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Review

The Role of Long Non-Coding RNAs in Hepatocarcinogenesis

Manuela Lanzafame 1,†, Gaia Bianco 1,†, Luigi M. Terracciano 1, Charlotte K. Y. Ng 1,2 and Salvatore Piscuoglio 1,*

1 Institute of Pathology, University Hospital Basel, Basel 4031, Switzerland; manuela.lanzafame@usb.ch (M.L.); gaia.bianco@usb.ch (G.B.); luigi.terracciano@usb.ch (L.M.T.); kiuyancharlotte.ng@usb.ch (C.K.Y.N.)
2 Department of Biomedicine, University of Basel, Basel, 4056 Switzerland
* Correspondence: salvatore.piscuoglio@usb.ch; Tel.: +41-61-613-286-874
† These authors contributed equally to this work.

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Abstract: Whole-transcriptome analyses have revealed that a large proportion of the human genome is transcribed in non-protein-coding transcripts, designated as long non-coding RNAs (lncRNAs). Rather than being “transcriptional noise”, increasing evidence indicates that lncRNAs are key players in the regulation of many biological processes, including transcription, post-translational modification and inhibition and chromatin remodeling. Indeed, lncRNAs are widely dysregulated in human cancers, including hepatocellular carcinoma (HCC). Functional studies are beginning to provide insights into the role of oncogenic and tumor suppressive lncRNAs in the regulation of cell proliferation and motility, as well as oncogenic and metastatic potential in HCC. A better understanding of the molecular mechanisms and the complex network of interactions in which lncRNAs are involved could reveal novel diagnostic and prognostic biomarkers. Crucially, it may provide novel therapeutic opportunities to add to the currently limited number of therapeutic options for HCC patients. In this review, we summarize the current status of the field, with a focus on the best characterized dysregulated lncRNAs in HCC.

Keywords: long non-coding RNA; hepatocellular carcinoma; liver cancer; carcinogenesis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the several malignancies in which mortality has been increasing, in particular, in Western populations [1]. HCCs typically arise on a background of cirrhosis and are usually associated with chronic hepatitis B (HBV) or hepatitis C virus (HCV) infection, exposure to aflatoxin B1, alcoholic liver disease, obesity or metabolic disorders. Treatment options for early-stage HCC involve resection and/or liver transplantation. On the other hand, for late-stage patients, only three systemic agents, namely sorafenib [2], regorafenib (both kinase inhibitors [3]), and nivolumab (an immune checkpoint inhibitor) [4], have been approved. Novel therapeutic targets may improve the dismal prognosis of late-stage HCC patients.

An increasing body of evidence suggests that the non-coding regions of DNA play fundamental roles in the regulation of many biological processes, including physiological processes such as cell growth and cell proliferation [5], cell migration [6], metabolism, and apoptosis [7]. Indeed, it is now believed that ~70–80% of the human genome does not encode for proteins but is transcribed as non-coding RNA (ncRNA) molecules [8,9]. A substantial portion of this “genomic dark matter” is long non-coding RNA (lncRNA), defined as ncRNA greater than ~200 nucleotides in length, accounting for 68% of RNA molecules [10]. lncRNA transcripts share some of the properties of protein-coding transcripts. For instance, lncRNA transcription is regulated by histone modification and canonical
spliceosome machinery [11–13]. Mechanistically, lncRNAs interact with transcription factors and may variably guide them to [14] or prevent them from binding to their target genes [15]. They may also act as enhancers by rearranging chromatin or may act as sponges to bind proteins or microRNAs [16–19]. Of their many roles, the best described is the recruitment of chromatin modifying complexes to specific genomic regions [6,11,13,20–23] via chromosomal looping [24,25].

Given their multiple functions in transcriptional, post-transcriptional, and epigenetic regulation of gene expression, they are emerging as new players in tumorigenesis. Indeed, increasing evidence demonstrates that dysregulation of lncRNAs is involved in several pathological conditions, including various types of cancer, such as those of the breasts, the lungs, prostate, and liver [26]. Two pan-cancer studies using The Cancer Genome Atlas (TCGA) data have revealed that lncRNA expression is tissue-, cell-type- and cancer-specific [10,27]. Of these two studies, one described 7942 lineage- or cancer-associated lncRNAs across cancer types [10], while the other found that 60% of the dysregulated lncRNAs is cancer type-specific [27].

Although there have been an increasing number of studies on lncRNAs in the past decade, the contribution of lncRNAs to HCC development, metastasis, and recurrence remains largely unknown. In the last years, many studies have been directed to the discovery and characterization of the contribution of lncRNAs to carcinogenesis and their potential use as diagnostic markers or therapeutic targets for HCC treatment. In this review, we will describe the biological roles of lncRNAs, their mechanisms of action, and the lncRNAs dysregulated in HCC. We will further provide an overview of the latest studies that are aimed at elucidating the potential uses of lncRNAs as diagnostic/prognostic markers and as therapeutic targets in HCC.

2. LncRNAs: Characteristics and Subclassification

Among the many subclasses of ncRNA molecules, lncRNAs are defined as non-coding transcripts that are more than ~200 nucleotides in length [28]. The most comprehensive characterization of this class of non-coding RNA was carried out by the GENCODE consortium, which reported on the extensive annotation of 14,880 human lncRNA species [12]. LncRNAs share many common features with mRNA transcripts; they are both transcribed by RNA polymerase II, they both undergo splice-processing and post-transcriptional modifications (5′-capping and polyadenylation), and they share similar chromatin states. Unlike mRNAs, lncRNAs tend to be shorter, are expressed at lower levels, and display fewer but longer exons [29]. Although lncRNAs show poor sequence conservation among species, their peculiar secondary structures, mechanisms of action, and localization appear to be highly conserved [30]. These features allow for lncRNAs to be classified according to several divergent criteria [31]. LncRNA subcellular localization, for instance, provides valuable information related to their functions and mechanisms of action. The known subcellular localization of lncRNAs based on RNA sequencing data has been collated into the lncATLAS database [32]. In general, lncRNAs tend to be more abundant in the nucleus [31], with some of them being reported to be chromatin-associated RNAs (CARs) [23] and some others that are directly related to the formation of nuclear bodies, such as NEAT1 and MALAT1 [33,34]. Single molecule RNA FISH analysis, revealed that even nuclear localization can be further categorized in distinct nuclear patterns [35], with the presence of both bright nuclear foci with distinct lncRNAs and single dispersed nuclear lncRNAs. Of note, some lncRNAs have been reported to be enriched in the cytosol and to localize with ribosomes [36]. Interestingly, lncRNAs have also been reported to be encoded in the small mitochondrial genome [37].

Despite the diverse features that are displayed by lncRNAs, as a general rule, they are broadly classified according to their biogenesis and genomic positions in relation to protein-coding genes, lncRNAs can be broadly classified into: (i) antisense RNAs or natural antisense transcripts (NATs); (ii) bidirectional RNAs; (iii) long intergenic RNAs (lincRNAs); and (iv) sense intronic RNAs [12,38,39] (Figure 1).
2.1. Antisense RNAs or Natural Antisense Transcripts (NATs)

NATs are endogenous RNAs that partially or totally overlap transcripts originating from their opposite strand. Yelin et al., estimated that more than 8% of the predicted 40,000 human genes have an antisense partner [40]. A substantial portion of eukaryotic promoters may indeed be transcribed in both the sense and the antisense directions [41]. Sense and antisense transcripts are usually regulated in a coordinated way, such as that high levels of the sense transcript usually lead to high levels of the antisense transcript, and vice versa.

2.2. Bidirectional RNAs

Bidirectional RNAs are also known as promoter-associated non-coding RNAs (pancRNAs) [42]. Slightly different from NATs, bidirectional RNAs are transcribed in the opposite direction with respect to the protein coding gene, but are located within 1 kb from its promoter region [42–45]. An example of this class of ncRNA is Linc00441, the bidirectional transcribed IncRNA of the Retinoblastoma gene RB1. Linc00441 has recently been reported to be aberrantly upregulated and inversely correlated to RB1 expression in human HCC samples [46]. More specifically, Linc00441 has also been reported to epigenetically suppress RB1 expression in HCC by recruiting DNMT3A methyltransferase [46].

2.3. Long Intergenic RNAs (lincRNA)

LincRNA refers to the class of non-coding RNAs that are transcribed from intergenic regions between two protein-coding genes [47]. The majority of lincRNAs are enhancer RNAs (eRNAs) that are located in enhancer regions and usually act in cis by inducing chromatin modifications in the promoters of the downstream genes [24]. A classic example of eRNA is the HOXA transcript at the distal tip (HOTTIP), a lncRNA situated in the 5′ distal region of the HOXA locus [25]. As one of the...
distal tip (HOTTIP), a lncRNA situated in the 5′ distal region of the HOXA locus [25]. As one of the best characterized lncRNAs implicated in HCC, HOTTIP will be extensively described in one of the following sections.

2.4. Sense Intronic RNAs

Sense intronic RNAs are transcribed from the introns of protein-coding genes and do not overlap exonic sequences. Examples of sense intronic RNAs are small nuclear-lncRNAs (sno-lncRNAs) and circular intronic lncRNAs (circRNAs). Sno-lncRNAs are lncRNAs that are flanked by two small nuclear RNAs (sno-RNAs) and thereby lack any 5′ and 3′ processing [48]. CircRNAs, instead, form a peculiar class of lncRNA that undergoes a special splicing (back-splicing) thus resulting in chemically circularized molecules [49].

3. LncRNAs: Mechanisms of Action

RNAs are very versatile molecules; they can interact with other nucleic acid molecules by simple base pair coupling and they can interact with proteins by folding into three-dimensional (3D) structures and generating complex recognition surfaces. RNAs are also dynamic; they can be both transcribed and degraded rapidly [50]. The versatility and dynamic nature are particularly evident for lncRNAs whose ability to bind both nucleic acids and proteins enables them to regulate gene expression on the transcriptional, post-transcriptional, and protein levels (Figure 2).

Figure 2. Mechanism of function of lncRNAs dysregulated in hepatocellular carcinoma (HCC). LncRNAs may act as sponges for miRNAs, bind transcripts or proteins and induce epigenetic modifications or chromatin remodeling. Their deregulation leads to hepatocellular carcinogenesis by regulating different cellular processes such as migration, proliferation, invasion, cell cycle, apoptosis and epithelial mesenchymal transition (EMT). Examples of the mechanisms of action of lncRNAs dysregulated in HCC are reported. See text for details.
3.1. Transcriptional Regulation and Chromatin Modification

One of the best described mechanisms of action of lncRNAs is their capacity to induce epigenetic modifications by acting as a scaffold for chromatin modification complexes. This discovery provided insight into the previously unresolved question on how chromatin modification complexes are able to act on the whole genome in a time-dependent and a cell-specific manner. Indeed, lncRNAs can guide chromatin remodeling complexes to specific genomic regions, regulating gene expression either in cis or in trans, as enhancers and mediators for long-range chromatin interactions [20,21].

The role of lncRNA as a scaffold for chromatin remodeling complexes was first described for the HOX transcript antisense RNA (HOTAIR). HOTAIR was reported to interact with the Polycomb repressive complex 2 (PRC2), thereby repressing the expression of the HOXD gene locus by inducing histone methylation and heterochromatin formation [51]. The same mechanism has now been demonstrated for other lncRNAs, such as XIST [52], the lncRNA that is responsible for X-chromosome inactivation, and it appears to be a general mechanism by which lncRNAs regulate gene expression during imprinting, development, cell differentiation, and disease [53,54].

Chromatin modification is not the only way through which lncRNAs modulate transcription. NATs, for instance, are able to directly inhibit the transcription of their sense transcripts in cis by competing for RNA polymerase II [55] or by forming an RNA-DNA triplex that prevents the binding of the transcription initiation complex [15]. Additionally, lncRNAs can fold into secondary structures that mimic DNA binding sites, further inhibiting the nuclear export of transcriptional factors by directly interacting with and repressing their associated transport proteins [56].

3.2. Post-Transcriptional Regulation and Maintenance of mRNA Stability

On the post-transcriptional level, lncRNAs play a role in regulating mRNA splicing. For example, NATs can form RNA-RNA duplexes which can mask splice sites [57]. Other lncRNAs, such as the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), have been reported to regulate splicing by directly modulating the activity of Ser/Arg-domain rich splicing factors [58].

LncRNAs may also influence mRNA stability by acting as competing endogenous RNAs (ceRNAs) [59–61] that compete for the binding of shared miRNAs. In particular, the circRNA subclass almost exclusively acts as miRNA decoy [17]. An example is circMTO1 that has been recently described to promote HCC cell proliferation and invasion by binding miR-9 and down-regulating p21 [62]. In general, miRNA sponging is a common mechanism among lncRNAs, owing to the presence of miRNAs competing target sites in their sequences. When the lncRNA with the complementary sequence becomes transcriptionally active, it competes for miRNA targeting and binding of RISC complexes, thus resulting in increased parent gene expression [18]. Several examples have been reported in HCC, such as the lncRNA highly upregulated in liver cancer (HULC) [16], MALAT1 [63], and nuclear enriched abundant transcript 1 (NEAT1) [64]. LncRNAs may also help to destabilize mRNA transcripts by activating a specific type of mRNA decay, called Staufen-mediated decay. This is the case for Alu repeats-containing lncRNAs, which can bind Alu sequences in the 3’UTR of target genes, thus mediating the binding of Staufen1 and the subsequent mRNA degradation [65].

3.3. Protein Activity Regulation and Scaffolding

Several lncRNAs have been reported to regulate cellular processes by direct binding to proteins, including RNA-binding proteins (RBPs) and transcription factors [66]. For example, Gadd7 and MALAT1 bind to and modulate the expression of RBP TDP43 [67], which is a protein that is implicated in mRNA splicing, transport, and stability [68]. Moreover, in silico prediction suggested that the HCC-associated lncRNAs HOTTIP, H19, HOTAIR, MALAT1, AIRN, MEG3, and uc002mb may interact with the RBPs eIF4AIII, PTB, and FUS [69]. In addition, lncRNAs harbor several distinct domains, each able to bind to distinct effector molecules, thus enabling them to serve as adaptors to bring proteins into complexes [66]. Apart from the role that lncRNAs play in chromatin remodeling, they...
may also serve as scaffolds for nuclear domains [70]. One such example is NEAT1, which has been implicated in the de novo assembly of the subnuclear organelles paraspeckles [71].

4. Widespread lncRNA Dysregulation in HCC

Significant effort has been made to examine the expression of lncRNAs and its relationship with carcinogenesis. The use of lncRNA microarrays and next generation sequencing techniques has allowed for researchers to perform genome-wide analyses to identify a large number of lncRNAs aberrantly expressed in HCC tissue and may be involved in hepatocarcinogenesis.

Cui et al. [72] performed a comprehensive investigation into lncRNA expression profile in HCC and matched non-tumor counterpart using two RNA sequencing datasets (including that of TCGA), and two lncRNA microarray datasets. The authors identified 347 lncRNAs that were consistently up- or down-regulated in at least two datasets [72]. They found that 31 and 41 lncRNA loci were located in genomic regions with recurrent DNA gains or losses, respectively, suggesting that genomic copy number alterations may be involved in the dysregulation of some lncRNAs in HCC. Furthermore, by comparing lncRNA expression pattern in HCC with or without invasion and metastasis, they also identified lncRNAs that may be involved in cancer cell metastasis and HCC recurrence [72].

Similar genome-wide lncRNA profiling studies carried out by other groups have invariably pointed to the general conclusion of widespread lncRNA dysregulation in HCC. An RNA-sequencing study of HBV-related HCC samples revealed a total of 1242 dysregulated lncRNA transcripts (983 up-regulated and 259 down-regulated) [73]. In another study of 12 HCC tissues and paired adjacent normal tissues, the authors identified 214 differentially expressed lncRNAs, among which 17 were further confirmed in 21 paired HCC and normal liver tissues via quantitative real-time PCR [74]. Finally, an RNA-sequencing analysis from 20 HCC patients recently identified 8603 novel dysregulated lncRNAs, including 917 recurrently dysregulated lncRNAs that were associated with clinicopathologic features [75]. Of particular interest was the observation that approximately 76% of the HCC-related lncRNAs were not previously annotated by the MiTranscriptome [10] or GENCODE [76], suggesting that at least some of the dysregulated lncRNAs might be HCC-specific [75].

4.1. Molecular and Functional Alterations of lncRNAs in HCC

Despite the huge number of lncRNAs described to be dysregulated in HCC by genome-wide approaches, not many have been comprehensively characterized (Table 1 and S1).

The vast majority of them is reported to be up-regulated in HCC and have been shown to have an oncogenic effect by promoting cell proliferation, invasion, metastasis formation, and/or angiogenesis. Investigations into the expression of these oncogenic lncRNAs have found them to be positively correlated with clinicopathological features of the patients. In this section, we will describe some of the well-characterized lncRNAs dysregulated in HCC in detail, giving some examples of their molecular mechanisms in cancer and their specific role in hepatocellular carcinogenesis. An extended list of the lncRNAs, their dysregulation, and molecular functions in HCC can be found in Table S1.
Table 1. LncRNAs dysregulated in HCC.

| IncRNA  | Class       | Expression in HCC | Effect on HCC                                                                                           | Molecular Mechanism                                                                                                                                                                                                 | Reference |
|---------|-------------|-------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| H19     | intergenic  | downregulated/upregulated | Inhibits migration and invasion; associated with HCC aggressiveness and poor outcome; promotes cell growth | Recruits HnRNP U/PCAF/RNAPolII complex to activate miR-200 family through histone acetylation; is involved in the miR675/ Akt/GSK-3beta/Cdc25A signaling pathway; interacts with EZH2 and represses E-caderin expression | [77–79]   |
| HEIH    | intergenic  | upregulated       | Promotes tumor progression and inhibits G0/G1 cell cycle arrest                                         | Interacts with EZH2 and represses target genes                                                                                                                                                                    | [80,81]   |
| HOTAIR  | intergenic  | upregulated       | Promotes cell proliferation, viability, invasion, migration and metastasis; suppresses apoptosis        | Regulates miR-331-3p/HER2, miR-1/FOXC1, miR-218/BMI1/Ink4a/ARF, DDX5/PRC2, STAT3, GLUT1/mTOR signaling pathways                                                                                               | [82–88]   |
| HOTTIP  | intergenic  | upregulated       | Promotes cell proliferation, migration, tumorigenesis and metastasis                                   | Interacts with WDR5/MLL promoting H3K4me3                                                                                                                                                                       | [89,90]   |
| HULC    | intergenic  | upregulated       | Promotes cell growth, proliferation, EMT, migration, tumor progression, metastasis, angiogenesis; modulates lipid metabolism | Regulates several signaling pathways including miR-9/PPARA/ACSL1, miR-200a-3p/ZEβ1, miR-107/E2F1/SPHK1, miR-488/ADAM, mR186/HMGA2; regulates the ubiquitin-mediated degradation of Sirt1 | [91–98]   |
| MALAT1  | antisense   | upregulated       | Promotes cell invasion, migration, growth, motility and metastasis                                     | Sponges miR-125b, miR-146b-5p, miR-204, miR-143-3p, miR-195; regulates p53/DBC1 signaling pathway                                                                                                              | [63,99–101] |
| MEG3    | intergenic  | downregulated     | Promotes proliferation and apoptosis                                                                  | Regulates p53 transcription                                                                                                                                                                                        | [102–107] |
| NEAT1   | intergenic  | upregulated       | Promotes tumorigenesis, EMT, cell proliferation, migration and metastasis                               | Regulates the miR-129-5p/VCP/IKB axis; sponges miR-613; regulates STAT3 expression through miR-485; regulates hnRNP A2 expression by sequestrating U2AF65; is involved in paraspeckle formation | [108–112] |
| UCA1    | intergenic  | upregulated       | Promotes EMT; is associated with tumor size, vascular invasion, TNM stage, metastasis and postoperative survival | Activates ERK signaling pathway; regulates SNAIL2 expression                                                                                  | [113–116] |

EMT: epithelial to mesenchymal transition; TNM: tumor/node/metastasis.
4.1.1. HOTAIR

One of the most well studied lncRNAs in HCC is the HOX transcript antisense intergenic RNA (HOTAIR) identified from a custom tiling array of the HOXC locus (12q13.13). HOTAIR represses transcription in trans acting as a scaffold for at least two distinct histone modification complexes to the target gene promoters: PRC2 and the lysine-specific demethylase 1 (LSD1)/co-repressor of RE1-silencing transcription factor (coREST)/REST complex [21,51,117].

Several studies showed that HOTAIR levels are elevated in HCC [82–87], and that its expression is associated with patients with increased risk of recurrence or metastasis [82,86], poor prognosis [84] and significantly shorter recurrence-free survival [83]. At the cellular level, HOTAIR is involved in proliferation, cell motility, viability and invasion, cell cycle progression, apoptosis, autophagy, and chemotherapeutic sensitivity of cancer cells to cisplatin and doxorubicin [83–88,117–120].

Recently, several studies have revealed novel insights into the functional mechanisms of HOTAIR in HCC cells. Su et al., demonstrated that HOTAIR expression is regulated by FOXC1 and that the oncogenic activity of HOTAIR is in part based on its sponging of miR-1 [85]. Indeed, miRNA sponging appears to be a general mechanism of HOTAIR, as HOTAIR also targets miR-218, resulting in increased cell viability, cell cycle upregulation, and tumorigenicity [120]. In primary human HCC specimens, HOTAIR was shown to be concordantly upregulated with the oncogene BMI1, which is a target of miR-218. Interestingly, HOTAIR silencing activates the main BMI1 downstream targets P16(Ink4a) and P14(ARF), by enhancing miR-218 and inhibiting BMI1 expression, thus resulting in the suppression of tumorigenesis in HCC [120].

HOTAIR also binds to transcripts and proteins. An integrated transcriptomic and quantitative proteomic analysis revealed that a total of 673 transcripts and 293 proteins are regulated by HOTAIR [121]. The analysis also showed that HOTAIR controls cell proliferation by regulating opioid growth factor receptor (OGFR) expression [121]. Cell proliferation in HCC could also be driven by HOTAIR-dependent regulation of cell cycle via STAT3 signaling [119]. Besides cell proliferation, HOTAIR has also been shown to be involved in the regulation of pluripotency. In fact, the binding of HOTAIR with the DDX5-PRC2 complex in the HBx-expressing hepatocytes 4pX-1 regulates the transcription of the epithelial cell adhesion marker EpCAM and pluripotency genes Nanog, Oct4, and Sox2 [122]. Emerging evidence also suggests a novel relationship between HOTAIR and glucose metabolism in HCC cells by upregulating glucose transporter isoform 1 (GLUT1) and activating the mammalian target of rapamycin (mTOR) signaling pathway [87].

4.1.2. HOTTIP

Among the lncRNAs dysregulated in HCC, HOTTIP deserves a special mention. This 3764 nucleotide RNA molecule is transcribed 330 base pairs upstream of the HOXA locus on chromosome 7p15.2. It could be considered a classical eRNA acting in cis. Mechanistically, it is a clear example of an lncRNA that serves as a scaffold for chromatin remodeling complexes. Wang et al. [25] showed that, similar to HOXA genes, HOTTIP is normally expressed at a very low level in distal/posterior anatomical sites and it is implicated in the transcriptional regulation of the HOXA locus. Briefly, they demonstrated that in distal fibroblast (foreskin) cells, HOTTIP binds to the WDR5-MLL complex and is able to position the complex in close proximity to the downstream HOXA genes by chromosomal looping, thus inducing their H3K4me3 and H3K4me4 methylation and subsequent transcriptional activation [25].

HOTTIP has been found dysregulated in several types of cancers. Its role in human carcinogenesis was firstly revealed in HCC [89] and has since been described in colorectal [123,124], gastric [125–127], pancreatic [128,129], and lung cancers [130], as well as in osteosarcoma [131] and glioma [132]. The results from these studies were collectively analyzed in three parallel meta-analyses, all of which clearly showed that the high expression of HOTTIP correlates with shorter overall survival, higher tumor grade and poor prognosis [133–135].
Quagliata et al. [89] reported the upregulation of the HOTTIP transcript in 52 snap-frozen HCC biopsies from therapy naive patients. The authors reported a higher expression of HOTTIP in non-neoplastic liver disease (excluding steatosis) when compared to normal tissue. For the first time, HOTTIP expression was found to be correlated with tumor progression and metastasis formation, as well as with overall patient survival, thus proposing HOTTIP as a possible prognostic factor for HCC [89]. Furthermore, the study showed that HOTTIP positively regulates HOXA13 expression in HCC cell lines and that its upregulation induces proliferation in vitro. Similarly, Tsang et al., also reported increased HOTTIP expression in HCC, highlighting the progressive upregulation of HOTTIP from cirrhotic tissue to pre-neoplastic lesion to early stage HCC [90]. They further confirmed the oncogenic potential of HOTTIP in a mouse xenograft model and reported that HOTTIP can be regulated by miRNA, specifically by miR-125b [90].

The role of miRNAs in HOTTIP regulation has been further unraveled by Ge et al., who observed a negative correlation between HOTTIP and miR-192/204 in 48 tumor-normal paired liver samples and showed that HOTTIP expression can be regulated by miR-192 and miR-204 via the canonical Argonaute2 mediated interference (siRNA) [136]. Specifically, the authors showed that miR-192 and miR-204 directly suppress HOTTIP in vitro and further identified the GLS1 gene, which plays a critical role in glutaminolysis and tumorigenesis, as a putative downstream target of HOTTIP. Ge et al., thus proposed a novel mechanism of action for HOTTIP, in which it explicates its oncogenic potential by directly upregulating glutaminolysis in HCC cells and promoting cancer cell proliferation in a time and dose dependent manner [136].

Despite the extensive functional studies, there remains a lot to be discovered in the functional relevance of HOTTIP in HCC. For instance, a meta-analysis of 393 HCC from the TCGA study revealed an association between HOTTIP expression and the genes that are involved in the PPAR signaling pathway, opening the doors to the further characterization of the role of HOTTIP in HCC [137].

4.1.3. MALAT1

MALAT1 is transcribed from chromosome 11q1 and was originally identified as a prognostic marker for metastasis and patient survival in non-small cell lung carcinoma [99]. Subsequent studies have shown that MALAT1 is aberrantly up-regulated in various tumor entities [138,139]. Its upregulation promotes tumor growth and metastasis through a variety of mechanisms, including regulating gene expression by recruiting or regulating the level of serine/arginine-rich protein (SR) family members that are involved in alternative splicing [58,140,141] or binding to active genomic sites [34]. High expression of MALAT1 has been associated with high grade, metastasis, and poor prognosis of cancer patients [141,142].

MALAT1, together with NEAT1, is one of the few lncRNAs to be described as frequently mutated in HCC leading to the dysregulation of gene expression and regulatory functions [143]. In HCC, Lai et al., reported that MALAT1 is overexpressed both in vitro and in vivo [100]. Patients with high expression level of MALAT1, associated with elevated levels of α-fetoprotein (AFP), have a significantly increased risk of tumor recurrence after liver transplantation [100]. Mechanistically, what is known about MALAT1 regulation in HCC is that it is transcriptionally regulated by HIF-2α, forming a positive feedback loop involved in the malignant transformation induced by arsenite [144]. It has also been suggested that MALAT1 could be regulated by the transcription factor, specificity proteins 1 and 3 (Sp1/3) [145].

The mechanisms by which MALAT1 promotes cell invasion, migration, growth, motility and metastasis in HCC have been shown to be principally related to its ability to bind to miRNAs and function as a sponge, capturing miRNA and regulating their activities. There are at least two miR-216b binding sites in MALAT1 and the HIF-2α-MALAT1-miR-216b axis regulates multidrug resistance of HCC cells by modulating autophagy [146]. By sponging and competitive binding to miR-204, MALAT1 releases the miR-204-mediated suppression of sirtuin 1, which in turn promotes HCC migration and invasion [63]. Furthermore, the sponging of miR-146b-5p by MALAT1 has also been shown to promote
tumor growth and metastasis and has been associated with poor survival in HCC patients [147]. Another example is the binding of miR-143-3p, which in turn, regulates the tumor suppressor gene ZEB1 [148]. Recently, MALAT1 has been found to act as a ceRNA for miR-195 that is no longer able to suppress its downstream target EGFR [149].

A high-throughput strategy by combining RNA pull-down, quantitative proteomics, bioinformatics, and experimental validation has resulted in the identification of interacting protein partners of MALAT1 in HCC. Indeed, the interactome of MALAT1 involves ribosomal proteins and proteins critical in RNA processing, gene transcription, protein degradation, and metabolism regulation [150]. The interaction between MALAT1 and the depleted in breast cancer 1 protein (DBC1) was further validated and characterized, revealing a novel mechanism by which MALAT1 regulates p53 activity through the interaction with DBC1 [150].

4.1.4. NEAT1

LncRNA nuclear enriched abundant transcript 1 (NEAT1) is so called because of its peculiar and exclusive localization in the sub-nuclear compartment paraspeckle [33]. In this compartment, NEAT1 can modulate gene expression by retaining mRNA molecules in the nucleus and by mRNA editing [151]. Of note, NEAT1 is genomically in close proximity to MALAT1 and both are frequently mutated in HCC [143]. NEAT1 has also been reported to co-localize with MALAT1 on active chromatin sites where both interact with proteins that are resident in the nuclear bodies [34]. Despite its emerging relevance in the regulation of gene expression, studies on the role of NEAT1 in human malignancies have remained limited so far. It is known that NEAT1 is a crucial regulator in several cancers and acts as a pivotal player in tumorigenesis and metastasis of HCC. Guo et al., firstly reported the clinical relevance of NEAT1 overexpression in HCC tissues and its association with several clinical features such as the number and size of tumor nodes, metastasis formation, TNM stage, vascular invasion, and tumor cell infiltration [109].

The overexpression and relevance of NEAT1 in HCC tissues and cell lines have been further confirmed in several recent studies aiming to delineate the functional mechanisms of NEAT1 in HCC pathogenesis [108,110,111]. These studies have shown that NEAT1 may act both as a miRNA sponge and as a protein-binding competitor. The ability of NEAT1 in sponging miRNAs was first described by Fang et al. [108], who reported NEAT1 overexpression in HCC tissues, as well as its negative correlation with miR-129-5p expression. They also proposed a mechanism of action involving the miR-129-5p, valosin-containing protein (VCP) and IkB axis. Other studies have described similar negative correlations with miR-613 [111] and miR-485 [64]. Interestingly, Zhang et al., showed that by acting as ceRNA for miR-485, NEAT1 is indeed able to enhance STAT3 expression in HCC [64].

The function of NEAT1 is not restricted to miRNA sponging, as it has also been reported to bind to and compete for the assembling of protein complexes. Mang et al., for instance, demonstrated that NEAT1 forms a protein complex with the splicing factor U2AF65, thus regulating the heterogeneous nuclear ribonucleoprotein hnRNP A2 expression [110]. hnRNP A2 is also an essential splicing factor that promotes cell proliferation and invasion, and correlates with poor outcome in HCC patients. Since hnRNP A2 is normally inhibited by U2AF65, the authors proposed a mechanism by which NEAT1 may favor HCC development by sequestrating U2AF65 and releasing hnRNP A2 activity [110].

Last but not least, two independent studies have associated NEAT1 with epithelial-to-mesenchymal transition (EMT) [112,152]. In a study using breast cancer tissues and cell lines, Choudhry et al., identified NEAT1 as a new transcriptional target of HIF-2α and described its ability to induce paraspeckle formation under hypoxic condition [152]. Similarly, Zheng et al., found that the overexpression of HIF-2α upregulates the level of NEAT1, thus promoting EMT and metastasis in hepatoma cell lines [112].
4.1.5. H19

H19 is transcribed from the critical imprinted locus IGF2/H19 on chromosome 11p15.5 and it was the first lncRNA identified [153]. In most normal adult tissues, only the paternal allele of IGF2 is expressed, whereas the maternal imprinted allele of H19 is usually expressed at high levels during embryonic development, but is rapidly repressed in most tissues after childbirth [154]. H19 is involved in transcription regulation by binding to hnRNP U and disrupting the hnRNP U-actin complex, thus inhibiting the phosphorylation of the RNA Pol II C-terminal domain at Ser5 and consequently preventing RNA Pol II-mediated transcription [155]. Many studies have shown a strong association between H19 expression and dysregulated imprinting of the IGF2/H19 locus with carcinogenesis in several types of cancer, including HCC [156–160].

H19 is also a ceRNA that acts as a sponge for miRNAs ([161] and references therein). For example, in breast cancer H19 regulates EMT and mesenchymal-epithelial transition (MET) by differentially acting as a sponge for miR-200b/b and let-7b [162].

Recently, a new role of the H19-IGF2 axis in regulating hepatocyte proliferation has been described in mice. It was demonstrated that H19 and Igf2 are negatively regulated by PHB1 and CTCF, which cooperatively bind the imprinting control region (ICR) of the Igf2/H19 locus [79].

Whether H19 acts as an oncogene or as a tumor suppressor gene is controversial. Zhang et al. [163] demonstrated that H19, in association with hnRNP U/PCAF/RNAPol II, activates miR-200 family by increasing histone acetylation, thus contributing the suppression of EMT and tumor metastasis. Moreover, they showed that H19 is significantly downregulated in intratumoral (T) HCC tissues compared with peritumoral tissues (L), and that patients with low T/L ratio of H19 were linked to poor prognosis [163]. H19 is also a precursor for miR-675 and both were found downregulated in HCC cells and their downregulation promotes migration and invasion of HCC via the AKT/GSK-3beta/Cdc25A signaling pathway [77]. On the contrary, Yang et al., demonstrated that H19 is overexpressed in HBV-infected patients and is a risk factor for reduced disease-free survival and increased tumor aggressiveness in HCC patients [78].

4.1.6. Other lncRNAs Dysregulated in HCC

Highly up-regulated in liver cancer (HULC) is a 500 nucleotide lncRNA on chromosome 6p24.3 and it was first identified as one of the most upregulated genes in HCC [93]. It was described to modulate the deregulation of lipid metabolism in HCC through a signaling pathway involving miR-9, PPARA, and ACSL1 [96]. It was also shown to promote hepatocarcinogenesis by perturbing the circadian rhythm through upregulating circadian oscillator CLOCK in hepatoma cells [164]. Recently, HULC has been described to regulate several signaling pathways by acting as a sponge for miRNAs. For instance, it promotes tumor progression and metastasis through the miR-200a-3p/ZEB1 signaling pathway [92] and promotes tumor angiogenesis in liver cancer through miR-107/E2F1/SPHK1 signaling [97]. HULC also plays an epigenetic role by enhancing the level of ubiquitin-specific peptidase 22 (USP22) and stabilizing the COX2 protein [94]. Finally, together with USP22/Sirt1, HULC attenuates the sensitivity of HCC cells to chemotherapeutic agents by inducing “protective autophagy” [98].

Maternally Expressed Gene 3 (MEG3) encodes a tumor suppressor lncRNA that is expressed in many normal tissues [165]. Methylation of MEG3 promoter and its marked downregulation have been reported in HCC cell lines and tissues [102,103]. MEG3 expression negatively correlates with tumor size and TNM stage, thus acting as a potential prognostic biomarker [107]. The forced expression of MEG3 in HCC cells significantly reduces both anchorage-dependent and -independent cell growth, and induces apoptosis [103], at least partially via the accumulation of p53 [107]. Indeed, it has been demonstrated that MEG3 is able to interact with the p53 DNA binding domain [106], thus enhancing its stability and transcriptional activity.

LincRNA-Ubiquitin-Fold Modifier Conjugating Enzyme 1 (lincRNA-UFC1) is also upregulated in HCC tissues and its expression associates with tumor size, stage, and patient outcome. Its expression in HCC cells promotes cell proliferation and cell-cycle progression and inhibits apoptosis [166]. Levels of
lincRNA-UFC1 were described to correlate with those of β-catenin in HCC tissues through a mechanism that involves the stabilization of the HuR protein (encoded by ELAVL1) by directly binding with the mRNA [166].

Urothelial carcinoma-associated 1 (UCA1) was reported to be markedly upregulated in HCC tissues and its expression in HCC is positively associated with tumor size, vascular invasion, TNM stage, metastasis, and postoperative survival [114,115]. Moreover, higher levels of UCA1 were also detected in serum of HCC patients [167] and are associated with higher grade, larger tumor size, higher TNM stage, and vascular invasion, acting as an independent unfavorable prognostic factor for HCC [113]. Acting as a miRNA sponge, UCA1 can either promote EMT [114] or activate the ERK signaling pathway in HCC [115]. Of note for hepatocarcinogenesis associated with HBV infection, UCA1 was found to be frequently upregulated in HBx-positive tissues and was shown to be upregulated by HBx in hepatoma cells, thus promoting cell growth by facilitating G1/S transition through CDK2 [168].

LncRNA-activated by TGF-β (lncRNA-ATB) is significantly upregulated in HCC tissues and metastasis, and its expression is associated with poor prognosis [169,170]. At the molecular level, it has been shown that lncRNA-ATB can promote the invasion-metastasis cascade, either by inducing EMT through the upregulation of ZEB1 and ZEB2 or by binding IL-11 mRNA and thus triggering STAT3 signaling [170]. These findings suggest that lncRNA-ATB predisposes HCC patients to metastasis and may potentially serve as a target for anti-metastatic therapies.

High Expression In HCC (HEIH) is another lncRNA whose high expression levels in HBV-related HCC were found to be significantly associated with recurrence and it was considered as an independent prognostic factor for survival. In patients with HCV-related HCC, HEIH expression in serum and exosomes is increased, but the ratio of HEIH expression in serum versus exosomes is decreased compared to patients with combined hepatocellular cholangiocarcinoma [81]. It was also described to play a key role in G0/G1 arrest and the same authors demonstrated that HEIH binds the enhancer of zeste homolog 2 (EZH2) factor inducing the repression of EZH2 target genes [80].

PCNA Antisense RNA 1 (PCNA-AS1) acts as a scaffold for mRNA molecules and was found significantly upregulated in HCC. Indeed, one of the roles of PCNA-AS1 is the regulation of PCNA mRNA stability [171].

5. Putative Diagnostic and Prognostic lncRNAs in HCC

The identification of lncRNAs whose expression levels correlated with clinicopathological characteristics of patients led to many studies of their diagnostic and/or prognostic potential in HCC tissues and in liquid biopsies (Figure 3).

For instance, UCA1 levels in HCC tissues [114,115] and in serum [113] were associated with high tumor grade, large tumor size, positive vascular invasion, and advanced TNM stage and may be an independent prognostic indicator [113]. Similarly, high levels of MALAT1 were associated with reduced disease-free survival in patients after liver transplantation [100]. The association between MALAT1 and prognosis appears to extend to plasma, with increased levels of MALAT1 correlating with liver damage and predicting progression to HCC [172]. Interestingly, it has also been reported that germline variants of MALAT1 and HULC may be associated with a decreased risk of HBV-associated HCC in the Chinese population [173].
Besides UCA1, MALAT1, and well-known lncRNAs, such as HOTAIR [82,84], HULC [92,93,174], a number of other lncRNAs whose expression was associated with disease stage and/or other clinicopathologic parameters have also been described. Recently, Yang et al., identified HAND2-AS1 as a potential biomarker for HCC tumorigenesis and metastasis [75]. Similarly, high expression levels of CASC15 [175], CYTOR (also known as Linc00152) [174], HANR [176], ICR (ICAM-1-Related ncRNA) [177], linc-UFC1 [166], IncRNA-ATB [170], IncSHRG [178], MVIH [179], PANDAR [180], PCAT14 [181], SNHG6 [182], SNHG20 [183], TINCR [184], TMCC1-AS1 [72], UBE2CP3 [185], WRAP53 [116]), ZEB1-AS1 [186], as well as the downregulation of LOC728290 [187], GAS5 [188], DILC [189], or WT1-AS [190], have been variably shown to be correlated with clinical severity, aggressive pathological features, metastasis, and/or poor outcome in HCC patients (Table S1). However, it should be noted that IncRNA is a fairly young research field, many of these associations have thus far been reported in single studies. Moreover, these studies differ substantially in their cohort sizes, etiologies and detection methods, and therefore the clinical utility for many of these IncRNAs remains to be validated and further tested in independent studies.

6. Therapeutic Potential of IncRNA in HCC

Tumor suppressor genes are notoriously difficult to target therapeutically, since a gain of function is difficult to achieve using current generations of therapeutic options [191]. In this context, the ability for IncRNAs to variably up- or down-regulate coding genes makes them attractive therapeutic targets. In particular, one possibility is the modulation of cis-acting IncRNAs, which may result in specific, endogenous alteration of the expression level of their target genes [192]. Several approaches have been proposed to target the various aspects of IncRNA mechanisms of action (Table 2). It should, however, be noted that IncRNAs as therapeutics is currently largely speculative based on the biological functions of IncRNAs and data observed in in vitro/in vivo studies. The development of therapeutic agents against IncRNAs is still far from clinical application.

**Figure 3.** Diagnostic/prognostic and therapeutic potentials of IncRNAs. IncRNAs isolated from liquid biopsies or tissues could be analyzed at the sequence or expression levels and may serve as potential biomarkers for HCC diagnosis, prognosis and therapy response prediction. IncRNAs may also be targeted for therapeutic interventions by silencing their expression using canonical Argonaute2 mediated interference (siRNA) molecules or antisense oligonucleotides (ASO), by blocking the interactions with DNA, RNA, or proteins using small synthetic molecules or by CRISPR/Cas9 editing.
Table 2. Therapeutic use of lncRNAs in HCC.

| lncRNA       | Molecular Strategy                                 | Reference |
|--------------|---------------------------------------------------|-----------|
| Ad5-AlncRNA  | Overexpressed to target miRNAs                    | [193]     |
| DANCR        | Silenced by shRNA                                 | [194]     |
| lncRNA-ATB   | Silenced by siRNA molecules                        | [195]     |
| MALAT1       | Silenced by antisense oligonucleotides (ASO)       | [196]     |
| MALAT1       | Silenced by CRISPR/Cas9                            | [197]     |

The first proposed approaches directly target lncRNAs to induce their degradation or destabilization. These methods include RNA interference mediated gene silencing and antisense oligonucleotides (ASO). For example, the delivery of siRNA molecules using ultrasound-targeted microbubble destruction was used to silence lncRNA-ATB, suppressing HCC migration and invasion in vitro [195]. Some in vivo evidence of successful inhibition of MALAT1 and metastasis by injecting ASO into subcutaneous tumors of nude mice has been reported for lung cancer cells [196].

An alternative therapeutic approach could be to block the interactions of lncRNA with DNA, RNA, or proteins using antagonistic sequences or small synthetic molecules that cover the lncRNA binding sites [198]. In addition, gene therapy represents an emerging and very promising strategy. Indeed, it was recently shown that the CRISPR/Cas9 technology could be successfully used to target an enhancer and exonic fragment of MALAT1 in human cells [197].

In view of their miRNA binding capacity, lncRNAs can be used not only as targets but also to target miRNAs involved in HCC. For example, the miRNAs miR-21, miR-153, miR-216a, miR-217, and miR-494 and miR-10a-5p have been shown to be upregulated in sorafenib-resistant cells and to participate in the mechanisms that are underlying sorafenib resistance [193]. The simultaneous targeting of these miRNAs using an artificial lncRNA expressed by an adenoviral vector (Ad5-AlncRNA) inhibits proliferation and induces apoptosis of sorafenib-resistant cells and enhances the effects of sorafenib in vitro and in vivo [193]. This may represent a potential strategy to overcome sorafenib resistance in the treatment of HCC.

7. Conclusions

Whole-transcriptome analyses are beginning to provide important insights into the biological and clinical relevance of lncRNAs in cancer. When compared to protein-coding genes, our knowledge in lncRNAs is in its infancy and many, many more studies are required to define which lncRNAs are genuinely critical in hepatocarcinogenesis. For HCC, the lack of molecular targets may benefit from exploiting lncRNAs as therapeutic targets. Future development in this area will be particularly exciting to increase the number of treatment options.

Supplementary Materials: Supplementary materials can be found at www.mdpi.com/1422-0067/19/3/682/s1.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| LncRNA | Long non-Coding RNA |
| HCC | Hepatocellular Carcinoma |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| TCGA | The Cancer Genome Atlas |
| Sno-RNA | Small nuclear RNA |
| CircRNA | Circular Intronic Long non-Coding RNA |
| SnolncRNA | Small Nuclear Long non-Coding RNA |
| NAT | Natural Antisense Transcript |
| LincRNA | Long intergenic RNA |
| PancRNA | Promoter Associated non-Coding RNA |
| CeRNA | Competing Endogenous RNA |
| EMT | Epithelial to Mesenchymal Transition |
| TNM | Tumor Node Metastasis |
| eRNA | Enhancer RNA |
| siRNA | Small interference RNA |
| MET | Mesenchimal to Epithelial Transition |
| ASO | Antisense Oligonucleotides |

References

1. El-Serag, H.B. Hepatocellular carcinoma. *N. Engl. J. Med.* 2011, 365, 1118–1127. [CrossRef] [PubMed]
2. Llovet, J.M.; Ricci, S.; Mazzaferro, V.; Hilgard, P.; Gane, E.; Blanc, J.F.; de Oliveira, A.C.; Santoro, A.; Raoul, J.L.; Forner, A.; et al. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 2008, 359, 378–390. [CrossRef] [PubMed]
3. Bruix, J.; Qin, S.; Merle, P.; Granito, A.; Huang, Y.H.; Bodoky, G.; Pracht, M.; Yokosuka, O.; Rosmorduc, O.; Breder, V.; et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (resorce): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017, 389, 56–66. [CrossRef]
4. El-Khoueiry, A.B.; Sangro, B.; Yau, T.; Crocenzi, T.S.; Kudo, M.; Hsu, C.; Kim, T.Y.; Choo, S.P.; Trojan, J.; Welling, T.H.R.; et al. Nivolumab in patients with advanced hepatocellular carcinoma (checkmate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017, 389, 2492–2502. [CrossRef]
5. Meola, N.; Pizzo, M.; Alfano, G.; Surace, E.M.; Banfi, S. The long noncoding rna vax2os1 controls the cell cycle progression of photoreceptor progenitors in the mouse retina. *RNA* 2012, 18, 111–123. [CrossRef] [PubMed]
6. Gupta, R.A.; Shah, N.; Wang, K.C.; Kim, J.; Horlings, H.M.; Wong, D.J.; Tsai, M.C.; Hung, T.; Argani, P.; Rinn, J.L.; et al. Long non-coding rna hotair reprograms chromatin state to promote cancer metastasis. *Nature* 2010, 464, 1071–1076. [CrossRef] [PubMed]
7. Kino, T.; Hurt, D.E.; Ichijo, T.; Nader, N.; Chrousos, G.P. Noncoding rna gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. *Sci. Signal.* 2010, 3, ra8. [CrossRef] [PubMed]
8. Carninci, P.; Kasukawa, T.; Katayama, S.; Gough, J.; Frith, M.C.; Maeda, N.; Oyama, R.; Ravasi, T.; Lenhard, B.; Wells, C.; et al. The transcriptional landscape of the mammalian genome. *Science* 2005, 309, 1559–1563. [CrossRef] [PubMed]
9. Consortium, E.P. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012, 489, 57–74. [CrossRef]
10. Iyer, M.K.; Niknafs, Y.S.; Malik, R.; Singhal, U.; Sahu, A.; Hosono, Y.; Barrette, T.R.; Prensner, J.R.; Evans, J.R.; Zhao, S.; et al. The landscape of long noncoding rnas in the human transcriptome. *Nat. Genet.* 2015, 47, 199–208. [CrossRef] [PubMed]
11. Cabili, M.N.; Trapnell, C.; Goff, L.; Koziol, M.; Tazon-Vega, B.; Regev, A.; Rinn, J.L. Integrative annotation of human large intergenic noncoding rnas reveals global properties and specific subclasses. *Genes Dev.* 2011, 25, 1915–1927. [CrossRef] [PubMed]
12. Derrien, T.; Johnson, R.; Bussotti, G.; Tanzer, A.; Djebali, S.; Tilgner, H.; Guernec, G.; Martin, D.; Merkel, A.; Knowles, D.G.; et al. The gencode v7 catalog of human long noncoding rnas: Analysis of their gene structure, evolution, and expression. *Genome Res.* 2012, 22, 1775–1789. [CrossRef] [PubMed]

13. Guttman, M.; Amit, I.; Garber, M.; French, C.; Lin, M.F.; Feldser, D.; Huarte, M.; Zuk, O.; Carey, B.W.; Cassady, J.P.; et al. Chromatin signature reveals over a thousand highly conserved large non-coding rnas in mammals. *Nature* 2009, 458, 223–227. [CrossRef] [PubMed]

14. Feng, J.; Bi, C.; Clark, B.S.; Mady, R.; Shah, P.; Kohtz, J.D. The evf-2 noncoding rna is transcribed from the dlx-5/6 ultraconserved region and functions as a dlx-2 transcriptional coactivator. *Genes Dev.* 2006, 20, 1470–1484. [CrossRef] [PubMed]

15. Martianov, I.; Ramadass, A.; Serra Barros, A.; Chow, N.; Akoulitchev, A. Repression of the human dihydrofolate reductase gene by a non-coding interfering transcript. *Nature* 2007, 445, 666–670. [CrossRef] [PubMed]

16. Wang, J.; Liu, X.; Wu, H.; Ni, P.; Gu, Z.; Qiao, Y.; Chen, N.; Sun, F.; Fan, Q. Creb up-regulates long non-coding rna, hulc expression through interaction with microrna-372 in liver cancer. *Nucleic Acids Res.* 2010, 38, 5366–5383. [CrossRef] [PubMed]

17. Hansen, T.B.; Jensen, T.I.; Clausen, B.H.; Bramsen, J.B.; Finsen, B.; Damgaard, C.K.; Kjems, J. Natural rna circles function as efficient microrna sponges. *Nature* 2013, 495, 384–388. [CrossRef] [PubMed]

18. Thomson, D.W.; Dinger, M.E. Endogenous microrna sponges: Evidence and controversy. *Nat. Rev. Genet.* 2016, 17, 272–283. [CrossRef] [PubMed]

19. Bayoumi, A.S.; Sayed, A.; Broskova, Z.; Teoh, J.P.; Wilson, J.; Su, H.; Tang, Y.L.; Kim, I.M. Crosstalk between long noncoding rnas and micrornas in health and disease. *Int. J. Mol. Sci.* 2016, 17, 356. [CrossRef] [PubMed]

20. Khalil, A.M.; Guttman, M.; Huarte, M.; Garber, M.; Raj, A.; Rivea Morales, D.; Thomas, K.; Presser, A.; Bernstein, B.E.; van Oudenaarden, A.; et al. Many human large intergenic noncoding rnas associate with chromatin-modifying complexes and affect gene expression. *Proc. Natl. Acad Sci. USA* 2009, 106, 11667–11672. [CrossRef] [PubMed]

21. Tsai, M.C.; Manor, O.; Wan, Y.; Mosammamparast, N.; Wang, J.K.; Lan, F.; Shi, Y.; Segal, E.; Chang, H.Y. Long noncoding rna as modular scaffold of histone modification complexes. *Science* 2010, 329, 689–693. [CrossRef] [PubMed]

22. Magistri, M.; Faghihi, M.A.; St Laurent, G., 3rd; Wahlestedt, C. Regulation of chromatin structure by long noncoding rnas: Focus on natural antisense transcripts. *Trends Genet.* 2012, 28, 389–396. [CrossRef] [PubMed]

23. Mondal, T.; Rasmussen, M.; Pandey, G.K.; Isaksson, A.; Kanduri, C. Characterization of the rna content of chromatin. *Genome Res.* 2010, 20, 899–907. [CrossRef] [PubMed]

24. Orom, U.A.; Derrien, T.; Beringer, M.; Gumireddy, K.; Gardini, A.; Bussotti, G.; Lai, F.; Zytnicki, M.; Notredame, C.; Huang, Q.; et al. Long noncoding rnas with enhancer-like function in human cells. *Cell* 2010, 143, 46–58. [CrossRef] [PubMed]

25. Wang, K.C.; Yang, Y.W.; Liu, B.; Sanyal, A.; Corces-Zimmerman, R.; Chen, Y.; Lajoie, B.R.; Protacio, A.; Flynn, R.A.; Gupta, R.A.; et al. A long noncoding rna maintains active chromatin to coordinate homeotic gene expression. *Nature* 2011, 472, 120–124. [CrossRef] [PubMed]

26. Sun, M.; Kraus, W.L. From discovery to function: The expanding roles of long noncoding rnas in physiology and disease. *Endocr. Rev.* 2015, 36, 25–64. [CrossRef] [PubMed]

27. Yan, X.; Hu, Z.; Feng, Y.; Hu, X.; Yuan, J.; Zhao, S.D.; Zhang, Y.; Yang, L.; Shan, W.; He, Q.; et al. Comprehensive genomic characterization of long non-coding rnas across human cancers. *Cancer Cell* 2015, 28, 529–540. [CrossRef] [PubMed]

28. Kopp, F.; Mendell, J.T. Functional classification and experimental dissection of long noncoding rnas. *Cell* 2018, 172, 393–407. [CrossRef] [PubMed]

29. Ulitsky, I.; Bartel, D.P. Lincrnas: Genomics, evolution, and mechanisms. *Cell* 2013, 154, 26–46. [CrossRef] [PubMed]

30. Torarinsson, E.; Sawera, M.; Havigaard, J.H.; Fredholm, M.; Gorodkin, J. Thousands of corresponding human and mouse genomic regions unalignable in primary sequence contain common rna structure. *Genome Res.* 2006, 16, 885–889. [CrossRef] [PubMed]

31. St Laurent, G.; Wahlestedt, C.; Kapranov, P. The landscape of long noncoding rna classification. *Trends Genet.* 2015, 31, 239–251. [CrossRef] [PubMed]
32. Mas-Ponte, D.; Carlevaro-Fita, J.; Palumbo, E.; Hermoso Pulido, T.; Guigo, R.; Johnson, R. Lncatlas database for subcellular localization of long noncoding rnas. RNA Biol. 2017, 14, 1771–1777. [CrossRef] [PubMed]

33. Peng, J.C.; Shen, J.; Ran, Z.H. Transcribed ultraconserved region in human cancers. Mol. Cell 2014, 55, 791–802. [CrossRef] [PubMed]

34. Cabili, M.N.; Dunagin, M.C.; McClanahan, P.D.; Biaesch, A.; Padovan-Merhar, O.; Regev, A.; Rinn, J.L.; Raj, A. Localization and abundance analysis of human Incrnas at single-cell and single-molecule resolution. Genome Biol. 2015, 16, 20. [CrossRef] [PubMed]

35. Van Heesch, S.; van Iterson, M.; Jacobi, J.; Boymans, S.; Essers, P.B.; de Bruijn, E.; Hao, W.; MacInnes, A.W.; Cuppen, E.; Simonis, M. Extensive localization of long noncoding rnas to the cytosol and mono- and polyribosomal complexes. Genome Biol. 2014, 15, R6. [CrossRef] [PubMed]

36. Rackham, O.; Shearwood, A.M.; Mercer, T.R.; Davies, S.M.; Mattick, J.S.; Filipovska, A. Long noncoding rnas are generated from the mitochondrial genome and regulated by nuclear-encoded proteins. RNA 2011, 17, 2085–2093. [CrossRef] [PubMed]

37. Esteller, M. Non-coding rnas in human disease. Nat. Rev. Genet. 2011, 12, 861–874. [CrossRef] [PubMed]

38. He, Y.; Vogelstein, B.; Velculescu, V.E.; Papadopoulos, N.; Kinzler, K.W. The antisense transcriptomes of human cells. Science 2008, 322, 1855–1857. [CrossRef] [PubMed]

39. Seila, A.C.; Calabrese, J.M.; Levine, S.S.; Yeo, G.W.; Rahl, P.B.; Flynn, R.A.; Young, R.A.; Sharl, P.A. Divergent transcription from active promoters. Science 2008, 322, 1849–1851. [CrossRef] [PubMed]

40. Preker, P.; Nielsen, J.; Kammler, S.; Lykke-Andersen, S.; Christensen, M.S.; Mapendano, C.K.; Schierup, M.H.; Jensen, T.H. RNA exosome depletion reveals transcription upstream of active human promoters. Science 2008, 322, 1851–1854. [CrossRef] [PubMed]

41. Tang, J.; Xie, Y.; Xu, X.; Yin, Y.; Jiang, R.; Deng, L.; Tan, Z.; Gangarapu, V.; Tang, J.; Sun, B. Bidirectional transcription of linc00441 and rb1 via h3k27 modification-dependent way promotes hepatocellular carcinoma. Cell Death Dis. 2017, 8, e2675. [CrossRef] [PubMed]

42. Hangauer, M.J.; Vaughn, I.W.; McManus, M.T. Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding rnas. PLoS Genet. 2013, 9, e1003569. [CrossRef] [PubMed]

43. Yin, Q.F.; Yang, L.; Zhang, Y.; Xiang, J.F.; Wu, Y.W.; Carmichael, G.G.; Chen, L.L. Long noncoding rnas with snorna ends. Mol. Cell 2012, 48, 219–230. [CrossRef] [PubMed]

44. Salzman, J.; Gawad, C.; Wang, P.L.; Lacayo, N.; Brown, P.O. Circular rnas are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS ONE 2012, 7, e30733. [CrossRef] [PubMed]

45. Geisler, S.; Coller, J. RNA in unexpected places: Long non-coding rna functions in diverse cellular contexts. Nat. Rev. Mol. Cell Biol 2013, 14, 699–712. [CrossRef] [PubMed]

46. Rinn, J.L.; Kertesz, M.; Wang, J.K.; Squazzo, S.L.; Xu, X.; Brugmann, S.A.; Goodnough, L.H.; Helms, J.A.; Farnham, P.J.; Segal, E.; et al. Functional demarcation of active and silent chromatin domains in human hox loci by noncoding rnas. Cell 2007, 129, 1311–1323. [CrossRef] [PubMed]

47. Zhao, J.; Sun, B.K.; Erwin, J.A.; Song, J.J.; Lee, J.T. Polycomb proteins targeted by a short repeat rna to the mouse x chromosome. Science 2008, 322, 750–756. [CrossRef] [PubMed]
53. Tang, Y.; Wang, J.; Jian, Z.; Chen, G.G.; Lai, P.B. Cancer specific long noncoding rnas show differential expression patterns and competing endogenous rna potential in hepatocellular carcinoma. *PLoS ONE* 2015, 10, e0141042. [CrossRef] [PubMed]

54. Zhang, X.N.; Wang, C.C.; Zhou, J. The long non-coding rna neat1 contributes to hepatocellular carcinoma progression. *Hepatol. Mon.* 2017, 39. [CrossRef] [PubMed]

55. Tripathi, V.; Ellis, J.D.; Shen, Z.; Song, D.Y.; Pan, Q.; Watt, A.T.; Freier, S.M.; Bennett, C.F.; Sharma, A.; Bubulya, P.A.; et al. The nuclear-retained noncoding rna malat1 regulates alternative splicing by modulating sr splicing factor phosphorylation. *PLoS ONE* 2015, 10, e0141042. [CrossRef] [PubMed]

56. Han, D.; Li, J.; Wang, H.; Su, X.; Hou, J.; Gu, Y.; Qian, C.; Lin, Y.; Liu, X.; Huang, M.; et al. Circular rna ccrmto1 acts as the sponge of microrna-9 to suppress hepatocellular carcinoma progression. *Hepatology* 2017, 66, 1151–1164. [CrossRef] [PubMed]

57. Hou, Z.; Xu, X.; Zhou, L.; Fu, X.; Tao, S.; Zhou, J.; Tan, D.; 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.* 2017, 39. [CrossRef] [PubMed]

58. Zhang, X.N.; Wang, C.C.; Zhou, J. The long noncoding rna neut1 contributes to hepatocellular carcinoma development by sponging mir-485 and enhancing the expression of the stat3. *J. Cell Physiol.* 2017. [CrossRef] [PubMed]

59. Gong, C.; Maquat, L.E. Incrnas transactivate stau1-mediated mrna decay by duplexing with 3′ utrs via alu elements. *Nature* 2011, 470, 284–288. [CrossRef] [PubMed]

60. Ferre, F.; Colantoni, A.; Helmer-Citterich, M. Revealing protein-incrna interaction. *Brief. Bioinform.* 2016, 17, 106–116. [CrossRef] [PubMed]

61. Tollervey, J.R.; Curk, T.; Rogel, B.; Briese, M.; Cereda, M.; Kayikci, M.; Konig, J.; Hortobagyi, T.; Nishimura, A.L.; Zupunski, V.; et al. Characterizing the rna targets and position-dependent splicing regulation by tdp-43. *Nat. Neurosci.* 2011, 14, 452–458. [CrossRef] [PubMed]

62. Buratti, E.; Baralle, F.E. The multiple roles of tdp-43 in pre-mrna processing and gene expression regulation. *RNA Biol.* 2010, 7, 420–429. [CrossRef] [PubMed]
74. Yao, J.; Wu, L.; Meng, X.; Yang, H.; Ni, S.; Wang, Q.; Zhou, J.; Zhang, Q.; Su, K.; Shao, L.; et al. Profiling, clinicopathological correlation and functional validation of specific long non-coding rnas for hepatocellular carcinoma. Mol. Cancer 2017, 16, 164. [CrossRef] [PubMed]

75. Yang, Y.; Chen, L.; Gu, J.; Zhang, H.; Yuan, J.; Lian, Q.; Lv, G.; Wang, S.; Wu, Y.; Yang, Y.T.; et al. Recurrently deregulated incrnas in hepatocellular carcinoma. Nat. Commun. 2017, 8, 14421. [CrossRef] [PubMed]

76. Harrow, J.; Frankish, A.; Gonzalez, J.M.; Tapanari, E.; Diekhsans, M.; Kokocinski, F.; Aken, B.L.; Barrell, D.; Zadissa, A.; Searle, S.; et al. Gencode: The reference human genome annotation for the encode project. Genome Res. 2012, 22, 1760–1774. [CrossRef] [PubMed]

77. Lv, J.; Ma, L.; Chen, X.L.; Huang, X.H.; Wang, Q. Downregulation of Incrnah19 and mir-675 promotes migration and invasion of human hepatocellular carcinoma cells through akt/gsk-3beta/cdc25a signaling pathway. J. Huazhong Univ. Sci. Technolog Med. Sci. 2014, 34, 363–369. [CrossRef] [PubMed]

78. Yang, Z.; Lu, Y.; Xu, Q.; Tang, B.; Park, C.K.; Chen, X. Hulc and h19 played different roles in overall and disease-free survival from hepatocellular carcinoma after curative hepatectomy: A preliminary analysis from gene expression omnibus. Dis. Markers 2015, 2015, 191029. [CrossRef] [PubMed]

79. Ramani, K.; Mavila, N.; Ko, K.S.; Mato, J.M.; Lu, S.C. Prohibitin 1 regulates the h19-igf2 axis and proliferation in hepatocytes. J. Biol. Chem. 2016, 291, 24148–24159. [CrossRef] [PubMed]

80. Yang, F.; Zhang, L.; Huo, X.S.; Yuan, J.H.; Xu, D.; Yuan, S.X.; Zhu, N.; Zhou, W.P.; Yang, G.S.; Wang, Y.Z.; et al. Long noncoding rna high expression in hepatocellular carcinoma facilitates tumor growth through enhancer of zeste homolog 2 in humans. Hepatology 2011, 54, 1679–1689. [CrossRef] [PubMed]

81. Zhang, C.; Yang, X.; Qi, Q.; Gao, Y.; Wei, Q.; Han, S. Lncnrnah1 in serum and exosomes as a potential biomarker in the hcv-related hepatocellular carcinoma. Cancer Biomark 2017. [CrossRef] [PubMed]

82. Geng, Y.J.; Xie, S.L.; Li, Q.; Ma, J.; Wang, G.Y. Large intervening non-coding rna hotair is associated with hepatocellular carcinoma progression. J. Natl. Cancer Inst. 2011, 103, 817–834. [CrossRef] [PubMed]

83. Ramani, K.; Mavila, N.; Ko, K.S.; Mato, J.M.; Lu, S.C. Prohibitin 1 regulates the h19-igf2 axis and proliferation in hepatocytes. J. Biol. Chem. 2016, 291, 24148–24159. [CrossRef] [PubMed]

84. Ishibashi, M.; Kogo, R.; Shibata, K.; Sawada, G.; Takahashi, Y.; Kurashige, J.; Akiyoshi, S.; Sasaki, S.; Iwaya, T.; Sudo, T.; et al. Clinical significance of the expression of long non-coding rna hotair in primary hepatocellular carcinoma. Oncol. Rep. 2011, 26, 1243–1250. [CrossRef] [PubMed]

85. Su, D.N.; Wu, S.P.; Chen, H.T.; He, J.H. Hotair, a long non-coding rna driver of malignancy whose expression is activated by foxc1, negatively regulates mirna-1 in hepatocellular carcinoma. Oncol. Lett. 2016, 12, 4061–4067. [CrossRef] [PubMed]

86. Su, D.N.; Wu, S.P.; Chen, H.T.; He, J.H. Hotair, a long non-coding rna driver of malignancy whose expression is activated by foxc1, negatively regulates mirna-1 in hepatocellular carcinoma. Oncol. Lett. 2016, 12, 4061–4067. [CrossRef] [PubMed]

87. Yang, Z.; Zhou, L.; Wu, L.M.; Lai, M.C.; Xie, H.Y.; Zhang, F.; Zheng, S.S. Overexpression of long non-coding rna hotair predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. Ann. Surg. Oncol. 2011, 18, 1243–1250. [CrossRef] [PubMed]

88. Ding, C.; Cheng, S.; Yang, Z.; Lv, Z.; Xiao, H.; Du, C.; Peng, C.; Xie, H.; Zhou, L.; Wu, J.; et al. Long non-coding rna hotair promotes cell migration and invasion via down-regulation of mirna-1 in hepatocellular carcinoma cells. Int. J. Mol. Sci. 2014, 15, 4060–4076. [CrossRef] [PubMed]

89. Quagliata, L.; Matter, M.S.; 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 2014, 59, 911–923. [CrossRef] [PubMed]

90. Tsang, F.H.; Au, S.L.; Wei, L.; Fan, D.N.; Lee, J.M.; Wong, C.C.; Ng, I.O.; Wong, C.M. Long non-coding rna hottip is frequently up-regulated in hepatocellular carcinoma and is targeted by tumour suppressive mir-125b. Liver Int 2015, 35, 1597–1606. [CrossRef] [PubMed]

91. Du, Y.; Kong, G.; You, X.; Zhang, S.; Zhang, T.; Gao, Y.; Ye, L.; Zhang, X. Elevation of highly up-regulated in liver cancer (hulc) by hepatitis b virus x protein promotes hepatoma cell proliferation via down-regulating p18. J. Biol. Chem. 2012, 287, 26302–26311. [CrossRef] [PubMed]

92. Li, S.P.; Xu, H.X.; Yu, Y.; He, J.D.; Wang, Z.; Xu, Y.J.; Wang, C.Y.; Zhang, H.M.; Zhang, R.X.; Zhang, J.J.; et al. Lncrna hulc enhances epithelial-mesenchymal transition to promote tumorigenesis and metastasis of hepatocellular carcinoma via the mir-200a-3p/zeb1 signaling pathway. Oncotarget 2016, 7, 42431–42446. [CrossRef] [PubMed]
93. Panzitt, K.; Tschernatsch, M.M.; Guelly, C.; Moustafa, T.; Stradner, M.; Strohmaier, H.M.; Buck, C.R.; Denk, H.; Schroeder, R.; Trauner, M.; et al. Characterization of hulc, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding rna. *Gastroenterology* 2007, 132, 330–342. [CrossRef] [PubMed]

94. Xiong, H.; Li, B.; He, J.; Zeng, Y.; Zhang, Y.; He, F. Lncrna hulc promotes the growth of hepatocellular carcinoma cells via stabilizing cox-2 protein. *Biochem. Biophys. Res. Commun.* 2017, 490, 693–699. [CrossRef] [PubMed]

95. Wang, Y.; Chen, F.; Zhao, M.; Yang, Z.; Li, J.; Zhang, S.; Zhang, W.; Ye, L.; Zhang, X. The long noncoding rna hulc promotes liver cancer by increasing the expression of the hmga2 oncogene via sequestration of the microrna-186. *J. Biol. Chem.* 2017, 292, 15395–15407. [CrossRef] [PubMed]

96. Cui, M.; Xiao, Z.; Wang, Y.; Zheng, M.; Song, T.; Cai, X.; Sun, B.; Ye, L.; Zhang, X. Long noncoding rna hulc modulates abnormal lipid metabolism in hepatoma cells through an mir-9-mediated rxra signaling pathway. *Cancer Res.* 2015, 75, 846–857. [CrossRef] [PubMed]

97. Lu, Z.; Xiao, Z.; Liu, F.; Cui, M.; Li, W.; Yang, Z.; Li, J.; Ye, L.; Zhang, X. Long non-coding rna hulc promotes tumor angiogenesis in liver cancer by up-regulating sphingosine kinase 1 (sphk1). *Oncotarget* 2016, 7, 241–254. [CrossRef] [PubMed]

98. Xiong, H.; Ni, Z.; He, J.; Jiang, S.; Li, X.; He, J.; Gong, W.; Zheng, L.; Chen, S.; Li, B.; et al. Lncrna hulc triggers autophagy via stabilizing sirt1 and attenuates the chemosensitivity of hcc cells. *Oncogene* 2017, 36, 3528–3540. [CrossRef] [PubMed]

99. Ji, P.; Diederichs, S.; Wang, W.; Boing, S.; Schneider, P.M.; Tidow, N.; Brandt, B.; Buerger, H.; Bulk, E.; et al. Malat-1, a novel noncoding rna, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003, 22, 8031–8041. [CrossRef] [PubMed]

100. Lai, M.C.; Yang, Z.; Zhou, L.; Zhu, Q.Q.; Xie, H.Y.; Zhang, F.; Wu, L.M.; Chen, L.M.; Zheng, S.S. Long non-coding rna malat-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med. Oncol.* 2012, 29, 1810–1816. [CrossRef] [PubMed]

101. Hou, Z.; Xu, X.; Fu, X.; Tao, S.; Zhou, J.; Liu, S.; Tan, D. Hbx-related long non-coding rna malat1 promotes cell metastasis via up-regulating ltbp3 in hepatocellular carcinoma. *Am. J. Cancer Res.* 2017, 7, 845–856. [PubMed]

102. Anwar, S.L.; Krech, T.; Hasemeier, B.; Schipper, E.; Schweitzer, N.; Vogel, A.; Kreipe, H.; Lehmann, U. Loss of imprinting and allelic switching at the dlk1-meg3 locus in human hepatocellular carcinoma. *PLoS ONE* 2012, 7, e49462. [CrossRef] [PubMed]

103. Braconi, C.; Kogure, T.; Valeri, N.; Huang, N.; Nuovo, G.; Costinean, S.; Negrini, M.; Miotto, E.; Croce, C.M.; Patel, T. MircoRNA-29 can regulate expression of the long non-coding rna gene meg3 in hepatocellular cancer. *Oncogene* 2011, 30, 4750–4756. [CrossRef] [PubMed]

104. He, J.H.; Han, Z.P.; Liu, J.M.; Zhou, J.B.; Zou, M.X.; Lv, Y.B.; Li, Y.G.; Cao, M.R. Overexpression of long non-coding rna meg3 inhibits proliferation of hepatocellular carcinoma huh7 cells via negative modulation of mirna-664. *J. Cell Biochem.* 2017, 118, 3713–3721. [CrossRef] [PubMed]

105. Guo, S.; Chen, W.; Luo, Y.; Ren, F.; Zong, T.; Rong, M.; Dang, Y.; Feng, Z.; Chen, G. Clinical implication of long non-coding rna neu1 expression in hepatocellular carcinoma patients. *Int. J. Clin. Exp. Pathol.* 2015, 8, 5395–5402. [PubMed]
110. Mang, Y.; Li, L.; Ran, J.; Zhang, S.; Liu, J.; Li, L.; Chen, Y.; Liu, J.; Gao, Y.; Ren, G. Long noncoding rna neat1 promotes cell proliferation and invasion by regulating hnrnp a2 expression in hepatocellular carcinoma cells. *Onco Targets Ther.* **2017**, *10*, 1003–1016. [CrossRef] [PubMed]

111. Wang, Z.; Zou, Q.; Song, M.; Chen, J. Neat1 promotes cell proliferation and invasion in hepatocellular carcinoma by negative regulating mir-613 expression. *Biomed. Pharmacother.* **2017**, *94*, 612–618. [CrossRef] [PubMed]

112. Zheng, X.; Zhang, Y.; Liu, Y.; Fang, L.; Li, L.; Sun, J.; Pan, Z.; Xin, W.; Huang, P. Hif-2alpha activated Incrna neat1 promotes hepatocellular carcinoma cell invasion and metastasis by affecting the epithelial-mesenchymal transition. *J. Cell Biochem.* **2017**. [CrossRef]

113. Zheng, Z.K.; Pang, C.; Yang, Y.; Duan, Q.; Zhang, J.; Liu, W.C. Serum long noncoding rna urothelial carcinoma-associated 1: A novel biomarker for diagnosis and prognosis of hepatocellular carcinoma. *J. Int. Mol. Res.* **2018**, *46*, 348–356. [CrossRef] [PubMed]

114. Xiao, J.N.; Yan, T.H.; Yu, R.M.; Gao, Y.; Zeng, W.L.; Lu, S.W.; Que, H.X.; Liu, Z.P.; Jiang, J.H. Long non-coding rna uca1 regulates the expression of snai1 by mir-203 to promote hepatocellular carcinoma progression. *J. Cancer Res. Clin. Oncol.* **2017**, *143*, 981–990. [CrossRef] [PubMed]

115. Wang, F.; Ying, H.Q.; He, B.S.; Pan, Y.Q.; Deng, Q.W.; Sun, H.L.; Chen, J.; Liu, X.; Wang, S.K. Upregulated Incrma-uca1 contributes to progression of hepatocellular carcinoma through inhibition of mir-216b and activation of fgfr1/erk signaling pathway. *Onco target* **2015**, *6*, 7899–7917. [CrossRef] [PubMed]

116. Kamel, M.M.; Matboli, M.; Sallam, M.; Montasser, I.F.; Saad, A.S.; El-Tawadi, A.H.F. Investigation of long noncoding rnas expression profile as potential serum biomarkers in patients with hepatocellular carcinoma. *Transl. Res.* **2016**, *168*, 134–145. [CrossRef] [PubMed]

117. Kogo, R.; Shimamura, T.; Mimori, K.; Kawahara, K.; Imoto, S.; Sudo, T.; Tanaka, F.; Shibata, K.; Suzuki, A.; Komune, S.; et al. Long noncoding rna hotair regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res.* **2011**, *71*, 6320–6326. [CrossRef] [PubMed]

118. Zhong, D.N.; Luo, Y.H.; Mo, W.J.; Zhang, X.; Tan, Z.; Zhao, N.; Pang, S.M.; Chen, G.; Rong, M.H.; Tang, W. High expression of long noncoding hotair correlates with hepatocarcinogenesis and metastasis. *Mol. Med. Rep.* **2017**. [CrossRef]

119. Zhou, J.J.; Cheng, D.; He, X.Y.; Meng, Z.; Li, W.Z.; Chen, R.F. Knockdown of hotair suppresses proliferation and cell cycle progression in hepatocellular carcinoma cell by downregulating ccnd1 expression. *Mol. Med. Rep.* **2017**, *16*, 4980–4986. [CrossRef] [PubMed]

120. Fu, W.M.; Zhu, X.; Wang, W.M.; Lu, Y.F.; Hu, B.G.; Wang, H.; Liang, W.C.; Wang, S.S.; Ko, C.H.; Waye, M.M.; et al. Hotair mediates hepatocarcinogenesis through suppressing mirna-218 expression and activating p14 and p16 signaling. *J. Hepatol.* **2015**, *63*, 886–895. [CrossRef] [PubMed]

121. Wu, Y.; Xiong, Q.; Li, S.; Yang, X.; Ge, F. Integrated proteomic and transcriptomic analysis reveals long noncoding rna hotair promotes hepatocellular carcinoma cell proliferation by regulating opioid growth factor receptor (ogfr). *Mol. Cell Proteomics* **2017**. [CrossRef]

122. Zhang, H.; Xing, Z.; Mani, S.K.; Bancel, B.; Durante, D.; Zoulif, F.; Tran, E.J.; Merle, P.; Andrisani, O. RNA helicase dead box protein 5 regulates polycomb repressive complex 2/hox transcript antisense intergenic rna function in hepatitis b virus infection and hepatocarcinogenesis. *Hepatology* **2016**, *64*, 1033–1048. [CrossRef] [PubMed]

123. Ren, Y.K.; Xiao, Y.; Wan, X.B.; Zhao, Y.Z.; Li, J.; Li, Y.; Han, G.S.; Chen, X.B.; Zou, Q.Y.; Wang, G.C.; et al. Association of long non-coding rna hottip with progression and prognosis of colorectal cancer. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 11458–11463. [PubMed]

124. Liu, Y.; Ding, J.; Zhang, Z.; Shi, Y.; Zhu, Y.; Li, J.; Peng, P.; Wang, J.; Fan, Y.; De, W.; et al. The long noncoding rna hoxa transcript at the distal tip promotes colorectal cancer growth partially via silencing of p21 expression. *Tumour Biol.* **2016**, *37*, 7431–7440. [CrossRef] [PubMed]

125. Ye, H.; Liu, K.; Qian, K. Overexpression of long noncoding rna hottip promotes tumor invasion and predicts poor prognosis in gastric cancer. *Onco Targets Ther.* **2016**, *9*, 2081–2088. [PubMed]

126. Wang, S.S.; Wuputra, K.; Liu, C.J.; Lin, Y.C.; Chen, Y.T.; Chai, C.Y.; Lin, C.S.; Kuo, K.K.; Tsai, M.H.; Wang, S.W.; et al. Oncogenic function of the homeobox a13-long noncoding rna hottip-insulin growth factor-binding protein 3 axis in human gastric cancer. *Onco target* **2016**, *7*, 36049–36064. [CrossRef] [PubMed]

127. Chang, S.; Liu, J.; Gou, S.; He, S.; Qiu, G.; Lu, J.; Wang, J.; Fan, L.; Zhao, W.; Che, X. Hottip and hoxa13 are oncogenes associated with gastric cancer progression. *Oncol. Rep.* **2016**, *35*, 3577–3585. [CrossRef] [PubMed]
128. Wang, Y.; Li, Z.; Zheng, S.; Zhou, Y.; Zhao, L.; Ye, H.; Zhao, X.; Gao, W.; Fu, Z.; Zhou, Q.; et al. Expression profile of long non-coding rnas in pancreatic cancer and their clinical significance as biomarkers. Oncotarget 2015, 6, 35684–35698. [CrossRef] [PubMed]

129. Fu, Z.; Chen, C.; Zhou, Q.; Wang, Y.; Zhao, Y.; Zhao, X.; Li, W.; Zheng, S.; Ye, H.; Wang, L.; et al. Lncrna hottip modulates cancer stem cell properties in human pancreatic cancer by regulating boxa9. Cancer Lett. 2017, 410, 68–81. [CrossRef] [PubMed]

130. Sun, Y.; Zhou, Y.; Bai, Y.; Wang, Q.; Bao, J.; Luo, Y.; Guo, Y.; Guo, L. A long non-coding rna hottip expression is associated with disease progression and predicts outcome in small cell lung cancer patients. Mol. Cancer 2017, 16, 162. [CrossRef] [PubMed]

131. Li, F.; Cao, L.; Hang, D.; Wang, F.; Wang, Q. Long non-coding rna hottip is up-regulated and associated with poor prognosis in patients with osteosarcoma. Int. J. Clin. Exp. Pathol. 2015, 8, 11414–11420. [PubMed]

132. Zhang, S.; Wang, W.; Liu, G.; Xie, S.; Li, Q.; Li, Y.; Lin, Z. Long non-coding rna hottip promotes hypoxia-induced epithelial-mesenchymal transition of malignant glioma by regulating the mir-101/zeb1 axis. Biomed. Pharmacother. 2015, 95, 711–720. [CrossRef] [PubMed]

133. Jin, N.; Yang, L.Y.; Xu, Z.P. Long non-coding rna hotspot is able to predict poor prognosis in various neoplasms: A meta-analysis. Mol. Clin. Oncol. 2017, 7, 263–266. [CrossRef] [PubMed]

134. Li, W.; Li, N.; Kang, X.; Shi, K.; Chen, Q. Prognostic value of the long noncoding rna hotspot in human cancers. Oncotarget 2017, 8, 59563–59569. [CrossRef] [PubMed]

135. Fan, Y.; Yan, T.; Chai, Y.; Jiang, Y.; Zhu, X. Long noncoding rna hottip as an independent prognostic marker of cancer. Clin. Chim. Acta 2017. [CrossRef] [PubMed]

136. Ge, Y.; Yan, X.; Jin, Y.; Yang, X.; Yu, X.; Zhou, L.; Han, S.; Yuan, Q.; Yang, M. Mirna-192 and mirna-204 directly suppress incrna hotspot and interrupt gls1-mediated glutaminolysis in hepatocellular carcinoma. PLoS Genet. 2015, 11, e1005726. [CrossRef] [PubMed]

137. Zhang, Y.; Huang, J.C.; Cai, K.T.; Yu, X.B.; Chen, Y.R.; Pan, W.Y.; He, Z.L.; Lv, J.; Feng, Z.B.; Chen, G. Long noncoding rna hotspot promotes hepatocellular carcinoma tumorigenesis and development: A comprehensive investigation based on bioinformatics, qrtpcr and metaanalysis of 393 cases. Int. J. Oncol. 2017, 51, 1705–1721. [CrossRef] [PubMed]

138. Gutschner, T.; Hammerle, M.; Eissmann, M.; HSU, J.; Kim, Y.; Hung, G.; Revenko, A.; Arun, G.; Stentrup, M.; Gross, M.; et al. The noncoding rna malat1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res. 2013, 73, 1180–1189. [CrossRef] [PubMed]

139. Han, Y.; Liu, Y.; Nie, L.; Gui, Y.; Cai, Z. Inducing cell proliferation inhibition, apoptosis, and motility reduction by silencing long noncoding ribonucleic acid metastasis-associated lung adenocarcinoma transcript 1 in urothelial carcinoma of the bladder. Urology 2013, 81, 209.e1–209.e7. [CrossRef] [PubMed]

140. Wang, J.; Su, L.; Chen, X.; Li, P.; Cai, Q.; Yu, B.; Liu, B.; Wu, W.; Zhu, Z. Malat1 promotes cell proliferation in gastric cancer by recruiting sf2/asf. Biomed. Pharmacother. 2014, 68, 557–564. [CrossRef] [PubMed]

141. Tian, Y.; Zhang, X.; Hao, Y.; Fang, Z.; He, Y. Potential roles of abnormally expressed long noncoding rna uca1 and malat-1 in metastasis of melanoma. Melanoma. Res. 2014, 24, 335–341. [CrossRef] [PubMed]

142. Ma, K.X.; Wang, H.J.; Li, X.R.; Li, T.; Su, G.; Yang, P.; Wu, J.W. Long noncoding rna malat1 associates with the malignant status and poor prognosis in glioma. Tumour Biol. 2015, 36, 3355–3359. [CrossRef] [PubMed]

143. Fujimoto, A.; Furuta, M.; Totoki, Y.; Tsunoda, T.; Kato, M.; Shiraishi, Y.; Tanaka, H.; Taniguchi, H.; Kawakami, Y.; Ueno, M.; et al. Whole-genome mutational landscape and characterization of noncoding and structural mutations in liver cancer. Nat. Genet. 2016, 48, 500–509. [CrossRef] [PubMed]

144. Luo, F.; Sun, B.; Li, H.; Xu, Y.; Liu, Y.; Liu, X.; Lu, L.; Li, J.; Wang, Q.; Wei, S.; et al. A malat1/hif-2alpha feedback loop contributes to arsenite carcinogenesis. Oncotarget 2016, 7, 5769–5787. [CrossRef] [PubMed]

145. Huang, Z.; Huang, L.; Shen, S.; Li, J.; Lu, H.; Mo, W.; Dang, Y.; Luo, D.; Chen, G.; Feng, Z. Spl1 cooperates with sp3 to upregulate malat1 expression in human hepatocellular carcinoma. Oncol. Rep. 2015, 34, 2403–2412. [CrossRef] [PubMed]

146. Yuan, P.; Cao, W.; Zang, Q.; Li, G.; Guo, X.; Fan, J. The hif-2alpha-malat1-mir-216b axis regulates multi-drug resistance of hepatocellular carcinoma cells via modulating autophagy. Biochem. Biophys. Res. Commun. 2016, 478, 1067–1073. [CrossRef] [PubMed]

147. Li, C.; Miao, R.; Liu, S.; Wan, Y.; Zhang, S.; Deng, Y.; Bi, J.; Qu, K.; Zhang, J.; Liu, C. Down-regulation of mir-146b-5p by long noncoding rna malat1 in hepatocellular carcinoma promotes cancer growth and metastasis. Oncotarget 2017, 8, 28683–28695. [CrossRef] [PubMed]
148. Cui, M.; Zheng, M.; Sun, B.; Wang, Y.; Ye, L.; Zhang, X. A long noncoding RNA perturbs the circadian rhythm and growth and motility of human hepatoma cells via modulation of mir-195. *J. Cell Biochem.* 2017. [CrossRef] [PubMed]

149. Liu, D.; Zhu, Y.; Pang, J.; Weng, X.; Feng, X.; Guo, Y. Knockdown of long non-coding RNA MALT1 inhibits growth and motility of human hepatoma cells. *J. Cell Biochem.* 2017. [CrossRef] [PubMed]

150. 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 MALT1 interacts with DBC1 to regulate P53 acetylation. *Nucleic Acids Res.* 2017, 45, 9947–9959. [CrossRef] [PubMed]

151. Clemson, C.M.; Hutchinson, J.N.; Sara, S.A.; Ensminger, A.W.; Fox, A.H.; Chess, A.; Lawrence, J.B. An architectural role for a nuclear noncoding RNA: Neat1 RNA is essential for the structure of paraspeckles. *Mol. Cell* 2009, 33, 717–726. [CrossRef] [PubMed]

152. Choudhry, H.; Albu khari, A.; Morotti, M.; Haider, S.; Moralli, D.; Smythies, J.; Schodel, J.; Green, C.M.; Camps, C.; Buffa, F.; et al. Tumor hypoxia induces nuclear paraspeckle formation through HIF-2alpha dependent transcriptional activation of Neat1 leading to cancer cell survival. *Oncogene* 2015, 34, 4482–4490. [CrossRef] [PubMed]

153. Brannan, C.I.; Dees, E.C.; Ingram, R.S.; Tilghman, S.M. The product of the h19 gene may function as an RNA. *Mol. Cell Biol.* 1990, 10, 28–36. [CrossRef] [PubMed]

154. Vennin, C.; Dahmani, F.; Spruyt, N.; Adriaenssens, E. Role of long non-coding RNA in cells: Example of the H19/IGF2 locus. *Adv. Biosci. Biotechnol.* 2013, Vol.04No.05. [CrossRef]

155. Bi, H.S.; Yang, X.Y.; Yuan, J.H.; Yang, F.; Xu, D.; Guo, Y.J.; Zhang, L.; Zhou, C.C.; Wang, F.; Washimi, O.; et al. Allelic-expression imbalance of the insulin-like growth factor 2 gene in hepatocellular carcinoma. *Oncotarget* 2015, 6, 9728–9740. [CrossRef]

156. Takeda, S.; Kondo, M.; Kumada, T.; Koshikawa, T.; Ueda, R.; Nishio, M.; Osada, H.; Suzuki, H.; Nagatake, M.; Vennin, C.; Dahmani, F.; Spruyt, N.; Adriaenssens, E. Role of long non-coding RNA in cells: Example of the H19/IGF2 locus. *Biochim. Biophys. Acta* 2013, 1830, 4899–4906. [CrossRef] [PubMed]

157. Zhou, W.; Ye, X.L.; Xu, J.; Cao, M.G.; Fang, Z.Y.; Li, L.Y.; Liu, Q.; Qian, Y.H.; Xie, D. The lncRNA h19 inhibits RNA polymerase II-mediated transcription by disrupting the hnrnp U-actin complex. *Oncogene* 2016, 35, 1926–1938. [CrossRef]

158. Lv, J.; Yu, Y.Q.; Li, S.Q.; Luo, L.; Wang, Q.; Aflatoxin B1 promotes cell growth and invasion in hepatocellular carcinoma HepG2 cells through h19 and e2fi. *Asian Pac. J. Cancer Prev.* 2014, 15, 2565–2570. [CrossRef] [PubMed]

159. Wu, J.; Qin, Y.; Li, B.; He, W.Z.; Sun, Z.L. Hypomethylated and hypermethylated profiles of h19dmr are associated with the aberrant imprinting of igf2 and h19 in hepatic cell carcinoma. *Genomics* 2008, 91, 443–450. [CrossRef] [PubMed]

160. Jing, W.; Zhu, M.; Zhang, X.W.; Pan, Z.Y.; Gao, S.S.; Zhou, H.; Qiu, S.L.; Liang, C.Z.; Tu, J.C. The significance of long noncoding RNA H19 in predicting progression and metastasis of cancers: A meta-analysis. *Biomed. Res. Int.* 2016, 2016, 5902678. [CrossRef] [PubMed]

161. Collette, J.; Le Bourhis, X.; Adriaenssens, E. Regulation of human breast cancer by the long non-coding RNA H19. *Int. J. Mol. Sci.* 2017, 18, 2319. [CrossRef] [PubMed]

162. Zhou, W.; Ye, X.L.; Xu, J.; Cao, M.G.; Fang, Z.Y.; Li, L.Y.; Guan, G.H.; Liu, Q.; Qian, Y.H.; Xie, D. The lncRNA h19 mediates breast cancer cell plasticity during emt and met plasticity by differentially sponging mir-200b/c and let-7b. *Sci. Signal.* 2017, 10. [CrossRef] [PubMed]

163. Zhang, L.; Yang, F.; Yuan, J.H.; Yuan, S.X.; Zhou, W.P.; Huo, X.S.; Xu, D.; Bi, H.S.; Wang, F.; Sun, S.H. Epigenetic activation of the mir-200 family contributes to h19-mediated metastasis suppression in hepatocellular carcinoma. *Carcinogenesis* 2013, 34, 577–586. [CrossRef] [PubMed]

164. Cui, M.; Zheng, M.; Sun, B.; Wang, Y.; Ye, L.; Zhang, X. A long noncoding RNA perturbs the circadian rhythm of hepatoma cells to facilitate hepatocarcinogenesis. *Neoplasia* 2015, 17, 79–88. [CrossRef] [PubMed]

165. He, Y.; Luo, Y.; Liang, B.; Ye, L.; Lu, G.; He, W. Potential applications of meg3 in cancer diagnosis and prognosis. *Oncotarget* 2017, 8, 73282–73295. [CrossRef] [PubMed]

166. Cao, C.; Sun, J.; Zhang, D.; Guo, X.; Xie, L.; Li, X.; Wu, D.; Liu, L. The long intergenic noncoding RNA UCFC1, a target of microRNA 34a, interacts with the mRNA stabilizing protein Hur to increase levels of beta-catenin in HCC cells. *Gastroenterology* 2015, 148, 415–26.e18–426. [CrossRef] [PubMed]
167. El-Tawdi, A.H.; Matboli, M.; El-Nakeep, S.; Azazy, A.E.; Abdel-Rahman, O. Association of long noncoding RNA and c-jun expression in hepatocellular carcinoma. *Expert Rev. Gastroenterol. Hepatol.* 2016, 10, 869–877. [CrossRef] [PubMed]

168. Hu, J.J.; Song, W.; Zhang, S.D.; Shen, X.H.; Qiu, X.M.; Wu, H.Z.; Gong, P.H.; Lu, S.; Zhao, Z.J.; He, M.L.; et al. Hbx-upregulated lncrna uca1 promotes cell growth and tumorigenesis by recruiting ezh2 and repressing p27kip1/cdk2 signaling. *Sci. Rep.* 2016, 6, 23521. [CrossRef] [PubMed]

169. Jang, S.Y.; Kim, G.; Park, S.Y.; Lee, Y.R.; Kwon, S.H.; Kim, H.S.; Yoon, J.S.; Lee, J.S.; Kweon, Y.O.; Ha, H.T.; et al. Clinical significance of lncrna-atb expression in human hepatocellular carcinoma. *Oncotarget* 2017, 8, 78588–78597. [CrossRef] [PubMed]

170. Yuan, J.H.; Yang, F.; Wang, F.; Ma, J.Z.; Guo, Y.J.; Tao, Q.F.; Liu, F.; Pan, W.; Wang, T.T.; Zhou, C.C.; et al. A long noncoding rna activated by tgf-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma. *Cancer Cell* 2014, 25, 666–681. [CrossRef] [PubMed]

171. Yuan, S.X.; Tao, Q.F.; Wang, J.; Yang, F.; Liu, L.; Wang, L.L.; Zhang, J.; Yang, Y.; Liu, H.; Wang, F.; et al. Antisense long non-coding rna pcna-as1 promotes tumour growth by regulating proliferating cell nuclear antigen in hepatocellular carcinoma. *Cancer Lett.* 2014, 349, 87–94. [CrossRef] [PubMed]

172. Konishi, H.; Ichikawa, D.; Yamamoto, Y.; Arita, T.; Shoda, K.; Hiramoto, H.; Hamada, J.; Itoh, H.; Fujita, Y.; Komatsu, S.; et al. Plasma level of metastasis-associated lung adenocarcinoma transcript 1 is associated with liver damage and predicts development of hepatocellular carcinoma. *Cancer Sci.* 2016, 107, 149–154. [CrossRef] [PubMed]

173. Liu, Y.; Pan, S.; Liu, L.; Zhai, X.; Liu, J.; Wen, J.; Zhang, Y.; Chen, J.; Shen, H.; Hu, Z. A genetic variant in long non-coding rna hulc contributes to risk of hbv-related hepatocellular carcinoma in a chinese population. *PLoS ONE* 2012, 7, e35145. [CrossRef] [PubMed]

174. Li, J.; Wang, X.; Tang, J.; Jiang, R.; Zhang, W.; Ji, J.; Sun, B. Hulc and linc00152 act as novel biomarkers in predicting diagnosis of hepatocellular carcinoma. *Cell Physiol. Biochem.* 2015, 37, 687–696. [CrossRef] [PubMed]

175. He, T.; Zhang, L.; Kong, Y.; Huang, Y.; Zhang, Y.; Zhou, D.; Zhou, X.; Yan, Y.; Zhang, L.; Lu, S.; et al. Long non-coding rna casc15 is upregulated in hepatocellular carcinoma and facilitates hepatocarcinogenesis. *Int. J. Oncol.* 2017, 51, 1722–1730. [CrossRef] [PubMed]

176. Xiao, J.; Lv, Y.; Jin, F.; Liu, Y.; Ma, Y.; Xiong, Y.; Liu, L.; Zhang, S.; Sun, Y.; Tipoe, G.L.; et al. Lncrna hanr promotes tumorigenesis and increase of chemoresistance in hepatocellular carcinoma. *Cell Physiol. Biochem.* 2017, 43, 1926–1938. [CrossRef] [PubMed]

177. Guo, W.; Liu, S.; Cheng, Y.; Lu, L.; Shi, J.; Xu, G.; Li, N.; Cheng, K.; Wu, M.; Cheng, S.; et al. Icam-1-related noncoding rna in cancer stem cells maintains icam-1 expression in hepatocellular carcinoma. *Clin. Cancer Res.* 2016, 22, 2041–2050. [CrossRef] [PubMed]

178. Xu, Y.C.; Liang, C.J.; Zhang, D.X.; Li, G.Q.; Gao, X.; Fu, J.Z.; Xia, F.; Ji, J.J.; Zhang, L.J.; Li, G.M.; et al. Lncshrg promotes hepatocellular carcinoma progression by activating hes6. *Oncotarget* 2017, 8, 70630–70641. [CrossRef] [PubMed]

179. Yuan, S.X.; Yang, F.; Yang, Y.; Tao, Q.F.; Zhang, J.; Huang, G.; Yang, Y.; Wang, R.Y.; Yang, S.; Huo, X.S.; et al. Long noncoding RNA associated with microvascular invasion in hepatocellular carcinoma promotes angiogenesis and serves as a predictor for hepatocellular carcinoma patients’ poor recurrence-free survival after hepatectomy. *Hepatology* 2012, 56, 2231–2241. [CrossRef] [PubMed]

180. Peng, W.; Fan, H. Long non-coding rna pandar correlates with poor prognosis and promotes tumorigenesis in hepatocellular carcinoma. *Biomed. Pharmacother.* 2015, 72, 113–118. [CrossRef] [PubMed]

181. Wang, Y.; Hu, Y.; Wu, G.; Yang, Y.; Tang, Y.; Zhang, W.; Wang, K.; Liu, Y.; Wang, X.; Li, T. Long noncoding rna pcat-14 induces proliferation and invasion by hepatocellular carcinoma cells by inducing methylation of mir-372. *Oncotarget* 2017, 8, 34429–34441. [CrossRef] [PubMed]

182. Birgani, M.T.; Hajjari, M.; Shahrisa, A.; Khoshnevisan, A.; Shojaa, Z.; Motahari, P.; Farhangi, B. Long non-coding rna snhgf6 as a potential biomarker for hepatocellular carcinoma. *Pathol. Oncol. Res.* 2017. [CrossRef] [PubMed]

183. Liu, J.; Lu, C.; Xiao, M.; Jiang, F.; Qu, L.; Ni, R. Long non-coding rna snhg20 predicts a poor prognosis for hcc and promotes cell invasion by regulating the epithelial-to-mesenchymal transition. *Biomed. Pharmacother.* 2017, 89, 857–863. [CrossRef] [PubMed]
184. Tian, F.; Xu, J.; Xue, F.; Guan, E.; Xu, X. Tincr expression is associated with unfavorable prognosis in patients with hepatocellular carcinoma. *Biosci. Rep.* 2017, 37. [CrossRef] [PubMed]

185. Cao, S.W.; Huang, J.L.; Chen, J.; Hu, Y.W.; Hu, X.M.; Ren, T.Y.; Zheng, S.H.; Lin, J.D.; Tang, J.; Zheng, L.; et al. Long non-coding rna ubc2cp3 promotes tumor metastasis by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. *Oncotarget* 2017, 8, 65370–65385. [CrossRef] [PubMed]

186. Li, T.; Xie, J.; Shen, C.; Cheng, D.; Shi, Y.; Wu, Z.; Deng, X.; Chen, H.; Shen, B.; Peng, C.; et al. Upregulation of long noncoding rna zeb1-as1 promotes tumor metastasis and predicts poor prognosis in hepatocellular carcinoma. *Oncogene* 2016, 35, 1575–1584. [CrossRef] [PubMed]

187. Zhang, S.G.; Li, Y.F.; Zhao, N.N.; Lai, C.C.; Cheng, S.J.; Yan, J.; Zhang, P.; Wang, Z.; Wang, X.L.; Yang, P.H. Decreased expression of long non-coding rna loc728290 in human hepatocellular carcinoma. *Oncol. Lett.* 2017, 14, 4551–4556. [CrossRef] [PubMed]

188. Tu, Z.Q.; Li, R.J.; Mei, J.Z.; Li, X.H. Down-regulation of long non-coding rna gas5 is associated with the prognosis of hepatocellular carcinoma. *Int. J. Clin. Exp. Pathol.* 2014, 7, 4303–4309. [PubMed]

189. Wang, X.; Sun, W.; Shen, W.; Xia, M.; Chen, C.; Xiang, D.; Ning, B.; Cui, X.; Li, H.; Li, X.; et al. Long non-coding rna dilc regulates liver cancer stem cells via il-6/stat3 axis. *J. Hepatol.* 2016, 64, 1283–1294. [CrossRef] [PubMed]

190. Lv, L.; Chen, G.; Zhou, J.; Li, J.; Gong, J. Wt1-as promotes cell apoptosis in hepatocellular carcinoma through down-regulating of wt1. *J. Exp. Clin. Cancer Res.* 2015, 34, 119. [CrossRef] [PubMed]

191. Morris, L.G.; Chan, T.A. Therapeutic targeting of tumor suppressor genes. *Cancer* 2015, 121, 1357–1368. [CrossRef] [PubMed]

192. Wahlestedt, C. Targeting long non-coding rna to therapeutically upregulate gene expression. *Nat. Rev. Drug Discov.* 2013, 12, 433–446. [CrossRef] [PubMed]

193. Tang, S.; Tan, G.; Jiang, X.; Han, P.; Zhai, B.; Dong, X.; Qiao, H.; Jiang, H.; Sun, X. An artificial Incrna targeting multiple mirnas overcomes sorafenib resistance in hepatocellular carcinoma cells. *Oncotarget* 2016, 7, 73257–73269. [CrossRef] [PubMed]

194. Yuan, S.X.; Wang, J.; Yang, F.; Tao, Q.F.; Zhang, J.; Wang, L.L.; Yang, Y.; Liu, H.; Wang, Z.G.; Xu, Q.G.; et al. Long noncoding rna dancr increases stemness features of hepatocellular carcinoma by derepression of ctnnb1. *Hepatology* 2016, 63, 499–511. [CrossRef] [PubMed]

195. Chen, F.; Li, Y.; Feng, Y.; He, X.; Wang, L. Evaluation of antimitastatic effect of Incrna-atb sirna delivered using ultrasound-targeted microbubble destruction. *DNA Cell Biol.* 2016, 35, 393–397. [CrossRef] [PubMed]

196. Gutschner, T.; Hammerle, M.; Diederichs, S. Malat1—A paradigm for long noncoding rna function in cancer. *J. Mol. Med.* 2013, 91, 791–801. [CrossRef] [PubMed]

197. Pulido-Quetglas, C.; Aparicio-Prat, E.; Arnan, C.; Polidori, T.; Hermoso, T.; Palumbo, E.; Ponomarenko, J.; Guigo, R.; Johnson, R. Scalable design of paired crispr guide rnas for genomic deletion. *PLoS Comput. Biol.* 2017, 13, e1005341. [CrossRef] [PubMed]

198. Tsai, M.-C.; Spitale, R.C.; Chang, H.Y. Long intergenic non-coding rnas—new links in cancer progression. *Cancer Res.* 2011, 71, 3–7. [CrossRef] [PubMed]

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