Long Noncoding RNAs as a Key Player in Hepatocellular Carcinoma

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ABSTRACT: Hepatocellular carcinoma (HCC) is a major malignancy in the liver and has emerged as one of the main cancers in the world with a high mortality rate. However, the molecular mechanisms of HCC are still poorly understood. Long noncoding RNAs (lncRNAs) have recently come to the forefront as functional non–protein-coding RNAs that are involved in a variety of cellular processes ranging from maintaining the structural integrity of chromosomes to gene expression regulation in a spatiotemporal manner. Many recent studies have reported the involvement of lncRNAs in HCC which has led to a better understanding of the underlying molecular mechanisms operating in HCC. Long noncoding RNAs have been shown to regulate development and progression of HCC, and thus, lncRNAs have both diagnostic and therapeutic potentials. In this review, we present an overview of the lncRNAs involved in different stages of HCC and their potential in clinical applications which have been studied so far.

KEYWORDS: Long noncoding RNAs, microRNAs, hepatocellular carcinoma, cancer

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Introduction

Hepatocellular carcinoma (HCC) is the primary cancer of the liver. It has become one of the most frequent cancer conditions accounting for the third leading cause of deaths caused by cancer.[1] Hepatocellular carcinoma–caused mortality is higher especially in developing countries, such as Asian and African region countries,[2] where hepatitis B virus (HBV) and hepatitis C virus (HCV) have been related to HCC.[3] Hepatocellular carcinoma is associated with a poor prognosis rate and various risk factors that are not limited to chronic infections with HBV, HCV, alcohol-induced liver disease, cirrhosis, and diabetes mellitus, to name just a few.[4–6] It has been a common observation that patients with a history of liver cirrhosis and chronic liver diseases have a predisposition toward developing HCC. An additional risk is posed by environmental factors, nutritional factors, endocrine factors, obesity, and certain hereditary conditions such as hemochromatosis.[7] Moreover, there is a multitude of causal factors which influence the onset of HCC, and they include nonalcoholic steatohepatitis, alcohol abuse, and chronic HBV/HCV.[8]

The complexity of HCC pathology has made it challenging to identify the main causative agents for its onset and development.[2] Different protein-coding genes have been shown to have roles in development and progression of the disease. These genes include genes involved in regulation of cell cycle, apoptosis, DNA damage response, and cell signaling.[9] However, there is a discordance between the expression patterns of these genes, which has made it difficult to generate a model for genes involved in HCC.[9] Due to the limited knowledge and nonuniformity in HCC symptoms, many different treatment strategies have been developed in the past with limited success. The most commonly used clinical therapy for HCC treatment is liver transplantation and resection of the liver. However, these treatments have their own limitations and the risk of recurrence of cancer. Therefore, other clinical therapies have also been developed including radio frequency ablation[10] and chemotherapy,[11] however, with limited success. Currently, there are no suitable treatment options because many of the target genes of these treatments are part of different pathways critical to cell function. Therefore, it can be stated that there are many knowledge gaps in our understanding and the molecular processes involved in HCC. In the recent years, increasing amounts of research have focused on the causative noncoding RNAs (ncRNAs) involved in HCC that may shed some light in understanding the still unclear molecular processes and agents involved in HCC.[12–14]

Advances in techniques used for studying transcriptome have led to the emergence of ncRNAs as a vital regulatory essence of the genome. Recently, a study based on the Encyclopedia of DNA Elements (ENCODE) revealed that more than 90% of the genome is transcribed, and therefore, there is an enormous number of RNA transcripts generated apart from messenger RNAs (mRNAs).[15] These transcribed ncRNAs are non–protein-coding RNAs which act as their own functional entity. Examples of ncRNAs include transfer RNAs, small nucleolar RNA, ribosomal RNAs, small interfering RNAs, small nuclear RNAs, microRNAs (miRNAs), Piwi-interacting RNAs (piRNAs), and long non coding RNAs (lncRNAs). These ncRNAs

form a vast and overlapping network of transcripts which have largely unknown functions. Although much of the research on HCC has focused on the gene expression patterns of traditional protein-coding genes, many research groups have recently attempted the expression-based identification of ncRNAs.[16] These studies have discovered several ncRNAs which show differential expression patterns and regulatory effects on initiation, progression, and aggressiveness of HCC.[16] MicroRNAs such as *miR-21*, *miR-122*, *miR-221/222*, *miR-520*, and *miR-657* have been shown to be promising biomarkers and therapeutic targets for HCC.[17–20] The piRNAs also hold some therapeutic potential according to a recent study by Rizzo et al[21] who identified 125 piRNAs deregulated in HCC and cirrhotic liver cells. They identified many important regulatory genes targeted by these piRNAs such as cell cycle regulators, tumor suppressor genes, and genes involved in apoptosis.[21] PIWI proteins have also been found dysregulated in HCC. For example, although increased levels of PIWIL1 protein was observed in HCC cell lines, decreased expression of PIWIL1 led to arrest of metastasis and invasion.[22,23]

Long noncoding RNAs have also been shown as important regulators of HCC. Long noncoding RNAs, as the name implies, are 200 bp (base pairs) to several kilobases (kb) long and are generally transcribed by RNA polymerase II,[24,25] spliced, polyadenylated, and sometimes localized in the nucleus or cytoplasm. They hold a significant place in the HCC development, and these have recently emerged as one of the major players in regulating genome dynamics. This is in part achieved by their highly specialized expression patterns in response to signals and different cell types[26] which are highly regulated in a spatiotemporal manner.[27] Due to their varied nature, the functions of lncRNAs have not been fully unraveled, and many lncRNAs are still uncharacterized functionally.[25] Their involvement in the regulation of different stages of HCC is an exciting and rapidly evolving area of research. In this review, we bring forward a few significant studies and highlight the roles of different lncRNAs in HCC.

HCC: Complexity and Known Mechanisms

As stated in the "Introduction" section, HCC is the primary cancer in the liver. Its incidence and mortality rates mostly correlate with increasing age, whereas it is 3 times prevalent in men than women.[28] As alcohol use and chronic liver diseases are known risk factors for this cancer, ~70% to 90% of the HCC cases derive from chronic liver disease and cirrhosis.[29] Liver hepatocytes undergo extensive proliferation, development of fibrous tissue, formation of cancerous nodules, and apoptosis during HCC development.[29] The ultimate liver failure leads to the poor prognosis and high mortality rates associated with HCC.

Telomere shortening and dysfunction in hepatocytes have been shown to contribute to the chromosome instability in HCC. Moreover, studies across multiple countries have identified allelic loss from chromosome arms, mutations in protein-coding genes such as the tumor suppressor gene *p53*, the oncogene β catenin (*CTNNB1*) and Janus kinase 1 (*JAK1*), telomerase reverse transcriptase (*TERT*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), phosphatase and tensin homolog (*PTEN*), myeloid-lymphoid leukemia (*MLL*), fibroblast growth factor 19 (*FGF19*), and *AXIN1* were found to be associated with patients with HCC.[30–33] For this reason, Wnt/β-catenin and JAK/STAT pathways are considered to be the most affected cellular signaling pathways in HCC.[31] The presence of mutations these genes have been shown to be elevated by infections with HBV or HCV.[30,34] More sophisticated molecular analyses (Figure 1) such as exome sequencing have revealed that the gene groups that are the most affected in HCC include leucine-rich repeat–containing family, histone methyltransferases, nucleotide-binding domain, calcium channel subunits, chromatin remodelers, and oxidative stress–associated genes.[33,35] Although these molecular targets have provided many critical insights regarding HCC pathogenesis and potential treatment targets, there is still a need for finding more efficient and druggable molecular targets. The studies summarized in this review regarding the role of lncRNAs in HCC provide hope for this goal.

LncRNAs: Functions and Regulation

Functions of lncRNAs

Widespread use of high-throughput sequencing technology has enabled identifications of new functional aspects of lncRNAs. Their function is known to be dependent on their origin within the genome and their structure. Long noncoding RNAs can originate from different genomic locations where they can be intragenic (long intronic RNAs, sense lncRNAs, antisense lncRNAs), intergenic (long intergenic ncRNAs), enhancer-associated, promoter-associated, and telomere repeat–containing RNAs[36,37] (Figure 2). Once transcribed, they can function through interactions with DNA, RNA, as well as protein components of a genome, due to which they can have such a wide impact on gene expression by modulating transcription, translation, and other regulatory processes.[26,36,38] There is a vast heterogeneity in known functions of lncRNAs. There is no single categorization of their functions, and they can be broadly classified as a major gene regulator. It appears that they are involved in almost all regulatory pathways.

Protein–lncRNA interactions. For instance, most lncRNAs form associations with different proteins assembling into ribonucleoprotein complexes which are the main effector molecules. Long noncoding RNAs possess the ability to form different 3-dimensional structures which provide them the capacity to bind and regulate different protein components.[39] According to Rinn and Chang,[40] lncRNAs can serve as guides where they aid proper localization of various protein complexes. For instance, the *lincRNA-p21* helps in the localization of hnRNP-K to specific promoters.[41] Some lncRNAs such as *PANDA* may also serve as decoys, which prevents p53-mediated apoptosis by associating with NF-YA transcription

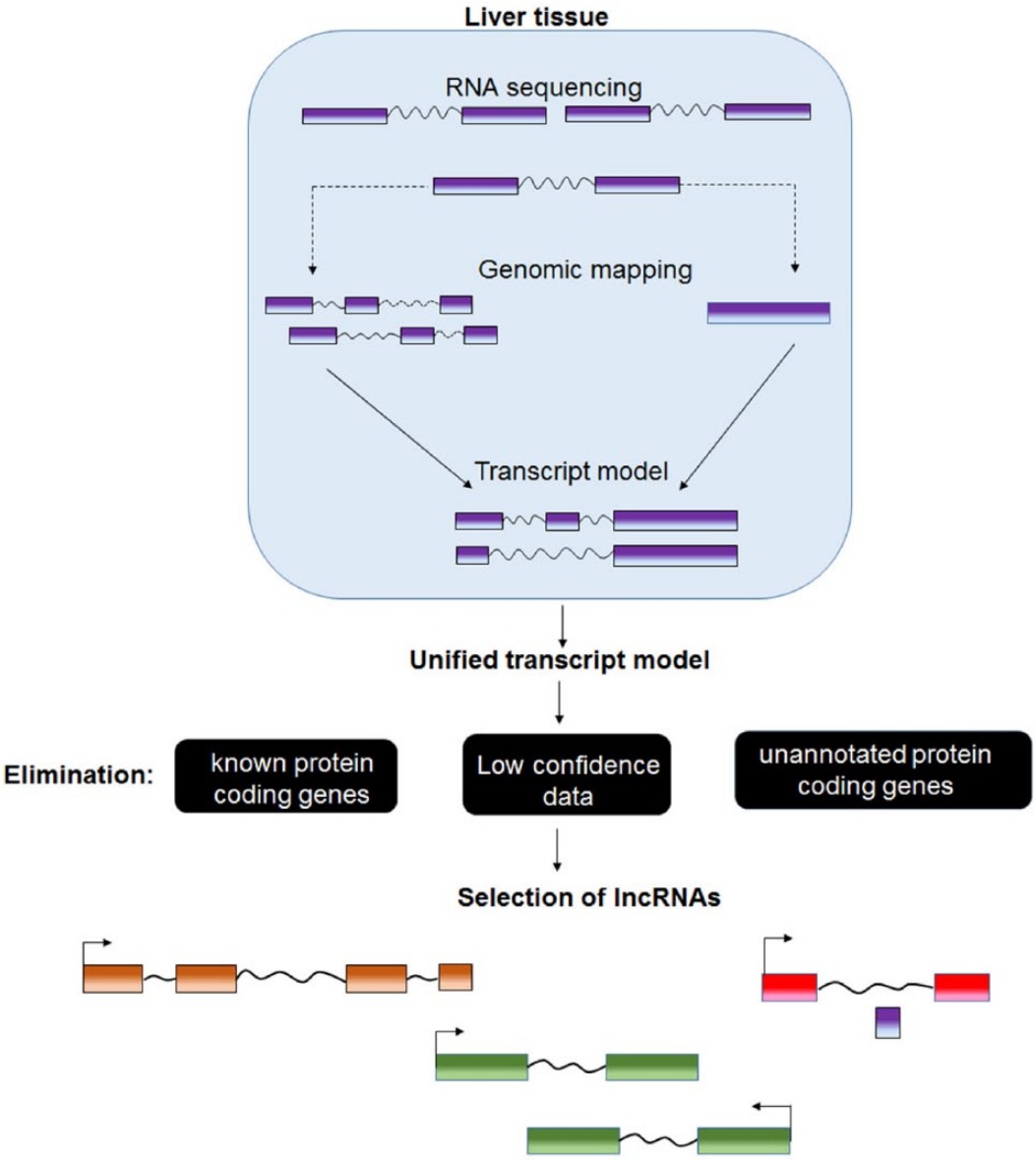

Figure 1. The different genomic localizations and biogenesis of long noncoding RNAs.

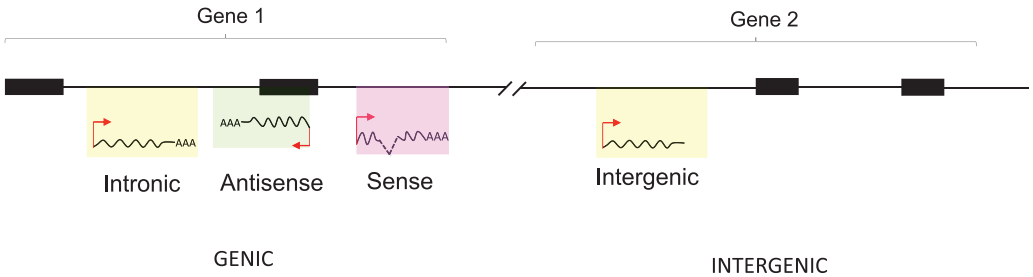

Figure 2. Sequencing methods used in identification of long noncoding RNAs.

factor.[42] Many other lncRNAs can serve as scaffolds such as the telomerase RNA *TERC*.[43] Long noncoding RNAs regulate alternative splicing machinery through protein interactions. The alternatively spliced lncRNA transcripts are tissue and developmental stage specific which helps in achieving the delicate balance of gene expression in a spatiotemporal manner.[44–46] Notable examples include metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) and nuclear-enriched abundant transcript 1 (*NEAT1*). *MALAT1* regulates serine-arginine–rich proteins involved in alternative splicing. *MALAT1* relocates these proteins to splicing speckles, influencing the alternative splicing process.[45] The function of *NEAT1* has not been fully elucidated. However, it was found to localize in the paraspeckles adjacent to the nuclear speckles of

MALAT1 and has been proposed to play a role in regulating alternative splicing during adipocytes differentiation.[46]

Many lncRNAs also influence the expression of genes present in their vicinity by transcriptional interference. These lncRNAs have been observed to be transcribed beyond the promoter region of the genes in their vicinity and therefore prevent the gene expression either by interfering with the binding of different transcription factors to their binding sites or by causing changes in the epigenetic marks leading to transcriptional silencing of the gene.[47,48] Therefore, it can be stated that transcription of lncRNAs regulates expression of genes in their vicinity or the neighbor genes, mainly functioning as antisense lncRNAs in *cis* or in *trans*[49] (Figure 2). Antisense transcription of lncRNAs has been known to regulate neighboring genes at multiple levels including transcription, posttranscription, translation, and posttranslation.[49] Positive regulation of genes or transcriptional activation due to transcription of the nearby lncRNAs has also been reported[50] where certain lncRNAs have been found associated with promoters (promoter-associated RNAs) and enhancers (enhancer-associated RNAs). These lncRNAs can directly influence the expression of genes leading to transcriptional activation as well as repression.[51,52] Another example of lncRNA having regulatory impacts on protein-coding genes is the β-APP–cleaving enzyme 1 antisense (*BACE1AS*) which regulates translation of β-APP–cleaving enzyme 1 (BACE1).[53] This enzyme is a major player in the Alzheimer disease. The interaction between *BACE1AS* and BACE1 stabilizes this protein resulting in increased abundance of BACE1.[53]

Chromatin-lncRNA interactions. At the genomic level, lncRNAs interact with DNA and function as scaffold molecules which regulate the chromatin structure and function. Scaffold lncRNAs have also been shown to have influence genome epigenetically.[43,54] They are also able to cause chromatin structural changes and gene expression changes through altering epigenetic mechanisms which include DNA methylation, histone posttranslational modifications, and ncRNAs such as miRNAs.[55] As stated in the previous section, lncRNAs mediate transcriptional silencing or activation through modulating epigenetic changes at specific gene loci. Long noncoding RNAs also have an impact on the epigenetic modifications, by aiding in altering the epigenetic landscape in different conditions. These alterations occur primarily due to the recruitment of different epigenetic regulatory proteins to specific gene loci. Many lncRNAs such as *HOTAIR*, *Rep A*, and *ANRIL* have been known to recruit epigenetic proteins which then create alternative epigenetic marks.[56,57] *ANRIL* which interacts with polycomb repressive complex (PRC) proteins (I and II) and *HOTAIR* which also interacts with PRC complex II and regulate chromatin remodeling.[56] Other than causing epigenetic modifications, many lncRNAs also regulate genetic imprinting. These lncRNAs influence the expression of a gene in a parent-specific manner.[58]

RNA-lncRNA interactions. Long noncoding RNAs are also capable of interacting with RNA molecules either as target-mimetic or sponge/decoy manner. One of the best examples of lncRNA interactions with RNA in both of these ways can be found with miRNAs where miRNA-lncRNA interactions lead to reduced activity of miRNAs.[59,60] Long noncoding RNAs have also been shown to regulate small RNAs and thereby regulate expression of their target genes. Many lncRNAs such as *Xist* and *Tsix* serve as precursor molecules for small RNAs where the small RNAs are transcribed from these lncRNA molecules.[61,62] As opposed to their function as progenitors or giving rise to miRNAs, lncRNAs also have the capability to inhibit the actions of miRNAs by interfering miRNA binding to their target genes, which is usually referred to as miRNA sponges.[63–66] As this requires lncRNAs to compete with miRNAs, they are also called competing endogenous RNAs.[67] Examples include *Linc-MD1* which acts as a sponge for *miR-133* and *miR-135* in gastric cancer and many examples from HCC that are not limited to *H19*:*let-7*, *linc-RoR*: *miR-145*, and *lncRNA-ATB*: *miR-200*.[68]

Many lncRNAs play important roles in embryonic stem cell development thereby increasing their potential regulatory manifolds.[69] Also, many lncRNAs are involved in the regulation of various aspects of differentiation of cells where these have been shown to regulate cellular identity development by changing the patterns of gene expression.[70] The cellular differentiation–associated functions performed by lncRNAs include programming and reprogramming of cell fate (eg, *Evf2* lncRNA) and self-renewal (eg, *ANCR* and *TINCR*).[71] Moreover, pluripotency of cells is regulated by lncRNAs *AK028326* and *AK141205* which regulate transcription factors Oct and Nanog and aid in maintaining the pluripotent state of stem cells.[72] This whole plethora of functions performed by lncRNAs seems to be just the edge of a horizon which needs to be further explored.

Collectively, lncRNAs have shown a vast variability, not only in their biogenesis but also in their functionality. Long noncoding RNAs have proven to be the silent key of genome and are increasingly being linked to many different types of functions. These studies discussed above provide convincing proof of the regulatory potential of lncRNAs reinforcing the currently developing notion that "protein-coding genes are slaves of their regulatory ncRNAs." Therefore, in the future, many new aspects of lncRNAs will be unraveled which will help to further the knowledge not only of the lncRNAs but also about different regulations imposed by these elements. This knowledge will empower us with new ways to fight various human diseases with a focus on cancer.

Regulation of lncRNA expression

To target lncRNAs in therapy for associated diseases, a thorough understanding of regulatory mechanisms of lncRNA expression is necessary. Long noncoding RNAs appear to follow regulatory processes similar to mRNA, such as transcription by RNA Pol

II, and RNA modifications, such as polyadenylation, 5′ capping, and splicing.[73,74] Protein-coding genes and lncRNAs seem to share many of the common transcription factors such as SP1, which is involved in transcription of lncRNAs with bidirectional promoters.[75] In addition, lncRNA expression is regulated by epigenetic mechanisms such as DNA methylation and miRNAs. For instance, the maternally expressed gene 3 (*MEG3*) lncRNA promoter is regulated by DNA methylation, and hypermethylation of the *MEG3* promoter is associated with reduced expression in HCC.[76] Moreover, the same gene is regulated by *miR-29* in HCC in which *miR-29* prevents DNMT1 methylating *MEG3* promoter.[76] MicroRNAs can cause cleavage and decay of lncRNAs such as *miRNA-let-7b* and *lincRNA-p21* and *miRNA-141* and *HOTAIR* in cancer conditions.[60] Posttranscriptional regulation and lncRNA decay have been important functions carried out mainly by miRNA-lncRNA interactions.[73]

Involvement of LncRNAs in Human Diseases and Cancer

Long noncoding RNAs form an important layer in the regulatory circuit of a genome, and their dysregulation has been associated with different diseases and malignancies. Whenever there is a dysregulation of lncRNA expression, its target genes are affected which in turn leads to various diseases. In different cancer types, mutations and expression deficits of lncRNAs have been detected in, but are not limited to, prostate cancer, lung cancer, colon cancer, bladder cancer, and breast cancer.[77,78] Long noncoding RNAs have also been linked to neurodegenerative diseases such as Alzheimer diseases, cardiovascular diseases, diabetes, and HIV/AIDS, to name a few.[78]

Aberrant expression of lncRNAs with important roles in cell cycle regulation and other regulatory pathways has been associated with different diseases including cancer.[79,80] Examples of cell cycle regulating lncRNAs are growth-arrested DNA damage–inducible gene 7 (*Gadd7*) which regulates TAR DNA-binding protein (TDP-43) and cyclin-dependent kinase 6 (Cdc6), in turn regulating the progression of the cell cycle.[81] In cancer conditions, many lncRNAs possess both oncogenic and tumor suppressor activities depending on their localization.[23] Steroid receptor RNA activator (*SRA*) is a lncRNA which regulates steroid-responsive genes. *SRA* was found to be dysregulated and showing high-expression patterns in different types of cancers including breast, uterus, and ovarian cancers.[82,83] A lncRNA that acts as oncogenes and aids in tumor development and progression is prostate cancer gene expression marker 1 (*PCGEM1*) and was found upregulated in prostate cancer, contributing to initiation and progression of prostate cancer. Furthermore, *PCGEM1* is a target of *miR-145*, an miRNA that plays a tumor suppressive role in prostate cancer.[84,85] Certain lncRNAs function as tumor suppressor genes. Growth arrest–specific 5 (GAS5) is one such tumor suppressor, which regulates the cellular inhibitor of apoptosis 2 (*cIAP2*) gene in response to starvation and it has been found to be downregulated in prostate and breast cancers.[86,87] Many previous studies have shown that any change in the epigenetic landscape of the genome may predispose the cells toward cancer, and lncRNAs have been shown to create varying epigenetic marks.[88] Many lncRNAs cause changes in promoter DNA methylation of tumor suppressor genes by directing DNA methyltransferases (DNMTs) to these genes and in turn silencing them.[89] Long noncoding RNAs also aid in chromatin remodeling and nucleosome reorganization of tumor suppression genes silencing them.[90] This is carried out by interaction of lncRNAs and recruitment of chromatin remodeling complexes such as SWI/SNF and NuRD to target gene promoters which subsequently alter histone modifications and positioning of nucleosomes at the promoter regions. Increased nucleosome occupancy and rendering a repressive chromatin structure lead to silencing of genes.[91] In addition, many lncRNAs such as *MALAT1* are involved in metastasis and progression of cancer.

Gene regulatory activities of lncRNAs at the epigenomic, transcriptional, posttranscriptional, and posttranslational level have also contributed to diseases other than cancer. The Alzheimer disease is one of the most common irreversible neurodegenerative diseases which occurs due to the degeneration of synapse and neurons in the brain leading to memory loss and decline in cognitive abilities.[92] Recent studies have suggested the possible involvement lncRNA *BACE1AS* to influence the accumulation of amyloid precursor protein in patients with Alzheimer disease.[93] Although lncRNAs have been shown to influence gene expression in *cis*, in Prader-Willi syndrome, *IPW* lncRNA was found to be upregulating the *DLK1-DIO3* region in *trans*. This association caused the downregulation of maternally expressed genes in the paternally imprinted region.[94] Furthermore, the authors observed that *IPW* created chromatin modifications to achieve the upregulated gene expression.[94] Moreover, deregulation of *Fendrr*, *Trpm3*, and *Scarb2* lncRNAs has been seen in heart failure.[95] In facioscapulohumeral muscular dystrophy, *DBE-T* is deregulated.[96,97] All these studies point toward the fact that there are many aspects that need to be explored about lncRNAs.

Roles of LncRNAs in HCC

Hepatocellular carcinoma is one of the most prevalent forms of cancer, and its incidence is increasing at a very high rate. However, its pathophysiology is less understood, and the underlying causes are even less understood. Recently, lncRNAs have been shown to have a high stake in HCC, and many lncRNAs have been associated with HCC which include *MVIH*, *H19*, *HEIH*, *HULC*, *TUC338*, and *MEG3*.[98–104] In this review, we have discussed the lncRNAs whose functions have been deduced and their involvement in onset, progression, and apoptosis of liver cancer cells (Table 1). There is a large number of lncRNAs which have been found to be important regulators of cancer development, progression, and metastasis. Many lncRNAs have been identified to be involved in HCC and will be discussed in the following sections.

Table 1. Expression and functions of known lncRNAs which have regulatory roles in HCC.

LONG NCRNA	FUNCTIONS	EXPRESSION	REFERENCES
HULC	Tumor growth and high proliferation rate	Upregulated	Geng et al,[105] Kim and Lee[106]
HOTAIR	Proliferation of tumor cells	Upregulated	Lu et al[107]
H19	HCC development; metastasis and invasion of HCC through AKT/GSK-3β/Cdc25A signaling pathway	Upregulated	Kim et al,[108] Lv et al[109]
HEIH	Recurrence in HBV-HCC	Upregulated	Wu et al[110]
MALAT1	Increased HCC cell migration; tumor metastasis and recurrence through Wnt/TCF/β-catenin and Hippo/yes-associated protein (YAP) signaling pathways	Upregulated	Nordin et al,[111] Wang et al[112]
MEG3	Decrease the anchorage-dependent and anchorage-independent cell growth and the introduction of apoptosis; regulation of HCC progression by UHRF1/DNMT1/MEG3/p53 axis signaling pathway	Downregulated	Gabory et al,[113] Zhou et al[114]
HOTTIP	Cell proliferation and viability	Upregulated	Yap et al[115]
TUG1	Regulate the cell growth	Upregulated	Wu et al[116]
DILC	Suppress liver cancer by inhibiting the autocrine signaling pathway of IL-6/STAT3	Downregulated	Jones and Baylin[117]
CCAT1	Proliferation of cancerous cells	Upregulated	Nakagawa and Kageyama[118]
URHC	Facilitate cell proliferation	Upregulated	Saxena and Carninci[119]
ANRIL	Cell proliferation, invasion, and migration of HCC cells	Upregulated	Hayashi et al[120]
CUDR	Inhibits H3K27me3, increases HULC expression	Upregulated	Gui et al[121]
LncRNA-ATB	Promotes cell invasion and metastasis	Upregulated	Yuan et al[122]
BANCR	Cell proliferation, migration, and invasion	Upregulated	Zhou and Gao[123]
CAMTA1	Promotes proliferation, stem cell–like properties, and tumorigenesis	Upregulated	Ding et al[124]
FTX	Acts as sponge for miR-374a, inhibits HCC cell epithelial-mesenchymal transition, and invasion	Downregulated	Liu et al[125]
GIHCG	Promotes HCC cells' proliferation, migration, and invasion	Upregulated	Sui et al[126]
GPC3-AS1	Promotes cell proliferation and migration and xenograft tumor growth	Upregulated	Zhu et al[127]
PCAT1	Higher level PCAT1 is associated with poor prognosis and survival	Upregulated	Yan et al[128]
PlncRNA-1	Promotes cell proliferation, migration, and invasion	Upregulated	Dong et al[129]
linc-ROR	Activates cellular stress pathways and modulation of cellular responses to chemotherapy	Upregulated	Takahashi et al[130]
SNHG15	Proposed to be a tumor promoter	Upregulated	Zhang et al[131]
SOX2OT	Promotes HCC cell migration	Upregulated	Shi and Teng[132]
LncSox4	Initiates liver TIC self-renewal through Stat3-Sox4 pathway	Upregulated	Chen et al[133]
SRHC	Tumor suppressor	Downregulated	Zheng et al[134]
CPS1-IT1	Reduced cell proliferation, migration, and invasion capacities	Downregulated	Wang et al[135]
TCF7	Induces liver self-renewal and tumor propagation by activating Wnt pathway	Upregulated	Wang et al[136]
BRM	Tumor initiation through YAP signaling	Upregulated	Zhu et al[137]
ZEB2-AS1	Regulates tumor growth and metastasis	Upregulated	Lan et al[138]
LINC00152	Promotes cell proliferation and tumor growth	Upregulated	Ji et al[139]
LINC01225	Invasion and cell proliferation by regulating EGFR/Ras/Raf-1/MEK/MAPK signaling pathway	Upregulated	Wang et al[140]

Table 1. (Continued)

LONG NCRNA	FUNCTIONS	EXPRESSION	REFERENCES
AFAP1-AS1	Promotes cell proliferation, migration, and invasion	Upregulated	Lu et al[141]
uc.338	Promotes cell proliferation and induces cell cycle progression	Upregulated	Bo et al[142]
CCHE1	Regulates the ERK/MAPK pathway and serves as an oncogene	Upregulated	Peng and Fan[143]
GAS5	Binds to glucocorticoid receptor and modulates mTOR signaling	Downregulated	Tu et al[144]
lnc-β-Catm	Promotes methylation of β-catenin in HCC cancer stem cells	Upregulated	Zhu et al[145]
lncRNA-LALR1	Facilitates cyclin D1 expression and activating Wnt-catenin pathway	Upregulated	Xu et al[146]
HBx-LINE1	Activates the Wnt β-catenin signaling in HBV-HCC	Inducer	Liang et al,[147] Chauhan et al,[148] Mulrooney-Cousins et al[149]
DANCR	Associated with CTNNB1 and β-catenin	Upregulated	Yuan et al[150]
ZNF674-AS1	Drives self-renewal of liver cancer stem cells	Downregulated	Zhang et al[151]
lncRNA-HAND2-AS1	Hypermethylated in portal vein tumor thrombosis and liver metastasis	Downregulated	Yang et al[152]
Linc00974	Invasion and proliferation of HCC through TGF-β and Notch signaling pathways	Deregulated biomarker	Tang et al[153]
hPVT1	Promotes cell cycle and stem cell–like properties in HCC	Upregulated	Ding et al[154]
PTENP1	Represses tumorigenic properties of HCC	Downregulated	Chen et al[155]
ZNRD1	DNA damage and repair via ERCC	Upregulated	Wen et al[156]
UCF1	Promotes HCC by inhibition of miR216b and activation of FGFR1/ERK signaling pathway	Upregulated	Cao et al[157]
MT1D	Proliferates HCC via accumulation of p53	Upregulated	Yu et al[158]

Abbreviations: HCC, hepatocellular carcinoma; lncRNAs, long noncoding RNAs; ncRNA; noncoding RNA; TGF-β, transforming growth factor β.

HULC

HULC is a lncRNA ~1.6 kb in length and contains 2 exons. It has been found to be upregulated in HCC and colorectal cancers which metastasize to the liver[101,159] (Figure 3). It has been reported that cyclic adenosine monophosphate response element binding protein (CREB) transcription factor upregulates the expression of *HULC*, especially in Hep3B cells[160] (Figure 3). Furthermore, the expression of *HULC* in HepG2 cells was also reported to be upregulated by the interaction of HBV HBx protein with CREB.[161] In a study by Hammerle et al,[162] another regulator of expression of *HULC* was discovered to be insulinlike growth factor 2 mRNA-binding protein (IGF2BP). The upregulation of *HULC* has been associated with tumor growth and a higher proliferation rate which is caused due to downregulation of the tumor suppressor gene *p18*. In addition, *HULC* has also been reported to influence HCC cells by regulating the expression of peroxisome proliferator–activated receptor α (PPARA) transcriptional factor by creating methylation marks at the CpG islands in the promoter of *miR-9*.[163] Thereby, it elevates the expression of PPARA which in turn increases expression of *ACSL1* gene. This leads to the high recurrence rates of HCC.[163]

It has been proposed that *HULC* acts as a sponge for *miR-372* and thereby causing upregulated expression of its target genes.[160] Patients with HCC have shown high levels of *HULC* in plasma which can be developed as a biomarker for prognosis of HCC.[164,165] Although *HULC* was the first lncRNA found to have upregulated expression in HCC, the mechanisms of its action have not yet been fully determined.[166]

HOTAIR

HOTAIR is a ~2.2-kb-long lncRNA, transcribed from the *HOXC* locus in antisense manner and hence named as HOX antisense intergenic RNA.[167] It was first observed in fibroblast causing the silencing of HOXD locus via establishing trimethylation on H3K27.[56] *HOTAIR* recruits PRC2 and lysine specific demethylase 1 (LSD1) protein complexes to the *HOXD* gene cluster and changes its histone methylation status and chromatin configuration.[168] Thereby, it causes silencing of tumor suppressor genes.[167] It has been implicated in breast, colorectal, gastrointestinal, and pancreatic cancers apart from HCC.[108,168,169] *HOTAIR* interacts with PRC2 through an 89-mer domain at the 5′ end of the sequence.[110] This region is

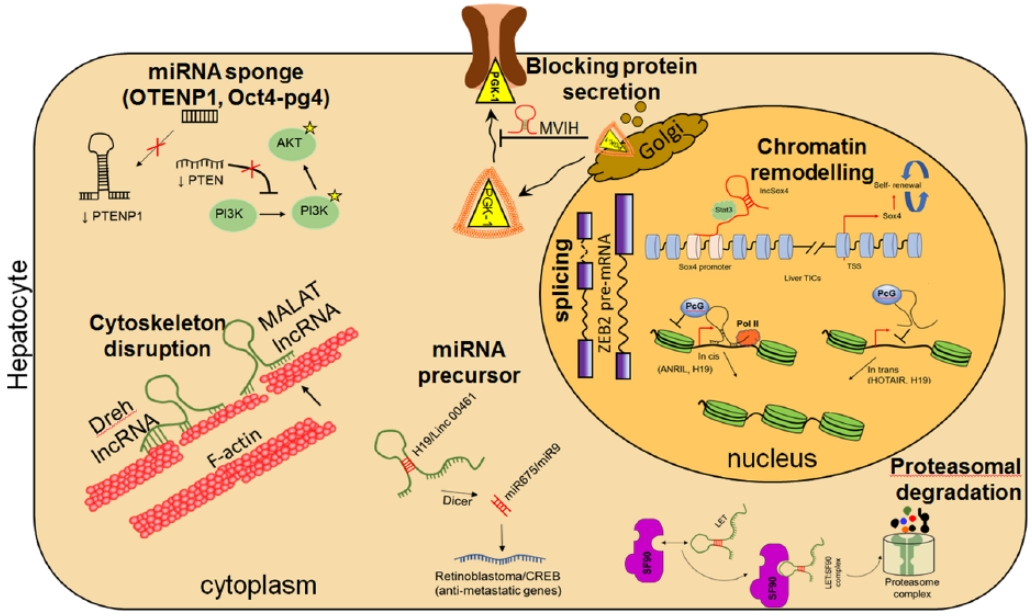

Figure 3. A general overview of the 3 basic mechanisms opted by lncRNAs to regulate different aspects of hepatocellular carcinoma. (A) cyclic adenosine monophosphate response element binding protein prevents the expression of *HULC* by binding to it and in turn preventing the growth and/or recurrence of hepatocellular carcinoma. (B) *H19* and many other lncRNAs have been shown to act as miRNA sponges; here, *H19* encodes *miR-675* in its first exon and thereby it can prevent the function of *miR-657*. Furthermore, knockdown of this lncRNA was shown to prevent hepatocellular carcinoma. (C) Another lncRNA *ANRIL* binds to the PRC complex II (polycomb repressive complex II) forming a complex which causes the epigenetic silencing of KLF2 (Krüppel-like factor 2). LncRNA indicates long noncoding RNA.

also known as the minHOTAIR, whereas LSD1 protein interacts with *HOTAIR* via the 646-mer at the 3′ end.[167] It has been reported that *HOTAIR* is overexpressed in HCC, and knockdown of *HOTAIR* reduces HCC proliferation.[105] Furthermore, the cells having lower expression of *HOTAIR* become more responsive to chemotherapy.[169]

H19

H19 is expressed from a ~2.3-kb-long, maternally imprinted gene. This lncRNA acts as both an oncogene and a tumor suppressor gene. However, its exact mechanism of action is still uncertain.[111] *H19* is expressed during embryogenesis, whereas transcriptionally silent in adult tissues.[113] It was also shown that this lncRNA was expressed in response to maternal undernutrition. In relation to cancer pathogenesis, it was found to be involved in metastasis and angiogenesis.[113,170] *H19* is coexpressed with another maternally imprinted gene, namely, insulinlike growth factor 2 (*IGF-2*) which has been proposed to play a role in cancer onset via different epigenetic modifications.[106] This observation is further strengthened by epigenetic abnormalities observed at *IGF-2* and *H19* loci in HCC.[171] However, many other studies have reported that many different mechanisms are operating at this locus, and no single process can be attributed to cancer onset and progression with certainty.[172–175] The association of *H19* with the development of HCC was further validated by the observation that knockdown of *H19* prevented the development of HCC.[99] Another interesting characteristic of the *H19* lncRNA is that it encodes *miR-675* in its first exon, and therefore, it can act as an miRNA sponge as well as a reservoir of *miR-675*.[176,177] *H19* has been shown to have versatile functions which entail epigenetic domains as well. It was reported that *H19* interacts with enhancer of zeste homolog 2 (EZH2) which is a part of a protein complex called as PRC2[178] (Figure 3).

HEIH

High expression in HCC (*HEIH*) is a lncRNA which was found to have elevated expression patterns in HCC as is evident from its name.[100] It is an oncogene and it interacts with EZH2. Furthermore, high expression of *HEIH* has been associated with recurrence of hepatitis B–related HCC (HBV-HCC). *HEIH* has been used as a biomarker for prognosis of HCC, and an elevated expression is an indication of advanced stage of HCC.[100]

MALAT1

The lncRNA *MALAT1* stands for metastasis-associated lung adenocarcinoma transcript 1. In the cancerous state, this locus harbors chromosomal translocations and mutations.[179] This lncRNA was also found to have an upregulated expression in HCC cell lines.[105] Differential expression of *MALAT1* has been found in different cancer types found in lung, liver, pancreas, colon, breast, prostate, and ovaries. *MALAT1* expression can be used as a biomarker for detection of recurrence of liver cancer after liver transplantation, and therefore, it can be developed as a therapeutic target.[102]

MEG3

MEG3 is a lncRNA ~1.7 kb in length and is a maternally imprinted gene.[180] This lncRNA has been observed to be downregulated in HCC cell lines, and its reintroduction has been reported to decrease the anchorage-dependent and anchorage-independent cell growth and apoptosis.[104] Braconi et al[104] reported that due to the absence of *MEG3*, the promoter regions of some genes involved in HCC show hypermethylation. *MEG3* expression has been observed to be downregulated in a number of cancer conditions including liver, lung, glioma, and cervical cancers.[107,181–184] For instance, reduced levels of MEG3 was found in cervical cancer tissues in contrast to the adjacent healthy tissues in 108 patients in association with increasing tumor size and metastasis.[185] In a study by Anwar et al[184] *MEG3* was observed to be the most commonly downregulated lncRNA in HCC. Demonstrating its connection with the epigenetic landscape, 60% of HCC cases reported by Anwar et al[184] correlated with increased DNA methylation. It was also reported that *MEG3* competes for *miR-181* family and thereby regulates the progression of gastric cancer.[186]

HOTTIP

HOX A transcript at distal tip (*HOTTIP)* is a lncRNA generated from the distal tip of *HOXA13* gene, and *HOTTIP* expression was found to be upregulated in HCC and pancreatic cancer.[187–189] *HOTTIP* interacts with WD-repeat–containing protein 5/mixed lineage leukemia (WDR5/MLL) complex regulating the expression of *HOXA* locus. It in turn under the regulation of *HOXA13* gene creates a feedback loop regulation.[188] In a recent study, Ge et al[190] demonstrated that *miR-192* and *miR-204* could suppress the expression of *HOTTIP* through the involvement of Argonaute 2 (AGO2)-mediated RNA interference in HCC cells. The suppression of *HOTTIP* by these miRNAs was shown to be reducing HCC cell viability, whereas induced *HOTTIP* expression by inhibiting these miRNAs increased cellular proliferation. These observations suggest that *HOTTIP* and its associated miRNAs could potentially be developed as a potential therapeutic strategy for HCC.

TUG1

Taurine upregulated gene 1 (*TUG1*) is a lncRNA that is ~7.1 kb in length. It has been shown to be involved in lung cancer, bladder cancer, and osteosarcoma apart from its involvement in liver cancer.[191–193] It was initially identified in mouse retinal cells responding to taurine signals in a screen designed to identify upregulated genes.[194] *TUG1* shows a high expression in HCC. It also regulated cell growth by epigenetic silencing of Krüppel-like factor 2 (KLF2) transcription factor.[195] Furthermore, knockdown of *TUG1* induced apoptosis of HCC cells and in hepatoblastomas.[195,196] Therefore, *TUG1* has potential therapeutic applications for treatment of HCC.[195,196]

DILC

This lncRNA was observed to have reduced expression in all HCC cell lines as deduced from microarray expression data and was so named as lncRNA downregulated in liver cancer (*DILC*).[197] This lncRNA was reported to be able to suppress liver cancer by inhibiting the autocrine signaling pathway of IL-6/STAT3.[197]

CCAT1

Colon cancer–associated transcript 1 (*CCAT1*) is a lncRNA that was initially found to be upregulated in gastric and colon cancer.[198,199] It is ~2.6 kb in length and located in the vicinity of the *c-Myc* gene.[198] *CCAT1* was also found to be upregulated in HCC as compared with noncancerous liver tissue.[200] It was associated with poor prognosis as well as aiding proliferation of cancerous cells in HCC. *CCAT1* influences proliferation of cancer cells as it acts as a sponge for *let-7* miRNA thereby increasing the expression of *HMGA2* and *c-Myc*.[200] Therefore, *CCAT1* holds potential therapeutic application as a molecular marker for HCC diagnosis as well as a target for HCC therapy.

URHC

This lncRNA was identified as the most frequently encountered lncRNA having an upregulated expression in HCC, and therefore, the name upregulated in HCC (*URHC*).[201] *URHC* was observed to downregulate *ZAK* and thereby facilitate cell proliferation.[201] As downregulation of *URHC* was shown to induce apoptosis and decrease proliferation of HCC cells, this can be potentially developed as a therapeutic target for therapy.[201]

ANRIL

ANRIL stands for antisense ncRNA, a 3.8-kb lncRNA found within in the *INK4* locus. It is transcribed by RNA polymerase II and subsequently alternatively spliced.[202] It was initially identified in familial melanoma tissues.[203] Since then, it has been observed to be involved in a number of cancer conditions including HCC, prostate cancer, gastric cancer, and non–small-cell lung cancer (NSCLC) development.[202,204–207] It is a *trans*-lncRNA which recruits the chromobox 7 (CBX7) domain of PRC1 and PRC2 (Figure 3) to the *CDKN2A/CDKN2B* loci. This recruitment generates H3K27 methylation which in turn silences the genomic loci.[115,208] As a result, the *p14*, *p15*, and *p16* genes get suppressed which are involved negative regulation of cell cycle, senescence, and apoptosis mechanisms.[115,208] Moreover, an alternatively spliced transcript of *ANRIL*, namely, p15 antisense (*p15AS*) has been shown to downregulate the expression of *p15*.[209] *ANRIL* was overexpressed in HCC tissues.[205] Increased expression and increased binding of *ANRIL*

to PRC2 caused epigenetic silencing of *KLF-2* in HCC.[205] However, downregulation of *ANRIL* was shown to inhibit cell proliferation, invasion, and migration of HCC cells.[210] They also showed the positive regulatory role of the transcription factor SP1 in regulating *ANRIL* in HCC and the potential of SP1 knockdown in downregulating *ANRIL* expression in HCC cells. Thus, *ANRIL* can be potentially developed as a therapeutic target for HCC treatment.[209,210]

Other lncRNAs involved in HCC

There are many other lncRNAs which have been shown to take part in different aspects of HCC, and much more will be identified in future experiments. Certain notable lncRNAs include microvascular invasion (*MVIH*) in HCC which has been reported to be involved in HBV-related HCC tissues.[98] *MVIH* interacts with protein phosphoglycerate kinase 1 (PGK1) which causes increased angiogenesis and tumor growth.[98] Another lncRNA which has been shown to be involved in HCC is extra-coding CEBPA (*ecCebpa*) which is a functional lncRNA derived from *CEBPA* gene. *EcCebpa* binds to the promoter of *CEBPA* gene and interacts with DNMT1, preventing the promoter methylation. This has led to the increased expression of *CEBPA*.[211]

Influence of LncRNA on Epigenetic Landscape of HCC

Changes to the epigenetic landscape of a cell are indications of deviations which are very frequently associated with diseases and cancer. Furthermore, many studies have shown that epigenetic modifications may also play important roles in regulation of lncRNA expression.[116] One major epigenetic modification influenced by lncRNAs is DNA methylation. In support of this notion, global hypomethylation has also been observed in HCC.[212] Hypermethylation at specific promoters leading to the silencing of tumor suppressor genes and activation of oncogenes have also been reported in HCC.[117,213] Long noncoding RNAs are involved in many different epigenetic processes where they may help in the recruitment of various proteins to sites of modifications and in altering the specificities and action of different protein complexes. Many lncRNAs provide a platform by functioning as scaffold molecules in the chromatin and recruiting different regulatory proteins to their sites of action. Examples of such lncRNAs include *ANRIL* and *HOTAIR*. Many lncRNAs have been found to regulate HCC via epigenetic mechanisms in many recent reports.[118,119,214] DNA methylation and histone modification patterns are changed in HCC leading to the onset and progression of cancer.[203] However, hypermethylation of DNA at specific gene loci (eg, angiogenesis inactivation gene) has been shown to inactivate the tumor suppressor genes in HCC.[215] Methylation patterns have been used to develop epigenetic signatures in HCC and normal liver cells which possess diagnostic value and thus can be used for predetermination of HCC candidates.[216] Many different approaches have been described previously to develop as therapeutic markers to identify and categorize HCC onset and progression. As mentioned earlier, different oncogenes and their methylation patterns have been studied in normal and cancer tissues.[216] A method using gene re-expression after epigenetic unmasking has also been proposed to identify differential methylation patterns of tumor suppressor genes.[217] Another approach has been developed to study cancer-related promoters, where differentially methylated promoter regions in HCC, other cancers, as well as normal tissues are studied.[218] Song et al[219] proposed the consideration of promoters as well as surrounding methylated regions to be developed as markers for epigenetic modifications.

Other than the direct influence on the expression of tumor suppression genes, epigenetic modifications can also be influenced via the proteins and enzymes involved in creating epigenetic marks. The most important player among these proteins is DNA DNMTs, which have been shown to have an elevated expression in HCC tissues. These elevated DNMT levels might be considered as a reason behind differential methylation states.[220] DNA methyltransferases are also targets of miRNAs which negatively regulate DNMTs. One such DNMT-targeting miRNA is *miRNA-29* which can inhibit levels of DNMTs including DNMT3A and 3B enzymes in many cancer conditions such as lung cancer cell lines and primary NSCLC.[221] This further influences the abundance of miRNAs in HCC which is also decreased.[222]

Variations in histone modifications have also been found between normal and HCC tissues. Histone modifications have also been proposed to be used as potential biomarkers for detection and diagnostic purposes. It has been shown that acetylation and the trimethylation at the H3K27 (H3K27Ac, H3K27me3), hyperacetylation at H3K9 (H3K9Ac), hyperacetylation of H4K8 (H3K8Ac), and trimethylation at the H3K4 (H3K4me3) are more pronounced in HCC.[120,223] Other than these modifications, HCC epigenetic states can also be altered by the differential expression patterns of the components of protein complexes such as PRC I and PRC II. There is accumulating evidence for the involvement of EZH2 subunit of PRC II which has been found to be a target of different miRNAs and lncRNAs.[224] SuZ12 and Bmi1 components of PRC II have also been shown to have differential expression patterns in HCC and may thus be important regulatory components of HCC pathways.[225,226]

Significance of LncRNAs in Clinical Applications

Long noncoding RNAs show tissue-specific expression patterns,[227] and therefore, they have a high usability as biomarkers for various types of cancers. Moreover, they are expressed in low copy numbers and show high diversity in transcripts in different tissues. Due to these characteristics displayed by lncRNAs, they can be developed as biomarkers for various types of cancers and disease conditions. It is very likely that techniques based on lncRNAs will show high sensitivity and low costs thereby having significant clinical applications.

Development of combinatorial therapy targeting different long and small ncRNAs together may yield better results which have been shown for *H19*, *MEG3*, and HULC.[104,160,228] *H19* can suppress HCC as mentioned previously and it also interacts with a protein complex hnRNP U/PCAF/RNA Pol II which in turn activates the *miR-200* family by increasing histone acetylation.[228] *MiR-29* regulates the expression of *MEG3* lncRNA in HCC.[104] *HULC* inhibits *miR-372* indirectly regulating the expression of different genes in HCC.[160] As *HULC* has also been observed in plasma and the level of plasma *HULC* has also been correlated with a positive HBV status, *HULC* can be developed as a biomarker for early detection of HCC.[187]

Conclusions

More than 600 000 people worldwide are affected by HCC, demanding urgent discoveries on therapeutic targets and early diagnostic markers. Unfortunately, our current knowledge about the molecular pathways influencing HCC is incomplete. Studies so far have demonstrated that HCC occurs due to genetic, epigenetic, transcriptional, and translational imbalances. The studies that revealed lncRNAs as a cause for HCC and their implications as diagnostic markers have created a shift in focus of HCC research from protein-coding genes to lncRNAs and other ncRNAs as key players in HCC pathogenesis. Due to their diverse functions as tumor suppressors, oncogenes, transcriptional regulators, and epigenetic modifiers, involvement in intricate cellular networks have made them a molecular tool that can potentially be developed into suitable therapeutic and clinical strategies for treatment of HCC. The availability of new and improved techniques has enabled the study of different factors involved in HCC and hold promise for the discovery of many lncRNAs influencing HCC in the future. There is an urgent need to explore expression, functions, and regulation of lncRNAs further to fully understand their role in different phases of HCC onset, progression, and development. Their role in modulating epigenetic landscape of HCC should also be taken into account when these lncRNAs are developed as diagnostic or therapeutic tools for HCC.

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Author Contributions

MM and RC reviewed and approved the final manuscript.

REFERENCES

1. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009;27:1485–1491.
2. Venook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist*. 2010;15:5–13.
3. Varnholt H, Drebber U, Schulze F, et al. MicroRNA gene expression profile of hepatitis C virus-associated hepatocellular carcinoma. *Hepatology*. 2008;47:1223–1232.
4. Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. *World J Gastroenterol*. 2008;14:4300–4308.
5. Aravalli RN, Cressman EN, Steer CJ. Cellular and molecular mechanisms of hepatocellular carcinoma: an update. *Arch Toxicol*. 2013;87:227–247.
6. Aravalli RN, Steer CJ, Cressman EN. Molecular mechanisms of hepatocellular carcinoma. *Hepatology*. 2008;48:2047–2063.
7. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;132:2557–2576.
8. Kirchner G, Kirovski G, Hebestreit A, et al. Epidemiology and survival of patients with hepatocellular carcinoma in Southern Germany. *Int J Clin Exp Med*. 2010;3:169–179.
9. Röcken C, Carl-McGrath S. Pathology and pathogenesis of hepatocellular carcinoma. *Dig Dis*. 2001;19:269–278.
10. Witczak-Malinowska K, Zadrozny D, Studniarek M, et al. Preliminary assessment of utility of radiofrequency ablation technique in treatment of primary hepatocellular carcinoma (HCC) in patients with hepatic cirrhosis. *Med Sci Monit*. 2003;9:68–72.
11. Hann HW. Active antiviral therapy for chronic hepatitis B and hepatocellular carcinoma. *Minerva Gastroenterol Dietol*. 2008;54:19–30.
12. Klingenberg M, Matsuda A, Diederichs S, Patel T. Non-coding RNA in hepatocellular carcinoma: mechanisms, biomarkers and therapeutic targets. *J Hepatol*. 2017;67:603–618.
13. Shi L, Peng F, Tao Y, Fan X, Li N. Roles of long noncoding RNAs in hepatocellular carcinoma. *Virus Res*. 2016;223:131–139.
14. Zou H, Shao CX, Zhou QY, et al. The role of lncRNAs in hepatocellular carcinoma: opportunities as novel targets for pharmacological intervention. *Expert Rev Gastroenterol Hepatol*. 2016;10:331–340.
15. Consortium EP, Birney E, Stamatoyannopoulos JA, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature*. 2007;447:799–816.
16. Zhu J, Liu S, Ye F, et al. The long noncoding RNA expression profile of hepatocellular carcinoma identified by microarray analysis. *PLoS ONE*. 2014;9:e101707.
17. Braconi C, Henry JC, Kogure T, Schmittgen T, Patel T. The role of microRNAs in human liver cancers. *Semin Oncol*. 2011;38:752–763.
18. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology*. 2007;133:647–658.
19. Song K-s, Han C, Wu T. Epigenetic regulation of miR-122 by PPARgammar and hepatitis B virus X protein in hepatocellular carcinoma cells. *FASEB J*. 2013;27:872.10.
20. Pineau P, Volinia S, McJunkin K, et al. miR-221 overexpression contributes to liver tumorigenesis. *Proc Natl Acad Sci U S A*. 2010;107:264–269.
21. Rizzo F, Rinaldi A, Marchese G, et al. Specific patterns of PIWI-interacting small noncoding RNA expression in dysplastic liver nodules and hepatocellular carcinoma. *Oncotarget*. 2016;7:54650–54661.
22. Zhao YM, Zhou JM, Wang LR, et al. HIWI is associated with prognosis in patients with hepatocellular carcinoma after curative resection. *Cancer*. 2012;118:2708–2717.
23. Siddiqi S, Matushansky I. Piwis and piwi-interacting RNAs in the epigenetics of cancer. *J Cell Biochem*. 2012;113:373–380.
24. Guttman M, Amit I, Garber M, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature*. 2009;458:223–227.
25. Clark MB, Mattick JS. Long noncoding RNAs in cell biology. *Semin Cell Dev Biol*. 2011;22:366–376.
26. Dinger ME, Amaral PP, Mercer TR, et al. Long noncoding RNAs in mouse embryonic stem cell pluripotency and differentiation. *Genome Res*. 2008;18:1433–1445.
27. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell*. 2011;43:904–914.
28. McGlynn KA, London WT. The global epidemiology of hepatocellular carcinoma: present and future. *Clin Liver Dis*. 2011;15:223–243, vii-x.
29. Sanyal AJ, Yoon SK, Lencioni R. The etiology of hepatocellular carcinoma and consequences for treatment. *Oncologist*. 2010;15:14–22.
30. Kawai-Kitahata F, Asahina Y, Tanaka S, et al. Comprehensive analyses of mutations and hepatitis B virus integration in hepatocellular carcinoma with clinicopathological features. *J Gastroenterol*. 2016;51:473–486.
31. Kan Z, Zheng H, Liu X, et al. Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma. *Genome Res*. 2013;23:1422–1433.
32. Pineau P, Marchio A, Battiston C, et al. Chromosome instability in human hepatocellular carcinoma depends on p53 status and aflatoxin exposure. *Mutat Res*. 2008;653:6–13.
33. Gu DL, Chen YH, Shih JH, Lin CH, Jou YS, Chen CF. Target genes discovery through copy number alteration analysis in human hepatocellular carcinoma. *World J Gastroenterol*. 2013;19:8873–8879.
34. Tornesello ML, Buonaguro L, Tatangelo F, Botti G, Izzo F, Buonaguro FM. Mutations in TP53, CTNNB1 and PIK3CA genes in hepatocellular carcinoma

associated with hepatitis B and hepatitis C virus infections. *Genomics*. 2013;102:74–83.
35. Cleary SP, Jeck WR, Zhao X, et al. Identification of driver genes in hepatocellular carcinoma by exome sequencing. *Hepatology*. 2013;58:1693–1702.
36. Djebali S, Davis CA, Merkel A, et al. Landscape of transcription in human cells. *Nature*. 2012;489:101–108.
37. Meseure D, Drak Alsibai K, Nicolas A, Bieche I, Morillon A. Long noncoding RNAs as new architects in cancer epigenetics, prognostic biomarkers, and potential therapeutic targets. *BioMed Res Int*. 2015;2015:320214.
38. Cabili MN, Dunagin MC, McClanahan PD, et al. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. *Genome Biol*. 2015;16:20.
39. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. *Nat Struct Mol Biol*. 2013;20:300–307.
40. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. *Annu Rev Biochem*. 2012;81:145–166.
41. Huarte M, Guttman M, Feldser D, et al. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. *Cell*. 2010;142:409–419.
42. Hung T, Wang Y, Lin MF, et al. Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet*. 2011;43:621–629.
43. Zappulla D, Cech T. RNA as a flexible scaffold for proteins: yeast telomerase and beyond. *Cold Spring Harb Symp Quant Biol*. 2006;71:217–224.
44. Stamm S, Ben-Ari S, Rafalska I, et al. Function of alternative splicing. *Gene*. 2005;344:1–20.
45. Bourgeois CF, Lejeune F, Stevenin J. Broad specificity of SR (serine/arginine) proteins in the regulation of alternative splicing of pre-messenger RNA. *Prog Nucleic Acid Res Mol Biol*. 2004;78:37–88.
46. Cooper DR, Carter G, Li P, Patel R, Watson JE, Patel NA. Long non-coding RNA NEAT1 associates with SRp40 to temporally regulate PPARγ2 splicing during adipogenesis in 3T3-L1 cells. *Genes*. 2014;5:1050–1063.
47. Martens JA, Laprade L, Winston F. Intergenic transcription is required to repress the *Saccharomyces cerevisiae* SER3 gene. *Nature*. 2004;429:571–574.
48. Camblong J, Iglesias N, Fickentscher C, Dieppois G, Stutz F. Antisense RNA stabilization induces transcriptional gene silencing via histone deacetylation in *S. cerevisiae*. *Cell*. 2007;131:706–717.
49. Villegas VE, Zaphiropoulos PG. Neighboring gene regulation by antisense long non-coding RNAs. *Int J Mol Sci*. 2015;16:3251–3266.
50. Hirota K, Miyoshi T, Kugou K, Hoffman CS, Shibata T, Ohta K. Stepwise chromatin remodelling by a cascade of transcription initiation of non-coding RNAs. *Nature*. 2008;456:130–134.
51. Schwartz JC, Younger ST, Nguyen NB, et al. Antisense transcripts are targets for activating small RNAs. *Nat Struct Mol Biol*. 2008;15:842–848.
52. Han J, Kim D, Morris KV. Promoter-associated RNA is required for RNA-directed transcriptional gene silencing in human cells. *P Natl A*. 2007;104:12422–12427.
53. Faghihi MA, Modarresi F, Khalil AM, et al. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of β-secretase expression. *Nature Med*. 2008;14:723–730.
54. Li Q_, Su Z, Xu X, et al. AS1DHRS4, a head-to-head natural antisense transcript, silences the DHRS4 gene cluster in cis and trans. *P Natl A*. 2012;109:14110–14115.
55. Wahid B, Ali A, Rafique S, Idrees M. New insights into the epigenetics of hepatocellular carcinoma. *Biomed Res Int*. 2017;2017:1609575.
56. Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell*. 2007;129:1311–1323.
57. Zhao J, Sun BK, Erwin JA, Song JJ, Lee JT. Polycomb proteins targeted by a short repeat RNA to the mouse X chromosome. *Science*. 2008;322:750–756.
58. He Y, Meng X-M, Huang C, et al. Long noncoding RNAs: novel insights into hepatocelluar carcinoma. *Cancer Lett*. 2014;344:20–27.
59. Paraskevopoulou MD, Hatzigeorgiou AG. Analyzing miRNA-lncRNA interactions. *Methods Mol Biol*. 2016;1402:271–286.
60. Jalali S, Bhartiya D, Lalwani MK, Sivasubbu S, Scaria V. Systematic transcriptome wide analysis of lncRNA-miRNA interactions. *PLoS ONE*. 2013;8:e53823.
61. Ogawa Y, Sun BK, Lee JT. Intersection of the RNA interference and X-inactivation pathways. *Science*. 2008;320:1336–1341.
62. Fejes-Toth K, Sotirova V, Sachidanandam R, et al; Affymetrix/Cold Spring Harbor Laboratory ENCODE Transcriptome Project. Post-transcriptional processing generates a diversity of 5′-modified long and short RNAs. *Nature*. 2009;457:1028–1042.
63. Ebert MS, Neilson JR, Sharp PA. MicroRNA sponges: competitive inhibitors of small RNAs in mammalian cells. *Nat Methods*. 2007;4:721–726.
64. Xiao H, Tang K, Liu P, et al. LncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging miR-200s in clear cell kidney carcinoma. *Oncotarget*. 2015;6:38005.
65. Su Z, Zhi X, Zhang Q_, Yang L, Xu H, Xu Z. LncRNA H19 functions as a competing endogenous RNA to regulate AQP3 expression by sponging miR-874 in the intestinal barrier. *FEBS Lett*. 2016;590:1354–1364.
66. Wang SH, Zhang WJ, Wu XC, et al. The lncRNA MALAT1 functions as a competing endogenous RNA to regulate MCL-1 expression by sponging miR-363-3p in gallbladder cancer. *J Cell Mol Med*. 2016;20:2299–2308.
67. Xia T, Liao Q_, Jiang X, et al. Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. *Sci Rep*. 2014;4:6088.
68. Sun J, Bie B, Zhang S, Yang J, Li Z. Long non-coding RNAs: critical players in hepatocellular carcinoma. *Int J Mol Sci*. 2014;15:20434–20448.
69. Sigova AA, Mullen AC, Molinie B, et al. Divergent transcription of long noncoding RNA/mRNA gene pairs in embryonic stem cells. *Proc Natl Acad Sci U S A*. 2013;110:2876–2881.
70. Hu W, Alvarez-Dominguez JR, Lodish HF. Regulation of mammalian cell differentiation by long non-coding RNAs. *EMBO Rep*. 2012;13:971–983.
71. Flynn RA, Chang HY. Long noncoding RNAs in cell-fate programming and reprogramming. *Cell Stem Cell*. 2014;14:752–761.
72. Sheik Mohamed J, Gaughwin PM, Lim B, Robson P, Lipovich L. Conserved long noncoding RNAs transcriptionally regulated by Oct4 and Nanog modulate pluripotency in mouse embryonic stem cells. *RNA*. 2010;16:324–337.
73. Wu Z, Liu X, Liu L, et al. Regulation of lncRNA expression. *Cell Mol Biol Lett*. 2014;19:561–575.
74. Zhang Y, Yang L, Chen LL. Life without a tail: new formats of long noncoding RNAs. *Int J Biochem Cell Biol*. 2014;54:338–349.
75. Uesaka M, Nishimura O, Go Y, Nakashima K, Agata K, Imamura T. Bidirectional promoters are the major source of gene activation-associated non-coding RNAs in mammals. *BMC Genomics*. 2014;15:35.
76. Braconi C, Kogure T, Valeri N, et al. MicroRNA-29 can regulate expression of the long non-coding RNA gene MEG3 in hepatocellular cancer. *Oncogene*. 2011;30:4750–4756.
77. Bartonicek N, Maag JL, Dinger ME. Long noncoding RNAs in cancer: mechanisms of action and technological advancements. *Mol Cancer*. 2016;15:43.
78. Chen X, Yan CC, Zhang X, You ZH. Long non-coding RNAs and complex diseases: from experimental results to computational models. *Brief Bioinform*. 2016;18:558–576.
79. Silva JM, Perez DS, Pritchett JR, Halling ML, Tang H, Smith DI. Identification of long stress-induced non-coding transcripts that have altered expression in cancer. *Genomics*. 2010;95:355–362.
80. Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov*. 2011;1:391–407.
81. Liu X, Li D, Zhang W, Guo M, Zhan Q. Long non-coding RNA gadd7 interacts with TDP-43 and regulates Cdk6 mRNA decay. *EMBO J*. 2012;31:4415–4427.
82. Leygue E, Dotzlaw H, Watson PH, Murphy LC. Expression of the steroid receptor RNA activator in human breast tumors. *Cancer Res*. 1999;59:4190–4193.
83. Ulveling D, Francastel C, Hubé F. When one is better than two: RNA with dual functions. *Biochimie*. 2011;93:633–644.
84. Wang C, Tao W, Ni S, et al. Tumor-suppressive microRNA-145 induces growth arrest by targeting SENP1 in human prostate cancer cells. *Cancer Sci*. 2015;106:375–382.
85. He JH, Zhang JZ, Han ZP, Wang L, Lv YB, Li YG. Reciprocal regulation of PCGEM1 and miR-145 promote proliferation of LNCaP prostate cancer cells. *J Exp Clin Cancer Res*. 2014;33:72.
86. Pickard MR, Williams GT. Regulation of apoptosis by long non-coding RNA GAS5 in breast cancer cells: implications for chemotherapy. *Breast Cancer Res Treat*. 2014;145:359–370.
87. Pickard MR, Mourtada-Maarabouni M, Williams GT. Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. *Biochim Biophys Acta*. 2013;1832:1613–1623.
88. Timp W, Feinberg AP. Cancer as a dysregulated epigenome allowing cellular growth advantage at the expense of the host. *Nat Rev Cancer*. 2013;13:497–510.
89. Li Q_, Su Z, Xu X, et al. AS1DHRS4, a head-to-head natural antisense transcript, silences the DHRS4 gene cluster in cis and trans. *Proc Natl Acad Sci U S A*. 2012;109:14110–14115.
90. Marquardt S, Escalante-Chong R, Pho N, et al. A chromatin-based mechanism for limiting divergent noncoding transcription. *Cell*. 2014;157:1712–1723.
91. Bohmdorfer G, Wierzbicki AT. Control of chromatin structure by long noncoding RNA. *Trends Cell Biol*. 2015;25:623–632.
92. Perl DP. Neuropathology of Alzheimer's disease. *Mt Sinai J Med*. 2010;77:32–42.
93. Massone S, Vassallo I, Fiorino G, et al. 17A, a novel non-coding RNA, regulates GABA B alternative splicing and signaling in response to inflammatory stimuli and in Alzheimer disease. *Neurobiol Dis*. 2011;41:308–317.
94. Stelzer Y, Sagi I, Yanuka O, Eiges R, Benvenisty N. The noncoding RNA IPW regulates the imprinted DLK1-DIO3 locus in an induced pluripotent stem cell model of Prader-Willi syndrome. *Nat Genet*. 2014;46:551–557.

95. Li D, Chen G, Yang J, et al. Transcriptome analysis reveals distinct patterns of long noncoding RNAs in heart and plasma of mice with heart failure. *PLoS ONE*. 2013;8:e77938.
96. Cabianca DS, Casa V, Bodega B, et al. A long ncRNA links copy number variation to a polycomb/trithorax epigenetic switch in FSHD muscular dystrophy. *Cell*. 2012;149:819–831.
97. Sun M, Kraus WL. From discovery to function: the expanding roles of long noncoding RNAs in physiology and disease. *Endocr Rev*. 2015;36:25–64.
98. Yuan S, Yang F, Yang Y, et al. Long non-coding RNA-MVIH promotes angiogenesis and serves as a predictor for HCC patients' poor recurrence-free survival after hepatectomy. *Hepatology*. 2012;56:2231–2241.
99. Matouk IJ, DeGroot N, Mezan S, et al. The H19 non-coding RNA is essential for human tumor growth. *PLoS ONE*. 2007;2:e845.
100. 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;54:1679–1689.
101. Panzitt K, Tschernatsch MM, Guelly C, et al. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. *Gastroenterology*. 2007;132:330–342.
102. Lai MC, Yang Z, Zhou L, et al. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol*. 2012;29:1810–1816.
103. Braconi C, Valeri N, Kogure T, et al. Expression and functional role of a transcribed noncoding RNA with an ultraconserved element in hepatocellular carcinoma. *Proc Natl Acad Sci U S A*. 2011;108:786–791.
104. Braconi C, Kogure T, Valeri N, et al. MicroRNA-29 can regulate expression of the long non-coding RNA gene MEG3 in hepatocellular cancer. *Oncogene*. 2011;30:4750–4756.
105. Geng Y, Xie S, Li Q, Ma J, Wang G. Large intervening non-coding RNA HOTAIR is associated with hepatocellular carcinoma progression. *J Int Med Res*. 2011;39:2119–2128.
106. Kim KS, Lee YI. Biallelic expression of the H19 and IGF2 genes in hepatocellular carcinoma. *Cancer Lett*. 1997;119:143–148.
107. Lu KH, Li W, Liu XH, et al. Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. *BMC Cancer*. 2013;13:461.
108. Kim K, Jutooru I, Chadalapaka G, et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. *Oncogene*. 2013;32:1616–1625.
109. Lv J, Ma L, Chen XL, Huang XH, Wang Q. Downregulation of LncRNAH19 and MiR-675 promotes migration and invasion of human hepatocellular carcinoma cells through AKT/GSK-3β/Cdc25A signaling pathway. *J Huazhong Univ Sci Technolog Med Sci*. 2014;34:363–369.
110. Wu L, Murat P, Matak-Vinkovic D, Murrell A, Balasubramanian S. Binding interactions between long noncoding RNA HOTAIR and PRC2 proteins. *Biochemistry*. 2013;52:9519–9527.
111. Nordin M, Bergman D, Halje M, Engstrom W, Ward A. Epigenetic regulation of the Igf2/H19 gene cluster. *Cell Prolif*. 2014;47:189–199.
112. Wang J, Wang H, Zhang Y, et al. Mutual inhibition between YAP and SRSF1 maintains long non-coding RNA, Malat1-induced tumourigenesis in liver cancer. *Cell Signal*. 2014;26:1048–1059.
113. Gabory A, Jammes H, Dandolo L. The H19 locus: role of an imprinted non-coding RNA in growth and development. *Bioessays*. 2010;32:473–480.
114. Zhuo H, Tang J, Lin Z, et al. The aberrant expression of MEG3 regulated by UHRF1 predicts the prognosis of hepatocellular carcinoma. *Mol Carcinog*. 2016;55:209–219.
115. Yap KL, Li S, Munoz-Cabello AM, et al. Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. *Mol Cell*. 2010;38:662–674.
116. Wu W, Bhagat TD, Yang X, et al. Hypomethylation of noncoding DNA regions and overexpression of the long noncoding RNA, AFAP1-AS1, in Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology*. 2013;144:956.e954–966.e954.
117. Jones PA, Baylin SB. The epigenomics of cancer. *Cell*. 2007;128:683–692.
118. Nakagawa S, Kageyama Y. Nuclear lncRNAs as epigenetic regulators—beyond skepticism. *Biochim Biophys Acta*. 2014;1839:215–222.
119. Saxena A, Carninci P. Long non-coding RNA modifies chromatin: epigenetic silencing by long non-coding RNAs. *Bioessays*. 2011;33:830–839.
120. Hayashi A, Yamauchi N, Shibahara J, et al. Concurrent activation of acetylation and tri-methylation of H3K27 in a subset of hepatocellular carcinoma with aggressive behavior. *PLoS ONE*. 2014;9:e91330.
121. Gui X, Li H, Li T, Pu H, Lu D. Long noncoding RNA CUDR regulates HULC and β-catenin to govern human liver stem cell malignant differentiation. *Mol Ther*. 2015;23:1843–1853.
122. Yuan JH, Yang F, Wang F, et al. A long noncoding RNA activated by TGF-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma. *Cancer Cell*. 2014;25:666–681.
123. Zhou T, Gao Y. Increased expression of LncRNA BANCR and its prognostic significance in human hepatocellular carcinoma. *World J Surg Oncol*. 2016;14:8.
124. Ding LJ, Li Y, Wang SD, et al. Long noncoding RNA lncCAMTA1 promotes proliferation and cancer stem cell-like properties of liver cancer by inhibiting CAMTA1. *Int J Mol Sci*. 2016;17:1617.
125. Liu F, Yuan JH, Huang JF, et al. Long noncoding RNA FTX inhibits hepatocellular carcinoma proliferation and metastasis by binding MCM2 and miR-374a. *Oncogene*. 2016;35:5422–5434.
126. Sui CJ, Zhou YM, Shen WF, et al. Long noncoding RNA GIHCG promotes hepatocellular carcinoma progression through epigenetically regulating miR-200b/a/429. *J Mol Med*. 2016;94:1281–1296.
127. Zhu 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;283:3739–3754.
128. Yan TH, Yang H, Jiang JH, et al. Prognostic significance of long non-coding RNA PCAT-1 expression in human hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2015;8:4126–4131.
129. Dong L, Ni J, Hu W, Yu C, Li H. Upregulation of long non-coding RNA PlncRNA-1 promotes metastasis and induces epithelial-mesenchymal transition in hepatocellular carcinoma. *Cell Physiol Biochem*. 2016;38:836–846.
130. Takahashi K, Yan IK, Kogure T, Haga H, Patel T. Extracellular vesicle-mediated transfer of long non-coding RNA ROR modulates chemosensitivity in human hepatocellular cancer. *FEBS Open Bio*. 2014;4:458–467.
131. Zhang JH, Wei HW, Yang HG. Long noncoding RNA SNHG15, a potential prognostic biomarker for hepatocellular carcinoma. *Eur Rev Med Pharmacol Sci*. 2016;20:1720–1724.
132. Shi XM, Teng F. Up-regulation of long non-coding RNA Sox2ot promotes hepatocellular carcinoma cell metastasis and correlates with poor prognosis. *Int J Clin Exp Pathol*. 2015;8:4008–4014.
133. Chen ZZ, Huang L, Wu YH, Zhai WJ, Zhu PP, Gao YF. LncSox4 promotes the self-renewal of liver tumour-initiating cells through Stat3-mediated Sox4 expression. *Nat Comm*. 2016;7:12598.
134. Zheng H, Yang S, Yang Y, et al. Epigenetically silenced long noncoding-SRHC promotes proliferation of hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2015;141:1195–1203.
135. Wang TH, Yu CC, Lin YS, et al. Long noncoding RNA CPS1-IT1 suppresses the metastasis of hepatocellular carcinoma by regulating HIF-1α activity and inhibiting epithelial-mesenchymal transition. *Oncotarget*. 2016;7:43588–43603.
136. Wang Y, He L, Du Y, et al. The long noncoding RNA lncTCF7 promotes self-renewal of human liver cancer stem cells through activation of Wnt signaling. *Cell stem cell*. 2015;16:413–425.
137. Zhu P, Wang Y, Wu J, et al. LncBRM initiates YAP1 signalling activation to drive self-renewal of liver cancer stem cells. *Nat Commun*. 2016;7:13608.
138. Lan T, Chang L, Wu L, Yuan Y. Downregulation of ZEB2-AS1 decreased tumor growth and metastasis in hepatocellular carcinoma. *Mol Med Rep*. 2016;14:4606–4612.
139. Ji J, Tang J, Deng L, et al. LINC00152 promotes proliferation in hepatocellular carcinoma by targeting EpCAM via the mTOR signaling pathway. *Oncotarget*. 2015;6:42813–42824.
140. 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:e2130.
141. Lu X, Zhou C, Li R, et al. Critical role for the long non-coding RNA AFAP1-AS1 in the proliferation and metastasis of hepatocellular carcinoma. *Tumour Biol*. 2016;37:9699–9707.
142. Bo C, Li N, Li X, Liang X, An Y. Long noncoding RNA uc.338 promotes cell proliferation through association with BMI1 in hepatocellular carcinoma. *Human Cell*. 2016;29:141–147.
143. Peng W, Fan H. Long noncoding RNA CCHE1 indicates a poor prognosis of hepatocellular carcinoma and promotes carcinogenesis via activation of the ERK/MAPK pathway. *Biomed Pharmacother*. 2016;83:450–455.
144. Tu ZQ, Li RJ, Mei JZ, Li XH. Down-regulation of long non-coding RNA GAS5 is associated with the prognosis of hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2014;7:4303–4309.
145. Zhu P, Wang Y, Huang G, et al. lnc-β-Catm elicits EZH2-dependent β-catenin stabilization and sustains liver CSC self-renewal. *Nat Struct Mol Biol*. 2016;23:631–639.
146. Xu D, Yang F, Yuan JH, et al. Long noncoding RNAs associated with liver regeneration 1 accelerates hepatocyte proliferation during liver regeneration by activating Wnt/β-catenin signaling. *Hepatology*. 2013;58:739–751.
147. Liang HW, Wang N, Wang Y, et al. Hepatitis B virus-human chimeric transcript HBx-LINE1 promotes hepatic injury via sequestering cellular microRNA-122. *J Hepatol*. 2016;64:278–291.
148. Chauhan R, Churchill ND, Mulrooney-Cousins PM, Michalak TI. Initial sites of hepadnavirus integration into host genome in human hepatocytes and in the woodchuck model of hepatitis B-associated hepatocellular carcinoma. *Oncogenesis*. 2017;6:e317.

149. Mulrooney-Cousins PM, Chauhan R, Churchill ND, Michalak TI. Primary seronegative but molecularly evident hepadnaviral infection engages liver and induces hepatocarcinoma in the woodchuck model of hepatitis B. *PLoS Pathog*. 2014;10:e1004332.
150. Yuan SX, Wang J, Yang F, et al. Long noncoding RNA DANCR increases stemness features of hepatocellular carcinoma by derepression of CTNNB1. *Hepatology*. 2016;63:499–511.
151. Zhang L, He T, Yan Y, et al. Expression and clinical significance of the novel long noncoding RNA ZNF674-AS1 in human hepatocellular carcinoma. *BioMed Res Int*. 2016;2016:3608914.
152. Yang Y, Chen L, Gu J, et al. Recurrently deregulated lncRNAs in hepatocellular carcinoma. *Nat Comm*. 2017;8:14421.
153. 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:e1549.
154. Ding C, Yang Z, Lv Z, et al. Long non-coding RNA PVT1 is associated with tumor progression and predicts recurrence in hepatocellular carcinoma patients. *Oncol Lett*. 2015;9:955–963.
155. Chen CL, Tseng YW, Wu JC, et al. Suppression of hepatocellular carcinoma by baculovirus-mediated expression of long non-coding RNA PTENP1 and microRNA regulation. *Biomaterials*. 2015;44:71–81.
156. Wen J, Liu Y, Liu J, et al. Expression quantitative trait loci in long non-coding RNA ZNRD1-AS1 influence both HBV infection and hepatocellular carcinoma development. *Mol Carcinog*. 2015;54:1275–1282.
157. 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;148:415–426.e418.
158. Yu W, Qiao Y, Tang X, et al. Tumor suppressor long non-coding RNA MT1DP is negatively regulated by YAP and Runx2 to inhibit FoxA1 in liver cancer cells. *Cell Signal*. 2014;26:2961–2968.
159. Liu Y, Pan S, Liu L, et al. A genetic variant in long non-coding RNA HULC contributes to risk of HBV-related hepatocellular carcinoma in a Chinese population. *PLoS ONE*. 2012;7:e35145.
160. Wang J, Liu X, Wu H, et al. CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer. *Nucleic Acids Res*. 2010;38:5366–5383.
161. Du Y, Kong G, You X, et al. Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18. *J Biol Chem*. 2012;287:26302–26311.
162. Hammerle M, Gutschner T, Uckelmann H, et al. Posttranscriptional destabilization of the liver-specific long noncoding RNA HULC by the IGF2 mRNA-binding protein 1 (IGF2BP1). *Hepatology*. 2013;58:1703–1712.
163. Cui 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;75:846–857.
164. 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.
165. Li J, Wang X, Tang J, et al. HULC and Linc00152 act as novel biomarkers in predicting diagnosis of hepatocellular carcinoma. *Cell Physiol Biochem*. 2015;37:687–696.
166. Panzitt K, Tschernatsch MM, Guelly C, et al. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. *Gastroenterology*. 2007;132:330–342.
167. Tsai M-C, Manor O, Wan Y, et al. Long noncoding RNA as modular scaffold of histone modification complexes. *Science*. 2010;329:689–693.
168. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature*. 2010;464:1071–1076.
169. Yang Z, Zhou L, Wu LM, et al. Overexpression of long non-coding RNA HOTAIR predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. *Ann Surg Oncol*. 2011;18:1243–1250.
170. Kwong WY, Miller DJ, Ursell E, et al. Imprinted gene expression in the rat embryo-fetal axis is altered in response to periconceptional maternal low protein diet. *Reproduction*. 2006;132:265–277.
171. Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet*. 2002;31:339–346.
172. Vernucci M, Cerrato F, Besnard N, et al. The H19 endodermal enhancer is required for Igf2 activation and tumor formation in experimental liver carcinogenesis. *Oncogene*. 2000;19:6376–6385.
173. Czarny MJ, Babcock K, Baus RM, Manoharan H, Pitot HC. Hepatocellular carcinomas of the albumin SV40 T-antigen transgenic rat display fetal-like re-expression of lgf2 and deregulation of H19. *Mol Carcinog*. 2007;46:747–757.
174. Manoharan H, Babcock K, Willi J, Pitot HC. Biallelic expression of the H19 gene during spontaneous hepatocarcinogenesis in the albumin SV40 T antigen transgenic rat. *Mol Carcinog*. 2003;38:40–47.
175. Manoharan H, Babcock K, Pitot HC. Changes in the DNA methylation profile of the rat H19 gene upstream region during development and transgenic hepatocarcinogenesis and its role in the imprinted transcriptional regulation of the H19 gene. *Mol Carcinog*. 2004;41:1–16.
176. Raveh E, Matouk IJ, Gilon M, Hochberg A. The H19 Long non-coding RNA in cancer initiation, progression and metastasis—a proposed unifying theory. *Mol Cancer*. 2015;14:184.
177. Kallen AN, Zhou XB, Xu J, et al. The imprinted H19 lncRNA antagonizes let-7 microRNAs. *Mol Cell*. 2013;52:101–112.
178. Luo M, Li Z, Wang W, Zeng Y, Liu Z, Qiu J. Long non-coding RNA H19 increases bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression. *Cancer Lett*. 2013;333:213–221.
179. Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neurooncol*. 2015;121:101–108.
180. Zhang X, Rice K, Wang Y, et al. Maternally expressed gene 3 (MEG3) noncoding ribonucleic acid: isoform structure, expression, and functions. *Endocrinology*. 2010;151:939–947.
181. Zhou Y, Zhang X, Klibanski A. MEG3 noncoding RNA: a tumor suppressor. *J Mol Endocrinol*. 2012;48:R45–R53.
182. Wang P, Ren Z, Sun P. Overexpression of the long non-coding RNA MEG3 impairs in vitro glioma cell proliferation. *J Cell Biochem*. 2012;113:1868–1874.
183. Qin R, Chen Z, Ding Y, Hao J, Hu J, Guo F. Long non-coding RNA MEG3 inhibits the proliferation of cervical carcinoma cells through the induction of cell cycle arrest and apoptosis. *Neoplasma*. 2013;60:486–492.
184. Anwar SL, Krech T, Hasemeier B, et al. Loss of imprinting and allelic switching at the DLK1-MEG3 locus in human hepatocellular carcinoma. *PLoS ONE*. 2012;7:e49462.
185. Zhang J, Yao T, Wang Y, Yu J, Liu Y, Lin Z. Long noncoding RNA MEG3 is downregulated in cervical cancer and affects cell proliferation and apoptosis by regulating miR-21. *Cancer Biol Ther*. 2016;17:104–113.
186. Peng W, Si S, Zhang Q_, et al. Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression. *J Exp Clin Cancer Res*. 2015;34:79.
187. Wang KC, Yang YW, Liu B, et al. A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. *Nature*. 2011;472:120–124.
188. Quagliata L, Matter MS, Piscuoglio S, et al. Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. *Hepatology*. 2014;59:911–923.
189. Cheng Y, Jutooru I, Chadalapaka G, Corton JC, Safe S. The long non-coding RNA HOTTIP enhances pancreatic cancer cell proliferation, survival and migration. *Oncotarget*. 2015;6:10840–10852.
190. Ge Y, Yan X, Jin Y, et al. MiRNA-192 [corrected] and miRNA-204 directly suppress lncRNA HOTTIP and interrupt GLS1-mediated glutaminolysis in hepatocellular carcinoma. *PLoS Genet*. 2015;11:e1005726.
191. Zhang EB, Yin DD, Sun M, et al. P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. *Cell Death Dis*. 2014;5:e1243.
192. Han Y, Liu Y, Gui Y, Cai Z. Long intergenic non-coding RNA TUG1 is overexpressed in urothelial carcinoma of the bladder. *J Surg Oncol*. 2013;107:555–559.
193. Zhang Q_, Geng PL, Yin P, Wang XL, Jia JP, Yao J. Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and promotes apoptosis. *Asian Pac J Cancer Prev*. 2013;14:2311–2315.
194. Young T, Matsuda T, Cepko C. The noncoding RNA taurine upregulated gene 1 is required for differentiation of the murine retina. *Current Biol*. 2005;15:501–512.
195. Huang M-D, Chen W-M, Qi F-Z, et al. Long non-coding RNA TUG1 is up-regulated in hepatocellular carcinoma and promotes cell growth and apoptosis by epigenetically silencing of KLF2. *Mol Cancer*. 2015;14:165.
196. Dong R, Liu GB, Liu BH, et al. Targeting long non-coding RNA-TUG1 inhibits tumor growth and angiogenesis in hepatoblastoma. *Cell Death Dis*. 2016;7:e2278.
197. 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;64:1283–1294.
198. Yang F, Xue X, Bi J, et al. Long noncoding RNA CCAT1, which could be activated by c-Myc, promotes the progression of gastric carcinoma. *J Cancer Res Clin Onco*. 2013;139:437–445.
199. Nissan A, Stojadinovic A, Mitrani-Rosenbaum S, et al. Colon cancer associated transcript-1: a novel RNA expressed in malignant and pre-malignant human tissues. *Int J Cancer*. 2012;130:1598–1606.
200. Deng L, Yang S-B, Xu F-F, Zhang J-H. Long noncoding RNA CCAT1 promotes hepatocellular carcinoma progression by functioning as let-7 sponge. *J Exp Clin Cancer Res*. 2015;34:18.
201. Xu W-H, Zhang J-B, Dang Z, et al. Long non-coding RNA URHC regulates cell proliferation and apoptosis via ZAK through the ERK/MAPK signaling pathway in hepatocellular carcinoma. *Int J Biol Sci*. 2014;10:664–676.
202. Pasmant E, Sabbagh A, Masliah-Planchon J, et al. Role of noncoding RNA ANRIL in genesis of plexiform neurofibromas in neurofibromatosis type 1. *J Natl Cancer Inst*. 2011;103:1713–1722.
203. Herceg Z, Paliwal A. Epigenetic mechanisms in hepatocellular carcinoma: how environmental factors influence the epigenome. *Mutat Res/Rev Mutat Res*. 2011;727:55–61.
204. Pasmant E, Laurendeau I, Heron D, Vidaud M, Vidaud D, Bieche I. Characterization of a germ-line deletion, including the entire INK4/ARF locus, in a

melanoma-neural system tumor family: identification of ANRIL, an antisense noncoding RNA whose expression coclusters with ARF. *Cancer Res*. 2007;67:3963–3969.
205. Huang M, Chen W, Qi F, 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;8:50.
206. Zhang EB, Kong R, Yin DD, et al. Long noncoding RNA ANRIL indicates a poor prognosis of gastric cancer and promotes tumor growth by epigenetically silencing of miR-99a/miR-449a. *Oncotarget*. 2014;5:2276–2292.
207. Nie FQ, Sun M, Yang JS, et al. Long noncoding RNA ANRIL promotes non–small cell lung cancer cell proliferation and inhibits apoptosis by silencing KLF2 and P21 expression. *Molecular cancer therapeutics*. 2015;14:268–277.
208. Kotake Y, Nakagawa T, Kitagawa K, et al. Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15(INK4B) tumor suppressor gene. *Oncogene*. 2011;30:1956–1962.
209. Yu W, Gius D, Onyango P, et al. Epigenetic silencing of tumour suppressor gene p15 by its antisense RNA. *Nature*. 2008;451:202–206.
210. Hua L, Wang CY, Yao KH, Chen JT, Zhang JJ, Ma WL. High expression of long non-coding RNA ANRIL is associated with poor prognosis in hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2015;8:3076–3082.
211. Di Ruscio A, Ebralidze AK, Benoukraf T, et al. DNMT1-interacting RNAs block gene-specific DNA methylation. *Nature*. 2013;503:371–376.
212. Herceg Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. *Mutagenesis*. 2007;22:91–103.
213. Lambert MP, Paliwal A, Vaissiere T, et al. Aberrant DNA methylation distinguishes hepatocellular carcinoma associated with HBV and HCV infection and alcohol intake. *J Hepatol*. 2011;54:705–715.
214. Lee JT. Epigenetic regulation by long noncoding RNAs. *Science*. 2012;338: 1435–1439.
215. Calvisi DF, Ladu S, Gorden A, et al. Mechanistic and prognostic significance of aberrant methylation in the molecular pathogenesis of human hepatocellular carcinoma. *J Clin Invest*. 2007;117:2713–2722.
216. Nishida N, Kudo M, Nagasaka T, Ikai I, Goel A. Characteristic patterns of altered DNA methylation predict emergence of human hepatocellular carcinoma. *Hepatology*. 2012;56:994–1003.
217. Revill K, Wang T, Lachenmayer A, et al. Genome-wide methylation analysis and epigenetic unmasking identify tumor suppressor genes in hepatocellular carcinoma. *Gastroenterology*. 2013;145:1424–1435.e1-25.
218. Hernandez-Vargas H, Lambert MP, Le Calvez-Kelm F, et al. Hepatocellular carcinoma displays distinct DNA methylation signatures with potential as clinical predictors. *PLoS ONE*. 2010;5:e9749.
219. Song MA, Tiirikainen M, Kwee S, Okimoto G, Yu H, Wong LL. Elucidating the landscape of aberrant DNA methylation in hepatocellular carcinoma. *PLoS ONE*. 2013;8:e55761.
220. Saito Y, Kanai Y, Sakamoto M, Saito H, Ishii H, Hirohashi S. Expression of mRNA for DNA methyltransferases and methyl-CpG–binding proteins and DNA methylation status on CpG islands and pericentromeric satellite regions during human hepatocarcinogenesis. *Hepatology*. 2001;33:561–568.
221. Griffiths EA, Gore SD. MicroRNA: mIR-ly regulators of DNMT? *Blood*. 2009;113:6269–6270.
222. Parpart S, Roessler S, Dong F, et al. Modulation of miR-29 expression by alpha-fetoprotein is linked to the hepatocellular carcinoma epigenome. *Hepatology*. 2014;60:872–883.
223. Bai X, Wu L, Liang T, et al. Overexpression of myocyte enhancer factor 2 and histone hyperacetylation in hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2008;134:83–91.
224. Wang L, Zhang X, Jia LT, et al. c-Myc-mediated epigenetic silencing of MicroRNA-101 contributes to dysregulation of multiple pathways in hepatocellular carcinoma. *Hepatology*. 2014;59:1850–1863.
225. Studach LL, Menne S, Cairo S, et al. Subset of Suz12/PRC2 target genes is activated during hepatitis B virus replication and liver carcinogenesis associated with HBV X protein. *Hepatology*. 2012;56:1240–1251.
226. Effendi K, Mori T, Komuta M, Masugi Y, Du W, Sakamoto M. Bmi-1 gene is upregulated in early-stage hepatocellular carcinoma and correlates with ATP-binding cassette transporter B1 expression. *Cancer Sci*. 2010;101:666–672.
227. Chauhan R, Lahiri N. Tissue- and serum-associated biomarkers of hepatocellular carcinoma. *Biomark Cancer*. 2016;8:37–55.
228. Zhang L, Yang F, Yuan JH, et al. Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. *Carcinogenesis*. 2013;34:577–586.