Interaction between lncRNAs and RNA binding proteins, and their potential as drug targets in the therapy of liver cancer (Review)

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Abstract. Liver cancer, including hepatocellular carcinoma (HCC) as the major type, is a serious malignant tumor with high morbidity and mortality worldwide. Long noncoding RNAs (lncRNAs) play an essential role in the pathogenesis and development of liver cancer, as they can cooperate with and modulate other molecules, particularly RNA binding proteins (RBPs), to perform regulatory functions. Conversely, RBPs also deeply influence the functional manner of lncRNAs in cancer cells. Thus, it is critical to decipher how lncRNAs and RBPs interact with each other, affect the expression, localization, structure, modification, or function of their partners, and induce the following biological programs. In the present review, the interactions between lncRNAs and RBPs identified over the past years are examined, and their modes of cooperation and downstream effects on liver cancer progression are explored. Briefly, lncRNA-RBP pairs were classified into different categories according to their mechanisms of interaction and their influence on liver cancer development, including how their interactions affect one another, how they cooperate to regulate targets, and the resulting functional outcomes on liver cancer. In addition, the current state-of-the-art databases and technologies used to identify potential interactions between lncRNAs and RBPs were also emphasized, including crosslinking and immunoprecipitation, RNA immunoprecipitation, RNA pull-down and mass spectrometry. In summary, the present review systematically summarized the regulatory functions of lncRNA-RBP pairs in liver cancer, which suggests the potential to harness RNA-based therapeutics as an alternative treatment modality for liver cancer.

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Contents

1. Introduction

The dysfunction of cells and their induced diseases may result from the dysregulated progression of expression of massive RNAs, including mRNAs and noncoding RNAs (ncRNAs) (1). In addition, up to 98% of the human genome can be transcribed into RNAs, most of which may represent RNAs that do not encode proteins (2), indicating that these transcribed RNAs are regarded as ncRNAs. ncRNAs longer than 200 nucleotides are called long ncRNAs (lncRNAs) (3), which were widely considered to be just transcriptional noise previously (4-6). With the emergence of sensitive and high-throughput sequencing technology, numerous lncRNAs have been detected and recognized. According to the NONCODE (v5.0) database, 172,216 lncRNA transcripts have been identified in the human genome (7). Currently, research has found that an increasing number of lncRNAs have regulatory functions and participate in various biological processes through different mechanisms, such as pluripotency, differentiation, proliferation, or cell survival (8). For example, lincRNA regulator of reprogramming (lincRNA-RoR) promotes the survival of liver cancer

cells during hypoxic stress by regulating the hypoxic signaling pathway, or plays a role in pluripotent or embryonic stem cells by blocking the activation of cell stress pathways (9,10).

LncRNA can bind to proteins, RNA, and DNA, thereby controlling gene expression levels in epigenetics, transcriptional regulation, and other mechanisms through genetic imprinting, chromatin remodeling, cell cycle regulation, splicing regulation, mRNA degradation, and translation regulation (11,12). Scientists are increasingly paying attention to the functional annotation of lncRNAs, especially their role in diseases (13). Liver cancer, including hepatocellular carcinoma (HCC), has become an important cancer in both developing and developed countries. Genetic research has shown that ncRNAs are involved in the initiation, regulation, and progression of HCC (14). LncRNA is receiving increasing attention in the pathogenesis of liver diseases and has potential diagnostic, prognostic, and therapeutic significance (15). The expression of highly upregulated liver cancer (HULC) lncRNA in plasma is known to be a novel mRNA-like lncRNA biomarker for the diagnosis of HCC (16). LncRNA participates in the pathogenesis of HCC by regulating cancer-related signaling pathways such as the MAPK signaling pathway (17).

RNA binding proteins (RBPs) control almost all aspects of RNA fate, including transcription, splicing, modification, cellular transport, translation, and degradation (18,19). Therefore, changes in the expression level, structure, localization, or function of RBPs may have far-reaching effects on various RNAs (19). RBPs interact with RNAs through the RNA binding domain (RBD), which include typical RNA recognition motifs, K homology domains, Piwi/Argonaute/Zwille domains, DEAD/DEAH helicases, and zinc finger domains (20-22). Previous studies have demonstrated that similar to lncRNAs, numerous RBPs are altered in cancer (23,24). In the field of RNA research, the search for the role of RNAs and RBPs in cancer has always been a focus of research (12). The traditional view suggests that RBPs regulate RNAs, but it has been proven that RNAs can also regulate the function of RBPs. In addition, there are also numerous reports suggesting that lncRNAs can also influence the functions of RBPs (25,26). Thus, it is a crucial issue to elucidate the underlying mechanism of how lncRNAs and RBPs interact and influence the progression of liver cancer.

A previous study summarized the interaction between lncRNAs and RBPs in liver cancer, but it was conducted ten years ago, and did not clearly elucidate the exact interaction mechanism between lncRNAs and RBPs in liver cancer (27). Due to the lack of information on lncRNA-RBP interactions, it hinders a better understanding of the mechanisms of lncRNA RBP interaction networks in the occurrence and development of liver cancer. With the deepening of research, more and more RBDs in RBPs have been discovered, providing a theoretical basis for the development of more drugs targeting RBDs in proteins. In the present review, the interaction between lncRNAs and RBPs specifically in liver cancer disease was examined. Notably, how lncRNA-RBP pairs affect the development or progression of liver cancer, as well as their downstream targets, was elucidated, and the mechanism of abnormal interaction networks in the occurrence and development of liver cancer was investigated.

2. LncRNA and RBP interactions form RNA-protein complexes

Through the application of high throughput sequencing technologies, the discovery and functional studies of lncRNAs have been expanded with blowout style (6). Numerous lncRNAs have been identified and verified in association of cancer development (28). As ncRNAs, lncRNAs in most cases interact with other molecules to modulate the tumorigenesis or progression of cancers, indicating the essential functions of lncRNA partners. RBPs are the most important type of lncRNA partners and can form RNA-protein (RNP) complexes with lncRNAs (29). Canonical RBPs have a wide range of substrates, including various types of RNAs, such as those associated with the heterogeneous nuclear ribonucleoprotein (hnRNP) family. In terms of functionality, RBPs can regulate the localization and function of lncRNAs (30). Conversely, lncRNAs can also alter the localization, modification, or even structure of associated RBPs to modulate their functions. In addition, the most important functions of RNP complexes are to regulate the downstream targets and influence the development of cancers (31). Thus, it is essential to identify the interactions between lncRNAs and RBPs to investigate their functions in liver cancer.

LncRNA-RBP pairs modulate the stability of each other or their substrates in liver cancer. An important function of lncRNAs is to interact with target proteins to stabilize their expression (32). In liver cells, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was shown to upregulate the expression of sterol regulatory element-binding protein 1c (SREBP-1c) by stabilizing the SREBP-1c protein, thereby promoting hepatic steatosis and insulin resistance (33). Similarly, lncRNA family with sequence similarity 215 member A (FAM215A) was found to be highly expressed in HCC, and increased the stability of lysosome-associated membrane protein 2 (LAMP2). FAM215A could prevent the ubiquitination of LAMP2, thereby reducing its degradation. FAM215A interacted with LAMP2 and stabilized LAMP2 to increase tumor progression (34). Through global identification and experimental validation, a novel RBP-lncRNA pair, non-canonical RBP CCT3 and LINC00326, was identified, which controls hepatocarcinogenic lipid metabolism and affects tumor growth (35). Notably, a downregulated lncRNA in HCC, NONHSAT024276, has been shown to interact with polypyrimidine tract-binding protein (PTBP)1, downregulate its expression and form a feedback loop. NONHSAT024276 was demonstrated to increase the ratio of M1 and M2 isoforms of pyruvate kinase (PKM1/PKM2) and to obstruct the PTBP1/PKM-mediated glycolysis, thus inhibiting HCC progression (36). In liver cancer, DEAD/H-box helicase 11 (DDX11)-antisense RNA 1 (AS1) has been shown to be upregulated and to promote cell-cycle progression. Mechanistically, DDX11-AS1 was demonstrated to interact with poly (ADP-ribose) polymerase 1 (PARP1), leading to downregulated expression of p53 and inhibition of the transcription of downstream genes such as p21 (37).

Conversely, RBPs have the ability to stabilize or destabilize the expression of lncRNAs. At the post-transcriptional level, RBPs can modulate the stability, degradation, and

functions of lncRNAs by interacting with them and forming RNP complexes (12). In hepatoma cells, the lncRNA small nucleolar RNA host gene (SNHG)6 was shown to interact with two important RBPs, including PTBP1 and hnRNPL. The interaction between SNHG6 and hnRNPL adsorbed hnRNPL from SET domain containing lysine methyltransferase 7 (SETD7) mRNA, inducing the degradation of SETD7 mRNA. In addition, SNHG6 and PTBP1 interaction facilitated the degradation of leucine zipper transcription factor like 1 mRNA. These two functional mechanisms both promote HCC progression, suggesting that SNHG6 promotes HCC progression by functioning as a 'decoy plus guide' (38). As an important RBP, PTBP1 can also interact with other lncRNAs. LncRNA OIP5-AS1 was upregulated in hepatoblastoma cells and could promote their proliferation and stemness. Mechanistically, OIP5-AS1 interacted with PTBP1 to increase the mRNA stability of β-catenin (39). In summary, these findings demonstrate that lncRNAs and RBPs interact with each other and affect the expression and functions of their partners, ultimately regulating liver cancer development or progression. LncRNA HULC, shown to be highly upregulated in liver cancer, demonstrated specific binding interaction with insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), which could lead to a decreased HULC half-life and lower steady-state expression levels (40).

As an important RBP, human antigen R [HuR; also known as embryonic lethal abnormal visual-like protein 1 (ELAVL1)], an ELAV family protein, can stabilize mRNA levels (41). LINC02381 (also named HOXC10 mRNA stabilizing lncRNA (HMS), has been shown to physically interact with HuR, and stabilize HOXC10 mRNA, which is overexpressed in numerous cancers. The findings indicate that the HuR and HMS interaction can maintain the invasive phenotypes of cancer cells (42). In HCC cells, HuR has been demonstrated to directly interact with lncRNA ubiquitin-fold modifier conjugating enzyme 1 (UFC1). In addition, HuR and lncRNA-UFC1 have been shown to cooperate to increase the mRNA level of CTNNB1. LncRNA-UFC1 has the ability to promote proliferation and cell cycle progression of HCC cells, which may be achieved by the increased level of catenin β1 (CTNNB1) (43). From the description and summary, it is observed that lncRNA-RBP pairs can modulate the stability and expression of each other; furthermore, they can also form complexes to influence the stability of other molecules, indicating that they have broad functional roles in regulating the stability of molecules in liver cancer.

Expanded tumor suppressor lncRNA-RBP interactions. While the majority of characterized lncRNA-RBP interactions in liver cancer promote tumorigenesis, several tumor-suppressive networks have been identified that warrant equal attention for therapeutic restoration. Understanding these protective mechanisms provides crucial insights for developing strategies to reactivate endogenous tumor suppression.

The lncRNA growth arrest-specific transcript 5 (GAS5) represents a paradigm of tumor-suppressive lncRNA-RBP interactions. GAS5 exemplifies tumor-suppressive lncRNA function through interactions with RBPs. In contrast to oncogenic lncRNAs, GAS5 was reported to be significantly downregulated in HCC tissues and was found to function as a potent suppressor of proliferation and metastasis (44). Mechanistically, GAS5 was shown to interact with the eukaryotic translation initiation factor 4E binding protein 2, acting as a translational inhibitor that suppresses cap-dependent protein synthesis, a critical requirement for rapidly dividing cancer cells (45). Additionally, GAS5 was demonstrated to serve as a competing endogenous RNA (ceRNA) sponge for multiple oncogenic microRNAs (miRNAs or miRs) in liver cancer, including miR-222 and miR-21, thereby derepressing their tumor-suppressive targets (46,47). Notably, GAS5 expression was shown to be correlated with enhanced natural killer (NK) cell cytotoxicity against HCC cells by interacting with miR-544 to regulate expression of runt-related transcription factor 3 (RUNX3), highlighting its role in tumor immunosurveillance (48). The restoration of GAS5 levels through RBP-mediated stabilization (such as via UPF1 interaction) or antisense oligonucleotide (ASO)-based delivery represents a promising therapeutic strategy distinct from oncogenic lncRNA inhibition (49).

Another lncRNA which has been shown to repress HCC progression is maternally expressed gene 3 (MEG3), a p53-activating tumor suppressor. MEG3 represents another critical tumor-suppressive lncRNA frequently silenced in HCC through both genetic and epigenetic mechanisms. MEG3 expression was shown to be induced in a p53-dependent manner following DNA damage and interacted with the RBP PTBP3. This interaction paradoxically inhibited p53 activation, forming a negative feedback loop that modulated DNA damage responses (50). However, in the context of HCC, MEG3 downregulation, often mediated by m^6A modification via methyltransferase-like protein 3 (METTL3), has been shown to disrupt this regulatory axis, contributing to unchecked proliferation (51). Thus, it is proposed that the restoration of MEG3 expression or stabilization of MEG3-PTBP3 interactions may reactivate p53 signaling and suppress hepatocarcinogenesis.

The lncRNA NONHSAT024276 was shown to form a tumor-suppressive feedback loop with PTBP1 to inhibit HCC progression and glycolysis. Unlike oncogenic lncRNAs that stabilize PTBP1, NONHSAT024276 was found to interact with and downregulate PTBP1 expression, thereby increasing the PKM1/PKM2 ratio and obstructing glycolysis-dependent tumor progression (36). This interaction illustrates how lncRNA-RBP pairs can function as molecular brakes on carcinogenic metabolism, offering a distinct therapeutic target for metabolic reprogramming in HCC. Another famous lncRNA is H19. While H19 is predominantly characterized as oncogenic in liver cancer, it exhibits tumor-suppressive functions under specific conditions through RBP-mediated mechanisms. H19 was shown to be associated with the hnRNPU, p300/CBP-associated factor (PCAF)/RNA polymerase II (RNA polII) complex, facilitating its nuclear translocation and subsequent epigenetic activation of the miR-200 family via histone acetylation. This mechanism was found to suppress epithelial-to-mesenchymal transition (EMT) and metastasis in HCC (52). The dual functionality of H19 highlights the importance of cellular context and specific RBP partnerships in determining lncRNA function, suggesting that therapeutic strategies must account for the dynamic nature of these interactions.

3. LncRNAs cooperate with RBPs to regulate transcription in liver cancer

Transcriptional regulation establishes and maintains specific cell states and its misregulation can cause a broad range of diseases (53). In this regulatory area, a large proportion of lncRNAs localize in the nucleus and can regulate transcriptional programs (54). Mechanistically, lncRNAs can regulate gene expression at the transcriptional and post-transcriptional levels by targeting local or distant genes (6). LncRNAs not only bind to transcription factors (TFs) or other protein complexes, but also recruit them to promoters. In this case, TFs are specific RBPs that interact with lncRNAs. The common mechanism for transcriptional regulation by lncRNAs is to recruit or block components of chromatin or histone-modifying complexes (20,55). At the transcriptional level, a novel regulatory pattern has been widely observed in which lncRNAs bind to histone-modifying complexes and recruit these complexes to specific locations. In this section, the lncRNA-RBP pairs controlling transcription in liver cancer are summarized. LncRNA heart and neural crest derivatives expressed 2-antisense RNA 1 (HAND2-AS1) was shown to recruit the INO80 chromatin remodeling complex to activate bone morphogenetic protein (BMP) receptor type 1A (BMPR1A) transcription and BMP signaling transduction, thus promoting stem cell self-renewal of liver cancer. In addition, BMPR1A was found to promote liver cancer stem cell (CSC) self-renewal through BMP signaling (56). BMP signaling has been shown to involve the regulation of stem cells, including hair follicle stem cells, blood stem cells, and pluripotent stem cells (57-59). These findings also indicate that INO80 is a novel RBP that interacts with HAND2-AS1. A previous study demonstrated that hnRNPK, an RBP from the hnRNP family, interacts with small nucleolar RNA SNORD126, an orphan C/D box snoRNA. The formed RNP complex was shown to regulate fibroblast growth factor receptor 2 (FGFR2) expression at the transcriptional level, then activate the PI3K-AKT pathway, and ultimately promote HCC development (60). In addition, hnRNPs can interact with lncRNAs and inhibit gene expression. For example, in macrophages, lncRNA lnc13 was shown to form a complex with the p42 subtype of hnRNPD, which can promote histone deacetylase 1 (HDAC1) binding to the promoter regulated by lnc13 and ultimately inhibit the expression of inflammatory factors, indicating that hnRNPD and lnc13 play an important role in recruiting HDAC1 to promoter regions (61).

Another important lncRNA, HOX transcript antisense RNA (HOTAIR) was shown to reduce the recruitment of the cAMP response element-binding protein (CREB), p300, RNA polII onto the SET domain-containing 2 (SETD2) promoter region that inhibits SETD2 expression and its phosphorylation, and finally promote human liver cancer stem cell malignant growth (62). Notably, two lncRNAs, including HULC and MALAT1, can cooperate to aggravate liver cancer stem cell growth by increasing telomeric reapeat binding factor 2 expression via transcriptional regulation (63). The highly expressed LINC00324 in liver cancer has been shown to regulate Fas ligand (FASL) expression by interacting with Spi-1 proto-oncogene (PU.1) (64). By recruiting the nucleosome remodeling and deacetylase (NuRD) complex, long non-coding RNA histone deacetylase 2 (lncHDAC2) was demonstrated to localize on the promoter of promoter of patched 1 (PTCH1) to inhibit its expression, leading to activation of Hedgehog signaling (65). LncRNA HOTTIP was shown to function in a cis manner to directly control the homeobox A locus gene expression by interacting with the WD repeat domain 5/mixed-lineage leukemia complex, thereby promoting HCC progression and predicting patient outcome (66). A recent study demonstrated the molecular and cellular functions of lncRNA linc01134. Linc01134 was shown to interact with RBP IGF2BP1 to promote the stability of Yin Yang-1 (YY1) expression, and YY1 also promoted the transcription of linc01134, forming a positive feedback loop to dictate the progression of HCC. In addition, linc01134 was demonstrated to act as a miR-324-5p sponge to exert its function (67).

LncRNAs not only interact with TFs, but also recruit them to promoter regions to regulate the transcription process. At the transcriptional level, a new pattern has been widely observed in which lncRNAs bind to histone-modifying complexes and recruit histone-modifying complexes to specific locations. Enhancer of zeste 2 (EZH2) is the subunit of polycomb repressive complex 2 (PRC2), which is involved in maintaining the transcriptional repressive state of genes by modifying histones. In liver cancer, DDX11-AS1 was shown to interact with EZH2 and DNA methyltransferase 1, and to suppress large tumor sppressor kinase 2 (LATS2) expression through a histone modification mechanism, indicating DDX11-AS1 may be a novel oncogene in hepatocarcinogenesis by repressing LATS2 (68). With regard to lncRNA SNHG9, it was also shown to interact with EZH2 and recruit EZH2 to the promoter region of phosphatase and tensin homolog (PTEN), thereby inhibiting transcription of PTEN by increasing histone H3 lysine 27 trimethylation levels in the promoter region. As PTEN is a canonical tumor suppressor, these findings indicated that SNHG9 promotes liver CSC self-renewal and tumor formation, and exacerbates HCC progression by inhibiting PTEN (69).

4. RNA modification and regulators of lncRNA stability and expression

RNA modifications, including N6-methyladenosine (m^6A) and 5-methylcytosine (m^5C), have been shown to significantly influence the functions of lncRNAs in cancer (70). It has been reported that m^6A modification plays an important role in liver carcinoma and lipid metabolism (71). The m^6A reader has been shown to play a crucial role in the stability of lncRNAs. Expression of lncRNA MEG3 was downregulated in HCC tissues, which was probably induced by N^6-methyladenosine modification mediated by m^6A writer METTL3. In addition, overexpression of MEG3 was shown to inhibit the proliferation, migration and invasion of HCC cells through miR-544b/BTG anti-proliferation factor 2 signaling (51). It was shown that METTL3 mediates the modification of lncRNA nucleolar protein interacting with the FHA domain of MKI67 (NIFK)-AS1 and increases its expression. Highly expressed NIFK-AS1 was demonstrated to promote the proliferation, colony formation, migration, and invasion of HCC cells through a ceRNA network involving an NIFK-AS1/miR-637/AKT1 axis (72). Peng *et al* explored the role of lipopolysaccharide

(LPS) in immune regulation of HCC, and detected the participation of lncRNA m^6A modification. LPS treatment increased the expression of methyltransferase-like protein 14 (METTL14), which promotes m^6A modification of miR-155 host gene (MIR155HG). The expression of MIR155HG was then stabilized by m^6A 'reader' protein ELAVL1. Finally, MIR155HG functioned as a ceRNA to modulate the expression of programmed death-ligan 1 by the miR-223/signal transducer and activator of transcription (STAT)1 axis (73). METTL14 was also shown to mediate m^6A modification of lncRNA Rho GTPase acitvating protein 5 (ARHGAP5)-AS1, which is significantly increased in HCC by m^6A reader IGF2BP2. The high expression of ARHGAP5-AS1 was demonstrated to interact with cold shock domain containing E1 (CSDE1) and attenuate the interaction between CSDE1 and tripartite motif containing 28, preventing CSDE1 degradation via the proteasome, finally contributing to HCC prognosis (74). Compared with m^6A, m^5C modification is less known and reported. A previous study showed that the expression of lncRNA H19 is also regulated by m^5C modification. RNA methyltransferase NOP2/Sun RNA methyltransferase 2 increased the m^5C level of H19, thus increasing its stability. The m^5C-modified H19 lncRNA could be specifically bound by G3BP stress granule assembly factor 1, leading to MYC accumulation and finally associated with poor differentiation of HCC (75). In summary, these findings demonstrated that RBP-mediated RNA modification can profoundly regulate the expression and function of lncRNAs, which can modulate the function of downstream targets and affect the progression of liver cancer.

5. RBP-lncRNA interactions regulate their transport and localization in liver cancer

The subcellular localization of molecules can indicate their potential functions and influences on biological processes. Increasing evidence suggests that RBPs can affect the cellular localization of lncRNAs, and vice versa. The functions of lncRNAs are tightly associated with their subcellular localizations, and have been previously summarized (54). It has been shown that RBP HuR can affect the stability and localization of its target RNA (76). The oncoprotein Yes associated protein (YAP) was shown to upregulate the expression of MALAT1 at the transcriptional and post-transcriptional levels, while serine and arginine rich splicing factor 1 (SRSF1) played the opposite role. SRSF1 inhibited YAP activity and downregulated MALAT1 expression by preventing co-occupation of T-cell factor/β-catenin on YAP and MALAT1 promoters. Conversely, overexpression of YAP impaired the nuclear preservation of SRSF1 and itself by interacting with angiokinetin. This effect eliminated the inhibitory effect of SRSF1 on MALAT1 in the nucleus. In addition, the high expression of YAP was consistent with the low nuclear accumulation of SRSF1 in human liver cancer tissue. Thus, RBP SRSF1 was demonstrated to exert important regulation on MALAT1 expression via protein-protein interaction, but not by directly interacting with MALAT1 RNA (77).

In most cases, H19 is a carcinogenic lncRNA. However, H19 can suppress HCC progression metastasis and the expression of markers of EMT. Mechanistically, H19 has been shown to be associated with the protein complex hnRNPU/PCAF/RNA polII, and to transport this complex into nucleus, thus activating the miR-200 family by increasing histone acetylation. Ultimately, the epigenetic activation of the miR-200 family was demonstrated to contribute to H19-mediated suppression of HCC metastasis (52). Concurrently, it has also been observed that lncRNA H19 can accelerate the occurrence of liver cancer. miR-675 embedded in the first exon of H19 can promote H19 transcription through histone modification and subsequent early growth response 1 transcription in an indirect manner. Finally, H19 may promote tumorigenesis by activating PKM2 to alter the expression and function of oncogenes with an as-yet unknown mechanism in human liver cancer (78). These findings suggest that lncRNAs can have various functions under specific conditions, which is probably induced by their interacting partners.

As one of the first identified cancer-related lncRNAs, HOTAIR has been shown to be aberrantly expressed in numerous tumors, including liver cancer, and is closely related to the occurrence and development of tumors (79). HOTAIR is reported to influence the localization of its interacting proteins. SETD2 is a lysine methyltransferase that catalyzes histone H3 lysine 36 trimethylation and has been revealed to play important roles in the regulation of transcriptional elongation, RNA splicing, and DNA damage repair (80). LncRNA HOTAIR was shown to reduce the reappearance of CREB, p300, and RNA polII in the SETD2 promoter region, thereby inhibiting SETD2 expression and its phosphorylation. Therefore, HOTAIR greatly impaired the DNA damage repair ability and increased microsatellite instability of liver stem cells, ultimately promoting their malignant growth (62). A similar mechanism was also observed for lncRNA LEF1-AS1, which recruits TF CCAAT/enhancer-binding protein (CEBP)β to the promoter region of cell division cycle associated 7 (CDCA7) to promote CDCA7 expression, therefore upregulating EZH2 expression and promoting proliferation and invasion of HCC cells (81).

LncRNA CEBPA-divergent transcript (DT), a divergent transcript of CEBPA, was revealed to have the ability to promote growth, migration and invasion of hepatoma cells. CEBPA-DT could bind to hnRNPC, facilitating cytoplasmic translocation of hnRNPC, and enhancing the interaction between hnRNPC and discoidin domain receptor 2 mRNA. In addition, CEBPA-DT could also facilitate nuclear translocation of β-catenin, which promotes Snail family transcriptional repressor 1 expression and finally induces the EMT process (82).

In addition, hnRNPK has been identified as a driving factor for RNA nuclear retention. MALAT1 lacks short scattered nuclear elements (SINEs), which can easily translocate to the cytoplasm and bind more strongly to TAR DNA protein 43 (TDP-43). TDP-43 can even be guided to the cytoplasm by MALAT1, leading to a decrease in the TDP-43 expression. Notably, the SINEs of MALTA1 can regulate the interaction between hnRNPK and MALAT1, which increases the nuclear retention of MALAT1. This may occur through direct interaction between SINEs and KH RNA binding domain containing, signal transduction associated 1, containing the KH RNA binding domain, as well as transformer-2α homolog protein, which binds to hnRNPK (83).

6. LncRNAs act as ceRNAs to modulate gene expression in liver cancer

LncRNAs can also sponge miRNA, acting as ceRNAs, to modulate expression of downstream genes, the regulatory mechanism of which is more abundant and deeper explored in cancers (84). This process is predominantly regulated by RBPs such as the miRNA partner Argonaute 2 (AGO2). AGO2 contains four functional core domains and has catalytic activity; its interaction with miRNAs guides the complex to the target RNA body, and can induce gene silencing at the post-transcriptional level (85). For example, lncRNA proliferating cell nuclear antigen pseudogene 1 (PCNAP1) was shown to contribute to hepatitis B virus (HBV) replication by attracting miR-154, thus increasing the expression level of PCNA, finally accelerating the growth of HCC (86). HOXD-AS1 was demonstrated to also act as a ceRNA to attract miR-130a-3p and upregulate expression of SRY-box containing transcription factor 4, thus activating the expression of EZH2 and matrix metalloproteinase (MMP)2 and ultimately facilitating HCC metastasis (87). LncRNA BCAR4 has also been shown to act as a ceRNA to promote liver cancer progression by sponging miR-1261 and upregulating anaphase promoting complex subunit 11 expression (88). As a well-known lncRNA, MALAT1 has been demonstrated to promote liver cancer progression, and one of the underlying mechanisms was reported to be that MALAT1 sponges miR-204 to release the expression and function of sirtuin 1 (SIRT1), which can significantly promote HCC migration and invasion (89). LncRNA growth arrest-specific transcript 5 (GAS5) was shown to be downregulated in the NK cells of patients with liver cancer. By exploring the underlying mechanism, it was found that GAS5 serves as a sponge of miR-544, and GAS5 overexpression was demonstrated to increase RUNX3 expression, interferon-gamma (IFN-γ) secretion, and NK cell cytotoxicity, indicating the killing effect of GAS5 on cancer cells (48). LncRNA HOTAIR can also act as a ceRNA to promote growth of liver cancer by targeting miR-217 (90). In addition, lncRNAs have been shown to not only sponge miRNA, but also RBPs and act as ceRNAs. Specifically, lncRNAs have been demonstrated to serve as 'bait' to prevent protein binding to target RNA. These lncRNAs can bind to RBPs and regulate the post-transcriptional fate of target mRNA (91). Furthermore, circular RNAs (circRNAs), a specific type of lncRNAs, have also been shown to be crucial ceRNAs that sponge miRNAs (92,93). Previous studies have described the functions and mechanisms of circRNAs in liver cancer (94,95). For example, circDLC1 can attract RBP HuR to subsequently reduce the interaction between HuR and MMP1 mRNAs, thus inhibiting the expression of MMP1 and ultimately contributing to inhibition of HCC progression (96). With regard to clinical application, circRNAs exhibit potential as novel biomarkers and therapeutic targets in HCC (97).

Moreover, numerous lncRNAs involved in liver cancer were reported to not be associated with RBPs. Knockdown of ACTA2-AS1 has been shown to promote liver cancer cell proliferation, migration and invasion, however the underlying mechanism has not been clearly elucidated (98). High expression of SNHG4 was shown to indicate a poor overall survival of patients with liver cancer, while the underlying mechanisms remain unclear (99). Ding *et al* demonstrated that lncRNA HOTAIR inhibits the mRNA and protein levels of RNA binding motif protein (RBM38) in HCC cells, thus promoting cell migration and invasion; whereas, how HOTAIR and RBM38 interact or cooperate to promote HCC progression has yet to be determined (100). Another well-known lncRNA, H19, can be detected in the exosomes released by $CD90^+$ liver cancer cells, and was reported to mediate the phenotype of endothelial cells (101). LncRNA deleted in lymphocytic leukemia 2 (DLEU2) has been shown to interact with EZH2. DLEU2 knockdown inhibited the proliferation of HCC cells, while EZH2 knockdown attenuated this inhibition. However, how DLEU2 and EZH2 interact and their molecular functions remain unclear (102).

7. LncRNAs regulate the post-translational modification of RBPs

The function of proteins is usually regulated by introducing chemical modifications after translation. Different types of post-translational modifications (PTMs) can affect multiple functions of proteins, thereby influencing cellular function and ultimately leading to the occurrence and development of cancer (103,104). To date, it has been found that some lncRNAs can regulate PTMs of their binding proteins through mechanisms such as phosphorylation, ubiquitination, and acetylation, thereby regulating protein degradation or production, and affecting protein expression levels and activity (105). p53 determines cell fate by regulating the transcription ability of multiple target genes, and its PTMs play a crucial role in its activity. However, how the PTMs of p53 are dysregulated remains a question worth exploring. MALAT1, a transcript associated with lung adenocarcinoma metastasis, has been shown to be involved in the PTMs of p53 and to affect the occurrence and development of tumors. According to previous studies, MALAT1 is widely present in various cancers, including HCC (106), and is associated with the proliferation and metastasis of cancer cells. MALAT1 was shown to reduce the acetylation of p53 by competing with the interaction of SIRT1 and deleted in breast cancer 1, thereby releasing SIRT1 and thus regulating the activity of SIRT1 (107). Similarly, APAL [also referred to as a Polo-like kinase 1 (PLK1)-related lncRNA] was shown to promote Aurora kinase A (AURKA)-mediated PLK1 phosphorylation by increasing the interaction between PLK1 and AURKA (108). In addition, lncRNA mesenchymal stem cell upregulation factor (lncRNA-MUF), was demonstrated to specifically interact with glycogen synthase kinase-3 β (GSK-3β) and annexin A2 (ANXA2) through different but partially overlapping sites, thereby regulating the progression of HCC. In addition, the increased expression of lncRNA-MUF promoted the interaction between ANXA2 and GSK-3β. Conversely, depletion of lncRNA MUF inhibited these binding effects (109).

In a recent study, lncRNA tetraspanin 12 (TSPAN12) was shown to be stabilized and partially increased by METTL3-mediated m^6A modification in HCC. Subsequently, TSPAN12 directly interacted with eukaryotic translation initiation factor 3 subunit I (EIF3I) and sentrin-specific protease 1 (SENP1), and also enhancde EIF3I-SENP1 interaction.

This interaction was shown to inhibit the SUMOylation of EIF3I, ultimately activating the Wnt/β-catenin signaling pathway and stimulating EMT and metastasis in HCC (110). By competing with HOTAIR to bind to EZH2, lncRNA-p21 not only broke down the PRC2 complex to release EZH2, but also enhanced the interaction between EZH2 and STAT3 to trigger STAT3 methylation (111). It is worth noting that the interaction between GAS5 and YAP was shown to enhance YAP phosphorylation, promoting its ubiquitination and degradation, thereby inhibiting YAP signaling. Therefore, lncRNA-GAS5 was demonstrated to inhibit the progression of colorectal cancer by dysregulating YAP *in vivo* and *in vitro* (112). Previous research has shown that lncRNAs can serve as regulatory factors for ubiquitin-mediated protein hydrolysis, promoting the degradation of ubiquitin-binding proteins. HOTAIR was shown to interact with E3 ubiquitin ligase and its substrates, thereby enhancing the ubiquitination and degradation of Ataxin-1 and Snuportin-1 (113). Although the aforementioned studies were not completely derived from liver cancer research, the findings on these important lncRNAs and RBPs indicate that these regulatory mechanisms may also occur and play important roles in liver cancer, which should be further explored in the future.

8. Databases that summarize the interactions between lncRNAs and RBPs

Based on the current literature research, there are several lncRNA and RBP databases that have summarized the identified lncRNAs and RBPs, their functions, subcellular localizations, association with diseases, and even their interaction pairs. LncBook2.0 (https://ngdc.cncb.ac.cn/lncbook/) is a curated database that integrates human lncRNAs with multi-omics annotations (114). In this version, LncBook2.0 identified the lncRNA-protein interaction pairs using the RNA binding sites of 356 RBPs from HepG2 and K562 cells, which are obtained by the eCLIP-seq experiments (115). Specifically, HepG2 is a type of liver cancer cell line, indicating that the identified lncRNA-RBP interaction pairs from LncBook2.0 can provide an abundant resource for the functional interactions between lncRNAs and RBPs in liver cancer cells. Typically, specific motifs exist within the lncRNA binding site of protein regulatory factors. High throughput CLIP-seq technology has provided comprehensive RBP datasets from various cell types. The recently established database CLIPdb collected 395 public CLIP-seq datasets for 111 RBPs from four organisms, providing a valuable resource to search and visualize the interactions between RBPs and RNAs, including lncRNAs (116).

In addition, the experimentally validated lncRNAs and circRNAs associated with human cancers have been collected and categorized in Lnc2Cancer 3.0 database, which includes 9,254 lncRNA-cancer associations, with 2,659 lncRNAs and 216 cancer subtypes. This database provides an abundant resource for the identification of lncRNAs associated with liver cancer. There were 117 entries related with liver cancer when the database was searched (117). However, this database does not provide detailed functional information for these validated lncRNAs. Finally, a review article has been published that listed the RNA-protein interaction database resources, which can help scientists quickly search for lncRNAs and proteins of interest (118).

In addition to database resources, the rapidly developing technologies and methods have also aided in identifying the lncRNA-RBP complexes in various diseases. Specifically, next generation sequencing technology has been shown to facilitate the identification of novel lncRNAs, as well as the interaction sites between RBPs and RNAs. The aforementioned CLIP and RNA immunoprecipitation methods can identify the sites bound by a specific RNA-binding protein on endogenous RNAs (119). In addition, RNA pulldown, RNA antisense purification, and chromatin isolation by RNA purification methods can help scientists identify interacting proteins given a lncRNA of interest (120-122). In addition to experimental methods to capture lncRNA-RBP pairs, *in silico* inference methods have also been developed for the prediction of these RNP complexes. With the increased accuracy of predictive algorithms, inference methods can provide highly confident prediction results, which accelerates the discovery of functional RNP complexes (123).

9. Therapeutic targeting of lncRNA-RBP interactions: Strategies and challenges

The identification of disease-driving lncRNA-RBP interactions in liver cancer has opened unprecedented opportunities for therapeutic intervention. Unlike traditional protein-targeting drugs, RNA-based therapeutics offer the unique advantage of targeting 'undruggable' molecules by sequence-specific recognition. Subsequently, the current therapeutic strategies targeting lncRNA-RBP networks, including ASOs, small molecule inhibitors, and clustered regularly interspaced short palindromic repeats (CRISPR)-based approaches, are presented alongside the critical challenges facing clinical translation.

ASOs and small interfering RNA (siRNA)-based approaches. ASOs represent the most clinically advanced strategy for targeting oncogenic lncRNAs in liver cancer. These single-stranded DNA constructs (16-20 nucleotides) bind complementary RNA sequences and mediate target degradation via RNase H1-dependent cleavage or steric blockade of RBP binding sites (124). The liver presents a privileged organ for ASO delivery due to its fenestrated endothelium and high metabolic activity, facilitating accumulation of systemically administered oligonucleotides.

Recent clinical progress highlights the translational potential of ASO technology. Bepirovirsen, an investigational ASO targeting HBV RNA, has demonstrated statistically significant functional cure rates in Phase III trials and was accepted for regulatory review in Japan in 2026 (125). While primarily an antiviral agent, the success of bepirovirsen validated ASO delivery to hepatocytes and established a regulatory pathway for liver-targeted RNA therapeutics. For HCC-specific applications, ASOs could be designed to degrade oncogenic lncRNAs such as HULC, MALAT1, or HOTAIR, thereby disrupting their pro-tumorigenic interactions with RBPs including IGF2BP1, PTBP1, and EZH2, respectively (126-128).

Chemical modifications have substantially improved ASO pharmacological properties. Substitution with

Table I. Summary of the therapeutic potential of lncRNA-RBP pairs in liver cancer.

First author/s, year	LncRNAs	RBPs	Functions	Targeting strategies	(Refs.)
Klec *et al*, 2019	HULC	IGF2BP1	Promote HCC progression	ASO	(126)
Tian *et al*, 2021	HOTAIR	EZH2	Epigenetic regulation	Small molecule inhibitors	(127)
Amodio *et al*, 2018	MALAT1	SRSF1	Activate mTOR pathway	ASO	(128)
Ali *et al*, 2020	RP11-156p1.3	Not identified	Regulate TNF-α and NF-κB pathways	CRISPR-Cas9	(137)
Xu *et al*, 2021	DDX11-AS1	PARP1	Promote cell-cycle progression	Small molecule inhibitors	(37)
Ye *et al*, *2021*	SNHG9	GSTP1	Promote cell proliferation, migration, and invasion	CRISPR-dCas9	(138)

lncRNA-RBP, long non-coding ribonucleic acid-ribonucleic acid-binding protein; ASO, antisense oligonucleotide; CRISPR, clustered regularly interspaced short palindromic repeats; Cas, CRISPR-associated protein; CRISPR-dCas9, clustered regularly interspaced short palindromic repeats-dead CRISPR-associated protein 9; DDX11-AS1, DEAD-box helicase 11 antisense RNA 1; EZH2, enhancer of zeste homolog 2; GSTP1, glutathione S-transferase Pi 1; HCC, hepatocellular carcinoma; HOTAIR, HOX transcript antisense RNA; HULC, highly upregulated in liver cancer; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PARP1, poly(ADP-ribose) polymerase 1; RBP, ribonucleic acid-binding protein; RP11-156p1.3, ribonucleic acid clone RP11-156p1.3; SRSF1, serine/arginine-rich splicing factor 1; SNHG9, small nucleolar RNA host gene 9; TNF-α, tumor necrosis factor-α.

2'-O-methoxyethyl, locked nucleic acids, or phosphorothioate backbones was shown to enhance nuclease resistance, reduce immunogenicity, and improve binding affinity (129). Notably, the development of N-acetylgalactosamine (GalNAc) conjugation technology has revolutionized liver-specific delivery, achieving >80% hepatocyte uptake after subcutaneous administration (130), which enables precise targeting of hepatocyte-specific lncRNA-RBP interactions while minimizing systemic toxicity.

RNA interference approaches using siRNAs offer an alternative mechanism for lncRNA silencing. Unlike ASOs, siRNAs operate through the RNA-induced silencing complex and can achieve potent, long-lasting knockdown. However, siRNA delivery to hepatocytes requires sophisticated nanoparticle formulations, typically lipid nanoparticles or GalNAc conjugation (131).

Small molecule inhibitors of lncRNA-RBP interactions. The development of small molecules disrupting lncRNA-RBP interactions represents a paradigm shift toward 'druggable' RNA targets. Unlike ASOs that degrade the entire RNA transcript, small molecules can selectively inhibit specific protein-binding interfaces while preserving other lncRNA functions, potentially reducing off-target effects (132). The interaction between lncRNAs and RBPs often depends on discrete structural motifs, including kissing loops, bulges, and G-quadruplexes, which present binding pockets for small molecule intervention. Advances in structural biology and computational screening have enabled rational design of inhibitors targeting these interfaces (133). The therapeutic strategy offers dual targeting flexibility: Inhibitors can be designed to bind either the lncRNA interface or the RBD of the protein. For liver cancer, this approach could disrupt pathological interactions such as HOTAIR-EZH2, MALAT1-SRSF1, or DDX11-AS1-PARP1, thereby reactivating tumor suppressor pathways or inhibiting oncogenic signaling (Table I). Preclinical studies suggest that small molecule disruption of lncRNA-RBP interactions can restore normal RNA metabolism and suppress tumor growth with favorable pharmacokinetic properties compared with biologics (134,135).

CRISPR-based and gene editing strategies. CRISPR-CRISPR associated protein (Cas) systems offer permanent, heritable disruption of oncogenic lncRNA loci, providing a potential curative approach for liver cancer. Unlike transient ASO or siRNA effects, CRISPR-mediated deletion or transcriptional repression ensures sustained silencing of disease-driving lncRNAs. The catalytically dead Cas9 (dCas9) fused to transcriptional repressors (KRAB) enables specific epigenetic silencing of lncRNA promoters without DNA cleavage, minimizing genotoxicity risks (136). Previous studies have successfully applied CRISPR-dCas9 to investigate lncRNA function in HCC. For instance, CRISPR-mediated knockout of lncRNA RP11-156p1.3 in HepG2 cells significantly decreased cell viability and reversed oncogenic signaling through TNF-α and NF-κB pathways (137). Similarly, CRISPR-dCas9 targeting of SNHG9 revealed its role in promoting glutathione S-transferase Pi 1 (GSTP1) methylation and HCC progression, suggesting that permanent SNHG9 silencing could represent a therapeutic strategy (138) (Table I). However, delivery remains the primary obstacle for CRISPR-based therapies in liver cancer. While viral vectors (such as AAV or lentivirus) offer efficient hepatocyte transduction, concerns regarding immunogenicity, insertional mutagenesis, and manufacturing complexity limit clinical applicability (139). Non-viral delivery using lipid nanoparticles or polymer carriers shows promise but requires optimization for efficient nuclear delivery of large CRISPR-Cas complexes (140).

Challenges in therapeutic targeting. Despite notable technological advances, significant hurdles impede clinical translation of lncRNA-RBP-targeted therapies for liver

Table II. Interactions between lncRNAs and RBPs and their functions in liver cancer.

LncRNAs	RBPs	Functions	Results	(Refs.)
FAM215A	LAMP2	Stabilizes LAMP2	Promotes HCC progression	(34)
HAND2-AS1	INO80	Recruits INO80	Promotes stem cell self-renewal of liver cancer	(56)
LINC00324	PU.1	Recruits PU.1	Regulates FASL expression	(64)
lncHDAC2	NuRD complex	Recruits NuRD	Inhibits PTCH1 expression	(65)
HULC	IGF2BP1	Destabilizes HULC expression	Promotes HCC progression	(40)
LINC00326	CCT3	Cooperates with CCT3	Regulates hepatocarcinogenic lipid metabolism	(35)
DDX11-AS1	PARP1	Interacts with PARP1	Promotes cell cycle progression	(37)
Linc01134	IGF2BP1	Cooperates to stabilize YY1 mRNA	Mediates HCC progression	(67)
UFC1	HuR	Cooperates to stabilize CTNNB1 mRNA	Promotes HCC progression	(42)
snoRD126	hnRNPK	Regulates FGFR2 expression and activate the PI3K-AKT pathway	Promotes HCC development	(60)
NONHSAT024276	PTBP1	Downregulates PTBP1 expression	Inhibits HCC progression	(36)
OIP5-AS1	PTBP1	Increases the mRNA stability of β-catenin	Promotes hepatoblastoma cell proliferation and stemness	(39)

lncRNA-RBP, long non-coding ribonucleic acid-ribonucleic acid-binding protein; AKT, protein kinase B; AS1, antisense RNA 1; AKT, protein kinase B; CCT3, chaperonin containing TCP1 subunit 3; CTNNB1, catenin β1; DDX11-AS1, DEAD-box helicase 11 antisense RNA 1; FASL, Fas ligand; FGFR2, fibroblast growth factor receptor 2; FAM215A, family with sequence similarity 215 member A; HAND2-AS1, heart and neural crest derivatives expressed 2 antisense RNA 1; HCC, hepatocellular carcinoma; HULC, highly upregulated in liver cancer; HuR, human antigen R (ELAV-like RNA binding protein 1); IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; INO80, INO80 complex subunit; LAMP2, lysosome-associated membrane protein 2; LINC00324, long intergenic non-protein coding RNA 324; LINC00326, long intergenic non-protein coding RNA 326; LINC01134, long intergenic non-protein coding RNA 1134; LncHDAC2, long non-coding RNA histone deacetylase 2-associated; mRNA, messenger ribonucleic acid; NONHSAT024276, non-human study transcript 024276; OIP5-AS1, Opa interacting protein 5 antisense RNA 1; PARP1, poly(ADP-ribose) polymerase 1; PI3K, phosphoinositide 3-kinase; PTBP1, polypyrimidine tract-binding protein 1; PTCH1, patched 1; PU.1, purine-rich box 1; RBP, ribonucleic acid-binding protein; snoRD126, small nucleolar RNA SNORD126; SNORD126, small nucleolar RNA C/D box 126; UFC1, ubiquitin-fold modifier conjugating enzyme 1; YY1, yin yang 1.

cancer, including specificity and off-target effects. Both ASOs and small molecules risk disrupting non-target RNA-protein interactions due to sequence homology or structural similarities. LncRNAs often contain repetitive elements and conserved structural motifs shared across multiple transcripts, potentially leading to unintended RBP sequestration or RNA mis-localization. Thus, comprehensive transcriptome-wide binding assays and structural characterization are essential to minimize off-target engagement. Another challenge is delivery or biodistribution. While the anatomical features of the liver facilitate oligonucleotide accumulation, achieving therapeutic concentrations specifically within HCC cells while sparing normal hepatocytes remains challenging. Tumor heterogeneity and desmoplastic stroma further impede drug penetration. Third is immunogenicity and toxicity. RNA therapeutics can activate innate immune sensors [such as Toll-like receptor (TLR)3, TLR7/8, and RIG-I] and induce inflammatory cytokine responses, potentially causing hepatotoxicity or systemic inflammation. Chemical modifications mitigate but do not eliminate immunogenicity. Additionally, repeated dosing may trigger anti-drug antibodies, particularly against polyethylene glycol coatings used in nanoparticle formulations, leading to accelerated blood clearance and reduced efficacy (141). In summary, further clinical experiments are urgently needed to identify highly efficient, safe, and economic therapeutic options targeting lncRNA-RBP pairs in liver cancer treatment.

10. Future directions

The convergence of advanced delivery technologies, structural biology, and artificial intelligence-driven drug design promises to overcome current limitations. Novel approaches including antibody-oligonucleotide conjugates enable cell-specific targeting beyond hepatocytes, while exosome-based delivery systems offer biocompatible, immunologically inert alternatives to synthetic nanoparticles. As our understanding of lncRNA-RBP structural dynamics expands, the development of orally bioavailable small molecule modulators may finally unlock the full therapeutic potential of these critical regulatory networks in liver cancer.

As a key achievement of this review, a clinically oriented summary of the lncRNA-RBP interactions catalogued in Table II is presented, stratified by therapeutic accessibility, biomarker potential, and druggability. This framework provides actionable guidance for prioritizing interactions in drug development pipelines. For example, the HULC-IGF2BP1 interaction can be treated as a diagnostic biomarker, as plasma HULC levels were shown to be associated with HCC diagnosis,

while IGF2BP1 was demonstrated to destabilize HULC providing a druggable node (16,40). Another interaction pair is MALAT1-SRSF1, which can serve as a prognostic indicator for patients with HCC. The mutual inhibition of SRSF1 with YAP was shown to create a synthetic lethality opportunity by maintaining MALAT1 expression; thus, targeting SRSF1 or MALAT1 may represent a potential therapeutic strategy for HCC in future. Other than these two illustrated pairs, other lncRNA-RBP pairs can also be further investigated to identify their potential in clinical translation of HCC treatment.

11. Conclusions and future perspectives

The interactions between lncRNAs and RBPs are diverse and complex. At the transcriptional and/or post-transcriptional level, lncRNAs can recruit interacting proteins to specific sites in the genome to regulate cis or trans gene expression (12). LncRNAs can serve as scaffolds to promote the assembly of protein complexes. In addition, lncRNAs can also serve as bait to weaken the interaction between proteins and biological macromolecules (DNA, RNA, and proteins). As the topic of lncRNAs and RBPs has been widely discussed in previous studies (30,142,143), their interactions and biological outcomes in liver cancer were emphasized in the present review, especially in studies from the last 5 years. The identified lncRNA-RBP pairs were found to have profound effects on the tumorigenesis or progression of liver cancer, and most of these lncRNA-RBP interactions were shown to promote liver cancer development, indicating that these interactions can serve as potential therapeutic targets for liver cancer. However, it has also been reported that the functions of RBPs are diverse in both cancer and normal cellular activity, making them difficult or undruggable targets for liver cancer therapy (143). Additionally, lncRNAs were shown to exhibit more tissue-specific expression pattern and have less functions compared with proteins, making them desirable targets for liver cancer therapy, as was reported in a recent study (144). Thus, the identified lncRNA-RBP interactions in liver cancer can be further explored to identify the exact interacting sites or functional domains, which should be preferentially considered in drug design and testing.

Of note, some points and issues were not discussed in the present review. Numerous lncRNAs identified in recent years were shown to lack functional annotation and interacting partners, and many RBPs were demonstrated to play important roles in liver cancer development, but were not shown to interact with lncRNAs. These lncRNAs and RBPs were not considered, but their importance is not excluded. In addition, not all the lncRNA-RBP pairs were included, especially those involving lncRNAs, including circRNAs, as ceRNAs (94). Finally, some special interaction mechanisms were not fully described in the present review. In summary, the field of lncRNA-RBP interactions is growing rapidly and attracting more attention than before. It is predictable that the protein-lncRNA interaction network will provide essential resources for the understanding of lncRNA and RBP biological mechanisms, as well as the abundant molecular targets for the drug design and treatment of liver cancer in the near future.

Despite the rapid expansion of lncRNA-RBP interaction research in liver cancer, several fundamental limitations constrain clinical translation. First, the overwhelming majority of reported interactions rely exclusively on *in vitro* experiments using established cell lines, which fail to recapitulate the complex tumor microenvironment, heterogeneity, and stromal interactions characteristic of human HCC. Second, the lack of robust *in vivo* validation represents a significant translational bottleneck. Animal models, particularly patient-derived xenografts and genetically engineered mouse models that faithfully replicate human hepatocarcinogenesis, are essential for assessing pharmacokinetics, biodistribution, and off-target effects of RNA-targeted therapies. Third, clinical validation is conspicuously absent. Prospective cohort studies with well-annotated clinical parameters (etiology, cirrhosis status, treatment history) are urgently needed to validate the prognostic and therapeutic relevance of specific lncRNA-RBP pairs. Fourth, mechanistic studies often fail to establish causal relationships vs. correlative associations. Rigorous genetic rescue experiments, structure-function mapping of interaction domains, and competitive inhibition studies are required to distinguish direct regulatory interactions from indirect effects. Finally, the dynamic and context-dependent nature of lncRNA-RBP interactions presents therapeutic challenges. The same lncRNA (for example H19) can exert opposing effects depending on RBP availability, metabolic state, or cellular stress (145). This functional plasticity complicates target validation and necessitates sophisticated conditional knockout models to dissect context-specific functions.

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JL designed the study, performed structured literature searches, wrote the draft manuscript, and finalized the manuscript. DC also wrote the draft manuscript. Both authors critically synthesized and interpreted the findings, and read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Cooper TA, Wan L and Dreyfuss G: RNA and disease. Cell 136: 777-793, 2009.
2. Brosnan CA and Voinnet O: The long and the short of noncoding RNAs. Curr Opin Cell Biol 21: 416-425, 2009.
3. Quinn JJ and Chang HY: Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet 17: 47-62, 2016.
4. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, *et al*: The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res 22: 1775-1789, 2012.
5. Ma L, Bajic VB and Zhang Z: On the classification of long non-coding RNAs. RNA Biology 10: 924-933, 2013.
6. Yao RW, Wang Y and Chen LL: Cellular functions of long noncoding RNAs. Nat Cell Biol 21: 542-551, 2019.
7. Fang S, Zhang L, Guo J, Niu Y, Wu Y, Li H, Zhao L, Li X, Teng X, Sun X, *et al*: NONCODEV5: A comprehensive annotation database for long non-coding RNAs. Nucleic Acids Res 46(D1): D308-D314, 2018.
8. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, Chen R, Dean C, Dinger ME, Fitzgerald KA, *et al*: Long non-coding RNAs: Definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol 24: 430-447, 2023.
9. Loewer S, Cabili MN, Guttman M, Loh YH, Thomas K, Park IH, Garber M, Curran M, Onder T, Agarwal S, *et al*: Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. Nat Genet 42: 1113-1117, 2010.
10. Takahashi K, Yan IK, Haga H and Patel T: Modulation of hypoxia-signaling pathways by extracellular linc-RoR. J Cell Sci 127 (Pt 7): 1585-1594, 2014.
11. Yang G, Lu X and Yuan L: LncRNA: A link between RNA and cancer. Biochim Biophys Acta 1839: 1097-1109, 2014.
12. Yao ZT, Yang YM, Sun MM, He Y, Liao L, Chen KS and Li B: New insights into the interplay between long non-coding RNAs and RNA-binding proteins in cancer. Cancer Commun (Lond) 42: 117-140, 2022.
13. Wapinski O and Chang HY: Long noncoding RNAs and human disease. Trends Cell Biol 21: 354-361, 2011.
14. Sun X and Malhotra A: Noncoding RNAs (ncRNA) in hepato cancer: A review. J Environ Pathol Toxicol Oncol 37: 15-25, 2018.
15. Huang Z, Zhou JK, Peng Y, He W and Huang C: The role of long noncoding RNAs in hepatocellular carcinoma. Mol Cancer 19: 77, 2020.
16. Xie H, Ma H and Zhou D: Plasma HULC as a promising novel biomarker for the detection of hepatocellular carcinoma. Biomed Res Int 2013: 136106, 2013.
17. Pan YF, Qin T, Feng L and Yu ZJ: Expression profile of altered long non-coding RNAs in patients with HBV-associated hepatocellular carcinoma. J Huazhong Univ Sci Technolog Med Sci 33: 96-101, 2013.
18. Hentze MW, Castello A, Schwarzl T and Preiss T: A brave new world of RNA-binding proteins. Nat Rev Mol Cell Biol 19: 327-341, 2018.
19. Gerstberger S, Hafner M and Tuschl T: A census of human RNA-binding proteins. Nat Rev Genet 15: 829-845, 2014.
20. Tang Q and Hann SS: HOTAIR: An oncogenic long non-coding RNA in human cancer. Cell Physiol Biochem 47: 893-913, 2018.
21. Gebauer F, Schwarzl T, Valcárcel J and Hentze MW: RNA-binding proteins in human genetic disease. Nat Rev Genet 22: 185-198, 2021.
22. Corley M, Burns MC and Yeo GW: How RNA-Binding proteins interact with RNA: Molecules and mechanisms. Mol Cell 78: 9-29, 2020.
23. Mohibi S, Chen X and Zhang J: Cancer the'RBP'eutics-RNA-binding proteins as therapeutic targets for cancer. Pharmacol Ther 203: 107390, 2019.
24. Pereira B, Billaud M and Almeida R: RNA-Binding proteins in cancer: Old players and new actors. Trends Cancer 3: 506-528, 2017.
25. Sun M, Gadad SS, Kim DS and Kraus WL: Discovery, annotation, and functional analysis of long noncoding RNAs controlling cell-cycle gene expression and proliferation in breast cancer cells. Mol Cell 59: 698-711, 2015.
26. Morris KV and Mattick JS: The rise of regulatory RNA. Nat Rev Genet 15: 423-437, 2014.
27. Takahashi K, Yan I, Haga H and Patel T: Long noncoding RNA in liver diseases. Hepatology 60: 744-753, 2014.
28. Yang M, Lu H, Liu J, Wu S, Kim P and Zhou X: lncRNAfunc: A knowledgebase of lncRNA function in human cancer. Nucleic Acids Res 50(D1): D1295-D1306, 2022.
29. Ferre F, Colantoni A and Helmer-Citterich M: Revealing protein-lncRNA interaction. Brief Bioinform 17: 106-116, 2016.
30. Jonas K, Calin GA and Pichler M: RNA-Binding proteins as important regulators of long non-coding RNAs in cancer. Int J Mol Sci 21: 2969, 2020.
31. Xia A, Yuan W, Wang Q, Xu J, Gu Y, Zhang L, Chen C, Wang Z, Wu D, He Q, *et al*: The cancer-testis lncRNA lnc-CTHCC promotes hepatocellular carcinogenesis by binding hnRNP K and activating YAP1 transcription. Nat Cancer 3: 203-218, 2022.
32. Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, Khalil AM, Zuk O, Amit I, Rabani M, *et al*: A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell 142: 409-419, 2010.
33. Yan C, Chen J and Chen N: Long noncoding RNA MALAT1 promotes hepatic steatosis and insulin resistance by increasing nuclear SREBP-1c protein stability. Sci Rep 6: 22640, 2016.
34. Huang PS, Lin YH, Chi HC, Tseng YH, Chen CY, Lin TK, Yeh CT and Lin KH: Dysregulated FAM215A Stimulates LAMP2 expression to confer drug-resistant and malignant in human liver cancer. Cells 9: 961, 2020.
35. Sondergaard JN, Sommerauer C, Atanasoai I, Hinte LC, Geng K, Guiducci G, Bräutigam L, Aouadi M, Stojic L, Barragan I and Kutter C: CCT3-LINC00326 axis regulates hepatocarcinogenic lipid metabolism. Gut 71: 2081-2092, 2022.
36. Li Y, Chen X, Huang H, Liao L, Chong H, Li G, Yuan T, Lu W, Deng S and Huang Q: A feedback loop between NONHSAT024276 and PTBP1 inhibits tumor progression and glycolysis in HCC by increasing the PKM1/PKM2 ratio. Cancer Sci 114: 1519-1540, 2023.
37. Xu M, Zhao X, Zhao S, Yang Z, Yuan W, Han H, Zhang B, Zhou L, Zheng S and Li MD: Landscape analysis of lncRNAs shows that DDX11-AS1 promotes cell-cycle progression in liver cancer through the PARP1/p53 axis. Cancer Lett 520: 282-294, 2021.
38. Wang H, Ma P, Liu P, Guo D, Liu Z and Zhang Z: lncRNA SNHG6 promotes hepatocellular carcinoma progression by interacting with HNRNPL/PTBP1 to facilitate SETD7/LZTFL1 mRNA destabilization. Cancer Lett 520: 121-131, 2021.
39. Jiang W, Ou ZL, Zhu Q, Yao YB and Zai HY: LncRNA OIP5-AS1 aggravates the stemness of hepatoblastoma through recruiting PTBP1 to increase the stability of beta-catenin. Pathol Res Pract 232: 153829, 2022.
40. Hammerle M, Gutschner T, Uckelmann H, Ozgur S, Fiskin E, Gross M, Skawran B, Geffers R, Longerich T, Breuhahn K, *et al*: Posttranscriptional destabilization of the liver-specific long noncoding RNA HULC by the IGF2 mRNA-binding protein 1 (IGF2BP1). Hepatology 58: 1703-1712, 2013.
41. Peng SS, Chen CY, Xu N and Shyu AB: RNA stabilization by the AU-rich element binding protein, HuR, an ELAV protein. EMBO J 17: 3461-3470, 1998.
42. Priyanka P, Sharma M, Das S and Saxena S: The lncRNA HMS recruits RNA-binding protein HuR to stabilize the 3'-UTR of HOXC10 mRNA. J Biol Chem 297: 100997, 2021.
43. Cao C, Sun J, Zhang D, Guo X, Xie L, Li X, Wu D and Liu L: The long intergenic noncoding RNA UFC1, a target of MicroRNA 34a, interacts with the mRNA stabilizing protein HuR to increase levels of β-catenin in HCC cells. Gastroenterology 148: 415-426 e18, 2015.
44. Tu ZQ, Li RJ, Mei JZ and Li XH: Down-regulation of long non-coding RNA GAS5 is associated with the prognosis of hepatocellular carcinoma. Int J Clin Exp Pathol 7: 4303-4309, 2014.
45. Hu G, Lou Z and Gupta M: The long non-coding RNA GAS5 cooperates with the eukaryotic translation initiation factor 4E to regulate c-Myc translation. PLoS One 9: e107016, 2014.
46. Hu L, Ye H, Huang G, Luo F, Liu Y, Liu Y, Yang X, Shen J, Liu Q and Zhang J: Long noncoding RNA GAS5 suppresses the migration and invasion of hepatocellular carcinoma cells via miR-21. Tumour Biol 37: 2691-2702, 2016.
47. Zhao P, Cui X, Zhao L, Liu L and Wang D: Overexpression of growth-arrest-specific transcript 5 improved cisplatin sensitivity in hepatocellular carcinoma through sponging miR-222. DNA Cell Biol 39: 724-732, 2020.
48. Fang P, Xiang L, Chen W, Li S, Huang S, Li J, Zhuge L, Jin L, Feng W, Chen Y and Pan C: LncRNA GAS5 enhanced the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3. Innate Immun 25: 99-109, 2019.

49. Lin G, Wu T, Gao X, He Z and Nong W: Research progress of long non-coding RNA GAS5 in malignant tumors. Front Oncol 12: 846497, 2022.
50. Shihabudeen Haider Ali MS, Cheng X, Moran M, Haemmig S, Naldrett MJ, Alvarez S, Feinberg MW and Sun X: LncRNA Meg3 protects endothelial function by regulating the DNA damage response. Nucleic Acids Res 47: 1505-1522, 2019.
51. Wu J, Pang R, Li M, Chen B, Huang J and Zhu Y: m6A-Induced LncRNA MEG3 suppresses the proliferation, migration and invasion of hepatocellular carcinoma cell through miR-544b/BTG2 signaling. Onco Targets Ther 14: 3745-3755, 2021.
52. Zhang L, Yang F, Yuan JH, Yuan SX, Zhou WP, Huo XS, Xu D, Bi HS, Wang F and Sun SH: Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. Carcinogenesis 34: 577-586, 2013.
53. Lee TI and Young RA: Transcriptional regulation and its misregulation in disease. Cell 152: 1237-1251, 2013.
54. Bridges MC, Daulagala AC and Kourtidis A: LNCcation: LncRNA localization and function. J Cell Biol 220: e202009045, 2021.
55. Pintacuda G, Wei G, Roustan C, Kirmizitas BA, Solcan N, Cerase A, Castello A, Mohammed S, Moindrot B, Nesterova TB and Brockdorff N: hnRNPK recruits PCGF3/5-PRC1 to the Xist RNA B-Repeat to establish polycomb-mediated chromosomal silencing. Mol Cell 68: 955-969.e10, 2017.
56. Wang Y, Zhu P, Luo J, Wang J, Liu Z, Wu W, Du Y, Ye B, Wang D, He L, *et al*: LncRNA HAND2-AS1 promotes liver cancer stem cell self-renewal via BMP signaling. EMBO J 38: e101110, 2019.
57. Genander M, Cook PJ, Ramsköld D, Keyes BE, Mertz AF, Sandberg R and Fuchs E: BMP signaling and its pSMAD1/5 target genes differentially regulate hair follicle stem cell lineages. Cell Stem Cell 15: 619-633, 2014.
58. Kirmizitas A, Meiklejohn S, Ciau-Uitz A, Stephenson R and Patient R: Dissecting BMP signaling input into the gene regulatory networks driving specification of the blood stem cell lineage. Proc Natl Acad Sci USA 114: 5814-5821, 2017.
59. Andersen P, Tampakakis E, Jimenez DV, Kannan S, Miyamoto M, Shin HK, Saberi A, Murphy S, Sulistio E, Chelko SP and Kwon C: Precardiac organoids form two heart fields via Bmp/Wnt signaling. Nat Commun 9: 3140, 2018.
60. Xu W, Wu Y, Fang X, Zhang Y, Cai N, Wen J, Liao J, Zhang B, Chen X and Chu L: SnoRD126 promotes the proliferation of hepatocellular carcinoma cells through transcriptional regulation of FGFR2 activation in combination with hnRNPK. Aging (Albany NY) 13: 13300-13317, 2021.
61. Castellanos-Rubio A, Fernandez-Jimenez N, Kratchmarov R, Luo X, Bhagat G, Green PH, Schneider R, Kiledjian M, Bilbao JR and Ghosh S: A long noncoding RNA associated with susceptibility to celiac disease. Science 352: 91-95, 2016.
62. Li H, An J, Wu M, Zheng Q, Gui X, Li T, Pu H and Lu D: LncRNA HOTAIR promotes human liver cancer stem cell malignant growth through downregulation of SETD2. Oncotarget 6: 27847-27864, 2015.
63. Wu M, Lin Z, Li X, Xin X, An J, Zheng Q, Yang Y and Lu D: HULC cooperates with MALAT1 to aggravate liver cancer stem cells growth through telomere repeat-binding factor 2. Sci Rep 6: 36045, 2016.
64. Gao J, Dai C, Yu X, Yin XB and Zhou F: Long noncoding RNA LINC00324 exerts protumorigenic effects on liver cancer stem cells by upregulating fas ligand via PU box binding protein. FASEB J 34: 5800-5817, 2020.
65. Wu J, Zhu P, Lu T, Du Y, Wang Y, He L, Ye B, Liu B, Yang L, Wang J, *et al*: The long non-coding RNA LncHDAC2 drives the self-renewal of liver cancer stem cells via activation of Hedgehog signaling. J Hepatol 70: 918-929, 2019.
66. Quagliata L, Matter MS, Piscuoglio S, Arabi L, Ruiz C, Procino A, Kovac M, Moretti F, Makowska Z, Boldanova T, *et al*: Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. Hepatology 59: 911-923, 2014.
67. Rong Z, Wang Z, Wang X, Qin C and Geng W: Molecular interplay between linc01134 and YY1 dictates hepatocellular carcinoma progression. J Exp Clin Cancer Res 39: 61, 2020.
68. Li Y, Zhuang W, Huang M and Li X: Long noncoding RNA DDX11-AS1 epigenetically represses LATS2 by interacting with EZH2 and DNMT1 in hepatocellular carcinoma. Biochem Biophys Res Commun 514: 1051-1057, 2019.
69. Yang S, Ruan X, Hu B, Tu J and Cai H: lncRNA SNHG9 enhances liver cancer stem cell self-renewal and tumorigenicity by negatively regulating PTEN expression via recruiting EZH2. Cell Tissue Res 394: 441-453, 2023.
70. Cusenza VY, Tameni A, Neri A and Frazzi R: The lncRNA epigenetics: The significance of m6A and m5C lncRNA modifications in cancer. Front Oncol 13: 1063636, 2023.
71. Pan XY, Huang C and Li J: The emerging roles of m(6)A modification in liver carcinogenesis. Int J Biol Sci 17: 271-284, 2021.
72. Chen YT, Xiang D, Zhao XY and Chu XY: Upregulation of lncRNA NIFK-AS1 in hepatocellular carcinoma by m(6)A methylation promotes disease progression and sorafenib resistance. Hum Cell 34: 1800-1811, 2021.
73. Peng L, Pan B, Zhang X, Wang Z, Qiu J, Wang X and Tang N: Lipopolysaccharide facilitates immune escape of hepatocellular carcinoma cells via m6A modification of lncRNA MIR155HG to upregulate PD-L1 expression. Cell Biol Toxicol 38: 1159-1173, 2022.
74. Liu J, Zhang N, Zeng J, Wang T, Shen Y, Ma C and Yang M: N(6) -methyladenosine-modified lncRNA ARHGAP5-AS1 stabilises CSDE1 and coordinates oncogenic RNA regulons in hepatocellular carcinoma. Clin Transl Med 12: e1107, 2022.
75. Sun Z, Xue S, Zhang M, Xu H, Hu X, Chen S, Liu Y, Guo M and Cui H: Aberrant NSUN2-mediated m(5)C modification of H19 lncRNA is associated with poor differentiation of hepatocellular carcinoma. Oncogene 39: 6906-6919, 2020.
76. Schultz CW, Preet R, Dhir T, Dixon DA and Brody JR: Understanding and targeting the disease-related RNA binding protein human antigen R (HuR). Wiley Interdiscip Rev RNA 11: e1581, 2020.
77. Wang J, Wang H, Zhang Y, Zhen N, Zhang L, Qiao Y, Weng W, Liu X, Ma L, Xiao W, *et al*: Mutual inhibition between YAP and SRSF1 maintains long non-coding RNA, Malat1-induced tumourigenesis in liver cancer. Cell Signal 26: 1048-1059, 2014.
78. Li H, Li J, Jia S, Wu M, An J, Zheng Q, Zhang W and Lu D: miR675 upregulates long noncoding RNA H19 through activating EGR1 in human liver cancer. Oncotarget 6: 31958-31984, 2015.
79. Gao JZ, Li J, Du JL and Li XL: Long non-coding RNA HOTAIR is a marker for hepatocellular carcinoma progression and tumor recurrence. Oncol Lett 11: 1791-1798, 2016.
80. Yu M, Qian K, Wang G, Xiao Y, Zhu Y and Ju L: Histone methyltransferase SETD2: An epigenetic driver in clear cell renal cell carcinoma. Front Oncol 13: 1114461, 2023.
81. Gao J, Dai C, Yu X, Yin XB and Zhou F: LncRNA LEF1-AS1 silencing diminishes EZH2 expression to delay hepatocellular carcinoma development by impairing CEBPB-interaction with CDCA7. Cell Cycle 19: 870-883, 2020.
82. Cai Y, Lyu T, Li H, Liu C, Xie K, Xu L, Li W, Liu H, Zhu J, Lyu Y, *et al*: LncRNA CEBPA-DT promotes liver cancer metastasis through DDR2/beta-catenin activation via interacting with hnRNPC. J Exp Clin Cancer Res 41: 335, 2022.
83. Nguyen TM, Kabotyanski EB, Reineke LC, Shao J, Xiong F, Lee JH, Dubrulle J, Johnson H, Stossi F, Tsoi PS, *et al*: The SINEB1 element in the long non-coding RNA Malat1 is necessary for TDP-43 proteostasis. Nucleic Acids Res 48: 2621-2642, 2020.
84. Zhang Y, Xu Y, Feng L, Li F, Sun Z, Wu T, Shi X, Li J and Li X: Comprehensive characterization of lncRNA-mRNA related ceRNA network across 12 major cancers. Oncotarget 7: 64148-64167, 2016.
85. Li X, Wang X, Cheng Z and Zhu Q: AGO2 and its partners: A silencing complex, a chromatin modulator, and new features. Crit Rev Biochem Mol Biol 55: 33-53, 2020.
86. Feng J, Yang G, Liu Y, Gao Y, Zhao M, Bu Y, Yuan H, Yuan Y, Yun H, Sun M, *et al*: LncRNA PCNAP1 modulates hepatitis B virus replication and enhances tumor growth of liver cancer. Theranostics 9: 5227-5245, 2019.
87. Wang H, Huo X, Yang XR, He J, Cheng L, Wang N, Deng X, Jin H, Wang N, Wang C, *et al*: STAT3-mediated upregulation of lncRNA HOXD-AS1 as a ceRNA facilitates liver cancer metastasis by regulating SOX4. Mol Cancer 16: 136, 2017.
88. Zhang Y and Zhou H: LncRNA BCAR4 promotes liver cancer progression by upregulating ANAPC11 expression through sponging miR-1261. Int J Mol Med 46: 159-166, 2020.
89. Hou Z, Xu X, Zhou L, Fu X, Tao S, Zhou J, Tan D and Liu S: The long non-coding RNA MALAT1 promotes the migration and invasion of hepatocellular carcinoma by sponging miR-204 and releasing SIRT1. Tumour Biol 39: 1010428317718135, 2017.

90. Wang LP, Wang JP and Wang XP: HOTAIR contributes to the growth of liver cancer via targeting miR-217. Oncol Lett 15: 7963-7972, 2018.
91. Liu J, Li W, Zhang J, Ma Z, Wu X and Tang L: Identification of key genes and long non-coding RNA associated ceRNA networks in hepatocellular carcinoma. PeerJ 7: e8021, 2019.
92. Zhong Y, Du Y, Yang X, Mo Y, Fan C, Xiong F, Ren D, Ye X, Li C, Wang Y, *et al*: Circular RNAs function as ceRNAs to regulate and control human cancer progression. Mol Cancer 17: 79, 2018.
93. Liu CX and Chen LL: Circular RNAs: Characterization, cellular roles, and applications. Cell 185: 2016-2034, 2022.
94. Shen H, Liu B, Xu J, Zhang B, Wang Y, Shi L and Cai X: Circular RNAs: Characteristics, biogenesis, mechanisms and functions in liver cancer. J Hematol Oncol 14: 134, 2021.
95. Louis C, Leclerc D and Coulouarn C: Emerging roles of circular RNAs in liver cancer. JHEP Rep 4: 100413, 2022.
96. Liu H, Lan T, Li H, Xu L, Chen X, Liao H, Chen X, Du J, Cai Y, Wang J, *et al*: Circular RNA circDLC1 inhibits MMP1-mediated liver cancer progression via interaction with HuR. Theranostics 11: 1396-1411, 2021.
97. Meng H, Niu R, Huang C and Li J: Circular RNA as a novel biomarker and therapeutic target for HCC. Cells 11: 1948, 2022.
98. Zhou RJ and Lv HZ: Knockdown of ACTA2-AS1 promotes liver cancer cell proliferation, migration and invasion. Mol Med Rep 19: 2263-2270, 2019.
99. Jiao Y, Li Y, Jia B, Chen Q, Pan G, Hua F and Liu Y: The prognostic value of lncRNA SNHG4 and its potential mechanism in liver cancer. Biosci Rep 40: BSR20190729, 2020.
100. Ding C, Cheng S, Yang Z, Lv Z, Xiao H, Du C, Peng C, Xie H, Zhou L, Wu J and Zheng S: Long non-coding RNA HOTAIR promotes cell migration and invasion via down-regulation of RNA binding motif protein 38 in hepatocellular carcinoma cells. Int J Mol Sci 15: 4060-4076, 2014.
101. Conigliaro A, Costa V, Lo Dico A, Saieva L, Buccheri S, Dieli F, Manno M, Raccosta S, Mancone C, Tripodi M, *et al*: CD90+ liver cancer cells modulate endothelial cell phenotype through the release of exosomes containing H19 lncRNA. Mol Cancer 14: 155, 2015.
102. Guo Y, Bai M, Lin L, Huang J, An Y, Liang L, Liu Y and Huang W: LncRNA DLEU2 aggravates the progression of hepatocellular carcinoma through binding to EZH2. Biomed Pharmacother 118: 109272, 2019.
103. Pan S and Chen R: Pathological implication of protein post-translational modifications in cancer. Mol Aspects Med 86: 101097, 2022.
104. Sharma B, Prabhakaran V, Desai A, Bajpai J, Verma R and Swain P: Post-translational modifications (PTMs), from a cancer perspective: An overview. Oncogen 2: 12, 2019.
105. Zhang X, Wang W, Zhu W, Dong J, Cheng Y, Yin Z and Shen F: Mechanisms and functions of long non-coding RNAs at multiple regulatory levels. Int J Mol Sci 20: 5573, 2019.
106. Toraih EA, Ellawindy A, Fala SY, Al Ageeli E, Gouda NS, Fawzy MS and Hosny S: Oncogenic long noncoding RNA MALAT1 and HCV-related hepatocellular carcinoma. Biomed Pharmacother 102: 653-669, 2018.
107. Chen R, Liu Y, Zhuang H, Yang B, Hei K, Xiao M, Hou C, Gao H, Zhang X, Jia C, *et al*: Quantitative proteomics reveals that long non-coding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. Nucleic Acids Res 45: 9947-9959, 2017.
108. Luo ML, Li J, Shen L, Chu J, Guo Q, Liang G, Wu W, Chen J, Chen R and Song E: The role of APAL/ST8SIA6-AS1 lncRNA in PLK1 activation and mitotic catastrophe of tumor cells. J Natl Cancer Inst 112: 356-368, 2020.
109. Yan X, Zhang D, Wu W, Wu S, Qian J, Hao Y, Yan F, Zhu P, Wu J, Huang G, *et al*: Mesenchymal Stem Cells Promote Hepatocarcinogenesis via lncRNA-MUF Interaction with ANXA2 and miR-34a. Cancer Res 77: 6704-6716, 2017.
110. Li B, Xiong X, Xu J, Peng D, Nie G, Wen N, Wang Y and Lu J: METTL3-mediated m(6)A modification of lncRNA TSPAN12 promotes metastasis of hepatocellular carcinoma through SENP1-depentent deSUMOylation of EIF3I. Oncogene 43: 1050-1062, 2024.
111. Luo J, Wang K, Yeh S, Sun Y, Liang L, Xiao Y, Xu W, Niu Y, Cheng L, Maity SN, *et al*: LncRNA-p21 alters the antiandrogen enzalutamide-induced prostate cancer neuroendocrine differentiation via modulating the EZH2/STAT3 signaling. Nat Commun 10: 2571, 2019.
112. Ni W, Yao S, Zhou Y, Liu Y, Huang P, Zhou A, Liu J, Che L and Li J: Long noncoding RNA GAS5 inhibits progression of colorectal cancer by interacting with and triggering YAP phosphorylation and degradation and is negatively regulated by the m(6)A reader YTHDF3. Mol Cancer 18: 143, 2019.
113. Yoon JH, Abdelmohsen K, Kim J, Yang X, Martindale JL, Tominaga-Yamanaka K, White EJ, Orjalo AV, Rinn JL, Kreft SG, *et al*: Scaffold function of long non-coding RNA HOTAIR in protein ubiquitination. Nat Commun 4: 2939, 2013.
114. Li Z, Liu L, Feng C, Qin Y, Xiao J, Zhang Z and Ma L: LncBook 2.0: Integrating human long non-coding RNAs with multi-omics annotations. Nucleic Acids Res 51(D1): D186-D191, 2023.
115. Van Nostrand EL, Freese P, Pratt GA, Wang X, Wei X, Xiao R, Blue SM, Chen JY, Cody NAL, Dominguez D, *et al*: A large-scale binding and functional map of human RNA-binding proteins. Nature 583: 711-719, 2020.
116. Yang YC, Di C, Hu B, Zhou M, Liu Y, Song N, Li Y, Umetsu J and Lu ZJ: CLIPdb: A CLIP-seq database for protein-RNA interactions. BMC Genomics 16: 51, 2015.
117. Gao Y, Shang S, Guo S, Li X, Zhou H, Liu H, Sun Y, Wang J, Wang P, Zhi H, *et al*: Lnc2Cancer 3.0: An updated resource for experimentally supported lncRNA/circRNA cancer associations and web tools based on RNA-seq and scRNA-seq data. Nucleic Acids Res 49(D1): D1251-D1258, 2021.
118. Yi Y, Zhao Y, Huang Y and Wang D: A Brief Review of RNA-Protein interaction database resources. Noncoding RNA 3: 6, 2017.
119. Hafner M, Katsantoni M, Köster T, Marks J, Mukherjee J, Staiger D, Ule J and Zavolan M: CLIP and complementary methods. Nat Rev Methods Primers 1: 20, 2021.
120. Torres M, Becquet D, Guillen S, Boyer B, Moreno M, Blanchard MP, Franc JL and François-Bellan AM: RNA pull-down procedure to identify RNA targets of a long Non-coding RNA. J Vis Exp 57379, 2018.
121. Chu C, Quinn J and Chang HY: Chromatin isolation by RNA purification (ChIRP). J Vis Exp 61: 3912, 2012.
122. Engreitz J, Lander ES and Guttman M: RNA antisense purification (RAP) for mapping RNA interactions with chromatin. Methods Mol Biol 1262: 183-197, 2015.
123. Liu ZP: Predicting lncRNA-protein interactions by machine learning methods: A review. Curr Bioinf 15: 831-840, 2020.
124. Lu K, Fan Q and Zou X: Antisense oligonucleotide is a promising intervention for liver diseases. Front Pharmacol 13: 1061842, 2022.
125. Cremer J, Elston R, Campbell FM, Kendrick S, Paff M, Quinn G and Theodore D: B-Clear phase 2b study design: Establishing the efficacy and safety of bepirovirsen in patients with chronic hepatitis B virus infection. Adv Ther 40: 4101-4110, 2023.
126. Klec C, Gutschner T, Panzitt K and Pichler M: Involvement of long non-coding RNA HULC (highly up-regulated in liver cancer) in pathogenesis and implications for therapeutic intervention. Expert Opin Ther Targets 23: 177-186, 2019.
127. Tian NN, Zheng YB, Li ZP, Zhang FW and Zhang JF: Histone methylatic modification mediates the tumor-suppressive activity of curcumol in hepatocellular carcinoma via an Hotair/EZH2 regulatory axis. J Ethnopharmacol 280: 114413, 2021.
128. Amodio N, Raimondi L, Juli G, Stamato MA, Caracciolo D, Tagliaferri P and Tassone P: MALAT1: A druggable long non-coding RNA for targeted anti-cancer approaches. J Hematol Oncol 11: 63, 2018.
129. Shen W, De Hoyos CL, Migawa MT, Vickers TA, Sun H, Low A, Bell TA III, Rahdar M, Mukhopadhyay S, Hart CE, *et al*: Chemical modification of PS-ASO therapeutics reduces cellular protein-binding and improves the therapeutic index. Nat Biotechnol 37: 640-650, 2019.
130. Debacker AJ, Voutila J, Catley M, Blakey D and Habib N: Delivery of oligonucleotides to the liver with GalNAc: From research to registered therapeutic drug. Mol Ther 28: 1759-1771, 2020.
131. Smekalova EM, Kotelevtsev YV, Leboeuf D, Shcherbinina EY, Fefilova AS, Zatsepin TS and Koteliansky V: lncRNA in the liver: Prospects for fundamental research and therapy by RNA interference. Biochimie 131: 159-172, 2016.
132. Zhong L, Li Y, Xiong L, Wang W, Wu M, Yuan T, Yang W, Tian C, Miao Z, Wang T and Yang S: Small molecules in targeted cancer therapy: Advances, challenges, and future perspectives. Signal Transduct Target Ther 6: 201, 2021.

133. Suravajhala R, Gupta S, Kumar N and Suravajhala P: Deciphering LncRNA-protein interactions using docking complexes. J Biomol Struct Dyn 40: 3769-3776, 2022.
134. Zhang N and Wen K: The role of lncRNA binding to RNA-binding proteins to regulate mRNA stability in cancer progression and drug resistance mechanisms (Review). Oncol Rep 52: 142, 2024.
135. Zhu J, Mo YY and Peng WX: RNA binding protein-mediated competing endogenous RNA mechanism in cancer. Gene 963: 149606, 2025.
136. Wang H, Guo R, Du Z, Bai L, Li L, Cui J, Li W, Hoffman AR and Hu JF: Epigenetic targeting of granulin in hepatoma cells by synthetic CRISPR dCas9 Epi-suppressors. Mol Ther Nucleic Acids 11: 23-33, 2018.
137. Ali HS, Boshra MS, El Meteini MS, Shafei AE and Matboli M: lncRNA-RP11-156p1.3, novel diagnostic and therapeutic targeting via CRISPR/Cas9 editing in hepatocellular carcinoma. Genomics 112: 3306-3314, 2020.
138. Ye S and Ni Y: lncRNA SNHG9 promotes cell proliferation, migration, and invasion in human hepatocellular carcinoma cells by increasing GSTP1 methylation, as revealed by CRISPR-dCas9. Front Mol Biosci 8: 649976, 2021.
139. Tong LW, Hu YS, Yu SJ, Li CL and Shao JW: Current application and future perspective of CRISPR/cas9 gene editing system mediated immune checkpoint for liver cancer treatment. Nanotechnology 35: 2024.
140. Paunovska K, Loughrey D and Dahlman JE: Drug delivery systems for RNA therapeutics. Nat Rev Genet 23: 265-280, 2022.
141. Sioud M: How the initial discovery of modified RNA enabled evasion of innate immune responses and facilitated the development of RNA therapeutics. Scand J Immunol 98: e13282, 2023.
142. Eun JW, Cheong JY, Jeong JY and Kim HS: A new understanding of long non-coding RNA in hepatocellular carcinoma-From m(6)A modification to blood biomarkers. Cells 12: 2272, 2023.
143. Zhang K, Barry AE, Lamm R, Patel K, Schafer M and Dang H: The role of RNA binding proteins in hepatocellular carcinoma. Adv Drug Deliv Rev 182: 114114, 2022.
144. Xing L, Wang ZK, Li DM, Li J and Liu M: RNA-based therapies in hepatocellular carcinoma: state of the art and clinical perspectives. Hepatoma Res 10: 24, 2024.
145. Wang Y, Hylemon PB and Zhou H: Long Noncoding RNA H19: A key player in liver diseases. Hepatology 74: 1652-1659, 2021.