

Long non-coding RNAs in HBV-related hepatocellular carcinoma (Review)

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Abstract. Hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) is a global health problem that accounts for more than half of total liver cancer cases in developing countries. Despite the growing number of researches conducted, the molecular mechanism underlying the development of HCC remains elusive. Long non-coding RNAs (lncRNAs), which are non-coding RNAs >200 nt in length that were previously considered to be transcriptional noise, have been found to be dysregulated in HBV-related HCC with the help of high-throughput omics techniques. Subsequent investigations revealed that aberrant expression of lncRNAs may affect the risk of HBV-related HCC through diverse mechanisms, including epigenetic silencing of transcriptional activation, alternative splicing, molecular sponging, modulating protein stability, and by serving as precursors of miRNAs. Although the sensitivity and specificity of lncRNAs must be further validated, a number of circulating lncRNAs have been identified as useful biomarkers for HBV-related HCC. In addition to these findings, recent studies also unveiled that certain genetic polymorphisms in lncRNAs may affect the occurrence and prognosis of HBV-related HCC. The aim of the present review was to provide an overview of the mechanisms underlying the involvement of lncRNAs in HBV-related HCC. Subsequently, lncRNAs found to be dysregulated in HBV-related HCC were focused on and current findings on circulating lncRNAs and their genetic polymorphisms were discussed.

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1. Introduction

Hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality worldwide, accounts for 70-85% of all liver cancer cases (1). Epidemiological data reveal that hepatitis B virus (HBV)-related HCC accounts for a large proportion of liver cancer cases, particularly in developing countries (2). Although the management of HBV-related HCC has improved in recent decades, its prognosis remains poor (3). Therefore, exploring the underlying mechanism is crucial for improving the prevention, diagnosis and treatment of HBV-related HCC. Although HBV-related HCC is associated with HBV genotype, mutation status, integration and dysregulation of signalling pathways, its detailed mechanism remains elusive (4,5).

According to the central dogma, genes exert their effects by encoding proteins. Most previous research has focused on protein-coding genes. In recent years, with the development of high-resolution microarrays and massive parallel sequencing, ~70-90% of the human genome is confirmed to be actively transcribed into RNA, although only a minority of the transcripts encode proteins (6). Long non-coding RNAs (lncRNAs), which are non-coding RNA molecules >200 nucleotides (nt) in length, are usually transcribed by RNA polymerase II and may be polyadenylated. Compared with mRNAs, lncRNAs usually have fewer exons and are expressed at lower levels (7,8). Based on genomic position and strand orientation, lncRNAs are classified into five categories, including intergenic, intronic, bidirectional, sense

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and antisense lncRNAs (Fig. 1) (9). Although considered to be transcriptional noise in the past, lncRNAs are involved in the tumourigenesis of several cancers (10). By functioning as signals, decoys, guides and scaffolds, lncRNAs regulate invasion, tumourigenicity and metastasis of HCC (11). In recent years, several lncRNAs have been found to be aberrantly expressed in HBV-related HCC and to affect the risk and prognosis of HBV-related HCC. Further research has screened out circulating lncRNAs and genetic polymorphisms in lncRNAs as risk factors for the occurrence and prognosis of HBV-related HCC.

The aim of the present review was to briefly outline the main mechanisms underlying the involvement of lncRNAs in HBV-related HCC and introduce current findings on lncRNAs in HBV-related HCC. Mounting evidence suggests that lncRNAs are crucial regulators of HBV-related HCC, and investigation of lncRNAs may help to further elucidate the molecular mechanisms implicated in the development of HBV-related HCC.

2. Main mechanisms of action of lncRNAs in HBV-related HCC

A number of lncRNAs are dysregulated in HBV-related HCC. As illustrated in Fig. 2, these lncRNAs affect the risk and prognosis of HBV-related HCC through diverse mechanisms, such as epigenetic silencing, transcriptional activation, alternative splicing regulation, molecular sponging, modulating protein stability, and by serving as precursors for miRNAs (Fig. 2). These mechanisms will be briefly delineated below.

Epigenetic silencing. Epigenetic silencing, which decreases the expression of target genes without changing DNA sequences, is a well-known mechanism through which lncRNAs regulate the expression of target genes. LncRNAs participate in epigenetic silencing in two different ways: First, lncRNAs interact with polycomb-group proteins directly, and then promote the epigenetic silencing of target genes. Several lncRNAs, such as high expression in HCC (HEIH) (12), urothelial carcinoma associated 1 (UCA1) (13), HOX transcript antisense RNA (HOTAIR) (14) and long intergenic ncRNA 152 (LINC00152) (15), repress gene expression by interacting with enhancer of Zeste homolog 2 (EZH2), a core component of polycomb repressive complex 2 (PRC2). CDKN2B antisense RNA 1 (ANRIL), through binding with PRC2, can repress the transcription of Kruppel-like factor 2 (KLF2) (16). Second, lncRNAs participate in epigenetic silencing by altering the expression level of polycomb-group proteins. For example, HOTAIR affects epigenetic reprogramming by enhancing Plk1-dependent proteasomal degradation of suppressor of Zeste 12 homolog (SUZ12), a key subunit of PRC2, in HBV-related HCC (17,18).

Transcriptional activation. Several lncRNAs are implicated in the occurrence of HBV-related HCC by activating the transcription of target genes in *cis* and in *trans*. HOXA transcript at the distal tip (HOTTIP), which was originally found to activate the transcription of distal HOXA genes through interaction with the WDR5/MLL complex during embryonic development (19), also promotes expression of neighbouring

homeobox A genes (HOXA genes) in HCC (20-22). Epithelial cell adhesion molecule (EpCAM) is a mammalian target of rapamycin (mTOR)-related oncogene near LINC00152. In HCC patients, LINC00152 activates the transcription of EpCAM by binding to its promoter (23). Although the detailed mechanism remains elusive, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is able to increase the expression of latent transforming growth factor β -binding protein 3 (LTBP3) (24).

Regulation of alternative splicing. Through alternative splicing, a single pre-mRNA produces several different mRNAs. Certain lncRNAs have been found to participate in alternative splicing. MALAT1 is a nuclear-retained lncRNA that regulates alternative splicing in HCC. By interacting with the serine/arginine-rich family of nuclear phosphoproteins (SR proteins), MALAT1 affects the distribution of splicing factors in nuclear speckle domains, changes the cellular levels of the phosphorylated forms of SR proteins, and modulates alternative splicing (25,26).

Competitive endogenous RNA. The competitive endogenous RNA (ceRNA) hypothesis, originally proposed by Salmena *et al* in 2011 (27), states that lncRNAs exert their effects by acting as molecular sponges for miRNAs. A general model for this process is that lncRNAs sequester miRNAs and then de-repress the expression of miRNA target genes. As proposed by Thomson and Dinger, instead of being a general mechanism for predicting the function of individual lncRNAs, the ceRNA hypothesis is of great value in exploring the mechanisms of lncRNAs in cancer (28). Several lncRNAs, such as Unigene56159 (29), highly upregulated in liver cancer (HULC) (30-35), HBx-LINE1 (36), UCA1 (37) and ANRIL (38), are involved in the development of HBV-related HCC by titrating miRNAs away from their targets. Several limitations of current research, such as the lack of a physiological expression system and overdependence on the application of miRNA-target prediction algorithms, should be taken into consideration in future research.

Modulating protein stability. LncRNAs alter the stability of proteins via different mechanisms. By upregulating ubiquitin-specific peptidase 22 (USP22), HULC decreases ubiquitin-mediated degradation of cyclooxygenase-2 (COX2) and silent information regulator 1, and then stabilizes these two proteins in HCC (34,39). Moreover, lncRNAs modulate the stability of proteins by direct binding. Vimentin is a type III intermediate filament (IF) and the major cytoskeletal component of mesenchymal cells. Its filament structure in liver cells can be altered through binding with lncRNA downregulated expression by HBx (lncRNA-Dreh) (40).

Precursors of miRNAs. LncRNAs may be precursors of miRNAs. The Ftx transcript, a conserved lncRNA in the X-inactivation centre, encodes two clusters of miRNAs in its introns. miR-374a and miR-545, located in one of these two clusters, are induced by HBV X protein (HBx) and are upregulated in HBV-related HCC. These two miRNAs are correlated with poor prognosis of HCC patients and promote the proliferation, migration and invasion of HCC cells (41).

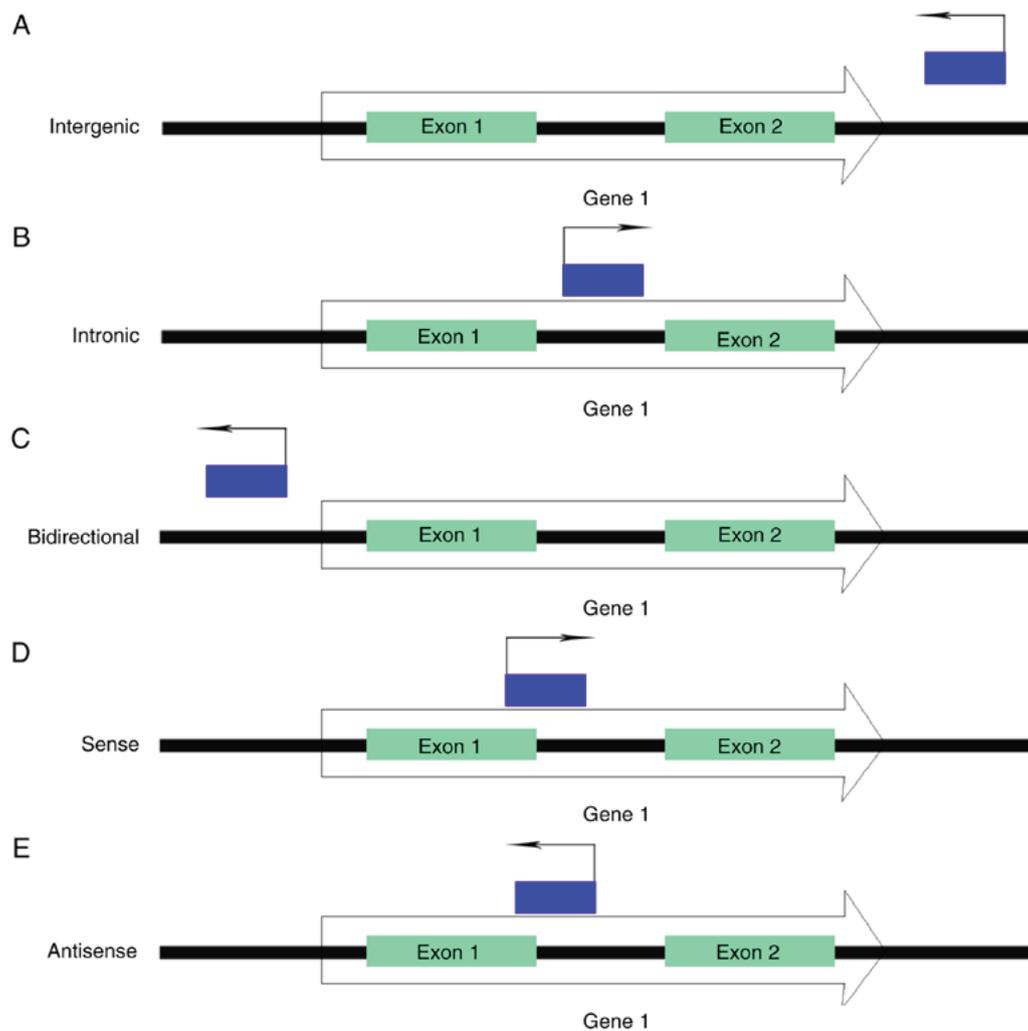


Figure 1. Overview of lncRNAs. (A) Intergenic lncRNA is located between two protein-coding genes. (B) Intronic lncRNA lies in an intron of a protein-coding gene. (C) Bidirectional lncRNA is transcribed in the opposite direction near a protein-coding gene. (D) Sense lncRNA is transcribed in the same direction as a protein-coding gene and overlaps with one or more exons. (E) Antisense lncRNA is transcribed in the opposite direction of a protein-coding gene and overlaps with one or more exons. lncRNA, long non-coding RNA.

3. lncRNAs dysregulated in HBV-related HCC

As mentioned above, lncRNAs may affect the risk of HBV-related HCC through diverse mechanisms. Thus, investigating lncRNAs aberrantly expressed in HBV-related HCC is an effective way for exploring the molecular mechanism of HBV-related HCC. In this review, well-studied lncRNAs that affect the occurrence and prognosis of HBV-related HCC are summarized in Table I and are discussed in detail below.

HULC. HULC, an oncogenic lncRNA of ~500 nt on chromosome 6p24.3, contains one intron, one canonical and two non-canonical polyadenylation signals. Through microarray analysis and qPCR, HULC was the first lncRNA identified to be specifically upregulated in HCC (42,43). Further research has demonstrated that cAMP response element-binding protein (CREB) increases the expression of HULC by binding to its promoter (30).

As an lncRNA mainly localized in the cytoplasm, HULC acts as a competitive endogenous RNA for miR-372 (30),

miR-186 (31), miR-488 (32), miR-200a-5p (33), miR-6825-5p, miR-6845-5p and miR-6886-3p (34), in HCC tissues and cell lines. By titrating these miRNAs away from their target mRNAs, HULC augments the expression of PRKACB, HMGA2, ADAM9, ZEB1 and USP22, and promotes HCC development. Moreover, via deubiquitination mediated by USP22, HULC increases the stability of COX2 and promotes the growth of HCC cell lines (39).

The function of HULC in HBV-related HCC has been investigated in recent years. By interacting with CREB, HBx increases the expression of HULC in HBV-related HCC tissues and cell lines. The expression of p18, a tumour suppressor gene located near HULC, is decreased by HULC and promotes the proliferation of hepatoma cells both *in vitro* and *in vivo* (44). Moreover, HULC also acts as a molecular sponge for miR-107 in HBV-related HCC. By sequestering miR-107, HULC upregulates E2F1 and then activates transcription of SPHK1 in HBV-related HCC tissues and cell lines. This process promotes tumour angiogenesis *in vitro* and *in vivo* (35). In 2017, Jiang *et al* revealed that metformin is able to inhibit the expression of HULC and suppress the

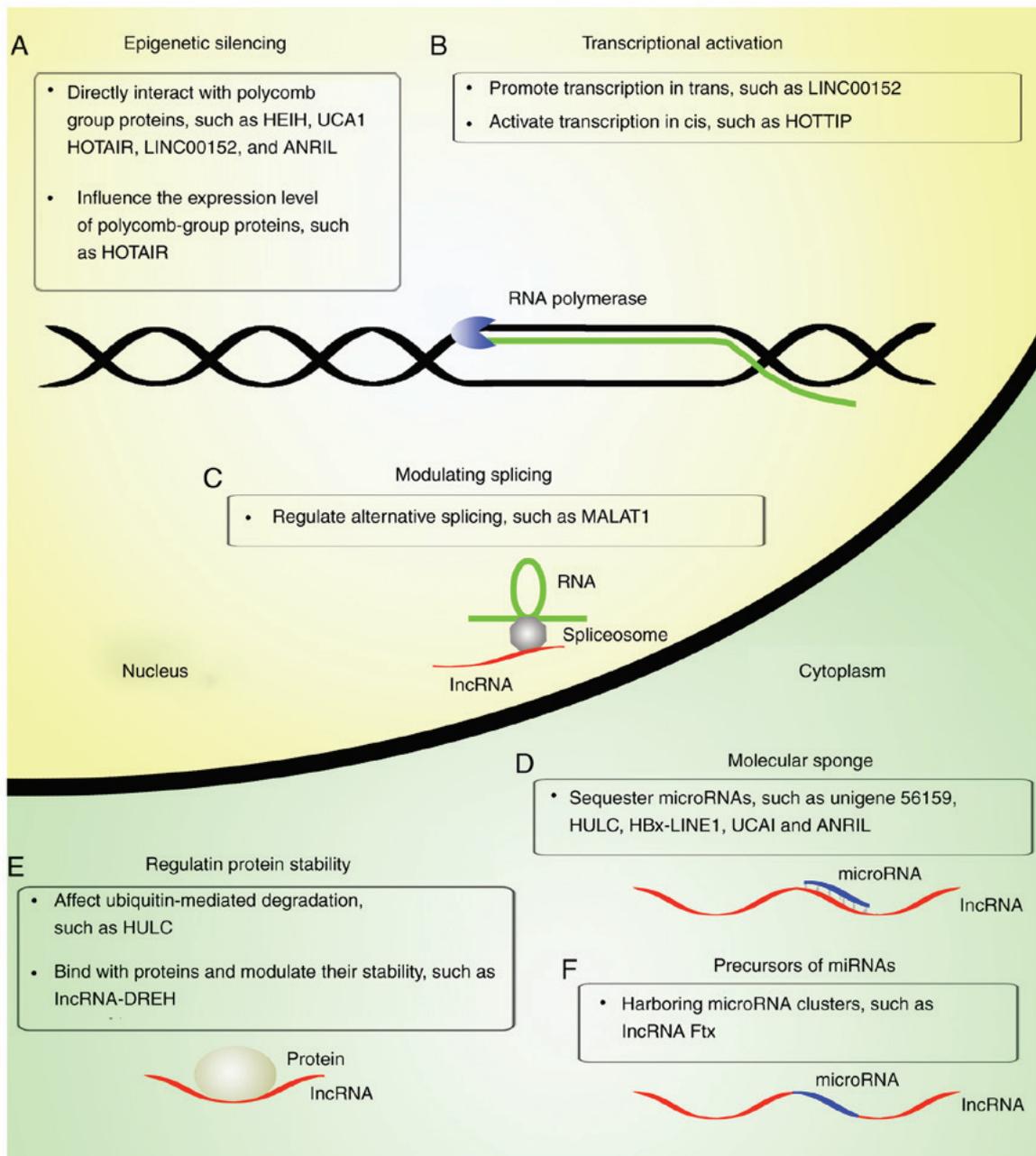


Figure 2. Main mechanisms of action of lncRNAs in HBV-related HCC. (A) Epigenetic silencing. (B) Transcriptional activation. (C) Modulating splicing. (D) Molecular sponge. (E) Regulating protein stability. (F) Precursors of microRNAs. lncRNA, long non-coding RNA; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

progression of HBV-related HCC (45). Although it must be further investigated, this finding suggests that HULC is a potential therapeutic target for HBV-related HCC.

Taken together, these findings demonstrate that HULC is an important oncogene in HBV-related HCC.

HOTAIR. The HOTAIR gene is ~12.6 kb in length and has six exons. lncRNA HOTAIR, a 2,158-nt transcript of the HOTAIR gene, was originally discovered by Rinn *et al* using tiling microarray analysis in 2007 (46). Further analyses revealed that HOTAIR interacts with PRC2 and enhances repression of the HOXD locus by PRC2 (46). Growing evidence has demonstrated that HOTAIR contributes to the risk of several cancers, including HCC (47).

In 2011, the expression of HOTAIR was reported to be increased in HCC tissues and cell lines (48). This finding was confirmed by a series of studies (14,49-55). Subsequent research has suggested that elevated expression of HOTAIR promotes migration and invasion of HCC cells by inhibiting RNA-binding motif protein 38 (49), and affects the symptoms and prognosis of HCC patients (48,51,55). Furthermore, overexpression of HOTAIR promotes autophagy by elevating the expression of ATG3 and ATG7 (52), and promotes glycolysis by activating glucose transporter isoform 1 and mTOR signalling (53). Inhibition of HOTAIR suppresses tumorigenesis, proliferation, viability, migration and invasion of HCC cells (14,48,54,56). Functional analyses have indicated that HOTAIR promotes HCC through repression

Table I. Dysregulated lncRNAs in HBV-related HCC.

lncRNA	Chromosome location	Classification	Subcellular location	Expression	Molecular mechanism	Biological function	Clinical impact	(Refs.)
HULC	Chr6:8652209-8653846	Intergenic	Cytoplasm	Upregulated	Sequesters a series of microRNAs and decreases the expression of p18	Promotes proliferation of hepatoma cells and tumour angiogenesis <i>in vitro</i> and <i>in vivo</i>	A potential therapeutic target	(30-34,42,44,45)
HOTAIR	Chr12:53962308-53974956	Antisense	Nucleus and cytoplasm	Upregulated	Participates in epigenetic silencing in hepatoma cells	Promotes migration and invasion of HCC cells	Affects symptoms and prognosis of HCC patients	(14,46,48-55,57,58)
MALAT1	Chr11: 65497688-65506431	Intergenic	Nucleus	Upregulated	Activates the transcription of LTBP3 in HBV-related HCC	Promotes migration and invasion of HCC cells <i>in vitro</i> and tumour growth <i>in vivo</i>	Affects the prognosis of HCC patients	(24,61-65)
UCA1	Chr19:15828206-15836136	Intergenic	Nucleus and cytoplasm	Upregulated	Recruits EZH2 to the promoter of p27 in the nucleus and sequesters miR-216b and miR-203 in the cytoplasm	Promotes growth, metastasis and EMT of HCC cell lines	Correlates with tumour size, vascular invasion, metastasis, postoperative survival and disease stage of HCC patients	(13,37,70)
HEIH	Chr5:180829954-180831605	Intergenic	Nucleus and cytoplasm	Upregulated	Binds with EZH2 and participates in repression of EZH2 targets	Promotes cell proliferation and tumour growth, modulates cell cycle	Correlates with the prognosis of HBV-related HCC	(12,72)
LINC00152	Chr2:87455368-87584075	Intergenic	Nucleus	Upregulated	Inhibits the expression of E-cadherin and activates the mTOR pathway	Promotes the proliferation and EMT of HCC cell lines and tumourigenesis	Correlates with tumour size, HBV infection, tumour number and HBx	(15,23)
HOTTIP	Chr7:27201844-27207259	Intergenic	Nucleus	Upregulated	Promotes the expression of HOXA genes	Inhibits proliferation and migration of HCC cells <i>in vitro</i> and reduces tumourigenesis and pulmonary metastasis <i>in vivo</i>	Correlates with increased metastasis formation and decreased OS	(20-22,77,78)
HBx-LINE1	Chr8p11	Not known	Nucleus	Upregulated	Activates Wnt/ β -catenin signalling pathway and sequesters miR-122	Promotes cell motility through EMT and causes mouse liver injury	Correlates with poorer patient survival	(36,80)
ANRIL	Chr9:22113678-22121097	Antisense	Nucleus	Upregulated	Represses the transcription of KLF2 and sequesters miR-122-5p	Inhibits apoptosis of HCC cells <i>in vitro</i> and promotes proliferation, invasion and migration of HCC cells <i>in vitro</i>	Correlates with tumour size, BCLC stage, OS, histological grade and TNM stage of HCC patients	(16,8,4)

Table I. Continued.

LncRNA	Chromosome location	Classification	Subcellular location	Expression	Molecular mechanism	Biological function	Clinical impact	(Refs.)
Unigene56159	Chr3	Intronic	Not known	Upregulated	Sequesters miR-140-5p	Promotes EMT, migration and invasion of hepatoma cells	Highly expressed in HBV-related HCC tissues	(29)
BALAP2-AS1	Chr17:81029130-81034573	Antisense	Cytoplasm	Upregulated	May function as a ceRNA	May be an oncogene for HCC	Highly expressed in HBV-related HCC tissues	(91)
WEE2-AS1	Chr7:141704338-141738230	Antisense	Not known	Upregulated	Up-regulate FERMT3 and activate PI3K/AKT/GSK3 β signal pathway	Promotes the proliferation, migration and invasion of HCC <i>in vitro</i> and	Correlates with hepatic vascular invasion, poor tumour differentiation and HBV infection	(94)
DBH-AS1	Chr9:133654586-133657313	Antisense	Nucleus	Uncertain	Activates MAPK signal pathway	Inhibits serum starvation-induced apoptosis of HCC cells, promotes tumour growth, proliferation and cell-cycle progression of HCC cell	Correlated with tumour size and seropositivity of HBsAg	(73,6)
DREH	Chr5:109213218-109213911	Sense	Not known	Downregulated	Inhibits the expression of vimentin and alters its filament structure	Inhibits proliferation of HCC cells <i>in vitro</i> and tumour growth <i>in vivo</i>	Associates with RFS and OS of HCC patients and correlates with tumour size and HBsAg in HCC patients	(40,73,87)
uc.306	Chr10	Intronic	Not known	Downregulated	May participate in the Wnt pathway	Not known	Affects the prognosis and correlates with OS of HCC patients	(90)
n346077	Chr11	Antisense	Not known	Downregulated	Not known	Suppresses HCC cell migration and invasion <i>in vitro</i>	Not known	(89)
lncRNA-6195	Chr3:125647611-125650486	Intergenic	Not known	Downregulated	Binds with ENO1, inhibits its enzymatic activity	Repressed energy metabolism in HCC cells, reduces proliferation of HCC cells <i>in vitro</i> and suppresses tumorigenesis <i>in vivo</i>	Lower expression level correlates with high Edmondson-Steiner grade of the tumours and shorter OS	(93)

LncRNA, long non-coding RNA; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; EMT, epithelial-to-mesenchymal transition; OS, overall survival; RFS, recurrence-free survival; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; BCLC, Barcelona Clinic Liver Cancer; ENO1, α -enolase; FERMT3, Fermitin family member 3.

of miR-1, and is involved in the recruitment of macrophages and myeloid-derived suppressor cells to the tumour micro-environment (57). Moreover, knockdown of HOTAIR was shown to increase the chemosensitivity of HCC cells to cisplatin (58).

HOTAIR is also involved in the occurrence of HBV-related HCC. qPCR has demonstrated that the expression of HOTAIR is markedly increased in liver tumour tissues from X/c-myc bitransgenic mice and HBV-infected patients (17). In HBV replicating cells, HOTAIR is regulated by DEAD box protein 5 and participates in proteasomal degradation of SUZ12 (18). In addition, HOTAIR reduces the stability of SUZ12 and ZNF198 by enhancing Plk1-dependent ubiquitination of these two proteins, and it may affect epigenetic reprogramming involved in oncogenic transformation (17). Taken together, this evidence indicates that HOTAIR promotes the occurrence of HCC and contributes to the risk of HBV-related HCC.

MALAT1. MALAT1 (also known as nuclear-enriched abundant transcript 2) is ~8,000 nt in length and localized in the nucleus (25). MALAT1 tends to be a nucleus-retained lncRNA and affects alternative splicing and gene expression (25,26). It was one of the first lncRNAs that was identified to be associated with a disease. In 2003, Ji *et al* demonstrated that MALAT1 predicts prognosis of early-stage lung cancer (59). MALAT1 is also an important oncogene in several other cancers, including esophageal squamous cell carcinoma, gastric and colorectal cancer (60).

MALAT1 is downregulated in HCC tissues and is associated with the overall survival (OS) of HCC (43). Higher expression of MALAT1 contributes to the risk of HCC recurrence after liver transplantation (61). Loss-of-function experiments have revealed that inhibition of MALAT1 in HepG2 cells reduces cell viability, motility and invasiveness and increases sensitivity to apoptosis (61). With the help of bioinformatics, MALAT1 was found to promote HCC progression, metastasis and multidrug resistance by sequestering a number of miRNAs, including miR-216b (62), miR-143-3p (63) and miR-146-5p (64). However, none of these studies investigated the subcellular localization or cytoplasmic abundance of MALAT1 (62-64). As an lncRNA mainly located in nuclear speckles (25), it does not appear likely that MALAT1 can sponge miRNAs in the cytoplasm.

qPCR has revealed that Sp1, Sp3 and MALAT1 are upregulated in HBV-related HCC tissues and cell lines. Further investigation has indicated that Sp1 and Sp3 bind to the proximal promoter region of MALAT1 and enhance its transcriptional activity (65). The expression of MALAT1 is elevated by HBx in HCC tissues and cell lines (24,66). Loss- and gain-of-function experiments have indicated that MALAT1 regulates HBx-induced cancer stem cell properties, promotes migration and invasion of HCC cells *in vitro* and tumour growth *in vivo*. Further research demonstrated that MALAT1 promotes tumour growth and metastasis by upregulating LTBP3. These findings indicate that MALAT1 mediates the oncogenic effect of HBx by increasing the expression of LTBP3 (24).

Although the detailed mechanism requires further investigation, MALAT1, a key oncogene for several cancers, contributes to the risk of HBV-related HCC.

UCA1. The UCA1 gene is ~7.3 kb in length and contains three exons (67). It is mapped to chromosome 19p13.12 and has three transcriptional isoforms. UCA1, a transcription isoform of the UCA1 gene that is ~1,400 nt in length, is the most abundant isoform of UCA1 in various cancers (68). It was originally identified in the bladder cancer cell line BLZ-211 and is a sensitive and specific marker for bladder cancer (67). UCA1 is also an oncogene for a number of other cancers, including HCC (68). UCA1 is also involved in anticancer drug resistance (69).

To determine whether UCA1 is involved in HBV-related HCC, the expression of UCA1 was detected in HCC cell lines and several groups of HCC patients mainly infected with HBV. Their results demonstrated that UCA1 was upregulated in cancerous tissues and HCC cell lines, and higher UCA1 expression in HCC was positively associated with tumour size, vascular invasion, metastasis, postoperative survival and disease stage (13,37,70). These findings indicate the important role of UCA1 in HBV-related HCC.

As an lncRNA localized in both the nucleus and cytoplasm (13,71), UCA1 has diverse functions. In hepatocytes, UCA1 is upregulated by HBx. Then, UCA1 recruits EZH2 to the promoter of p27 in the nucleus, suppresses the expression of p27 and activates CDK2. This process contributes to G1/S transition and promotes the growth of hepatic and hepatoma cells. These findings unveil the crucial role of the HBx/UCA1/EZH2/p27 signalling pathway in HCC (13). In the cytoplasm, UCA1 acts as a molecular sponge for miR-216b and miR-203. By sequestering miR-216b, UCA1 increases the expression of fibroblast growth factor receptor 1, activates the extracellular signal-regulated kinase signalling pathway and promotes the growth and metastasis of HCC cell lines (70). In addition, sponging miR-203 promotes epithelial-to-mesenchymal transition (EMT) in HCC cells via the upregulation of Snail2 (37). In conclusion, UCA1, a crucial oncogene in several cancers, is regulated by HBx and contributes to the risk of HBV-related HCC.

HEIH. The lncRNA HEIH is ~1,600 nt in length and maps to chromosome 5. It is located in the nucleus and cytoplasm of HCC cells. With the use of microarray analysis and qPCR, HEIH was found to be upregulated in HBV-related HCC tumour tissues (12). In addition to being upregulated in HCC cell lines, further investigation revealed that HEIH is significantly increased only in HBV-related HCC tumour tissues (72,73). Logistic multivariate regression has demonstrated that the expression of HEIH is associated with disease recurrence and OS in HCC patients. These findings suggest that HEIH is an independent prognostic factor for OS in HBV-related HCC (12).

Rather than DNA amplification, DNA methylation or histone acetylation, upregulation of HEIH is induced by the transcription factor Sp1. Loss- and gain-of-function experiments were performed to evaluate the effect of HEIH on cell biological behaviour. *In vitro* experiments demonstrated that HEIH promotes cell proliferation by upregulating proliferating cell nuclear antigen and modulating the cell cycle by decreasing the expression of p16, p21 and p27 in HCC cell lines. *In vivo* studies revealed that HEIH promotes tumour growth in nude mice. RNA immunoprecipitation and pulldown

revealed that HEIH is physiologically associated with EZH2 and is required for repression of EZH2 target genes (12). These findings indicate that, by participating in epigenetic silencing, HEIH contributes to the risk of HBV-related HCC.

LINC00152. LINC00152, an lncRNA located on chromosome 2p11.2, contains four exons and encodes an 828-bp transcript. It is mainly localized in the nucleus of HCC cells (23) and plays a vital role in carcinogenesis of several cancers (74).

In a group of HCC patients with different aetiologies, LINC00152 was found to be hypomethylated during hepatocarcinogenesis (75). This finding was confirmed in a group of HCC patients mainly infected with HBV (23). The expression of LINC00152 was found to be significantly increased in HCC patients and cell lines (15,23). These results suggest that LINC00152 is involved in HCC. The expression of LINC00152 is correlated with tumour size, HBV infection, tumour number and HBx expression (15,23). Kaplan-Meier analysis has revealed that higher expression of LINC00152 results in significantly shorter OS time (15).

LINC00152 is activated by HBx and promotes proliferation and EMT of HCC cell lines *in vitro* and tumorigenesis *in vivo* (15,23). With the use of microarray analysis, the Gal4- λ N/BoxB reporter system and antisense oligonucleotide technology, LINC00152 has been shown to activate the mTOR pathway by binding to the promoter of EpCAM in a *cis*-regulation pattern (23). In addition, LINC00152 promotes cell EMT by decreasing the binding of EZH2 to the promoter of E-cadherin and inhibiting expression of E-cadherin in HCC cell lines (15). These findings indicate that LINC00152 contributes to the risk of HBV-related HCC.

HOTTIP. LncRNA HOTTIP is mapped to the HOXA locus and encodes a 3,764-nt transcript. It was originally identified in anatomically distal human fibroblasts. HOTTIP activates and then promotes the development of several cancers by recruiting histone-modifying enzymes to HOX genes and silencing tumour suppressor genes (76).

The expression of HOTTIP is increased in HCC tumour tissues and cell lines (20,21,77,78). By analysing the expression of lncRNAs in HCC patients infected with different hepatitis viruses, HOTTIP has been shown to be significantly upregulated in HCV- and HBV-related HCC patients (73). Higher expression levels of HOTTIP are correlated with increased metastasis and decreased OS (21). These findings show that HOTTIP may be a prognostic indicator for HCC and should prompt further investigation of its function.

Loss-of-function experiments have revealed that knockdown of HOTTIP inhibits the proliferation and migration of HCC cells *in vitro* and reduces tumorigenesis and pulmonary metastasis *in vivo* (20). *In vitro* and *in vivo* investigations have also revealed that the expression of HOTTIP is suppressed by miR-192, miR-204 and miR-125b (20,78), and it promotes the expression of a panel of HOXA genes, including HOXA 10, 11 and 13, in HCC (20-22). In addition to being inhibited by miRNAs, the expression of HOTTIP is also repressed by HOXA13. This suggests the existence of a bidirectional regulatory loop between HOTTIP and HOXA13 (21). These findings suggest that HOTTIP is a crucial oncogene in HBV-related HCC.

HBx-LINE1. As 85-90% of HBV-related HCC tumours harbour at least one HBV insertion site (79), it was reasonable to hypothesize that integration of HBV into the host genome may play an important role in the development of HBV-related HCC. To investigate the effect of such integration on genome disruption, transcriptome sequencing was performed to analyse six HBV-positive HCC cell lines for viral integration. With the use of ViralFusionSeq, a specific algorithm for accurate and unbiased detection of HBV integration, a virus-human chimeric transcript named HBx-LINE1 was detected in HKCI-4. Hemi-nested reverse transcription-PCR revealed that HBx-LINE1 was expressed in 21 of 90 HBV-related HCC tumours. Subsequent research demonstrated that HBx-LINE1 is an lncRNA that promotes cell motility by activating the Wnt/ β -catenin signalling pathway (80).

HBx-LINE1 was detected in 17 of 40 HCC tissues by qPCR. Subsequent investigations have revealed that the expression of HBx-LINE1 is inversely correlated with miR-122 in HBV-related HCC tissues and HuH7 cells. Functional analysis demonstrated that HBx-LINE1 sponges miR-122 in HuH7 cells and mouse liver cells. By sequestering miR-122, HBx-LINE1 activates the β -catenin signalling pathway, promoting hepatic cell migration and causing mouse liver injury (36).

However, these findings were not consistent with those of other studies. In 2015, Ding *et al* reported that HBx-LINE1 was not detected in 30 HCC tissues. In addition, HBx-LINE1 integration was not detected using primers designed to detect the HBx-LINE1 virus-host junction sequences at the DNA level (81).

There are several possible reasons for this discrepancy. HBV integration is a complex process, and its mechanism remains unclear. Cellular and viral factors affecting HBV integration also remain unclear. Combined with the fact that these studies were conducted in different areas, the small sample size may have caused the discrepancy. More research with larger samples may help further elucidate the role of HBx-LINE1 in the occurrence and prognosis of HBV-related HCC.

ANRIL. ANRIL, originally identified in familial melanoma patients, is transcribed as a 3,800-nt lncRNA in the antisense direction of the INK4BARF-INK4A gene cluster (82). Accumulating evidence indicates that ANRIL is upregulated in several cancers and acts as an oncogene (83).

In HCC patients and cell lines, the expression of ANRIL was found to be increased by qPCR (16,38,84). A recent study revealed that ANRIL was upregulated in HCV- and HBV-related HCC patients (73). The expression of ANRIL was associated with tumour size, Barcelona Clinic Liver Cancer (BCLC) stage, histological grade, TNM stage and OS in HCC patients (16,38). These findings suggest that ANRIL contributes to the risk of HCC, particularly HBV-related HCC.

Loss-of-function experiments have been conducted to elucidate the effect of ANRIL on HCC cell behaviour. Knockdown of ANRIL expression induced apoptosis and suppressed proliferation, invasion and migration of HCC cells *in vitro* (16,38,84). Inhibition of ANRIL led to slower tumour growth *in vivo* (16,38). Functional analyses revealed that ANRIL is activated by the transcription factor Sp1 and represses the transcription of KLF2 through binding with PRC2 (16). ANRIL also exerts its effects by sponging

miR-122-5p (38). These findings indicate that ANRIL is a crucial oncogene and contributes to the risk of HBV-related HCC.

DBH-AS1. DBH-AS1, an lncRNA of ~2 kb residing at chr9q34, is downregulated by quercetin in HepG2 cells (85). The expression of DBH-AS1, which is induced by HBx and repressed by p53, is upregulated in HCC cell lines and tumour tissues. The expression of DBH-AS1 is positively correlated with tumour size and hepatitis B surface antigen (HBsAg). *In vitro* and *in vivo* experiments have demonstrated that DBH-AS1 inhibits serum-starvation-induced apoptosis of HCC cells, promotes proliferation and cell cycle progression of HCC cells, and contributes to tumour growth. DBH-AS1 activates the mitogen-activated protein kinase (MAPK) signalling pathway. Through activation of MAPK signalling, DBH-AS1 contributes to the risk of HBV-related HCC (86).

However, a recent study by Zhang *et al* demonstrated opposite results regarding the expression pattern of DBH-AS1. In 11 HBV-related HCC patients, the expression of DBH-AS1 was significantly decreased in tumour tissues compared with peritumoural tissues (73). There are several possible reasons for this discrepancy. First, the sample size of these two studies was small. Second, in the former study, HCC patients with different viral aetiologies were included in the HCC group. As the expression of lncRNAs in HCC patients with different aetiologies may be different, this may have led to the different results. To elucidate the expression pattern and functional role of DBH-AS1 in HBV-related HCC, more studies on HBV-related HCC with larger sample sizes are required.

DREH. DREH is ~700 nt in length and located on chromosome 5. By analysing the expression profile of lncRNAs induced by HBx with the use of microarrays and qPCR, lncRNA-Dreh, the mouse ortholog of DREH, was found to be downregulated in HBx transgenic mice and mouse liver cells expressing HBx. By binding to vimentin, lncRNA-Dreh inhibits its expression and alters its filament structure. This process represses tumour growth and inhibits tumour metastasis *in vivo*. Loss-of-function experiments have demonstrated that inhibition of Dreh promotes proliferation and migration of mouse liver cell lines (40). These findings suggest that lncRNA-Dreh acts as a tumour suppressor in HBV-related HCC.

The importance of lncRNA-Dreh led researchers to investigate the function of its human orthologue in HBV-related HCC. Although DREH is upregulated in HCV-related HCC tissues, qPCR revealed that DREH is significantly downregulated in HBV-related HCC tissues (40,73,87). The expression of DREH was found to be inversely correlated with HBx in HCC tissues and downregulated by HBx in HCC cell lines. Inhibition of DREH promotes proliferation of HCC cells *in vitro* and tumour growth *in vivo* (87). Survival and correlation analyses have demonstrated that lower expression of DREH is closely associated with the recurrence-free survival (RFS) and OS of HCC patients (40) and is correlated with tumour size and HBsAg in HCC patients (87). Although its detailed mechanism of action in HCC patients remains elusive, DREH acts as a tumour suppressor in HBV-related HCC.

Other lncRNAs in HBV-related HCC. In recent years, a growing number of lncRNAs are found to be aberrantly expressed in HBV-related HCC via microarray analyses and high-throughput sequencing. For example, the expression of XLOC_007433 and AC144449.1 was found to be increased and decreased, respectively, in male patients with HBV-related HCC (88). In HBV-related HCC tissues and cell lines, n346077 (89) and uc.306 (90) are downregulated, while BAIAP2-AS1, PRC1-AS1, LINC00665 and AC092171.4 are upregulated (91,92). n346077 is associated with invasion and migration of HCC cells (89), and uc.306 is negatively correlated with the OS of HBV-related HCC patients (90). lncRNA-6195, a tumour repressor for HBV-related HCC, suppresses HCC cell proliferation both *in vitro* and *in vivo* through binding with α -enolase and then inhibiting its enzymatic activity (93). The expression level of Unigene56159, a 2653-nt-long lncRNA located in the second intron of ROBO1, is significantly higher in HBV-positive compared with HBV-negative HCC tissues and cell lines. Subsequent investigation revealed that Unigene56159 is induced by HBV and promotes EMT, migration and invasion of hepatoma cells via sequestering miR-140-5p and increasing the expression of Slug (29). Upregulated by HBx, WEE2-AS1 is able to accelerate the proliferation, migration, invasion and cell cycle progression of HCC cells through increasing the expression of Fermitin family member 3 (94). Additionally, recent studies have shown that the expression levels of lncRNAs are regulated by HBx (95-99).

Mining gene expression databases is also an effective method for identifying lncRNAs that are involved in HBV-related HCC. Through analysing data from the Gene Expression Omnibus database and the Cancer Genome Atlas, a LINC00346-miR-10a-5p-CDK1 axis was found to affect the progression of HBV-related HCC (100). Another research using bioinformatics identified MSC-AS1, POLR2J4, EIF3J-AS1, SERHL, RMST and PVT1 as risk factors for RFS of HBV-related HCC (101).

4. Circulating lncRNAs serve as novel biomarkers for HBV-related HCC

Despite the marked advances in diagnostic methods and surgical techniques, the prognosis of HBV-related HCC remains poor. A number of serum markers, such as α -fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of AFP and des- γ -carboxy prothrombin, are used for diagnosis and outcome prediction in HCC (102,103). However, the specificity and sensitivity of these tumour markers are not sufficient. This has encouraged researchers to search for novel serum markers of HCC. As an increasing number of lncRNAs have been demonstrated to affect the risk of HBV-related HCC, researchers have tried to determine whether these lncRNAs may be used as serum biomarkers for HBV-related HCC.

As the first lncRNA confirmed to be upregulated in HCC, the expression of HULC in the peripheral blood cells of HCC patients was first found to be markedly increased in 3 of 4 HCC patients in a pilot experiment in 2007 (42). Later research revealed that the plasma HULC-positive rate was higher in HBV-positive HCC patients compared with that in HBV-negative HCC patients, and that the level of HULC

was correlated with Edmondson grade (104). By screening in the training set and validation in the validation set, plasma HULC was confirmed to be increased in the HCC group and exhibited adequate diagnostic accuracy for HCC (105). These results indicate that plasma HULC is a useful biomarker for HBV-related HCC.

In addition to HULC, a number of other circulating lncRNAs, such as MALAT1 (106), LINC00152 (105,107), RP11-160H22.5 (107), XLOC014172 (107), PVT1 (108) and uc002mbe.2 (108), are upregulated in HCC patients. The serum levels of lncRNA uc003wbd (109), lncRNA-AF085935 (109), uc001ncr (110) and AX800134 (110) are elevated in HBV-related HCC patients. These results indicate that circulating lncRNAs may be useful biomarkers for predicting the risk and prognosis of HBV-related HCC.

However, there are several limitations to these studies. First, several studies recruited HCC patients with different aetiologies. Although the detailed mechanism remains elusive, Zhang *et al* observed that HCC patients with different viral aetiologies had different dysregulated lncRNAs (73). Assigning patients with different aetiologies to one group may cause bias. Second, as several studies included small samples, the results may not be as reliable. Future research with larger samples and recruiting of only HBV-related HCC patients will validate the findings and yield more reliable results. Third, a number of these circulating lncRNAs identified to be dysregulated in HBV-related HCC are also aberrantly expressed in other tumours. Future research in patients with different tumours using high-throughput technology will help us identify circulating lncRNAs specific for HBV-related HCC.

However, despite these limitations, the research mentioned above provides valuable clues for further screening of circulating lncRNAs that may serve as biomarkers for HBV-related HCC.

5. Genetic polymorphisms in lncRNAs and HBV-related HCC

Genetic polymorphisms are the most abundant genetic markers in the human genome. Association studies are widely used to identify genetic variations that contribute to the occurrence and prognosis of several cancers, including HBV-related HCC. Since genome-wide association studies have discovered that the majority of single-nucleotide polymorphisms (SNPs) associated with complex disease are located in genomic regions not coding for proteins (111,112), researchers started to explore the associations between several SNPs in lncRNAs and cancer (113). The effect of SNPs in lncRNAs on HBV-related HCC has also been investigated. In 2012, the variant genotype of rs7763881 in HULC was shown to decrease the risk of HBV-related HCC in a group of unrelated ethnic Han Chinese patients (114). As shown in Table II, a number of SNPs in lncRNAs affect the occurrence and prognosis of HBV-related HCC (Table II).

As mentioned above, HOTAIR contributes to the susceptibility to HBV-related HCC. Recently, a case-control study was conducted to evaluate the association between SNPs in HOTAIR and the risk of HBV-related HCC. The minor allele of rs920778 was found to be a risk factor for HBV-related HCC. With the use of qPCR, functional investigation using

luciferase activity and CCK-8 assays revealed that the minor allele of rs920778 increased the expression of HOTAIR and was associated with a higher proliferation rate of HCC cells. These findings suggest that the minor allele of rs920778 promotes the occurrence of HBV-related HCC by upregulating HOTAIR and increasing proliferation of HCC cells (115).

Growth arrest special 5 (GAS5), an lncRNA identified in a mouse thymoma cell line, has been found to be down-regulated in most HCC patients (116,117). rs145204276 is a 5-bp indel polymorphism in the promoter region of GAS5. Association studies have demonstrated that the deletion allele of rs145204276 significantly increases the risk of HBV-related HCC. Subsequent analyses have revealed that rs145204276 increases the expression of GAS5 in HCC tissues and cell lines by altering the methylation status of the GAS5 promoter region (118).

A 4-bp deletion allele of rs10680577 in RERT-lncRNA, an lncRNA whose sequence overlaps with Ras-related GTP-binding protein 4b and prolyl hydroxylase 1 (EGLN2), promotes the occurrence of HBV-related HCC. This allele leads to increased expression of RERT-lncRNA and EGLN2 in HCC tissues and cell lines. Bioinformatics analyses have demonstrated that this allele may alter the structure of RERT-lncRNA. Thus, rs10680577 may affect the occurrence of HBV-related HCC by regulating the expression of RERT-lncRNA and EGLN2 and altering the structure of RERT-lncRNA (119).

rs35622507, a novel short tandem repeat (STR) polymorphism in the coding region of KCNQ1-overlapping transcript 1 (KCNQ1OT1), affects the occurrence of HBV-related HCC. In a group of unrelated Han Chinese subjects, the homozygous 10-10 genotype was shown to increase the risk of HCC. qPCR indicated that HCC cell lines with the homozygous 10-10 genotype exhibited significantly lower expression of KCNQ1OT1 and higher expression of cyclin-dependent kinase inhibitor 1C (CDKN1C) compared with HCC cell lines with other genotypes. Bioinformatics prediction indicated that this STR polymorphism may alter the structure of KCNQ1OT1. Thus, rs35622507 may affect the risk of HBV-related HCC by altering the structure of KCNQ1OT1 and modulating the expression of KCNQ1OT1 and CDKN1C (120).

Recently, a genome-wide association study explored risk loci for familial HBV-related HCC. Although the detailed molecular mechanism remained unclear, a cluster of SNPs overlapping with LINC00272 was associated with increased risk of HBV-related HCC (121).

Expression quantitative trait loci (eQTLs) are genetic variants that may affect the expression of a specific gene and contribute to the risk of complex diseases (122). They are significantly enriched for disease-associated polymorphisms. Several SNPs in lncRNAs, such as rs7248320 (123), rs3757328 (124), rs6940552 (124,125), rs9261204 (124,125), rs11489585 (126), rs79037040 (127) and rs2055822 (127), are eQTLs for a series of genes and may contribute to the risk of HBV-related HCC. In addition to affecting the risk of HBV-related HCC, some eQTLs, such as rs1110839 (128) and rs4848320 (128), may affect the prognosis of HBV-related HCC.

However, all the abovementioned studies were conducted in Chinese populations. Future research in other populations

Table II. Genetic mutations in lncRNAs and HBV-related HCC.

Polymorphism ID	Substitutes	lncRNA	SNP location	Clinical impact	Biological function	(Refs.)
rs7763881	A>C	HULC	Chr6:8653014	Decreases the risk of HCC	Not known	(114)
rs920778	C>T	HOTAIR	Chr12:53966448	Increases the risk of HCC	Increases the expression of HOTAIR and promotes the proliferation of HCC cells	(115)
rs145204276	AGGCA>-	GAS5	Chr1:173868254	Increases the risk of HCC	Regulates the expression of GAS5 via an epigenetic mechanism	(118)
rs10680577	TACT>-	RERT-lncRNA	Chr19:40798691	Increases the risk of HCC	Increases expression of RERT-lncRNA and EGLN2, may change structure of RERT-lncRNA	(119)
rs35622507	GAGT repeats	KCNQ1OT1	Not known	Decreases the risk of HCC	Alters the structure of KCNQ1OT1 and modulates expression of KCNQ1OT1 and CDKN1C	(120)
rs7248320	A>G	AC008392.1	Chr19:48256972	Increases the risk of HCC	eQTLs for CARD8	(123)
rs3757328,	G>A	ZNRD1-AS1	Chr6:30060575	Increases the risk of HCC	eQTLs for ZNRD1	(124)
rs6940552	G>A	ZNRD1-AS1	Chr6:30044563	Increases the risk of HCC	eQTLs for ZNRD1	(124,125)
rs9261204	A>G	ZNRD1-AS1	Chr6:30037466	Increases the risk of HCC	eQTLs for ZNRD1	(124,125)
rs11489585	A>G	APTR	Chr7:77685535	Increases the risk of HCC	eQTLs for PTPN12	(126)
rs79037040	G>T	RP11-1149O23.3	Chr8:23225458	Decreases the risk of HCC	eQTLs for TNFRSF10A	(127)
rs2055822	A>G	RP11-459E5.1	Chr8:22779707	Increases the risk of HCC	eQTLs for TNFRSF10B	(127)
rs1110839	T>G	AC016683.6	Chr2:113236840	Is associated with better prognosis of HCC	eQTLs for PAX8	(128)
rs4848320	C>T	AC016683.6	Chr2:113253214	Is associated with better prognosis of HCC	eQTLs for PAX8	(128)

lncRNA, long non-coding RNA; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

will help to better understand the effect of SNPs in lncRNAs on HBV-related HCC. Taken together, although preliminary, the evidence suggests that genetic polymorphisms in lncRNAs may affect the occurrence and prognosis of HBV-related HCC.

6. Conclusions

During recent years, with the use of various approaches, including loss- and gain-of-function experiments and *in vitro* and *in vivo* analyses, the important role of lncRNAs in the occurrence and prognosis of HBV-related HCC has started to emerge. Several circulating lncRNAs and genetic polymorphisms in lncRNAs are also screened out to affect the risk and prognosis of HBV-related HCC. These studies will hopefully elucidate the mechanism of action of lncRNAs and help in the prevention, diagnosis and treatment of HBV-related HCC.

However, although the findings of these studies are valuable, the functions of a large proportion of lncRNAs dysregulated in HBV-related HCC remain elusive. Although Zhang *et al* found that HCC patients infected with different hepatitis viruses had different dysregulated lncRNAs (73), their mechanism of action remains unclear. Moreover, a recent study indicated that an lncRNA was able to exert its function by encoding a small polypeptide (129). Whether any lncRNAs affect the risk of HBV-related HCC in this manner is yet to be investigated. Future research in these areas will help unravel the function of lncRNAs in HBV-related HCC.

In conclusion, although the functions of lncRNAs have yet to be fully elucidated, recent studies indicate that lncRNAs play key roles in HBV-related HCC, and investigation of lncRNAs will pave the way for fully understanding the mechanism underlying the development of HBV-related HCC.

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Authors' contributions

ZH, CXB and LSL were involved in the conception and design of this study. ZH summarized relevant literature and wrote the manuscript; CXB revised the manuscript; ZJ, WXW, CHJ and LL collected and evaluated relevant literature; LSL revised the manuscript according to the reviewers' comments and was responsible for further support. All authors have read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that there are no potential conflicts of interest and no financial support related to this study.

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