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## Long non-coding RNAs in hepatocellular carcinoma: Potential roles and clinical implications

Zhao-Shan Niu, Xiao-Jun Niu, Wen-Hong Wang

Zhao-Shan Niu, Laboratory of Micromorphology, School of Basic Medicine, Medical Department of Qingdao University, Qingdao 266071, Shandong Province, China

Xiao-Jun Niu, Oncology Specialty, Medical Department of Qingdao University, Qingdao 266071, Shandong Province, China

Wen-Hong Wang, Department of Pathology, School of Basic Medicine, Medical Department of Qingdao University, Qingdao 266071, Shandong Province, China

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**Correspondence to:** Zhao-Shan Niu, MD, Laboratory of Micromorphology, School of Basic Medicine, Medical Department of Qingdao University, Room 201, Building Boya, 308 Ningxia Road, Qingdao 266071, Shandong Province, China. [z.s.niu@qdu.edu.cn](mailto:z.s.niu@qdu.edu.cn)  
Telephone: +86-532-83780012  
Fax: +86-532-83780012

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### Abstract

Long non-coding RNAs (lncRNAs) are a subgroup of non-coding RNA transcripts greater than 200 nucleotides in length with little or no protein-coding potential. Emerging evidence indicates that lncRNAs may play important regulatory roles in the pathogenesis and progression of human cancers, including hepatocellular carcinoma (HCC). Certain lncRNAs may be used as diagnostic or prognostic markers for HCC, a serious malignancy with increasing morbidity and high mortality rates worldwide. Therefore, elucidating the functional roles of lncRNAs in tumors can contribute to a better understanding of the molecular mechanisms of HCC and may help in developing novel therapeutic targets. In this review, we summarize the recent progress regarding the functional roles of lncRNAs in HCC and explore their clinical implications as diagnostic or prognostic biomarkers and molecular therapeutic targets for HCC.

**Key words:** Hepatocellular carcinoma; Long non-coding RNAs; Function; Biomarker; Therapeutic target

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**Core tip:** Emerging evidence indicates that long non-coding RNAs (lncRNAs) may play important regulatory roles in the pathogenesis and progression of human cancers, including hepatocellular carcinoma (HCC). Therefore, elucidating the functional roles of lncRNAs in tumors can contribute to a better understanding of the molecular mechanisms of HCC and may help in developing novel therapeutic targets. In this review, we summarize the recent progress regarding the functional

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## INTRODUCTION

Hepatocellular carcinoma (HCC), a major type of primary liver cancer, is the second leading cause of cancer death worldwide<sup>[1]</sup>. Unfortunately, the incidence and mortality rates of HCC have continued to increase globally. The high mortality of HCC patients is mainly due to late diagnosis, leading to limited therapeutic options. Accordingly, there is an urgent need to elucidate the molecular mechanisms involved in the initiation and progression of HCC to identify reliable biomarkers for early diagnosis and therapeutic targets to improve the survival of these patients. Recent data have demonstrated that the complexity of human carcinogenesis cannot be accounted for by genetic alterations alone and that epigenetic changes may also be involved<sup>[2]</sup>. In fact, it is becoming increasingly evident that dysregulated epigenetic regulatory processes play a central role in cancer onset and progression<sup>[3]</sup>. In human HCC, for example, epigenetic changes in various cancer-related genes are more frequently observed than genetic changes<sup>[4]</sup>, suggesting the crucial impact of epigenetic alterations in hepatocarcinogenesis.

Epigenetic alterations include changes in DNA methylation, histone modifications, and non-coding RNA-mediated gene silencing<sup>[5]</sup>. Recent studies have revealed that the vast majority of the human genome is actively transcribed into non-coding RNAs (ncRNAs), only 1%-2% of which encode proteins<sup>[6,7]</sup>. As most cancer studies to date have principally focused on protein-coding genes, the function of ncRNAs in cancer remains largely unknown. Nonetheless, accumulating evidence is shedding light on the functional importance of ncRNAs in cancer biology, and these molecules are emerging as new regulators of diverse biological functions, with important roles in oncogenesis and tumor progression<sup>[8]</sup>. ncRNAs can be roughly classified into the following two groups based on length: small ncRNAs (< 30 nucleotides) and long ncRNAs (lncRNAs; > 200 nucleotides)<sup>[9]</sup>. Small ncRNAs, especially microRNAs (miRNAs), have been studied extensively. In contrast, lncRNAs are the least studied transcripts and their functions remain largely unknown, even though they constitute the majority of ncRNAs.

lncRNAs were initially regarded as "transcriptional

noise" of the transcriptome. However, the recent application of next-generation sequencing, particularly RNA-sequencing (RNA-Seq), has broadened and deepened our knowledge of lncRNAs related to various types of diseases, including cancer. It is clear that lncRNAs act as critical regulators of multiple cellular processes, especially gene expression. It has been well documented that many lncRNAs are frequently aberrantly expressed in human cancers in which they may serve as oncogenes or tumor suppressors<sup>[10-12]</sup>, suggesting that they may act as novel drivers of tumorigenesis. Compared with protein-coding genes, lncRNA alterations are highly tumor- and cell line-specific<sup>[13]</sup>, and this characteristic of specificity makes lncRNAs promising biomarkers for diagnosis. Importantly, lncRNAs play critical regulatory roles in the pathogenesis and progression of cancers, including cell proliferation, differentiation, apoptosis, tumorigenesis, and progression<sup>[14-17]</sup>. All of these findings point to lncRNAs as promising diagnostic or prognostic biomarkers and potential therapeutic targets for cancer.

Given the critical roles of lncRNAs in the initiation and progression of cancer, it is not surprising that lncRNAs have aroused considerable interest in HCC research. To date, multiple HCC-related lncRNAs have been identified. *In vitro* and *in vivo* functional experiments have shown that in HCC cells, lncRNAs are involved in the regulation of diverse biological processes, such as proliferation, migration, apoptosis, the cell cycle, tumorigenesis, and metastasis. Moreover, increasing evidence indicates that lncRNAs may play irreplaceable roles in the initiation and progression of HCC. As lncRNAs may serve as diagnostic or prognostic biomarkers and therapeutic targets for HCC, elucidating the roles of lncRNAs in tumors can contribute to a better understanding of the molecular mechanisms of HCC and assist in the development of novel therapeutic targets. In this review, we summarize the recent progress regarding the functions of lncRNAs in HCC and explore their clinical implications as diagnostic or prognostic biomarkers and molecular therapeutic targets.

## CLASSIFICATION OF LNCRNAs

As they can be categorized according to their various properties, such as transcript length, genomic location and context, sequence and structure conservation, effects on DNA sequences, functional mechanisms and targeting mechanisms, association with protein-coding genes or subcellular structures, many different classifications of lncRNAs have been proposed<sup>[18,19]</sup>. For example, according to their genomic location relative to neighboring protein-coding genes, lncRNAs have generally been categorized into five classes: sense, antisense, intronic, intergenic, and bidirectional lncRNAs<sup>[20]</sup>. lncRNAs may also be classified according to their targeting mechanisms: signal, decoy, guide,

and scaffold<sup>[21]</sup>.

However, there has been no systematic and unambiguous classification of lncRNAs to date, and many existing lncRNA classifications are conflicting and overlapping. Different criteria (databases, projects, and methodologies) used to classify lncRNAs may be primarily responsible for the classification overlap. In reality, lncRNAs are not a homogeneous class of molecules but rather a mixture of multiple functional classes with distinct biological mechanisms and/or roles<sup>[22]</sup>. Many lncRNAs are not easily classified into any particular category, and it is likely that the same lncRNAs may be listed in different groups in all classifications<sup>[23,24]</sup>. In addition, the vast majority of lncRNAs remain functionally uncharacterized, which hampers their functional classification.

Given their complexity, from biogenesis to function, these overlapping and conflicting classifications would inevitably add another layer of difficulty to our understanding of lncRNA biology. Interestingly, the authors of a recent review highlight the roles of large systems biology-based datasets as conceptual guidelines for lncRNA classification and functional annotation<sup>[19]</sup>. Specifically, advances in high-throughput transcriptome sequencing technologies will contribute to uncovering previously unknown functions of lncRNAs, and as such, the arbitrary classifications will need to be redefined.

## SUBCELLULAR LOCALIZATION PATTERNS OF LNCRNAs

lncRNAs have diverse subcellular localization patterns, ranging from bright sub-nuclear foci to almost exclusive cytoplasmic localization; some lncRNAs are found in both compartments<sup>[25,26]</sup>, with the majority preferentially localized to the nucleus and chromatin<sup>[20,27-29]</sup>. Importantly, it is becoming increasingly clear that the function of lncRNAs depends on their subcellular localization<sup>[30]</sup>. In general, nuclear lncRNAs are recognized as important transcriptional and epigenetic modulators of nuclear functions<sup>[15,31,32]</sup>, whereas cytoplasmic lncRNAs have been described as modulating mRNA stability and translation<sup>[32,33]</sup>. Compared with the mostly highly abundant cellular RNAs, the vast majority of lncRNAs that are typically less abundant in a population of cells can be highly abundant in individual cells<sup>[25,34]</sup>. To more precisely locate and confirm the sub-cellular localization of lncRNAs, two recent reports have suggested that rather than using conventional RNA fluorescence *in situ* hybridization (FISH) techniques that have a relatively low sensitivity, it may be more effective to study lncRNAs by applying single-molecule RNA FISH<sup>[25,35]</sup>.

## MECHANISMS OF LNCRNA-MEDIATED GENE EXPRESSION

To date, the biological functions and molecular

mechanisms of most lncRNAs remain largely elusive, with only very few being partially characterized. Nevertheless, existing evidence demonstrates that these molecules play critical roles in the regulation of specific cellular processes, specifically in protein-coding gene expression at the epigenetic, transcriptional and post-transcriptional levels<sup>[36-40]</sup>.

### Epigenetic regulation

Epigenetic regulatory mechanisms can act at genomic (DNA methylation or demethylation) or nucleosomal and chromatin (post-translational histone modifications and chromatin remodeling complexes) levels<sup>[41]</sup>. As stated above, the majority of lncRNAs localize preferentially to the nucleus and chromatin, and increasing evidence indicates that some nuclear lncRNAs epigenetically regulate gene expression by altering chromatin structure<sup>[42]</sup>. There are two underlying mechanisms by which lncRNAs mediate changes in chromatin and gene expression. First, they can directly interact with chromatin-modifying enzymes, functioning as guides in *cis* or *trans* by recruiting chromatin modifiers to specific genomic loci to mediate DNA methylation or histone modification, thereby modulating chromatin states and impacting gene expression<sup>[32,43-47]</sup>. Second, lncRNAs function as adaptors that link specific chromatin loci with ATP-dependent chromatin-remodeling complexes<sup>[48,49]</sup>, serving as guides to target these complexes to regulate nucleosome remodeling and gene expression<sup>[47,50,51]</sup>.

In addition, lncRNAs have been identified as crucial regulators of epigenetic processes such as X-chromosome inactivation<sup>[52,53]</sup>, genomic imprinting<sup>[53,54]</sup>, cellular differentiation determination<sup>[55,56]</sup>, and cell identity maintenance<sup>[57]</sup>. Thus, lncRNAs play crucial roles in the epigenetic regulation of gene expression. In particular, investigation of the interrelationships between lncRNAs and epigenetic modifications will provide new insight into cancer diagnosis and therapy.

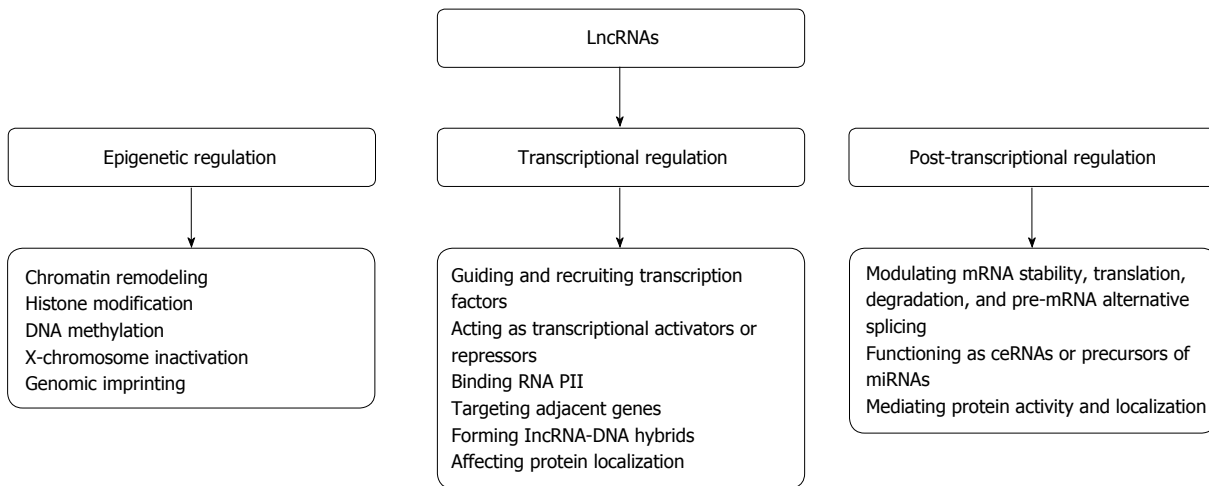
### Transcriptional regulation

At the level of transcriptional regulation, lncRNAs regulate gene expression by (1) recruiting and guiding transcription factors to the promoter region of target genes to regulate their transcription; (2) functioning as transcriptional activators or repressors to mediate gene transcription; (3) interacting with RNA polymerase II to regulate gene transcription; (4) interfering with transcription of adjacent genes in *cis*; (5) forming lncRNA-DNA hybrids to repress transcription of a target; and (6) affecting protein localization to regulate gene expression<sup>[24,58-63]</sup>.

### Post-transcriptional regulation

lncRNAs regulate the expression of genes responsible for biological functions at the post-transcriptional level by modulating messenger RNA (mRNA) stability, translation, degradation, and pre-mRNA alternative





**Figure 1 The regulatory mechanisms of long non-coding RNAs.** LncRNAs: Long non-coding RNAs; RNA PII: RNA polymerase II; ceRNAs: Competing endogenous RNAs; mRNA: Messenger RNA; miRNAs: MicroRNAs.

splicing genes. These molecules also function as competing endogenous RNA (ceRNA) or endogenous microRNA (miRNA) sponges, act as precursors of miRNAs, and interact with proteins to mediate their activity or alter their localization<sup>[58,64-71]</sup>. Through these mechanisms, lncRNAs play crucial roles in the post-transcriptional regulation of gene expression.

Taken together, these distinct molecular mechanisms allow dysregulated lncRNAs to up-regulate or down-regulate gene expression, thereby determining their regulatory functions in various biological processes. Nevertheless, the complicated mechanisms underlying such regulatory behaviors need further investigation. The biological functions and molecular mechanisms of action of lncRNAs are presented in Figure 1.

## FUNCTIONAL ROLES OF LNCRNAs AND MECHANISMS UNDERLYING LNCRNAs DYSREGULATION IN CANCER

Numerous investigations have indicated that aberrantly expressed lncRNAs play critical roles in cancer initiation and progression. However, the biological functions and mechanisms of the majority of lncRNAs in cancer remain largely unknown. In general, lncRNAs regulate gene expression in cancer at the epigenetic, transcriptional, and post-transcriptional levels. Consequently, lncRNAs affect cell proliferation, survival, migration, or genomic stability<sup>[72]</sup>, thereby contributing to tumor development. Specifically, evidence to date demonstrates that lncRNAs are frequently aberrantly expressed in human cancers in which they may serve as oncogenes or tumor suppressors<sup>[73,74]</sup>. These lncRNAs can mediate several cancer-associated processes, including epigenetic regulation, the DNA damage response, cell cycle control, and miRNA silencing<sup>[75]</sup>. Furthermore, dysregulated lncRNAs

can disrupt multiple cellular oncogenic pathways by exerting oncogenic and/or tumor suppressive functions. LncRNAs also drive many important cancer phenotypes through interactions with other cellular macromolecules, including DNA, protein, and RNA<sup>[76]</sup>. In brief, the role of lncRNAs in cancer initiation and progression is evident, yet the detailed mechanisms of their involvement in this process need to be clarified.

To date, researchers have elucidated genetic, epigenetic, and transcriptional regulatory mechanisms responsible for dysregulation of lncRNAs in cancer<sup>[77]</sup>. For instance, genetic regulatory factors, such as genetic instability and single-nucleotide polymorphisms, can be found in lncRNAs and might contribute to their aberrant expression in cancer<sup>[77]</sup>. Additionally, aberrant expression of lncRNAs with oncogenic properties can be caused by gene amplifications and point mutations<sup>[78]</sup>. Epigenetic regulation, such as DNA methylation or histone acetylation in the promoter region of lncRNAs, can alter their expression in cancer<sup>[79,80]</sup>, and expression of some cancer-associated lncRNAs can also be initiated by some key transcription factors, such as Myc and p53<sup>[81,82]</sup>, or signaling cascades such as Notch<sup>[83]</sup>. Taken together, the above-mentioned regulatory factors contribute to aberrant expression of lncRNAs in cancer, with the dysregulated lncRNAs consequently acting as important regulators of cancer initiation and progression.

## DYSREGULATED EXPRESSION OF LNCRNAs IN HCC

It has been proven that aberrant lncRNA expression leads to dysregulation of downstream effectors and that lncRNAs may provide a cellular growth advantage resulting in HCC<sup>[84]</sup>, suggesting that lncRNAs may serve as promising diagnostic biomarkers and potential therapeutic targets for HCC. Thus far, multiple

**Table 1** Hepatocellular carcinoma associated long non-coding RNAs in this review

LncRNA	Chromosomal location	Dysregulation	Biological roles	Ref.
<i>H19</i>	11p15.5	Up-regulated	Promotes HCC growth	Matouk <i>et al</i> <sup>[93]</sup>
		Down-regulated	Inhibits migration and invasion of HCC cells	Lv <i>et al</i> <sup>[98]</sup>
<i>HOTAIR</i>	12q13.13	Up-regulated	Promotes HCC growth	Geng <i>et al</i> <sup>[107]</sup>
<i>HOTTIP</i>	7p15.2	Up-regulated	Promotes proliferation of HCC cells	Quagliata <i>et al</i> <sup>[115]</sup>
<i>HULC</i>	6p24.3	Up-regulated	Promotes HCC growth	Zhang <i>et al</i> <sup>[127]</sup>
<i>MALAT1</i>	11q 13.1	Up-regulated	Promotes invasion	Lai <i>et al</i> <sup>[148]</sup>
<i>MVIH</i>	10q22-q23	Up-regulated	Promotes HCC growth, microvascular invasion, and intrahepatic metastasis	Shi <i>et al</i> <sup>[153]</sup>
<i>MEG3</i>	14q32.2	Down-regulated	Inhibits cell growth	Zhu <i>et al</i> <sup>[166]</sup>
<i>Lnc-FTX</i>	Xq13.2	Up-regulated	Promotes proliferation and cell cycle progression of HCC cells	Liu <i>et al</i> <sup>[175]</sup>
		Down-regulated	Inhibits proliferation and cell cycle progression of HCC cells	Liu <i>et al</i> <sup>[176]</sup>

HCC: Hepatocellular carcinoma; LncRNA: Long non-coding RNA; *H19*: *H19*, imprinted maternally expressed transcript; *HOTAIR*: HOX antisense intergenic RNA; *HOTTIP*: HOXA transcript at the distal tip; *HULC*: Highly up-regulated in liver cancer; *MALAT1*: Metastasis-associated lung adenocarcinoma transcript 1; *MEG3*: Maternally expressed gene 3; *MVIH*: Microvascular invasion in HCC; *FTX*: Five prime to Xist.

dysregulated lncRNAs have been identified as participating in the initiation and progression of HCC. Here, we briefly summarize seven well-documented lncRNAs in HCC: *H19*, *HOTAIR*, *HULC*, *HOTTIP*, *MALAT1*, *MVIH*, and *MEG3*. *FTX*, a novel lncRNA associated with HCC, is also discussed. Up-regulated expression of lncRNAs in HCC is thought to have an oncogenic function, whereas a few lncRNAs exhibiting down-regulated expression in HCC may act as tumor suppressors (Table 1).

### **H19**

The human *H19* gene (*H19*) is a paternally imprinted gene located on human chromosome 11p15.5, a locus that contains several imprinted genes, such as insulin-like growth factor 2 (*IGF2*) and *H19*. Although *H19* has been investigated for years, its role in tumorigenesis is still controversial. Increasing evidence suggests that *H19* is highly expressed in many human cancers<sup>[73,85-88]</sup>, indicating that it acts as an oncogene and that its activation may play a critical role in tumorigenesis. Nonetheless, several studies have shown that *H19* functions as a tumor suppressor<sup>[89-92]</sup>. Apparently, *H19* has a dual role in tumorigenesis, reflecting the complexity of *H19* function. According to the literature, *H19* function in HCC is seemingly much more complicated than that in other types of cancers; indeed, its function in hepatocarcinogenesis is largely debated. Numerous investigations have shown that the *H19* gene behaves as an oncogene, with its activation contributing to hepatocarcinogenesis. For example, hypoxia induces *H19* expression in HCC cells both *in vitro* and *in vivo*. Furthermore, silencing *H19* expression attenuates tumor growth *in vivo*, suggesting that *H19* behaves as an oncogene and enhances the tumorigenic potential of HCC cells *in vivo*<sup>[93]</sup>. A mechanism by which *H19* exerts its oncogenic activity in hepatocarcinogenesis has been proposed. Alterations in gene expression at the *H19/IGF2* locus are associated with malignancies<sup>[87]</sup>. In

particular, *H19* is a precursor of *miR-675*, and *H19* and *miR-675* are increasingly described as having key roles in the progression and metastasis of cancers of different tissue origins<sup>[94]</sup>. Recent data indicate that *H19*-derived *miR-675* favors tumor progression in HCC by repressing expression of twist-related protein 1<sup>[95]</sup>, and *miR-675* up-regulates *H19* by activating *EGR1* in human liver cancer<sup>[96]</sup>. These findings suggest that the oncogenic role of *H19* is mediated through *miR-675*. Aflatoxin B1 (AFB1) presents another mechanism related to the oncogenic function of *H19*. AFB1 induces expression of transcriptional factor *E2F1* (*E2F1*), and AFB1-induced *E2F1* up-regulates the expression of *H19* in HCC HepG2 cells, thereby promoting cellular growth and invasion<sup>[97]</sup>.

Regardless, current evidence supports a role of *H19* as a tumor suppressor. A study investigating the effect and mechanism of *H19* and *miR-675* on HCC cell migration and invasion reported that inhibition of *H19* and *miR-675* expression can promote the migration and invasion of HCC cells via the AKT/GSK-3 $\beta$ /Cdc25A signaling pathway<sup>[98]</sup>. This finding suggests that *H19* acts as a tumor suppressor in HCC cells. Intriguingly, recent data indicate that *H19* is down-regulated in intratumoral HCC tissues compared with peritumoral tissues<sup>[99]</sup>. Additionally, *H19* plays a role in promoting tumor initiation but exerts its tumor-suppressive effect on subsequent tumor progression and metastasis in HCC<sup>[99]</sup>. These findings suggest a tumor-promoting mechanism for *H19* in peritumoral HCC tissues and also indicate that *H19* has distinct roles at different stages of HCC development. Given the complexity of *H19* function in HCC, there is a need for further investigation to resolve the discrepancy.

In particular, a recent study found that up-regulation of *H19* has a statistically significant linear correlation with *AFP* mRNA levels in HCC tumor samples<sup>[95]</sup>, suggesting its role as a potential non-invasive diagnostic biomarker in HCC. Therefore, it should be feasible to detect both *AFP* and *H19* simultaneously to achieve

better performance in HCC management.

### **HOTAIR**

HOX transcript antisense intergenic RNA (*HOTAIR*) is a human gene located on chromosome 12q13.13 that is co-expressed with *HOXC* genes. *HOTAIR* has been identified as regulating chromatin silencing of the adjacent *HOX* locus<sup>[100]</sup>. Recent studies have revealed that *HOTAIR* functions as a molecular scaffold to link polycomb repressive complex 2 (*PRC2*) and lysine-specific demethylase 1/REST corepressor 1/RE1-silencing transcription factor (*LSD1/CoREST/REST*) complexes and direct them to specific gene sites, leading to altered histone H3 lysine 27 (*H3K27*) methylation and *H3K4* demethylation and ultimately resulting in epigenetic gene silencing<sup>[46,101]</sup>. Accumulating evidence demonstrates that *HOTAIR* is dysregulated in a variety of human cancers and that overexpression of *HOTAIR* is associated with cancer cell proliferation, apoptosis, invasion, progression, and metastasis as well as poor survival<sup>[102-105]</sup>.

It has been reported that *HOTAIR* expression in HCC tissues is significantly higher than that in adjacent non-cancerous tissues<sup>[106,107]</sup>. In addition, the expression levels of *HOTAIR* in liver cancer cell lines were found to be higher than those in normal liver cell lines<sup>[106]</sup>. These findings suggest that *HOTAIR* exhibits oncogenic activity in HCC. Thus far, several studies have investigated the clinical implications of *HOTAIR* in HCC. Patients with HCC that overexpress *HOTAIR* have an increased risk of recurrence following hepatectomy, and there is also a correlation between *HOTAIR* overexpression and increased risk of lymph node metastasis<sup>[108]</sup>. A high level of *HOTAIR* expression has potential as a candidate biomarker for predicting HCC recurrence in liver transplantation (LT) patients<sup>[106]</sup>. Furthermore, patients with high expression of *HOTAIR* have a significantly shorter recurrence-free survival than patients with low expression of *HOTAIR*<sup>[109]</sup>. Taken together, these findings support the role of *HOTAIR* as a metastatic biomarker. Indeed, just as in most other types of cancer, *HOTAIR* is considered most valuable as a prognostic indicator in HCC, particularly as a metastatic biomarker rather than as a diagnostic biomarker<sup>[110]</sup>.

Various mechanisms have been proposed for the oncogenic activity of *HOTAIR* in HCC. For example, a regulatory network between *miR-218* and *HOTAIR* was elucidated, whereby *HOTAIR* inactivates P16 (Ink4a) and P14 (ARF) signaling by down-regulating *miR-218* expression in HCC via *EZH2* targeting of the *miR-218-2* promoter regulatory axis and enhancing *Bmi-1* expression, resulting in hepatocarcinogenesis<sup>[111]</sup>. In addition, up-regulation of *HOTAIR* promotes proliferation, migration, and invasion of human HCC cells by activating autophagy<sup>[112]</sup>, by inhibiting RNA binding motif protein 38 (RBM38)<sup>[113]</sup>, or in part by modulating *miR-1*<sup>[114]</sup>.

### **HOTTIP**

HOXA transcript at the distal tip (*HOTTIP*), which is transcribed from the 5' tip of the *HOXA* locus, has been observed to be up-regulated in various cancers, including HCC<sup>[115]</sup>. For example, a recent meta-analysis demonstrated that a higher expression level of *HOTTIP* is correlated with positive lymph node metastasis (LNM) and poor overall survival (OS) in patients with diverse cancers<sup>[116]</sup>, suggesting that *HOTTIP* might be a potentially promising predictor of LNM and survival in human cancer.

Another recent study showed that *HOTTIP* expression is significantly up-regulated in HCC tissues compared with adjacent non-neoplastic tissues<sup>[115]</sup>. Patients with higher levels of *HOTTIP* and homeobox protein Hox-A13 (*HOXA13*) showed increased metastasis formation and decreased OS. Moreover, knockdown of *HOTTIP* inhibited the proliferation of liver cancer-derived cell lines<sup>[115]</sup>. These findings indicate that *HOTTIP* might serve as a potential predictor of LNM and survival in patients with HCC. Intriguingly, these authors have also observed marked up-regulation of *HOXA13* in HCC, with *HOTTIP* and *HOXA13* having a highly positive correlation. In addition, knock-down of *HOTTIP* expression led to a reduction in *HOXA13* expression in HCC cell lines<sup>[115]</sup>, suggesting that *HOTTIP* may serve as a transcriptional regulator of *HOXA13* in HCC cells. *HOTTIP* is located at the 5' end of the *HoxA* cluster, and can enhance expression of upstream *HoxA* genes, most prominently *HOXA13*<sup>[117]</sup>. Furthermore, *HOXA13* has been shown to play a critical role in hepatocarcinogenesis. In a recent study, *HOXA13* expression was found to be significantly up-regulated in HCC tissues compared with corresponding paracarcinomatous tissues, and all *HOXA13*-positive paracarcinomatous tissues exhibited different levels of atypical hyperplasia. Moreover, *HOXA13* overexpression may be associated with tumor angiogenesis in HCC<sup>[118]</sup>. These findings indicate that *HOXA13* may play a crucial role in hepatocyte carcinogenesis. Another study found that *HOXA13* was the only *HOX* network gene to be constitutively overexpressed in all tested HCCs, independently of stage<sup>[119]</sup>, suggesting its involvement in the tumorigenic process of HCC. These authors speculated that *HOXA13* deregulation is involved in HCC, possibly through nuclear export of eIF4E-dependent transcripts<sup>[119]</sup>. In addition, overexpression of *HOXA13* was shown to rescue the phenotype of *HOTTIP* knock-down HCC cells, further supporting that up-regulation of *HOTTIP* in HCC may enhance expression of *HOXA13* and eventually mediate HCC carcinogenesis<sup>[120]</sup>. Overall, *HOTTIP* exerts its oncogenic functions in hepatocarcinogenesis at least partly by modulating *HOXA13*. Additionally, the *HOTTIP/HOXA13* axis may represent a predictor of prognosis in patients with HCC and a potential therapeutic target for this fatal disease.

Increasing evidence reveals that lncRNAs can

interact with miRNAs. Indeed, lncRNAs can act as miRNA sponges, reducing their regulatory effect; in turn, miRNAs may directly interact with lncRNAs and silence their expression<sup>[121,122]</sup>. *MiR-125b* has been shown to be a post-transcriptional regulator of *HOTTIP* in HCC, whereby loss of *miR-125b* expression might contribute to the frequent up-regulation of *HOTTIP*<sup>[120]</sup>. In another recent study, the authors found that both *miR-192* and *miR-204* function as tumor suppressors to reduce *HOTTIP* expression via the Argonaute2-mediated RNA interference pathway in HCC. Furthermore, glutaminase has been identified as a potential downstream target of the *miR-192/-204-HOTTIP* axis in HCC<sup>[123]</sup>.

In summary, the afore-mentioned results suggest the existence of a complex regulatory interaction between *HOTTIP* and *HoxA* genes or miRNAs. Up-regulation of *HOTTIP* contributes to hepatocarcinogenesis at least partly by regulating expression of *HoxA* genes, especially *HOXA13*, and interacting with miRNAs. Further studies are required to determine whether the regulatory loop between *HOTTIP* and *HOXA13* or miRNAs may serve as potential therapeutic targets for HCC.

### **HULC**

Expression of the highly up-regulated in liver cancer (*HULC*) gene, which is located on chromosome 6p24.3, is increased in HCC<sup>[124]</sup>, and several recent studies have helped shed light on the factors that contribute to its aberrant up-regulation. For example, research has found that expression of *HULC* can be enhanced by the transcription factor CREB (cAMP response element-binding protein) through interaction with *miR-372*<sup>[125]</sup>. In addition, up-regulation of *HULC* by the hepatitis B virus (HBV) X protein promotes the proliferation of hepatoma cells through down-regulation of the tumor suppressor p18<sup>[126]</sup>. Furthermore, it has been shown that *HULC* might function as an miRNA sponge for *miR-372* in HCC and may thereby regulate gene expression at the post-transcriptional level<sup>[125]</sup>.

As an oncogene, *HULC* is implicated in hepatocarcinogenesis via regulation of multiple biological processes. *HULC* promotes the proliferation of HCC cells by regulating tumor cell proliferation-associated genes, especially cell cycle-related genes to alter the cell cycle in HCC cells<sup>[127]</sup>. *HULC* also contributes to HCC growth by acting mechanistically to deregulate lipid metabolism through a signaling pathway involving *miR-9*, peroxisome proliferator-activated receptor alpha (*PPARA*), and acyl-CoA synthetase long chain family member 1 (*ACSL1*)<sup>[128]</sup>. In addition, *HULC* is responsible for perturbations in the circadian rhythm by up-regulating the circadian oscillator *CLOCK* (clock circadian regulator) in hepatoma cells, resulting in the promotion of hepatocarcinogenesis<sup>[129]</sup>. Other biological processes, such as angiogenesis, alterations in cell metabolism, activation of a precursor cell

compartment, and tissue remodeling, as well as survival, invasion and migration<sup>[124,130]</sup>, may also contribute to hepatocarcinogenesis. Furthermore, *HULC* functions as a ceRNA to activate the epithelial-mesenchymal transition, stimulating HCC progression and metastasis through the *miR-200a-3p/ZEB1* signaling pathway<sup>[130]</sup>. A recent study provides new insight into the molecular mechanisms underlying the functions of *HULC* in hepatocarcinogenesis. The authors demonstrate that *HULC* specifically binds to Y-box protein-1 (YB-1) to promote its phosphorylation through ERK kinase and in turn regulates the interaction of YB-1 with certain oncogenic mRNAs, consequently accelerating the translation of these oncogenic mRNAs in hepatocarcinogenesis<sup>[131]</sup>. All of these findings indicate that *HULC* might be involved in the pathogenesis and progression of HCC.

However, there are conflicting data in the literature regarding whether *HULC* in HCC is associated with a favorable or an unfavorable prognosis. According to a recent study from China, high *HULC* expression is significantly associated with higher clinical stage and probability of intrahepatic metastasis, and HCC patients with high expression of *HULC* had worse survival than those with low or no *HULC* expression<sup>[130]</sup>. Conversely, two recent studies from South Korea and Germany, propose that high *HULC* expression is significantly associated with a low stage and grade and less vascular invasion and that HCC patients with high *HULC* expression have better survival than those with low or no *HULC* expression<sup>[132,133]</sup>. These conflicting findings might be largely due to the inclusion of different racial and regional groups. Future studies with larger patient cohorts and various geographic and etiologic backgrounds are needed to confirm the prognostic value of *HULC* in HCC.

Compared with healthy controls, the plasma level of *HULC* was found to be dramatically increased in a large cohort of HCC patients, and higher *HULC* expression was significantly associated with larger tumor size, and no tumor encapsulation<sup>[134]</sup>, as well as higher Edmondson grades and HBV-positive status<sup>[135]</sup>. Therefore, plasma *HULC* might act as a potential noninvasive biomarker for predicting the growth, progression and metastasis in HCC.

In summary, the afore-mentioned findings suggest that *HULC* may contribute to the carcinogenesis and progression of HCC. Therefore, *HULC* may act as a potential noninvasive biomarker for predicting the growth, progression, metastasis, and prognosis of HCC.

### **MALAT1**

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is also known as non-coding nuclear-enriched abundant transcript 2. The *MALAT1* locus at 11q13.1 has been reported to harbor chromosomal translocation breakpoints, deletions, translocations, and



point mutations linked to cancer<sup>[136,137]</sup>. These studies have suggested that patients with these phenotypes are more susceptible to cancer.

Nonetheless, the molecular mechanism of *MALAT1* in cancer is currently uncertain. Previous cell culture studies have shown that *MALAT1* is specifically retained in nuclear speckles to regulate alternative splicing of pre-mRNAs by modulating the functional levels of serine/arginine (SR) splicing proteins<sup>[138,139]</sup>. Moreover, a recent study suggests that *MALAT1* function is only apparent in particular cell types, such as metastatic cancer cells<sup>[140]</sup>. These studies indicate that aberrant *MALAT1* expression promotes tumor metastasis by modulating alternative pre-mRNA splicing. However, another study has suggested a mechanism of gene regulation<sup>[141]</sup>. Two molecular functions of *MALAT1* in cell-based models, contributing to its association with tumor metastasis, have been proposed: regulation of gene expression and alternative splicing<sup>[142-144]</sup>. For example, regulation of expression of metastasis-associated genes, rather than alternative splicing, is the critical function of *MALAT1* in lung cancer metastasis<sup>[145]</sup>. Although alternative splicing is critical for regulating gene expression, it may not be a major mechanism for modulating gene expression, and alternative splicing alone cannot explain the role of *MALAT1* in some cancer cell lines or tissues. Overall, *MALAT1* functions as a regulator of alternative splicing or gene expression, governing the hallmarks of cancer metastasis.

Increasing evidence shows that *MALAT1* is frequently up-regulated in both liver cancer cell lines and human HCC tissue samples<sup>[146]</sup>, suggesting that it plays an oncogenic role in HCC. A few studies to date have investigated the roles and clinical implications of *MALAT1* in HCC. In one study, *MALAT1* expression was found to be significantly up-regulated in HCC tumor tissues compared with corresponding non-tumor tissues. Furthermore, *MALAT1* was found to act as a marker with high sensitivity for human HCCs at both early and late stages<sup>[147]</sup>, suggesting that the gene can serve as a potential diagnostic tool for HCC. In another study, patients with high expression levels of *MALAT1* had a significantly increased risk of tumor recurrence after LT, and silencing *MALAT1* with siRNA in HepG2 cells effectively reduced cell viability, motility, and invasiveness and also increased susceptibility to apoptosis<sup>[148]</sup>. These findings suggest that *MALAT1* may play a critical role in HCC progression and serve as a potential predictor of HCC recurrence after LT. Importantly, inhibition of *MALAT1* may be a potential therapeutic target for treatment of HCC.

A recent study investigated the role of specificity protein 1/3 (Sp1/3) in the regulation of *MALAT1* transcription in HCC cells, and the authors found that Sp1 and Sp3 play roles in up-regulating *MALAT1* expression<sup>[149]</sup>. Several potential mechanisms linking *MALAT1* with HCC oncogenesis have been proposed.

For instance, *MALAT1* was found to be up-regulated in HCC and to act as a proto-oncogene to promote HCC cell growth through Wnt pathway activation and induction of oncogenic serine/arginine-rich splicing factor 1 (SRSF1). In addition, inhibition of SRSF1 expression or mTOR activity abolished the oncogenic properties of *MALAT1*, and the authors concluded that *MALAT1* promotes HCC development through SRSF1 up-regulation and mTOR activation<sup>[150]</sup>. Nevertheless, the molecular mechanisms underlying the biological functions of *MALAT1* in HCC remain largely elusive and require further investigation.

### **MVIH**

The lncRNA microvascular invasion in hepatocellular carcinoma (*MVIH*) is located in the intron of the *RPS24* gene, which encodes a protein belonging to the S24E family of ribosomal proteins<sup>[151]</sup>. *MVIH* functions as a tumor promoter and is thus up-regulated in many human cancers. Furthermore, *MVIH* has been shown to activate angiogenesis<sup>[152]</sup>. Thus far, only a few studies have shown that *MVIH* is involved in the pathogenesis and progression of HCC, and the function and mechanism of *MVIH* in HCC still need to be fully investigated.

A recent study found that *MVIH* expression was significantly increased in HCC tissues and cells and that *MVIH* promoted HCC cell growth and inhibited apoptosis by inhibiting *miR-199a* expression *in vitro* and *in vivo*<sup>[153]</sup>. Taken together, these findings provide evidence that *MVIH* acts as an *miR-199a* sponge, linking regulation of gene expression in HCC pathogenesis. In addition to its role in HCC pathogenesis, *MVIH* has also been shown to activate angiogenesis. A previous study demonstrated that *MVIH* is generally overexpressed in HCC and plays a key role in activating angiogenesis; consequently, dysregulation of *MVIH* might serve as a predictor of poor recurrence-free survival of HCC patients after hepatectomy<sup>[154]</sup>. It is well-known that pathological angiogenesis is essential for oncogenesis, tumor invasion and metastasis. The above-mentioned results suggest that blocking *MVIH* function might inhibit tumor angiogenesis. Thus, *MVIH* might serve as a promising therapeutic target for HCC antiangiogenic therapy.

### **MEG3**

Maternally expressed gene 3 (*MEG3*) is an imprinted gene located at chromosome 14q32.3; imprinting of this gene is controlled by the upstream intergenic differentially methylated region (IG-DMR)<sup>[155]</sup>. Although *MEG3* is expressed in many normal tissues, its expression is lost in various human cancers or cancer cell lines. Numerous studies have verified the functional role of *MEG3* as a tumor suppressor in many human cancers<sup>[156-158]</sup>. Therefore, loss of *MEG3* expression may contribute to tumor pathogenesis in

a wide range of tissues of different origin. In recent years, hypermethylation of the *MEG3* promoter or the *MEG3*-3IG-DMR has been shown to contribute to loss of *MEG3* expression in human cancer cells<sup>[159-161]</sup>, and increasing evidence shows that hypermethylation of the *MEG3* promoter plays an important role in loss of *MEG3* expression in tumors<sup>[156,158,162-165]</sup>. Overall, hypermethylation in specific *MEG3* regions might result in permanent gene transcriptional silencing and the consequent loss of its antiproliferative function, thus contributing to oncogenesis<sup>[159]</sup>.

*MEG3* expression was found to be markedly reduced in HCC tissues and cell lines compared with that in adjacent normal liver tissues and normal hepatocytes<sup>[79,166]</sup>. Furthermore, ectopic expression of *MEG3* in hepatoma cells significantly inhibits proliferation and induces apoptosis<sup>[166,167]</sup>, and forced expression of *MEG3* in HCC cells significantly decreases both anchorage-dependent and -independent growth and induces apoptosis<sup>[79,160]</sup>. These data therefore indicate that *MEG3* functions as a tumor suppressor in hepatoma cells and plays an important role in hepatocarcinogenesis. Several studies have investigated the mechanism underlying loss of or reduction in *MEG3* expression in HCC. Similar to many other cancers, it has been revealed that loss of *MEG3* expression in HCC is associated with hypermethylation of its promoter region<sup>[79,160,167,168]</sup>.

It has been proven that *MEG3* can inhibit cell proliferation and promote apoptosis through a p53-related pathway<sup>[169]</sup>. Several studies have also confirmed that overexpression of *MEG3* results in an increase in p53 protein and stimulates its transactivational activity in HCC cells<sup>[166,170,171]</sup>. Further investigation showed that *MEG3* functions as a tumor suppressor in hepatoma cells by interacting with p53 to enhance p53-mediated transcriptional activity and influence the expression of partial p53 target genes<sup>[166]</sup>. In addition, dysregulated tissue-specific expression of *miR-29a* in HCC epigenetically modulates *MEG3* expression through promoter hypermethylation<sup>[79]</sup>.

Kaplan-Meier analysis demonstrated that patients with low *MEG3* expression have worse overall and relapse-free survival compared with those with high expression of *MEG3*, and Cox proportional hazard analyses showed *MEG3* expression to be an independent prognostic factor for HCC patients<sup>[171]</sup>. These findings suggest that decreased expression of *MEG3* contributes to HCC development and progression. Overall, *MEG3* may serve as a useful molecular diagnostic marker and a potential therapeutic target for HCC.

### FTX

The gene five prime to *XIST* (*FTX*) is located upstream of *XIST*, within the X-inactivation center (XIC). *FTX* is thought to positively regulate the expression of *XIST*, which is essential for the initiation and spread of X-inactivation<sup>[172]</sup>, and recent studies have indicated

the pro-oncogenic potential of *FTX* in several types of cancer, including renal cell carcinoma<sup>[173]</sup> and glioma<sup>[174]</sup>.

Surprisingly, there are two opposite findings regarding the role of *FTX* in HBV-related HCC in a Chinese population. In one study, *FTX* and *FTX*-derived *miR-545* were found to be up-regulated in HCC tissues compared with matched tumor-adjacent tissues, and patients with high *FTX* expression exhibited poor survival<sup>[175]</sup>, indicating that *FTX* functions as an oncogenic lncRNA in HCC. Conversely, in another study, *FTX* was found to be significantly down-regulated in HCC tissues compared with that in normal liver tissues, and patients with higher *FTX* expression exhibited longer survival, suggesting that *FTX* acts as a tumor suppressor in HCC<sup>[176]</sup>. There are several possible explanations for these two contradictory findings. First, *FTX* might play distinct roles in HCC because it can function as a precursor for miRNAs and as an endogenous miRNA sponge (also termed ceRNA). *FTX* can encode a related cluster of miRNAs (*miR-374a* and *miR-545*) in most mammalian species<sup>[177]</sup>. Accordingly, in HCC, *FTX* can function as an oncogene when it serves as the precursor of *miR-545*, with which it is co-transcribed, or as a tumor suppressor when it acts as a microRNA sponge for *miR-374a* to inhibit the binding of *miR-374a* to its targets. Second, in two studies, *FTX* was either up-regulated or down-regulated in HCC compared with non-tumor liver samples, suggesting a high *FTX* variability across different cohorts of patients. Third, different levels of *FTX* distribution at different sites of the HCC nodule may exist, and inadequate tumor sampling may also be a factor. Fourth, different methods were used to detect *FTX* in these two studies, with the former using quantitative reverse transcription-quantitative polymerase chain reaction, and the latter *in situ* hybridization.

## PROBLEMS AND PERSPECTIVES

In this review, we summarize the recent progress regarding the functional roles of lncRNAs associated with HCC, including *H19*, *HOTAIR*, *HULC*, *HOTTIP*, *MALAT1*, *MVIH*, *MEG3*, and *FTX*. As potent gene regulators, these HCC-related lncRNAs are involved in diverse biological functions, such as cell proliferation, apoptosis, migration, invasion, metastasis, and angiogenesis, thereby contributing to the initiation and progression of HCC. In addition, these HCC-related lncRNAs may serve as potential diagnostic or prognostic biomarkers and also as therapeutic targets for HCC.

Intriguingly, due to their highly specific expression patterns in particular types of cancer<sup>[178]</sup>, efficient detection in the bodily fluids of patients (e.g., blood, plasma, and urine) and relatively stable local secondary structures, lncRNAs have the potential to serve as novel noninvasive biomarkers<sup>[13]</sup>. For example, *HULC* is detected with a higher frequency in the

plasma of HCC patients than in healthy controls<sup>[135]</sup>, suggesting the possibility of using *HULC* as a potent circulating biomarker to facilitate early diagnosis of HCC. Nevertheless, further investigations in larger patient cohorts are necessary to validate the diagnostic effectiveness of circulating *HULC* in HCC.

Despite the importance of lncRNAs in HCC, our current understanding of HCC-related lncRNAs remains rather limited. First, the behavioral characteristics and mechanisms underlying HCC-related lncRNAs contributing to HCC remain largely unclear. Second, “driver lncRNAs” associated with tumorigenesis and progression of HCC have not yet been identified. To gain insight into lncRNA functions and mechanisms of action in HCC, several major issues need to be addressed: (1) technological advances in high-throughput RNA-Seq and high-resolution imaging of RNAs are required. In addition, computational algorithm analysis and integrated datasets are also essential; (2) rather than acting alone, the regulatory role of lncRNAs typically occurs through a large complex network that involves mRNAs, miRNAs, DNA, and proteins<sup>[179]</sup>. Therefore, it is critical to understand how lncRNAs interact with RNA, DNA, and proteins and how aberrant crosstalk may be regulated in HCC; and (3) most of the previous studies concerning lncRNAs have been retrospective single-center analyses with a relatively small sample size. Thus, a multicenter prospective cohort study with a large sample is needed to gain a deeper understanding of the explicit roles of lncRNAs in HCC in various ethnic populations<sup>[185]</sup>.

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