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**Emerging role of long noncoding RNAs in recurrent hepatocellular carcinoma**

Fang Y *et al*. Role of lncRNAs in recurrent HCC

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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.

**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 RNAs (lncRNAs) are 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 (vlncRNAs)[14]. LncRNA characteristics cover unique regulatory mechanisms, alternative forms of biogenesis, 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 *GHICG* 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).

***Up-regulated lncRNAs 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-TRAF6 axis and studied its function in NF-κB signal transduction activated by DNA damage. The study on this axis implied that the upregulation of *PDIA3P1* may confer chemoresistance. Targeting *PDIA3P*1 represents a promising strategy to inactivate NF-κB signaling and enhance cancer cell chemosensitivity. The same study also verified one of the main working models of a cytoplasmic lncRNA: 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 ch11q13.1 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 5ʹ end and a poly A tail at its 3ʹ 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 lncRNAs 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[54]. 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 lncRNA 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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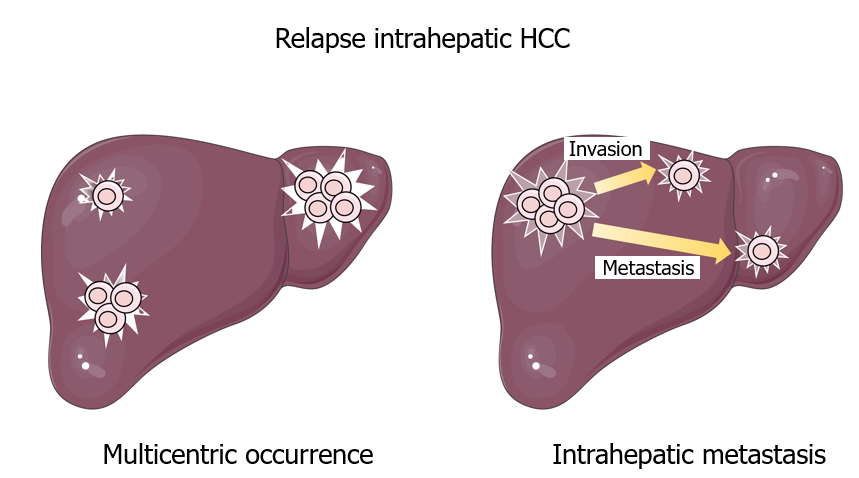
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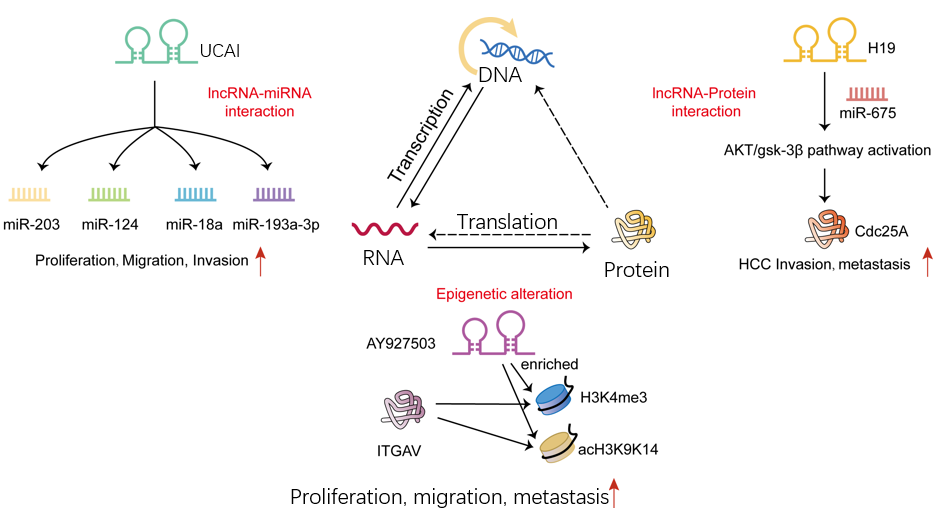
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**Figure Legends**



**Figure 1 Recurrence of intrahepatic hepatocellular carcinoma is caused by two different ways.** HCC: Hepatocellular carcinoma.



**Figure 2 Molecular mechanisms of long non-coding RNAs in recurrent hepatocellular carcinoma.** lncRNA: Long non-coding RNA; HCC: Hepatocellular carcinoma.

**Table 1 Recurrent hepatocellular carcinoma associated long non-coding RNAs**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Gene | Gene ID | Location | Expression | miRNA | Processes | Clinical association | Ref. |
| PTTG3P | 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] |
| PDIA3P1 | 171423 | 1q21.1 | ↑ | miR-125a/b, miR-124 | Proliferation, migration, invasion | Tumor size, metastasis, TNM stage, poor RFS and OS | [43,67] |
| MALAT1 | 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] |
| UCA1 | 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] |
| MEG3 | 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] |
| GAS5 | 60674 | 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] |
| CASC2 | 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] |
| H19 | 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 | [32,95-103] |

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



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