 binding and recruitment (81) (82). For instance, lncRNA taurine upregulated gene 1 (TUG1) has been found overexpressed in HCC tissues and cell lines (81). High expression of lncRNA TUG1 in HCC patients was correlated with tumour size and the Barcelona Clinic Liver Cancer (BCLC) stage (81). It was also discovered that promoter regions of TUG1 interact with nuclear transcription factor SP1 to epigenetically regulates the expression of tumour suppressor, Kruppel-like factor 2 (KLF2) in HCC cells (81). Silencing of KLF2 leads to increased HCC proliferation and repressed cell apoptosis (81). A ChIP experiment has demonstrated that EZH2 directly binds to the KLF2 promoter regions to suppress KLF2 transcription and that mechanistically, the knockdown of TUG1 reduces the binding ability of EZH2 in HCC cells. Xu et al. revealed that lncRNA LINC00978 is significantly overexpressed in HCC (82). Meanwhile, fractionation experiments revealed that LINC00978 expression is higher in the nucleus than in the cytosol of HCC cells, further reflecting that LINC00978 acts as a regulator of gene transcription (82). Mechanistically, LINC00978 binds to EZH2 to epigenetically downregulate the expression of cyclin-dependent kinase inhibitors, p21 and E-cadherin. Together. these results showed that LINC00978/EZH2 complexes promote HCC cell proliferation, migration and invasion (82).

The lncRNA-regulated Gene Expression at Post-transcriptional Level

Cytoplasmic lncRNA also could regulate gene expression at the post-transcriptional level. The expression of cytoplasmic lncRNAs in HCC is modulated by miRNAs and RNA-binding proteins (83). High expression of lncRNA can competitively combine with miRNA, acting as a molecular sponge to induce miRNA dysfunction and promotes cancer. lncRNA also serves as competitive endogenous RNAs (ceRNAs) for miRNA and reduces the regulatory effects of miRNA on its mRNA target. For example, lncRNA DLGAP1-AS1 functions as a ceRNA of miRNA to impair miR-26a-5p and miR-26b-5p, thus activating the oncogenic cytokine IL-6 [84]. Through bioinformatic analysis, it was shown that miR-26a-5p and miR-26b-5p were complementarily bound to the DLGAP-AS1 to suppress its expression (84). Moreover, an RNA pulldown experiment demonstrated that DLGAP-AS1 directly bind to miR-26a-5p and miR-26b-5p. The study also found that the overexpression of DLGAP-AS1 in HCC competes with miR-26a-5p and miR-26b-5p expression, which functions as a ceRNA to promote IL-6 expression and drives HCC progression (84). In another study, lncRNA double homeobox A pseudogene 8 (DUXAP8) acted as ceRNA of miR-422a to regulate the expression of pyruvate dehydrogenase kinase 2 (PDK2), thereby promoting the growth and progression of HCC (85). Besides, it was observed that DUXAP8 targeted miR-422a and directly regulated PDK2 to affect the growth and progression of HCC (85). Notably, lncRNA

was also reported to regulate protein stabilisation in HCC. A study by Liu et al. (86) found that lncRNA snoRNA host gene 17 (SNGH17) overexpression in HCC was associated with poor survival in HCC. Moreover, SNGH17 interacted with oncogenic c-Myc, thereby inhibiting ubiquitin-proteosome-dependent degradation of the c-Myc protein (86).

THE MICRORNA

Unlike lncRNA, miRNA is a short, small non-coding single-stranded RNA transcript with approximately 18-24 nucleotides in length that can regulate gene expression at the post-transcriptional level by inducing translational repression or mRNA degradation via Watson-Crick base pairing to the 3'UTR of its specific mRNA gene (87). The biogenesis of miRNA occurs in the nucleus and cytoplasm. The pri-miRNA consists of an imperfectly paired stem-loop structure, long flanking sequences and some internal loops (bulges). These structural characteristics contribute to an efficient miRNA processing event. After transcription, the pri-miRNA hairpin is further cleaved by the microprocessor complex Drosha enzyme (RNase III exonuclease) and its cofactor, the RNA-binding protein DiGeorge critical region 8 (DGCR8) or Drosha-DGCR8 complexes. The cleaved transcript which is 70-100 nucleotides long, is referred to as a stem-loop structure known as precursor miRNAs (pre-miRNAs) with 2-nt 3' overhang. The pre-miRNAs are then exported from the nucleus to the cytoplasm through nuclear pore complexes, which are large proteinaceous channels embedded in the nuclear membrane. The pre-miRNAs are transported by Exportin-5 (Exp-5) in a complex with RanGTP. In the cytoplasm, the stem-loop pre-miRNA is further processed by Dicer (a double-stranded RNA-specific, RNase III endonuclease). Dicer and its partner HIV-1 trans-activating response RNA-binding protein (TRBP) and protein-kinase RNA activator (PACT) bind to the end of pre-miRNA and cleave both strands of the duplex, resulting in 18-25 nucleotides double-stranded mature miRNA duplex with 2-nucleotide at 3' overhangs. The mature miRNA duplex could give rise to two different mature miRNAs; guide strand and passenger strand (87). Mature miRNA negatively regulates gene expression by either translational repression or mRNA degradation which is dependent on the complementary sequence between miRNA and target mRNA (88). The guide strand is bound by the Argonaute proteins (AGO) and retained in the miRNA-induced silencing complex (miRISC) matches with the transcript in the 3'UTR of the target mRNAs for post-transcriptional silencing. Other strands, known as passenger strands are released and degraded. The miRNAs recognise their target mRNAs by one and several motif site sequences; seed matches are located within the 3'UTR of the target mRNA that is complementary to 2-8 bases in the 5'end of the miRNA (88).

THE ROLES OF MICRORNA IN HCC

The miRNAs in HCC Growth and Progression

Some miRNAs have been identified to possess anticancer properties. In cancer, miRNAs can be classified as oncogenic miRNA (oncomiR) and tumour suppressor miRNA (tsmiR) relatively based on which gene they control (89). In general, oncomiRs are found upregulated in cancers and have been shown to act as an oncogene while tsmiRs are low expressed (89). The expression of oncomiRs and tsmiRs expressed in HCC is listed in Table IV.

Table IV: Oncogenic and tumour suppressor miRNAs in HCC

Expression	miRNA	mRNAs or Proteins Target	Biological Functions	References
Upregulated	miR-21	• PTEN	• Promotes proliferation, EMT, invasion and evasion of apoptosis. • Activation of PDK1/AKT pathway.	[90]
Upregulated	miR-96-5p	• CASP9	• Inhibits apoptosis.	[91]
Upregulated	miR-25	• RhoGDI1	• Promotes growth of HCC cells *in vitro*. Enhances migration, invasion and EMT of cells.	[92]
Upregulated	miR-33a	• PPARα	• Induces proliferation and inhibits apoptosis in HCC cells.	[93]
Upregulated	miR-107	• Cofilin-1	• Induces cell death by ROS accumulation.	[94]
Upregulated	miR-135a	• FOXO1	• Promotes cell migration and invasion	[95]
		• TONSL-AS1	• Promotes cell proliferation.	[96]
Upregulated	miR-155-5p	• PTEN	• Promotes proliferation, migration, invasion and reduced apoptosis of HCC cells.	[97]
Upregulated	miR-181a	• Atg5	• Suppress apoptosis of HCC cells and promotes tumour growth *in vivo*.	[98]
Upregulated	miR-183	• PDCD4	• Inhibits apoptosis by targeting TGF-β1.	[99]
Upregulated	miR-210	• FGFRL1	• Promotes HCC cell angiogenesis.	[100]
Upregulated	miR-224	• PP2R1B	• Promotes cell proliferation, migration and invasion by modulating the AKT pathway.	[101]
Upregulated	miR-302d	• TGFBR2	• Increases HCC cell growth. • Inhibits apoptosis and promotes migration.	[102]
Upregulated	miR-519a	• PTEN	• Promotes cell proliferation and cell cycle progression *in vitro* by activating the PI3K/Akt pathway.	[103]

CONTINUE

Table IV: Oncogenic and tumour suppressor miRNAs in HCC (CONT.)

Expression	miRNA	mRNAs or Proteins Target	Biological Functions	References
Upregulated	miR-873	• NDFIP1	• Promotes cell proliferation, migration and invasion.	[104]
Upregulated	miR-4417	• TRIM35	• Promotes cell proliferation and inhibits apoptosis in HCC cell lines. • Regulates PKM2 phosphorylation.	[105]
Downregulated	miR-1	• FOXC1	• Inhibits proliferation.	[106]
Downregulated	miR-26b	• NF-kB	• Enhances chemosensitivity and apoptosis by targeting TAK1 and TAB3.	[107]
Downregulated	miR-29c-3p	• TRIM31	• Suppress cell proliferation and migration. • Suppress tumorigenicity *in vivo.*	[108]
Downregulated	miR-125-5p	• BCL2L2, TRIAP1	• Inhibits cell viability and migration and induces apoptosis of HCC cells.	[109]
Downregulated	miR-133b	• Caspase-3/8 • Bax/Bcl2	• Inhibits proliferation and increases LDH activity and apoptosis in HCC cells.	[110]
Downregulated	miR-145-5p	• KLF5	• Inhibits cell proliferation and migration.	[111]
Downregulated	miR-186	• YAP1	• Inhibits proliferation, migration and invasion of HCC cells.	[112]
Downregulated	miR-195		• Inhibits cell migration, invasion and metastasis	[113]
Downregulated	miR-206	• c-MET	• Suppress c-Met/Akt/mTOR signalling.	[114]
Downregulated	miR-216b	• IGF2BP2	• Inhibits cell proliferation, migration and invasion of HCC cells.	[115]
Downregulated	miR-217	• MTDH	• Suppress proliferation, migration and invasion.	[116]
Downregulated	miR-223	• NLRP3	• Suppress proliferation and induces apoptosis.	[117]
Downregulated	miR-361-5p	• MAP3K9	• Induces HCC cell apoptosis and enhances drug sensitivity.	[118]
Downregulated	miR-424	• c-Myb	• Inhibits cell proliferation, migration and invasion.	[119]
Downregulated	miR-451	• IL-6R	• Suppress proliferation and migration. • Suppress angiogenesis by targeting the IL-6R-STAT2-VEGF signalling.	[120]
Downregulated	miR-527	• GPC3	• Inhibits expression of oncogenic factor, GPC3 in HCC cells.	[121]
Downregulated	miR-663b	• GAB2	• Suppress cell proliferation and invasion.	[122]
Downregulated	miR-4782-3p	• USP14	• Inhibits cell growth and induces apoptosis.	[123]

Abbreviations: Tripartite motif-containing 35 (TRIM35), pyruvate kinase muscle 2 (PKM2), Rho GDP dissociation inhibitor alpha (RhoGDI1), serine/threonine-protein phosphatase 2A 65kDa regulatory subunit A β isoform (PPP2R1B), caspase 9 (CASP9), metadherin (MTDH), Yes-associated protein 1 (YAP1), Grb2-associated binding 2 (GAB2), Kruppel-like factor 5 (KLF5), IL-6 receptor (IL-6R), fibroblast growth factor receptor-like 1 (FGFRL1), forkhead box C1 (FOXC1), glypican 3 (GPC-3), NOD-like receptor family, pyrin domain containing 3 (NLRP3), tripartite motif containing 31 (TRIM31), programmed cell death (PDCD4).

The miRNA in HCC Diagnosis

In recent years, miRNAs have gained significant attention for their potential as diagnostic and prognostic non-invasive biomarkers in HCC, since they are regarded as being highly specific and sensitive. Numerous miRNAs are aberrantly expressed in cell, tissue, serum, plasma and saliva (124) (125) (126). For instance, the level of miR-487a in the tissues of HCC patient is elevated compared to that in non-tumorous liver tissues (125). Additionally, the expression of miRNA is closely related to disease severity and clinicopathological features of HCC (125). For example, the level of miR-487a expression was observed to be correlated with tumour size, nodule number and microvascular invasion (125). Further analysis found that overexpression of miR-487a in HCC tissues is significantly correlated to low overall survival (OS) rate and disease-free survival (DFS) (125). In another study, a high level of miR-497 was reported in HCC tissue and its expression was significantly correlated with the malignant and invasiveness of HCC (127). In vitro experiments showed that miR-497 overexpression significantly suppressed the PDCD4 expression which induced proliferation and migration (127). In addition, Chen and colleagues found that miR-1246 potentially serves as a biomarker for early HCC diagnosis. Furthermore, miR-1246 is overexpressed in tissue and serum of HCC patients, which may be used for early diagnosis of HCC (102). The level of miR-1246 expression in HCC patients was significantly correlated with clinicopathological characteristics including tumour size, TNM staging and metastasis (102). In addition, Kaplan-Meier survival analysis revealed that a low level of miR-1246 was significantly associated with a low survival probability of HCC patients, indicating the potential of miR-1246 as a prognostic marker for monitoring HCC (102).

The miRNA in HCC Therapy

The main goal of miRNA-based therapy is to restore normal function of deregulated signalling pathways. miRNA-based therapeutics lie in their ability to target mRNAs simultaneously, thereby controlling multiple signalling pathways (128). Some promising approaches aimed at manipulating miRNA expression can be achieved through miRNA replacement therapy and inhibition of oncogenic miRNAs (129). Mounting studies have validated the efficiency of miRNA replacement therapy in in vitro and in vivo models. For example, a study demonstrating that miR-140 was among the most downregulated miRNAs in HCC and was closely correlated with clinicopathological features and the BCLC stage (130). Overexpression of miR-140 in vitro by transfection of synthetic miR-140 mimics markedly inhibited cell proliferation, migration and invasion. It was further demonstrated that, in vitro transient transfection of miR-140 mimic significantly blocked the G1 phase and inhibited the HCC cycle from the G0/G1 phase to the S phase (130). Employing an in vivo experimental model of HCC, xenograft mice were subcutaneously injected with LM3-LV-miR-188 to stably overexpress

the miR-188 (131). Wu et al. (131) demonstrated that oncogene forkhead box N2 (FOXN2) mRNA expression was shown to be downregulated in LM3-LV-miR-188-inoculated mice compared to the control group. At the same time, restoration of miR-188 in mice models has been shown to reduce the tumour volume and weight in the LM3-LV-miR-188-inoculated mice compared to those in the control group (131).

OncomiRs which are highly expressed in cancer can be inhibited by the introduction of synthetic DNA or RNA molecules that suppress miRNA biogenesis and restore its normal expression (132). Chang et al. (125) demonstrated that well-established oncomiR, miR-487 is as promising potential target in the treatment of HCC. A high level of miR-487a has been found to target tumour suppressor genes such as sprout-related EVH1 domain containing 2 (SPRED2) and phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1), which facilitates metastasis and proliferation of HCC cells. Through an in vivo study, Chang and colleagues developed a potent and specific 23-mer in vivo-morpholino (Morpholino-Anti-miR-487a) designed for silencing miR-487a in HCC mouse model. They showed that intravenous administration of morpholino-anti-miR-487a in HCC mouse models resulted in a significant reduction in tumour growth and metastasis nodules in vivo (125). Another study reported that miR-500a expression significantly increased in HCC cell lines (SMMC-7721 and HepG2) compared to the immortalised normal hepatic cell line (132). Utilising an in vitro study, inhibition of miR-500a by miR-500a inhibitor was shown to remarkably reduce the miR-500a expression, thereby suppressing HCC cell proliferation and promoting apoptosis (133). A study by Bao et al. intratumorally injected antogomiR-500a 3p into the HCC-xenograft nude mice model, indicating that the inhibition of miR-500a was shown to inhibit the growth of transplanted tumours in nude mice (133).

THE CROSSTALK OF lncRNA-miRNA-mRNA AXIS IN HCC

Accumulating evidence reported the interconnection of lncRNA-miRNA-mRNA in HCC. This regulatory mechanism allows lncRNA and mRNA to compete with each other to bind to a shared miRNA via common miRNA recognition elements (MREs). For example, Dong et al. (134) discovered that HOTAIR acted as a sponge for miR-1 in HCC cells, which promoted the expression of FOXC1 and modulated its oncogenic activities in HCC cells. In addition, the overexpression of DUXAP8 diminished the inhibitory effects of miR-9-3p on IGF1R expression thereby promoting HCC proliferation, migration and invasion (134). A similar regulatory mechanism has been observed through the lncRNA ZFPM2-AS1/miR-139/GDF10 axis (135). ZFPM2-AS1 was reported to be a target of miR-139, which regulated the expression levels of GDF10, a target of miR-139 (135). They also found that ZFPM2-AS1 putatively bound to miR-139 and prevented miR-139 from inhibiting its target gene GDF10, thereby regulating GDF10 post-transcriptionally (135).

LIMITATION AND FUTURE PERSPECTIVE

There are challenges and considerable gaps in understanding ncRNAs role in HCC progression, diagnosis and therapy. However, it remains a hurdle and a major challenge whether these ncRNA therapeutic approaches from preclinical model systems can be translated into clinical models while considering their efficacy and safety. Thus, clinical trials are required to further validate the functional role and mechanism of ceRNAs in the clinical setting of HCC.

CONCLUSION

This review sheds light on the expression profile of lncRNA and miRNA profiles in HCC growth, progression, diagnostic and therapeutic biomarkers. It has also discussed how ncRNAs exert their biological functions by targeting various signalling pathways involved in HCC. It is hoped that a deeper understanding of the gene regulation mechanism of lncRNAs and miRNAs in HCC will provide the opportunity for develop an effective, actionable and safe treatment strategy for HCC.

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