

Long non-coding RNAs era in liver cancer

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies leading to high mortality rates in the general population and the sixth most common cancer worldwide. HCC is characterized by deregulation of multiple genes and signalling pathways. These genetic effects can involve both protein coding genes as well as non-coding RNA genes. Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nt, constituting a subpopulation of ncRNAs. Their biological effects are not well understood compared

to small non-coding RNA (microRNAs), but they have been recently recognized to exert a crucial role in the regulation of gene expression and modulation of signalling pathways. Notably, several studies indicated that lncRNAs contribute to the pathogenesis and progression of HCC. Investigating the molecular mechanisms underlying lncRNAs expression opens potential applications in diagnosis and treatment of liver disease. This editorial provides three examples (MALAT-1 metastasis associated lung adenocarcinoma transcript, HULC highly upregulated in liver cancer and HOTAIR HOX transcript antisense intergenic RNA) of well-known lncRNAs upregulated in HCC, whose mechanisms of action are known, and for which therapeutic applications are delineated. Targeting of lncRNAs using several approaches (siRNA-mediated silencing or changing their secondary structure) offers new possibility to treat HCC.

Key words: Hepatocellular carcinoma; Epigenetics; Sequencing; Liver; Long non-coding RNAs

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Core tip: The long non-coding RNAs discovery opens a meaningful collision with epigenetics and reveals new roles of RNA in most of cellular processes. This focus explores the functional potentiality of RNAs in the liver in light of most recent knowledge.

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TEXT

Recent advances in massive parallel sequencing, especially RNA sequencing (RNAseq), reveal that at least 90% of the human genome is transcribed into

non-coding RNAs (ncRNAs), while surprisingly less than 2% encodes protein-coding genes. Besides the different types of ncRNAs smaller than 200 nucleotides, such as microRNAs (miRNAs) or PIWI-interacting RNAs, a large proportion of human transcriptome results in RNAs that are longer than 200 nucleotides. Speaking in terms of numbers, this means that about 9000 small ncRNAs and about 32000 long ncRNAs (lncRNAs) have been identified vs 21000 protein coding genes^[1]. The importance of the lncRNAs has been proven in recent years, as multiple research groups functionally characterized the relevant lncRNAs role in development, epigenetics, cell differentiation and cancer^[2]. Basically, lncRNAs can be defined as often polyadenylated RNA, lacking clear open reading frames (ORFs)^[2]. The sequence length of this family gives them the ability to have complex secondary structures and to turn inward revealing a tertiary structure^[3]. *De novo* discovery and expression analysis of lncRNAs by RNAseq allowed them to be classified along the cell lines, highlighting that lncRNAs expression is strikingly tissue-specific compared with coding genes. Batista *et al*^[4] also underline the “address code”, both spatial and temporal, of the lncRNAs as key components in cell fate during the development. The repertoire of the functions of lncRNAs seems to be getting more and more increasing and spans between transcription and regulation of messenger RNA (mRNA) processing or translation. They can act *in cis* or *in trans* and the cells can use them to modulate gene expression as well as to bind miRNAs, thereby behaving like a sponge in order to protect the mRNAs target from degradation (ceRNAs)^[1].

This editorial focuses on three well-known lncRNAs in the liver and on their potential application as therapeutic targets: metastasis associated lung adenocarcinoma transcript 1 (MALAT-1), highly upregulated in liver cancer (HULC) and HOX transcript antisense intergenic RNA (HOTAIR).

lncRNA MALAT-1 is frequently upregulated in both liver cancer cell lines and hepatocellular carcinoma (HCC) tissue samples; moreover analysis of clinical data demonstrated that its level is an independent prognostic factor for HCC recurrence after liver transplantation^[5], potentially acting as a novel biomarker. MALAT-1 is involved in mRNA splicing^[6] and may play an essential role in cell cycle regulation^[7]. Recent and encouraging studies indicate that antisense oligonucleotides specific to match MALAT-1 disrupt its function, attenuating the corresponding phenotype in cancer cell^[8]. A treatment targeting MALAT-1 may be a significant approach in patients following liver transplantation.

One example of ceRNAs class, which has been well characterized in the liver, is HULC. The lncRNA HULC is upregulated in HCC and was found to contain mir-372 binding sites. HULC overexpression can reduce mir-372 level, leading to an induction of PRKACB, which in turn induces CREB phosphorylation^[9]. Phosphorylated CREB protein binds to a cAMP response element region, and is then bound to by CBP, which coactivates it, leading to

the acetylation of the histone tail and maintaining the open configuration of the chromatin. This regulatory circuitry provides an example of gene reprogramming during tumorigenesis. Interestingly, a recent paper showed that hepatitis B virus X protein (HBx) positively correlated with HULC in clinical HCC tissues. Moreover, HBx also activated the HULC promoter in HepG2 cell lines^[10]. Liu *et al*^[11] demonstrated that a single nucleotide polymorphism at HULC was associated with decreased sponge activity and decreased HCC risk. It suggests that therapeutic agents that compete with miRNA binding may be useful to treat HCC patients^[11].

The third well-known lncRNA is HOTAIR, which is always overexpressed in HCC and liver cancer cell lines. HOTAIR increases PCR2 recruitment to the genomic loci and in this way, it mediates the epigenetic repression of PCR2 target genes, modifying the profile of positive (H3K4me3) or negative (H3K27me3) chromatin marks^[12]. Notably, this kind of lncRNA fits into the universe of the chromatin world by changing its structure. An increasing number of chromatin-associated proteins have been implicated in RNA binding, supporting the idea that epigenetic effects are RNA-dependent. Altering the secondary structure of HOTAIR may prevent to embed PCR2 and the consequent aberrant epigenome^[13].

All together, these evidences suggest that lncRNAs are strongly associated with liver cancer and they have real potential roles as biomarkers for disease diagnosis, prognosis, or therapeutic response as well as direct targets for therapeutic intervention.

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