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Review Article

The emerging landscape of long non-coding RNAs in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common and aggressive cancers. HCC shows high prevalence and lethality caused by a variety of etiologic factors. However, the underlying mechanisms and the diagnostic markers identifying patients at risk in advance has not been entirely elucidated. Long non-coding RNAs (lncRNAs) are a subgroup of non-coding RNAs greater than 200 nucleotides in length with no protein-coding capability. With the progress in sequencing technologies and bioinformatic tools, the landscape of lncRNAs is being revealed. Numerous discoveries point out that lncRNAs participate in HCC carcinogenesis and metastasis through altering cell proliferation and invasion ability, apoptosis, and chemo- or radio-sensitivity. Moreover, lncRNA is easy to detect compared to the traditional diagnostic methods. This review summarizes the mechanisms of major lncRNAs in HCC discovered in recent years and lncRNAs as early diagnostic markers for HCC.

Keywords: Long non-coding RNAs, miRNAs, hepatocellular carcinoma, valuable biomarker, pathway, landscape

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, causing approximately 90% of all human liver cancers [1], and is the third-leading cause of cancer-related death [2]. Factors that lead to HCC mainly include chronic infection with hepatitis B or C virus (HBV or HCV) and other alcohol consumption-related or non-related factors-which can harm the liver and lead to cirrhosis-such as non-alcoholic steatohepatitis (NASH) or long-term exposure to aflatoxin [3]. Even though HBV and HCV sufferers account for a large proportion of liver cancer patients, metabolic syndromes, such as NASH, are the major cause of liver diseases, and risk developing into HCC [4, 5].

HCC therapies depend on diagnosis, and hepatic resection and liver transplantation are the first choices for early-stage treatment (Barcelona Clinic Liver Cancer, BCLC 0 & BCLC A) [4]. The five-year survival rate of early stage HCC is > 50% if treated properly [2]. For the intermediate stage (BCLC B), trans-arterial chemoembolization is used as a first-line treatment, with a median survival of 40 months among well-selected candidates. In the advanced stage, which most patients present with, the effects of chemotherapy and radiotherapy are limited [6]. Patients in this stage can receive systemic therapies along with drugs, such as sorafenib [7]. The median survival for terminal stage HCC is 3-4 months, with 11% of the patients showing survival for one year; at this stage of HCC, patients can only be provided supportive care [8].

The earlier the diagnosis, the greater the chance of curing HCC, and the longer the patient can survive. However, there are many difficulties in HCC prognosis. Serum α-fetoprotein (AFP) has been widely used as a serum biomarker for the past few decades in the screening and diagnosis of early-stage HCC [9]. However, AFP has limited sensitivity and low prognostic value because not all HCC cells secrete AFP, and the AFP level is also elevated in other conditions, such as cirrhosis or hepatitis [10, 11]. Dual-phase CT scanning and MRI can effectively detect HCC when the nodules

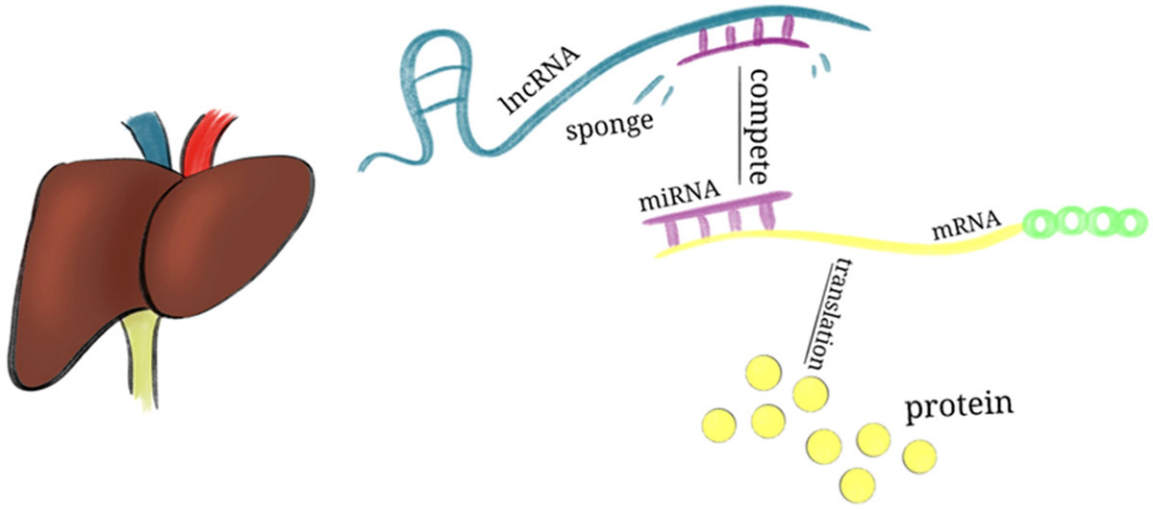

Figure 1. Schematic diagram of biologic function of the lncRNA in regulating mRNA translation. The blue, purple, and yellow lines respectively represent lncRNA, miRNA and mRNA. Generally, lncRNA functions as a 'sponge' in the regulation network which competes with mRNA to bind to miRNAs. In this way, acting as a competitive endogenous RNA (ceRNA), the overexpression of many kinds of lncRNAs may activate the mRNA translation by inhibiting miRNA activation.

are 1-2 cm in size. It is necessary to identify a sensitive early biomarker for HCC detection. A non-invasive diagnostic method with high sensitivity and specificity is required. Recently, the discovery of RNAs has led to several deficiencies in this field.

Various studies have found that > 70% of the human genome sequences are transcribed into RNAs. However, among them, only 2% are translated into protein. There are a large number of non-coding RNAs (ncRNAs) that also have essential biologic functions. These transcripts dramatically altered our understanding of complicated diseases, including cancer [12]. Generally, ncRNAs are classified into microRNAs (miRNAs), small interfering RNAs, PIWI-interacting RNAs, circular RNAs, and various types of long non-coding RNAs (lncRNAs) [13]. lncRNAs are RNAs longer than 200 nucleotides in length and do not translate into proteins [14]. The landscape of lncRNAs has been unraveled by the progress in sequencing technology and bioinformatic tools [12]. These RNAs function with sequence-specific regulation, which has altered our understanding of numerous complex diseases [14].

Under many circumstances, lncRNAs function as an important part of the miRNA network as miRNA sponges, compete with mRNA for binding to miRNA, and consequently regulate mRNA expression [15]. lncRNAs can interact with proteins, functioning as an important component of the holoprotein, or simply help with protein localization into certain positions [16, 17]. Research on lncRNA-miRNA or lncRNA-protein interactions might contribute to a better understanding of HCC and other liver diseases (**Figure 1**).

lncRNAs are involved in the pathophysiology of a wide range of diseases, the majority of which are genetic and inflammatory disorders and cancers [18]. Several lncRNAs have important functions in the biologic progression of HCC, including cell proliferation, apoptosis, invasion, metastasis, and angiogenesis [19, 20]. Abnormal lncRNA expression plays an important role in the modulation of malignant phenotypes [18]. Since lncRNAs can be easily detected in the plasma and urine [21], these transcripts are potential biomarkers and drug targets for HCC diagnosis and treatment.

This review mainly focuses on the relationship between lncRNA and HCC progression, which has been reported in the last decade. The interaction between lncRNAs and miRNAs or proteins or epigenetics that contribute to tumorigenesis, HCC cell proliferation, metastasis, and metabolism are evaluated. Furthermore, the regulation of lncRNA expression is discussed. These discussions provide an essential refer-

ence for HCC diagnosis and therapy and provide novel insights for a better understanding of this cancer.

lncRNAs as valuable biomarkers of HCC

The means of HCC diagnosis mentioned above lack sensitivity and specificity, which makes their use inappropriate for diagnosis in the early stages of cancer. It is of vital importance to detect HCC emergence in patients as early as possible to guarantee survival; therefore, a new biomarker is needed for HCC prognosis and diagnosis. lncRNAs play an important role in the regulation of gene expression in HCC, can be easily tested in urine and plasma, and are much more sensitive than AFP, which is currently used. lncRNAs may be biomarkers for the prognosis and diagnosis of HCC (**Table 1**).

lncRNA HULC in HCC

Highly upregulated in liver cancer (HULC) is characterized as an mRNA-like lncRNA in HCC, which is markedly upregulated [22]. Several *in vivo* experiments have shown an aberrant expression of HULC and downstream miRNAs in HCC; this aberrant expression is easily detectable [23, 24]. Direct evidence obtained from 30 HCC patients showed an upregulated HULC expression in liver tissue and blood samples compared with 20 healthy volunteers without HCC or other liver diseases [25]. Moreover, the expression was linked to HCC grade and HBV status. HULC expression is likely to be associated with tumor progression and can be easily detected in plasma, making it a possible biomarker for the diagnosis of HCC [25].

lncRNA MALAT1 in HCC

MALAT1 is another highly conserved lncRNA that is upregulated in human HCC. It was first detected to be elevated in metastasizing non-small cell lung carcinomas (NSCLCs); thus, it has a considerably broader role in the mechanism of tumor formation and has the potential to be a general biomarker in many carcinoma types, including HCC [26, 27]. Hepcarcin (HCN) is a murine ortholog of human MALAT1, with a highly conserved structure and function [27]. HCN is thought to be a marker of procarcinogen-induced HCC. In human HCC patients, MALAT1 is a genetic biomarker of HCC, and can be detected using an RNA antisense probe (hAS). Furthermore, from the data gained in a 2006 study, MALAT1 expression in liver tissue samples is approximately six times greater than that in healthy samples following hAS detection [27].

lncRNA HOTAIR in HCC

HOTAIR, another lncRNA that was first observed in breast cancer, is involved in the molecular mechanisms of cancer formation and metastasis [28, 29]. Studies have shown that it could be a candidate biomarker for human HCC detection. Both *in vitro* and *in vivo* experiments have shown a positive correlation between HCC and HOTAIR expression in HCC cell lines and 50 HCC patients, respectively [30, 31]. The statistics obtained from 60 HCC patients who underwent liver transplantation (LT) revealed a negative correlation between HOTAIR expression and recurrence-free survival rate in liver cancer [30]. These results make it significant to evaluate HOTAIR levels for HCC prognosis, and for survival rate prediction after LT surgery.

lncRNA CCAT1 in HCC

CCAT1 expression plays an important role in human HCC. Eighty-six samples gained from HCC patients showed a relationship between CCAT1 and the survival rate of the patients. The overall survival rate and relapse-free survival rate were both higher when the CCAT1 levels were low. CCAT1 expression can be analyzed by quantitative real-time polymerase chain reaction (RT-qPCR) in liver tissues, which makes it a possible biomarker for predicting HCC patient survival [32].

lncRNA SNHG3 in HCC

In the study by Zhang *et al.,* SNHG3 was examined in 51 pairs of fresh HCC tissues and 144 pairs of formalin-fixed tissues derived from the livers of HCC patients. SNHG3 was detected using RT-qPCR and an *in situ* hybridization of liver tissues. A significant upregulation was observed in HCC tissues, which confirms the potential of SNHG as an HCC predictor [33]. Further studies also showed a correlation between SNHG3 and the portal vein tumor thrombus (PVTT) in HCC patients [33]. However, additional data should be analyzed to further gain a thorough understanding of this relationship.

Table 1. Possible lncRNA prognostic markers for HCC

LncRNA	Expression level in HCC	Samples for expression level dectetion	Samples for diagnosis	Diagnosis detection methods	Reference
HULC	upregulated	46 HCCs, 4 FNHs, 7 cirrhoses, and 2 non-neoplastic livers	9 healthy volunteers, 10 patients with liver cirrhosis, and 4 HCC patients	RT-qPCR	[22]
		30 HCC tumor samples and 20 healthy control liver tissue samples	20 healthy volunteers and 30 HCC patients	RT-qPCR	[25]
MALAT1	upregulated	6 human HCC samples	2 HCC and 2 healthy samples for Northern blot; 4 HCC tissues for ISH.	ISH and Northern blot	[27]
HOTAIR	upregulated	50 paired primary cancerous and adjacent non-cancerous tissues of the HCC patients	60 HCC patients and 50 additional patients underwent liver transplantation	RT-qPCR	[30]
CCAT1	upregulated	HCC samples from 86 patients	HCC samples from 86 patients	RT-qPCR	[32]
SNHG3	upregulated	51 pairs of fresh HCC samples	144 pairs of formalin-fixed, paraffin-embedded HCC samples	RT-qPCR and ISH	[33]
HAND2-AS1	downregulated	50 HCC tissues and 50 paired adjacent non-tumor liver tissues	50 HCC tissues and 50 paired adjacent non-tumor liver tissues	RT-qPCR	[35]
PANDAR	upregulated	482 pairs of HCC tissues	482 patients with HCC	RT-qPCR	[36]
HEIH	upregulated	85 HCC patients who underwent liver surgery	50 paired HCC/nontumor tissue specimens, along with 20 HBV-infected cirrhotic liver tissues and 20 normal liver tissue, and additional 85 HCC tissues.	Microarray and RT-qPCR	[37]
TP73-AS1	upregulated	84 pairs of HCC samples	84 samples collected from tumor surgical resection	RT-qPCR	[39]

lncRNA HAND2-AS1 in HCC

HAND2-AS1 is a lncRNA that is downregulated in HCC, especially in PVTTs. In addition, HAND2-AS1 has been shown to be associated with HCC metastasis [34]. Data obtained from 50 HCC surgical tissues showed downregulated HAND2-AS1 levels. The survival rate of HCC patients was positively correlated with the HAND2-AS1 level. HAND2-AS1 can significantly reduce the viability of HCC by targeting the miR-300/SOCS5 axis, which makes it a good target for therapy and a possible biomarker for diagnosis [35].

lncRNA PANDAR in HCC

PANDAR predicts a poor prognosis in HCC. According to Peng *et al.*, 482 pairs of liver tissues were obtained from HCC patients, and RT-qPCR was performed to investigate the concentration of PANDAR. PANDAR overexpression is correlated with the clinical outcome of HCC, including liver cirrhosis, HBV surface antigen levels, APF, tumor nodules, vascular invasion, and TNM stage [36]. In addition, overexpression is related to poor survival rate, and in HCC cell lines, PANDAR silencing inhibited HCC cell growth.

lncRNA HEIH in HCC

The lncRNA-HEIH has been reported to be an independent prognostic factor for HCC. In athe respective study, HBV-related HCC samples were examined using RT-qPCR. HEIH overexpression was detected and was found to be significantly related to tumor recurrence and negatively correlated with overall survival rate [37].

lncRNA TP73-AS1 in HCC

TP73-AS1 is involved in tumor proliferation and development [38]. According to Li *et al.*, 84 pairs of HCC specimens and corresponding adjacent non-tumor tissues were used in RT-qPCR to examine the TP73-AS1 concentration. High TP73-AS1 levels correlate with poor prognosis [39].

lncRNAs can be detected in numerous ways. Some studies have reported that lncRNAs can be easily detected in plasma and urine with the progress of sequencing technology [40]. Non-invasive methods for HCC prediction are particularly important. The earlier the cancer is detected, the better the patients can respond to therapy, which will then increase survival. lncRNAs present a new possibility for HCC prognosis.

Mechanism of lncRNA action in HCC

lncRNAs interact with miRNAs in HCC

lncRNAs play an important role in miRNA regulation networks (**Table 2**). They are equivalent to competitive endogenous RNAs and have also been described as miRNA sponges. This sponge mechanism works by the binding of the lncRNA to other miRNAs with its antisense region to prevent the miRNAs from binding to the target mRNAs [41]. lncRNA and miRNA regulation can achieve a measurable effect on target mRNA expression, which is of vital importance in tumors [42]. The lncRNA-miRNA-mRNA regulatory network plays a critical role in cancer biology, including that of breast cancer [43], nasopharyngeal carcinoma [44], colorectal cancer [45], and HCC cell lines. In these cases, lncRNAs serve as novel biomarkers as well as potential therapeutic targets for non-invasive prognosis and medical treatment.

lncRNA H19 in HCC

lncRNA H19 regulates miRNAs such as miR-675 [46-49], miR-193a-3p [50], miR-138 [49], and miR-200 [51] which affect HCC progression. Unlike in other cases, H19 is a precursor of miR-675 [52]. In a study by Li, miR-675 accelerated liver cancer cell growth in mice, and importantly, by reducing the activity of HP1 isoforms, EGR1 expression was elevated and consequently increased H19 expression by occupying the H19 imprinting control region [48]. The amplification of H19 in this way multiplies the effect of the lncRNA H19 on other targets. In AFP-secreting HCC, which is often associated with a worse prognosis, miR-675 suppresses the Twist1 and retinoblastoma proteins, which is a key epithelial-to-mesenchymal transition (EMT) mediator [47]. miR-675 overexpression is also associated with sorafenib resistance in HCC [46]. In another study conducted by Ge *et al.*, miR-675 bound to FADD, while miR-138 interacted with PTK2 or was sponged by H19. PTK2 upregulation elevated FAK expression. FADD inhibition decreased the caspase-8 and caspase-3 levels. Both path-

Table 2. Interaction between lncRNAs and miRNAs and the downstream pathways as well as the biological effects in HCC

lncRNA	miRNA	downstream proteins or pathways	biological function
HULC	miRNA-372	PRKACB, CREB	tumorigenesis
	miRNA-203	ADAM9	tumorigenesis
DLX6-AS1	miR-203a	MMP-2	proliferation, migration, and invasion of HCC cells, tumorigenesis
	miR-424-5p	WEE1	cell cycle arrest, proliferation, migration, and invasion of HCC cells
MALAT1	miR-146a	PI3K/Akt/mTOR	proliferation, apoptosis, and autophagy of HCC cells
	miR-124	PI3K/Akt	CSC generation, stemness-related factor activation and tumorigenicity
	miR-200a		proliferation, migration, invasion, and apoptosis under hypoxia
	miR-375	YAP1	cancer stem cell features of HCC cells
	miR-140-5p	Aurora-A	Sorafenib resistance, proliferation, migration, and EMT of HCC cells
H19	miR-675		Sorafenib resistance
	miR-675	Twist1, Rb protein	cell adhesion, cell cycle initiation, proliferation, cell morphology, and invasive potential
	miR-675	HP1α, EGR1, PKM2	histone methylation and acetylation, proliferation of HCC cells
	miR-675	FADD	cell apoptosis, tumorigenesis
	miR-138	PTK2	cell apoptosis, tumorigenesis
	miR-193a-3p	PSEN1	radio-resistance and chemo-resistance
	miR-200	hnRNP U/PCAF/RNAPol II	metastasis, EMT marker expression, histone acetylation
lncRNA-ATB	miR-200	ZEB1, ZEB2, IL-11, STAT3	EMT, invasion and metastatis in HCC cells
CCAT1	let-7b	HMGA2	proliferation, migration invasion, and apoptosis of HCC cells
	let-7	HMGA2, c-Myc	tumor size, microvascular invasion, AFP expression in patients, and proliferation and migration of HCC cells
NEAT1	miR-187	IGF-1R	proliferation, migration, and invasion of HCC
	mIR-101-3p	WEE1	radiosensitivity of HCC cells
	miR-335	c-Met-Akt	Sorafenib resistance
	miR-22-3p	Akt2	tumorigenesis, proliferation, invasion, apoptosis of HCC cells
	miR-204	ATG3	Sorafenib resistance, autophagy in HCC cells
	miR-124-3p	ATGL, DAG, FFA	lipolysis disruption
	miR-155	Tim-3	$CD8^+$ T cells cytolysis activity
SNHG6	miR-101-3p	Zeb1, UPF1, Smad7	apoptosis, cell cycle progression, tumorigenesis, EMT, and metastasis
	miR-26a/b	TAK1	proliferation, drug resistance, apoptosis in HCC cells
	miR-139-5p	SERPINH1	proliferation, cell cycle, migration, and invasion of HCC cells
	miR-1297	FUS, MAT1A, MAT2A	genome-wide hypomethylation
TP73-AS1	miR-200a	HMGB1, RAGE, NF-κB	proliferation of HCC cells
ZFAS1	miR-150	ZEB1, MMP14, MMP16	metastasis
HAND2-AS1	miR-300	SOCS5	tumorigenesis, metastasis

ways inhibit cancer cell apoptosis and lead to hepatoblastoma tumorigenesis [49]. Besides its function as a precursor, H19 also sponges miR-193-3p and subsequently activates PSEN1. PSEN1 is involved in inducing chemo- and radiosensitivity in liver cancer [50]. Aberrant H19 expression also upregulates the miR-200 family by increasing histone acetylation, followed by the activation of miR-200 family members, including miR-200a, miR-200b, miR-200c, miR-141, and miR-429. The target gene of the miR-200 family is ZEB1/2, which results in EMT reversal when overexpressed. Conversely, knockdown of H19 may cause a reduction in the levels of the miR-200 family and result in ZEB1/2 downregulation [51]. Accordingly, inhibition of invasion and metastasis was found in H19-overexpressed cells.

The role of lncRNA HULC in HCC

HULC is upregulated in HCC. Wang *et al.* revealed the relationship between HULC and miR-372 in liver cancer [53], and Wan *et al.* showed a connection between HULC and miR-203 in liver cancer [54]. In liver cancer cell

lines, HULC downregulates miR-372 activity, which, in turn, reduces the repression of its target gene PRKACB. PRKACB activation facilitates cAMP response element binding protein (CREB) phosphorylation. Phospho-CREB binds to *Hulc,* the core promoter of liver cancer. CREB binding protein was detected in the *Hulc* promoter *in vivo.* Additional experiments showed that phospho-CREB recruits the HAT P300 enzyme and Brg I to the *Hulc* promoter, which leads to the activation of epigenetic markers and chromatin remodeling. A histone modification was also observed around the promoter. These processes contribute to the activation of HULC transcription and subsequently repress miR-372 transcription. HULC expression is driven by a decrease in the levels of miR-372 [53]. This regulatory loop may amplify the influence of the lncRNA HULC on other molecular pathways contributing to HCC development, such as that involving an overexpression of miR-203, which leads to the inhibition of cell proliferation [54].

The role of lncRNA MALAT1 in HCC

MALAT1 is involved in complicated miRNA regulatory networks. MALAT1 overexpression in HCC results in accelerated tumor progression and a reduction in the overall survival rate [55, 56]. MALAT1 sponges miR-146a [57] and miR-124 [58], and both miRNAs can target PI3K, which is a well-known apoptosis and autophagy modulator [59]. The PI3K-Akt pathway is activated, particularly in high-grade HCC patients, and Akt phosphorylation is positively correlated with a decrease in overall survival rate and poor prognosis [58]. Downstream effectors, such as mTOR and p70S6k, are upregulated up to 45% in HCC [60], providing multiple effects of the regulatory network of MALAT1-miR-146a/miR-124 on the PI3K/Akt pathway. MALAT1 can sponge miR-200a, which is a target of the lncRNA TP73-AS1 [39, 61]. Under hypoxic conditions, MALAT1 sponges miR-200a *in vitro*. miR-200a activity repression suppresses apoptosis and induces the metastasis and proliferation of HCC cells [61]. According to Li *et al.*, the same interaction was found between the lncRNA TP73-AS1 and miR-200a [39]. This study verified that the HMGB1/RAGE pathway is inhibited by miR-200a and NF-κB. miR-200a inhibition can initiate the transcription of several inflammatory cytokines [62]. MALAT1 also regulates the expression of other miRNAs; for instance, miR-375 is sponged by MALAT1. The direct target of miR-375 is Yes-associated protein 1 (YAP1), which can rescue the features of liver cancer stem cells (CSCs) [63]. Stem cell-like abilities may contribute to self-renewal and metastasis. Recent research has shown that miR-140-5p is another miRNA that targets the Aurora-A pathway and contributes to sorafenib resistance under MALAT1 regulation [64].

The role of lncRNA NEAT1 in HCC

NEAT1 also sponges let-7 miRNA and according to Liu *et al.*, induces HCC cell proliferation. Furthermore, the target gene of let-7b has been shown to be the gene encoding IGF-1r, which is considered a critical regulator in HCC and is involved in HCC development, proliferation, and apoptosis [65, 66].

NEAT1 has noteworthy regulatory effects on many other miRNAs, which has made it an important research target in recent years. NEAT1 acts as a competing endogenous RNA (ceRNA) sponging the miRNA hsa-mir-139-5p, the direct target of which is TGF-β [67]. TGF-β is involved in HCC progression and is involved in the activation of other lncRNAs, such as lncRNA-ATB [68]. A NEAT1 splicing variant with a stronger tendency to form an RNA binding protein complex, namely NEAT1_2, is capable of sponging miR-101-3p and consequently upregulating the oncogene *WEE1* [69]. *WEE1* is an important oncogene and is regulated by the lncRNA DLX6-AS1, as described above [70]. The Akt family is a regulatory target of NEAT1. By sponging miR-335, NEAT1 upregulates the c-Met/Akt pathway, which enhances sorafenib resistance and inhibits HCC cell apoptosis [71, 72]. Besides, NEAT1 contributes to sorafenib resistance by sponging miR-204, which is an ATG3 inhibitor. Rescue assays also showed that NEAT1 promotes HCC autophagy through the same signaling pathway [73]. NEAT1 sponges miR-22-3p and upregulates Akt2, an isoform of the Akt family. Increased Akt2 is correlated with cell proliferation and invasion, which was verified in an HCC mouse model. Interestingly, NEAT1 can downregulate miR-124-3p, which upregulates ATGL expression. ATGL can mediate lipolysis in HCC cells, indicating that NEAT1 can control lipid metabolism in HCC [74]. The NEAT1 gene, as described above, has two splic-

ing variants, NEAT1_1 and NEAT 1_2. The precursor of miR-612 (pre-miR-612) is part of the NEAT1_2 DNA sequence. The splicing balance between NEAT1 and miR-612 was controlled by PTBP3. NEAT1 downregulates p53 and results in cell proliferation, while miR-612 increases Akt2 expression and induces EMT and cell metastasis. Moreover, NEAT1 can also repress the antitumor effect of $CD8^+$ T cells by regulating the miR-155/Tim3 signaling pathway. NEAT1 downregulation restrained the apoptosis of $CD8^+$ T cells and enhanced their cytolysis activity against HCC cells; NEAT1 thus presents another novel therapeutic target [75].

The role of lncRNA SNHG6 in HCC

lncRNA SNHG6 plays an important role in human HCC development [76, 77]. SNHG6 is a lncRNA that shares some of its downstream miRNAs with NEAT1, such as miR-101 [78] and miR-139 [67]. SNHG6 also acts as a ceRNA to bind to miR-101-3p. Consequently, ZEB1 is upregulated due to miR-101-3p repression, thus inducing EMT in HCC cells and increasing invasion and metastasis [78]. SNHG6 sponges miR-139-5p, activating SERPINH1 expression and inducing the proliferation and viability of HCC cells [67]. Human SNHG6 consists of five transcripts from SNHG6-003 to SNHG6-007. SNHG6-003 and SNHG6-006 were highly expressed in HCC cell lines, whereas the others were barely detected. SNHG6-003 plays an oncogenic role in HCC by functioning as a sponge for miR-26a and miR-26b [79]. Guo *et al.* reported the genome-wide hypomethylation induced by SNHG6. SNHG regulates MAT1A and MAT2A levels by sponging miR-1297. In this case, MAT1A is suppressed through the miR-1297/FUS pathway, while MAT2A is promoted by removing the inhibitor miR-1297 during its mRNA translation. Both above-mentioned pathways determine SAM expression in HCC cells, which has a positive feedback on the regulation of MAT1A and MAT2A [80, 81]. This mechanism provides a new perspective that the abnormal expression of a single lncRNA may have an effect on genome-wide regulation; this idea could guide further innovative research [81].

The role of lncRNA CCAT1 in HCC

CCAT1 is a lncRNA linked to the proliferation and migration of HCC cells in human HCC. It functions as a let-7 sponge [82, 83]. Let-7 is a miRNA that targets HMGA2 and c-Myc. The former plays an important role in the transcriptional modulation of proliferating genes [82], while the latter is an oncogene that induces proliferation when overexpressed [84].

The role of lncRNA ATB in HCC

The miR-200 family is involved in the lncRNA ATB regulatory network. Contrary to the effects of H19, lncRNA ATB downregulates miR-200 [68, 85]. Subsequently, ZEB1/2 is upregulated, leading to EMT in HCC cells. ATB was found to promote the invasion-metastasis cascade of HCC cells in nude mice [68].

The role of lncRNA TP73-AS1 in HCC

A study on TP73-AS1, found that NF-κB is repressed by miR-200, and miR-200 downregulation induces the expression of various cytokines [39]. However, in this study, a different mechanism for the overexpression of IL-1 was observed, in which the mRNA directly bound to miR-200 to increase its stability [68].

The role of lncRNA DLX6-AS1 in HCC

lncRNA DLX6-AS1 is upregulated in HCC tissues. It is involved in the miRNA regulatory network which involves miR-203a [86] and miR-424-5p [70]. DLX6-AS1 knockdown inhibits the proliferation, migration, and invasion of HCC cells. In addition, DLX6-AS1 silencing inhibited tumor growth in the subcutaneous tissues of nude mice. DLX6-AS1 sponges miR-203a, which reduces the repression of its target gene matrixmetalloproteinase-2 (MMP-2). MMP-2 was previously verified to be a critical protein involved in HCC cell proliferation, migration, and invasion [87]. Another target of DLX6-AS1 is miR-424-5p, and upon miR-424-5p downregulation, the inhibitory effect on WEE1, a G2 checkpoint kinase, was abolished. WEE1 overexpression has been verified in many cancer types, and WEE1 repression could be a therapeutic target for cancer treatment [88].

lncRNAs interact with certain critical proteins in HCC

lncRNAs mainly function as miRNA sponges. However, under several conditions, they directly interact with proteins, as has been observed in many cases of tumorigenesis. lncRNAs interact with proteins through their RNA structural ele-

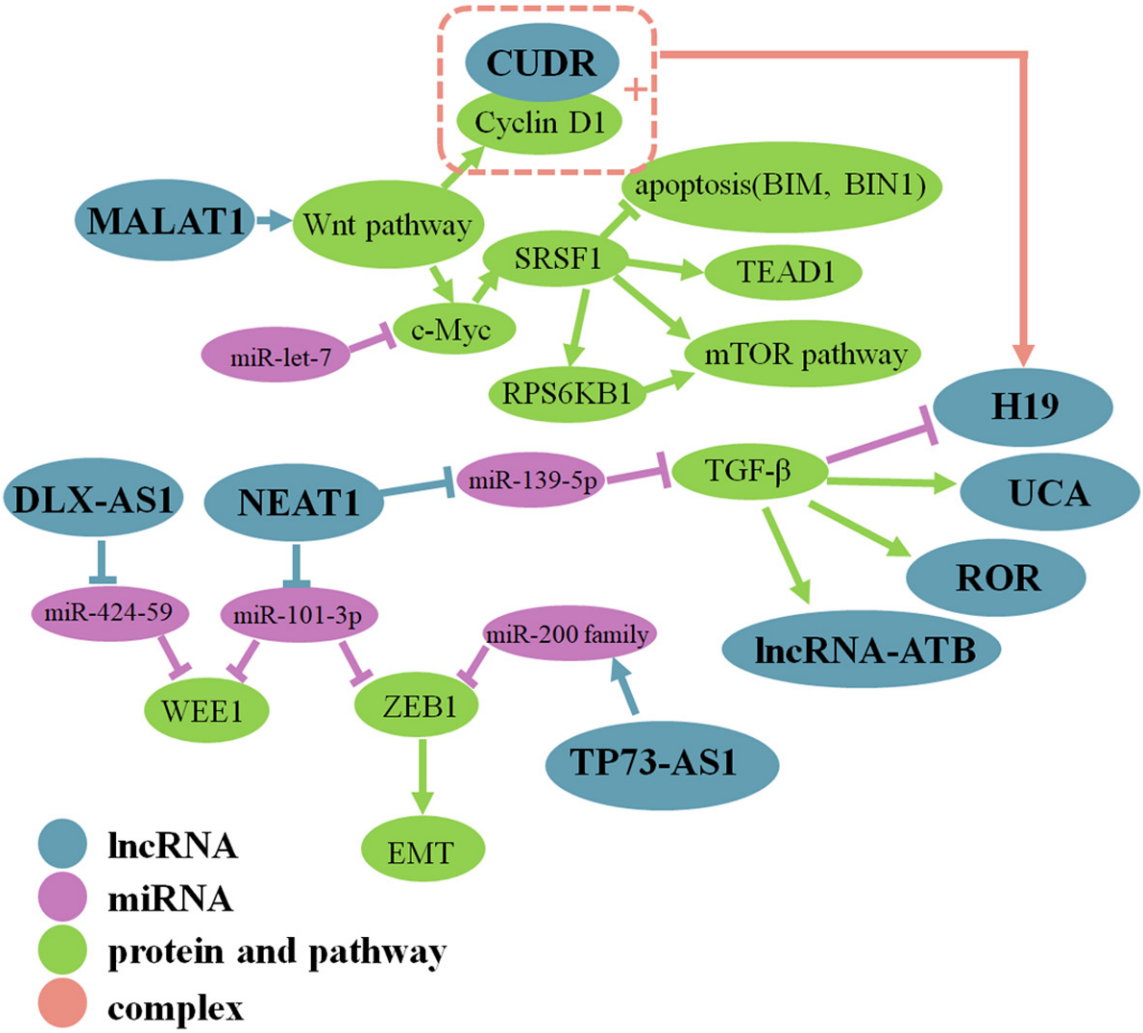

Figure 2. Regulation network of the lncRNA in HCC. LncRNAs are involved in a complicated network. Part of the interaction and important pathways are presented in this figure. LncRNAs sponge miRNAs in order to regulate their target mRNAs. LncRNAs directly activate or deactivate some signaling pathways by interacting with proteins. LncRNAs also bind with proteins to form a complex which has novel biological functions. The aberrant expression of a single lncRNA may trigger upheaval of the whole network and influence other lncRNAs.

ments. In the nucleus, lncRNAs affect the polycomb recessive complex (PRC), thus affecting chromatin accessibility and gene expression. In the cytoplasm, lncRNAs can scaffold multiple proteins or participate in the formation of stable complexes [89]. It is common for lncRNAs to modulate protein functions, regulate protein-protein interactions, and affect protein localization [90]. In HCC, many important signaling pathways are influenced by the direct action of lncRNAs on proteins (**Figure 2**).

lncRNA HULC interacts with some proteins in HCC

lncRNA HULC interacts with certain important proteins and consequently regulates the cellular metabolism, cell cycle, and expression of certain oncogenes in HCC. Tobramycin affinity purification and mass spectrometric analysis suggested the interaction ability of HULC with several critical enzymes in the glycolysis pathway. Wang *et al.* demonstrated that HULC interacts with lactate dehydrogenase A (LDHA) and pyruvate kinase 2 (PKM2)-which catalyzes the final step of glycolysis and plays a pivotal role in tumorigenesis and cancer progression. LDHA overexpression is often observed in HCC. HULC can activate LDHA by directly binding to it and mediating its phosphorylation. HULC represses PKM2 activity through a similar direct binding mechanism, mediating PKM2 phosphorylation and preventing PKM2 from forming a functional

tetramer. However, neither *in vitro* nor *in vivo* experiments have found evidence suggesting that HULC affects the interaction between LDHA and PKM2. Instead, it acts as an adaptor that enhances the interaction between LDHA, PKM2, and fibroblast growth factor receptor type 1, which also mediates the phosphorylation of LDHA and PKM2. The modulation of these two critical proteins promotes aerobic glycolysis in HCC cells and enhances cell proliferation [91]. Y box protein 1 (YB-1) is a multifunctional protein that participates in transcriptional or translational regulation and mRNA splicing, DNA repair, and stress response to extracellular signals [92]. Dan *et al.* observed specific binding between HULC and YB-1. HULC is reported to promote YB-1 phosphorylation, which is mediated by ERK kinase. Moreover, phospho-YB-1 activates the silenced oncogenes, subsequently accelerating the expression of these genes and promoting cell proliferation and HCC progression. Interestingly, similar to YB-1, many other ERK substrates are found to be phosphorylated under HULC regulation, such as RSK, which requires further study [93, 94].

lncRNA MALAT1 interacts with some proteins in HCC

MALAT1 targets several proteins that are highly associated with tumorigenesis and CSC stemness. SR protein splicing factor 1 (SRSF1) directly binds to MALAT1, is upregulated in HCC, and acts as a proto-oncogene [95]. The Wnt-β-catenin pathway is activated by MALAT1 and activates c-Myc, which is a transcriptional activator of SRSF1 [96]. Malakar *et al.* reported that SRSF1 regulated oncogenic alternative splicing. The frequency of this event increased following MALAT1 upregulation. An increased concentration of the extra short isoform of BIM, inclusion of exon 12A in BIN1, inclusion of exon 5 in TEAD1, and the emergence of a shorter splicing variant Iso-2 was observed in cells overexpressing MALAT1; all of these molecular events contribute to HCC tumorigenesis and proliferation. Iso-2 with oncogenic activity can bind to mTOR and thus activate mTORC1 (mTOR complex 1), which is essential for MALAT1 transformation and tumorigenesis. Activation of the Wnt pathway contributes to cyclin D upregulation, which is a critical factor for cell proliferation [97]. By interacting with the Wnt-β-catenin pathway, MALAT1 modulates HCC oncogenicity and stemness, contributing to a low differentiation rate and tumorigenesis in HCC [98].

lncRNA NEAT1 interacts with some proteins in HCC

NEAT1 interacts widely with many proteins. In a study by Koyama *et al.*, NEAT1 is required for CD44 expression, which is an essential CSC marker. According to their study, CD44 expression was positively correlated with NEAT1_1 expression. In CD44-deficient cells, NEAT1_1 restores CSC stemness in the cells, indicating another uncovered CD44-independent pathway [99]. NEAT1 promotes heterogeneous nuclear ribonucleoprotein A2 (hnRNPA2) expression. The regulation is not through direct binding between NEAT1 and hnRNPA2, but through the formation of the NEAT1-U2AF65 complex. Neat1 induces an elevated level of hnRNP and consequently promotes cell proliferation and invasion in HCC [100].

lncRNAs have epigenetic effects on histone modification and DNA methylation in HCC

Besides working as an mRNA sponge or interacting with different protein types to affect cell functions, lncRNAs can regulate HCC progression by epigenetic mechanisms. Epigenetics is the study of the inheritable changes that are induced by the modification of gene expression rather than the alteration of the genetic code itself. Epigenetic changes mainly include chromatin accessibility, DNA methylation, and histone modifications, such as methylation, acetylation, and ubiquitination [101]. With a greater realization of the importance of epigenetics in tumorigenesis, more research is being conducted in this direction and more details about the underlying mechanisms and processes are being revealed.

In HCC tumors, lncRNA AY927503 can enrich H3K4Me3, H3K9Ac, and H3K14Ac but reduce H3K27Me3 and histone protein H1FX occupancy in the ITGAV promoter region [102]. The pattern of histone modification remodels the chromatin structure and promotes RNA polymerase II recruitment on the ITGAV promoter. The overexpressed integrin is known to boost HCC metastasis.

lncRNA lnc34a suppresses miR-34a expression through an epigenetic mechanism. lnc34a

recruits DNMT3a and histone deacetylase 1 (HDAC1) on the miR-34a promoter region to facilitate their DNA methylation and histone deacetylation, respectively; thus, arresting miR-34a transcription. The downstream miRNA miR-34a is a tumor suppressor that binds Smad4 to suppress both the TGF-β pathway and hepatoma cell migration. Therefore, the inhibition of miR-34a expression contributes to HCC metastasis [103].

lncRNA ID2-AS1 localizes adjacent to the gene *ID2*. ID2-AS1 can block histone deacetylase 8 from binding to the enhancer region of *ID2*, subsequently blocking *ID2* transcription, which finally leads to the suppression of tumor metastasis by the regulation of the EMT process [104].

lncRNA HOTAIR upregulates DNA methyltransferase (DNMT) expression and thus promotes DNA methylation on CpG islands located in the miR-122 promoter region, epigenetically suppressing miR-122 expression. miR-122 suppression activates cyclin G1 expression and promotes tumorigenicity in HCC [105].

It has been reported that the genome-encoded lncRNA MALAT1 can interact with different coding and non-coding regions on mitochondrial DNA. MALAT1 is important for the maintenance of mitochondrial DNA CpG methylation and also its biological functions, including oxidative phosphorylation, ATP production, and apoptosis. Dysregulation of these pathways is positively correlated with HCC progression [106].

Regulation of lncRNA expression in HCC

In HCC, lncRNA plays an important role in cancer progression by interacting with proteins and miRNAs to regulate all the characteristics of HCC cells. Many lncRNAs are abnormally expressed in HCC cells. While many of them are overexpressed, several others are downregulated. The regulation of lncRNA expression could serve as a novel strategy for HCC therapy and the extensive study of this process would also extend our understanding of the molecular mechanism of HCC development, and warrants further in-depth research.

It is noteworthy that many lncRNAs have a positive feedback mechanism in their expression regulation. Consequently, these lncRNAs are able to amplify their effect by themselves and have better opportunities to interact with their downstream target miRNAs or proteins. HULC, as described above, is able to upregulate itself by sponging miR-203, which subsequently upregulates PRKACB. PRKACE phosphorylates CREB and consequently activates the *Hulc* promoter [53]. Similarly, H19 upregulates miR-675 and promotes EGR1 activity, occupying the imprinted control region of H19 and increasing H19 expression [48].

As demonstrated above, MALAT1 upregulates SRSF1 [96]. However, according to a study by Wang *et al.*, SRSF1 inhibits MALAT1 expression through the negative regulation of YAP transcriptional activity. YAP interacts with TCF4/β-catenin at the *Malat1* promoter, thus promoting the transcription of MALAT1. SRSF1 has a negative effect on YAP transcription, while YAP is capable of regulating its localization and SRSF1 in order to inhibit the degradation effect of SRSF1 on *Malat1*. The results of the analyses conducted in this study presented a network in which the balance between SRSF1 and YAP could largely affect MALAT1 levels and tumorigenesis [107].

There are many other proteins and signaling pathways that regulate the function of lncRNAs in HCC. HBV is a common factor that leads to HCC. HBV protein X (HBx) activates CREB; therefore, the promoter of *Hulc* is activated [108]. TGF-β is a regulator of multiple lncRNAs, including H19 [109], ATB [68], UCA1 [110], and ROR [111]. TGF-β activates the lncRNA ATB, and the regulatory effect is implied through the TGF-β/Smad pathway, but this needs further verification [68]. TGF-β is a positive UCA1 regulator, which upregulates HXK2 and increases lactate production, glucose uptake, and ATP production in HCC [110]. Extracellular vesicle signaling, such as lncRNA ROR, responds to TGF-β. TGF-β upregulates ROR and enhances chemoresistance [111]. Notably, according to the study by Zhang *et al.*, TGF-β repressed H19 expression in tumor-initiating hepatocytes (TICs). It has been demonstrated that the Sox2 level is downregulated by TGF-β, which results in decreased H19 expression, affecting the survival, proliferation, and progenitor capacity of TICs. Furthermore, H19 transcription is activated by the lncRNA CUDR. CUDR overexpression, as well as its combination with cyclin D1,

reduces methylation at the promoter region of H19 and upregulates its expression [112].

NEAT1 expression is linked with many other signaling pathways. HIF-2α is reported to be a direct regulator of NEAT1 in breast cancer [113], and has been shown to be the same in HCC [114]. Zheng *et al.* reported that HIF-2α is an activator of NEAT1 transcription and promotes EMT activity. p53 is a tumor suppressor, and one of its target genes was NEAT1. p53 induces NEAT1, particularly NEAT1_2 expression and paraspeckle formation [115]. This can enhance chemosensitivity and prevent DNA damage accumulation during replication [115]. The promoter region of NEAT1 is the direct binding target of BCLF1, which induces HCC cell proliferation and invasion by promoting NEAT1 expression.

Conclusion and prospects

The study of non-coding RNAs is recent [116]. HULC was discovered in 2007 and is regarded as the most upregulated gene expressed in HCC [22]. HULC may downregulate miRNAs by acting as a sponge, thus regulating the translation of target mRNA [18]. Besides HULC, lncRNA-H19 is another lncRNA that is associated with advanced HCC stage, particularly when highly expressed [117]. Abnormal H19 lncRNA expression is linked to inflammation caused by NASH, HBV, HCV, or alcohol-related causes, which results in HCC. A high MALAT1 level is a marker for a high HCC risk after liver surgery [118, 119]. lncRNAs can function as either oncogenes or tumor suppressors. Overexpressed lncRNA-maternally expressed gene 3 induces apoptosis and decreases cell proliferation in HCC, which makes it an independent prognostic factor for HCC patients [120]. *In vitro* lncRNA-amine oxidase copper containing 4, pseudogene overexpression significantly reduced tumor growth [121].

With the progression of sequencing technology and bioinformatics tools, the functions of lncRNAs can be predicted, and the underlying molecular mechanisms of lncRNAs can be explained. Meanwhile, updated technologies, such as chromatin immunoprecipitation (ChIP) and RT-qPCR are widely used in the evaluation of the lncRNA-miRNA or lncRNA-protein interaction and aid in HCC diagnosis at an early stage. Some lncRNAs have been reported to have conflicting effects on HCC generation. H19 is often overexpressed, whereas, in some cases, its inhibition contributes to HCC cell apoptosis [49]. NEAT1 also has multiple effects. In addition, many other reports verified that NEAT1 overexpression leads to tumor progression, and NEAT1 contributes to chemosensitivity and sensitivity to p53 therapy [115]. SNHG6 has a contrary regulatory effect on MAT1A and MAT2A, which leads to genome-wide hypomethylation [81]. Certain lncRNAs may also lead to histone acetylation to regulate the target genes.

The majority of studies have focused on HCC cell lines or tissues from HCC patients. HCC is rarely diagnosed using a small surgery. Therefore, in order to prove that lncRNAs are biomarkers for prognosis and diagnosis, additional studies should focus on the *in vivo* conditions and the concentration of lncRNA in the plasma and urine, which can be easily collected and examined.

Disclosure of conflict of interest

None.

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