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Long noncoding RNAs in hepatocellular carcinoma: Novel insights into their mechanism

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Abstract

Hepatocellular carcinoma (HCC) is the predominant subject of liver malignancies which arouse global concern. Advanced studies have found that long non-coding RNAs (lncRNAs) are differentially expressed in HCC and implicate they may play distinct roles in the pathogenesis and metastasis of HCC. However, the underlying mechanisms remain largely unclear. In this review, we summarized the functions and mechanisms of those known aberrantly expressed lncRNAs identified in human HCC tissues. We hope to enlighten more comprehensive researches on the detailed mechanisms of lncRNAs and their application in clinic, such as being used as diagnostic and prognostic biomarkers and the targets for potential therapy. Although studies on lncRNAs in HCC are still deficient, an improved understanding of the roles played by lncRNAs in HCC will lead to a much more effective utilization of those lncRNAs as novel candidates in early detection, diagnosis, prevention and treatment of HCC.

Key words: Hepatocellular carcinoma; Long noncoding RNA; Dysregulation; Mechanism; Pathway

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Core tip: Hepatocellular carcinoma (HCC) is a global concern. Long noncoding RNAs (lncRNAs) are likely to play crucial roles in various pathogenesis of HCC, including tumor growth, proliferation, invasion, metastasis and recurrence. Here, we focus on recent studies of human HCC associated lncRNAs and highlight their functions, mechanisms, as well as their potential to act as novel candidates for early detection, diagnosis, prevention and treatment of HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC), one of the most common histologic subtype of primary liver cancers, accounting for 70%-85% of liver cancer cases in most countries, is the third-leading cause of worldwide mortality for various cancers^[1-3]. It causes nearly 695900 deaths per year, half of which occur in China, as a result of the high chronic hepatitis B virus (HBV) infection incidence^[4]. Besides, infection with hepatitis C virus, hepatosteatosis and chronic exposure to toxic chemical substances are the major HCC risk factors^[5,6]. Especially, exposure to aflatoxin plays a key role in inducing HCC in our Guangxi Zhuang Autonomous Region^[7]. In addition, many key signal transduction pathways have been verified to be involved in the pathogenesis of HCC, including PI3K/Akt/mTOR pathway, Raf/MAPK/ERK pathway, Jak/Stat pathway, WNT- β -catenin pathway, so on and so forth^[8-12]. Usually, the treatments for HCC are finite and are only available in the early stage, while most HCC are only detected in their advanced stage when traditional chemotherapy has marginal effects and leads to poor prognosis. Because of its dismal outcome, etiology and carcinogenesis investigation are in urgent need. Recently, human genome analysis in non-protein coding has made new progress. It discovers massive transcription of large RNA transcripts which lack coding protein function, termed as long noncoding RNAs (lncRNAs).

With recent application of next generation sequencing techniques, significant numbers of non-coding RNAs (ncRNAs) and lncRNAs have been discovered to be associated with HCC. And HCC is characterized by dysregulation of numerous gene networks while both protein-coding genes and ncRNA genes are involved, just like many other cancers. It is estimated that protein-coding genes only account for less than 2% of the human genome while nearly 70% of the human genome is transcribed pervasively^[13]. Accordingly, ample ncRNAs are transcribed from human genome, for instance lncRNAs, microRNAs (miRNAs), small interfering RNAs

and PIWI-interacting RNAs^[14-16].

NcRNAs were once thought to be body "garbage" or transcriptional "noise". However, accumulating reports have demonstrated that miRNAs and lncRNAs play valid regulatory roles in cancer^[17-22]. Recent studies^[23] have also elucidated that lncRNAs possess a significant role in epigenetic regulation. Via regulating gene expression by miscellaneous mechanisms, including genomic imprinting, chromatin modification, regulation of protein function, transcription and post-transcriptional processing^[24-26], lncRNAs are involved in multitudinous physiological functions and pathological processes.

lncRNAs, larger than 200 nucleotides (nt) in length, are commonly defined as endogenous cellular RNA molecules, which are poorly conserved and not capable of being translated into proteins^[21,23,27]. They can be monitored by a high-throughput analysis such as transcriptome analysis and microarrays, or through bioinformatics prediction^[28]. lncRNAs can be transcribed by RNA polymerase II, and then undergo cotranscriptional modifications including polyadenylation and pre-RNA splicing^[29]. Many studies have pointed out that lncRNA transcripts play vital roles in various biological processes as they function in gene imprinting and splicing, chromatin modification, immunosurveillance, cell fate specification, cell cycle control and cell apoptosis, or act as nuclear architecture, subnuclear compartments, RNA processing enhancer and promoter^[30,31].

lncRNAs have assorted mechanisms in biological processes. Generally speaking, the role of lncRNA as a gene expressing regulator could be found in transcriptional level and posttranscriptional level. Cis-regulation and trans-regulation are two main transcriptional regulation means, by which lncRNAs can target local and distant genes, respectively. The posttranscriptional regulating mechanism is involved in posttranscriptional process of mRNAs which includes splicing, editing, trafficking, translation and degradation. lncRNAs can also function as competing endogenous RNAs for shared miRNA^[32,33]. In brief, there are four known molecular functions of lncRNAs: Signal, decoy, guide, and scaffold^[21,34].

There are five species of lncRNAs, listed as follow^[31,35,36]: Sense or antisense (when overlapping at least one exon of another transcript on the opposite or same strand), bidirectional (when a neighboring coding transcript or its expression on the opposite strand is initiated in close genomic proximity), intronic (when derived from an intron of a second transcript), and intergenic (when it lies as an independent unit within the genomic interval between two genes). An updated definition was given to lncRNAs by other researchers regardless of their length and non-protein coding capability^[37]. It described lncRNAs as RNA molecules who may have the function as primary or spliced transcripts which do not confirm to the known varieties of small RNAs or structural RNAs^[38]. In recent years, the number of articles focused on lncRNAs has increased greatly. Recent studies have demonstrated that certain

Table 1 Upregulated long noncoding RNAs in hepatocellular carcinoma

Name	Gene locus	Size (bp)	Dysregulation	Potential role in HCC	Ref.
HULC	6p24.3	1638	Upregulated	Associate with HBV infection or histological grade. Associate with tumor growth	[22,29,44-50]
H19	11p15.5	2660	Upregulated	Suppress progression, metastasis. Promote cell proliferation	[22,29,50-57]
TUC338	12q13.13	590	Upregulated	Increased in liver cirrhosis. Modulate cell growth	[58]
MALAT1	11q13.1	8708	Upregulated	Associate with tumor metastasis, recurrence	[21,22,29,59,60]
HOTAIR	12q13.13	12649	Upregulated	Associate with invasion and metastasis. Increases chemosensitivity	[21,22,29,61-65]
HOTTIP	7p15.2	6839	Upregulated	Associate with tumor progression and disease outcome	[28,66-68]
HEIH	5q35.3	1665	Upregulated	Associated with HBV-HCC. Associate with prognosis	[21,29,69]
MDIG	3q11.2	30635	Upregulated	Associate with DNA repair and prognosis	[70]
PVT1	8q24.21	210626	Upregulated	Associate with HCC progression and predict recurrence	[71,72]
Linc00974	17q21.31	4890	Upregulated	Predict tumor growth and metastasis	[73]
UFC1	1q23.3	5113	Upregulated	Promote HCC cell proliferation, inhibit cell apoptosis and induce cell cycle progression	[10,12,74]
PCNA-AS1	20p12.3	384	Upregulated	Promote tumor growth	[75]
UCA1	19p13.12	7375	Upregulated	Involved in chemotherapeutic resistance. Associate with TNM stage, metastasis and postoperative survival	[50,76]
CCAT1	8q24.21	11887	Upregulated	Promotes HCC progression	[77-79]
ATB	19q13.3	2895	Upregulated	Associate with poor prognosis	[80,81]
URHC	2q24.2	192173	Upregulated	Promote cell proliferation and inhibit apoptosis	[82]

HCC: Hepatocellular carcinoma; HULC: Highly upregulated in liver cancer; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; HOTAIR: HOX transcript antisense RNA; HEIH: Long noncoding RNA high expression in HCC; CCAT1: Colon cancer associated transcript-1; ATB: Long noncoding RNA-activated by transforming growth factor- β ; URHC: Up-regulated in hepatocellular carcinoma; HBV: Hepatitis B virus; TNM: Tumor node metastasis.

Table 2 Downregulated long noncoding RNAs in hepatocellular carcinoma

Name	Gene locus	Size (bp)	Dysregulation	Potential role in HCC	Ref.
MEG3 (GTL2)	14q32.3	34919	Downregulated	Associate with methylation. Predictive biomarker for monitoring epigenetic therapy	[21,83-87]
LncRNA-LET	15q24.1	2606	Downregulated	Reduces hepatic invasion and abdominal metastases	[88]
PTENP1	9p13.3	3917	Downregulated	Repress the tumorigenic properties of HCC cells	[22,89]
SRHC	5p15.31	6365	Downregulated	Inhibit cancer proliferation	[90]
MT1DP	16q13	1255	Downregulated	Act as a tumor suppressor. Overexpression of MT1DP decreases cell proliferation but increases apoptosis	[91]

HCC: Hepatocellular carcinoma; MT1DP: Metallothionein 1D, pseudogene; MEG3: Maternally expressed gene 3; LncRNA: Long noncoding RNA.

lncRNAs are specifically correlated with certain classes of cancer and the different expression level of lncRNAs may function as an indicator for metastasis and prognosis^[39-41]. Genome-wide transcriptomic analyses have found that a number of lncRNAs are dysregulated in HCC cell lines or cancer tissues^[21,28,29,42,43]. Given the fact that such large scales of lncRNAs are aberrantly regulated in HCC, it is of highly possibility that lncRNAs are directly associated with carcinogenesis of HCC. In this review, we concentrated on cancer-related lncRNAs which have been validated in human HCC. Furthermore, we summarized their mechanism and signaling pathways in HCC.

REPRESENTATIVE LNCRNAS DYSREGULATED IN HCC

Abnormal expressed lncRNAs have been found to be associated with hepatocarcinogenesis and play a key role in metastasis and prognosis^[29,34,42]. Accumulating studies recently have focused on the contributions of lncRNAs in HCC development. Here, we summarized differential expressions of lncRNAs and their potential roles in HCC (Tables 1 and 2).

MECHANISMS AND SIGNALING PATHWAY IN HCC

After attentive study, we divided the researched lncRNAs into 3 groups and made the above conclusive table. And with the purpose of identifying the roles of different lncRNAs who might play in the early detection and diagnosis or prevention and treatment of HCC, we further summarized their function and mechanism as follow.

LNCRNAS ASSOCIATED WITH TUMOR GROWTH AND PROLIFERATION IN HCC

Highly upregulated in liver cancer

Highly upregulated in liver cancer (HULC), a well-researched lncRNA who associates with HBV infection and HCC tumor growth is upregulated in HCC and associated with its grades^[45]. By viewing dozens of research articles, we found that HULC can accelerate the growth of HCC *via* downregulating its neighbor gene p18 (known as eukaryotic translation elongation factor 1, EEF1E1 or AIMP3) and can disturb the circadian rhythm of HCC *via* upregulating oscillator CLOCK^[47].

The complementary base which pairs between 5'UTR of CLOCK mRNA and HULC takes responsibility for the modulation of CLOCK mediated by HULC^[91]. With regard to the mechanism of HULC upregulation, HBx regulates the transcription of CREB-dependent promoters by interacting with CREB, and then, the transcription factor CREB contributes to the activation of HULC promoter^[47,48]. The variant genotypes of rs7763881 in HULC contribute to decreasing HCC susceptibility in persistent HBV carriers. And single nucleotide polymorphisms (SNPs) in HULC contribute to the risk of HBV chronic infection and HCC^[92]. Besides, HULC acts as an endogenous "sponge", who downregulates a series of miRNAs activities, including miR-372. Studies indicate that inhibition of miR-372 results in decreased translational repression of its target gene, PRKACB, and inducing phosphorylation of CREB in turn^[48].

Based on the above mechanisms, HULC may have the potential of predicting prognosis in clinical practice. However, only cell lines research were done by researchers, other confirmatory experiments are requisite.

LncRNA-hPVT1

Two studies investigated closely into lncRNA-hPVT1 and concluded that it has a function of promoting cell proliferation, cell cycling and it also functions as an acquisition of stem-cell like contents in HCC cells. lncRNA-hPVT1 upregulates nucleolar protein p120 (NOP2) *via* enhancing the stability of NOP2 proteins and its above functions depend on the presence of NOP2. Studies show that the transforming growth factor (TGF)- β 1/lncRNA-hPVT1/NOP2 pathway is compromised in the progression of HCC. Hence, lncRNA-hPVT1 influences the stem-cell like potential of HCC cells and promotes the growth of HCC. Regulation of the lncRNA-hPVT1/NOP2 pathway has a beneficial effect in the treatment of HCC^[71]. More researches are needed to be done in order to find effective therapy targeted at lncRNA-hPVT1.

UFC1

Other than the above three lncRNAs, another well-studied lncRNA associated with HCC proliferation is lncRNA-UFC1 (GenBank Accession No. KJ809564), who promotes HCC cell proliferation, induces cell cycle progression and inhibits cell apoptosis^[73]. It induces HuR translocation and by silencing HuR expression can abrogate the function of lncRNA-UFC1 function in HCC. Moreover, lncRNA-UFC1 is targeted by miR-34a and the overexpression of miR-34a significantly suppresses the expression levels of cell cycle related proteins, cellular proliferation and HuR expression in lncRNA-UFC1-overexpressing cells^[10]. As molecularly targeted therapies are heated studied, UFC1 offers us a new aspect, clinical research are in the urgent need.

ZNRD1 antisense RNA 1

A large case-control study including 1344 HBV natural-clearance subjects, 1344 HBV persistent carriers and

1300 HBV-positive HCC patients was done^[93]. The study found out that ZNRD1 antisense RNA 1 (ZNRD1-AS1) is a crucial regulator of ZNRD1 (human zinc ribbon domain containing 1). In ZNRD1-AS1, several SNPs (nucleotide polymorphisms) is identified as expression quantitative trait loci (eQTLs) SNPs, which are connected with the expression of ZNRD1^[94,95]. ZNRD1 is involved in DNA damage and repair *via* regulating the expression of excision repair cross-complementing 1 (ERCC1)^[96], to restrain cell proliferation and to regulate the expression of miRNAs in cancers^[97,98]. Furthermore, ZNRD1 eQTLs SNPs in lncRNA ZNRD1-AS1 have an increased risk for persistent HBV-carriers HCC but a protective influence against chronic HBV infection^[93]. As a result, the different roles which ZNRD1-AS1 play make a difference in the treatment of HBV-positive HCC patients and HBV-negative HCC patients.

Colon cancer associated transcript-1

Dysregulation of colon cancer associated transcript-1 (CCAT1) is in association with tumor size, microvascular invasion, AFP and prognosis in patients with HCC. Besides, it is demonstrated that *in vitro* CCAT1 could promote proliferation and migration in HCC by binding to let-7, which contributes to the up-regulation of HMGA2 and c-Myc^[76]. Herein, the complex of CCAT1 and let-7 may have the diagnostic function in early detection of HCC and its migration.

Maternally expressed gene 3

Maternally expressed gene 3 (*MEG3*) regulates tumor cell proliferation and apoptosis in HCC partially through the accumulation of p53^[83]. UHRF1, as a new identified oncogene, contributes to the upregulation of *MEG3* in HCC by regulating DNMT1, while upregulation of *MEG3* in HCC cells can partially diminish the promotion of proliferation produced by UHRF1. In addition, UHRF1/DNMT1/*MEG3*/p53 axis signaling pathway is involved in HCC progression^[99]. Furthermore, loss of *MEG3* gene expression is related to hypermethylation of the promoter region in HCC^[82]. Impressively, enforced expression of *MEG3* in HCC remarkably decreases both anchorage-independent and anchorage-dependent cell growth, and induces cell apoptosis^[83]. Associated with anti-oncogene p53, *MEG3* shows a promising future in being one of the therapeutic targets for HCC treatment.

PTENP1

The over-expression of PTENP1 (a pseudogene of PTEN) represses the oncogenic PI3K/AKT pathway and elicits pro-death autophagy by sequestering miR-20a, miR-19b and miR-17 *in vitro*. It also inhibits tumor growth *in vivo*. These are accompanied by dampened angiogenesis or neovasculature maturation, enhanced apoptosis and autophagy^[88]. It's necessary to do further *in vivo* experiments to confirm its detailed mechanism.

The above 7 lncRNAs have been widely studied, and they are considered to be associated with tumor growth and proliferation in HCC. With further clinical trials, their

application in the prediction and diagnosis of HCC would be possible.

LNCRNAs ASSOCIATED WITH METASTASIS AND PROGNOSIS IN HCC

Invasion and metastasis often adumbrate an advanced stage while recurrence often indicates a poor prognosis. It's the same in HCC development. The following lncRNAs were found associated with metastases and recurrence which may predict a dismal outcome.

H19

A dozen of studies have elucidated that H19 serves as a potential prognostic marker as well as potential target for HCC therapy. By decreasing the expression of markers for epithelial-to-mesenchymal transition, such as claudin 1, cytokeratin-8 (KRT-8), KRT-19 and CDH1 (E-cadherin), H19 suppresses the progression of HCC. By mediating hnRNP/PCAF/RNAPol II, H19 suppresses the migration of HCC. By increasing histone acetylation, H19 can epigenetically activates miR-200 family, and thus, it suppresses HCC metastasis^[50]. Moreover, the identification of AKT/GSK-3 β /Cdc25A signaling pathway as the downstream signaling pathway of H19 explains the molecular mechanism of metastasis and invasion in HCC^[100]. And it has also been demonstrated that the deletion of H19 endodermal enhancer can regulate expression of insulin-like growth factor 2 (IGF2) and H19 in the early stage of liver carcinogenesis as well as that paternal inheritance of the deletion of H19 endodermal enhancer can delay tumor formation by increasing apoptosis of the hepatocytes and reducing IGF2 expression^[101]. In the main, by various signaling pathway, H19 can be a promising indicator for prognosis and can be targeted in the treatment of HCC.

Metastasis-associated lung adenocarcinoma transcript 1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a critical regulator of maintaining the transformative phenotype in HCC, it associates with tumor metastasis and recurrence^[102]. MALAT1 is a genuine target gene of the Wnt/TCF/ β -catenin and Hippo/yes associated protein (YAP) signaling pathway. It is negatively regulated by SRSF1 *via* the following two pathways. The first pathway is by accelerating the degradation of MALAT1 which is blocked by YAP at the stage of post-transcriptional. When overexpressed, YAP stimulates the translocation of SRSF1 from the nucleus to the cytoplasm, thus the nuclear-retained MALAT1 avoids degradation^[103]. The second pathway is by binding to YAP. SRSF1 inhibits the transcriptional activity of YAP and prevents the recruitment of YAP on the MALAT1 promoter at a transcriptional stage^[104].

MALAT1 can interact with the arginine/serine SR proteins and modulate their distribution to the nuclear speckles. Furthermore, MALAT1 can regulate alternative splicing of pre-mRNAs *via* controlling active SR proteins'

levels^[103].

To sum up, by participating in different pathway, MALAT1 shows a crucial role in the carcinogenesis of HCC which lays the foundation of early detection of metastases and assessment of recurrence.

HOX transcript antisense RNA

High expression of HOX transcript antisense RNA (HOTAIR) indicates a notably poorer prognosis with respect to overall survival (OS) and a remarkably larger tumor size in HCC patients^[62]. HOTAIR is selectively required to target polycomb repressive complex 2 (PRC2) occupancy, thus, induces histone H3 tri-methylated at lysine 27 (H3K27) trimethylation and silenced transcription of the HOXD locus^[105]. The 5' domain of HOTAIR can bind to PRC2, while the 3' domain of HOTAIR can bind to the LSD1 (lysine specific demethylase 1)/CoREST (Co-repressor of RE1-silencing transcription factor)/REST complex; after that, the complexes are targeted and assembled to the HOXD locus; and co-ordinately regulate histone H3K27 methylation and histone histone 3 methylated at lysine 4 demethylation; consequently, the transcription across 40 kb of the HOXD locus is silenced in trans by DNA methylation^[106]. These indicate that the HOTAIR-induced assembly and targeting of LSD1 and PRC2 complexes is a general mechanism for gene silencing across the genome, which plays a vital role in the association with invasion and metastasis in HCC^[64]. Expression of HOTAIR is also associated with tumor size and lymph node metastasis in HCC patients^[62]. Knockdown of HOTAIR reduces the levels of matrix metalloproteinase 9 and vascular endothelial growth factor, which play an important role in metastasis and cell motility^[60].

In addition, HOTAIR is found to promote invasion and migration in HCC by inhibiting RBM38. Silencing of RBM38 restores cell motility, while knockdown of HOTAIR conspicuously reduces cell motility as the downregulation of HOTAIR increases the expression of RBM38 both on mRNA levels and protein levels^[63].

With its association with tumor size, tumor metastasis and OS, HOTAIR is regarded as one of the prognosis indicator. It's of great potential value to use it in the clinic in the future.

HOTTIP

HOTTIP (the transcript of HOXA at the distal tip with 3.8 kb), transcribed from the 5' tip of the HOXA locus, coordinates the activation of some 5' HOXA genes and is negatively regulated by miR-125b. High HOTTIP expression indicates an increased metastasis formation and a decreased overall survival^[65]. HOTTIP binds the adaptor protein WDR5 directly and targets WDR5/MLL complexes across HOXA, thereby driving histone H3 lysine 4 trimethylation and the gene transcription and influences HCC cell proliferation rates as a result^[27]. Its overexpression contributes to hepatocarcinogenesis through regulating the expression of its neighboring protein-coding genes^[67]. With these function, HOTTIP

can be potentially used in clinic as a prognosis predictor.

LncRNA high expression in HCC

LncRNA high expression in HCC (HEIH), associated with recurrence and overall survival in HBV-related HCC, is overexpressed in HCC tissues^[68]. HEIH influences the expression of enhancer of zeste homolog 2 (EZH2) target genes by increasing the binding of EZH2 levels. Downregulation of HEIH induces G(0)/G(1) arrest which is caused by the interaction of EZH2 with HEIH. Thus, level of HEIH is significantly associated with recurrence and is an independent prognostic factor for survival in HCC^[68]. In summary, HEIH connects with HBV-related HCC and plays a role as the risk factor for HCC recurrence. Therefore, predicting the possibility of HCC recurrence by detecting the relative change of the HBV virus and HEIH level in serum is worth further studying.

ATB

Overexpression of lncRNA-ATB (lncRNA-activated by TGF- β) significantly correlates with EMT gene signature expression, macrovascular invasion, microvascular invasion, portal vein tumor thrombus and encapsulation. Moreover, higher expression of lncRNA-ATB is significantly correlated with shorter recurrence-free survival and overall survival, suggesting that lncRNA-ATB contributes to HCC progression^[27].

LncRNA-ATB upregulates ZEB1 and ZEB2 *via* competitively binding with the miR-200 family, then it induces EMT and invasion. Besides, lncRNA-ATB promotes organ colonization of disseminated HCC tumor cells through binding with autocrine induction of interleukin 11 (IL-11), IL-11 mRNA and triggering signal transducer and activator of transcription 3 signaling^[79,80]. On the whole, lncRNA-ATB facilitates the invasion-metastasis cascade, which makes it a predictor for HCC prognosis.

LncRNA-p21

LncRNA-p21, located upstream of *CDKN1A* gene, who triggers apoptosis in HCC, is a transcriptional target of p53 and *p53* gene is an important tumor suppressor gene^[107,108]. Importantly, lncRNA-p21 can bind to heterogeneous nuclear ribonucleoprotein K (hnRNP-K), therefore it contributes to the localization of hnRNP-K and transcriptional repression of p53-regulated genes^[109] and as a result, triggers apoptosis. Theoretically, lncRNA-p21 should be down-regulated in HCC, however, corroborating experiments are needed to delineate the exact underlying mechanism. As the transcriptional target of anti-oncogene p53, p21 shows a promising future in being one of the therapeutic targets for inducing cellular apoptosis.

The above 7 lncRNAs are considered to be associated with metastasis and prognosis in HCC. Although many researches have been complicated, studies with more cases and further ward clinical trials would be needed in order to develop novel therapeutics and treatment for

HCC patients.

LATEST FIND OF LNCRNAs RELATED TO HCC

Linc00974

Dysregulation of Linc00974 increases KRT19 levels, which results in the activation of both TGF- β and Notch signaling pathways, which causes the invasion and proliferation of HCC both *in vivo* and *in vitro*. Linc00974 influenced KRT19 expression by interacting with miR-642^[72]. Being significantly correlated with tumor differentiation grade, size and metastasis makes Linc00974 a feasible predictor in the carcinogenesis of HCC.

Up-regulated in hepatocellular carcinoma

High level of up-regulated in hepatocellular carcinoma (URHC) expression is significantly associated with tumor size, tumor number and shorter overall survival after surgery^[81]. URHC can regulate cell proliferation and apoptosis by repressing ZAK expression. ZAK, also known as MLK-like MAP triple kinase- α or ZAK- α , belongs to the mixed lineage kinase family and functions as a tumor-suppressor gene in HCC^[110]. Inactivation of the ERK/MAPK pathway is required for the increase in HCC growth, which is induced by URHC-ZAK regulation^[81]. However, only microarray analysis was done, which limited its conviction. Experiments *in vivo* and *in vitro* are desperately needed.

SRHC

SRHC (NCBI No: uc003jdr) is an important downstream target gene of HNF-4A and it is correlated with α -feto-protein (AFP) levels and the degree of differentiated tumors^[89]. SRHC is combined with HNF-4A to promote its transcription, thus inhibiting the proliferation of tumor cells and promoting cell differentiation in HCC^[89]. Serum AFP level monitoring is well developed and have been used as a standardized index of HCC diagnosis, therefore, detecting SRHC in predicting HCC may have great value in clinical practice as well.

Metallothionein 1D, pseudogene

Metallothionein 1D, pseudogene (MT1DP) inhibits tumor cell growth could be rescued by a combination of overexpression of Runt related transcription factor 2, FoxA1 and YAP. In addition, MT1DP inhibited transformative phenotype of liver cancer cells and cell proliferation by reducing protein synthesis of FoxA1^[90]. With this inhibiting function, it's of great research value whether MT1DP can be a potential therapeutic target in the treatment of HCC or not.

LncRNA low expression in tumor

LncRNA low expression in tumor (LncRNA-LET) plays a decisive role in hypoxia-induced metastasis in HCC through a hypoxia-inducible factor 1, alpha subunit

(HIF-1 α)/histone deacetylase 3 (HDAC3)/LET/NF90 pathway^[110]. Precisely, HDAC3 represses LET by decreasing the LET promoter region's histone acetylation-mediated modulation under hypoxic conditions. And then, down-regulation of LET recedes the direct interactions between LET and NF90, then enhances the stabilization of NF90 and increases the expression of HIF-1 α (a target mRNA of NF90 involved in hypoxia-induced metastasis). As a result, LET inhibits the metastasis of HCC *via* this positive feedback loop^[87]. Therefore, when LET is downregulated, patients usually face a poor prognosis.

For these 5 newly found lncRNAs, investigations with more preclinical models of HCC would be desired in order to further strengthen the conclusions and provide a more rational support for ward clinical application.

CONCLUSION

In conclusion, lncRNAs play a crucial role in various biological processes in HCC, such as initiation, progression, metastasis, treatment and prognosis.

Two latest published articles also reached the same conclusion. On the basis of dozens of studies, Yang *et al.*^[111] discussed the probable molecular mechanisms depended on lncRNA level change, and drew the conclusion that lncRNAs can be applied in HCC diagnosis and treatment. However, their summary was ommissive as they only analyzed the upregulated lncRNAs, and even some upregulated lncRNAs were left out, such as HOTTIP, MVIH, UFC1, UCA1, CCAT1, *etc.* In our article, we not only analyzed the differential expression of lncRNAs in human HCC (upregulated as well as downregulated), but also summarized their specific mechanisms and pathways and gave an outlook in their potential as candidates in diagnosis and treatment of HCC. Another review^[111] provided different lncRNAs compared to us, such as RP11-160H22.5, XLOC_014172 and LOC149086. However, these lncRNAs were not embodied in NCBI database, and their mechanisms were unavailable, which brought us new research direction.

Although plenty of studies^[28,112-115] cast light on the characteristics and mechanisms of different lncRNAs involved in HCC as we summarized above, till now, research on lncRNA still remains in its infancy and a large portion of lncRNAs surely remains to be further discovered. As systematic identification of lncRNAs and their well-understanding of mechanisms can pave the way for early diagnosis and therapeutics designing for HCC, there is still a long way to go in the research field of HCC-related lncRNAs.

Continuous researches are needed to verify the detailed function and mechanisms of revealed lncRNAs and to find innovative lncRNAs and sequentially, the predictive and diagnostic roles of lncRNAs in HCC can be validated. Thereby, diagnosis of HCC in an early stage and controlling its development and progression will become possible. Further clinical and ward trials are also in the urge, so that we can develop therapeutic roles of lncRNAs in HCC. In a word, future studies should aim

at investigating how can a discovered lncRNA be used to identify HCC patients and used as a guidance being applied in treatment to have optimal responses and to reduce the likelihood of relapse.

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