Emerging role of long noncoding RNAs in recurrent hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) remains one of the most frequent types of liver cancer and is characterized by a high recurrence rate. Recent studies have proposed that long non-coding RNAs (lncRNAs) are potential biomarkers in several recurrent tumor types. It is now well understood that invasion, migration, and metastasis are important factors for tumor recurrence. Moreover, some of the known risk factors for HCC may affect the expression levels of several types of lncRNAs and thus affect the recurrence of liver cancer through lncRNA regulation. In this paper, we review the biological functions, molecular mechanisms, and roles of lncRNAs in HCC and summarize current knowledge about lncRNAs as potential biomarkers in recurrent HCC.

Key Words: Long non-coding RNAs; Hepatocellular carcinoma; Liver cancer; Biomarker; Recurrence

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Core Tip: Hepatocellular carcinoma (HCC) is one of the most recurring malignant tumors in the world. Intrahepatic metastasis and multicenter occurrence are two ways of recurrence of HCC. Currently, a growing number of studies have shown that long non-coding RNAs (lncRNAs), regulators of human gene expression, are abnormally expressed and influence the development of HCC. So, we need to further understand
the significance of lncRNAs in the clinical diagnosis and treatment of recurrent HCC and explore the regulatory mechanisms of lncRNAs in the occurrence and treatment of recurrent HCC.

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INTRODUCTION

In most countries, the trend of hepatocellular carcinoma (HCC) mortality has increased in recent decades[1]. It is also the third leading cause of cancer-related deaths worldwide. For all stages combined, the 5-year relative survival rate is lowest for cancers of the liver (18%)[2]. Owing to insidious symptoms and early metastases, most HCC patients are diagnosed at an advanced stage, resulting in limited or ineffective treatments. Although the treatment for HCC, including surgical intervention and sorafenib, has ameliorated the disease in the past few decades, the overall survival rate of HCC patients is still alarmingly high owing to its high recurrence rate[3]. Tumor recurrence is the most critical factor affecting mortality in HCC patients regardless of surgery[4].

The recurrence of intrahepatic HCC is caused by two different ways: (1) Intrahepatic metastasis (IM) descending from the primary cancer; and (2) Independent carcinogenesis leading to multicentric occurrence (MO)[5-7]. It is worth noting that these two mechanisms are not mutually exclusive, and both factors can lead to the recurrence of intrahepatic HCC. So far, there has been no definite standard to accurately distinguish the origin of multifocal HCC from IM or MO. Hence, histopathological features are still the most convenient strategy. Treatment options for recurrent intrahepatic HCC include repeat liver resection and ablative therapy[8] (Figure 1). Generally, after radical resection, the overall survival (OS) and recurrence-free survival (RFS) rates of MO-HCC patients are better than those of IM-HCC patients[9]. IM is more metastatic and has greater migratory ability than MO. HCC with IM recurs earlier and has a poorer prognosis than HCC with MO[10]. In recent decades, OS and RFS after hepatectomy have remained unsatisfactory due to the high rates of IM and MO[11]. Histopathological analysis is still the most convenient strategy, and it is objective and accurate. Pathology remains a cornerstone in the clinical treatment of patients with HCC, as it allows a definitive diagnosis and provides prognostic information. However, most current studies focus on primary liver cancer, but there are few studies on recurrent HCC. Therefore, precise diagnostic/prognostic biomarkers are urgently needed to improve the clinical outcomes of recurrent intrahepatic HCC.

Long non-coding RNA (lncRNA) can be defined as transcripts of more than 200 nucleotides that are not translated into proteins and act as important regulators in gene expression networks[12]. In recent years, with the development of next-generation sequencing, lncRNAs have become the focus of research[13]. A few studies suggest that annotated lncRNA transcripts in the whole human genome are involved in the biological processes of recurrent HCC.

In this review, we summarize the current understanding of the molecular mechanisms, differential expression, and biological functions of lncRNAs in recurrent HCC. Furthermore, we discuss the potential prospects of lncRNAs as precise diagnostic/prognostic biomarkers for recurrent intrahepatic HCC.

BIOLOGICAL FUNCTIONS OF LncRNAs

We often divide noncoding RNAs into two categories: (1) Noncoding RNAs shorter than 200 nucleotides, including PIWI-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), tRNA-derived small RNAs (tsRNAs), and microRNAs (miRNAs); and (2) RNAs longer than 200 nucleotides (long ncRNAs; lncRNAs), including large intergenic ncRNAs (lincRNAs) and very long ncRNAs (v-lncRNAs)[14]. LncRNA characteristics cover unique regulatory mechanisms, alternative forms of biogenesis,
Figure 1 Recurrence of intrahepatic hepatocellular carcinoma is caused by two different ways. HCC: Hepatocellular carcinoma.

cis-regulatory activities, and functional structured RNA domains[15]. Therefore, lncRNAs are emerging as important regulators of tissue physiology and disease processes, including cancer[16]. Increasing evidence has shown that lncRNAs play important roles in transcriptional regulation, cell growth, and tumorigenesis through a variety of mechanisms[17]. Some studies have shown that certain lncRNAs are potential targets and biomarkers for the diagnosis and prognosis of malignant tumors. For instance, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was included in the first batch of lncRNAs to be employed in the lncRNA-targeted therapy of lung cancer[18]. Shi et al[19] discovered that AC069513.4 and four other lncRNAs could be used as independent prognostic biomarkers to predict the survival of patients with clear cell renal cell carcinoma. The lncRNA PCAL7 is overexpressed in prostate cancer (PCa) and promotes PCa by strengthening androgen receptor signaling[20]. An increasing number of studies have shown that lncRNAs play vital roles in the pathogenesis and therapeutic response of IM and MO[21,22].

Molecular Mechanisms of LncRNAs in Recurrent HCC

We believe that elucidating the molecular mechanisms related to liver cancer invasion and metastasis can help prevent and treat liver cancer recurrence. The molecular mechanisms by which lncRNAs play an important role in the regulation of approximately all steps of cancer progression include epigenetic regulation, miRNA regulation, cell growth, and epithelial-mesenchymal transition (EMT)[23] (Figure 2).

Epigenetics involves the modification of DNA molecules that regulate gene activity uninfluenced by the DNA sequence, and mitosis is stable. To date, in recurrent HCC, the most recognized epigenetic mechanisms are chromatin modification and DNA methylation. It is widely acknowledged that epigenetic regulation plays a key role in invasion and metastasis in diverse types of cancer, including recurrent HCC. In colorectal neoplasia, the lncRNA CRNDE directly binds to EZH2, SUZ12, and SUV39H1, and mediated their inhibition of tumor suppressor genes, including CELF2 and LATS2[24]. Kang et al[25] showed that a high level of AY927503 could promote HCC metastasis and is related to the poor prognosis of HCC patients. The promotion of metastasis by AY927503 is related to the activation of ITGAV transcription by recruiting chromatin modification mechanisms to the ITGAV promoter and reducing H1FX binding[25].

Furthermore, through bioinformatics analyses using the TCGA and GEO databases, it has been found that the mutual regulatory network between lncRNAs and miRNAs is involved in the progression of cancer[26]. The recurrence and metastasis of tumors are closely related to complex regulatory networks among protein-coding genes, lncRNAs, and miRNAs. Recently, many studies have reported that miRNAs and lncRNAs are involved in miRNA regulation[27]. Xu et al[28] and Chen et al[29] demonstrated the molecular mechanisms by which lncRNAs and miRNAs act in the process of recurrence in low-grade glioma and ovarian cancer. Similarly, the complex regulatory network between lncRNAs and miRNAs will help clarify the molecular mechanism of lncRNAs in recurrent liver cancer. H19 is a 2.3-kb lncRNA that is composed of five exons and four small introns and is located on ch11p15.5 as an imprinting gene with maternal expression[30]. H19 has been characterized to work either as a tumor suppressor or an oncogene in vitro and in vivo[31]. Lv et al[32]
revealed that the inhibition of H19 and miR-675 promoted the invasion and metastasis of HCC by activating the AKT/GSK-3β/Cdc25A signaling pathway. Interestingly, Sui et al.[33] found that through contact with EZH2 and miR-200b/a/429, GIHCG recruits EZH2 and DNMT1 to the promoter of miR-200b/a/429 and increases H3K27me3 and DNA methylation levels in the promoter of miR-200b/a/429. Functional experiments showed that GIHCG promotes the proliferation, migration, and invasion of HCC cells in vitro and promotes the growth and metastasis of xenografts in vivo.[33]. This result is fully in line with the characteristics of IM and OM. Moreover, the discovery of this pathway showed a new mechanistic link between lncRNAs, epigenetic modulations, and miRNAs.

Research has revealed that lncRNAs play an irreplaceable role in the development of recurrent HCC through EMT. EMT is a crucial cell remodeling process during embryonic development and organogenesis. During EMT, epithelial cells lose their polarized structure and gain migration and invasion capabilities.[34]. A large amount of evidence has revealed the activation of EMT in cancer metastasis, which contributes to metastasis to the surrounding tissue and distant organs. Huang et al.[35] explored whether the cancer susceptibility candidate 2 (CASC2)/miR-367/FBXW7 axis suppresses the migration, invasion, and EMT progression of HCC cells. Among the players in this pathway, the lncRNA CASC2 was determined to inhibit the migration and invasion abilities of HCC cells in vitro and in vivo.

The list of lncRNAs is still under development, and their molecular mechanisms are continuously being elucidated. Therefore, in recurrent HCC, lncRNAs act not only through a certain mechanism but through multiple molecular mechanisms. Next, we discuss the role of lncRNA expression in recurrent HCC.

**ROLE OF LNCRNA EXPRESSION IN RECURRENT HCC**

Early HCC-related research focused mainly on protein-coding genes because of their central position in the regulation of biological processes. However, increasing evidence indicates that lncRNAs play an important role in diverse physiological and pathological processes. These lncRNAs are differentially expressed in different tissues and cancers, thereby affecting cancer invasion and metastasis. Aberrant expression of lncRNAs is associated with epigenetic reprogramming during tumor development and progression, mainly due to their ability to interact with DNA, RNA, or proteins to regulate gene expression[36]. The following section of this review discusses characteristics of the candidate lncRNAs in recurrent HCC according to their expression (upregulated or downregulated) (Table 1).
### Table 1 Recurrent hepatocellular carcinoma associated long non-coding RNAs

| Gene ID | Location | Expression | miRNA | Processes | Clinical association | Ref. |
|---------|----------|------------|-------|-----------|---------------------|------|
| 26255   | 8q13.1   | †          | miR-383 | Proliferation, migration, invasion, metastasis, cell apoptosis, cell cycle progression, tumorigenesis, EMT | Tumor size, TNM stage, poor prognosis, metastasis | [40, 41] |
| 171423  | 1q21.1   | †          | miR-125a/b, miR-124 | Proliferation, migration, invasion | Tumor size, metastasis, TNM stage, poor RFS and OS | [43, 67] |
| 378938  | 11q13.1  | †          | miR-146a, miR-22, miR-3064-5p, miR-125a-3p, miR-140, miR-124-3p, miR-124, miR-30a-5p, miR-195 | Proliferation, apoptosis, autophagy, proliferation, migration, invasion, angiogenesis, immunosuppression, glucose metabolism | Poor RFS and OS, metastasis | [68-79] |
| 652995  | 19p13.12 | †          | miRNA-193a-3p, miR-18a, miR-124, miR-203, miR-216B | Proliferation, migration, invasion, apoptosis, EMT | TNM stage, intrahepatic metastasis, postoperative recurrence, postoperative survival, shorter OS, tumor size, vascular invasion | [49, 50, 80-84] |
| 55384   | 14q32.2  | †          | miR-9-5p, miR-10a-5p, miR-493-5p, miR-483-3p, miR-26a, miR-29a | Cell apoptosis, growth inhibition, proliferation, apoptosis, cell cycle progression, migration, invasion, EMT | Poor RFS and OS, metastasis, | [55-58, 61] |
| 60874   | 1q25.1   | †          | miR-21, miR-1323, miR-182, miR-135B | Proliferation, invasion, apoptosis, metastasis | Drug resistance, metastasis, shorter RFS, poor prognosis, TNM stage, differentiation, glucose levels, portal vein tumor thrombosis, tumor size, lymph node metastasis | [63, 65, 66, 85-88] |
| 255082  | 10q26.11 | †          | miR-183, miR-362-5p, miR-24-3p, miR-367 | Proliferation, migration, invasion, colony formation, cell cycle, apoptosis, metastasis, EMT | Tumor size, metastasis | [89-94] |
| 283120  | 11p15.5  | †          | miR-675, miR-193B, miR-15b, miR-675, miR-326 | Proliferation, motility, migration, invasion, apoptosis, EMT | Differentiation, drug resistance, metastasis, growth, shorter survival time, lymph node metastasis, distant metastasis | [32, 95-105] |

EMT: Epithelial-mesenchymal transition; RFS: Recurrence-free survival; OS: Overall survival.

### Up-regulated IncRNAs in recurrent HCC

**PTTG3P**: Previous studies have suggested that pituitary tumor-transforming 3, pseudogene (PTTG3P) serves as an oncogene in human cancers. The PTTG3P gene is mapped to ch8q13.1 in humans. PTTG3P is upregulated in several types of cancer. In addition, PTTG3P regulates migration and invasion in multiple types of tumors, such as gastric cancer, colorectal cancer, and breast cancer.[37-39] Similarly, several studies have shown that PTTG3P is upregulated in HCC tissues and cells. To date, PTTG3P has been shown to affect PI3K/AKT signaling by upregulating PTTG1 and the PTTG3P-miR-383-CCND1/PARP2 axis in HCC.[40, 41] Bai et al.[42] showed that high PTTG3P expression was an independent indicator associated with a short OS and RFS regardless of the pathological stage or tumor grade, suggesting the potential usage as a prognostic biomarker for recurrence.

**PDIA3P1**: Protein disulfide isomerase family A member 3 pseudogene 1 [PDIA3P1 (gene ID: 171423)] is located on ch1q21.1 with a 2099-bp segment and is located primarily in the cytoplasm. PDIA3P1 has been reported to be upregulated in HCC and is highly expressed under hypoxic conditions. PDIA3P1 regulates the p53 pathway to promote cell proliferation, migration, and invasion and suppresses apoptosis in HCC. Moreover, in patients with HCC, high PDIA3P1 expression is significantly related to tumor size, metastasis, TNM stage, and a poorer survival outcome than patients with low PDIA3P1 expression. Furthermore, Xie et al.[43] found the hMTR4-PDIA3P1-miR-125/124-TRAFF6 axis and studied its function in NF-kB signal transduction activated by DNA damage. The study on this axis implied that the upregulation of PDIA3P1 may confer chemoresistance. Targeting PDIA3P1 represents a promising strategy to inactivate NF-kB signaling and enhance cancer cell chemosensitivity. The same study also verified one of the main working models of a cytoplasmic IncRNA: As a combination of a ceRNA and miRNA, it upregulates the expression of miRNA targets. In addition, PDIA3P1 may be useful as a new biomarker for multidrug resistance and
progression of recurrent HCC.

**MALAT1**: MALAT1, also known as NEAT2, is a key lncRNA gene that is located on ch1q13.1 and encodes a 6-kb protein. A meta-analysis of a transcriptome dataset showed that MALAT1 is upregulated in several cancers, including lung cancer, prostate cancer, and breast cancer[44]. Additionally, high MALAT1 expression is associated with invasion and metastasis in lung, breast, and liver cancers, suggesting the pivotal role of MALAT1 in MO and IM[45-47]. In both HCC cell lines and clinical tissue samples, MALAT1 is upregulated and is associated with invasion, metastasis, migration, cell proliferation, apoptosis, and a short OS and RFS. In particular, Lai et al [48] demonstrated that higher MALAT1 expression was associated with a shortened RFS and suggested that MALAT1 could serve as an independent prognostic factor for predicting HCC recurrence. These findings suggest that MALAT1 may selectively affect the spread of cancer cells or residual cancer cells after surgery to cause liver cancer recurrence, showing important clinical significance.

**UCA1**: Urothelial carcinoma associated 1 (UCA1), a novel vital oncogenic lncRNA, is located on ch19p13.12 with a TATA box at its 5' end and a poly A tail at its 3' end. UCA1 was first discussed in bladder cancer and is highly expressed in multiple cancers. In HCC, Wang et al[49] found that UCA1 was significantly upregulated in tumor tissues and associated with TNM stage, metastasis, and a poor survival. In addition, high UCA1 expression in HCC was positively associated with tumor size, vascular invasion, and American Joint Committee on Cancer stage (P < 0.05)[50]. Furthermore, gain-of-function and loss-of-function analyses showed that UCA1 knockdown inhibited HCC cell proliferation, migration, and invasion in vitro and xenograft tumor growth in vivo. At the molecular level, miR-203, miR-124, miR-18a, and miR-193a-3p may affect the proliferation, migration, and invasion of cancer cells in hepatocellular carcinoma by altering UCA1. Consequently, these data indicate that UCA1 could serve as an oncogene in tumorigenesis and act as a novel serum biomarker for the diagnosis and prognosis of HCC recurrence.

**Down-regulated IncRNAs in recurrent HCC**

**MEG3**: Maternally expressed 3 (MEG3) is a maternally imprinted gene localized on ch14q32.2 that has been reported to be downregulated in multiple cancer tissues compared with nontumoral tissues of the same origin. MEG3 overexpression can reinforce cell apoptosis and decrease proliferation, migration, and invasion in breast cancer[51], colorectal carcinoma[52], and oral cancer stem cells[53]. In liver cancer, the loss of methylation at the MEG3 locus is linearly related to the overall loss of DNA methylation[34]. Several studies suggested that the methylation-dependent tissue-specific regulation of MEG3 by miR-29a and miR-10a-5p may contribute to HCC growth and that miR-9-5p, miR-493-5p, miR-483-3p, and miR-664 inhibit HCC growth [55-59]. After further evaluation of its biological function, it was determined that the stable overexpression of MEG3 can inhibit migration and invasion by regulating EMT [60,61]. Moreover, Kaplan-Meier analysis demonstrated that patients with low MEG3 expression had a worse OS and RFS than those with high expression[62]. This information provides valuable explanations for literature on the function of MEG3 and provides recommendations for new therapeutic targets.

**GAS5**: Growth arrest specific 5 (GAS5) is a novel tumor suppressor lncRNA located on ch1q25. Although GAS5 has a short open reading frame, it does not encode a protein and acts as a snoRNA host gene. Notably, GAS5 expression levels are downregulated in a number of human malignancies, and such aberrant expression is negatively associated with disease stage and prognosis. In HCC, low GAS5 expression is significantly associated with differentiation and TNM stage[63]. In addition, Kaplan-Meier survival curves revealed that low GAS5 expression was associated with a poor OS and RFS in HCC patients[64]. Through functional experiments, Chen et al[65] found that GAS5 could significantly inhibit the migration and invasion of HCC cells in vitro and suppress tumor metastasis in vivo. At the molecular level, GAS5 can suppress the migration, invasion, and metastasis of HCC via miR-21, miR-135b, miR-182, and miR-382-3p. Interestingly, GAS5-mediated miR-1323 promotes cell proliferation and invasion and inhibits apoptosis by targeting TP53INP1 in HCC[66]. Therefore, GAS5 may play an important role in the recurrence of liver cancer, and its expression is an independent prognostic factor for patients with HCC.
CONCLUSION

HCC is one of the most common malignant cancers in the world, but the underlying mechanism of the pathogenesis of recurrent HCC is still not clearly understood. However, research on lncRNA-related recurrence in liver cancer is still lacking. Therefore, this review focuses on the molecular mechanisms and expression of lncRNAs, classifies them according to their biological processes, and further subdivides them by their most common modes of molecular interactions in recurrent HCC. Currently, a growing number of studies have shown that lncRNAs, regulators of human gene expression, are abnormally expressed and influence the development of cancers. The lncRNA/miRNA/mRNA axis participates in diverse biological functions, including cancer migration, invasion, and metastasis. Analysis of lncRNAs in recurrent HCC can be interesting and will lead to the identification of novel diagnostic and prognostic markers because it is noninvasive and easily accessible. For recurrent HCC, the identification of early and prognostic biomarkers can help reveal the patient’s disease classification, formulate a personalized clinical treatment plan, improve efficacy and prognosis, and extend survival. At present, only a few lncRNAs that have been researched in recurrent HCC may serve as prognostic markers. However, much more research is required to apply lncRNAs in clinical practice along with the development of some standards for identifying lncRNA biomarkers in recurrent HCC. In summary, at present and in the future, we still need to further understand the significance of lncRNAs in the clinical diagnosis and treatment of recurrent HCC and explore the regulatory mechanisms of lncRNAs in the occurrence and treatment of recurrent HCC.

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