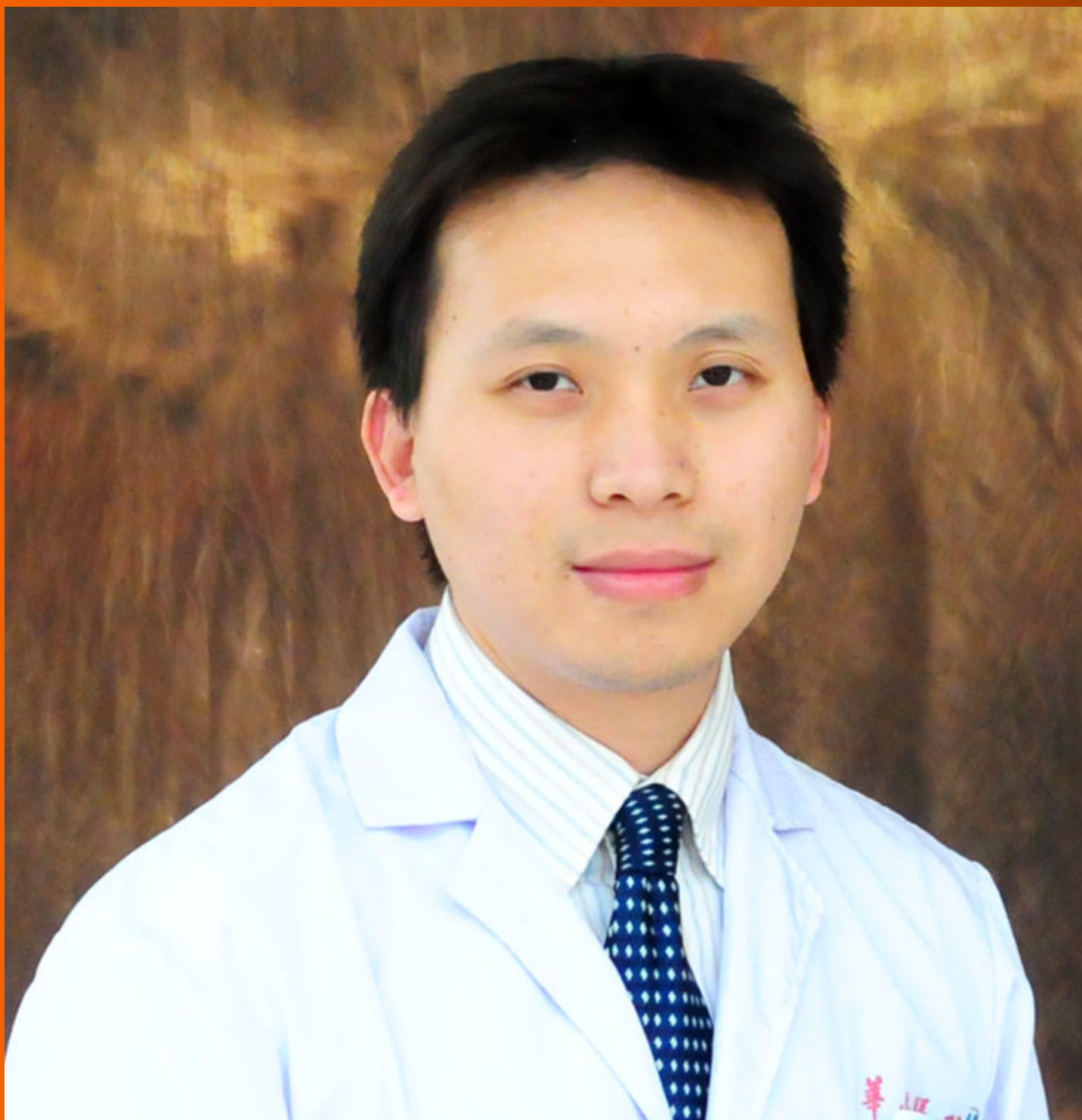


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Role of long noncoding RNA-mediated competing endogenous RNA regulatory network in hepatocellular carcinoma

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Abstract

Long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) are noncoding RNAs (ncRNAs) that occupy over 90% of the human genome, and their main function is to directly or indirectly regulate messenger RNA (mRNA) expression and participate in the tumorigenesis and progression of malignances. In particular, some lncRNAs can interact with miRNAs as competing endogenous RNAs (ceRNAs) to modulate mRNA expression. Accordingly, these RNA molecules are interrelated and coordinate to form a dynamic lncRNA-mediated ceRNA regulatory network. Mounting evidence has revealed that lncRNAs that act as ceRNAs are closely related to tumorigenesis. To date, numerous studies have established many different regulatory networks in hepatocellular carcinoma (HCC), and perturbations in these ceRNA interactions may result in the initiation and progression of HCC. Herein, we emphasize recent advances concerning the biological function of lncRNAs as ceRNAs in HCC, with the aim of elucidating the molecular mechanism underlying these HCC-related RNA molecules and providing novel insights into the diagnosis and treatment of HCC.

Key words: Hepatocellular carcinoma; Long noncoding RNA; MicroRNA; Competing endogenous RNA; Function; Mechanism

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Core tip: Mounting evidence has revealed that long noncoding RNA (lncRNA)-mediated competitive endogenous RNA (ceRNA) regulatory network plays a crucial role in tumorigenesis. To date, numerous studies have established many different regulatory networks in hepatocellular carcinoma (HCC), and perturbations in these ceRNA interactions may result in the initiation and progression of HCC. Herein, we emphasize recent advances concerning the biological function of lncRNAs as ceRNAs in HCC, with the aim of elucidating the molecular mechanism underlying these HCC-related RNA molecules and providing novel insights into the diagnosis and treatment of HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant tumor with high morbidity and mortality worldwide^[1]. However, the pathogenesis of HCC remains elusive. Although great progress has been made in the diagnosis and treatment of HCC in recent years, the overall and long-term effects of treatment in patients with advanced HCC are poor. Therefore, in-depth studies are needed to explore the mechanisms underlying HCC occurrence and development, which will contribute to the development of effective diagnostic biomarkers and therapeutic targets for HCC.

Protein-coding genes account for less than 2% of the human genome, while most of the genome is composed of genes that are transcribed into noncoding RNAs (ncRNAs)^[2]. ncRNAs are divided into long noncoding RNAs (lncRNAs), small ncRNAs, and intermediate-sized ncRNAs by length^[3]. lncRNAs have been identified as key regulators of transcription and translation and are involved in a variety of biological processes by regulating gene expression^[4]. MicroRNAs (miRNAs) are small ncRNAs that interact with the 3'-untranslated region (3'-UTR) of target mRNAs to facilitate their degradation or inhibit their translation. MiRNAs play a critical role in tumorigenesis and tumor cell proliferation, migration, and invasion^[5]. lncRNAs and miRNAs are regulatory ncRNAs, and dysregulation of lncRNAs or miRNAs is involved in tumor initiation and progression either *via* the activation or inhibition of target genes^[6].

Existing evidence indicates that there are interactions among RNA molecules, such as lncRNAs and miRNAs^[7], miRNAs and mRNAs^[8], and lncRNAs and mRNAs^[9]; these RNA molecules are interrelated and collaborate to form a dynamic regulatory network of lncRNAs acting as competitive endogenous RNAs (ceRNAs)^[10]. The ceRNA mechanism is one of the important ways by which an lncRNA exerts its posttranscriptional gene regulation in the cytoplasm, and perturbations in these ceRNA interactions contribute to tumor initiation and progression. Currently, the identified ceRNAs include protein-coding RNAs (mRNAs) and ncRNAs, such as lncRNAs, pseudogene transcripts, viral RNAs, and circular RNAs (circRNAs). lncRNAs are the main component of the ceRNA network, as they regulate mRNA expression by acting as miRNA sponges. To date, numerous different regulatory networks of lncRNAs acting as ceRNAs in HCC have been established. Accumulating evidence has revealed that lncRNAs acting as ceRNAs play pivotal roles in HCC initiation and progression^[11,12]. Herein, we emphasize recent advances concerning the biological function of lncRNAs acting as ceRNAs in HCC, with the aim of elucidating the molecular mechanism underlying these HCC-related RNA molecules and providing novel insights into the diagnosis and treatment of HCC.

MECHANISM OF ACTION OF LNCRNAs INVOLVED IN THE CERNA REGULATORY NETWORK

Theoretically, any RNA molecule with a miRNA binding site can bind to a miRNA to form an intricate ceRNA regulatory network. RNA transcripts in the ceRNA network

are in a state of equilibrium under physiological conditions; once perturbed, this will lead to the occurrence of disease^[13,14]. In the ceRNA regulatory network, miRNA acts as a bridge between ncRNA and mRNA and negatively regulates the expression of its target mRNA^[15]. There is growing evidence that each miRNA can regulate many transcripts. In turn, RNA transcripts with different miRNA response elements (MREs) may also be targets of multiple miRNAs^[16]. The multiplicity of targets allows RNA and RNA to interact with each other by competitively binding to a common MRE, and the same MRE is the structural basis for the binding of different RNAs^[16].

In addition to directly regulating mRNAs, lncRNAs can also indirectly affect the expression of target genes by sponging miRNAs^[10]. Structurally, most lncRNAs are similar to mRNAs, which makes their patterns of gene regulation more diverse and extensive and unaffected by translation^[17]. This may be the reason why many lncRNAs can act as ceRNAs to sponge miRNAs to inhibit miRNAs from degrading their target mRNAs. In general, the more miRNA binding sites there are on an lncRNA, the stronger the competition^[18]. When lncRNAs are expressed at low levels, they can bind only a few miRNAs, and the remaining miRNAs interact with mRNAs to promote their degradation. In contrast, when lncRNAs are expressed at high levels, they can combine with more miRNAs, thus relieving the inhibitory effect of miRNAs on their target mRNAs. The new regulatory pattern of lncRNA-miRNA-mRNA is an extension of the traditional miRNA-mRNA regulatory model^[10].

ROLE OF LNCRNAs AS CERNAS IN HCC

To date, mounting evidence indicates that oncogenic or tumor suppressive lncRNAs can regulate their target genes by acting as ceRNAs to sponge miRNAs^[19,20], thereby affecting glucose metabolism, immune escape, autophagy, angiogenesis, liver cancer stem cells (LCSCs), proliferation, apoptosis, epithelial-mesenchymal transition (EMT), migration, invasion, metastasis, chemoresistance, and radioresistance in HCC (Figure 1). Specifically, the majority of the identified lncRNAs exhibit oncogenic properties that function as ceRNAs for tumor suppressive miRNAs, thereby activating the expression of oncogenic mRNAs to promote HCC occurrence and progression (Figure 2A). In addition, some lncRNAs exhibit tumor suppressive properties, acting as ceRNAs for oncogenic miRNAs (oncomiRs), thus upregulating the expression of tumor suppressive targets to inhibit HCC occurrence and progression (Figure 2B). Here, we elucidate the functions of some lncRNA-mediated ceRNA regulatory networks in HCC (Table 1). Note that there are many abbreviations in this paper, so they are listed and expanded in Table 1 below.

Glucose metabolism

The “reprogramming” of glucose metabolism is regarded as a prominent characteristic of cancer cells. A large amount of lactic acid produced by glycolysis forms an inflammatory microenvironment around the tumor, which contributes to tumor cell proliferation, EMT, invasion, metastasis, immune escape, and resistance to chemotherapy and radiotherapy. Existing evidence indicates that aberrant glucose metabolism plays a pivotal role in the invasion and metastasis of HCC^[21,22]. The mechanism of abnormal activation of glycolysis in cancer cells is complex, and many studies have confirmed that lncRNAs play a significant role in modulating glycolysis by sponging miRNAs in HCC, among which oncogenic lncRNAs that act as ceRNAs can promote glycolysis. For instance, lactate dehydrogenase isoform A (LDHA), a glycolytic enzyme, can mediate aerobic glycolysis in cancer cells^[23]. The lncRNA *RAET1K*, as a miR-100-5p sponge, can enhance LDHA expression and facilitate hypoxia-induced glycolysis, thereby promoting HCC progression^[24]. In addition, hemikinas 2 (HK2) is another glycolytic enzyme related to glycolysis in cancer cells^[25], and the lncRNA *TUG1* induces glycolysis and promotes HCC metastasis by acting as a ceRNA to enhance HK2 expression by sponging miR-455-3p^[26]. Additionally, hypoxia-inducible factor (HIF) 1 has been confirmed to promote aerobic glycolysis in cancer^[27], and the lncRNA *HOTAIR* promotes glycolysis by acting as a ceRNA for miR-130a-3p to increase HIF1 expression in HCC cells^[28]. By contrast, tumor suppressive lncRNAs that act as ceRNAs can inhibit glycolysis in HCC. For example, endoplasmic reticulum protein 29 (ERp29), an endoplasmic reticulum protein, and the lncRNA *MEG3* are downregulated in high-glucose (HG) HCC cells, while miR-483-3p is upregulated in HG HCC cells. Mechanistically, the overexpression of *MEG3* inhibits glycolysis by sponging miR-483-3p to increase ERp29 expression in HCC^[29]. Currently, antitumor drugs that target glucose metabolism are being researched and developed;

Table 1 Long noncoding RNA-mediated competitive endogenous RNA network in hepatocellular carcinoma

LncRNA	Dysregulation	Sponged miRNA(s)	Affected mRNA(s)/ signaling pathway(s)	Biological functions	Ref.
<i>RAET1K</i>	Up-regulated	miR-100-5p	LDHA	Enhances HCC glycolysis and progression	Zhou <i>et al</i> ^[24]
<i>TUG1</i>	Up-regulated	miR-455-3p	HK2	Promotes HCC glycolysis and metastasis	Lin <i>et al</i> ^[26]
<i>HOTAIR</i>	Up-regulated	miR-130a-3p	HIF1	Promotes glycolysis	Hu <i>et al</i> ^[28]
		miR-218	Bmi-1	Promotes HCC cell proliferation	Fu <i>et al</i> ^[74]
		miR-1	FOXC1	Promotes HCC cell proliferation, migration, and invasion	Su <i>et al</i> ^[75]
		miR-214-3p	FLOT1	Promotes HCC cell proliferation, migration, and invasion	Liu <i>et al</i> ^[77]
<i>MEG3</i>	Down-regulated	miR-23b-3p	ZEB1	Promotes HCC invasion and metastasis	Yang <i>et al</i> ^[78]
		miR-483-3p	ERp29	Inhibits glycolysis	Li <i>et al</i> ^[29]
		miR-9-5p	SOX11	Promotes HCC cell apoptosis and inhibits cell growth	Liu <i>et al</i> ^[93]
<i>NEAT1</i>	Up-regulated	miRNA-10a-5p	PTEN	Inhibits HCC cell proliferation, migration, and invasion	Zhang <i>et al</i> ^[94]
		miR-155	Tim-3	Facilitates CD8+T cells-mediated immune escape	Yan <i>et al</i> ^[35]
		miR-335	c-Met-Akt pathway	Enhances HCC resistance to sorafenib	Chen <i>et al</i> ^[130]
<i>FENDRR</i>	Down-regulated	miR-423-5p	<i>GADD45β</i>	Suppresses Treg-mediated immune escape	Yu <i>et al</i> ^[38]
<i>PVT1</i>	Up-regulated	miR-365	ATG3	Promotes autophagy	Yang <i>et al</i> ^[44]
<i>HNF1A-AS1</i>	Up-regulated	hsa-miR-30b-5p	ATG5	Stimulates autophagy	Liu <i>et al</i> ^[45]
<i>CCAT1</i>	Up-regulated	miR-181a-5p	ATG7	Induces autophagy	Guo <i>et al</i> ^[46]
		Let-7	HMGA2 and c-Myc	Promotes HCC cell proliferation and migration	Deng <i>et al</i> ^[81]
		miR-490-3p	CDK1	Promotes HCC cell proliferation and invasion	Dou <i>et al</i> ^[82]
		miR-30c-2-3p	CCNE1	Promotes HCC cell proliferation	Zhang <i>et al</i> ^[83]
		miR-26a-5p	ATG12	Promotes autophagy	Li <i>et al</i> ^[47]
<i>LINC00665</i>	Up-regulated	miR-186-5p	MAP4K3	Facilitates autophagy	Shan <i>et al</i> ^[49]
<i>HULC</i>	Up-regulated	miR-107	SPHK1	Promotes angiogenesis	Lu <i>et al</i> ^[52]
		miR-200a-3p	ZEB1	Enhances EMT and promotes HCC growth and metastasis	Li <i>et al</i> ^[65]
		miR-2052	MET	Promotes HCC cell proliferation, migration, and invasion	Zhang <i>et al</i> ^[66]
		miR-186	HMGA2	Promotes HCC growth and metastasis	Wang <i>et al</i> ^[68]
		miR-372-3p	Rab11a	Promotes HCC growth and metastasis	Cao <i>et al</i> ^[71]
		miR-6825-5p, miR-	USP22	Increases HCC resistance	Xiong <i>et al</i> ^[142]

		6845-5p, and miR-6886-3p		to oxaliplatin	
MALAT1	Up-regulated	miR-3064-5p	FOXA1/CD24/Src pathway	Promotes angiogenesis	Zhang <i>et al</i> ^[53]
		miR-140	VEGF-A	Promotes angiogenesis	Hou <i>et al</i> ^[54]
		miR-124	PI3K/Akt pathway	Enhances HBx-induced CSC properties	He <i>et al</i> ^[59]
		miR-216b	HIF-2 α	Enhances HCC resistance to 5-FU	Yuan <i>et al</i> ^[155]
LINC00488	Up-regulated	miR-330-5p	TLN1	Facilitates angiogenesis	Gao <i>et al</i> ^[55]
DANCR	Up-regulated	miR-214, miR-320a and miR-199a	CTNNB1	Enhances the stemness of HCC cells	Yuan <i>et al</i> ^[61]
ANRIL	Up-regulated	miR-384	STAT3	Promotes HCC cell proliferation, migration, and invasion	Ji <i>et al</i> ^[85]
		miR-122-5p	N/A	Promotes HCC cell proliferation, metastasis, and invasion	Ma <i>et al</i> ^[86]
		miR-144	PBX3	Promotes HCC cell growth, migration, and invasion	Ma <i>et al</i> ^[87]
GAS5	Down-regulated	miR-21	PDCD4 and PTEN	Suppresses HCC cell migration and invasion	Hu <i>et al</i> ^[89]
		miR-135b	RECK	Inhibits HCC invasion	Yang <i>et al</i> ^[90]
		miR-1323	TP53INP1	Inhibits HCC cell proliferation and invasion and promotes apoptosis	Zhang <i>et al</i> ^[91]
		miR-222	N/A	Increases HCC sensitivity to cisplatin	Zhao <i>et al</i> ^[151]
ASB16-AS1	Up-regulated	miR-1827	FZD4 Wnt/ β -catenin pathway	Promotes HCC growth and invasion	Yao <i>et al</i> ^[97]
DSCR8	Up-regulated	miR-485-5p	FZD7 Wnt/ β -catenin pathway	Promotes HCC cell proliferation and cell cycle	Wang <i>et al</i> ^[99]
LINC00662	Up-regulated	miR-15a, miR-16, and miR-107	WNT3A Wnt/ β -catenin pathway	Promotes HCC growth and metastasis	Tian <i>et al</i> ^[101]
SNHG5	Up-regulated	miR-26a-5p	GSK3 β Wnt/ β -catenin pathway	Promotes HCC metastasis and EMT	Li <i>et al</i> ^[103]
SOX9-AS1	Up-regulated	miR-5590-3p	SOX9 Wnt/ β -catenin pathway	Facilitates HCC growth and metastasis	Zhang <i>et al</i> ^[105]
DLGAP1-AS1	Up-regulated	miR-26a-5p and miR-26b-5p	IL-6 JAK2/STAT3 pathway and CDK8/LRP6 Wnt/ β -catenin pathway	Facilitates HCC EMT and progression	Lin <i>et al</i> ^[109]
MIR22HG	Down-regulated	miR-10a-5p	NCoR2 Wnt/ β -catenin pathway	Inhibits HCC growth, migration, and invasion	Wu <i>et al</i> ^[111]
PTTG3P	Up-regulated	miR-383	CCND1/PARP2 and PI3K/Akt pathway	Promotes HCC cell proliferation, migration, and invasion and inhibits apoptosis	Zhou <i>et al</i> ^[115]
DLEU1	Up-regulated	miR-133a	IGF-1R PI3K/AKT pathway	Promotes HCC cell proliferation, migration, and invasion	Zhang <i>et al</i> ^[116]
TCL6	Down-regulated	miR-106a-5p	PTEN PI3K/AKT pathway	Inhibits HCC cell proliferation, migration, and invasion	Luo <i>et al</i> ^[117]
CDKN2B-AS1	Up-regulated	let-7c-5p	NAP1L1 PI3K/AKT/ mTOR pathway	Promote HCC growth and metastasis	Huang <i>et al</i> ^[118]
GAS6-AS2	Up-regulated	miR-493-5p	OTUB1 PI3K-AKT- FoxO3a pathway	Promotes HCC cell proliferation, migration, and invasion	Liang <i>et al</i> ^[119]

SNHG12	Up-regulated	miR-199a/b-5p	MLK3 NF-κB pathway	Promotes HCC cell proliferation and tumorigenicity	Lan <i>et al</i> ^[125]
CASC2	Down-regulated	miR-362-5p	CYLD NF-κB pathway	Inhibits HCC cell migration and invasion	Zhao <i>et al</i> ^[127] ; Ni <i>et al</i> ^[128]
		miR-222	N/A	Enhances HCC sensitivity to cisplatin	Liu <i>et al</i> ^[150]
LINC-ROR	Up-regulated	miR-876-5p	FOXO1	Increases HCC resistance to sorafenib	Zhi <i>et al</i> ^[134]
		miR-145	RAD18	Enhances radiation resistance of HCC cells	Chen <i>et al</i> ^[163]
LINC00160	Up-regulated	miR-132	PIK3R3	Promotes HCC resistance to sorafenib	Zhang <i>et al</i> ^[136]
FOXD2-AS1	Up-regulated	miR-150-5p	TMEM9	Facilitates HCC resistance to sorafenib	Sui <i>et al</i> ^[138]
SNHG3	Up-regulated	miR-128	CD151	Promotes HCC resistance to sorafenib	Zhang <i>et al</i> ^[140]
SNHG16	Up-regulated	miR-140-5p	N/A	Increases HCC resistance to sorafenib	Ye <i>et al</i> ^[141]
		let-7b-5p	N/A	Enhances HCC resistance to oxaliplatin	Li <i>et al</i> ^[149]
NR2F1-AS1	Up-regulated	miR-363	ABCC1	Enhances HCC resistance to oxaliplatin	Huang <i>et al</i> ^[144]
KCNQ1OT1	Up-regulated	miR-7-5p	ABCC1	Increases HCC resistance to oxaliplatin	Hu <i>et al</i> ^[145]
NRAL	Up-regulated	miR-340-5p	Nrf2	Facilitates HCC resistance to cisplatin	Wu <i>et al</i> ^[147]
LINC01234	Up-regulated	miR-31-5p	MAGEA3	Promotes HCC resistance to cisplatin	Chen <i>et al</i> ^[148]
CRNDE	Up-regulated	miR-33a	HMGA2	Promotes HCC resistance to 5-FU	Han <i>et al</i> ^[152]
KRAL	Down-regulated	miR-141	Keap1	Reverses HCC resistance to 5-FU	Wu <i>et al</i> ^[158]
NEAT1_2	Up-regulated	miR-101-3p	WEE1	Enhances radio-resistance of HCC cells	Chen <i>et al</i> ^[160]
LINC00473	Up-regulated	miR-345-5p	FOXO1	Promotes radio-resistance of HCC cells	Zhang <i>et al</i> ^[165]

HCC: Hepatocellular carcinoma; LncRNAs: Long noncoding RNAs; ceRNA: Competitive endogenous RNA; RAET1K: Retinoic acid early transcript 1K; LDHA: Lactate dehydrogenase isoform A; TUG1: Taurine up-regulation gene 1; HK2: Hemikinasin 2; HOTAIR: Homeobox transcript antisense RNA; HIF1: Hypoxia-inducible factor 1; Bmi-1: B lymphoma moloney murine leukemia virus insertion region 1; FOXC1: Forkhead box C1; FLOT1: Flotillin 1; ZEB1: Zinc finger E-box binding homeobox 1; MEG3: Maternally expressed gene 3; ERp29: ER protein 29; SOX11: SRY-related HMG-box transcription factor 11; PTEN: Phosphatase and tensin homolog; NEAT1: Nuclear enriched abundant transcript 1; Tim-3: T cell immunoglobulin mucin-3; FENDRR: Fetal-lethal noncoding developmental regulatory RNA; GADD45β: Growth arrest and DNA damage-inducible beta; PVT1: Plasmacytoma variant translocation 1; ATG3: Autophagy related genes 3; HNF1A-AS1: HNF1A antisense RNA 1; ATG5: Autophagy related genes 5; CCAT1: Colon cancer associated transcript 1; ATG7: Autophagy related genes 7; HMGA2: High mobility group AT-hook 2; CDK1: Cyclin-dependent kinase 1; CCNE1: Cyclin E1; HCG11: HLA complex group 11; ATG12: Autophagy related genes 12; LINC00665: Long intergenic non-protein coding RNA 665; MAP4K3: Mitogen-activated protein kinase kinase kinase kinase 3; HULC: Highly upregulated in liver cancer; SPHK1: Sphingosine kinase 1; MET: Hepatocyte growth factor receptor; Rab11a: Member RAS oncogene family; USP22: Ubiquitin-specific peptidase 22; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; FOXA1: Forkhead box A1; VEGF-A: Vascular endothelial growth factor A; PI3K/Akt pathway: Phosphoinositide-3-kinase/protein kinase B; CSC: Liver cancer stem cell; HIF-2α: Hypoxia-inducible factor 2α; TLN1: Talin 1; DANCER: Differentiation antagonizing non-protein coding RNA; CTNNB1: Catenin beta-1; ANRIL: Antisense noncoding RNA in the INK4 locus; STAT3: Signal transducer and activator of transcription 3; N/A: Not available; PBX3: Pre-B-cell leukemia homeobox 3; GAS5: Growth arrest-specific 5; PDCD4: Programmed cell death 4; RECK: Cysteine-rich protein with Kazal motifs; TP53INP1: Tumor protein p53-induced nuclear protein 1; ASB16-AS1: ASB16 antisense RNA 1; FZD4: Frizzled 4; DSCR8: Down syndrome critical region 8; FZD7: Frizzled-7; WNT3A: Wingless-type MMTV integration site family 3A; SNHG5: Small nucleolar RNA host gene 5; GSK3β: Glycogen synthase kinase 3β; EMT: Epithelial-mesenchymal transition; SOX9-AS1: SOX9 antisense RNA 1; SOX9: Sex determining region Y-box 9; DLGAP1-AS1: Long noncoding RNA DLGAP1 antisense RNA 1; IL-6: Interleukin-6; JAK2: Janus kinase 2; CDK8: Cyclin-dependent kinase 8; LRP6: Low-density lipoprotein receptor-related protein 6; MIR22HG: MIR22 host gene; NCOAR2: Nuclear receptor corepressor 2; PTTG3P: Pituitary tumor-transforming 3; CCND1: Cyclin D1; PARP2: Poly ADP-ribose polymerase 2; DLEU1: Deleted in lymphocytic leukaemia 1; IGF-1R: Insulin-like growth factor 1 receptor; TCL6: T cell leukemia/lymphoma 6; CDKN2B-AS1: CDKN2B antisense RNA 1; NAP1L1: Nucleosome assembly protein 1 like 1; mTOR: Mammalian rapamycin; GAS6-

AS2: Growth arrest specific 6 antisense RNA 2; OTUB1: OTU domain-containing ubiquitin aldehyde-binding protein 1; FOXO3a: Forkhead Box O3a; SNHG12: Small nucleolar RNA host gene 12; MLK3: Mixed-lineage kinase 3; NF- κ B: Nuclear factor kappa-B; CASC2: Cancer susceptibility candidate 2; CYLD: Cylindromatosis; LINC-ROR: Intergenic non-protein coding RNA, regulator of reprogramming; FoxM1: Forkhead box M1; RAD18: A RING-type ubiquitin ligase E3; PIK3R3: Phosphoinositide-3-kinase regulatory subunit 3; FOXD2-AS1: FOXD2 adjacent opposite strand RNA 1; TMEM9: Transmembrane protein 9; SNHG3: Small nucleolar RNA host gene 3; SNHG16: Small nucleolar RNA host gene 16; NR2F1-AS1: NR2F1 antisense RNA 1; ABCC1: Multidrug resistance-associated protein 1; KCNQ1OT1: KCNQ1 overlapping transcript 1; NRAL: Nrf2 regulation-associated lncRNA; Nrf2: Nuclear factor erythroid-2-related factor 2; MAGEA3: Melanoma-associated antigen A3; CRNDE: Colorectal neoplasia differentially expressed; KRAL: Keap1 regulation-associated lncRNA; Keap1: Kelch-like ECH-associated protein 1; NEAT1_2: Nuclear enriched abundant transcript 1_2; WEE1: WEE1 G2 checkpoint kinase; FOXF1: Forkhead box protein P1.

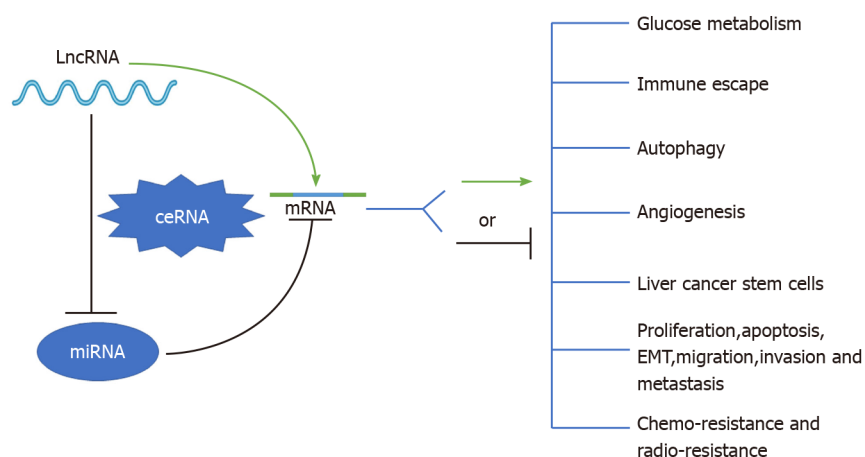


Figure 1 Schematic diagram of the role of long noncoding RNA-mediated competitive endogenous RNA regulatory network in hepatocellular carcinoma. See the text for details. LncRNA: Long noncoding RNA; ceRNA: Competing endogenous RNA; miRNA: MicroRNA; mRNA: Messenger RNA; EMT: Epithelial-mesenchymal transition.

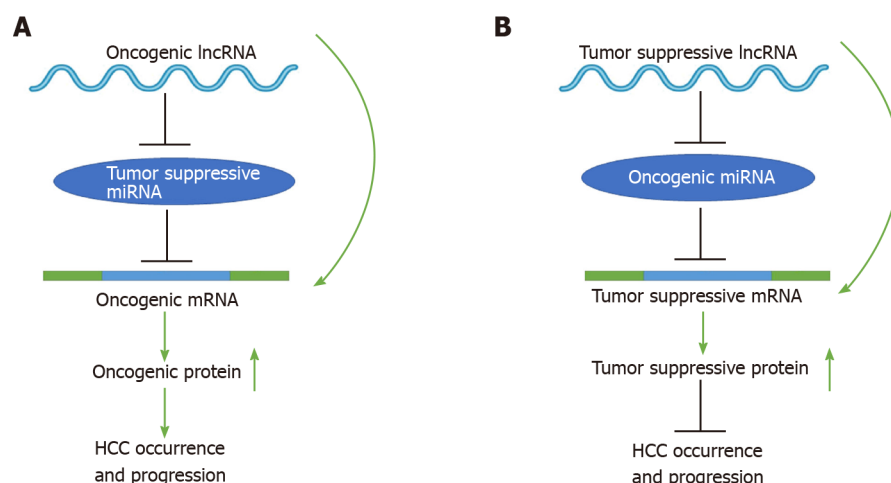


Figure 2 Schematic diagrams of long noncoding RNA-mediated competitive endogenous RNA regulatory network that mediates the occurrence and progression of hepatocellular carcinoma. See the text for details. LncRNA: Long noncoding RNA; miRNA: MicroRNAs; mRNA: Messenger RNA.

the above findings suggest that the lncRNA-mediated ceRNA network could provide new ideas for inhibiting glycolysis in HCC.

Immune escape

Tumor immune escape refers to the phenomenon that tumor cells can survive and proliferate by escaping immune system-mediated recognition and attack by changing themselves or their tumor microenvironment^[30]. Currently, the effectiveness of immunotherapy is limited by tumor immune escape. Thus, an in-depth exploration of the mechanisms of tumor immune escape may provide novel insights into tumor

immunotherapy. Current studies have shown that lncRNAs can modulate immune escape in HCC by acting as ceRNAs of miRNAs, among which oncogenic lncRNAs that function as ceRNAs can promote the immune escape of HCC cells. For example, *NEAT1*, a newly discovered oncogenic lncRNA, is specifically localized in nuclear paraspeckles and participates in paraspeckle formation and the transcriptional regulation of many genes^[31,32]. T cell immunoglobulin mucin-3 (Tim-3), an immune checkpoint molecule, can suppress the immune response^[33], and the increased expression of Tim-3 within the tumor can inactivate killer T cells, thus preventing the death of tumor cells^[34]. Mechanistically, *NEAT1* facilitates the CD8⁺ T cell-mediated immune escape of HCC cells by acting as a ceRNA for miR-155 to enhance Tim-3 expression^[35]. Conversely, tumor suppressive lncRNAs that act as ceRNAs can inhibit the immune escape of HCC cells. For instance, *GADD45β*, a tumor suppressor, is associated with antitumor immune responses^[36], and CD4⁺ T cells lacking *GADD45β* are less responsive to the stimulation of T cell receptors or inflammatory cytokines^[37]. *FENDRR*, a tumor suppressor lncRNA, upregulates *GADD45β* by sponging miR-423-5p, thereby suppressing the immune escape of HCC cells^[38]. These findings suggest that the lncRNA-mediated ceRNA network is involved in mediating immune evasion in HCC and thus may be a promising therapeutic target for HCC immunotherapy.

Autophagy

Autophagy is closely associated with the development of malignant tumors and can promote tumor survival and proliferation by regulating interactions between the tumor and tumor microenvironment^[39]. In HCC, autophagy plays a vital role in tumor immunity, oxidative stress, and the maintenance of hepatic homeostasis and thus participates in HCC initiation and progression and resistance to chemotherapy drugs^[40]. Identification of the mechanisms by which autophagy is activated in HCC will help clarify HCC pathogenesis and reveal novel treatments for HCC patients. Numerous investigations have indicated that oncogenic lncRNAs that function as ceRNAs are required for promoting autophagy in HCC. For example, autophagy-related genes 3, 5, 7, and 12 (*ATG3*, *ATG5*, *ATG7*, and *ATG12*, respectively) are major regulators of the induction of autophagosome formation^[41-43]. The lncRNA *PVT1* promotes autophagy in HCC by enhancing *ATG3* expression by sponging miR-365^[44]. The lncRNA *HNF1A-AS1* upregulates the expression of *ATG5* in HCC by acting as a sponge of hsa-miR-30b-5p, thus stimulating autophagy^[45]. The lncRNA *CCAT1* serves as a ceRNA for miR-181a-5p to induce autophagy in HCC by enhancing *ATG7* expression^[46]. The lncRNA *HCG11* promotes autophagy in HCC by enhancing *ATG12* expression by sponging miR-26a-5p^[47]. In addition, mitogen-activated protein kinase kinase kinase 3 (MAP4K3), an upstream kinase of the MAPK pathway, is a key node in the regulation of autophagy^[48]. The lncRNA *LINC00665* facilitates autophagy by sponging miR-186-5p to enhance MAP4K3 expression^[49]. Collectively, these results suggest that the lncRNA-mediated ceRNA network could provide novel treatments for HCC patients.

Angiogenesis

Angiogenesis is responsible for HCC growth, proliferation, invasion, and metastasis^[50]. The mechanisms underlying HCC angiogenesis are complex, and exploration of the factors involved in regulating HCC angiogenesis is of great significance for improving antiangiogenic treatments for HCC. Emerging evidence indicates that oncogenic lncRNAs that act as ceRNAs are tightly linked to HCC angiogenesis. For instance, sphingosine kinase 1 (SPHK1), a key metabolic enzyme, is correlated with tumor angiogenesis^[51]. A study found that the lncRNA *HULC* promotes angiogenesis by upregulating SPHK1 in HCC; *HULC* acts as a ceRNA to increase the expression of transcription factor E2F1 by competitively binding to miR-107 and subsequently results in the activation of the *SPHK1* promoter, thus promoting HCC angiogenesis *in vivo*^[52]. In addition, the lncRNA *MALAT1* can promote HCC angiogenesis by sponging miR-3064-5p to activate the forkhead box A1 (FOXA1)/CD24/Src pathway^[53] or by functioning as a miR-140 sponge to enhance vascular endothelial growth factor A expression^[54]. Similarly, *LINC00488*, another lncRNA, upregulates the expression of talin 1 to facilitate HCC angiogenesis by sponging miR-330-5p^[55]. These findings suggest that the lncRNA-mediated ceRNA network may be a promising target for antiangiogenic therapies for HCC.

Liver cancer stem cells

LCSCs exhibit high proliferation, self-renewal, high tumorigenicity, chemoresistance, and radioresistance^[56-58], and their abundance is positively associated with the degree

of HCC malignancy. Elucidation of the regulatory mechanisms of LCSCs will contribute to our understanding of the pathogenesis of HCC and the identification of novel therapeutic strategies. Existing evidence has shown that oncogenic lncRNAs help sustain cancer stem cell (CSC) traits by acting as ceRNAs for miRNAs to initiate HCC development. For instance, the lncRNA *MALAT1* activates the phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) pathway by acting as a miR-124 sponge to enhance HBx-induced CSC properties^[59]. In addition, catenin beta-1 (CTNNB1)/ β -catenin sustains the stemness properties of LCSCs^[60]. In another recent study, it was found that the lncRNA *DANCR* was highly expressed in HCC tissues and stem-like HCC cells; *DANCR* can act as a ceRNA to enhance CTNNB1 expression by sponging miR-214, miR-320a, and miR-199a, thereby enhancing the stemness of HCC cells^[61]. Thus, the lncRNA-mediated ceRNA network may serve as a potential therapeutic target for LCSCs.

Proliferation, migration, EMT, invasion, and metastasis

The lncRNA-mediated ceRNA regulatory network functions by regulating miRNA target genes: lncRNAs acting as ceRNAs can participate in cell proliferation, apoptosis, migration, EMT, invasion, and metastasis by modulating mRNAs in HCC. Currently, there are many lncRNA-miRNA-miRNA target gene (mRNA) networks reported in HCC. In this review, we provide only a few examples of lncRNA-miRNA-mRNA networks, including those involving oncogenic lncRNAs such as *HULC*, *HOTAIR*, *CCAT*, and *ANRIL* and tumor suppressive lncRNAs such as *GAS5* and *MEG3*.

lncRNA *HULC*-miRNA-mRNA: *HULC* has been identified as a specifically highly expressed lncRNA in HCC^[62]. In a recent study, high *HULC* expression in HCC was significantly connected to increased lymph node metastasis and advanced TNM stage^[63]. This finding indicates that *HULC* can facilitate the proliferation, migration, invasion, and metastasis of HCC cells, leading to the malignant development of HCC. Thus far, it has been reported that *HULC* may exert its oncogenic function in HCC through diverse molecular mechanisms, of which the *HULC*-mediated ceRNA network is important. For instance, zinc finger E-box binding homeobox 1 (ZEB1), a key regulator of EMT, contributes to HCC cell invasion and metastasis^[64]. As a ceRNA of miR-200a-3p, *HULC* increases the expression of ZEB1, thereby enhancing EMT and promoting HCC growth and metastasis^[65]. In addition, *HULC* can enhance the expression of hepatocyte growth factor receptor (MET) by sponging miR-2052, thus promoting HCC cell proliferation, migration, and invasion^[66]. High mobility group AT-hook 2 (*HMGA2*), an oncogene, has been shown to be closely associated with cancer progression and metastasis^[67]. *HULC* promotes HCC growth and metastasis by enhancing *HMGA2* expression by acting as a ceRNA of miR-186^[68]. Rablla, a central regulatory protein, promotes exosome secretion, and exosomes significantly promote HCC progression^[69,70]. A mechanistic investigation revealed that *HULC* increases RAS oncogene family member expression to induce exosome secretion by sponging miR-372-3p, contributing to HCC growth and metastasis^[71].

lncRNA *HOTAIR*-miRNA-mRNA: The lncRNA *HOTAIR* has been reported to exert an oncogenic role in a variety of malignances^[72,73]. Emerging evidence suggests that *HOTAIR* functions as a ceRNA and facilitates HCC cell proliferation, migration, invasion, and metastasis. For instance, a study confirmed that *HOTAIR* promotes HCC cell proliferation and tumorigenicity by competitively binding to miR-218 to activate B lymphoma Moloney murine leukemia virus insertion region 1 expression and inactivate P16^{Ink4a} and P14^{ARF}^[74]. Another study also demonstrated that Forkhead box C1-activated *HOTAIR* promotes HCC cell proliferation, migration, and invasion by acting as a sponge of miR-1^[75]. In addition, flotillin 1 (FLOT1), a marker of lipid rafts, is highly expressed in HCC and contributes to aggressive tumor characteristics^[76]. *HOTAIR* enhances FLOT1 expression by sponging miR-214-3p, thereby promoting HCC cell proliferation, migration, and invasion^[77]. Additionally, *HOTAIR* promotes HCC cell invasion and metastasis by sponging miR-23b-3p to upregulate ZEB1 expression^[78].

lncRNA *CCAT*-miRNA-mRNA: The lncRNA *CCAT1* is located on chromosome 8q24.21 and plays vital roles in promoting HCC cell proliferation and metastasis^[79]. *CCAT1* has been shown to upregulate the expression of its downstream gene *c-Myc*, thereby promoting tumorigenesis^[80]. Subsequently, many studies have explored the potential mechanism by which *CCAT1* upregulates *c-Myc* to promote tumorigenesis. In HCC, *CCAT1* functions as a ceRNA of miRNA let-7, thus counteracting the inhibitory effect of Let-7 on its target genes, *HMGA2* and *c-Myc*, which upregulates the

expression of *HMGA2* and *c-Myc* and ultimately facilitates HCC proliferation and migration^[81]. In addition, *CCAT1* upregulates cyclin-dependent kinase 1 expression by acting as a miR-490-3p sponge, thereby promoting HCC cell proliferation and invasion^[82]. Furthermore, *CCAT1* acts as a sponge of miR-30c-2-3p to upregulate the expression of cyclin E1, leading to HCC cell proliferation^[83].

lncRNA ANRIL-miRNA-mRNA: The lncRNA *ANRIL* is located on chromosome 9p21 and plays an oncogenic role in tumorigenesis^[84]. *ANRIL* functions as a ceRNA to sponge miRNAs, thereby regulating gene expression in HCC. The high expression of *ANRIL* in HCC is related to HCC cell proliferation, migration, and invasion; mechanistically, *ANRIL* exerts its biological action in HCC by sponging miR-384 to upregulate signal transducer and activator of transcription 3 (STAT3) expression^[85]. *ANRIL* can also promote HCC cell proliferation, metastasis, and invasion by acting as a ceRNA of miR-122-5p^[86]. In addition, *ANRIL* can upregulate the expression of pre-B-cell leukemia homeobox 3 by sponging miR-144 to facilitate HCC cell growth, migration, and invasion^[87].

lncRNA GAS5-miRNA-mRNA: The lncRNA *GAS5* is downregulated in diverse malignancies, including HCC^[88]. Increasing evidence indicates that the *GAS5*-mediated ceRNA network may be one of the important mechanisms by which *GAS5* exerts its biological functions in HCC. For example, *GAS5* restrains HCC cell migration and invasion by sponging miR-21 to upregulate its targets, programmed cell death 4 and phosphatase and tensin homolog (PTEN)^[89]. In addition, *GAS5* suppresses HCC invasion by sponging miR-135b to enhance cysteine-rich protein with Kazal motifs expression^[90]. *GAS5* also functions as a miR-1323 sponge to upregulate tumor protein p53-induced nuclear protein 1 expression, thus inhibiting HCC cell proliferation and invasion and promoting apoptosis^[91].

lncRNA MEG3-miRNA-mRNA: *MEG3* is an imprinted gene and a tumor suppressive lncRNA. *MEG3* is inversely related to tumorigenesis and plays an inhibitory role in many malignancies^[92]. Acting as a ceRNA against miRNA is an important mechanism of action of *MEG3* in HCC. For example, the overexpression of *MEG3* can promote cell apoptosis and inhibit HCC growth by upregulating SRY-related HMG-box transcription factor 11 expression by acting as an miR-9-5p sponge^[93]. In addition, *MEG3* enhances the expression of PTEN to restrain HCC cell proliferation, migration, and invasion by sponging miRNA-10a-5p^[94].

The lncRNA-mediated ceRNA regulatory network functions by modulating signaling pathways: lncRNAs acting as ceRNAs can also participate in HCC cell proliferation, migration, EMT, invasion, and metastasis by modulating various signaling pathways in HCC, including the Wnt/ β -catenin pathway, PI3K/AKT pathway, and nuclear factor kappa-B (NF- κ B) pathway.

Wnt/ β -catenin pathway: Abnormal activation of the Wnt/ β -catenin pathway, a key event implicated in HCC carcinogenesis, is believed to be a key target for the clinical diagnosis and treatment of HCC^[95]. Thus, elucidation of the regulatory mechanisms of the Wnt/ β -catenin pathway will provide new insights into a new anticancer therapy for HCC. Extensive evidence to date has indicated that lncRNAs can mediate the Wnt/ β -catenin pathway by acting as ceRNAs of miRNAs, thereby modulating HCC cell proliferation and invasion; oncogenic lncRNAs that act as ceRNAs can perform their biological actions by activating the Wnt/ β -catenin pathway in HCC. For example, frizzled (FZD) 4, a Wnt receptor, can activate the Wnt/ β -catenin pathway in HCC^[96], and the lncRNA *ASB16-AS1* enhances FZD4 expression to activate the Wnt/ β -catenin pathway by acting as a miR-1827 sponge and subsequently facilitates HCC growth and invasion^[97]. Likewise, another Wnt receptor, FZD7, can also activate the Wnt/ β -catenin pathway in HCC^[98]. The lncRNA *DSCR8* activates the Wnt/ β -catenin pathway by enhancing FZD7 expression by acting as a miR-485-5p sponge to facilitate HCC cell proliferation and the cell cycle^[99]. Wingless-type MMTV integration site family 3A (WNT3A) is one of the crucial components of the Wnt/ β -catenin pathway related to HCC progression^[100], and the lncRNA *LINC00662* activates the Wnt/ β -catenin pathway by enhancing WNT3A expression *via* the competitive sponging of miR-15a, miR-16, and miR-107, thereby promoting HCC growth and metastasis^[101]. Glycogen synthase kinase 3 β (GSK3 β) is a pivotal regulator of β -catenin signaling^[102], and the lncRNA *SNHG5* acts as a miR-26a-5p sponge to enhance GSK3 β expression, thereby activating the Wnt/ β -catenin pathway to facilitate HCC metastasis and EMT^[103]. In addition, sex determining region Y-box (SOX) 9 can activate the Wnt/ β -catenin pathway in HCC^[104], and the lncRNA *SOX9-AS1* facilitates HCC growth and

metastasis by increasing SOX9 expression to activate the Wnt/ β -catenin pathway by acting as a miR-5590-3p sponge^[105]. In HCC, interleukin (IL)-6 is associated with the activation of Janus kinase 2 (JAK2)/STAT3 signaling^[106]; cyclin-dependent kinase (CDK) 8 and low-density lipoprotein receptor-related protein 6 (LRP6) are associated with the activation of Wnt/ β -catenin signaling^[107,108], and the lncRNA *DLGAP1-AS1* increases the expression of IL-6 and CDK8/LRP6 by functioning as a sponge of miR-26a-5p and miR-26b-5p, thereby activating JAK2/STAT3 and Wnt/ β -catenin signaling to facilitate EMT and the progression of HCC, respectively^[109]. Instead, tumor suppressive lncRNAs that act as ceRNAs function by inactivating Wnt/ β -catenin signaling in HCC. For example, in HCC, nuclear receptor corepressor 2 is associated with inhibition of the activation of Wnt/ β -catenin signaling^[110]. *MIR22HG*, a tumor suppressive lncRNA, increases NCOR2 expression by sponging miR-10a-5p, thereby inactivating Wnt/ β -catenin signaling to inhibit HCC cell growth, migration, and invasion^[111]. The abovementioned findings suggest that different lncRNA-mediated ceRNA networks can exert their biological functions in HCC by mediating the Wnt/ β -catenin pathway; these networks may become effective therapeutic targets for treating HCC patients.

PI3K/AKT pathway: PI3K/AKT, a highly activated pathway in HCC, is implicated in HCC carcinogenesis and chemoresistance^[112-114]. At present, emerging evidence indicates that multiple lncRNA-mediated ceRNA networks can exert their biological functions by modulating the PI3K/AKT pathway, among which oncogenic lncRNAs that act as ceRNAs exert their biological function by activating the PI3K/AKT pathway in HCC. For instance, the lncRNA *PTTG3P* facilitates the proliferation, migration, and invasion and inhibits the apoptosis of HCC cells by increasing the expression of cyclin D1/poly ADP-ribose polymerase 2 and activating the PI3K/Akt pathway by acting as a ceRNA of miR-383^[115]. Similarly, the lncRNA *DLEU1* activates the PI3K/Akt pathway by increasing insulin-like growth factor 1 receptor-1R expression by sponging miR-133a, thereby facilitating HCC cell proliferation, migration and invasion^[116]. By contrast, tumor suppressive lncRNAs that act as ceRNAs can exert their biological function by inactivating the PI3K/Akt pathway in HCC. For instance, *TCL6*, a tumor suppressive lncRNA, upregulates PTEN expression by sponging miR-106a-5p to suppress the PI3K/AKT pathway, thereby inhibiting HCC cell proliferation, migration, and invasion^[117]. Intriguingly, several oncogenic lncRNAs that act as ceRNAs have been reported to exert their biological functions by activating the PI3K/AKT/mammalian rapamycin (mTOR) or PI3K/AKT/FoxO3a pathway in HCC. For example, the lncRNA *CDKN2B-AS1*, an oncogenic lncRNA, enhances nucleosome assembly protein 1 like 1 expression by acting as a ceRNA of let-7c-5p, thus activating the PI3K/AKT/mTOR pathway to promote HCC cell growth and metastasis^[118]. In addition, the lncRNA *GAS6-AS2* activates the PI3K/AKT/FoxO3a pathway by upregulating OTU domain-containing ubiquitin aldehyde-binding protein 1 expression by sponging miR-493-5p, which promotes HCC cell proliferation, migration, and invasion^[119]. In short, the lncRNA-miRNA-PI3K/AKT, PI3K/AKT/mTOR or PI3K-AKT-FoxO3a regulatory network is expected to be a potential therapeutic target for the treatment of HCC patients.

NF- κ B pathway: Numerous studies have shown that abnormal activation of the NF- κ B pathway is related to HCC growth, EMT, and invasion^[120-122]. Existing evidence suggests that lncRNAs can act as miRNA sponges and exert their biological function by mediating the NF- κ B pathway in HCC, among which oncogenic lncRNAs that act as ceRNAs can exert their biological function by activating the NF- κ B pathway in HCC. For example, in the NF- κ B pathway, mixed-lineage kinase (MLK) 3 contributes to cancer migration, invasion, and metastasis^[123,124], and the lncRNA *SNHG12* enhances MLK3 expression by competitively sponging miR-199a/b-5p, thereby activating the NF- κ B pathway to promote HCC proliferation and tumorigenicity^[125]. By contrast, a tumor suppressive lncRNA that acts as a ceRNA can exert its biological function by inactivating the NF- κ B pathway in HCC. For example, *CYLD*, a tumor suppressor, can negatively regulate the NF- κ B pathway in HCC^[126], and the lncRNA *CASC2*, a tumor suppressive lncRNA, suppresses the NF- κ B pathway by enhancing *CYLD* expression by sponging miR-362-5p, thereby inhibiting HCC cell migration and invasion^[127,128]. These findings indicate that the lncRNA-miRNA-NF- κ B pathway network may serve as a therapeutic target for patients with HCC.

Chemoresistance and radioresistance

Although current chemotherapy and radiotherapy regimens can prolong the survival of HCC patients, tumor recurrence and metastasis due to chemoresistance and

radioresistance lead to unsatisfactory long-term efficacy. The underlying mechanisms of therapeutic resistance in HCC are still unclear, and the exploration of such mechanisms will help improve the current treatment of HCC. Emerging evidence suggests that lncRNAs play a critical role in mediating chemoresistance and radioresistance by acting as ceRNAs of miRNAs in HCC.

Currently, the lncRNA-mediated ceRNA network has been proven to mediate HCC resistance to chemotherapy drugs, including sorafenib, oxaliplatin, cisplatin, and 5-fluorouracil (5-FU). Exploration of the resistance mechanisms to chemotherapy drugs in the treatment of HCC will provide new insights into overcoming chemoresistance.

Sorafenib has been approved for treating advanced HCC; however, the emergence of sorafenib resistance has affected the efficacy of HCC treatment. Existing studies have shown that the lncRNA-mediated ceRNA network is responsible for HCC resistance to sorafenib. Specifically, oncogenic lncRNAs that act as ceRNAs can enhance HCC resistance to sorafenib. For example, activation of the c-Met-Akt pathway can promote sorafenib resistance in HCC cells^[129], and the lncRNA *NEAT1* activates the c-Met-Akt pathway by sponging miR-335 to enhance sorafenib resistance in HCC cells^[130]. In addition, recent studies have suggested that the abnormal activation or expression of forkhead box M1 (FoxM1) contributes to chemotherapy resistance in various cancer cells^[131,132]. In HCC cells, FoxM1 knockout sensitizes drug-resistant HCC cells to sorafenib^[133], and the lncRNA *LINC-ROR* increases sorafenib resistance in HCC cells by elevating FOXM1 expression by sponging miR-876-5p^[134]. Phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3), a regulatory subunit of PI3K, activates the PI3K/AKT pathway to enhance the resistance of HCC cells to sorafenib-induced apoptosis^[135], and the lncRNA *LINC00160* acts as a miR-132 sponge to promote sorafenib resistance by increasing PIK3R3 expression in HCC cells^[136]. Transmembrane protein 9 (TMEM9) plays a vital role in HCC cell growth^[137], and the lncRNA *FOX2-AS1* upregulates TMEM9 expression by sponging miR-150-5p to facilitate the resistance of HCC cells to sorafenib^[138]. The tetraspanin protein CD151 has been shown to attenuate drug-induced apoptosis in cancer cell lines^[139], and the lncRNA *SNHG3* enhances CD151 expression by acting as a ceRNA for miR-128 to promote HCC resistance to sorafenib^[140]. Additionally, the lncRNA *SNHG16* is upregulated in sorafenib-resistant HCC cells, and *SNHG16* increases sorafenib resistance partly by competitively sponging miR-140-5p^[141].

Oxaliplatin has been approved for the treatment of patients with locally advanced and metastatic HCC who are not eligible for surgical resection or local treatment; however, oxaliplatin resistance affects the efficacy of HCC treatment. The lncRNA-mediated ceRNA network has been confirmed to modulate oxaliplatin resistance in HCC. In particular, oncogenic lncRNAs that act as ceRNAs can enhance HCC resistance to oxaliplatin. For instance, *HULC* can upregulate the expression of the ubiquitin-specific peptidase 22 (USP22) protein by suppressing miR-6825-5p, miR-6845-5p, and miR-6886-3p at the epigenetic or transcriptional level in HCC cells; USP22 enhances the *HULC*-induced deubiquitination of Sirt1 and stabilizes it, and Sirt1 stability induces the autophagy of HCC cells, thus increasing the resistance of HCC cells to oxaliplatin^[142]. Multidrug resistance-associated protein 1 (ABCC1) is indicative of chemotherapy resistance^[143], and the lncRNA *NR2F1-AS1* elevates ABCC1 expression by sponging miR-363 to enhance oxaliplatin resistance in HCC cells^[144]. Similarly, the lncRNA *KCNQ10T1* increases oxaliplatin resistance in HCC cells by sponging miR-7-5p to elevate ABCC1 expression^[145].

The antitumor efficacy of cisplatin in the treatment of advanced HCC patients is unsatisfactory due to drug resistance. The lncRNA-mediated ceRNA network has been demonstrated to modulate cisplatin resistance in HCC, among which oncogenic lncRNAs that act as ceRNAs can enhance HCC resistance to cisplatin. For example, nuclear factor erythroid-2-related factor 2 (Nrf2) is upregulated in HepG2/cisplatin cells and mediates the chemoresistance of HCC cells to cisplatin^[146]. The lncRNA *NRAL* increases Nrf2 expression by sponging miR-340-5p, thereby facilitating cisplatin resistance in HCC cells^[147]. Melanoma-associated antigen A3 (MAGEA3) enhances chemoresistance to cisplatin in HepG2 cells, and the lncRNA *LINC01234* enhances MAGEA3 expression by sponging miR-31-5p to promote cisplatin resistance in HCC^[148]. The lncRNA *SNHG16* enhances cisplatin resistance in HCC cells by sponging let-7b-5p^[149]. Conversely, tumor suppressive lncRNAs that act as ceRNAs can reduce HCC resistance to cisplatin. For example, the overexpression of *CASC2*, a tumor suppressor lncRNA, strengthens cisplatin sensitivity in HCC cells by sponging miR-222^[150]. In addition, the overexpression of *GAS5*, another tumor suppressor lncRNA, enhances the sensitivity of HCC cells to cisplatin by sponging miR-222^[151].

The inhibitory efficacy of 5-FU on HCC cells is limited by chemical resistance. Emerging evidence indicates that the lncRNA-mediated ceRNA network is correlated

with 5-FU resistance in HCC cells, among which oncogenic lncRNAs that act as ceRNAs can enhance HCC resistance to 5-FU. For example, the lncRNA *CRNDE* acts as a ceRNA of miR-33a in HCC to enhance HMGA2 expression, thereby promoting chemoresistance to 5-FU in HCC cells^[152]. HIF-2 α is related to the resistance of HCC cells to doxorubicin and sorafenib^[153,154], and the lncRNA *MALAT1* acts as a ceRNA to increase HIF-2 α expression by competitively sponging miR-216b, leading to the enhanced chemoresistance of HCC cells to 5-FU^[155]. In contrast, tumor suppressive lncRNAs that act as ceRNAs can reduce HCC resistance to 5-FU. For example, Kelch-like ECH-associated protein 1 (Keap1) inactivation enhances the resistance of HCC cells to chemotherapy drugs such as sorafenib^[156,157], and the overexpression of *KRAL*, a tumor suppressive lncRNA, enhances Keap1 expression by functioning as a ceRNA for miR-141 to reverse the resistance to 5-FU in HCC cell lines^[158].

Currently, an oncogenic lncRNA-mediated ceRNA network has been demonstrated to enhance HCC resistance to radiation therapy. For instance, AZD1775, an inhibitor of WEE1, has been reported to sensitize HCC cells to radiation^[159], suggesting that WEE1 can enhance radioresistance in HCC. The lncRNA *NEAT1_2* upregulates WEE1 expression by acting as a ceRNA for miR-101-3p to reduce the radiosensitivity of HCC^[160]. A RING-type ubiquitin ligase E3 (RAD18), an E3 ubiquitin-linked enzyme, can induce radiation resistance in glioma cells^[161,162]. The lncRNA *LINC-ROR* competes with sponge miR-145 to increase RAD18 expression, thereby enhancing the radiation resistance of HCC cells^[163]. Forkhead box protein P1 (FOXP1), a transcription factor, attenuates radioresistance in cervical cancer^[164]. The lncRNA *LINC00473* promotes radioresistance in HCC by increasing FOXP1 expression by sponging miR-345-5p^[165]. These findings suggest that the lncRNA-mediated ceRNA network may provide new clues for overcoming radioresistance in HCC.

PROBLEMS AND PERSPECTIVES

The lncRNA-mediated ceRNA regulatory network provides a new mode of posttranscriptional regulation and plays a critical role in the initiation and progression of HCC. Nevertheless, investigations into the detailed mechanism of the ceRNA network and its relationship with HCC are still in the preliminary stage. Although there are increasing reports about lncRNAs as ceRNAs in HCC, several fundamental problems facing these studies need to be addressed. First, information on the roles of lncRNAs that act as ceRNAs in current studies is derived from overexpression and/or knockout experiments, and only when the abundance of lncRNAs is remarkably high can lncRNAs act as ceRNAs. As a result, the abundance of artificially controlled lncRNAs often far exceeds the abundance range of any endogenous lncRNA. Therefore, it is urgent to verify whether the lncRNA-mediated ceRNA network has the same effects under normal cellular conditions. Second, most of the current research on ceRNAs is still in the prediction stage of bioinformatics, and most studies lack biological validation; the regulatory relationships in the ceRNA network need to be effectively verified. Third, methodologically, there are few predictive tools available; most miRNA-mRNA predictions focus only on the binding of a miRNA with its target in the 3'-UTR. However, this is not always the case; miRNAs can also target the 5'-untranslated region and coding sequences of mRNAs^[166-170]. Thus, provided that the prediction of a ceRNA is not limited to the 3'-UTR of its mRNA, the range of predicted ceRNAs should be improved. Fourth, one miRNA generally interacts with one target mRNA. However, some miRNAs may modulate many target mRNAs, and *vice versa*^[167,171]. Thus, it is necessary to model the effect of ceRNAs in real scenarios. Fifth, the ceRNA hypothesis maintains that a miRNA is stably expressed; in fact, intracellular miRNA expression is dynamic, which inevitably influences the effectiveness of ceRNAs. Sixth, although ceRNA prediction methods are constantly updated, the current prediction algorithms cannot fully encompass several factors affecting ceRNA susceptibility (quantity and characteristics of MREs, miRNA/mRNA abundance, and subcellular location of RNAs)^[172,173]. Therefore, the prediction methods and experimental methods still need to be further updated and improved. Seventh, the initiation and progression of HCC are a complex event, and it is unclear whether other mechanisms interact with lncRNAs acting as ceRNAs in HCC cells. Addressing the above problems will enable a better understanding of the lncRNA-mediated ceRNA network that can be used to more effectively diagnose and treat HCC.

Given the critical roles and the complex interactions among lncRNA-mediated ceRNA regulatory networks in HCC, future investigations with validation in large sample sizes and the exploration of in-depth molecular mechanisms are needed to

probe the HCC-specific lncRNA-mediated ceRNA axis, which should identify new diagnostic and prognostic markers of HCC and provide promising targets for the treatment of patients with HCC.

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