REVIEW ARTICLE

The paradoxical functions of long noncoding RNAs in hepatocellular carcinoma: Implications in therapeutic opportunities and precision medicine

Duguang Li a,b, Xiaoxiao Fan a,b, Yirun Li a,b, Jing Yang a,b,*, Hui Lin a,b,*

a Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310058, PR China
b Biomedical Research Center, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310058, PR China

Received 3 June 2020; received in revised form 22 October 2020; accepted 24 November 2020
Available online 1 December 2020

Abstract Hepatocellular carcinoma (HCC) is among the most aggressive and lethal diseases with poor prognosis, worldwide. However, the mechanisms underlying HCC have not been comprehensively elucidated. With the recent application of high-throughput sequencing techniques, a diverse catalogue of differentially expressed long non-coding RNAs (lncRNA) in cancer have been shown to participate in HCC. Rather than being "transcriptional noise," they are emerging as important regulators of many biological processes, including chromatin remodeling, transcription, alternative splicing, translational and post-translational modification. Moreover, lncRNAs have dual effects in the development and progression of HCC, including oncogenic and tumour-suppressive roles. Collectively, recently data point to lncRNAs as novel diagnostic and prognostic biomarkers with satisfactory sensitivity and specificity, as well as being therapeutic targets for HCC patients. In this review, we highlight recent progress of the molecular patterns of lncRNAs and discuss their potential clinical application in human HCC.

* Corresponding author. Department of General Surgery, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, 3 East Qingchun Road, Hangzhou, Zhejiang 310058, PR China.
** Corresponding author. Biomedical Research Center, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310058, PR China.
E-mail addresses: 11918306@zju.edu.cn (D. Li), fxxyoe@126.com (X. Fan), 11818184@zju.edu.cn (Y. Li), yangj2828@163.com (J. Yang), 369369@zju.edu.cn (H. Lin).

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2020.11.014
2352-3042/Copyright © 2020, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 90% of all cases of primary liver cancer, and is a common and aggressive human malignancy worldwide. The tumour may be curable by resection or liver transplantation when patients are diagnosed at early stages of the disease; however, most individuals with advanced HCC are not suitable candidates and their treatment options are limited. Hepatocarcinogenesis is a multi-stage process that involves changes in numerous gene networks and pathways, many of which have not yet been clarified. Therefore, further insights into the molecular pathogenesis of liver cancer are of great importance for the development of future effective therapeutic approaches.

Intensive investigations over the last few decades have widely explored the roles of protein-coding genes in HCC. Due to the general implementation of deep-sequencing technologies, it is now evident that less than 2% of the human genome can encode proteins, and at least 90% of the genome is actively transcribed into non-coding RNA (ncRNA) that has no protein encoding potential. Previously, ncRNAs were assumed to be exceptional curiosities or 'splicing noise', but accumulating evidence demonstrate their physiological function, as well as their crucial role in the disease context.

The widespread use of microarrays and high-throughput sequencing techniques have facilitated the detection of large quantities of dysregulated long non-coding RNAs (lncRNAs), in human HCC. Using next-generation sequencing technology, Yao and colleagues reported 214 differentially expressed lncRNAs (DELs) detected from 12 HCC tissues and paired adjacent normal tissues. A proportion of lncRNAs were significantly associated with tumour cell differentiation, portal vein tumour thrombosis, and serum or tissue alpha-fetoprotein levels. When categorizing tissues by viral status, 719 lncRNAs were significantly dysregulated in hepatitis B virus (HBV)-HCC tissues compared to paired non-tumour tissues using microarray analysis. Similar to reports on HBV-HCC, the lncRNA transcriptome was also altered in hepatitis C virus (HCV)-infected liver cancer. Recently, the relationship between lncRNAs specificity and metastasis of HCC has been extensively analysed. Comparative expressions of lncRNAs between HCC and portal vein tumour thrombi (PVTT) have identified 107 deregulated lncRNAs associated with metastasis. Additionally, expressions of oxaliplatin-resistant lncRNAs in HCC have been established, with the identification of 120 differentially expressed lncRNAs. Nonetheless, the depository of general transcription is far greater than the molecular properties of the transcripts in liver cancer. This review aims to classify HCC-associated lncRNAs that are closely linked to different biological processes according to their distinct molecular mechanisms. Finally, we discuss and summarize the potential value of lncRNAs as a diagnostic tool and therapeutic goal.

Classification and structural features of lncRNAs

In general, ncRNAs can be divided into short ncRNAs (sncRNAs) and lncRNAs, defined as ncRNA shorter or longer than approximately 200 nucleotides in length, respectively. MicroRNAs (MiRNAs), piwi-interacting RNAs (piRNAs) and small nucleolar RNA (snoRNA) are the most studied sncRNAs transcripts. Mature miRNAs are approximately 22-nucleotide-long single stranded RNA molecules that target a wide range of mRNA and block translation by binding their seed sequence to the 3’ untranslated region (3’UTR) of mRNA. SnoRNAs are small RNAs of 60–300 nucleotides in length that function as guide RNAs for the post-transcriptional modification of ribosomal RNAs and some spliceosomal RNAs. In addition, piRNAs are unique small ncRNAs that form into the piRNA-induced silencing complex (piRISC) to silence transposable elements in germline cells. In comparison to sncRNAs, lncRNAs can be classified according to the location and origin of the genome. Specific lncRNAs exist in the intergenic regions, while other lncRNAs are arranged in the form of antisense, bidirectional or are overlapping with protein-encoding genes. Intriguingly, a subset of lncRNAs originate from the enhancer regions of the genome and have enhancer-like functions (enhancer lncRNA). Two ncRNAs considered as lncRNAs include, circular RNAs (circRNAs) which are back-spliced from a 5’ splice site to an upstream 3’ splice site of protein-coding mRNAs or linear ncRNAs; and pseudogenes, which have lost their protein-coding capacity owing to imperfect copies of functional protein-coding genes and various mutations.

LncRNAs analysis shows specific consistency characteristics including paucity of introns, low GC level, poor start codon and open reading frame contexts. In addition to the main features of the sequence, recent research has developed genome-scale approaches and uncovered a variety of secondary lncRNAs structure elements, which can interact with many molecules, such DNA, RNA and/or protein. Emerging studies describe the central role lncRNAs play in many physiological and pathological processes, including differentiation, development and disease. Furthermore, lncRNAs, act as a driving factor in tumour inhibition and carcinogenicity in different types of cancer. Over the last ten years, discovery of hundreds of dysregulated lncRNAs has demonstrated their function as oncogene transcripts or tumour suppressor genes in liver cancer.
Overview of properties of IncRNAs in HCC

Various studies have shown that HCC-related IncRNAs regulate gene expression through different patterns, and categories of IncRNA functions are not single. In liver cancer, the principle routes of IncRNAs activity are divided into four categories. First, IncRNAs are considered as molecular signal markers for important functional biological events through modulating transcription activities or pathways. Decoy IncRNAs can act as molecular decoys to bind and titrate away targeted proteins or RNAs. IncRNAs can also act on near or distant genes as a guide for binding specific proteins, and then locate the molecular complex to specific targets. Finally, IncRNAs serve as central platforms on which different effector molecules can be assembled.

Moreover, IncRNAs referring to Wnt and STAT3 signal transduction in HCC have been separated comprehensively. The Wnt and STAT3 pathways are critical regulators of hepatoma stem cells and are involved in the induction of epithelial-mesenchymal transition (EMT) and metastasis. Similarly, Lv and colleagues have highlighted the role of IncRNAs in multiple liver cancer stem cells (LCSCs) regulatory signalling pathways, including the Wnt/β-catenin, STAT3, TGF-β, YAP and cell cycle-related signaling. IncRNAs are further distinguished by its effects on divergent phenotypes in HCC. A recent study summarises the basic characteristics and functions of IncRNAs, in relation to the liver cancer microenvironment. However, due to the variety of properties, the functions of IncRNA in HCC remains unclear. Notably, subcellular localization of IncRNA is another means to provide valuable information about its role and mode of action. Thus, most HCC-associated IncRNAs modulate the expression and stability of their downstream targets in relation to the specific cellular compartments through diverse biological processes, including epigenetic, transcriptional, and post-transcriptional levels.

Functional mechanisms of tumor-promoting IncRNAs in HCC

Chromatin remodelling regulation

A mechanistic action of IncRNAs is their capacity to induce epigenetic alterations of target genes as a scaffold or guide of chromatin modified complex. Polycomb repressive complex 2 (PRC2) is a well-known epigenetic repressor which can inhibit the transcription of various genes through histone H3 lysine 27 tri-methylated (H3K27me3) during the progression of HCC. In recent years, IncRNAs have been shown to control gene expression by binding to PRC2. Fu and colleagues described the function of pro-oncogene IncRNA HOX transcript antisense RNA (HOTAIR) as a bridge to interact with PRC2. This initiates chromatin remodelling and H3K27 trimethylation of miR-218, thus activating oncogene Bmi-1 in HCC. As expected, Bmi-1 targets, tumour suppressors P16(Ink4a) and P14ARF are downregulated, whereas MDM2 is activated. Additionally, another up-regulated IncRNA CDKN2B antisense RNA 1 (CDKN2B-AS1) has been demonstrated to epigenetically repress tumour suppressor kruppel-like factor 2 (KLF2) transcription in HCC cells by binding with PRC2 and recruiting it to the KLF2 promoter region. Through comparison of HBV-related HCC with paired peritumoral tissues, the level of specific differentially expressed IncRNA High Expression in HCC (HEIH) was analysed, which is significantly linked to recurrence and is an independent prognostic factor for survival. LncRNA-HEIH is also associated with enhancer of zeste homolog 2 (EZH2), a key component of PRC2, and is required for the repression of EZH2 target gene p16, which plays a key role in G (0)/G (1) arrest. While IncRNAs have been found to widely interact with PRC2, other chromatin remodellers have been also implicated. Elevated IncRNA translation regulatory long non-coding RNA 1 (TRERRNA1) levels can suppress cadherin 1 (CDH1) expression via the recruitment of euchromatic histone lysine methyltransferase 2 (EHMT2) to dimethylate H3K9 in the CDH1 promoter region, thus promoting cell metastasis and invasion of HCC.

Recent evidence showed upregulated LINC0441 being inversely correlated to tumour-suppressor gene retinoblastoma gene 1 (RB1) expression in human HCC samples. Furthermore, RNA pull-down assays demonstrated the decreased RB1 level induced by LINC0441 made in association with the incidental methylation by DNA methyltransferase 3 (DNMT3) recruited by LINC0441, thereby resulting in apoptosis suppression and cell-cycle rearrangement. Highly up-regulated in liver cancer (HULC) is a long non-coding RNA overexpressed in HCC which may elicit methylation of CpG islands in the miR-9 promoter through upregulation of DNA methyltransferase 1 (DNMT1), thus relieving the inhibitory effect on its target peroxisome proliferator activated receptor alpha (PPARA). Therefore, activation of transcriptional factor PPARA activates the acyl-CoA synthetase long chain family member 1 (ACSL1) promoter, inducing the deregulation of lipid metabolism in HCC, and stimulating the accumulation of intracellular triglycerides and cholesterol. Uncovering the role of oncogene IncRNA distal-less homeobox 6 antisense 1 (DLX6-AS1) showed its contribution to induce cell adhesion molecule 1 (CADM1) promoter methylation via increasing the enrichment of methyltransferase (DNMT1, DNMT3a, and DNMT3b) in LCSCs. This ultimately regulates downstream pluripotent genes-related to cancer stem cells including OCT4, SOX2, and Nanog through activating STAT3 signalling pathway (Fig. 1B).

Apart from gene transcription modulation through histone methylation and DNA methylation, histone acetylation is another important way of modifying chromatin. P300/CBP-associated factor (PCAF) is a well-known histone acetyltransferase, playing a major role in transcription elongation. Acting as an antisense RNA of Glypican 3 (GPC3), GPC3-AS1 overexpression and co-expression with GPC3 in HCC tissues has been shown through microarray analysis. RNA pull-down, RIP, and ChIP assays suggested GPC3-AS1 could directly bind with PCAF and recruit PCAF to the GPC3 gene body region, subsequently inducing an increase in euchromatic histone marks and activating GPC3 transcription (Fig. 1C).
Transcriptional regulation

Generally, lncRNAs regulate transcription through direct chromatin looping, recruitment or prevention of multiple transcription factors or disrupting the Pol II transcription machinery at target genes.\(^{48}\) Chen and colleagues discovered a role of lncSox4 in the self-renewal of liver tumour-initiating cells (TICs), tumour initiation, and propagation. Moreover, the specific binding of lncSox4 and STAT3 remarkably increases STAT3 enrichment at Sox4 promoter and induces Sox4 activation, leading the acquisition of LCSCs.\(^{52}\) Similarly, LINC00324, another lncRNA overexpressed in HCC tissue, contributes to the maintenance of LCSCs biological properties by upregulating the expression of fas ligand (FasL) through recruitment of transcription factor PU.1 to the FasL promoter region (Fig. 1 D).\(^{53}\)

Additionally, lncRNAs regulate target gene transcription through binding to their loci promoters directly. LncRNA calmodulin binding transcription activator 1 (CAMTA1) is vital to obtain CSC characteristics of HCC cells by regulating the expression CAMTA1. Chromatin isolation by RNA purification assay confirmed that the direct combination of lncCAMTA1 and CAMTA1 promoter alters chromatin structure and prevents the transcription of CAMTA1. Therefore, cancer stem cell-like properties could be maintained owing to the repression of CAMTA1 (Fig. 1 E).\(^{54}\)

Recent data suggested lncRNA HOTAIR can stimulate malignant proliferation of human LCSCs. SET Domain-Containing Protein 2 (SETD2) is a vital target of HOTAIR, and SETD2 expression at the transcriptional level is reduced through blocking RNA polymerase II (RNA pol II) catalytic function and by dissociating the cAMP responsive element binding protein 1 (CREB)-P300-RNA pol II complex from the promoter of SETD2. Decreased SETD2 level interferes with mismatch recognition and DNA damage repair, potentially causing tumourigenesis in LCSCs (Fig. 1 F).\(^{55}\)

Alternative splicing regulation

At the post-transcriptional level, lncRNAs may play a key role in alternative splicing processes, which can actively participate in tumourigenicity.\(^{56}\) Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a nucleus-enriched lncRNA and its close proximity to nuclear SC35 speckle actively controls pre-mRNA processing through modulating oncogenic alternative splicing factors.\(^{57}\) MALAT1 induces serine and arginine rich splicing factor 1 (SRSF1) to mediate its target cleavage, increasing the occurrence of anti-apoptotic splicing isoforms and activating the mTOR pathway by regulating the selective splicing of S6 kinase 1 (S6K1).\(^{58}\) Expression of lncRNA nuclear enriched abundant transcript 1 (NEAT1) is reportedly higher in HCC than normal tissues, and acted as a cancer driver promoting proliferation, invasion and migration.\(^{59}\) NEAT1 can form a protein complex with U2 small nuclear RNA auxiliary factor-2 (U2AF2), an essential splicing factor of polypyrimidine tract pre-mRNA, thus modulating heterogeneous nuclear ribonucleoprotein (HNRNP) A2 expression.\(^{59,60}\) HNRNPA2 is associated with the poor prognosis of hepatoma patients, and is an essential cleavage factor in facilitating the proliferation and invasion of liver cells (Fig. 2 A).\(^{61}\)

mRNA stability regulation

LncRNAs are also implicated in the control of mRNA stability through diverse post-transcriptional regulatory pathways.\(^ {62}\) The antisense lncRNAs, including those located antisense to tumour related genes, can affect the stability of mRNAs in complicated and accurate gene-net of malignant diseases.\(^ {63,64}\) The up-regulated antisense lncRNA, PCNA antisense RNA 1 (PCNA-AS1), and proliferating cell nuclear antigen (PCNA) form a double-stranded RNA to increase
PCNA stability, consequently prompting HCC growth. Moreover, lncRNA ICAM-1-related (ICR) that is specifically highly expressed in liver PVTT forms an RNA duplex with ICAM-1 to maintain its expression through approximately 800 bp complementary to the ICAM-1 mRNA sequence, thereby promoting the CSC characteristics of HCC cells. In comparison to tumour adjacent tissues, lncRNA associated with liver regeneration (LALR1) dramatically increases in HCC tissues. RNA pulldown analyses revealed lncRNA-LALR1 could upregulate oncogene ID2 expression through interaction with ID2 mRNA in HCC cells, highlighting an ID2-dependent effect of LALR1 on tumourigenicity (Fig. 2B).

Contrarily, lncRNA can act as legitimate bona fide microRNA competitor thereby actively competing with their parent protein-coding genes for the same pool of microRNAs through sets of conserved microRNA response element, thus enhancing the translation of target RNAs. TP73 antisense RNA 1 (TP73-AS1) is a type of lncRNA highly expressed in liver cancer, which shares a similar binding site of miR-200a with high mobility group box 1 (HMGB1). TP73-AS1 competes with HMGB1 for miR-200a binding, thus attenuating the inhibitory effect of miR-200a on HMGB1 expression. By sponging and competitively binding to miR-199a-3p, LINC00346 releases the miR-199a-3p-mediated suppression of CDK1/cyclin B1, thereby affecting p53 signalling pathways and regulating apoptosis, invasion and cell cycle of HCC cells. The newly discovered role of lncRNA LINC00160 in HCC showed LINC00160 silencing suppresses autophagy and drug resistance in HCC by decreasing the expression of phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3) via miR-132 promotion (Fig. 2C).

Aside from RNA-duplex formation and miRNA sponges, mRNA stabilizing protein Hu antigen R (HuR) can be guided by lncRNA-UFC1 to interact with β-catenin mRNA, ultimately enhancing β-catenin levels to promote HCC proliferation and inhibit apoptosis. In contrast, Lnc-UCID (lncRNA up-regulating CDK6 by interacting with DHX9) increases CDK6 expression in HCC cells by competitively binding to DEAH (Asp-Glu-Ala-His) box helicase 9 (DHX9) and sequestering DHX9 from CDK6-3' UTR. DHX9 is an RNA helicase, which could post-transcriptionally suppress CDK6 expression by binding to the 3′UTR of CDK6 mRNA (Fig. 2D).

Post-translational regulation

Regarding post-translational modification, lncRNAs modulate protein ubiquitination positively or negatively and influence the degradation of proteins mediated by ubiquitin proteasome. It is widely recognized that degradation of intracellular proteins by the ubiquitin proteasome system regulates a broad array of cellular processes. Higher lncRNA-PVT1 expression indicates a poor HCC clinical
prognosis. Fang and colleagues confirmed that lncRNA-PVT1 up-regulates nucleolar protein 2 (NOP2) by preventing the degradation of ubiquitin proteasome system. Moreover, the role of lncRNA-PVT1 depends on the presence of NOP2. In addition, the frequent DNA-gain regions of HCC produces a tumour-promoting lncRNA, LINC01138, which exerts its oncogenic activity through physical interaction with protein arginine methyltransferase 5 (PRMT5) and stabilizes PRMT5 through blocking ubiquitin/proteasome-dependent degradation in HCC (Fig. 3A). In HBV replicating cells, HOTAIR may serve as a ubiquitination scaffold through interaction with PRC2 and E3 ligases Mex-3 RNA-binding family member B (Mex3b) simultaneously. This facilitates the degradation of PRC2 and results in de-repression of PRC2 targets, including epithelial cell adhesion molecule (EPCAM) and pluripotency genes (Fig. 3B). In addition to the above, lncRNAs can also modify protein localization or activity, as well as the composition of protein complexes to exert various biological effects. Recent evidence demonstrated HCC cells grown together with HCC Mesenchymal stem cells (MSC) switch to a more aggressive phenotype. Subsequently, lncRNA MSC-upregulated factor (MUF) is activated by HCC-MSCs, and accountable for the formation of tumour sphere and EMT processes. Mechanistic investigations showed higher interaction between ANXA2 and glycogen synthase kinase 3β (GSK-3β) due to the combination of lncRNA-MUF and ANXA2, reducing GSK-3β-mediated phosphorylation of β-catenin and preventing its degradation of ubiquitin-proteasome system. Eventually, β-catenin translocates to the nucleus activating the Wnt cascade (Fig. 3C). A new lncRNA, gastric cancer metastasis associated long non-coding RNA (GMAN), is evidently responsible for anti-apoptosis and increasing the invasion and migration potential in HCC. Mechanistic analysis implied that GMAN and eukaryotic translation initiation factor 4B (eIF4B) directly combine to stabilize phosphorylation of eIF4B at serine-422 by preventing the binding and dephosphorization of eIF4B from the protein phosphatase 2 regulatory subunit B-alpha (PPP2R2A), thus increasing translation and expression of anti-apoptotic mRNA (Fig. 3D). Moreover, Ni and colleagues identified that oncogenic lncRNA uc.134 combines with cullin 4A (CUL4A) to prevent its nuclear export without changing its protein level in HCC cells, thus impeding the CUL4A-mediated ubiquitination of large tumour suppressor kinase 1 (LATS1), and increasing yes associated protein 1 (YAP) S127 phosphorylation to silence the YAP target genes (Fig. 3E).}

**Tumor-suppressive effect of lncRNAs in HCC**

Increasing reports focus on the characterization of oncogenic lncRNAs in HCC; however, there are lncRNAs, which...
play a suppressive role in liver cancer. These may influence distinct biological processes, such as pro-oncogene lncRNAs in HCC, being dependant on their cellular distribution. Regarding their modes of action, lncRNAs may be an important regulator of nuclear mechanisms once localized into the nucleus. Subsequent exportation of lncRNAs into the cytoplasm can affect mRNA turnover and controls protein stability (Table 1).

**Roles of lncRNAs in the nucleus**

The lncRNA MAGI2 antisense RNA 3 (MAGI2-AS3) is very prominent in the nucleus of HCC cells and markedly promotes H3K4me2 demethylation at the Rac GTPase activating protein 1 (RACGAP1) promoter through recruitment of lysine demethylase 1A (KDM1A), ultimately suppressing the expression of RACGAP1 and restraining tumourigenesis.82 Early studies supported the notion of a stimulatory role of lncRNA H19 in HCC. Zhang and colleagues have provided an explanation for the hitherto puzzling literature on the relationship between H19 and HCC. H19 associates with the protein complex hnRNPU/PCAF/RNAPolII and initiates the transcription of the miR-200 family by enhancing the histone H3 acetylation, thus impairing the aggressive and metastatic properties of HCC.83

Maternally expressed gene 3 (MEG3) encodes lncRNA whose expression is lost or downregulated in major human cancers. MEG3 compound is formed by association with p53 DNA binding domain, and is then recruited to its specific site where it influences the expression of partial p53 target genes and implements a suppressive role in hepatoma cells.84 LncRNA wilms tumour-associated antisense RNA (WT1-AS) may possess a tumour-inhibitory role by reversing WT1-mediated resistance to doxorubicin-based chemotherapy in HCC cells. Bioinformatics analysis revealed binding of WT1-AS to the TATA region of the WT1 promoter could inhibit WT1 transcription, which can negatively regulate HCC

| LncRNA      | Classification | Expression in HCC | Effect on HCC                                      | Molecular mechanism                                      | Reference |
|-------------|----------------|-------------------|---------------------------------------------------|----------------------------------------------------------|-----------|
| MAGI2-AS3   | antisense      | down              | inhibits cell growth, migration, invasiveness, and promote cell apoptosis | promotes H3K4me2 demethylation at RACGAP1 promoter through recruitment of KDM1A | [82]      |
| H19         | intergenic     | down              | inhibits EMT and tumor metastasis                 | recruits HnRNP U/PCAF/RNAPolII complex to activate miR-200 family through histone acetylation interacts with p53 DNA binding domain to activates p53-mediated transcriptional activity binds to the WT1 promoter to inhibit transcription | [83]      |
| MEG3        | intergenic     | down              | inhibits proliferation and induces apoptosis      | [84]                                                      |
| WT1-AS      | antisense      | down              | negatively regulates HCC chemotherapy resistance | [85]                                                      |
| FTX         | overlapping    | down              | inhibits EMT, cell metastasis and invasion        | competitively sponges miR-374a and upregulates WIFI1, PTEN and WNT5A | [86]      |
| LINC01093   | intergenic     | down              | suppresses cell proliferation and metastasis     | disrupts the association between IGF2BP1 and GLI1 mRNA, resulting in the degradation of GLI1 mRNA promotes the ubiquitin-mediated degradation of PKM2 and inhibits Akt/mTOR signaling pathway | [87]      |
| LINC01554   | intergenic     | down              | abolishes aerobic glycolysis, inhibits cell growth, colony formation, foci formation inhibit HCC invasion and metastasis | induce HNRNPA2B1 degradation via the ubiquitin-proteasome pathway | [88]      |
| MIR503HG    | intergenic     | down              | [89]                                              |                                                          |

LncRNA, long non-coding RNA; HCC, hepatocellular carcinoma; EMT, epithelial–mesenchymal transition.
chemotherapy resistance through JAK2/STAT3 and MAPK signalling.95

**Roles of IncRNAs in the cytoplasm**

In additional to their functional role in the nucleus, IncRNAs also govern gene expression post-transcriptionally following exportation into the cytoplasm. One study demonstrated the reduction of epithelial marker E-cadherin upon IncRNA-FTX interference, accompanied with increased mesenchymal markers N-cadherin, Snail, Vimentin, ZEB1, and Twist in SMMC 7721 cells. FTX acts as a repressive factor of HCC metastasis and invasion by competitively sponging miR-374a and upregulating multiple negative regulators of the Wnt/β-catenin signalling cascade, including WIF1, PTEN, and WNT5A.96

A novel liver-enriched IncRNA LIN01093 competitively pairs with oncofoetal protein insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), preventing glioma-associated oncogene homolog 1 (GLI1) mRNA binding to IGF2BP1 and promoting GLI1 degradation. Decreased level of GLI1 is crucial to repress its downstream molecules, thus avoiding HCC cell proliferation.97

In vitro assay and nude mice xenograft models have confirmed the role of LIN01554 as a tumour suppressor in HCC. Subcellular fractionation assay showed the cytoplasmic accumulation of LIN01554 in hepatoma cells. Mechanistic analyses suggested that LIN01554 downregulation impedes the ubiquitin-mediated degradation of pyruvate kinase M2 (PKM2) and facilitates Akt/mTOR signalling pathway, thereby empowering cancer cells to acquire high aerobic glycolysis to sustain cell growth.98 The host gene of mir503, IncRNA MIR503HG, interacts with HNRNPA2B1 to expose concealed ubiquitination sites and mediates protein degradation via the ubiquitin—proteasome pathways. Simultaneous formation of mir503HG-HNRNPA2B1 complex anchors to p52 and p65, making the mRNAs fragile and ultimately inactivating the NF-κB signalling pathway in HCC cells.99

**Putative diagnostic and prognostic IncRNAs in HCC**

Accumulating evidence supported the notion that the wide range of IncRNA expression patterns in various cancers holds significant promise for the discovery of novel cancer biomarkers.90 Differential expressions and mutations of IncRNAs in HCC are turning into reliable tools for predicting cancer prognosis and patients outcome.91 The majority of IncRNAs display strict tissue-specific and neoplasm-specific expression traits, opening up a new range of possibilities for the precise classification of distinct subcategories of tumours, and to predict therapeutic action.92,93

A retrospective study showed HCC-expressed IncRNA, called IncRNA regulator of Akt signalling associated with HCC and RCC (LNCARSR), is up-regulated in HCC patients and cell lines. High-incidence LNCARSR in patients correlates with large tumour volume, advanced clinical stage, and poor prognosis.94 Another study identified the strong correlation of IncRNA small nuclear RNA host gene 20 (SNHG20) expression with multiple clinicopathological characteristics in HCC patients.95 Moreover, screening deregulated genes in 46 HCCs, 4 focal nodular hyperplasia, and 7 cirrhosis, using cDNA arrays, characterized HULC with highly specific up-regulation in HCC tissues.96 HULC is detected at higher frequency in the plasma of early stage HCC compared to healthy controls.97 LncRNA ZEB1 antisense RNA 1 (ZEB1-AS1) is abnormally overexpressed in HCC samples, especially in metastatic tumour tissues. Patients with high ZEB1-AS1 expressions have shorter survival rates and higher recurrence ratio.98 In addition to those mentioned above, dysregulated LIN00974, LIN01225 and IncRNA downregulated in liver cancer stem cells (DILC) have been variably shown to correlate with clinicopathologic parameters, and/or poor outcome in HCC patients.99–101 Furthermore, combination of IncRNAs as candidate biomarkers in HCC has been proposed. Increased expression of IncRNA urothelial cancer associated 1 (UCA1) and WD repeat containing antisense to TP53 (WRAP53) is associated with advanced HCC clinical stage. It is noteworthy that two types of IncRNAs in combination with alpha-fetoprotein have surprisingly increase sensitivity to 100%.102 Additionally, the sensitivity and specificity values of a 2-IncRNA signature (PTV1 and uc002mbe.2) for distinguishing HCC patients from the healthy group reached 60.56% and 90.62%, respectively.103 A group of three up-regulated IncRNAs in liver cancer, RP11-160H22.5, XLOC_014172 and LOC149086, showed improved diagnosis efficiency and credible clinical potential, with a merged area under the curve training set and validation set of 0.999 and 0.896, respectively.104

The use of non-coding RNA molecules packaged in exosomes as non-invasive biomarkers are a promising field of research as they are free from degradation by RNases present in plasma or other body fluids.105 LncRNA focally amplified IncRNA on chromosome 1 (FAL1) is reportedly up-regulated in serum exosomes of HCC patients, and transfer of exosomal FAL1 to HCC cells may trigger non-positive effects.106 Additionally, major alterations of LIN00161 in extracellular vesicles obtained from hepatoma cells can significantly discriminate HCC patients from healthy individuals.107 Moreover, recent data from 301 participants showed higher levels of serum exosomal IncRNAs ENSG00000258332.1 and LIN00635 in the liver cancer group, which can be utilized as diagnostic biomarkers for detecting HCC.108

**Therapeutic potential of IncRNAs in HCC**

Advancement in IncRNA-targeting therapeutics provides an outstanding opportunity to impact various aspects of cancer progression. Currently there are two major approaches employing nucleic acid therapeutics; double stranded RNA-mediated interference (RNAi) and single stranded antisense oligonucleotides (ASOs).109 Although siRNA holds promise in therapeutic gene silencing, several barriers of in vivo systemic siRNA therapy still exists including circulating nuclease degradation, renal clearance, off-target effects and immune stimulation.110 However, a PEGylated PLGA nanoplatform (NP) loaded with LIN00958 siRNA for HCC systemic administration has been developed and characterized. PLGA-based nanosystem is controlled release, tumour targeting, safe, and presents satisfactory antitumor efficacy.111 Furthermore, in vivo interference with IncRNA

The paradoxical functions of long noncoding RNAs 365
differentiation antagonizing non-protein coding RNA (DANCR) action through shRNA leads to decreased tumour cell vitality, tumour shrinkage, and improved mouse survival.\textsuperscript{112} ASOs are single stranded oligonucleotides that offer specific complementarity and degrade mRNA or lncRNA via RNase H.\textsuperscript{113} This approach for targeting HCC-related lncRNAs has been reported recently. Targeting oncogenic linc00210 by ASOs substantially attenuate related lncRNAs has been reported recently. Targeting ERK signalling activity in HCC.\textsuperscript{118} These findings point to- and decreases KRAS protein level, as well as downstream NCBP2-AS2, is recognized as the first KRAS-binding protein conserved 99-amino acid microprotein encoded by lncRNA sequences for multiple miRNAs underlying sorafenib resistance with sorafenib on HCC animal models.\textsuperscript{115} Another adenovirus-expressed lncRNAi, representing an artificial interfering lncRNA demonstrated an optimal anti-tumor effect on HCC patient-derived xenograft tumour models in nude mice, due to its complementary sequence with oncogenic miRNAs.\textsuperscript{116}

Conclusions and future perspectives

In this review, we comprehensively describe how large amounts of oncogenic lncRNAs in HCC could be involved in gene modulation through epigenetic, transcriptional, and post-transcriptional regulation. In addition to promoting carcinogenesis, lncRNA can also act as negative regulators of HCC progression, impacting similar cellular processes. However, not all HCC-associated lncRNAs participate in gene regulation of molecular patterns proposed above. Particularly, lncRNA associated with microvascular invasion of HCC (MVIH) promotes tumour growth and intrahepatic metastasis by activating tumour-inducing angiogenesis through inhibiting the secretion of PGK.\textsuperscript{117} KRASIM, a generically highly conserved 99-amino acid microprotein encoded by lncRNA NCBP2-AS2, is recognized as the first KRAS-binding protein and decreases KRAS protein level, as well as downstream ERK signalling activity in HCC.\textsuperscript{118} These findings point towards the complexity of the lncRNA molecular mechanisms in HCC, warranting further investigations.

Mounting evidence demonstrate the suitability of lncRNAs as a molecular tool in the early diagnosis and prognosis prediction for patients with liver cancer. However, most studies have been conducted in a few cases. Collaborative projects with larger patient cohorts are necessary to identify more specific and sensitive markers for future diagnosis and prognosis. Apart from serving as biomarkers, novel strategies based on lncRNA therapy, such as RNAi and ASO, may provide potential opportunities for treating HCC. These methods can be promising alternatives in advanced liver cancer patients with limited therapeutic options. Considering the efficacy of targeting lncRNAs in animal models, careful application of these in human therapy will be critical in order to validate its stability, side effects and safety.

Authorship statement

Duguang Li: Conceptualization, Writing-Original draft preparation. Jing Yang and Hui Lin: Writing-Reviewing and Editing. Duguang Li, Xiaoxiao Fan and Yirun Li: Making tables and drawings.

Conflict of interests

The authors declare that there are no conflicts of interest.

Acknowledgements

This work was supported by the National Key Research and Development Project (No. 2017YFC0110802), Zhejiang province Key Research and Development Project (No. 2020C01059), National Natural Science Foundation of China (No. 81872297, and 81874059), Zhejiang Engineering Research Center of Cognitive Healthcare (No. 2017E10011) and the National Key Scientific Instrument and Equipment Development Project (No. 81827804).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2020.11.014.

References

1. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018.
2. Llovet JM. Liver cancer: time to evolve trial design after everolimus failure. Nat Rev Clin Oncol. 2014;11(9):506–507.
3. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379(9822):1245–1255.
4. Zucman-Rossi J, Villanueva A, Nault JC, Llovet JM. Genetic landscape and biomarkers of hepatocellular carcinoma. Gastroenterology. 2015;149(5):1226–1239. e1224.
5. Djebali S, Davis CA, Merkel A, et al. Landscape of transcription in human cells. Nature. 2012;489(7414):101–108.
6. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. Physiol Rev. 2016;96(4):1297–1325.
7. Yao J, Wu L, Meng X, et al. Profiling, clinicopathological correlation and functional validation of specific long non-coding RNAs for hepatocellular carcinoma. Mol Cancer. 2017;16(1):164.
8. Li Y, Chen X, Huang H, et al. Identification of novel lncRNAs for detection of HBV-associated hepatocellular carcinoma. OncoTargets Ther. 2019;12:10199–10211.
9. Zhang H, Zhu C, Zhao Y, et al. Long non-coding RNA expression profiles of hepatitis C virus-related dysplasia and hepatocel- lular carcinoma. Oncotarget. 2015;6(41):43770–43778.
10. Yang Y, Chen L, Gu J, et al. Recurrently deregulated lncRNAs in hepatocellular carcinoma. Nat Commun. 2017;8:14421.
11. Yin X, Zheng SS, Zhang L, et al. Identification of long non-coding RNA expression profile in oxaliplatin-resistant hepatocellular carcinoma cells. Gene. 2017;596:53–88.
12. Kapranov P, Cheng J, Dike S, et al. RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science. 2007;316(5830):1484–1488.
13. Taft RJ, Pang KC, Mercer TR, Dinger M, Mattick JS. Non-coding RNAs: regulators of disease. J Pathol. 2010;220(2):126–139.
14. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often ranked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120(1):15–20.
The paradoxical functions of long noncoding RNAs

15. Williams GT, Farzaneh F. Are snoRNAs and snoRNA host genes new players in cancer? *Nat Rev Cancer*. 2012;12(2):84–88.

16. Siomi MC, Sato K, Peczic D, Aravin AA. PIWI-interacting small RNAs: the vanguard of genome defence. *Nat Rev Mol Cell Biol*. 2011;12(4):246–258.

17. Qureshi IA, Mehler MF. Non-coding RNA networks underlying cancer. *Biol Nat Rev Mol Cell Biol*. 2012;13(1):19–31.

18. Williams GT, Farzaneh F. Are snoRNAs and snoRNA host genes new players in cancer? *Nat Rev Mol Cell Biol*. 2011;12(4):246–258.

19. Williams GT, Farzaneh F. Are snoRNAs and snoRNA host genes new players in cancer? *Nat Rev Mol Cell Biol*. 2011;12(4):246–258.

20. Niazi F, Valadkhan S. Computational analysis of functional long noncoding RNAs reveals lack of peptide-coding capacity and parallels with 3’ UTRs. *RNA*. 2012;18(4):825–843.

21. Volders PJ, Helsens K, Wang X, et al. LncRNApedia: a database for annotated human lncRNA transcript sequences and structures. *Nucleic Acids Res*. 2013;41(Database issue):D246–D251.

22. Uszczynska-Ratajczak B, Lagarde J, Frankish A, Guigo R, Johnson R. Towards a complete map of the human long non-coding RNA transcriptome. *Nat Rev Genet*. 2018;19(9):535–548.

23. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet*. 2016;17(1):47–62.

24. Premsner JR, Chinnaian VM. The emergence of lncRNAs in cancer biology. *Cancer Discov*. 2011;1(5):391–407.

25. Wong CM, Tsang FH, Ng IO. Non-coding RNAs in hepatocellular carcinoma: molecular functions and pathological implications. *Nat Rev Gastroenterol Hepatol*. 2018;15(3):137–151.

26. Klingenberg M, Matsuda A, Diederichs S, Patel T. Non-coding RNA in hepatocellular carcinoma: mechanisms, biomarkers and therapeutic targets. *J Hepatol*. 2017;67(3):603–618.

27. Yang W, Yan HX, Chen L, et al. Wnt/beta-catenin signaling contributes to activation of normal and tumorigenic liver progenitor cells. *Cancer Res*. 2008;68(11):4287–4295.

28. Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. *Nat Rev Cancer*. 2014;14(11):736–746.

29. Lv H, Lv G, Han Q, Yang W, Wang H. Noncoding RNAs in liver cancer stem cells: the big impact of little things. *Cancer Lett*. 2018;418:51–63.

30. Huang JL, Zheng L, Hu YW, Wang Q. Characteristics of long non-coding RNA and its relation to hepatocellular carcinoma. *Carcinogenesis*. 2014;35(3):507–514.

31. Lin YH, Wu MH, Yeh CT, Lin KH. Long non-coding RNAs as mediators of tumor microenvironment and liver cancer cell communication. *J Mol Biol*. 2018;419(2):3742.

32. Shi X, Sun M, Liu H, Yao Y, Song Y. Long non-coding RNAs: a new frontier in the study of human diseases. *Cancer Lett*. 2013;339(2):159–166.

33. Marchese FP, Huarte M. Long non-coding RNAs and chromatin modifiers: their place in the epigenetic code. *Epigenetics*. 2014;9(1):21–26.

34. Campos EI, Reinberg D. Histones: annotating chromatin. *Annu Rev Genet*. 2009;43:559–599.

35. Au SL, Wong CC, Lee JM, et al. Enhancer of zeste homolog 2 epigenetically silences multiple tumor suppressor microRNAs to promote liver cancer metastasis. *Hepatology*. 2012;56(2):622–631.

36. Khalil AM, Guttmann M, Huarte M, et al. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. *Proc Natl Acad Sci U S A*. 2009;106(28):11667–11672.

37. Fu WM, Zhu X, Wang WM, et al. Hotair mediates hepatocarcinogenesis through suppressing miRNA-218 expression and activating P14 and P16 signaling. *J Hepatol*. 2015;63(4):886–895.

38. Huang MD, Chen WM, Qi FZ, et al. Long non-coding RNA ANRIL is upregulated in hepatocellular carcinoma and regulates cell apoptosis by epigenetic silencing of KLF2. *J Hematol Oncol*. 2015;8(1):57.

39. Yang F, Zhang L, Huo XS, et al. Long noncoding RNA high expression in hepatocellular carcinoma facilitates tumor growth through enhancer of zeste homolog 2 in humans. *Hepatology*. 2011;54(5):1679–1689.

40. Song W, Gu Y, Lu S, et al. LncRNA TRERNA1 facilitates hepatocellular carcinoma metastasis by dimethylating H3K9 in the CDH1 promoter region via the recruitment of the EHMT2/S-NAIL1 complex. *Cell Prolif*. 2019;52(4):e12621.

41. Tang J, Xie Y, Xu X, et al. Bidirectional transcription of Linc00441 and RB1 via H3K27 modification-dependent way promotes hepatocellular carcinoma. *Cell Death Dis*. 2017;8(3):e2675.

42. Gai M, Xiao Z, Wang Y, et al. Long noncoding RNA HULC modulates abnormal lipid metabolism in hepatoma cells through an miR-9-mediated RXRA signaling pathway. *Cancer Res*. 2015;75(5):846–857.

43. Wu DM, Zheng ZH, Zhang YB, et al. Down-regulated lncRNA DLX6-A51 inhibits tumorigenesis through STAT3 signaling pathway by suppressing CADM1 promoter methylation in liver cancer stem cells. *J Exp Clin Cancer Res*. 2019;38(1):237.

44. Nosrati N, Kapoor NR, Kumar V. Combinatorial action of transcription factors orchestrates cell cycle-dependent expression of the ribosomal protein genes and ribosome biogenesis. *FEBS J*. 2014;281(10):2339–2352.

45. Feng M, Ho M. Glypican-3 antibodies: a new therapeutic target for liver cancer. *FEBS Lett*. 2014;588(2):377–382.

46. Zhou XT, Yuan JH, Zhu TT, Li YY, Cheng XY. Long noncoding RNA glypican 3 (GPC3) antisense transcript 1 promotes hepatocellular carcinoma progression via epigenetically activating GPC3. *FEBS J*. 2016;283(20):3739–3754.

47. Hung T, Wang Y, Lin MF, et al. Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet*. 2011;43(7):621–629.

48. Yang L, Lin C, Jin C, et al. lncRNA-dependent mechanisms of androgen-receptor-regulated gene activation programs. *Nature*. 2013;500(7464):598–602.

49. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell*. 2011;43(6):904–914.

50. Mariner PD, Walters RD, Espinoza CA, et al. Human Alu RNA is a modular transacting repressor of mRNA transcription during heat shock. *Mol Cell*. 2008;29(4):499–509.

51. Chen ZZ, Huang L, Wu YH, Zhao WJ, Zhu PP, Gao YF. LncSox4 promotes the self-renewal of liver tumour-initiating cells through Stat3-mediated Sox4 expression. *Nat Commun*. 2016;7:12598.

52. Gao J, Dai C, Yu X, Yin XB, Zhou F. Long noncoding RNA LINCO0324 exerts protumorigenic effects on liver cancer stem cells by upregulating fas ligand via PU box binding protein. *FASEB J*. 2020;34(4):5800–5817.

53. Ding LJ, Li Y, Wang SD, et al. Long noncoding RNA IncCAMTA1 promotes proliferation and cancer stem cell-like properties of liver cancer by inhibiting CAMTA1. *Int J Mol Sci*. 2016;17(10):1617.

54. Liu J, An J, Wu M, et al. LncRNA HOTAIR promotes human liver cancer stem cell malignant growth through downregulation of SETD2. *Onco target*. 2015;6(29):27847–27864.

55. Kreytanz M, Puig I, Pena C, et al. A natural antisense transcript regulates Zeb2/Sip1 gene expression during Snaill-induced
epithelial-mesenchymal transition. *Genes Dev.* 2008;22(6): 756–769.
57. Hutchinson JN, Ensminger AW, Clemson CM, Lynch CR, Lawrence JB, Chess A. A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. *BMN Genom.* 2007;8:39.
58. Malakar P, Shilo A, Mogilevsky A, et al. Long noncoding RNA MALAT1 promotes hepatocarcinoma development by SRSP1 upregulation and mtOR activation. *Cancer Res.* 2017; 77(5):1155–1167.
59. Mang Y, Li L, Ran J, et al. Long noncoding RNA NEAT1 promotes cell proliferation and invasion by regulating hnRNP A2 expression in hepatocarcinoma cells. *OncoTargets Ther.* 2017;10:1003–1016.
60. Agrawal AA, McLaughlin KJ, Jenkins JL, Kielkopf CL. Structure-guided U2AF65 variant improves recognition and splicing of a defective pre-mRNA. *Proc Natl Acad Sci U S A.* 2014; 111(49):17420–17425.
61. Shilo A, Ben Hur V, Denichenko P, et al. Splicing factor hnRNP A2 activates the Ras-MAPK-ERK pathway by controlling A-Raf splicing in hepatocarcinoma development. *RNA.* 2016;20(4):505–515.
62. Geissler S, Coller J. RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. *Nat Rev Mol Cell Biol.* 2013;14(11):699–712.
63. Mahmoudi S, Henriksson S, Corcoran M, Mendez-Vidal C, Wiman KG, Farnebo M. Wrap3S, a natural p53 antisense transcript required for p53 induction upon DNA damage. *Mol Cell.* 2009;33(4):462–471.
64. Yu W, Gius D, Onyango P, et al. Epigenetic silencing of tumour suppressor gene p15 by its antisense RNA. *Nature.* 2008; 451(7175):202–206.
65. Yuan SX, Tao QF, Wang J, et al. Antisense long non-coding RNA PCNA-AS1 promotes tumor growth by regulating proliferating cell nuclear antigen in hepatocarcinoma. *Cancer Lett.* 2014;349(1):87–94.
66. Guo W, Liu S, Cheng Y, et al. ICAM-1-Related noncoding RNA in cancer stem cells maintains ICAM-1 expression in hepatocarcinoma. *Clin Cancer Res.* 2016;22(8): 2041–2050.
67. Mao LH, Chen SY, Li XQ, et al. lncRNA-LALR1 upregulates small nucleolar RNA SNO D7Z2 to promote growth and invasion of hepatocarcinoma. *Aging (Albany NY).* 2020;12(5): 4527–4546.
68. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfo PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell.* 2011;146(3):353–358.
69. Li S, Huang Y, Huang Y, et al. The long non-coding RNA TP73-AS1 modulates HCC cell proliferation through miR-200a-dependent HMGB1/RAGE regulation. *J Exp Clin Cancer Res.* 2017;36(1):51.
70. Jin J, Xu H, Li W, Xu X, Liu H, Wei F. LINC00346 acts as a competing endogenous RNA regulating development of hepatocarcinoma via modulating CDK1/CCNB1 Axis. *Front Bioeng Biotechnol.* 2020;8:54.
71. Zhang W, Liu Y, Fu Y, et al. Long non-coding RNA LINC0160 functions as a decoy of microRNA-132 to mediate autophagy and drug resistance in hepatocarcinoma via inhibition of PI3K/Akt. *Cancer Lett.* 2020;478:22–33.
72. Cao C, Sun J, Zhang D, et al. The long intergenic noncoding RNA UFC1, a target of MicroRNA 34a, interacts with the mRNA stabilizing protein HuR to increase levels of beta-catenin in HCC cells. *Gastroenterology.* 2015;148(2): 425–426, e418.
73. Wang YL, Liu JY, Yang JE, et al. Lnc-UCID promotes G1/S transition and hepatoma growth by preventing DHX9-mediated CDK6 down-regulation. *Hepatology.* 2019;70(1): 259–275.
The paradoxical functions of long noncoding RNAs

94. Li Y, Ye Y, Feng B, Qi Y. Long noncoding RNA lncARSR promotes doxorubicin resistance in hepatocellular carcinoma via modulating PTEN-PI3K/Akt pathway. J Cell Biochem. 2017;118(12):4498–4507.

95. Liu J, Lu C, Xiao M, Jiang F, Qu L, Ni R. Long non-coding RNA SNHG20 predicts a poor prognosis for HCC and promotes cell invasion by regulating the epithelial-to-mesenchymal transition. Biomed Pharmacother. 2017;89:857–863.

96. Panzitt K, Tschenatsch MM, Guelly C, et al. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. Gastroenterology. 2007;132(1):330–342.

97. Xie H, Ma H, Zhou D. Plasma HULC as a promising novel biomarker for the detection of hepatocellular carcinoma. BioMed Res Int. 2013;2013:136106.

98. Li T, Xie J, Shen C, et al. Upregulation of long noncoding RNA ZEB1-AS1 promotes tumor metastasis and predicts poor prognosis in hepatocellular carcinoma. Oncogene. 2016;35(12):1575–1584.

99. Tang J, Zhuo H, Zhang X, et al. A novel biomarker Linc00974 interacting with KRT19 promotes proliferation and metastasis in hepatocellular carcinoma. Cell Death Dis. 2014;5(12):e1549.

100. Wang X, Zhang W, Tang J, et al. LINC01225 promotes occurrence and metastasis of hepatocellular carcinoma in an epidermal growth factor receptor-dependent pathway. Cell Death Dis. 2016;7(3):e2130.

101. Wang X, Sun W, Shen W, et al. Long non-coding RNA DILC regulates liver cancer stem cells via IL-6/STAT3 axis. J Hepatol. 2016;64(4):1283–1294.

102. Kamel MM, Matboli M, Sallam M, Montasser IF, Saad AS, El-Tawdi AHF. Investigation of long noncoding RNAs expression profile as potential serum biomarkers in patients with hepatocellular carcinoma. Transl Res. 2016;168:134–145.

103. Yu J, Han J, Zhang J, et al. The long noncoding RNAs PVT1 and uc002mbe.2 in sera provide a new supplementary method for hepatocellular carcinoma diagnosis. Medicine (Baltim). 2016;95(31):e4436.

104. Tang J, Jiang R, Deng L, Zhang X, Wang K, Sun B. Circulation long non-coding RNAs act as biomarkers for predicting tumorigenesis and metastasis in hepatocellular carcinoma. Oncotarget. 2015;6(6):4505–4515.

105. Record M, Subra C, Silvente-Poirot S, Poirot M. Exosomes as intercellular signalosomes and pharmacological effectors. Biochem Pharmacol. 2011;81(10):1171–1182.

106. Li B, Mao R, Liu C, Zhang W, Tang Y, Guo Z. LncRNA FAL1 promotes cell proliferation and migration by acting as a ceRNA of miR-1236 in hepatocellular carcinoma cells. Life Sci. 2018;197:122–129.

107. Sun L, Su Y, Liu X, et al. Serum and exosome long non coding RNAs as potential biomarkers for hepatocellular carcinomas. J Cancer. 2018;9(15):2631–2639.

108. Xu H, Chen Y, Dong X, Wang X. Serum exosomal non-coding RNAs ENSG00000258332.1 and LINC00635 for the diagnosis and prognosis of hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev. 2018;27(6):710–716.

109. Arun G, Diermeier SD, Spector DL. Therapeutic targeting of long non-coding RNAs in cancer. Trends Mol Med. 2018;24(3):257–277.

110. Singh A, Trivedi P, Jain NK. Advances in siRNA delivery in cancer therapy. Artif Cells Nanomed Biotechnol. 2018;46(2):274–283.

111. Xueliang Z, Zhiqiang C, Wen G, et al. M6A-mediated upregulation of LINC00958 increases lipogenesis and acts as a nanotherapeutic target in hepatocellular carcinoma. J Hematol Oncol. 2020;13(1):5.

112. Yuan SX, Wang J, Yang F, et al. Long noncoding RNA DANCR increases stemness features of hepatocellular carcinoma by derepression of CTNNB1. Hepatology. 2016;63(2):499–511.

113. Ideue T, Hino K, Kitao S, Yokoi T, Hirose T. Efficient oligonucleotide-mediated degradation of nuclear noncoding RNAs in mammalian cultured cells. RNA. 2009;15(8):1578–1587.

114. Fu X, Zhu X, Qin F, et al. Linc00210 drives Wnt/beta-catenin signaling activation and liver tumor progression through CTNNB1-dependent manner. Mol Cancer. 2018;17(1):73.

115. Tang S, Tan G, Jiang X, et al. An artificial lincRNA targeting multiple miRNAs overcomes sorafenib resistance in hepatocellular carcinoma cells. Oncotarget. 2016;7(45):73257–73269.

116. Li X, Su Y, Sun B, et al. An artificially designed interfering lincRNA expressed by oncolytic adenovirus competitively consumes OncomiRs to exert antitumor efficacy in hepatocellular carcinoma. Mol Cancer Ther. 2016;15(7):1436–1451.

117. Yuan SX, Yang F, Yang Y, et al. Long noncoding RNA associated with microvascular invasion in hepatocellular carcinoma promotes angiogenesis and serves as a predictor for hepatocellular carcinoma patients’ poor recurrence-free survival after hepatectomy. Hepatology. 2012;56(6):2231–2241.

118. Xu W, Deng B, Lin P, et al. Ribosome profiling analysis identified a KRAS-interacting microprotein that represses oncogenic signaling in hepatocellular carcinoma cells. Sci China Life Sci. 2020;63(4):529–542.