Review

The emergence of long non-coding RNAs in hepatocellular carcinoma: an update

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Abstract

Hepatocellular carcinoma (HCC) accounting for roughly 90% of all primary liver neoplasms is the sixth most frequent neoplasm and the second prominent reason of tumor fatality worldwide. As regulators of diverse biological processes, long non-coding RNAs (IncRNAs) are involved in onset and development of neoplasms. With the continuous booming of well-featured IncRNAs in HCC from 2016 to now, we reviewed the newly-presented comprehension about the relationship between IncRNAs and HCC in this study. To be specific, we summarized the overview function and study tools of IncRNAs, elaborated the roles of IncRNAs in HCC, and sketched the molecular mechanisms of IncRNAs in HCC. In addition, the application of IncRNAs serving as biomarkers in early diagnosis and outcome prediction of HCC patients was highlighted.

Key words: long non-coding RNAs, hepatocellular carcinoma, function, mechanism, diagnosis; prognostic biomarker

Introduction

Hepatocellular carcinoma (HCC) accounts for roughly 90% of all primary liver neoplasms, and is the sixth most frequent neoplasm and the second prominent reason of tumor fatality worldwide [1]. The highest morbidity of HCC has been found in China and the Asia-Pacific area, which accounts for >50% of HCC cases in the world [2]. Meanwhile, liver cancer is fatal in both developed and developing countries, with the 5-year overall survival rate generally lower than 20% [3]. HCC is the sole solid neoplasm that could be cured by liver transplant which can simultaneously heal the neoplasm and latent cirrhosis, and which is not influenced by the extent of liver function impairment [4]. However, the extreme shortage of liver donors results in procrastination before transplantation, and increasing the risk of tumor progression, and transplantation failure during this period [5]. These suggested that HCC is a devastating disease with disappointing outcomes and limited therapeutic options. Similar to other cancers, HCC is characterized by the gradual accumulation of genetic and epigenetic changes [6-8]. Among these alterations, long non-coding RNAs (IncRNAs) play crucial roles in the initiation and progression of HCC.
LncRNAs are transcripts with more than 200 bp in length, and have incrementally been recognized as the emerging star in neoplasm study as their essential function in tumor biology [9-11]. These transcripts are lack of the protein-coding potential in general and are particularly ubiquitous in almost whole livings [9]. LncRNAs have emerged as regulators in diverse biological processes [12-14] containing cellular proliferation, differentiation, motility, invasiveness, survival and so on [15-17]. Mounting evidences have demonstrated that IncRNAs are involved in tumor onset and development [18, 19], and their expression is frequently deregulated in cancers [20-27]. LncRNAs are strikingly cell type-specificity and cancer type-specificity in expression which are relatively stable [18, 28]. Therefore, IncRNAs stand a chance to serve as a kind of desired indicators with underlying utilizations in neoplasm divination, early-discovery, classification and treatment.

With the continuous booming of well-featured lncRNAs in HCC from 2016 to now, a great quantity of newly-presented researches is coming into being on the relationship between IncRNAs and HCC. Here, we reviewed the present comprehension of IncRNAs in HCC. To be specific, we summarized the overview function and study tools of IncRNAs, elaborated the roles of IncRNAs in HCC, and sketched the molecule mechanisms of IncRNAs in HCC. Meanwhile, the utilization of IncRNAs as markers in HCC early-diagnosis and outcome prediction was also highlighted.

Tools for the research of IncRNAs

A mounting number of databases about lncRNAs are developed to assist in the research of IncRNAs that include the functions of IncRNAs under the physiological state and pathological conditions. Over twenty databases touching upon the biological properties of IncRNAs are outlined in Table 1. These databases will dramatically facilitate a better understanding of IncRNAs which are essential members of epigenetic regulation, and their interaction with other RNAs.

Dysregulation and roles of IncRNAs in HCC

Tumor progression and recurrence

HCC is a complicated disease referred to multiple factors. A growing body of evidence suggested that IncRNAs involved in the occurrence and development of diverse neoplasm containing HCC. Importantly, some could affect the features of neoplasm, including proliferation, apoptosis, motility, invasiveness and angiogenesis. As an example, HOTAIR expression levels increased in both HCC tumor tissues and HepG2 cells, which promoted HCC progression [29] and were bound up with earlier relapse [30, 31]. Those showed the importance of HOTAIR in the evolvement and the relapse of HCC. Furthermore, IncRNAs could be involved in tumor progression and had potential to serve as an attractive target for precision therapy in HCC.

Invasiveness and metastasis

It is well known that invasiveness is an origin in worse disease prognosis and higher recurrence of neoplasm patients [32], which was partly correlated with certain behaviors of cancerous cells. Studies have showed that IncRNAs were related to vital growth-boosting properties and their deregulation dedicated to the survival of cancerous cells. LINC00052 [33], ZEB1-AS1 [34] and LINC01225 [35] was showed to accelerate cellular motility and invasiveness. In short, these IncRNAs could function as oncogenes via facilitating invasion and metastasis of HCC cells. Conversely, it was indicated that CPS1-IT1 [36], IncRNA XIST [37] and IncRNA FTX [38] were down-regulated in HCC samples and inhibited the relapse and metastasis of HCC cells. These IncRNAs act as tumor suppressor genes via restraining invasion and metastasis in HCC.

Proliferation and apoptosis

A flood of literatures have mirrored that IncRNAs participated in the development of HCC via modulating cell proliferation and apoptosis. On the one aspect, some IncRNAs could accelerate cell proliferation while inhibit cell apoptosis in HCC. It was demonstrated that the expression of XIST [39], IncRNA HOST2 [40], HOXA-AS2 [41], CCHE1 [42] and AFAP1-AS1 [43] was significantly elevated in HCC tumor tissues and/or cell lines, which promoted cell proliferation while protected cells from apoptosis in HCC. Conversely, IncRNA AK058003 [44], lincRNA-p21 [45] and IncRNA XIST [37] were revealed to decrease in HCC tumors, and act as a tumor suppressor, suppressing HCC cellular multiplication and clonality while accelerating cellular apoptosis. These results suggested that IncRNAs played important roles in proliferation and apoptosis of HCC and may serve as latent therapeutic targets of HCC.

Chemo-sensitivity and radio-resistance

LncRNAs have also been reported to function in chemo-sensitivity or radio-resistance through arrest of cell cycle, suppression of apoptosis as well as strengthening of DNA injury repair [46, 47]. For instance, IncRNA TUC338 [48] and MALAT1 [49] was involved in HCC evolution and drug-resistance (such as...
as sorafenib). These suggested that lncRNAs have the potential to serve as new targets for exploiting novel strategies of chemotherapy and radiotherapy in HCC patients.

**Angiogenesis**

Coupling with the increase of neoplasm sizes, angiogenesis is required. In order to supply nutrient substances and O₂, angiogenesis permits neoplasm to maintain its metabolism waste with following access to blood metastasis process. Frequently, neoplasm cell leads to induction of pro-angiogenic signs or blockage of anti-angiogenic markers, which could open an “on-off” of angiogenesis. LncRNAs are mirrored to serve as a key player in the regulation of angiogenesis. LncRNAs contributed to abnormal hypervascularity of HCC and afforded a novel landscape into the mechanism of neoplasm angiogenesis.

**Table 1. Main databases of long noncoding RNAs**

<table>
<thead>
<tr>
<th>NO.</th>
<th>Database name</th>
<th>Availability</th>
<th>Characteristics *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arraystar</td>
<td><a href="http://www.arraystar.com/">http://www.arraystar.com/</a></td>
<td>analysis for expression profiling and for the regulation of RNAs, especially the regulatory ncRNAs</td>
</tr>
<tr>
<td>2</td>
<td>C-It-Loci</td>
<td><a href="http://c-it-loci.uni-frankfurt.de/">http://c-it-loci.uni-frankfurt.de/</a></td>
<td>conserved loci and silico screening of tissue-enriched lncRNAs</td>
</tr>
<tr>
<td>3</td>
<td>ceRDB</td>
<td><a href="http://www.oncomir.umu.uen/cefind/">http://www.oncomir.umu.uen/cefind/</a></td>
<td>miRNA binding sites for a given mRNA target</td>
</tr>
<tr>
<td>4</td>
<td>CHIPBase</td>
<td><a href="http://rna.sysu.edu.cn/chipbase/">http://rna.sysu.edu.cn/chipbase/</a></td>
<td>the TF binding sites and motifs, co-expression patterns, ChIP-function and genome browser</td>
</tr>
<tr>
<td>5</td>
<td>Co-LncRNA</td>
<td><a href="http://www.bio-bigdata.com/Co-LncRNA/">http://www.bio-bigdata.com/Co-LncRNA/</a></td>
<td>GO annotations and KEGG pathways</td>
</tr>
<tr>
<td>6</td>
<td>DIANA-LncBase v2.0</td>
<td><a href="http://www.microrna.gr/LncBase">http://www.microrna.gr/LncBase</a></td>
<td>expression regulation and the annotation of MREs on the basis of ‘ceRNA hypothesis’</td>
</tr>
<tr>
<td>7</td>
<td>GEPIA</td>
<td><a href="http://gepia.cancer-pku.cn/index.html">http://gepia.cancer-pku.cn/index.html</a></td>
<td>customizable functions analysis, such as expression, survival and correlation analyses</td>
</tr>
<tr>
<td>8</td>
<td>Linc2GO</td>
<td><a href="http://www.bioinfo.tsinghua.edu.cn/~liuke/Linc2GO/index.html">http://www.bioinfo.tsinghua.edu.cn/~liuke/Linc2GO/index.html</a></td>
<td>comprehensive functional annotations on the basis of ‘ceRNA hypothesis’</td>
</tr>
<tr>
<td>9</td>
<td>Lnc2Cancer</td>
<td><a href="http://www.bio-bigdata.net/Lnc2cancer/">http://www.bio-bigdata.net/Lnc2cancer/</a></td>
<td>relationships between lncRNA and human tumors</td>
</tr>
<tr>
<td>10</td>
<td>LncACTdb</td>
<td><a href="http://www.bio-bigdata.net/LncACTdb/">http://www.bio-bigdata.net/LncACTdb/</a></td>
<td>interactions and annotations of lncRNA-miRNA-mRNA</td>
</tr>
<tr>
<td>11</td>
<td>lncATLAS</td>
<td><a href="http://atlas.crg.eu/">http://atlas.crg.eu/</a></td>
<td>subcellular localization of lncRNAs</td>
</tr>
<tr>
<td>12</td>
<td>lncCeDB</td>
<td><a href="http://gyanxet-beta.com/lncedb/">http://gyanxet-beta.com/lncedb/</a></td>
<td>lncRNAs acting potentially as ceRNAs</td>
</tr>
<tr>
<td>13</td>
<td>LNCipedia</td>
<td><a href="http://www.lncipedia.org">http://www.lncipedia.org</a></td>
<td>basic transcript information and structure; protein coding potential and transcript features, microarray probes and lncRNA expression</td>
</tr>
<tr>
<td>14</td>
<td>LncRBase</td>
<td><a href="http://bicresources.jcbose.ac.in/zhurm/lncbase/">http://bicresources.jcbose.ac.in/zhurm/lncbase/</a></td>
<td>functions, annotations, lncRNA expression values, associations between lncRNAs and functional terms, as well as known functions of human lncRNAs annotations of eukaryotic lncRNAs and references information about these RNAs</td>
</tr>
<tr>
<td>16</td>
<td>LncRNAdb</td>
<td><a href="http://www.lncrdb.net/">http://www.lncrdb.net/</a></td>
<td>resources of SNPs in human/mouse lncRNAs and functional SNP selection</td>
</tr>
<tr>
<td>17</td>
<td>LncRNADisease</td>
<td><a href="http://cmbi.bjmu.edu.cn/lncrnadisease/">http://cmbi.bjmu.edu.cn/lncrnadisease/</a></td>
<td>as a component of ScienceWikis, it affords community-curated resource of LncRNA knowledge</td>
</tr>
<tr>
<td>18</td>
<td>LncRNASNP</td>
<td><a href="http://bioinfo.life.hust.edu.cn/lncRNA">http://bioinfo.life.hust.edu.cn/lncRNA</a> SNP/</td>
<td>types, chromosomal locations, descriptions on the biological functions and disease associations, protein-lncRNA interactions, and genomic variations</td>
</tr>
<tr>
<td>20</td>
<td>LncRNAsome</td>
<td><a href="http://genome.igib.res.in/lncRNAsome/">http://genome.igib.res.in/lncRNAsome/</a></td>
<td>conservation annotations and lncRNAs–diseases relationships</td>
</tr>
<tr>
<td>21</td>
<td>miRcode</td>
<td><a href="http://www.microcode.org">http://www.microcode.org</a></td>
<td>gene expression information and ancillary data for featured ncRNAs</td>
</tr>
<tr>
<td>22</td>
<td>NONCODE</td>
<td><a href="http://www.noncode.org">http://www.noncode.org</a>, or <a href="http://www.bioinfo.org/noncode/">http://www.bioinfo.org/noncode/</a></td>
<td>—</td>
</tr>
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<td>24</td>
<td>RegRNA2.0</td>
<td><a href="http://regrna2.mbc.nctu.edu.tw/">http://regrna2.mbc.nctu.edu.tw/</a></td>
<td>functional RNA motifs and sites</td>
</tr>
<tr>
<td>25</td>
<td>StarBase v2.0</td>
<td><a href="http://starbase.sysu.edu.cn/">http://starbase.sysu.edu.cn/</a></td>
<td>miR-function and ceRNA-function web tools</td>
</tr>
<tr>
<td>26</td>
<td>TANRIC</td>
<td><a href="http://ipl.mdanderson.org/tanric/...design/basic/index.html">http://ipl.mdanderson.org/tanric/...design/basic/index.html</a></td>
<td>the expression profiles of lncRNAs in large patient cohorts of 20 cancer types including TCGA, CCLE and other independent datasets</td>
</tr>
<tr>
<td>27</td>
<td>TPGLDA</td>
<td><a href="https://github.com/USTC-HIlab/TPGLDA/">https://github.com/USTC-HIlab/TPGLDA/</a></td>
<td>prediction of relationships of lncRNAs and diseases</td>
</tr>
</tbody>
</table>

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References

[91] [92] [93] [94] [95] [96] [98] [99] [100] [101] [102] [103] [104] [105] [106] [107-112] [113] [114,115] [116, 117]
Molecular mechanisms of lncRNAs in HCC

Epigenetic regulatory lncRNAs
LncRNAs have been shown to exert regulatory roles at nearly all stages of gene expression [50], from targeting epigenetic modification, transcriptional regulation, interactions of lncRNAs-proteins, lncRNAs-miRNAs-mRNAs, lncRNA-lncRNA, autophagy as well as signaling pathway to modulation of mRNA stabilization. LncRNA GIHCG promoted HCC progression through epigenetically upregulating H3K27me3 levels and DNA methylation contents [51]. LncRNA ZNFX1-AS1 suppressed HCC cell growth through modulating miR-9 methylation [52]. Linc00441 promoted HCC tumorigenesis in a H3K27 modification-dependent manner [53].

Transcriptional regulatory lncRNAs
Several lncRNAs could serve as transcriptional regulators. It was reported that CCAT2 [54] and HOTAIR [55] accelerated EMT process mediated by transcription factor (TF) Slug and Snail in HCC, respectively. LncRNA ZEB1-AS1 promoted neoplasm invasiveness and indicated an adverse clinical outcome via positively regulating the ZEB1 expression in HCC [34]. Meanwhile, lncRNA CPS1-IT1 suppressed HCC aggressivity via controlling HIF-1α activity [36]. LncRNA uc.338 was found to promote cellular growth via modulating of CDKN1A transcription in HCC [56].

LncRNAs-proteins interactions
LncRNA HNF1A-AS1 repressed NKD1 and p21 expression via interacting with EZH2, and then promoted HCC cell proliferation [57]. LncRNA NEAT1 modulated hnRNP-A2 level to facilitate cellular multiplication and invasiveness in HCC cell lines [58]. LncRNA TUC338 targeted RASAL1 to be involved in sorafenib-sensitized HCC cells [48]. LncRNA BANCR elevated the protein level of VIM while lowered the protein content of E-cad to cripple cellular malignant degree [59]. The lncRNA EGFR-AS1, a target of GHR, up-regulated the expression of EGFR in HCC [60]. To summarize, lncRNAs-proteins interactions functioned as a vital mechanism of lncRNAs in HCC.

LncRNAs-miRNAs-mRNAs interactions
It has been demonstrated that microRNAs (miRNAs) functioned crucially in many caners, including HCC [61-63]. LncRNAs could share miRNA recognition elements (MREs) with mRNAs and modulate the function of mRNAs with miRNAs-mediated mechanisms, where lncRNAs were called competing endogenous RNAs (ceRNAs) [64-66]. For instance, lncRNA SNHG12 - miR-199a/b-5p - MLK3 - NF-κB signaling [67] accelerated tumorigenesis and metastasis in HCC. LncRNA UCA11 - miR-203 - Slug axis [68] and lncRNA Ftx - miR-545 - RIG-I network [69] were involvement in HCC progression. The HIF-2α - MALAT1 - miR-216b axis regulated multi-drug resistance of HCC cells [49]. Overall, lncRNAs could serve as “miRNA sponges” to share the same MREs with mRNAs.

Others
LncRNAs - lncRNAs interactions
LncRNAs functioned vitally in a variety of biology processes. Frequently, the occurrence and development of neoplasm frequently was attributed to the interaction effects of some lncRNAs. LncRNA-lncRNA synergistic networks were beneficial to explore clinically related lncRNAs in neoplasm [70]. Reports suggested that LncRNA HULC cooperated with MALAT1 to promote CSCs proliferation in HCC [71]. And the overexpression of HULC along with MALAT1 increased the binding of RNA pol II, P300, CREPT to TRF2, which triggered the upregulation, phosphorylation and SUMOylation of TRF2 [71]. Indeed, lncRNAs could interact with other lncRNAs.

Autophagy
Autophagy is a cellular degradation pathway that is essential to maintain cell physiology progress, and its disruption leads to multiple diseases in humans [72]. Recently, macro-autophagy/autophagy has emerged as a promising therapeutic target in various types of solid tumor treatment [73]. LncRNAs exerted crucial roles in the regulation of autophagy lately, which made them act as potential biomarkers of disease phenotypes [74]. LncRNA HULC could induce a protective autophagy [75]. LncRNA HNF1A-AS1 served as a autophagic accelerator in HCC [76]. And the lncRNA HOTAIR activated autophagy [30]. These studies indicated that the lncRNAs-autophagy networks are likely to supply additional insights into treatment interventions and markers evaluation in human diseases, especially in cancers.

Signaling pathway
As we all know, signaling pathways functioned considerably in the development of HCC and presented some therapeutic strategies based on in vivo and in vitro findings. LncRNA T-UCR severed as a potential growth driver gene modulated by the Wnt/β-catenin signaling in hepatobiliary carcinogenesis [77, 164]. LncRNA MEG3 could activate ER stress and p53 signaling related to NF-κB
pathway, which followed by suppressing cell multiplication and promoting apoptosis [78]. Lnc-DILC was downregulated in liver cancer stem cells and mediated intrahepatic inflammation via governing the cross-linking of TNF-α - NF-κB pathway with IL-6 - STAT3 pathway [79].

**mRNA stabilization**

Transcription activity and post-transcription mechanisms involved in IncRNAs could modulate ribonucleotide reductase followed by altering the stability of message RNAs [80]. In turn, mRNA steady state levels could directly influence their expression [80]. The IncRNA MALAT1 accelerated arsenite-induced glycolysis, which was mediated via HIF-1α mRNA stabilization in human liver L-02 cell lines [81]. LncRNA AK058003 could reduce the expression of mRNA stabilizing protein HuR and act as a precursor of miR-15a to suppress γ-synuclein-mediated cell proliferation and the metastasis of HCC [44]. In addition, IncRNA HULC triggered autophagy via stabilizing Sirt1 and attenuated the chemosensitivity of HCC cells [75]. These studies suggested that some lncRNAs participating biological processes may be mediated by selective stabilization of mRNAs.

**Potential clinical application of IncRNAs in HCC**

**LncRNAs as prognostic biomarkers for HCC**

Accumulating reports declared that lncRNAs have potential to serve as prognostic predictors in neoplasms containing HCC patients. A variety of lncRNAs were demonstrated to exhibit abnormal expression in HCC, which were significantly correlated with the survival time and were independent outcome predictors in HCC patients (Table 3). Therefore, lncRNAs might be acted as potential and useful prognostic indicators in HCC.

**Conclusion and future prospective**

In a nutshell, lncRNAs have the potential to serve as promising biomarkers for tumor progression and recurrence (lncRNA HOTAIR, SNHG1, HULC, MALAT1, CRNDE, GIHCG, UCA1, IncSox4 and IncBRM), as well as for invasion and metastasis (SNHG20, CCAT2, HOST2, Linc-cdh4-2, LINC00052, AFAP1-AS1, ZEB1-AS1, ZEB2-AS1, LINC01225, UCO01kfo, SPRY4-IT1, Unigene56159, HULC, plncRNA-1, SchLAI, IncRNA-AK058003, CPS1-IT1, XIST, FTX, TUSC7 and GA55). Besides, lncRNAs are involved in HCC through affecting on cell proliferation and apoptosis (UC001kfo, SPRY4-IT1, ZEB2-AS1, RBMY2FP, uc.338, UCA1, XIST, HOST2, HOXA-AS2, CCHE1, CCAT2, SNHG1, HNF1A-AS1, PCAT-1, AFAP1-AS1, HULC, MALAT1, IncCAMTA1, Inc-DILC, IncRNA-AK058003, ZNF1X-AS1, lincRNA-p21, XIST, FTX and GA55), as well as angiogenesis (lncRNA TUG1 and HULC). Additionally, lncRNAs serve as a conceivable indicator for chemo-sensitivity and radio-resistance (HULC, RP11-134G8.8, RP11-363E7.4, RP1-193H18.2, TUC338 and MALAT1; Figure 1, Table S1). Meanwhile, lncRNAs exerted their efficient and effective actions in mechanisms of interaction with proteins/ miRNAs/ mRNAs/ lncRNAs, in epigenetic regulation/transcriptional regulation, as well as in regulation of autophagy, signaling pathway and mRNA stabilization in HCC on the horizon of the current studies (Figure 1, Table S1). Furthermore, these lncRNAs might be promising indicators for disease diagnosis (Table 2), prognosis and recurrence prediction (Table 3), and even be new up-and-coming targets for therapeutic intervention of HCC.

Yet, the precise biological function and molecular mechanisms of IncRNAs in HCC remained uncharacterized. Thus, further exploration and validation researches are required for illuminating the intricate mechanisms (especially in epigenetic and transcriptional modulation of IncRNAs) as well as the clinical utilizations of lncRNAs in HCC.

http://www.jcancer.org
Figure 1. Dysregulation and functional roles of lncRNAs in hepatocellular carcinoma.

Table 2. Application as diagnostic index of lncRNA in hepatocellular carcinoma patients

<table>
<thead>
<tr>
<th>LncRNAs</th>
<th>Functions</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2’ lncRNA signature (PVT1 and uc002mbe.2)</td>
<td>distinguishes HCC patients from the healthy population</td>
<td>0.764 (0.684-0.833)</td>
<td>60.56 %</td>
<td>90.62 %</td>
<td>[119]</td>
</tr>
<tr>
<td>CCH1E1</td>
<td>discriminates tumor tissues from normal tissues</td>
<td>0.9262</td>
<td>—</td>
<td>—</td>
<td>[42]</td>
</tr>
<tr>
<td>CRNDE</td>
<td>discriminates tumor tissues from adjacent normal tissues in HCC</td>
<td>0.699</td>
<td>—</td>
<td>—</td>
<td>[120]</td>
</tr>
<tr>
<td>DANCR</td>
<td>differentiates patients with HCC from HVs and patients with CHB and cirrhosis</td>
<td>0.868</td>
<td>83.8 %</td>
<td>72.7 %</td>
<td>[121]</td>
</tr>
<tr>
<td></td>
<td>differentiates patients with HCC from CHB and cirrhosis</td>
<td>0.864</td>
<td>80.8 %</td>
<td>84.3 %</td>
<td>[121]</td>
</tr>
<tr>
<td>DGC8S</td>
<td>discriminates tumor tissues from normal tissues</td>
<td>0.782</td>
<td>63.3 %</td>
<td>83.3 %</td>
<td>[122]</td>
</tr>
<tr>
<td>LINC RP1130-1</td>
<td>discriminates HCC from adjacent normal tissues</td>
<td>0.74</td>
<td>—</td>
<td>—</td>
<td>[123]</td>
</tr>
<tr>
<td>MALAT1 (plasma)</td>
<td>discriminates HCC patients and hepatic disease patients</td>
<td>0.66</td>
<td>51.1 %</td>
<td>89.3 %</td>
<td>[124]</td>
</tr>
<tr>
<td>JPKX</td>
<td>discriminates between HCC patients and controls</td>
<td>0.814</td>
<td>100.0 %</td>
<td>52.4 %</td>
<td>[125]</td>
</tr>
<tr>
<td>JPKX and AFP</td>
<td>discriminates between HCC patients and controls</td>
<td>0.905</td>
<td>97.1 %</td>
<td>72.2 %</td>
<td>[125]</td>
</tr>
<tr>
<td>SPRY4-IT1</td>
<td>differentiates HCC patients from controls</td>
<td>0.702 (0.609-0.796)</td>
<td>87.3 %</td>
<td>50.0 %</td>
<td>[126]</td>
</tr>
<tr>
<td>SPRY4-IT1 and AFP</td>
<td>differentiates HCC patients from controls</td>
<td>0.800 (0.706-0.874)</td>
<td>87.3 %</td>
<td>65.0 %</td>
<td>[126]</td>
</tr>
<tr>
<td>UCA1</td>
<td>discriminates HCC patients from healthy controls</td>
<td>0.91</td>
<td>91.4 %</td>
<td>88.6 %</td>
<td>[127]</td>
</tr>
</tbody>
</table>
Table 3. Prognostic abilities of IncRNAs for hepatocellular carcinoma patients in Cox proportional hazards model

<table>
<thead>
<tr>
<th>IncRNAs</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th>References</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>OS</td>
<td>JPX (low vs. high)</td>
<td>2.283 (1.211-4.304)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>XIST (low vs. high)</td>
<td>2.155 (1.136-4.088)</td>
<td>0.003</td>
</tr>
<tr>
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<td>CCHE1 expression (Low vs. High)</td>
<td>0.977 (0.312-3.434)</td>
<td>0.414</td>
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<td>lncRNA SNHG15 (High vs. Low)</td>
<td>3.017 (1.448-6.221)</td>
<td>0.018</td>
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<td></td>
<td>SNHG20</td>
<td>4.440 (2.254-8.743)</td>
<td>0.000</td>
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<td>lncRNA GAS5 (Low vs. High)</td>
<td>—</td>
<td>&lt;0.0001</td>
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<tr>
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<td>CARLo-5 (Low vs. High)</td>
<td>3.267 (1.620-6.271)</td>
<td>0.014</td>
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<tr>
<td></td>
<td>SNHG3</td>
<td>4.442 (2.368-8.332)</td>
<td>0.006</td>
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<td>CCA12 expression (high vs low)</td>
<td>2.118 (1.245-3.603)</td>
<td>0.021</td>
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<tr>
<td></td>
<td>UC001kfo (High vs. Low)</td>
<td>1.876 (1.098-3.207)</td>
<td>0.024</td>
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<td>Inc-DILC (low vs. high)</td>
<td>2.618 (1.136-6.036)</td>
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<tr>
<td>RFS</td>
<td>CARLo-5 (Low vs. High)</td>
<td>2.873 (1.669-5.852)</td>
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<td>Inc-DILC (low vs. high)</td>
<td>2.142 (1.025-4.477)</td>
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<tr>
<td>PFS</td>
<td>UC001kfo (High vs. Low)</td>
<td>2.147 (1.260-3.658)</td>
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</table>

Supplementary Material

Acknowledgments
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Authors’ contributions
LP collected the references and drafted the manuscript. GCL and XQY participated in the design of the review and helped to draft the manuscript. CYZ, JYP, YQZ and XP revised critically the manuscript. All authors read and approved the final manuscript.

Competing Interests
The authors have declared that no competing interest exists.

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