Review article:

LNCRNA INVOLVEMENT IN HEPATOCELLULAR CARCINOMA METASTASIS AND PROGNOSIS

Maryam Abbastabar¹, Mohammad Sarfi¹, Abolfazl Golestani¹, Ehsan Khalili¹,*

¹ Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, I.R. Iran

* Corresponding author: Ehsan Khalili, PhD, Department of Clinical Biochemistry, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98 21 88953004, Fax: +98 21 64053385, E-mail: E-khalili@sina.tums.ac.ir

http://dx.doi.org/10.17179/excli2018-1541

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ABSTRACT

Eukaryotic IncRNAs are RNA molecules defined to be greater than 200 bp in length that are not translated to a protein and operate through several mechanisms, including participating in chromatin remodeling and methylation, influencing the integrity and stability of proteins and complexes, or acting as a sponge for miRNA inhibition. A number of recent studies have concentrated on the relationship between long non-coding RNAs (lncRNAs) and cancer. Hepatocellular carcinoma (HCC) is the most prevalent histological type of liver tumors, accounting for about 80 % of the cases worldwide. Lack of proper molecular markers for diagnosis of HCC and treatment evaluation is a significant problem. Dysregulated expression of HCC-related IncRNAs such as MEG-3, MALAT1, HULC, HOTAIR, and H19 have been identified and closely related with tumorigenesis, metastasis, prognosis and diagnosis. In this review, we summarized recent highlighted functions and molecular mechanisms of the most extensively studied lncRNAs in the pathophysiology of hepatocellular carcinoma and their potential for serving as probable therapeutic targets.

Keywords: Hepatocellular carcinoma (HCC), long non-coding RNA (lncRNAs), metastasis, prognosis, liver

INTRODUCTION

In humans, more than 85 % of the genome is transcribed. RNAs that do not encode proteins are called non-coding RNAs (ncRNAs). Non-coding RNAs are classified into two groups based on their size. One group is short RNAs with less than 200 nucleotides such as miRNA, siRNA, snoRNA and the other is long non-coding RNAs with more than 200 nucleotides. LncRNAs, in contrast with miRNAs, are less understood (Berretta and Morillon, 2009; Haggar and Boushey, 2009; ENCODE Project Consortium, 2012; Guttmann and Rinn, 2012). XIST (X-inactive specific transcript) and H19 were the first
lncRNAs discovered in the 1990s (Branman et al., 1990; Brockdorff et al., 1992).

XIST has a role in inactivation of X-chromosome in female zygotes (Marahrens et al., 1998). Many lncRNAs are transcribed and spliced by RNA polymerase II and several lncRNAs have both poly-A tail and 5' cap (Derrien et al., 2012). Similar to protein-coding genes, lncRNAs have certain epigenetic modifications like H3K4me3 in the promoter of the gene and H3K36me3 that are seen throughout their genome. They generally do not have functional open reading frames (ORFs). However, this discrepancy is obscured by the discovery of bifunctional RNAs that may possess both protein-coding and coding-free functions. Even though lncRNAs can be found in many tissues, the brain and central nervous system have the highest levels of expressed lncRNAs. The intracellular location of these molecules also varies, as they can be found in a wide range of intracellular components such as the nucleus, the cytoplasm, or in one or more focal regions of the cells. Their location may indicate their likely performance (Dinger et al., 2008; Warden et al., 2008; Ponjavic et al., 2009).

The basis for nomenclature of lncRNAs is different. Some of them are named based on their role, such as PRAL (P53 Regulation-Association Long Non-Coding RNA), or based on their tissue expression such as HULC (Highly upregulated in liver cancer), while some are named based on their genomic location such as HOTAIR (Hox antisense intergenic RNA) (Warden et al., 2008). LncRNAs have their own functional attributes due to their secondary structures; they usually have stem-loop secondary structures (Kino et al., 2010). They interact with other biological molecules such as RNA, DNA, and protein, and other critical factors in promoting the physiological activity of natural cells. These molecules play important roles in biological processes through multiple mechanisms, such as acting as a sponge for miRNAs inhibition, participating in chromatin remodeling and also influencing the stability of proteins (Quinn and Chang, 2016). Many of these molecules are associated with human diseases such as gastric cancer (Du et al., 2015), breast cancer (Gupta et al., 2010), colorectal cancer (Kogo et al., 2011), and non-small-cell lung cancer (NSCLC) (Sun et al., 2014).

Hepatocellular carcinoma (HCC) is the most prevalent histological type of liver tumors, accounting for about 80% of the cases (DeSantis et al., 2014). This malignancy is the seventh most common carcinoma in men and the ninth in women (Okuda, 1992). HCC has a wide variety of geographical disparity. It is more prevalent in China, Taiwan, Korea and other countries in Southeast Asia and Sub-Saharan Africa (Wang et al., 1991). The main risk factors for hepatocellular carcinoma are age, sex, and cirrhosis, but the main cause is an overdose of alcohol or chronic infection with hepatitis B or hepatitis C viruses (Trevisani et al., 1996; Velázquez et al., 2003). Several signaling pathways have been shown to be critical players in HCC such as the Wnt/β Catenin (Herbst and Kolligs, 2007), p53 (Hsu et al., 1993), Ras (Liao et al., 1997) and JAK/STAT pathway (Wormald and Hilton, 2004). Although many diagnostic and treatment methods are available for HCC, including surgical resection, liver transplantation, radioembolization, radiation therapy, and molecularly targeted therapies (Attwa and El-Etreby, 2015), the absence of suitable molecular markers for HCC diagnosis and therapy evaluation is a significant problem. Therefore, it is critical to develop novel strategies for early diagnosis, prognosis, prediction, and therapeutic targets of patients with HCC. In our study, we focused on abridging the conceivable functions and molecular mechanisms of the most extensively studied lncRNAs in HCC. Numerous lncRNAs have been reported to be involved in metastasis and prognosis of hepatocellular carcinoma. This review summarizes selected lncRNAs that are dysregulated in hepatocellular carcinoma studies, and discusses their mechanisms and clinical applications (Table 1).
Table 1: Summary of lncRNAs involved in the hepatocellular carcinoma

| LncRNA | Genomic location | Archetype         | Function            | Cancer Phenotype                      | Hcc-pathway examples                                      | Reference                                                                 |
|--------|------------------|-------------------|---------------------|---------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------------------|
| MALAT-1 | 11q13.1          | Decoy             | Oncogenic           | Migration; Proliferation; Invasion; Metastasis | MALAT-1 → LTBP3→metastasis MALAT-1-- mir-146-5p→migration, invasion MALAT-1-- mir-195→ EGFR→metastasis | Li and Chen, 2013; Hou et al., 2017; Li et al., 2017a; Liu et al., 2018 |
| MEG-3  | 14q32.2          | Decoy, scaffold   | Tumor suppressive   | Invasion; Metastasis                  | MEG-3--MIR-664→reduced tumor growth, invasion, and metastasis MEG-3--MDM2→P53→reduced tumor growth | Miyoshi et al., 2000; Vogelstein et al., 2000; Zhou et al., 2007; Yang et al., 2012; He et al., 2017b |
| GAS5   | 1q25.1           | Decoy, scaffold   | Tumor suppressive   | Metastasis                           | GAS5--vimentin→reduced metastasis                         | Coccia et al., 1992; Tu et al., 2014; Chang et al., 2016 |
| MVIH   | 10q22            | Decoy, scaffold   | Oncogenic           | Proliferation; Migration; Angiogenesis | MVIH --miR-199a→ Proliferation, migration MVIH--PGK1→ angiogenesis | Lay et al., 2000; Yuan et al., 2012b; Kinose et al., 2015 |
| HOTAIR | 12q13.13         | Scaffold          | Oncogenic           | Migration; Invasion; Metastasis       | HOTAIR→ matrix metalloproteinase-9→metastasis HOTAIR --mir-23b-3p→ ZEB1→EMT | Geng et al., 2011; Yan et al., 2016; Yang et al., 2018 |
| H19    | 11p15.5          | Decoy, scaffold   | Oncogenic           | Metastasis                           | H19→ hnRNP U/PCAF/RNAPol II and miR-200→metastasis H19-- mir372→ PRKACB H19→ZEB1→ EMT | Cai and Cullen, 2007; Keniry et al., 2012; Zhang et al., 2012 Panzitt et al., 2007; Wang et al., 2010; Li et al., 2016a |
| HULC   | 6p24.3           | Decoy, scaffold   | Oncogenic           | Metastasis                           | Dresh--vimentin→reduced metastasis                        | Huang et al., 2013 |
| DRESH  | 17 E1.1; 17      | Scaffold          | Tumor suppressive   | Metastasis                           | DRESH→vimentin→reduced metastasis                        | Huang et al., 2013 |
| MDIG   | 3q11.2           | Guide             | Oncogenic           | Proliferation; Transformation         | MDIG→modification of H3K9me3→expression of genes important for cell expression of genes important for cell proliferation or transformation | Ogasawara et al., 2010; Chen et al., 2013 |
| ZEB1-AS1 | 10p11.22        | -                 | Oncogenic           | Metastasis                           | ZEB1-AS1-- E-cadherin→EMT                                | Hashiguchi et al., 2013; Li et al., 2016b |
| UC.134 | 3                | Signal            | Tumor suppressive   | Metastasis                           | UC.134→ repressing YAP and stimulating Hippo kinase signaling | Ni et al., 2017 |
| PVT-1  | 8q24.21          | Scaffold          | Oncogenic           | Proliferation                         | PVT-1→stabilizing the NOP2 protein→proliferation          | Chapman et al., 2012; Wang et al., 2014a; Yu et al., 2016 |
| UCA1   | 19p13.12         | Decoy             | Oncogenic           | Metastasis; Invasion                  | UCA1--miR-216b→ FGFR1/ERK signaling                       | Li et al., 2014; Wang et al., 2015a |
| ATB    | -                | Decoy             | Oncogenic           | Metastasis; Invasion                  | ATB--miR-200 family→ ZEB1 and ZEB2→ EMT, invasion        | Yuan et al., 2014 |
**METASTASIS-ASSOCIATED LUNG ADENOCARCINOMA TRANSCRIPT 1 (MALAT-1)**

MALAT-1, also known as nuclear enriched abundant transcript-2 (NEAT-2), is located at human chromosome 11q13.1 and mostly situated in nuclear speckles (Li and Chen, 2013). This lncRNA interacts with serine/arginine (SR) proteins and regulates them and other splicing factors (Tripathi et al., 2010). It is highly expressed in the brain (Bernard et al., 2010) and overexpressed in many human carcinomas such as colorectal cancer (Yang et al., 2015), non-small-cell lung cancer (Ji et al., 2003), endometrial stromal sarcoma (ESS) (Yamada et al., 2006), breast cancer (Guffanti et al., 2009), and HCC. MALAT-1 has been elevated in both HCC lines and clinical tissue samples. Silencing of MALAT-1 by siRNA decreases cell proliferation and inhibits migration and invasion; therefore, it could be a novel biomarker for prediction of HCC recurrence following liver transplantation (Lai et al., 2012). Hou et al. (2017) demonstrated that hepatitis B virus X protein (HBx) could upregulate the long non-coding RNA MALAT-1 in HCC, and MALAT-1 could further influence the expression of latent transforming growth factor β-binding protein 3 (LTBP3), resulting in further progress and metastasis of HCC. In addition, Li et al. (2017a) reported that MALAT-1 acts as a molecular sponge for miR-146-5p to downregulate its expression in HCC. miR-146b-5p could obliterate amplification, migration, and invasion, and also induces apoptosis in vitro and in vivo. Remarkably, TNF receptor-associated factor 6 (TRAF6) has been justified as a lead target of miR-26a in HCC and miR-26a-5p applies the cancer inhibitory functions through repressing phosphorylation of Akt mediated by TRAF6. In addition, Liu et al. (2018) suggested that MALAT-1 acts as a circular endogenous RNA for miR-195. Epidermal growth factor receptor (EGFR) is a direct target of miR-195. Sponging of miR-195 by MALAT1 exerts oncogenic effects since miR-195 is no longer able to suppress the downstream target EGFR.

**MATERNALLY EXPRESSED GENE-3 (MEG-3)**

Maternally Expressed Gene 3 (MEG-3) is a human equivalent of mouse gene trap locus 2 (Gtl2) that is located at human chromosome 14q32.2 (Miyoshi et al., 2000). Evidence suggests that MEG3 is expressed in normal tissues, whereas its expression is downregulated in tongue squamous cell carcinoma (Wang et al., 2014b), gastric cardiac adenocarcinoma (Guo et al., 2017), nasopharyngeal carcinoma (Chak et al., 2017) and gastric cancer (Peng et al., 2015). This lncRNA is downregulated in HCC tissues, and its overexpression inhibits proliferation of the HCC HuH7 cell by negative modulation of miRNA-664 which reduces tumor growth, invasion, and metastasis in the orthotopic liver cancer model (Yang et al., 2012; He et al., 2017b). This lncRNA also functions as a tumor inhibitor through P53-dependent and P53-independent pathways. Zhou and his colleagues (2007) discovered that MEG3 induces P53 accumulation via repressing murine double minute 2 (MDM2) expression, which degrades p53. In addition it has been well documented that MEG3 has antitumor effects in the absence of p53 (Vogelstein et al., 2000). Li et al. (2017c) found that miR-26a, as a tumor suppressor, and MEG3 decreased significantly in HCC compared to matched non-malignant tissues. MiR-26a binds to 3'-UTR of DNA methyltransferase3b (DNMT3B) and suppresses its expression, resulting in the upregulation of MEG3. In this way, miR-26a inhibits cell proliferation, migration, and invasion in HCC.

**GROWTH ARREST-SPECIFIC 5 (GAS5)**

GAS5, which accumulates in growth-arrested cells, is located at 1q25.1. This gene encodes multiple snoRNAs and lncRNAs that act as a ribo-repressor of the glucocorticoid and associated receptors (Coccia et al., 1992). Various functions have been related to this transcript, including cell development prevention and apoptosis (Wang et al., 2018). It has therefore been recognized as a potential
tumor suppressor, with its inhibition linked to cancer in numerous diverse tissues. Tu et al. (2014) revealed that the expression level of GAS5 is reduced in HCC compared to normal matched tissues. It also has been proven that GAS5 expression is associated with HCC tumor size, lymph node metastasis, and clinical stage. Chang et al. (2016) reported that GAS5 participates in the epithelial mesenchymal transition (EMT) of HCC cells. Overexpression of GAS5 downregulates the vimentin and upregulates the E-cadherin level in hepatocellular carcinoma cells. There is a significant negative association between GAS5 and the vimentin level in vivo (Chang et al., 2016). Vimentin is a 57 kDa, type III intermediate filament whose function is to maintain cell and tissue integrity. Vimentin is linked with tumor incursion and a poor prognosis in various types of cancers, including hepatocellular carcinoma (Hu et al., 2004). These data suggest an essential role for GAS5 in the molecular etiology of HCC and implicate the potential application of GAS5 in HCC therapy.

**LncRNA with Associated Microvascular Invasion in HCC (MVIH)**

MVIH is located at human chromosome 10q22 at RPS24 (Ribosomal Protein S24) gene which is overexpressed in HCC (Yuan et al., 2012b), and breast cancer (Lei et al., 2016). Presently, little is known about MVIH. A current study showed that MVIH might control HCC cell vitality by sponging and repressing the expression of miR-199a (Shi et al., 2015). Several reports have shown that miR-199a acts as a tumor repressor, promotes tumor cell apoptosis, and inhibits cell proliferation and migration in several cancers (Tian et al., 2014; Wang et al., 2014b; Kinose et al., 2015). Yuan et al. (2012b) found that MVIH could activate tumor-inducing angiogenesis by diminishing the secretion of phosphoglycerate kinase 1 (PGK1), which is a glycolytic enzyme that catalyzes the conversion of 1,3-diphosphoglycerate to 3-phosphoglycerate. This enzyme can be secreted by tumor cells and contributes to inhibition of angiogenesis (Lay et al., 2000). The serum level of MVIH is inversely correlated with the level of PKG1. MVIH overexpression could predict the recurrence of early-stage HCC in patients (Yuan et al., 2012b).

**HOX Antisense Intergenic RNA (HOTAIR)**

This IncRNA's gene is situated inside the Homeobox C (HOXC) gene assemblage on chromosome 12 and is co-expressed with the HOXC genes (Wu et al., 2017). HOTAIR recruits the polycomb repressive complex-2 (PRC2) and Lysine-Specific Histone Demethylase 1 (LSD1) to the specific site and regulates the HOXD gene expression (Yan et al., 2016). This IncRNA has an essential function in the epigenetic control of gene expression. In this regard, HOTAIR is deregulated in various cancers like pancreatic cancer (Kim et al., 2013), lung cancer (Loewen et al., 2014), esophageal cancer (Lv et al., 2013), and HCC. In HCC, HOTAIR is increased compared to non-cancerous tissues; it acts by activating the Wnt/β catenin signaling pathway and is associated with metastasis, differentiation, and early recurrence (Gao et al., 2016). In vitro assays in the HCC cell line have demonstrated that knockdown of HOTAIR IncRNA diminishes cell proliferation and is associated with decreased levels of matrix metalloproteinase-9 and vascular endothelial growth factor protein, which are crucial for cell motility and metastasis (Geng et al., 2011). On the other hand, HOTAIR promotes invasion and metastasis of HCC cells by enhancing EMT. This IncRNA acts as a miR-23b-3p sponge to positively regulate zinc finger E-box-binding homeobox 1(ZEB1), a transcription factor associated with EMT (Yang et al., 2018). In addition, Wu et al. (2018) reported that HOTAIR bestows its impacts on cell multiplication via controlling the opioid growth factor receptor expression, which is a negative biological regulator of cell proliferation in HCC.
H19

H19 was the first imprinted non-coding transcript identified and has a highly conserved secondary structure (Cai and Cullen, 2007). H19 is co-expressed with another maternally imprinted gene, insulin-like growth factor 2 (IGF-2) (Jones et al., 1998). The H19 gene behaves as an oncogene and may serve as a potential new target for anti-tumor therapy (Matouk et al., 2007). Increased expression of H19 RNA has been shown in a large group of tumors such as pancreatic cancer (Ma et al., 2014), breast cancer (Zhang et al., 2016) and HCC. Many studies have shown that H19 can interact with microRNAs and proteins. H19 acts as a sponge for miR-675 that is encoded in its first exon (Keniry et al., 2012). Furthermore, H19 is associated with the protein complex hnRNP U/PCAF/RNAPol II and activates the miR-200 family by increasing histone acetylation. Zhang et al. (2012) demonstrated that H19 can alter the miR-200 pathway, thus contributing to mesenchymal-to-epithelial transition and repression of cancer metastasis.

HIGHLY UPREGULATED IN LIVER CANCER NON-CODING RNA (HULC)

HULC is located at human chromosome 6p24.3 and is the first ncRNA with highly specific upregulation in HCC. It can be detected in the blood of HCC patients (Panzitt et al., 2007). This IncRNA may act as an endogenous sponge that downregulates a series of miRNAs’ activities, including miR-372 and miR-200a-3p. Suppression of miR-372 reduces the translational repression of PRKACB (cAMP-dependent protein kinase catalytic subunit beta), which then triggers phosphorylation of CREB. Binding of phospho-CREB to the HULC promoter activates HULC expression (Wang et al., 2010). HULC expression is not confined to HCC alone, but also to those colorectal carcinomas that metastasize to the liver (Matouk et al., 2009). Li et al. (2016a) suggested that miR-200a-3p is negatively regulated by HULC, and HULC functions as a ceRNA to mediate EMT via up-regulating ZEB1 in HCC cells. Xiong and his colleagues (2017) found that ectopic expression of HULC stimulates the autophagy of HCC cells via harmonizing silent information regulator 1 (Sirt1) protein and dampening of HULC sensitized HCC cells to antitumor reagents through suppressing protective autophagy. In addition, it has also been found that HULC and Linc00152 can act as novel biomarkers in predicting the diagnosis of HCC, and a combination of HULC, Linc00152, and AFP has the highest prediction value in HCC (Li et al., 2015).

DRESH

Hepatitis B virus (HBV) has an important role in human hepatocellular carcinoma (HCC). Many non-coding RNAs including miRNAs such as miR-18a (Liu et al., 2016b), mir-148a (Yuan et al., 2012a), mir-21 (Qiu et al., 2013) and IncRNAs regulated by HBx in HCC have important biological functions in cell proliferation, apoptosis, invasion, and metastasis. HBx protein can decrease IncRNAs whose expression is downregulated by HBx (termed IncRNA-Dreh). LncRNA-Dreh acts as a cancer inhibitor and could attach to the intermediate filament protein vimentin, suppresses its expression, and alters the cytoskeletal structure and prevents tumor metastasis (Huang et al., 2013).

MDIG

MDIG was initially discovered as a mineral dust-induced transcript from coal miners’ alveolar macrophages (Zhang et al., 2005). The expression of MDIG is controlled by the c-Myc oncogene and termed as myc-induced nuclear antigen 53 (Mina53) (Ogasawara et al., 2010). High levels of MDIG expression have been found in lung cancer (Lu et al., 2009), renal cell carcinoma (Ishizaki et al., 2007), lymphoma (Teye et al., 2007), neuroblastoma (Fukahori et al., 2007), esophageal squamous cell carcinoma, and HCC (Tsuneoka et al., 2004). Chen et al. (2013) demonstrated that MDIG participates in mod-
ification of H3K9me3 to impact the heterochromatin structure of the genome, and the expression of genes important for cell proliferation or transformation. Ogasawara et al. (2010) proposed that Mina53 expression is accelerated in HCC with a lower histological grade, larger diameter, or cell growth competence, and Mina53 is linked to biological malignancy of HCC.

**ZEB1-AS1**

Zinc finger E-box-binding homeobox 1 is a protein encoded by the ZEB1 gene in humans. There is a non-coding antisense transcript emanating from the promoters of ZEB1, ZEB1 antisense1 (ZEB1-AS1). ZEB1-AS1 is frequently upregulated in HCC samples, especially in metastatic tumor tissues, and may serve as a valuable prognostic biomarker for HCC (Li et al., 2016b). Hashiguchi et al. (2013) revealed that positive ZEB-1 expression and loss of E-cadherin expression correlate with a poor prognosis and progression of HCC through their effect on the progression of EMT.

**UC.134 LNCRNA**

UC.134 is a novel lncRNA that inhibits liver tumor development by suppressing the CUL4A-mediated ubiquitination of LATS1 and augmenting YAP phosphorylation. Overexpression of uc.134 suppresses HCC cell proliferation, invasion, and metastasis in vitro and in vivo. The use of this lncRNA may provide a favorable therapeutic method by repressing YAP and stimulating Hippo kinase signaling (Ni et al., 2017).

**PVT-1 AND UC200MBE.2**

The lncRNA plasmacytoma variant translocation 1 (PVT1) is 1716 nucleotides long. It is located at 8q24.21 and is a recently identified long non-coding RNA. The human PVT1 oncogene level has been discovered to be high in a succession of human cancers (Barsotti et al., 2012; Chapman et al., 2012). Yu et al. reported that lncRNAs PVT1 and uc002mbe.2 are upregulated in the sera of HCC patients compared to healthy controls (Yu et al., 2016). They demonstrated that amalgamation of 2 lncRNAs in the serum produces a new supplementary approach for HCC diagnosis. In addition, Wang et al. (2014a) found that oncofetal long non-coding RNA PVT1 stimulates multiplication and acquisition of stem cell-like properties in hepatocellular carcinoma cells through stabilizing the NOP2 protein. The NOP2 nucleolar protein can intensify nucleolar activities and stimulate cell proliferation by modifying the cell cycle and the hPVT1/NOP2 pathway. It is also involved in promoting carcinogenesis and cell proliferation and acquiring stem cell-like properties in HCC cells.

**LNCRNA-UCA1 AND WRAP53**

Urothelial carcinoma associated antigen 1 (UCA1) is a bladder cancer-specific lncRNA with a total length of 1439 bp that is located at 19p13.12 (Li et al., 2014). UCA1 is a common molecular marker for lymph node metastasis and prognosis in various cancers, including colorectal cancer, breast cancer, esophageal cancer, lung cancer, and pancreatic cancer (Ni et al., 2015; Wang et al., 2015b; He et al., 2017a). The expression of serum UCA1 is significantly higher in patients with HCC, allowing differentiation of HCC from benign liver disease and healthy controls. High expression of serum UCA1 is significantly associated with a high tumor grade, large tumor size, positive vascular invasion, and advanced TNM stage (Heng et al., 2018). Kamel et al. (2016) provided evidence that lncRNA-UCA1 and WD repeat containing antisense to TP53 (WRAP53) are highly expressed in the serum of HCC patients and HCV patients. They reported that lncRNA-WRAP53 expression is a useful prognostic marker for RFS in HCC. Wang et al. (2015a) demonstrated that UCA1 may act as an endogenous sponge by directly binding to miR-216b, and downregulation of miR-216b expression results in repression of fibroblast growth factor receptor1 (FGFR1) expression and activation of an FGFR1/ERK signaling pathway in HCC.
Therefore, upregulated lncRNA-UCA1 levels in HCC tissues are associated with the TNM stage, metastasis, and postoperative survival.

**ATB**

LncRNA activated by transforming growth factor beta (TGF-β) (lncRNA-ATB) is involved in cell proliferation and metastasis in a variety of cancers, including renal cell carcinoma, colorectal cancer, non-small-cell lung cancer, glioma, etc. (Iguchi et al., 2015; Qiu et al., 2017; Ke et al., 2017; Li et al., 2017d). In addition, this lncRNA is upregulated in hepatocellular carcinoma metastases and is associated with a poor prognosis. LncRNA-ATB upregulates ZEB1 and ZEB2 by competitively binding to the miR-200 family, thereby inducing EMT and invasion (Yuan et al., 2014). Li et al. (2018) demonstrated that Astragaloside IV (AS-IV) significantly downregulates lncRNA-ATB expression in a dose- and time-dependent manner in HCC cells. AS-IV represses EMT and migration of HCC cells. Likewise, through downregulation of lncRNA-ATB, AS-IV inactivates IL-11/STAT3 signaling, induces HCC cell apoptosis, and reduces HCC cell viability.

**OTHER LNCRNAS IN HCC**

Recent studies have established that many other lncRNAs are abnormally regulated in HCC, including lncRNA-Low Expression in Tumor (lncRNA-LET), located at 15q24.1. It is involved in cancer suppression in numerous tumor types, such as cervical cancer (Jiang et al., 2015), nasopharyngeal carcinoma (Sun et al., 2015), lung adenocarcinoma (Liu et al., 2016a), and HCC. Hypoxia can suppress lncRNA-LET by decreasing the histone H3 and H4 acetylation levels in its promoter region. Furthermore, downregulation of lncRNA-LET may affect the accumulation and stability of HIF-1α mRNA under hypoxic conditions. It is worth noting that the transcript levels of the endogenous hypoxia marker CA9 are inversely correlated with the levels of lncRNA-LET in primary HCC tissues, and downregulated expression of lncRNA-LET is associated with HCC metastasis (Olive et al., 2001; Yang et al., 2013). The High Expression in HCC lncRNA (termed lncRNA-HEIH) is an oncogenic lncRNA with a high expression in hepatocellular carcinoma. This lncRNA facilitates tumor growth through enhancing Zeste Homolog 2 in humans and may act as a critical regulatory factor in HCC progression (Yang et al., 2011). P73 antisense RNA 1 T (TP73-AS1) is located at 1p36 on the human chromosome and is associated with cell proliferation and tumor progression (Zang et al., 2016). Previous studies have shown that TP73-AS1 might be upregulated in HCC. TP73-AS1 modulates HCC cell proliferation by miR-200a-dependent HMGB1/RAGE regulation. TP73-AS1 might compete with HMGB1 for miR-200a binding to inhibit miR-200a expression. High lncRNA-TP73-AS1 expression in HCC is associated with a poorer prognosis. This lncRNA might play a key role in regulating the proliferation of HCC cells and may be a potential therapeutic target for HCC treatment (Li et al., 2017b).

**CONCLUSIONS**

Hepatocellular carcinoma is one of the most prevalent and aggressive human malignancies. Despite the use of diverse treatment methods, clinical prognosis remains poor. A number of recent studies have focused on the functions of lncRNAs in the initiation and progression of HCC. Nonetheless, our present understanding of lncRNAs is limited. Further investigations are essential to clarify the biological functions and molecular characteristics of lncRNAs in HCC.

**Acknowledgments**

This work was financially supported by grants (95-01-30-31634) from the Deputy of Research, Tehran University of Medical Sciences.

**Conflict of interest**

The authors declare that they have no conflict of interest.
REFERENCES

Attwa MH, El-Etreby SA. Guide for diagnosis and treatment of hepatocellular carcinoma. World J Hepatol. 2015;7:1632-51.

Barsotti AM, Beckerman R, Laptenko O, Huppi K, Caplen NJ, Prives C. p53-Dependent induction of PVT1 and miR-1204. J Biol Chem. 2012;287:2509-19.

Bernard D, Prasanth KV, Tripathi V, Colasse S, Nakamura T, Xuan Z, et al. A long nuclear - retained non-coding RNA regulates synaptogenesis by modulating gene expression. The EMBO J. 2010;29:3082-93.

Berretta J, Morillon A. Pervasive transcription constitutes a new level of eukaryotic genome regulation. EMBO Rep. 1990;10:973-82.

Brannan CI, Dees EC, Ingram RS, Tilghman SM. The product of the H19 gene may function as an RNA. Mol Cell Biol. 1990;10:28-36.

Brockdorff N, Ashworth A, Kay GF, Mcmabe VM, Norris DP, Cooper PJ, et al. The product of the mouse Xist gene is a 15 kb inactive X-specific transcript containing no conserved ORF and located in the nucleus. Cell. 1992;71:515-26.

Cai X, Cullen BR. The imprinted H19 non-coding RNA is a primary microRNA precursor. RNA. 2007;13:313-6.

Chang L, Li C, Lan T, Wu L, Yuan Y, Liu Q, et al. Decreased expression of long non-coding RNA GAS5 indicates a poor prognosis and promotes cell proliferation and invasion in hepatocellular carcinoma by regulating vimentin. Mol Med Rep. 2016;13:1541-50.

Chapman MH, Tidswell R, Dooley JS, Sandanayake NS, Cerec V, Deheragoda M, et al. Whole genome RNA expression profiling of endoscopic biliary brushings provides data suitable for biomarker discovery in cholangiocarcinoma. J Hepatol. 2012;56:877-85.

Chen B, Yu M, Chang Q, Lu Y, Thakur C, Ma D, et al. Mdig de-represses H19 large intergenic non-coding RNA (lincRNA) by down-regulating H3K9me3 and heterochromatin. Oncotarget. 2013;4:1427-37.

Cocchia EM, Cicala C, Charlesworth A, Ciccarelli C, Rossi G, Philipson L, et al. Regulation and expression of a growth arrest-specific gene (gas5) during growth, differentiation, and development. Mol Cell Biol. 1992;12:3514-21.

Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long non-coding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 2012;22:1775-89.

DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64:252-71.

Dinger ME, Pang KC, Mercer T, Mattick JS. Differentiating protein-coding and non-coding RNA: challenges and ambiguities. PLoS Comput Biol. 2008;4: e1000176.

Du M, Wang W, Jin H, Wang Q, Ge Y, Lu J, et al. The association analysis of IncRNA HOTAIR genetic variants and gastric cancer risk in a Chinese population. Oncotarget. 2015;6:31255-62.

ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012;489(7414):57-74.

Fukahori S, Yano H, Tsuneoka M, Tanaka Y, Yagi M, Kuswano M, et al. Immunohistochemical expressions of Cap43 and Mina53 proteins in neuroblastoma. J Pediatr Surg. 2007;42:1831-40.

Gao JZ, Li J, Du JL, Li XL. Long non-coding RNA HOTAIR is a marker for hepatocellular carcinoma progression and tumor recurrence. Oncol Lett. 2016;11:1791-8.

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;39:2119-28.

Guffanti A, Iacono M, Pelucchi P, Kim N, Soldá G, Croft LJ, et al. A transcriptional sketch of a primary human breast cancer by 454 deep sequencing. BMC Genomics. 2009;10:163.

Guo W, Dong Z, Liu S, Qiao Y, Kuang G, Guo Y, et al. Promoter hypermethylation-mediated downregulation of miR-770 and its host gene MEG3, a long non-coding RNA, in the development of gastric cardia adenocarcinoma. Mol Carcinog. 2017;56:1924-34.

Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;464(7291):1071-6.

Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs. Nature. 2012;482(7385):339-46.
Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22:191-7.

Hashiguchi M, Ueno S, Sakoda M, Iino S, Hiwatashi K, Minami K, et al. Clinical implication of ZEB-1 and E-cadherin expression in hepatocellular carcinoma (HCC). BMC Cancer. 2013;13:572.

He A, Hu R, Chen Z, Liao X, Li J, Wang D, et al. Role of long non-coding RNA UCA1 as a common molecular marker for lymph node metastasis and prognosis in various cancers: a meta-analysis. Oncotarget. 2017a;8:1937-43.

He JH, Han ZP, Liu JM, Zhou JB, Zou MX, Lv YB, et al. Overexpression of long non-coding RNA MEG3 inhibits proliferation of hepatocellular carcinoma Huh7 cells via negative modulation of miRNA-664. J Cell Biochem. 2017b;118:3713-21.

Heng Z-K, Pang C, Yang Y, Duan Q, Zhang J, Liu WC. Serum long non-coding RNA urothelial carcinoma-associated 1: A novel biomarker for diagnosis and prognosis of hepatocellular carcinoma. J Int Med Res. 2018;46:348-56.

Herbst A, Kolligs FT. Wnt signaling as a therapeutic target for cancer. Methods Mol Biol. 2007;361:63-91.

Hou Z, Xu X, Fu X, Tao S, Zhou J, Liu S, et al. HBx-related long non-coding RNA MALAT1 promotes cell metastasis via up-regulating LTBP3 in hepatocellular carcinoma. Am J Cancer Res. 2017;7:845-56.

Hsu I, Tokiwa T, Bennett W, Metcalf R, Welsh J, Sun T, et al. p53 gene mutation and integrated hepatitis B viral DNA sequences in human liver cancer cell lines. Carcinogenesis. 1993;14:987-92.

Hu L, Lau SH, Tzang C-H, Wen J-M, Wang W, Xie D, et al. Association of Vimentin overexpression and hepatocellular carcinoma metastasis. Oncogene. 2004;23:298-302.

Huang JF, Guo YJ, Zhao CX, Yuan SX, Wang Y, Tang GN, et al. Hepatitis B virus X protein (HBx)-related long non-coding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma metastasis by targeting the intermediate filament protein vimentin. Hepatology. 2013;57:1882-92.

Iguchi T, Uchi R, Nambara S, Saito T, Komatsu H, Hirata H, et al. A long non-coding RNA, lncRNA-ATB, is involved in the progression and prognosis of colorectal cancer. Anticancer Res. 2015;35:1385-8.

Ishizaki H, Yano H, Tsuneko M, Ogasawara S, Akiba J, Nishida N, et al. Overexpression of the myc target gene Mina53 in advanced renal cell carcinoma. Pathol Int. 2007;57:672-80.

Ji P, Diederichs S, Wang W, Böing S, Metzger R, Schneider PM, et al. MALAT-1, a novel non-coding RNA, and thymosin [beta] 4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene. 2003;22:8031-41.

Jiang S, Wang H-L, Yang J. Low expression of long non-coding RNA LET inhibits carcinogenesis of cervical cancer. Int J Clin Exp Pathol. 2015;8:806-11.

Jones BK, Levorse JM, Tilghman SM. Igf2 imprinting does not require its own DNA methylation or H19 RNA. Genes Dev. 1998;12:2200-7.

Kamel MM, Mattholi M, Sallam M, Montasser IF, Saad AS, El-Tawdi AH. Investigation of long non-coding RNAs expression profile as potential serum biomarkers in patients with hepatocellular carcinoma. Transl Res. 2016;168:134-45.

Ke L, Xu S-B, Wang J, Jiang X-L, Xu M-Q. High expression of long non-coding RNA ATB indicates a poor prognosis and regulates cell proliferation and metastasis in non-small cell lung cancer. Clin Transl Oncol. 2017;19:599-605.

Keniry A, Oxley D, Monnier P, Kyba M, Dandolo L, Smits G, et al. The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r. Nat Cell Biol. 2012;14:659-65.

Kim K, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene. 2013;32:1616-25.

Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Non-coding RNA Gas5 is a growth arrest and starvation-associated repressor of the glucocorticoid receptor. Sci Signal. 2010;3:ra8.

Kinose Y, Sawada K, Nakamura K, Sawada I, Toda A, Nakatsuka E, et al. The hypoxia-related microRNA miR-199a-3p displays tumor suppressor functions in ovarian carcinoma. Oncotarget. 2015;6:11342-56.

Lai M-C, Yang Z, Zhou L, Zhu Q-Q, Xie H-Y, Zhang F, et al. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. Med Oncol. 2012;29:1810-6.
Lay AJ, Jiang X-M, Kisker O, Flynn E, Underwood A, Condron R, et al. Phosphoglycerate kinase acts in tumour angiogenesis as a disulphide reductase. Nature. 2000;408(6814):869-73.

Lei B, Xu S-P, Liang X-S, Li Y-W, Zhang J-F, Zhang G-Q, et al. Long non-coding RNA MVHI is associated with poor prognosis and malignant biological behavior in breast cancer. Tumor Biol. 2016;37:5257-64.

Li C, Miao R, Liu S, Wan Y, Zhang S, Deng Y, et al. Down-regulation of miR-146b-5p by long non-coding RNA MALAT1 in hepatocellular carcinoma promotes cancer growth and metastasis. Oncotarget. 2017a; 8:28683-95.

Li CH, Chen Y. Targeting long non-coding RNAs in cancers: progress and prospects. Int J Biochem Cell Biol. 2013;45:1895-910.

Li J, Wang X, Tang J, Jiang R, Zhang W, Ji J, et al. HULC and Linc00152 act as novel biomarkers in predicting diagnosis of hepatocellular carcinoma. Cell Physiol Biochem. 2015;37:687-96.

Li S-P, Xu H-X, Yu Y, He J-D, Wang Z, Xu Y-J, et al. LncRNA HULC enhances epithelial-mesenchymal transition to promote tumorigenesis and metastasis of hepatocellular carcinoma via the miR-200a-3p/ZEB1 signaling pathway. Oncotarget. 2016a; 7:42431-46.

Li CH, Chen Y. Targeting long non-coding RNAs in cancers: progress and prospects. Int J Biochem Cell Biol. 2013;45:1895-910.

Li J, Wang X, Tang J, Jiang R, Zhang W, Ji J, et al. HULC and Linc00152 act as novel biomarkers in predicting diagnosis of hepatocellular carcinoma. Cell Physiol Biochem. 2015;37:687-96.

Li S, Huang Y, Huang Y, Fu Y, Tang D, Kang R, et al. The long non-coding RNA TP73-AS1 modulates HCC cell proliferation through miR-200a-dependent HMG1/RAGE regulation. J Exp Clin Cancer Res. 2017b;36:51.

Li T, Xie J, Shen C, Cheng D, Shi Y, Wu Z, et al. Up-regulation of long non-coding RNA ZEB1-AS1 promotes tumor metastasis and predicts poor prognosis in hepatocellular carcinoma. Oncogene. 2016b; 35:1575-84.

Li Y, Ren M, Zhao Y, Lu X, Wang M, Hu J, et al. MicroRNA-26a inhibits proliferation and metastasis of human hepatocellular carcinoma by regulating DNM13B-MEG3 axis. Oncol Rep. 2017c;37:3527-35.

Li Y, Ye Y, Chen H. Astragaloside IV inhibits cell migration and viability of hepatocellular carcinoma cells via suppressing long non-coding RNA ATB. Biomed Pharmacother. 2018;99:134-41.

Li Z, Li X, Wu S, Xue M, Chen W. Long non-coding RNA UCA1 promotes glycolysis by upregulating hexokinase 2 through the mTOR-STAT3/microRNA143 pathway. Cancer Sci. 2014;105:951-5.

Li Z, Wu X, Gu L, Shen Q, Luo W, Deng C, et al. Long non-coding RNA ATB promotes malignancy of esophageal squamous cell carcinoma by regulating miR-200b/Kindlin-2 axis. Cell Death Dis. 2017d;8:e2888.

Liao Y, Tang Z-Y, Liu K-D, Ye S-L, Huang Z. Apoptosis of human BEL-7402 hepatocellular carcinoma cells released by antisense H-ras DNA-in vitro and in vivo studies. J Cancer Res Clin Oncol. 1997;123:25-33.

Liu B, Pan C-F, He Z-C, Wang J, Wang P-L, Ma T, et al. Long non-coding RNA-LET suppresses tumor growth and EMT in lung adenocarcinoma. Biomed Res Int. 2016;2016: 4693471.

Liu D, Zhu Y, Pang J, Weng X, Feng X, Guo Y. Knockdown of long non-coding RNA MALAT1 inhibits growth and motility of human hepatoma cells via modulation of miR-195. J Cell Biochem. 2018;119:1368-80.

Liu X, Zhang Y, Wang P, Wang H, Su H, Zhou X, et al. HBX protein-induced downregulation of microRNA-18a is responsible for upregulation of connective tissue growth factor in HBV infection-associated hepatocarcinoma. Med Sci Monit. 2016; 22:2492-500.

Loewen G, Jayawickramarajah J, Zhuo Y, Shan B. Functions of IncRNA HOTAIR in lung cancer. J Hematol Oncol. 2014;7:90.

Lu Y, Beezhold K, Chang Q, Zhang Y, Rojanasakul Y, Zhao H, et al. Lung cancer-associated JmJc domain protein mdig suppresses formation of tri-methyl lysine 9 of histone H3. Cell Cycle. 2009;8:2101-9.

Lv X-B, Lian G-Y, Wang H-R, Song E, Yao H, Wang M-H. Long non-coding RNA HOTAIR is a prognostic marker for esophageal squamous cell carcinoma progression and survival. PLoS ONE. 2013;8:e63516.

Ma C, Nong K, Zhu H, Wang W, Huang X, Yuan Z, et al. H19 promotes pancreatic cancer metastasis by derepressing let-7’s suppression on its target HMG2-mediated EMT. Tumor Biol. 2014;35:9163-9.

Marahrens Y, Loring J, Jaenisch R. Role of the Xist gene in X chromosome choosing. Cell. 1998;92:657-64.

Matouk IJ, Degroot N, Mezan S, Ayesh S, Abu-Lail R, Hochberg A, et al. The H19 non-coding RNA is essential for human tumor growth. PLoS ONE. 2007;2:e845.

Matouk IJ, Abbasi I, Hochberg A, Galun E, Dweik H, Akkawi M. Highly upregulated in liver cancer non-coding RNA is overexpressed in hepatic colorectal metastasis. Eur J Gastroenterol Hepatol. 2009;21:688-92.
Miyoshi N, Wagatsuma H, Wakana S, Shiroishi T, Nomura M, Aisaka K, et al. Identification of an imprinted gene, Meg3/Gtl2 and its human homologue MEG3, first mapped on mouse distal chromosome 12 and human chromosome 14q. Genes Cells. 2000;5:211-20.

Ni B, Yu X, Guo X, Fan X, Yang Z, Wu P, et al. Increased urothelial cancer associated 1 is associated with tumor proliferation and metastasis and predicts poor prognosis in colorectal cancer. Int J Oncol. 2015;47:1329-38.

Ni W, Zhang Y, Zhan Z, Ye F, Liang Y, Huang J, et al. A novel IncRNA uc. 134 represses hepatocellular carcinoma progression by inhibiting CUL4A-mediated ubiquitination of LATS1. J Hematol Oncol. 2017;10(1):91.

Ogasawara S, Komuta M, Nakashima O, Akiba J, Tsuneoka M, Yano H. Accelerated expression of a Myc target gene Mina53 in aggressive hepatocellular carcinoma. Hepatol Res. 2010;40:330-6.

Okuda K. Epidemiology of primary liver cancer. In: Tobe T, Kameda H, Okudaira M, Ohto M, Endo Y, Mito M, et al. (eds). Primary liver cancer in Japan (pp 3-15). Tokyo: Springer, 1992.

Olive PL, Aquino-Parsons C, Macphail SH, Liao S-Y, Raleigh JA, Lerman MI, et al. Carbonic anhydrase 9 as an endogenous marker for hypoxic cells in cervical cancer. Cancer Res. 2001;61:8924-9.

Panzitt K, Tschernatsch MM, Guelly C, Moustafa T, Stradner M, Strohmaier HM, et al. Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as non-coding RNA. Gastroenterology. 2007;132:330-42.

Peng W, Si S, Zhang Q, Li C, Zhao F, Wang F, 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.

Ponjavic J, Oliver PL, Lunter G, Ponting CP. Genomic and transcriptional co-localization of protein-coding and long non-coding RNA pairs in the developing brain. PLoS Genet. 2009;5:e1000617.

Qiu X, Dong S, Qiao F, Lu S, Song Y, Lao Y, et al. HBx-mediated miR-21 upregulation represses tumor-suppressor function of PDCD4 in hepatocellular carcinoma. Oncogene. 2013;32:3296-305.

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

Shi Y, Song Q, Yu S, Hu D, Zhuang X. Microvascular invasion in hepatocellular carcinoma overexpression promotes cell proliferation and inhibits cell apoptosis of hepatocellular carcinoma via inhibiting miR-199a expression. Onco Targets Ther. 2015;8:2303-10.

Sun M, Liu X, Lu K, Nie F, Xia R, Kong R, et al. EZH2-mediated epigenetic suppression of long non-coding RNA SPRY4-IT1 promotes NSCLC cell proliferation and metastasis by affecting the epithelial–mesenchymal transition. Cell Death Dis. 2014;5: e1298.

Sun Q, Liu H, Li L, Zhang S, Liu K, Liu Y, et al. Long non-coding RNA-LET, which is repressed by EZH2, inhibits cell proliferation and induces apoptosis of nasopharyngeal carcinoma cell. Med Oncol. 2015;32(9):226.

Teye K, Arima N, Nakamura Y, Sakamoto K, Sueoka E, Kimura H, et al. Expression of Myc target gene mina53 in subtypes of human lymphoma. Oncol Rep. 2007;18:841-8.

Tian Y, Zhang Y-Z, Chen W. MicroRNA-199a-3p and microRNA-34a regulate apoptosis in human osteosarcoma cells. Biosci Rep. 2014;34:e00132.

Trevisani F, D'intino PE, Grazi GL, Caraceni P, Gasbarrini A, Colantonio A, et al. Clinical and pathologic features of hepatocellular carcinoma in young and older Italian patients. Cancer. 1996;77:2223-32.

Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, et al. The nuclear-retained non-coding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell. 2010;39:925-38.

Tsuneoka M, Fujita H, Arima N, Teye K, Okamura T, Inutsuka H, et al. Mina53 as a potential prognostic factor for esophageal squamous cell carcinoma. Clin Cancer Res. 2004;10:7347-56.

Tu Z-Q, Li R-J, Mei J-Z, Li X-H. Down-regulation of long non-coding RNA GAS5 is associated with the prognosis of hepatocellular carcinoma. Int J Clin Exp Pathol. 2014;7:4303-9.

Velázquez RF, Rodriguez M, Navascués CA, Linares A, Pérez R, Sotomrios NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology. 2003;37:520-7.
Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature. 2000;408(6810):307-10.

Wang F, Yuan JH, Wang SB, Yang F, Yuan SX, Ye C, et al. Oncofetal long non-coding RNA PVT1 promotes proliferation and stem cell-like property of hepatocellular carcinoma cells by stabilizing NOP2. Hepatology. 2014a;60:1278-90.

Wang F, Ying H-Q, He B-S, Pan Y-Q, Deng Q-W, Su H-L, et al. Upregulated IncRNA-UCA1 contributes to progression of hepatocellular carcinoma through inhibition of miR-216b and activation of FGFR1/ERK signaling pathway. Oncotarget. 2015a;6:7899-917.

Wang H-M, Lu J-H, Chen W-Y, Gu A-Q. Upregulated lncRNA-UCA1 contributes to progression of lung cancer and is closely related to clinical diagnosis as a predictive biomarker in plasma. Int J Clin Exp Med. 2015b;8:11824-30.

Wang J, Liu X, Wu H, Ni P, Gu Z, Qiao Y, et al. CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer. Nucleic Acids Res. 2010;38:5366-83.

Wang S-H, Zhou J-D, He Q-Y, Yin Z-Q, Cao K, Luo C-Q. MiR-199a inhibits the ability of proliferation and migration by regulating CD44-Ezrin signaling in cutaneous squamous cell carcinoma cells. Int J Clin Exp Pathol. 2014b;7:7131-41.

Wang Y, Jing W, Ma W, Liang C, Chai H, Tu J. Down-regulation of long non-coding RNA GASS-AS1 and its prognostic and diagnostic significance in hepatocellular carcinoma. Cancer Biomark. 2018;22:227-36.

Wang Z, Xiang Q, Li D, Li S. Correlation between gene expression and chromatin conformation of c-fos and N-ras in human liver and hepatoma. Chin Med Sci J. 1991;6(1):6-8.

Warden CD, Kim S-H, Soojin VY. Predicted functional RNAs within coding regions constrain evolutionary rates of yeast proteins. PLoS ONE. 2008;3:e1559.

Wormald S, Hilton DJ. Inhibitors of cytokine signal transduction. J Biol Chem. 2004;279:821-4.

Wu L, Zhang L, Zheng S. Role of the long non-coding RNA HOTAIR in hepatocellular carcinoma. Oncol Lett. 2017;14:1233-9.

Wu Y, Xiong Q, Li S, Yang X, Ge F. Integrated proteomic and transcriptomic analysis reveals long non-coding RNA HOTAIR promotes hepatocellular carcinoma cell proliferation by regulating opioid growth factor receptor (OGFr). Mol Cell Proteom. 2018;17:146-59.

Yang T, He X, Chen A, Tan K, Du X. LncRNA HOTAIR contributes to the malignancy of hepatocellular carcinoma by enhancing epithelial-mesenchymal transition via sponging miR-23b-3p from ZEB1. Gene. 2018;670:114-22.

Yuan K, Lian Z, Sun B, Clayton MM, Ng IO, Feitelson MA. Role of miR-148a in hepatitis B associated hepatocellular carcinoma. PLoS ONE. 2012a;7:e35331.
Yuan SX, Yang F, Yang Y, Tao QF, Zhang J, Huang G, et al. Long non-coding 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. 2012b;56:2231-41.

Zang W, Wang T, Wang Y, Chen X, Du Y, Sun Q, et al. Knockdown of long non-coding RNA TP73-AS1 inhibits cell proliferation and induces apoptosis in esophageal squamous cell carcinoma. Oncotarget. 2016;7:19960-74.

Zhang K, Luo Z, Zhang Y, Zhang L, Wu L, Liu L, et al. Circulating lncRNA H19 in plasma as a novel biomarker for breast cancer. Cancer Biomark. 2016;17:187-94.

Zhang L, Yang F, Yuan J-H, Yuan S-X, Zhou W-P, Huo X-S, et al. Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. Carcinogenesis. 2012;34:577-86.

Zhang Y, Lu Y, Bao-Zhu Y, Castranova V, Shi X, Stauffer JL, et al. The human mineral dust-induced gene, mdig, is a cell growth regulating gene associated with lung cancer. Oncogene. 2005;24:4873-82.

Zhou Y, Zhong Y, Wang Y, Zhang X, Batista DL, Gejman R, et al. Activation of p53 by MEG3 non-coding RNA. J Biol Chem. 2007;282:24731-42.