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CANCER INNOVATION

REVIEW

The expression and function of long noncoding RNAs in hepatocellular carcinoma

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Abstract

With the deepening of the genome project study, attention on noncoding RNAs is increasing. Long noncoding RNAs (lncRNAs) have become a new research hotspot. A growing number of studies have revealed that lncRNAs are involved in tumorigenesis and tumor suppressor pathways. Aberrant expressions of lncRNAs have been found in a variety of human tumors including hepatocellular carcinoma (HCC). In this review, we provide a brief introduction to lncRNA and highlight recent research on the functions and clinical significance of lncRNAs in HCC.

KEYWORDS

carcinogenesis, hepatocellular carcinoma, long noncoding RNA, noncoding RNAs, tumor suppressor

1 | BACKGROUND

Primary hepatocellular carcinoma (HCC) is a common human malignancy. The fatality rate of HCC ranks third among all malignancies worldwide [1], and HCC is one of the main causes of cancer-related death in China. With the development of medical technology in recent years, strategies for the diagnosis and treatment of HCC have made increasing progress. However, the recurrence, metastasis and mortality rates of HCC have not sufficiently improved and early detection of HCC remains challenging. The main reason for these obstacles is that the molecules and factors involved in early symptoms and various pathological manifestations of primary HCC are still unclear. Therefore, the molecular mechanisms underlying the development and occurrence of HCC have become the focus of research studies in recent years.

A great deal of research has demonstrated that long noncoding RNAs (lncRNAs) are widely involved in physiological and pathological processes, and aberrations in lncRNAs have been found to be related to many human diseases, particularly cancer. Alterations in lncRNA expressions have been detected in a variety of human tumors, including HCC [2–6] and may be associated with tumor

Abbreviations: HCC, hepatocellular carcinoma; LncRNA, long noncoding RNA; MDR1, multidrug resistance 1 gene; ncRNA, noncoding RNA; PCG, protein-coding genes; pre-mRNA, precursor mRNA; T-DMR, tissue-dependent differentially methylated region; T-UCRs, transcribed ultra-conserved regions; UCRs, ultra-conserved regions.

Jingli Du and Yue Su contributed equally to this study and shared first authorship.

occurrence and development. Furthermore, several lncRNAs have been shown to be sensitive and specific tumor markers. Together, these findings have led to a new understanding of the molecular mechanisms of HCC with implications for HCC diagnosis.

2 | LncRNAs

Early scientific research suggested that RNA was the only medium for transmitting information between DNA and protein. RNA was considered an intermediate for transmitting information for protein synthesis but was not thought to participate in the regulation of this process. However, with the development of technology, later studies revealed that less than 2% of genes encode protein and most DNA is transcribed into noncoding RNA (ncRNA) [7, 8]. A large number of ncRNAs constitute a huge molecular network that plays important regulatory roles in eukaryotes.

LncRNAs are RNAs more than 200 nt long, and most lack protein coding ability [9, 10]. The update defines lncRNAs as RNA molecules that may function as either primary or spliced transcripts and excluding known classes of small RNAs, such as miRNAs, small nucleolar RNAs, piwi-interacting RNAs, or into classes of structural RNAs including transfer RNAs, small nuclear RNAs, spliceosomal RNAs and so on [11].

2.1 | Classification of lncRNAs

The classification of lncRNA has not been well established. According to the position of LncRNA relative to host *protein-coding genes (PCG)*, the classifications of LncRNA include nature antisense RNA, intronic antisense RNA, bidirectional RNA, exon-sense overlapping RNA, intergenic RNA, intron-sense RNA and promoter- or enhancer-correlated RNA [10, 11]. Other researchers classified lncRNA into three groups: lincRNAs, which are transcribed from intergenic regions; LucrRNAS, which are transcribed from ultra-conserved regions (UCRs); and other lncRNAs [12].

2.2 | Functions of lncRNAs

LncRNAs were initially believed to be a by-product of transcription or the "noise" generated from transcription of the genome with no biological function [13, 14]. However, research has confirmed that lncRNAs are involved in multiple regulatory roles and biological processes including genomic imprinting [15], X chromosome inactivation [16], chromatin structure [17], enhancer function [18, 19], transcriptional activation, transcriptional interference and gene expression regulation by cis or trans regulatory mechanisms [17, 20]. LncRNAs play important biological roles in multiple levels of chromosome modification, transcription, and posttranscription [21].

LncRNA has been shown to regulate the expression of genes by various mechanisms, including transcriptional regulation, chromatin modification, post-transcriptional regulation, and so on (Figure 1). LncRNAs silence or activate gene expression by regulating DNA methylation or histone modification and chromatin remodeling. For example, Imamura et al. found that *lncRNA Khpsla* originates from a CpG island and overlaps with a tissue-dependent differentially methylated region (T-DMR) of *SPHK1*. Overexpression of two fragments of *Khps1* caused demethylation of CG sites in the T-DMR [22]. Silencing of the *Kcnq1ot1* gene was found to involve H3K9me2 and H3K27me3 histone modifications, which are partly caused by G9a and Ezh2 histone methyltransferases, resulting in cluster-wide repressive histone marks, gene silencing and DNA methylation of CpG islands of promoters [23]. A similar observation was reported with *Ari*, *Xist*, and *BACE1-AS*, which bind PRC2, TRX, and G9a and impart specific silencing of genomic loci both in cis and trans [17, 24-26]. In a study in leukemia, Yu et al. found that lncRNA antisense *P15* expression resulted in *p15* silencing through heterochromatin formation [27].

LncRNAs act as transcriptional regulators or coregulators to modulate gene expression; they can inhibit gene transcription via transcriptional interference [28]; and interact with transcription inhibiting complexes to influence the expression of target genes. LncRNAs interact with RNA polymerase II, interfere with the formation of the transcription initiation complex and inhibit transcription initiation, resulting in rapid changes in gene expression patterns. For example, *B2* RNA in mice and *Alu* RNA in humans repress mRNA transcription in response to heat shock; these lncRNAs inhibit the polymerase and DNA contacts by binding with RNA polymerase II and assemble into complexes on the promoter [29].

LncRNAs regulate mRNA splicing, transport, editing, translation, and degradation. Base pairing between sense and antisense RNAs masks the splice sites that trigger alternate splicing [30]. LncRNA stabilize or promote target gene translation by extended base pairing [31]. For example, the upregulation of *BACE1-AS* is linked to BACE1 mRNA stabilization through extended base-pairing with BACE1, resulting in increased protein level [32]. Conversely, some base pairing facilitates mRNA decay or inhibits mRNA translation. For example, the cytoplasmic *1/2-sbsRNAs* promotes decay by partial base pairing with specific target mRNAs and recruitment of Staufen1 [31, 33]. Moreover, some lncRNAs form

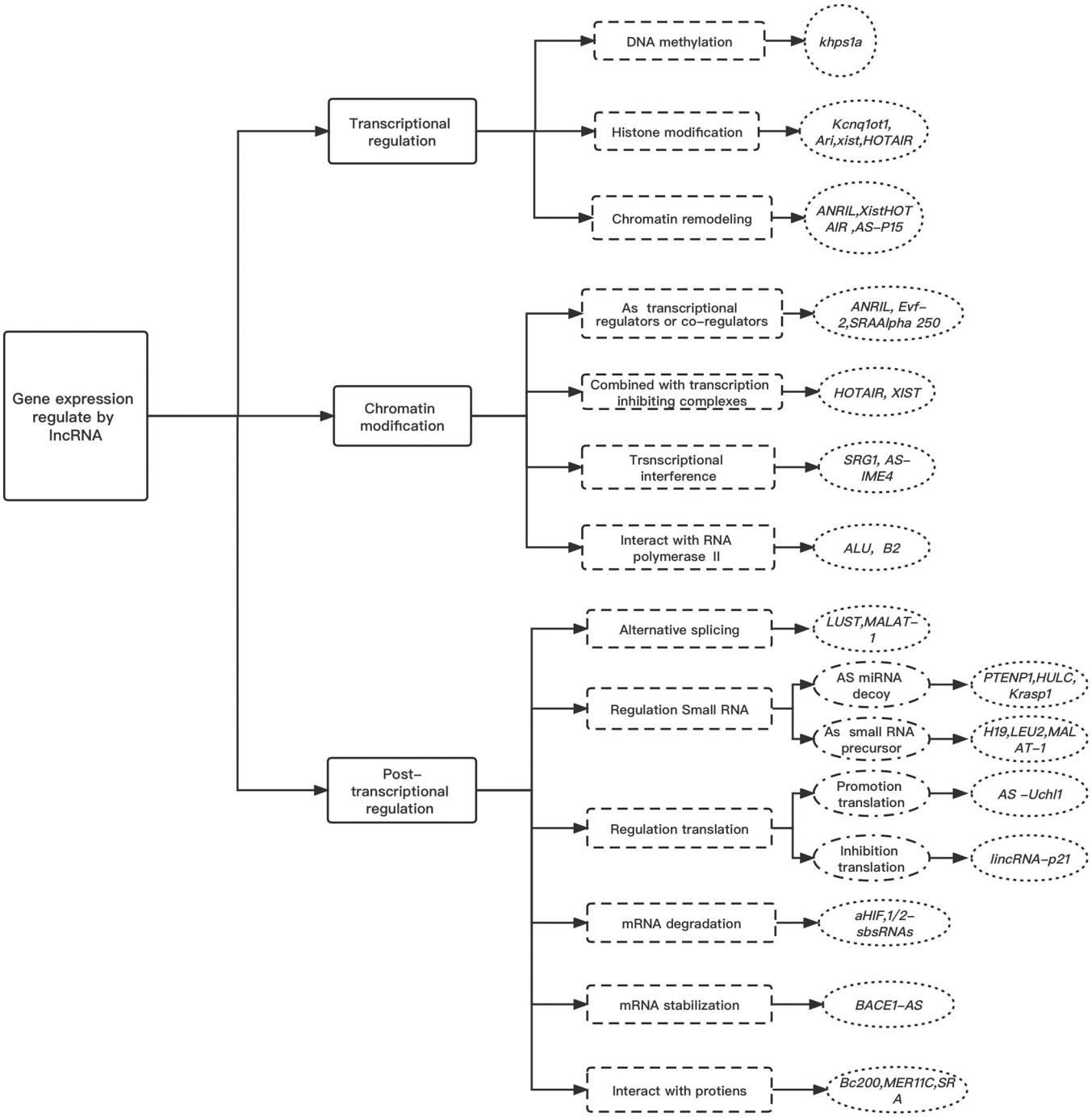

FIGURE 1 Regulation of gene expression by long noncoding RNA through transcriptional regulation, chromatin modification and posttranscriptional regulation mechanisms.

complementary double-stranded with transcripts of protein-coding genes, and further produced endogenous siRNA under Dicer cleavage, resulting in mRNA degradation and influencing gene expression levels [34]. LncRNAs also bind with RNA binding proteins to suppress mRNA splicing and translation and can function as ceRNAs to increase expression of mRNA, the miRNA target [31]. For example, lncRNA *MALAT1* was implicated in splicing of precursor mRNA (pre-mRNA) by influencing the distribution of serine/arginine-rich proteins [35]. LncRNA *BACE1-AS* competes with miR-485-5p to interact with BACE1 mRNA, representing another mechanism by which *BACE1-AS* controls the stability of BACE1 mRNA [36]. LncRNAs can act as a scaffold for various proteins to form ribonucleoprotein complexes [37].

In addition, LncRNA also directly interact with specific proteins to directly regulate their activity or alter their subcellular localization [38].

3 | LncRNAs RELATED TO HCC

Increasing research has shown that abnormal lncRNA expression is related to the occurrence and development of tumors, and lncRNAs have been shown to play important regulatory roles in these processes. Several studies have shown that some tumors did not harbor mutations in protein-encoding genes and instead exhibited abnormal expressions of lncRNAs [39]. Pan et al. [40] examined differentially expressed lncRNAs in a hepatoma carcinoma group and control group and found that the lncRNA expression profiles in the two groups were different, suggesting these differentially expressed lncRNAs may be involved in the molecular mechanisms of HCC. In the following section, we discuss the recent research related to lncRNAs in HCC (Table 1).

3.1 | LncRNAs promote the progression of HCC

Research has identified multiple lncRNAs that promote the occurrence or progression of HCC. The lncRNAs with oncogenic roles include *HULC, H19, MALAT1, HEIH, MVIH, HOTAIR*, and *HOTTIP/HOXA13*. Several lncRNAs associated with cell metabolism that promote HCC were recently reported, such as lncRNA *RP11-386G11.10* [41], *SNHG6* [42], *FASRL* [43], and *DACT3-AS1* [44].

3.1.1 | LncRNAs related to liver cancer cell proliferation

3.1.1.1 | Highly upregulated in liver cancer *(HULC)*

Various lncRNAs have been shown to regulate the proliferation of liver cancer cells, including *HULC*, *SNHG6*, *lncRNA RP11-386G11.10*, *MIAT*, and *ALKBH3-AS1*. Among these lncRNAs, HULC has been relatively well studied. *HULC* is located on chromosome 6p24.3 and has a length of approximately 500 nt. *HULC* is expressed at higher levels in human liver cancer cells compared with noncancerous liver cells. In contrast, *HULC* expression showed small differences or no differences in other tumor cells compared with the corresponding nontumor cells [45]. *HULC* is detectable in blood of HCC patients, and it is expected to be a potential biomarker of HCC [45]. Ruan et al. [46] found high expression of *HULC* in HCC, especially in HBV-related HCC. These studies suggest that *HULC* is a biological marker of HCC.

Knockdown of *HULC* in liver cancer cells resulted in changes in the expressions of tumor-related genes. Hepatitis B virus-related HCC was directly related with the upregulation of the expression of *HULC* [46]. Subsequent studies demonstrated that *HULC* prevented the proliferation of hepatic cells induced by hepatitis B virus through the upregulation of p18. This would provide a treatment ideal for hepatitis B virus-positive patients with HCC [47]. These effects of *HULC* are achieved by its targeting and inhibiting miRNAs, like miR-372. One study showed that different genotypic variations of rs7763881 in *HULC* reduced the susceptibility of Han Chinese patients with long-term hepatitis B virus [48].

3.1.2 | LncRNAs related to drug resistance in HCC

Several differentially expressed lncRNAs in HCC are closely related to drug resistance of liver cancer cells such as *H19*, *lncRNA GAS5* [49], *lncRNA NIFK-AS1* [50], *lncRNA CRNDE* [51], *MALAT1*, and *lncRNA PCGEM1* [52]. *H19* was the first identified lncRNA and is derived from a paternal gene. H19 is highly expressed in embryo somatic cells and is downregulated in most tissues rapidly after birth [53]. Notably, *H19* was found to be highly expressed in different types of tumor tissues [54]. A study revealed that *H19* upregulation was related to HCC [55]. Methylated forms of *H19* were related to the overexpression of *H19* in HCC. Researchers found that there are three methylated forms of *H19* in HCC: hyper-, medium-, and hypomethylated *H19*; the hypo- and hyper-profiles were related to *H19* aberrant imprinting [56].

H19 influences gene expression and affects cancer occurrence and development, but the mechanism is not completely understood. *H19* is believed to induce P-glycoprotein expression and *multidrug resistance 1 gene* (*MDR1*)-associated drug resistance through regulation of *MDR1* promoter methylation in HCC cells, which is involved in drug resistance, and thus knockdown of *H19* may be a target in HCC chemotherapy [57]. Knockdown of *H19* in HCC and gastric carcinoma cells prevented the anchoring growth of cancer cells after restoration from hypoxia [58]. Other research results also showed that *H19* prevents the development and growth of cells under hypoxia [59], which has specific implications for tumor tissues with high oxygen consumption, as tumor cells are in the hypoxic state because of the rapid growth of tumor tissues.

3.1.3 | LncRNAs related to liver cancer cell invasion, metastasis, and apoptosis

Multiple lncRNAs such as *lncRNA HOXD-AS1* [52], *MALAT1*, *CEBPA-DT* [60], *lnc-CTHCC* [61], and *HOTAIR* are associated with the metastasis of HCC. Below

TABLE 1 Long noncoding RNA (lncRNA) related to hepatocellular carcinoma (HCC).

	Function	Genes	Result
LncRNAs promotes the progression of HCC	Liver cancer cell proliferation	*HULC*	(1) *HULC* is not only that it is a biological mark of HCC, but more importantly, it has also been determined that it can be proven to promote HCC cells proliferation. (2) *HULC* could prevent the proliferation of hepatic cells induced by Hepatitis B virus through the upregulation of P18, which is one of the treatment methods for the Hepatitis B virus positive patients with HCC. (3) Different genotypic variations of rs7763881 in *HULC* can reduce the sensitive susceptibility degree of the patients with long-term carrying of Hepatitis B virus within the Han Chinese population. (4) *HULC* could be expected to be a novel biomarker of HCC.
	Drug resistance in HCC	*H19*	(1) *H19* could methylate the promoter of the multidrug resistance 1 gene (*MDR1* gene), by which the HCC cells produce the corresponding drug resistance, and could be used as a target for chemotherapy of HCC. (2) Knockdown of *H19* in HCC and gastric carcinoma cells could prevent the anchoring growth of cancer cells after their restoration from the hypoxia state. (3) *H19* could prevent the development and growth of cells under hypoxia, which had specific meaning for the tumor tissues with high oxygen consumption.
	Liver cancer cell invasion, metastasis, apoptosis	*MALAT1*	(1) The reduction of the expression of *MALAT1* in HCC cells can not only effectively reduce the invasion and metastasis of HCC cells, also promote apoptosis of cancer cells. (2) *MALAT1* may be a potential biomarker for predicting the metastasis of HCC and therapeutic targets. (3) The silencing and suppressing of the gene *MALAT1* by shRNA could block the cell growth cycle and invasive properties of many malignant tumors. (4) The inhibition of *MALAT1* could prevent the tumor cells proliferation and invasion in HCC and bladder cancer, also could promote tumor cell apoptosis.
		HOTAIR	(1) The inhibition of *HOTAIR* in HCC cells can decrease MMP9 production, as well as the vascular endothelial growth factor 68, which were found to be very important for the movement and transfer of the cells. (2) Decreasing its expression is expected to become a new type of treatment for HCC.
	HBV infection	*HEIH*	(1) The expression levels of *HEIH* could be as a biomarker for predicting the survival time. (2) lncRNA-HEIH participates in regulating cell cycles, which could recruit PRC2 might by combining with EZH2, and thereby inhibiting the expression of the downstream target genes, as well as affecting its regulation function.
	Liver cancer prognosis	*MVIH*	(1) The high expression of *MVIH* was closely related to microvascular invasion, intrahepatic metastasis, and poor prognosis. (2) *MVIH* could inhibit the secretion of PGK1, and also promote the angiogenesis of tumors.
		HOTTIP/ HOXA13	(1) *HOTTIP* has a possible as an early predictive marker of HCC.

TABLE 1 (Continued)

	Function	Genes	Result
			(2) Combined clinicopathological with *HOTTIP/HOXA13* expression data, which revealed that *HOTTIP/HOXA13* upregulation expression is related to metastasis of HCC patients and poor prognosis.
LncRNAs can inhibit the progression of HCC	Apoptosis of liver cancer cells	*MEG3*	(1) Increasing *MEG3* RNA could inhibit reduce the growth of HCC cells and induce cell apoptosis. (2) *Meg3* also plays an important role in other diseases such as ischemia-reperfusion injury and inflammation. (3) It can also directly bind to RNA-binding proteins, affecting the function of tumor cells.
	Tumor inhibitory	*LET*	(1) It was considered to have tumor suppressor activity. (2) The research on lncRNA *LET* has been reported in gastric cancer, bladder cancer, breast cancer, and so on. It mainly plays its tumor inhibitory function by competing to bind miRNA.
	Inhibit the growth and metastasis of HCC	*Dreh*	(1) It could inhibit HCC cells proliferation and metastasis. (2) *Dreh* could potentially interact with intermediate filament protein, inhibit its expression, and could also prevent HCC cells migration by changing the structure and morphology of cell cytoskeletons. (3) *Dreh*'s function mainly focuses on liver cancer and glucose transport, moreover, there are few reports on related signaling pathways.
		T-UCRs	(1) If *TUC338* was knocked down, the anchorage-dependent, as well as anchorage-independent growth of the HCC cells, would be inhibited. This suggested that *T-UCR* played significantly role in HCC cells, also provided new ideas for the therapy of HCC targeting lncRNA. (2) *T-UCR300a* also could block the malignant pathological manifestations of the invasive performance of tumor cells.
	Apoptosis of liver cancer cells	*uc002mbe.2*	(1) *uc002mbe.2* played regulatory role in inducing apoptosis of the HCC cells induced by Trichostatin A. (2) *uc002mbe.2* knockdown could reduce apoptosis induced by TSA and promote the proliferation of cancer HCC cells.

we describe several lncRNAs that have been extensively studied.

3.1.3.1 | *MALAT1*

The *MALAT1* gene is located on chromosome 11q13 and is over 8000 nt in length. *MALAT1* regulates gene expression and influences posttranscriptional modifications of the primary transcripts. *MALAT1* is conserved among all species, indicating the importance of its functions. *MALAT1* was found to be upregulated in multiple tumor types [4]. Reduced expression of *MALAT1* in HCC cells inhibited the invasion and metastasis and promoted the apoptosis of HCC cells. *MALAT1* may thus be a potential biomarker for predicting the metastasis of HCC and a therapeutic target. *MALAT1* was also shown to be an independent prediction index for the recurrence of HCC. Increased expression of *MALAT1* was identified in HCC cell lines and HCC tissues. Patients with highly expressed *MALAT1* in HCC cells, even following liver transplantation, still face the significant possibility of recurrence [62].

MALAT1 was found to be related with many malignant characteristics of tumors. Inhibition of *MALAT1* expression could reverse malignant characteristics of tumor cells, such as invasiveness, metastasis, and proliferation. Silencing of *MALAT1* by shRNA blocked cell growth and invasion activity of many malignant tumors through a mechanism involving the regulation of multiple genes, including *Caspase-3*, *Caspase-8*, and *Bax* genes [63]. Inhibition of *MALAT1* prevented tumor cell proliferation and

invasion in HCC and bladder cancer, and promoted tumor cell apoptosis [64].

3.1.3.2 | *HOTAIR*

HOTAIR is highly expressed in both primary and metastatic tumor tissues in breast carcinoma [65] and HCC [66]. The expression of *HOTAIR* in liver cancer tissue is significantly higher than that in adjacent tissues, and its expression level significantly correlated with tumor differentiation degree, tumor size, and TNM staging. Patients with distant metastasis, intravascular invasion, or advanced disease have significantly higher expression levels of *HOTAIR*, indicating that high expression of *HOTAIR* may play a role in promoting liver cancer proliferation, migration, and invasion. Furthermore, tumors with *HOTAIR* upregulation were associated with low survival rates [67] and a high recurrence rate [65]. Inhibition of *HOTAIR* in HCC cells decreased MMP9 production and vascular endothelial growth factor [68], which are critical for cell migration. These studies demonstrated that *HOTAIR* is related to the invasion and metastasis of HCC cells. Decreasing its expression may be a potential treatment strategy for HCC.

3.1.4 | LncRNAs associated with HBV infection

HEIH is a highly and specifically expressed lncRNA in HCC tissues that was discovered by Sun et al. in a study on the lncRNA expression spectrums in HCC in para-carcinoma tissues of hepatitis B virus-infected patients using lncRNA chip analysis [6]. Kaplan-Meier analysis determined that *HEIH* expression level may be a biomarker for predicting survival and its expression highly correlated with cancer recurrence. A functional study indicated that *lncRNA-HEIH* regulates the cell cycle and recruits PRC2 by interacting with EZH2 and affecting its transcriptional regulation function, thereby inhibiting the expression of downstream target genes. These findings indicate that *lncRNA-HEIH* plays an important regulatory role in hepatocarcinogenesis.

3.1.5 | LncRNA associated with liver cancer prognosis

3.1.5.1 | *MVIH*

Yuan et al. [69] reported that the level of *MVIH* (NCBI N0. AK094613) in HCC tissues was significantly higher than that in peri-carcinoma tissues and *MVIH* is involved in the angiogenesis of tumors. The authors performed a microarray analysis of tumor tissues and paired para-cancerous tissues of 40 patients with HCC related to hepatitis B. Clinical research data of 215 HCC patients revealed that high expression of *MVIH* was closely related to microvascular invasion, intrahepatic metastasis, and poor prognosis. *MVIH* was found to inhibit the secretion of PGK1 and promote tumor angiogenesis.

3.1.5.2 | *HOTTIP/HOXA13*

The *LncRNA HOXA* transcript at the distal tip (*HOTTIP*) is located in adjacent with *HOXA13* [70]. *HOTTIP*, similar to *lncRNA Xist* and *HOTAIR*, plays a key role in gene expression regulation by influencing chromatin modification [71]. *HOTTIP* and *HOXA13* are upregulated in HCC and are involved in hepatocarcinogenesis [72]. Upregulation of *HOTTIP* was also observed in nontumor liver diseases (such as cirrhosis and HCV-infected cirrhosis), which suggests that *HOTTIP* imbalance may be the early step of *HOXA13* leading to hepatocarcinogenesis [72]. Therefore, *HOTTIP* may be an early predictive marker of HCC. Upregulation of *HOTTIP/HOXA13* expression was found to be related to metastasis and poor prognosis of HCC.

3.2 | LncRNAs that inhibit the progression of HCC

In contrast to the lncRNAs described above, many lncRNAs function as tumor suppressors in HCC through their activities in promoting apoptosis and inhibiting metastasis and proliferation of tumor cells. For example, both *lncRNA CASC2* [73] and *RUNX1-IT1* [74] promote the apoptosis of HCC cells. Below we discuss several important lncRNAs that can inhibit HCC.

3.2.1 | *Maternally expression gene 3 (MEG3)*

MEG3 is expressed in various normal tissues and was found to exhibit a tumor suppression function. The *MEG3* lncRNA gene is a single-copy imprinted gene that contains 10 exons. As a result of various splicing patterns, 12 isoforms are expressed, which display three secondary domains [75, 76].

MEG3 is widely studied, and its expression has been reported in various tumors. *MEG3* was found to interact with cAMP and *p53* [77, 78]. The effect of *MEG3* on *p53* activation depends on the secondary structure of *MEG3* [78]. *MEG3* expression is controlled by epigenetic modifications, and abnormal methylation of CpGs in *MEG3* was observed in a variety of cancer types [79–82]. Compared with normal liver cells, HCC cells show

downregulation of MEG by 210-fold. Increasing *MEG3* RNA inhibited the growth of HCC cells and induced cell apoptosis [82]. Furthermore, the authors found that *miR-29* promotes *MEG3* expression. Compared with wild-type control mice, *miR-29a/b1* knock-out mice showed a downregulation of *MEG3* in liver tissues [82].

MEG3 plays an important role in diseases such as ischemia-reperfusion injury and inflammation. Its mechanism of action is relatively complex, and it regulates cell function by its action as a ceRNA [83]. *MEG3* also directly binds to RNA binding proteins, affecting the function of tumor cells. The role of *MEG3* in hepatocarcinogenesis and development is still under study.

3.2.2 | *LncRNA-LET*

LncRNA LET expression has been reported in gastric cancer, bladder cancer, breast cancer, and HCC. It mainly exerts a tumor inhibitory function through its activity as a ceRNA [84–87].

Yang et al. [88] found that *lncRNA-LET* (NCBI number AK055007) was downregulated in HBV-related HCC. Further study showed that *lncRNA-LET* exhibited reduced expression in HCC, colorectal, and squamous cell lung cancers. Furthermore, downregulated *lncRNA-LET* promoted HCC metastasis. Thus, *lncRNA-LET* was considered to have tumor suppressor activity. Hypoxia-induced histone deacetylase 3 inhibits *lncRNA-LET* by reducing histone acetylation of the *lncRNA-LET* promoter [88]. *lncRNA-LET* downregulation stabilizes nuclear factor 90, which leads to hypoxia-induced invasion of cancer cells.

3.2.3 | *Dreh*

Huang et al. [89] examined the alterations of lncRNA expression induced by *HBx* and found that *Dreh* inhibited the growth and metastasis of HCC. The authors found that *HBx* transgenic mice have a specific profile of liver lncRNAs compared with wild-type mice and identified *lncRNA-Dreh* as a lncRNA downregulated by *HBx*. Functional experiments showed that *Dreh* inhibits HCC cell proliferation and metastasis. *Dreh* may also interact with intermediate filament protein and inhibit its expression, and it prevents HCC cell migration by changing the structure and morphology of cell cytoskeletons. In HCC patients with high expression of *Dreh*, the recurrence rate was low and the prognosis was good. While research on *Dreh* function mainly focuses on liver cancer and glucose transport, some studies have investigated the related signaling pathways.

3.2.4 | *T-UCR338*

Transcribed ultra-conserved regions (T-UCRs), a class of lncRNAs, are transcribed from ultra-conserved regions [12]. *UCRs* are DNA noncoding genomic segments of at least 200 bp in length that are completely conserved across humans, mice, and rats. A total of 481 *UCRs* have been identified, some of which overlap with coding exons; more than half of them are noncoding genes [90]. Approximately 68% of *UCRs* are transcribed, constituting a new category of ncRNAs, the *T-UCRs* [91]. *T-UCR* expressions are altered in human tumorigenesis, such as leukemia, neuroblastoma, colorectal cancer, and HCC [91–93]. *T-UCRs* are aberrantly expressed in malignant hepatocytes. *T-UCR 338* is a *T-UCR* with a length of 590 nt. Knockdown of *TUC338* led to inhibition of anchorage-dependent and anchorage-independent growth of HCC cells. This suggested that *T-UCR* plays a significant role in regulating the growth of HCC cells [93]. Other studies have shown that reducing other *T-UCRs*, such as *T-UCR300a*, could block the invasion of HCC cells [94]. These findings may lead to the development of new therapeutic strategies for HCC.

3.2.5 | *uc002mbe.2*

The lncRNA *uc002mbe.2* is downregulated in liver cancer, and its downregulation inhibits the apoptosis of tumor cells. Furthermore, *uc002mbe.2* mediates trichostatin-induced apoptosis of liver cancer cells [95, 96]. Chen et al. [97] found that the interaction between *uc002mbe.2* and *hnRNPA2B1* can mediate AKT deactivation and p21 induction is related, thereby participating in the cytostatic effect of trichostatin in HCC cells. The global expression of lncRNAs and coding genes was analyzed with the Human LncRNA Array V2.0 after 24 h treatment of liver cancer cells with Trichostatin A. Among the differentially expressed lncRNAs, *uc002mbe.2* change the most. Knockdown of *uc002mbe.2* reduced the apoptosis induced by TSA and promoted the proliferation of HCC cells. Moreover, *uc002mbe.2* was significantly deregulated in HCC cell lines and tissues compared with normal human hepatocytes and adjacent noncancerous tissues. The function of *uc002mbe.2* in other tumors has not been reported yet.

4 | FUTURE PROSPECTS

The functions of lncRNA are complex and diverse. In cancer, lncRNAs can function as oncogenic factors that promote tumor occurrence and development or tumor suppressors that inhibit cancer growth. Some lncRNAs

promote tumor distant metastasis and are associated with poor prognosis while some lncRNAs are associated with improved prognosis. LncRNAs may serve as tumor molecular markers or therapeutic targets, providing new strategies for the diagnosis and treatment of tumors. More research on the relationship between lncRNAs and tumor development is required.

LncRNAs form very large and complex post-transcriptional and pre-protein translation regulatory networks. The number of lncRNAs is large, and the number of lncRNAs in human cells can reach up to tens of thousands. However, the lncRNAs that have been currently studied only account for a few of the total lncRNAs, and research on the function of lncRNA in tumors, including in HCC, remains in the initial stage. With further investigations on the molecular mechanism of HCC, new lncRNAs related to HCC will be continuously discovered, and the regulation mechanisms will be further revealed. These findings will help provide insights to aid in early diagnosis of HCC, establish molecular targeted therapies, and improve the survival of HCC patients.

AUTHOR CONTRIBUTIONS

Jingli Du: Conceptualization (equal); methodology (equal); resources (equal); writing—original draft (equal). **Yue Su**: Data curation (equal); resources (equal). **Jianzhi Gao**: Investigation (equal); supervision (equal). **Yanhong Tai**: Formal analysis (equal); Writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are openly available in a public repository that issues data sets with DOIs.

ETHICS STATEMENT

Not Applicable.

INFORMED CONSENT

Not Applicable.

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