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**Long noncoding RNAs in hepatitis B viral replication and oncogenesis**

LncRNAs in HBV replication and oncogenesis

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## Abstract

Several diverse long noncoding RNAs (lncRNAs) have been identified to be involved in hepatitis B viral (HBV) replication and oncogenesis, especially those dysregulated in HBV-related hepatocellular carcinoma (HCC). Most of these dysregulated lncRNAs are modulated by the HBV X protein (HBx). The regulatory mechanisms of some lncRNAs in HBV replication and oncogenesis have been characterized. Genetic polymorphisms of several lncRNAs affecting HBV replication or oncogenesis have also been studied. The prognosis of HCC remains poor. It is important to identify novel tumor markers for early diagnosis and find more therapeutic targets for effective treatments of HCC. Some dysregulated lncRNAs in HBV-related HCC may become biomarkers for early diagnosis and/or the therapeutic targets of HCC. This mini-review summarizes these findings briefly, focusing on recent developments.

**Key Words:** Hepatitis B virus; hepatocellular carcinoma; long non-coding RNAs; HBx; biomarker

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**Core Tip:** The prognosis of hepatocellular carcinoma (HCC) remains poor. It is important to identify novel tumor markers for early diagnosis and find more therapeutic targets for effective treatments of HCC. Several diverse long noncoding RNAs (lncRNAs) have been identified to be involved in HBV-related HCC. <sup>4</sup> A better understanding of the molecular mechanisms underlying lncRNA-mediated hepatocarcinogenesis may help for their use in early diagnosis and to identify appropriate targets for the prevention and treatment of HBV-related HCC.

## INTRODUCTION

Majority of the human genome (70–90%) is actively transcribed. Only approximately 2% of these transcribed RNAs translate into proteins, while more than 90% of them are noncoding RNAs (ncRNAs). Based on size, ncRNAs are classified into small ncRNAs (less than 200 nucleotides (nt)) and long noncoding RNAs (lncRNAs, more than 200 nt). Several kinds of small ncRNAs have been characterized, including transfer-, ribo-, small nucleolar-, piwi -and micro-RNAs (miRNAs). It is well known that miRNAs (generally 22–25 nt) can regulate gene expression by suppressing protein translation or by mRNA degradation through interacting with their target mRNA sequences, usually at the 3'-untranslated regions (3'UTR). Various miRNAs have been found to be dysregulated and play important roles in hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) progression [1].

Long ncRNAs (lncRNAs) are mostly transcribed by RNA polymerase II, sometimes polyadenylated and located in nuclear and/or cytosolic fractions. LncRNAs are divided into intergenic, intronic, bidirectional, sense, and antisense lncRNAs based on their genomic location and strand orientation. These lncRNAs may function as signals, decoys, guides, or scaffolds to regulate the expression of their target genes through interacting with their partner molecules [2]. In this way, lncRNAs can modulate gene expression at different levels, including epigenetic silencing, transcriptional control, post-transcriptional regulation, and protein stability modulation [2]. Thus, they are involved in many biological processes such as cell proliferation, invasion and metastasis, autophagy, and apoptosis. Indeed, dysregulation of lncRNAs has now been implicated in numerous human diseases, especially cancers, *e.g.*, HCC [2].

Liver cancer was the sixth most common cancer and the third leading cause of cancer death in the world in 2020 (<https://gco.iarc.fr/today/home>). HCC represents approximately 90% of all cases of primary liver cancer. The leading cause of HCC is persistent HBV infection, which occurs in more than half of the HCC cases [3]. The management of HBV-related HCC has improved in the past decade. However, the outcome of HCC is still poor. Understanding more regarding the underlying mechanism of HBV-related HCC is required for improving the prevention, diagnosis,

and treatment of HCC. The roles of lncRNAs in HBV-related HCC have received much more attention lately.

In this mini-review, we briefly outline the involvement of lncRNAs in HBV replication. We summarize the findings of dysregulated lncRNAs in HBV-related diseases, especially HCC, and discuss their roles and the potential clinical applications as diagnostic or therapeutic targets for HCC.

### **lncRNAs in hepatitis B viral replication**

HBV, belonging to the *Hepadnaviridae* family, is a small enveloped DNA virus. Ten HBV genotypes (A–J), which are based on eight percent or more sequence divergence across the viral genome, have been identified [4]. Even with the genotype differences, HBVs share the same pattern of replication cycle in the cells [5]. HBV infection begins with the attachment of virions to the surface proteoglycans on hepatocytes, followed by high affinity binding with more specific receptors (e.g., sodium taurocholate cotransporting polypeptide; NTCP) [6]. After entry into the cell, the viral compact, partially double-stranded genome (i.e., relaxed circular DNA (rcDNA)) will form the stable covalently closed circular DNA (cccDNA) by viral and host factors [7]. Then, the viral RNAs (including sub-genomic mRNAs and pre-genomic RNA (pgRNA)) are transcribed from cccDNA using the cellular transcriptional machinery. The pgRNAs and the viral polymerase proteins (HBpAg) will be encapsidated by HBV core proteins (HBcAg). The newly formed nucleocapsids containing partially double-stranded HBV DNA made from pgRNA by HBpAg then either re-enter the nucleus to produce more cccDNA or release as mature virions following the assembly with HBV surface proteins (HBsAg) [5].

The 3.2 kilobases (kb) HBV genome contains four open reading frames (ORFs): surface (S), precore (pre-C)/core (C), polymerase (P), and X. The S ORF encodes three viral envelope proteins initiated from different start codons: large, middle, and small surface antigens (HBsAg). HBV e antigen (HBeAg) and core antigen (HBcAg) are

encoded in the pre-C/C ORF [5]. The P ORF encodes viral polymerase (HBpAg) possessing reverse transcriptase, RNase H, and DNA polymerase activities. HBV X protein (HBxAg, HBx) derived from X ORF can transactivate the expression of both cellular and viral genes required for viral replication [5].

Nearly 257 million people worldwide have been infected with HBV, resulting in 887,000 people dying of liver cirrhosis or HCC annually. Therefore, identification of new therapeutic targets against HBV is urgently needed. LncRNAs could be potential targets as a growing number of them have been found to play a role in HBV replication [8] (Figure 1).

### **LncRNAs facilitating hepatitis B viral replication**

LncRNA DLEU2 (deleted in lymphocytic leukemia 2). HBx was found to bind the DLEU2 promoter to enhance its transcription. Nuclear DLEU2 could directly bind to HBx or the histone methyltransferase enhancer of zeste homolog 2 (EZH2). The interaction of HBx and DLEU2 on the viral cccDNA displaces EZH2 from the viral chromatin to boost viral transcription and replication [9].

HOTAIR (HOX Transcript Antisense RNA). HOTAIR was significantly upregulated in HBV-infected cells. HOTAIR promoted HBV transcription and replication by elevating the activities of HBV promoters *via* modulation of the levels of cccDNA-bound SP1 [10].

LncRNA PCNAP1 (proliferating cell nuclear antigen pseudogene 1). The expression levels of PCNAP1 and PCNA (proliferating cell nuclear antigen) were significantly elevated in the livers of HBV cccDNA-positive HCC patients. PCNA could interact with HBV cccDNA in a HBc-dependent manner. PCNAP1 enhanced PCNA through sponging miR-154, which targets the 3'UTR of PCNA mRNA. Moreover, PCNAP1 or PCNA enhanced HBV replication significantly both *in vitro* and *in vivo*. Thus, lncRNA PCNAP1 enhances HBV replication through the miR-154/PCNA/HBV cccDNA axis [11].

LncRNA HULC (highly upregulated in liver cancer). The HULC gene is located on chromosome 6p24.3 and contains two exons and one intron. HULC is an lncRNA of



around 500 nt mainly localized in the cytoplasm. <sup>29</sup> HULC was found to elevate HBx, which coactivated STAT3 to stimulate the miR-539 promoter. Elevated miR-539, which targets the 3'UTR of APOBEC3B mRNA, downregulated APOBEC3B and promoted HBV replication. Thus, HULC activates HBV through the HBx/ STAT3/miR-539/APOBEC3B axis <sup>[12]</sup>. Another study demonstrated that lncRNA HULC enhanced HBV replication through the HAT1/HULC/HBc complex responsible for the accumulation on cccDNA minichromosome <sup>[13]</sup>. Moreover, the HULC genetic variant rs7763881 is associated with HBV infection <sup>[14]</sup>.

<sup>11</sup> LncRNA ZNRD1-AS1 (ZNRD1 antisense RNA 1). A zinc ribbon domain containing 1 (ZNRD1), cloned from the human leukocyte antigen (HLA) region, should play an important role in immune response against HBV infection. ZNRD1-AS1 is an important regulator of ZNRD1. The variant allele of ZNRD1-AS1 (rs3757328) was reported to be associated with HBV clearance <sup>[15]</sup>.

<sup>6</sup> LncRNA HBx-LINE1 (HBx-long interspersed nuclear element 1). HBx-LINE1 suppresses miR-122 <sup>[16]</sup>, a miRNA that has been demonstrated to inhibit HBV replication by directly targeting the HBV pgRNA sequence <sup>[17]</sup>. Thus, by depleting miR-122, HBx-LINE1 enhances HBV replication.

LncRNA AP000253. AP000253 was found to promote HBV transcription and replication in hepatoma cells <sup>[18]</sup>. <sup>32</sup> However, the AP000253 expression in liver tissues and the molecular mechanism of its involvement in HBV infection are not clear yet.

### **LncRNAs suppressing hepatitis B viral replication**

<sup>35</sup> LncRNA HOTTIP (HOXA transcript at the distal tip). HOTTIP is a 3,764 nt transcript mapped to the HOXA locus. HOTTIP was found to be induced by HBV in vitro. Further studies demonstrated that HBpAg could bind to and stabilize CREB1 mRNA to facilitate its translation. Then, the CREB1 protein would bind to the regulatory element of HOTTIP to promote its expression. HOTTIP significantly suppresses HBV replication through its downstream factor HOXA13, which <sup>19</sup> was found to bind to HBV Enh I/Xp to reduce the production of pgRNA as well as HBV replication. Thus, HBpAg attenuates HBV replication *via* activation of the

CREB1/HOTTIP/HOXA13 axis. In this way, lncRNA HOTTIP could restrain HBV replication and contribute to viral persistent infection [19].

#### **Other lncRNAs involved in hepatitis B viral replication**

H11, a novel inhibitor of La protein, suppressed HBV replication by blocking the interaction between La protein and HBV RNA. Further studies have shown that 61 lncRNAs were upregulated and 74 lncRNAs were downregulated in an H11 treatment group when compared with the control group [20]. These lncRNAs should affect HBV replication though further verification is required.

The importance of lncRNAs in HBV replication has started to emerge. However, many unidentified lncRNAs critical for HBV replication should exist, such as those regulated by HBx (mentioned in the following sections). HBx is required for transcription from the viral cccDNA minichromosome. Thus, HBx modulates HBV replication. The lncRNAs affected by HBx may modulate HBV replication. The roles of these lncRNAs in HBV replication require further investigation.

#### **lncRNAs in HBV-related immune responses**

The roles of lncRNAs in the host immune system during HBV infection have just started to emerge (Figure 2). lncRNA ENST00000519726 (lncRNA-HEIM) was highly expressed in monocytes and was further upregulated upon HBV infection. Elevated lncRNA-HEIM expression was remarkably correlated with the TGF- $\beta$  signaling



pathway. Furthermore, altering the endogenous lncRNA-HEIM amount in monocytes significantly affected TGF- $\beta$  production [21].

LncRNA FTX downregulates the expression of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and NF- $\kappa$ B but upregulates the expression of Tim-3. This result demonstrated the effect of FTX on the expression of inflammatory cytokines through FTX-miR-545-Tim<sup>3</sup> axis [22].

High lncRNA-CD160 expression level can inhibit IFN- $\gamma$  and TNF- $\alpha$  secretion in CD8<sup>+</sup> T cells and decrease the immune response of CD8<sup>+</sup> T cells. LncRNA-CD160 can interact with HDAC11 (histone-modification enzyme gene histone deacetylase 11) to form a complex on the promoters of IFN- $\gamma$  and TNF- $\alpha$  to inhibit their expression. Thus, lncRNA-CD160 acts as an immune suppressor. Indeed, knockdown of lncRNA-CD160 can block HBV infection [23].

Lnc-DC is a specific group of lncRNAs in dendritic cells. Lnc-DC could be activated by HBV infection. In addition, Lnc-DC is important in regulating the growth, apoptosis, and immune response of dendritic cells mediated by TLR9/STAT3 signaling. Moreover, the regulation of Lnc-DC controlled the immune response by reduction in secreted TNF- $\alpha$ , IL-6, IL-12, and IFN- $\gamma$ , while increasing the IL-1 $\beta$  concentration in dendritic cells [24].

LncRNA#32 could positively regulate IFN-stimulated gene expression by interacting with activating transcription factor 2 (ATF2). Indeed, depletion of lncRNA#32 resulted in a significant increase in the replication of several viruses, including HBV. Thus, lncRNA#32 plays a role in host antiviral responses [25].

The role of lncRNAs in the HBV-related immune responses remains unclear. There should be many unidentified lncRNAs important for HBV-related immune responses, such as those involved in HBV-related HCC.

### LncRNAs in HBV-related chronic diseases

Progression of liver disease from chronic HBV infection to HCC may include several stages [26], such as fibrosis and cirrhosis (Figure 2). The roles of lncRNAs in these HBV-related chronic diseases are largely unknown.

Transforming growth factor- $\beta$  (TGF- $\beta$ ) plays an important role in various pathogenic processes, from inflammation, fibrosis, and cirrhosis to cancer. LncRNA-ATB, which is activated by TGF- $\beta$ , is a key regulator of the TGF- $\beta$  signaling pathway. The plasma levels of lncRNA-ATB in HBV-related cirrhosis patients were significantly higher than those in healthy controls [27].

Serum lincRNA-p21 Levels in CHB patients, those with hepatitis B cirrhosis, and HBV-related HCC, were higher than those in the control subjects. LincRNA-p21 Level was negatively correlated with levels of HBV DNA, ALT, and AST in patients with liver diseases. Thus, serum lincRNA-p21 may serve as a potential biomarker for liver cell damage in patients with hepatitis virus infection, hepatitis B cirrhosis, and HBV-related HCC [28].

Compared with that in healthy controls, HBV carriers, and CHB patients, the expression of lnc-TCL6 was obviously upregulated in Child-Pugh A patients with liver cirrhosis. Thus, lnc-TCL6 was identified as a sensitive biomarker for early diagnosis of liver cirrhosis (Child-Pugh A) [29].

LncRNA MALAT1 (metastasis associated in lung adenocarcinoma transcript 1) expression in CHB group was significantly upregulated compared to the control group. Moreover, the thioredoxin interacting protein (TXNIP) was also significantly upregulated in the CHB group. Further studies indicate that the MALAT1/hsa-miR-20b-5p/TXNIP axis may mediate CHB-induced inflammatory damage in chronic HBV infection complicated with non-alcoholic fatty liver disease [30].

LncRNA-MEG3 (maternally expressed gene-3) was reported to be significantly downregulated in human HCC cell lines possibly due to the MEG3 promoter being hyper-methylated. Further studies indicated that the serum level of lncRNA-MEG3 was lower in CHB patients, which is negatively correlated to the liver fibrotic degree. In

vitro experiments verified those results. Thus, LncRNA-MEG3 may serve as a diagnostic biomarker for CHB [31].

LncRNA GAS5 (long noncoding RNA-growth arrest specific transcript 5) is significantly downregulated in CHB patients due to its promoter methylation. Compared with the sera of healthy controls, lower GAS5 Levels were detected in the sera of CHB patients. Thus, LncRNA GAS5 is also reported as a biomarker for liver fibrosis in CHB patients [32].

CHB patients might progress to acute-on-chronic liver failure (ACLF) with a high fatality rate. Four lncRNAs (RP11-25K21.6, THRB, RAB27A, and GNPTAB) were found to be differentially expressed between the ACLF and the control groups. Aberrant lncRNAs might be used to develop novel diagnostic biomarkers and/or therapeutic targets for ACLF [33].

The role of lncRNAs in the HBV-related chronic diseases is not clear yet. Those lncRNAs involved in HBV-related HCC (mentioned in the following section) may also play roles in HBV-related chronic diseases. This requires further investigation.

### **LncRNAs dysregulated in HBV-related HCC**

HCC was the sixth most common cancer in world in 2020. Risk factors of HCC include external stimuli such as HBV or hepatitis C virus (HCV) infection, intake of aflatoxin B1, alcohol consumption, smoking, and host factors such as age, gender, genetics, and comorbidities. Globally, approximately 2 billion people have been infected with HBV. Among them, more than 350 million people are chronic HBV carriers. Chronic HBV infection has been implicated in HCC development. In fact, persistent HBV infection occurs in more than half of HCC, particularly in developing countries. Comparing with other solid malignancies, HCC is characterized by its highly invasive and metastatic potential. Indeed, HCC is the third leading cause of cancer death in world. This is in part due to the fact that patients may not exhibit symptoms at early stages of HCC [34]. Therefore, comprehensive approaches are warranted to identify

5 novel tumor markers and find more effective therapeutic targets to improve the diagnosis and treatment of HCC [8]. In recent years the idea has emerged that regulatory noncoding RNAs, such as miRNAs and lncRNAs, should play regulatory roles in cancers such as HCC [1]. Specifically, various lncRNAs were reported to regulate the expression of tumor suppressor genes or oncogenes involved in cancer development [2].

HCC caused by HBV infection is related to different HBV genotypes, the mutation status of viral genomes, integration of viral DNAs, and the dysregulation of signaling pathways affected by HBV. However, the detailed mechanisms of HBV-related HCC remain to be determined. The development of the majority of HBV-related HCCs is associated with (1) chronic inflammation, (2) insertion of viral sequences into the cellular chromosomes, (3) transactivation of growth regulatory genes by HBx, and (4) altered versions of the preS/S envelope proteins [35]. If the host immune system fails to clear HBV, the infection will become chronic. Then, HBV DNA may integrate into the cellular chromosome. Indeed, integrated viral DNA is found in 85%–90% of HBV-related HCCs. Insertion of the HBV DNA occurs preferentially at certain sites in the host genome, including repetitive elements such as long interspersed nuclear elements (LINEs) and Alu repeats [36]. The HBx gene is the smallest ORF encoding a 154-amino acid regulatory protein. HBx is reported to contribute to the pathogenesis of HCC by trans-modulating many growth regulatory genes and activating various signaling pathways, including p53, NF- $\kappa$ B, and Wnt signaling. Diverse lncRNAs involved in the events of viral immune responses, viral integration, and HBx regulatory activities should play roles in HBV-related HCC [37]. Studies on lncRNAs which are differentially expressed in HBV-HCC tissue samples may elucidate oncogenic pathways and identify novel diagnostic and therapeutic targets [8]. When compared to normal and/or non-HBV HCC samples, hundreds of dysregulated lncRNAs in HBV-related HCC tissues have been detected [38–40]. It is also reported that HBx could alter the expression of 2002 lncRNA [41]. In this mini-review, the better characterized lncRNAs in HBV-related HCC will be discussed.

#### Upregulated lncRNAs in HBV-related HCC (Table 1)



## 1. HULC

HULC was the first lncRNA reported to be specifically upregulated in HCC through microarray analysis and qRT-PCR. By interacting with cAMP-responsive element-binding protein (CREB), HBx up-regulates the HULC expression in hepatoma cell lines and HBV-related HCC tissues. HULC downregulates the expression of p18, a tumor suppressor gene close to HULC, and thus promotes the proliferation of hepatoma cells [42]. Moreover, HULC can act as a molecular sponge for miR-107. By sponging miR-107, HULC upregulates E2F1 and then activates SPHK1 transcription in hepatoma cell lines and HBV-related HCC tissues. Thus, HULC promotes tumor angiogenesis through miR-107/E2F1/SPHK1 signaling [43]. Altogether, these studies indicate that HULC serves as an oncogene important for HBV-related HCC. HULC is also demonstrated to act as an endogenous 'sponge' for various other miRNAs (e.g., miR-372, miR-186, miR-488, miR-200a-5p, miR-6825-5p, miR-6845-5p, and miR-6886-3p) in hepatoma cell lines and HCC tissues [44]. Those findings provide new insights into the mechanism of HULC in the HCC development.

## 2. HOTAIR (Hox transcript antisense intergenic RNA)

The HOTAIR gene is on chromosome 12. LncRNA HOTAIR is a 2,158 nt transcript derived from the HOTAIR gene. HOTAIR is involved in the occurrence of HBV-related HCC. HBV replication and, in particular, HBx production, stimulates expression of HOTAIR and Plk1. The combination of Plk1 and HOTAIR are involved in epigenetic reprogramming associated with oncogenic transformation [45]. In vitro studies have demonstrated that HOTAIR has sequence-specific effects and interacts with various chromatin modifying proteins, e.g., Polycomb repressive complex 2 (PRC2) [46]. Another study showed that HOTAIR might mediate hepatocarcinogenesis by down-regulating miR-218 and in-activating P14 and P16 signaling [47]. These findings suggest that lncRNA HOTAIR should play an important role in hepatocarcinogenesis.

## 3. HEIH (High Expression In HCC)

The HEIH gene is on chromosome 5. LncRNA HEIH is a polyadenylated, approximately 1,600 nt in length, lncRNA, whose expression is strongly linked to HBV-

associated HCC. It is located both in the nucleus and cytoplasm. HEIH could promote cell proliferation by upregulating PCNA and decreasing the expression of p16, p21, and p27 in cells. Moreover, HEIH could promote tumor growth in nude mice. Mechanistically, HEIH is physiologically associated with EZH2 (enhancer of zeste homolog 2), the catalytic subunit of the polycomb repressive complex 2 (PRC2). The association of HEIH with EZH2 is needed to repress the EZH2 target genes [48]. These studies demonstrate that HEIH contributes to HBV-related HCC through the participation of epigenetic silencing.

#### 4. HBx-LINE1

Almost all HBV-related HCC tumors (85–90%) have at least one HBV insertion site in the host genome. Thus, integration of HBV DNA should be important for the HCC development. LINEs appear to be a favored site for HBV DNA integration. To investigate the effect of HBV integration on genome disruption, HBx-LINE1, a viral-human chimeric fusion transcript derived from viral sequences containing HBx and cellular LINEs, was found functioning as a lncRNA. HBx-LINE1 was detected in 23.3% of HBV-related HCC patients [49, 50]. HBx-LINE1, on chromosome 8p11.21, was transcribed from the HBx promoter. HBx-LINE1 contains six miR-122-binding sites and serves as a molecular sponge to sequester cellular miR-122. By downregulating miR-122, HBx-LINE1 activates the  $\beta$ -catenin signaling pathway, and in turn enhances HCC cell proliferation, invasion, and migration [16]. However, these findings were not consistent with those from other studies [51]. More studies with a larger sample size should help further clarify the role of HBx-LINE1 in the HBV-related HCC.

#### 5. UCA1 (Urothelial carcinoma associated 1)

The UCA1 gene is approximately 7.3 kb in length on chromosome 19p13.12 and contains three exons. It has three transcriptional isoforms. UCA1, around 1,400 nt in length, is the most abundant isoform of the UCA1 gene [52]. UCA1 was originally identified in the bladder cancer cell line and also played an important role in HBV-related HCC. HBx could upregulate UCA1 expression [37, 53]. UCA1, an lncRNA detected in both the cytoplasm and nucleus [53], has diverse functions. In nucleus, UCA1



recruits EZH2 to the p27 promoter, reduces the p27 expression, and enhances CDK2. Thus, UCA1 could promote the growth of hepatic and hepatoma cells through the HBx/UCA1/EZH2/p27 axis [53]. In cytoplasm, UCA1 serves as a molecular sponge for miR-216b and miR-203. Through sequestering miR-216b, UCA1 could promote the growth and metastasis of HCC cell lines by up-regulating the expression of fibroblast growth factor receptor 1 and activating the extracellular signal-regulated kinase signaling pathway [54]. In addition, sequestering miR-203 facilitates epithelial-to-mesenchymal transition (EMT) in HCC cells through Snail2 upregulation [55]. Thus, UCA1 could promote cell cycle progression, enhance cell proliferation, and decrease cell apoptosis in HBx-related HCC [37].

#### 6. DBH-AS1

DBH-AS1 is an lncRNA of approximate 2 kb located on chromosome 9q34. HBx can upregulate the expression of DBH-AS1, which promotes HCC cell proliferation [37]. DBH-AS1 activates the ERK/p38/JNK MAPK signaling pathway. Once activated, ERK/p38/JNK MAPK can upregulate CDK6 (cyclin-dependent kinase), CCND1, and CCNE1 (members of cyclins) and downregulate p16, p21, and p27 (inhibitors of CDK). Thus, DBH-AS1 could induce the G1/S and G2/M transitions and promote cell proliferation. DBH-AS1 was also shown to protect HCC cells from serum starvation-induced apoptosis. These results suggested that DBH-AS1 acts as an oncogene [56]. However, a recent study showed contradicting results regarding the expression pattern of DBH-AS1 [57]. To elucidate the exact role of DBH-AS1 in HBV-related HCC, more research is required.

#### 7. HOTTIP (HOXA transcript at the distal tip)

LncRNA HOTTIP, a 3,764 nt transcript, is located on chromosome 7p15.2 and encodes from a genomic region in the 5'tip of the HOXA locus. LncRNA-HOTTIP was significantly overexpressed in tumor tissues compared to adjacent non-tumor tissues of the HCC patients. Patients with high HOTTIP expression were associated with increased metastasis formation and decreased overall survival. HOTTIP has also been detected to be upregulated significantly in HBV-related HCC patients [57]. Elevated

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HOTTIP expression could enhance cell proliferation and migration and contribute to metastasis of HCC partly by upregulating its neighboring HOXA genes (e.g., HOXA 10, 11 and 13), which are associated with various cancer types. These findings suggest that HOTTIP acts as an oncogene in HBV-related HCC.

#### 8. ANRIL (Antisense noncoding RNA in the INK4 Locus)

ANRIL, a 3,800 nt lncRNA, is in the INK4BARF-INK4A gene cluster [58]. ANRIL is upregulated in several cancers including HBV-related HCC [57]. The ANRIL expression was associated with tumor size, histological grade, and overall survival in HCC patients [59]. These findings indicate that ANRIL plays a role in the HCC development, particularly HBV-related HCC. Knockdown of ANRIL expression in HCC cells *in vitro* could induce apoptosis and reduce the proliferation, invasion, and migration of these HCC cells [60]. Furthermore, inhibition of ANRIL led to slower tumor growth *in vivo* [59, 60]. ANRIL represses the KLF2 transcription through binding with PRC2 [59]. ANRIL also serves as a molecular sponge for miR-122-5p, whose overexpression significantly repressed the proliferation, migration, and invasion of HCC cells [60]. These findings indicate that ANRIL is also an oncogene in HBV-related HCC.

#### 9. LINC00152.

LINC00152, an lncRNA of 828 nt, is mapped to chromosome 2p11.2 and contains four exons. It is mainly localized in the nucleus of HCC cells. The LINC00152 expression is associated with tumor size, HBV infection, and HBx amount [61]. Elevated LINC00152 expression also results in decreased overall survival [61]. LINC00152 is up-regulated by HBx protein and enhances proliferation and EMT of HCC cell lines *in vitro* and tumorigenesis *in vivo* [61]. LINC00152 has been shown to activate the mTOR pathway, which is a classic dysregulated pathway involved in the pathogenesis of HCC. In addition, LINC00152 promotes EMT by reducing the binding of EZH2 to the E-cadherin promoter and suppressing E-cadherin expression in HCC cell lines [61]. Ablation of E-cadherin will lose cell-cell contacts, resulting in EMT. These studies suggest that LINC00152 contributes to HBV-related HCC.

#### 17 10. MALAT1 (Metastasis-associated lung adenocarcinoma transcript 1)

MALAT1 (also known as nuclear-enriched abundant transcript 2, NEAT2), an lncRNA of approximate 8,000 nt in length, is mainly localized in the nucleus [62]. MALAT1 expression is elevated by HBx in HCC tissues and cell lines [63]. Sp1 and Sp3, also found upregulated, would bind to the proximal promoter region and enhance the transcription of MALAT1 [64]. MALAT1 affects alternative splicing and gene expression [62, 65]. MALAT1 could promote tumor growth and metastasis by upregulating LTBP3 (Latent-transforming growth factor beta-binding protein 3) expression. These results suggest that MALAT1 mediates the oncogenic effect of HBx through enhancing the LTBP3 expression, which promotes early metastatic events [63]. Moreover, a higher MALAT1 expression correlates to HCC recurrence after liver transplantation [66]. Additionally, knockdown of MALAT1 has been shown to reduce cell viability, motility, and invasiveness and increase sensitivity to apoptosis in HepG2 cells [66]. Therefore, MALAT1 is also an oncogene contributing to the risk of HBV-related HCC.

#### 11. Ftx

LncRNA Ftx is transcribed within the X-inactivation center [67]. Ftx encodes four miRNA clusters in its introns, among them, miR-545/374a located in intron b of Ftx has been implicated in HBV-associated HCC [22]. Expression of miR-374a and miR-545 was significantly higher in tumor tissues of HBV-related HCC. Further investigations suggested that miR-545/374a may contribute to poor prognosis by enhancing tumor invasion. This was supported by the observation that the proliferation of malignant cells was significantly suppressed in the presence of miR-545/374a inhibitors. On the other hand, overexpression of the miRNAs resulted in increased proliferation. miR-545/374a also enhanced migration and invasion abilities of HCC cells. Moreover, clinical samples positive for HBV DNA showed an increase in miR-545/374a. The upregulation of miR545 was also found to be HBx-dependent. Three targets for miR-545/374a were identified: estrogen-related receptor alpha (ESRRA), estrogen-related receptor gamma (ESRRG), and arginine and glutamate rich (ARGLU-I). Experimental evidence demonstrated that miR-545 could downregulate ESRRG expression.

Additionally, miR-374a had been shown to activate Wnt signaling pathway. In conclusion, lncRNA Ftx involves HBV-related HCC by serving as miRNAs precursor.

#### 12. MVIH (microvascular invasion in HCC)

MVIH is situated within the intron of the ribosomal protein S24 (RPS24) gene. The MVIH expression was significantly upregulated in HBV-related HCC. Highly expressed MVIH was associated with frequent microvascular invasion and decreased overall survival [68]. Further investigations found that MVIH could promote tumor growth and metastasis by enhancing angiogenesis through reducing the secretion of PGK1 (phosphoglycerate kinase 1) suppressing angiogenesis [68].

#### 13. Unigene56159

Unigene56159, an lncRNA of 2653 nt, is in the second intron of ROBO1. Unigene56159 was elevated in HBV-related HCC and HBV-producing cell line. Further investigations have found that Unigene56159, induced by HBV, could promote the EMT, migration, and invasion of hepatoma cells through sequestering miR-140-5p and up-regulating the Slug expression [69].

In addition to the abovementioned lncRNAs, the expression of LINC01232 [70], SAMD12-AS1 [71], lnc-HUR1 [72], n335586 [73], XIST [74], and SNHG5 [75] was found to be increased in HBV-related HCC. Moreover, the expression of WEE2-AS1 [76], MAFG-AS1 [77], lncRNA-ATB [78], TRERNA1 [79], lncRNA IHS [80], SNHG20 [81], and AX800134 [82] was upregulated by HBx.

Those upregulated lncRNAs by HBV and/or HBx may be involved in HCC progress through diverse mechanisms to enhance HCC cell proliferation, invasion, and metastasis, and/or prevent the death of HCC cells (e.g., apoptosis) [83].

### Downregulated lncRNAs in HBV related HCC (Table 2)

#### 1. Dreh (Downregulated expression by HBx)

Dreh, an lncRNA of approximate 700 nt in length, is mapped to chromosome 5. The Dreh expression was downregulated by HBx in HCC cell lines. Dreh is also significantly



downregulated in HBV-related HCC tissues. Suppression of DREH facilitates proliferation of hepatoma cells *in vitro* and also tumor growth *in vivo* [84]. Lower Dreh expression is associated with the recurrence-free survival and overall survival of HCC patients [84]. Playing as a tumor suppressor in the development of HBV-related HCC, Dreh suppressed cell proliferation and cell migration *in vitro* and *in vivo*. By binding to the intermediate filament protein vimentin, lncRNA Dreh inhibits its expression and alters its filament structure to repress tumor cell migration. Therefore, HBx inhibits Dreh expression and in turn facilitates HCC.

## 2. LET (Low expression in tumor)

LncRNA-LET is an lncRNA identified to be decreased in HBV-related HCC. LncRNA-LET and NF90 (nuclear factor 90) are associated with each other. LncRNA-LET could downregulate NF90. NF90 has been implicated in the stabilization of many factors (e.g., hypoxia induced factor 1  $\alpha$ , HIF-1 $\alpha$ ) related to tumor growth and metastasis [85, 86]. The LET/NF90/HIF-1 $\alpha$  axis may be critical for HCC invasion in hypoxic environments. Under hypoxia conditions, induced HDAC-3 (hypoxia-induced histone deacetylase 3) suppressed LET expression, which increased the expression of nuclear factor 90 (NF90) and HIF-1 $\alpha$ , and, hence, enhanced the invasiveness of HCC and contributed to HCC progression [85].

In addition to the abovementioned lncRNAs, the expression of uc.306 [87], UPAT [88], SEMA6A-AS1 [89], BANC1 [90], and miR143HG [91] was found to be decreased in HBV-related HCC. Moreover, the expression of LncRNA-6195 [92], LINC01352 [93], and F11-AS1 [94] was suppressed by HBx. These downregulated lncRNAs by HBV and/or HBx serve as tumor repressors and suppress HCC cell proliferation.

## Other lncRNAs in HBV-related HCC

### H19

The H19 gene is located adjacent to the insulin-like growth factor 2 (IGF-2) gene on chromosome 11p15.5. This gene produces a 2.3 kb lncRNA, which is exclusively expressed from the maternal allele. Reports of H19 expression in HCC are controversial. Recently, lncRNA H19 was found to be upregulated in CHB patients [95]. On the other

hand, lncRNA H19 could suppress the growth of hepatoblastoma cells by promoting their apoptosis [96].

Most of these dysregulated lncRNAs are modulated by HBx, it would help to know whether altered versions of the preS/S envelope proteins would modulate the expression of lncRNAs or not. The progress of research on the role of lncRNAs in HBV-related HCC is impressive. However, the functions of a large proportion of lncRNAs dysregulated in HBV-related HCC remain elusive. Future investigation on the function of lncRNAs in HBV-related HCC will shed the light on understanding the detailed mechanisms regarding the development of HBV-induced HCC. Understanding more regarding the molecular mechanisms underlying lncRNA-mediated oncogenesis should help for their use in diagnosis and to identify appropriate targets for prevention and treatment of HBV-related HCC.

### **Genetic polymorphisms of lncRNAs in HBV replication and oncogenesis**

A number of dysregulated lncRNAs have been identified in HBV replication and oncogenesis [2, 37]. Genetic polymorphisms affecting the expression (changes in the enhancer/promoter region) or activity (differences in the coding region) of these lncRNAs may also affect HBV replication and oncogenesis. Association studies are used to identify genetic variations of lncRNAs involved in HBV replication and oncogenesis [2].

### **Genetic polymorphisms in the enhancer/promoter of lncRNAs**

The intronic enhancer of HOTAIR had significantly higher HOTAIR levels in the rs920778 TT genotype than in the CC genotype. By upregulating HOTAIR, the rs920778 TT genotype promotes the development of HBV-related HCC and increases proliferation of HCC cells [97].



LncRNA GAS5 (growth arrest special 5) has been found to be downregulated in HCC patients [98]. A five-base-pair Ins/Del polymorphism (rs145204276) in the promoter region of GAS5 could affect the GAS5 expression. The deletion allele of rs145204276 increases the risk of HBV-related HCC significantly, though the detailed mechanism is unclear [99].

The sequence of RERT-lncRNA overlaps with those of the Ras-related GTP-binding protein 4b and prolyl hydroxylase 1 (EGLN2). An Ins/Del polymorphism (rs10680577) in the distal promoter of RERT-lncRNA may alter the structure of RERT-lncRNA and regulate the expression of RERT-lncRNA and EGLN2. A 4-bp deletion allele of rs10680577 in RERT-lncRNA increases expression of RERT-lncRNA and EGLN2 and promotes the occurrence of HBV-related HCC [100].

### Genetic polymorphisms in the coding region of lncRNAs

A polymorphism in the coding region of KCNQ1-overlapping transcript 1 (KCNQ1OT1), i.e. rs35622507, may alter the structure of KCNQ1OT1 and modulate the expression of KCNQ1OT1 and cyclin-dependent kinase inhibitor 1C (CDKN1C). The homozygous 10-10 genotype with significantly lower expression of KCNQ1OT1 and higher expression of CDKN1C was shown to increase the risk of HBV-related HCC [101].

LINC01149 variant rs2844512 was identified to facilitate HBV spontaneous recovery but increase the risk of HCC. Further studies indicated this variant created a binding site for miR-128-3p and upregulated MICA expression by serving as a miRNA sponge [102].

### Other genetic polymorphisms in lncRNAs

The variant allele of ZNRD1-AS1 (i.e., rs3757328) is reported to associate with HBV clearance [15].

The SNPs in glutamate-ammonia ligase [GLUL] overlapping with LINC00272 were associated with increased risk of HBV-related HCC [103].

CARD8 (Caspase recruitment domain family, member 8) can coordinate innate and adaptive immune responses and may participate in HBV-related HCC. Several SNPs (rs7248320) within a new identified lncRNA AC008392.1, which is located in the

upstream region of CARD8 in the long arm of the 9-chromosome, affect the CARD8 expression and may serve as a susceptibility marker for HBV-related HCC [104].

Three regulatory SNPs (rs3757328, rs6940552 and rs9261204) in the zinc ribbon domain-containing 1 antisense RNA 1 (ZNRD1-AS1) and the HBV genotype significantly affected HCC susceptibility. The results indicate that ZNRD1-AS1 accompanied by HBV genotypes may influence HCC risk [15].

TNFRSF10 (Tumor necrosis factor receptor superfamily member 10) including TNFRSF10A and TNFRSF10B is a death domain-containing receptor for the apoptotic ligand TNFSF10. In the upstream region of TNFRSF10A and downstream region of TNFRSF10B, lncRNAs RP11-1149O23.3 and RP11-459E5.1 were identified, respectively. The two lncRNAs are possibly involved in the regulation of TNFRSF10A and TNFRSF10B. Several SNPs (i.e., rs79037040-T and rs2055822-A) in RP11-1149O23.3 and RP11-459E5.1 may affect the expression of TNFRSF10A and TNFRSF10B and may be susceptibility markers for HCC and chronic HBV infection [105].

Paired-box family member PAX8 encodes a transcription factor that may participate in the prognosis of HCC. Several SNPs (rs4848320 and rs1110839) within AC016683.6 lncRNA may affect the PAX8 expression and affect the prognosis of HBV-related HCC [106].

The association of lnc-RP11-150O12.3 variants (rs2275959, rs1008547, and rs11776545) with HBV-related HCC risk and progression has been reported [107].

lncRNAs HULC and MALAT1 have been upregulated in HBV-related HCC. Genetic variants of lncRNA HULC (rs7763881) and lncRNA MALAT1 (rs619586) are associated with the decreased susceptibility to HCC [108].

These studies suggest that genetic polymorphisms in lncRNAs should affect the development and outcome of HBV-related HCC. This may help to identify appropriate targets for prevention and treatment of HCC in the age of personalized medicine.

## Regulatory mechanisms of lncRNAs in HBV replication and oncogenesis

lncRNAs can function as signals, decoys, guides, or scaffolds through interacting with their partner molecules and regulate gene expression at different levels. Up to now, at least seven mechanisms have been found to affect HBV replication and oncogenesis by dysregulated lncRNAs: epigenetic silencing, transcriptional control, splicing regulation, molecular sponge, production of miRNAs, protein stability modulation, and production of a small polypeptide (Figure 2) [2, 109, 110].

### Epigenetic silencing:

Polycomb group (PcG) proteins are epigenetic regulators of transcription. Through multiprotein complexes PRCs (polycomb repressive complexes), PcGs could modify histones (and other proteins) and silence target genes. lncRNAs may decrease the expression of their target genes through epigenetic silencing either by altering the expression level of PcGs or by interacting with PcGs directly and then silencing their target genes. HOTAIR enhances the degradation of suppressor of Zeste 12 homolog (SUZ12), a key subunit of PRC2, through Plk1<sup>[45]</sup>. Several lncRNAs interact with EZH2, a component of PRC2 to modulate (repress in most cases) the expression of their target genes, *e.g.*, HEIH<sup>[48]</sup>, UCA1<sup>[53]</sup>, HOTAIR<sup>[47]</sup>, LINC00152<sup>[61]</sup>, and PVT1<sup>[111]</sup>. ANRIL can interact with PRC2<sup>[112]</sup>.

### Transcriptional control:

lncRNAs can activate the transcription of their target genes in cis or in trans. HOTTIP could promote the expression of its neighboring homeobox A genes (HOXA genes) in HCC<sup>[57]</sup>. LINC00152 binds to the promoters of epithelial cell adhesion molecule (EpCAM) and IL23 to activate their transcription in HCC patients<sup>[113]</sup>. MALAT1 could up-regulate the expression of latent transforming growth factor  $\beta$ -binding protein 3 (LTBP3)<sup>[63]</sup>.

### Splicing regulation:

lncRNAs could affect the expression of their target genes through alternative splicing regulation. MALAT1, a nuclear lncRNA, could interact with the SR proteins

(serine/arginine-rich family of nuclear phosphoproteins) and change the cellular levels of the phosphorylated forms of SR proteins to modulate alternative splicing in HCC [62].

#### Molecular sponge:

LncRNAs could exert their effects by acting as molecular sponges for miRNAs, i.e., competitive endogenous RNA (ceRNA) [114]. Through molecular sponges, lncRNAs sequester miRNAs and then de-repress the expression of the miRNA target genes. Several lncRNAs, such as Unigene56159 [69], HULC [115], HBx-LINE1 [16], UCA1 [55], ANRIL [60], LINC01149 variant [102], LINC01352 [93], F11-AS1 [94], LINC01232 [70], n335586 [73], XIST [74], SNHG5 [75], SSTR5-AS1 [116], and TRERNA1 [79] are involved in the development of HBV-related HCC by sequestering miRNAs.

#### Production of miRNAs:

LncRNAs could produce miRNAs to regulate their target genes by serving as precursors of miRNAs. The Ftx transcript encodes two clusters of miRNAs (i.e., miR-374a and miR-545) in its introns in HBV-related HCC [117].

#### Protein stability modulation:

LncRNAs could stabilize their protein targets by direct interactions. LncRNA-Dreh could bind vimentin, a type III intermediate filament, and stabilize its filament structure [84]. LncRNAs could also stabilize their protein targets by reduced degradation of these proteins indirectly. By enhancing ubiquitin-specific peptidase 22 (USP22), HULC suppresses ubiquitin-mediated degradation of cyclooxygenase-2 and silent information regulator 1 in HCC [118].

#### Production of a small polypeptide:

A putative lncRNA HBVPTPAP could encode a small polypeptide to induce the apoptosis of HCC cells [110].

Through these different mechanisms, lncRNAs can regulate gene expression. As more lncRNAs are identified, more novel mechanisms will be revealed.

### LncRNAs as potential biomarkers for diagnosis and therapy of HBV-related HCC

It is suggested that HOTAIR may potentially be <sup>3</sup> a novel HBV diagnostic biomarker based on its ability to facilitate HBV transcription and replication. This may not be practical because the commercially available diagnostic kits for HBV infection already have high specificities and sensitivities. On the other hand, the specificity and sensitivity of currently available tumor markers for HBV-related HCC (e.g.,  $\alpha$ -fetoprotein) are not sufficient. This results in the poor prognosis of HBV-related HCC. This has encouraged researchers to search for novel potential biomarkers of HCC. Various miRNAs have been accepted to be biomarkers for diagnosis and therapy for HCC <sup>[119]</sup>. As an increasing number of lncRNAs, as well as the genetic polymorphisms in <sup>1</sup> lncRNAs, have been found to contribute in the development of HBV-related HCC, researchers have tried to study whether these lncRNAs could be used as novel biomarkers for HBV-related HCC <sup>[120]</sup>. To be tumor markers, lncRNAs have the advantage over proteins because they can be amplified easily, e.g., by RT-PCR. A number of lncRNAs dysregulated in HBV-related HCC have been suggested to be potential markers for HCCs. If these lncRNAs can be secreted to biological fluids, e.g., blood, they can be easily detected. Therefore, those secreted lncRNAs are suggested to be potential markers for HBV-related HCC, such as HULC <sup>[121]</sup>, IGF2AS <sup>[122]</sup>, Linc00152 <sup>[121]</sup>, lncRNA-uc003wbd <sup>[123]</sup>, lncRNA-AF085935 <sup>[123]</sup>, uc001ncr <sup>[124]</sup>, AX800134 <sup>[124]</sup>, and UCA1 <sup>[53-55]</sup>. However, most of these circulating lncRNAs aberrantly expressed in HBV-related HCC are also dysregulated in other tumors. It is better to identify a circulating lncRNAs specific for HBV-related HCC diagnosis <sup>[125]</sup>. Alternatively, detection of several lncRNAs together could be an option <sup>[126-130]</sup>.

Gene therapies such as RNA interference may become a common treatment for HCC in the future. In this way, lncRNAs can be the new therapeutic targets for HBV-related HCC. It is reported that metformin can suppress the HULC expression and block the progression of HBV-related HCC <sup>[131]</sup>. Thus, HULC could be a potential therapeutic target for RNA interference in HBV-related HCC treatment. Other lncRNAs



upregulated in HBV-related HCC are also reported to be potential therapeutic targets [8], such as MVIH [68] and HBx-LINE1 [16]. On the other hand, an effective way to deliver lncRNA MEG3 RNA using MS2 virus-like-particles to inhibit HCC cells has been developed [132]. Other lncRNAs downregulated in HBV-related HCC could use a similar approach to treat HBV-related HCC, such as DREH[84] and LET[85]. Other advances in gene and epigenetic editing will enable correcting the aberrations caused by the dysregulated lncRNAs in HBV-related HCC in the future.

## CONCLUSION

The important roles of lncRNAs in HBV replication and oncogenesis have started to emerge in recent years. Growing evidence indicates that some lncRNAs are dysregulated in HBV-infected cells and/or HBV-related HCC. Functional characterization of these lncRNAs has led to a more comprehensive understanding of HBV replication and oncogenesis. These lncRNAs have diverse functions, which are now beginning to be revealed. Although the progress regarding the role of lncRNAs in HBV-related HCC has been impressive, their roles in HBV replication, host immune responses, and HBV-related chronic diseases need further characterization. Even in HBV-related HCC, only a small part of lncRNAs has been well characterized, and a large portion of lncRNAs remains to be further explored. Thus, more efforts are required to understand the detailed mechanisms of these lncRNAs in the progression of HCC. The growing studies on the roles of lncRNAs in hepatocarcinogenesis could result in designing lncRNAs as potential biomarkers for diagnosis and therapy of HBV-related HCC.

Several technologies such as chromatin immunoprecipitation (ChIP), RNA sequencing (RNA-seq), ChIP sequencing, tiled RNA expression arrays, cap analysis of gene expression, and serial analysis of gene expression have been used to detect lncRNAs. Only recently, different types of post-transcriptional chemical modifications of RNAs have been detected and characterized through sequencing-based, transcriptome-wide studies, *e.g.*, pseudouridine ( $\Psi$ ), N6 -methyladenosine, (m6A) and



5-methylcytosine (m5C).<sup>6</sup> These modifications have been shown to affect the fate of RNA, including lncRNAs [133]. Further details about the roles of these chemical modifications of lncRNAs in HBV replication and oncogenesis are expected in the near future.

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