Review

Function of the Long Noncoding RNAs in Hepatocellular Carcinoma: Classification, Molecular Mechanisms, and Significant Therapeutic Potentials

Ahmad Khan and Xiaobo Zhang *

College of Life Sciences, Zhejiang University, Hangzhou 310058, China
* Correspondence: zxb0812@zju.edu.cn; Tel.: +86-571-88981129

Abstract: Hepatocellular carcinoma (HCC) is the most common and serious type of primary liver cancer. HCC patients have a high death rate and poor prognosis due to the lack of clear signs and inadequate treatment interventions. However, the molecular pathways that underpin HCC pathogenesis remain unclear. Long non-coding RNAs (lncRNAs), a new type of RNAs, have been found to play important roles in HCC. LncRNAs have the ability to influence gene expression and protein activity. Dysregulation of lncRNAs has been linked to a growing number of liver disorders, including HCC. As a result, improved understanding of lncRNAs could lead to new insights into HCC etiology, as well as new approaches for the early detection and treatment of HCC. The latest results with respect to the role of lncRNAs in controlling multiple pathways of HCC were summarized in this study. The processes by which lncRNAs influence HCC advancement by interacting with chromatin, RNAs, and proteins at the epigenetic, transcriptional, and post-transcriptional levels were examined. This critical review also highlights recent breakthroughs in lncRNA signaling pathways in HCC progression, shedding light on the potential applications of lncRNAs for HCC diagnosis and therapy.

Keywords: hepatocellular carcinoma; lncRNAs; mechanisms; biomarker

1. Introduction

Cancer, a major public health issue and one of the world’s lethal illnesses [1–6], is a multifaceted disorder characterized by uncontrolled cellular growth through genetic variations, epigenetic changes, chromosomal rearrangements, and amplification [7–9]. Various cancers have been linked to increased causes of death and mortality, despite the best efforts of experts to conduct comprehensive investigations to develop more effective therapeutic techniques [10,11]. As a consequence, finding effective screening tools, diagnostic biomarkers, and more effective treatment approaches to increase tumor patients’ long-term survival and treatment rates is essential [12–14].

Hepatocellular carcinoma (HCC), a severe specific type of primary liver cancer [15], accounts for 75–85% of cases of death [16–20]. The low survival rate of HCC is due to asymptomatic initiation in premature stages and loss of optimum treatment period after diagnosis in middle or late stages [17]. Hepatitis B or C virus infection, aflatoxin B1, drugs, alcohol, and metabolic diseases are the most common risk factors for HCC [21–25]. Moreover, there are a few uncommon diseases that increase HCC risks, including alpha1-antitrypsin deficiency (A1AT), tyrosinemia, and Wilson disease. Tyrosinemia is caused by deficiency of fumarylacetoacetate hydrolase, whereas Wilson’s disease is caused by a mutation in the ATP7B gene. All of these are complex multifactorial diseases that cause hepatotoxicity via various mechanisms, which can eventually lead to cirrhosis and HCC [24].

The initiation and persistence of HCC are complicated and are influenced by multiple variables [26,27]. HCC is associated with high levels of tumor growth, postoperative
relapse, and chemo resistance [28–32]. Hepatic fibrosis, a wound-healing condition that involves the dysregulation of extracellular matrix proteins and alteration of normal hepatic architecture, is a significant risk factor for HCC [33–35]. The regulatory mechanisms involved in HCC are still hot topics [36,37]. HCC progression is a complex mediated through accumulation of genetic and epigenetic modifications [38,39], accumulating the necessary amount of genetic and epigenetic variations, leading to the formation of dysplastic foci and nodules, eventually progressing into HCC (Figure 1). To elucidate the HCC progression, landscape, and biology, a complete transcriptome study of the specimens demonstrating diverse disease stages may offer a higher-resolution view of the essential mechanisms of progression [40]. Nonalcoholic fatty liver disease (NAFLD) has been increasing in prevalence and is defined as excessive fat accumulation in the liver and steatosis presence in >5% of hepatocytes [41]. NAFLD can develop to nonalcoholic steatohepatitis (NASH), with inflammation and ballooning with or without fibrosis. NASH further develops to liver cirrhosis in a significant proportion of the patients and eventually progresses into HCC [41]. Generally, NAFLD HCC patients have poor prognosis and are associated with a more progressive stage of the disease [42]. Improved control of virus C illnesses and latent liver cancer has resulted in an increasing number of patients with restored liver function in response to cirrhosis [43]. Systemic chemotherapy, molecule-targeted therapy, trans catheter artery chemoembolization, and immunotherapy are the most common and effective treatments [27].

![Figure 1](image_url)

Figure 1. Genetic alterations in HCC. After gaining necessary genetic and epigenetic variations, cirrhosis develops into dysplastic foci and nodules to form HCC.

To formulate new diagnostic and therapeutic approaches against HCC and to enhance the prognostic value of diagnosed patients, it is important to reveal the relationship among signs, symptoms, and molecular alterations [44]. Advances in biomedical technology to date, such as live transplantation, surgical excision, and radiofrequency ablation, has increased the 5-year survival rates of HCC patients [45–47]. Additional molecular mechanisms and the development of reliable biological indicators for HCC detection are critical at the initial stage of HCC development [26,48–52].

Carcinogenesis is frequently caused by abnormal expressions of genes [53,54]. Recent evidence suggests that RNA processing has been consistently changed in cancer [55–57], revealing the critical role of RNA in tumor genesis and cancer development [54,58]. The long noncoding RNAs (lncRNAs) are mainly categorized according to their positional relationship with adjacent coding genes [59]. Several reports have been published in the scientific literature, highlighting a potential role for lncRNAs in tissue pathophysiology and development [20,49,60,61]. Evidence has shown that lncRNAs are mostly dysregulated as tumor suppressors in various cancers [20,62], and many lncRNAs are intricately linked to the progression of cancer, including HCC [25,63–67], signifying that lncRNAs are potential therapeutic targets in HCC [68].

In this review article, we present an overview of the existing knowledge on lncRNAs in HCC progression and analyze their mechanisms in the cancer phenotype. We also discuss the prospective application of lncRNAs as prognostic and therapeutic targets for HCC patients with future prospective to recognize diverse mechanisms of lncRNAs in HCC.
2. Characteristics and Classification of RNAs

RNA sequencing technology has identified more than one hundred thousand (100,000) distinct RNA molecules of mammalian species [69–71]. Coding RNAs and noncoding RNAs (ncRNAs) are the two types of RNAs [72,73]. Based on the length of transcripts, ncRNAs can be divided into two classes (small ncRNAs and long ncRNAs). The miRNAs (microRNAs), snRNAs (small nucleolar RNAs), PIWI-interacting RNAs, and other endogenous RNAs are examples of small ncRNAs [53,54], which have a nucleotide number of less than 200 [74]. LncRNAs (long noncoding RNAs), lincRNAs (long intergenic noncoding RNAs), NATs (natural antisense transcripts), T-UCRs (transcribed ultra-conserved regions), long enhancer ncRNAs, and noncoding repeat sequences, as pseudo genes, are examples of long ncRNAs with more than 200 nucleotides (Figure 2) [74].

![Figure 2. Noncoding RNAs classified into small noncoding RNAs and long noncoding RNAs. Small noncoding RNAs include miRNAs (microRNAs), snRNAs (small nucleolar RNAs), PIWI-interacting RNAs, and endogenous small interfering RNAs. Long noncoding RNAs (lncRNAs) are composed of sense, antisense, bidirectional, enhancer, intergenic, and intronic lncRNAs based on their localizations as compared to the nearby protein-coding genes. LncRNAs could function as competing endogenous RNAs (ceRNAs).](image)

Small ncRNAs were first identified by exogenous RNA interference (RNAi) in plants and nematodes and were found to exist endogenously, functioning mostly as gene regulators through pairing to the target genes, hence directing their post-transcriptional activities in animals and plants [75]. It is well known that ncRNAs account for the majority of the human transcriptome, including miRNAs, IncRNAs, and circRNAs. MicroRNAs are single-stranded RNAs and participate in a series of physiological and pathological processes by facilitating post-transcriptional regulation of the target genes [76]. Numerous abnormally expressing miRNAs are associated with HCC initiation and progression [76,77]. Various studies have exposed the biological roles of IncRNAs as regulators of transcription, modulators of mRNA processing, and organizers of nuclear domains [76–79]. Compared with linear RNAs, circRNAs are more stable to exonuclease and ribonuclease, with conserved structure and stable sequence and tissue specificity [78,79]. It has been shown that circRNAs play significant pathophysiologial roles in the existence and development of alcoholic liver injury; hepatic fibrosis, HCC, and other liver diseases. CircRNAs have also been confirmed to exert effects with respect to regulation of cellular metabolisms of HCC [78].

For example, small ncRNAs, siRNAs, and/or miRNAs, have been well characterized [74,80,81]. LncRNAs, in comparison with small ncRNAs, are less understood in terms of their mechanisms and functions [74]. The prevalence of various forms of RNAs is altered...
in most eukaryotic cells. Ribosomal RNAs are responsible for approximately 80–85% of cellular RNA mass, accompanied mostly by tRNAs and mRNAs [82]. Although ncRNAs are not translated into proteins, they play important roles in the physiological functions of organisms [69,83]. In particular, IncRNAs are essential controllers of chromatin dynamics, growth, differentiation, and gene development [20,84]. At present, with the advancement of high-throughput sequencing and DNA tiling array technology, a number of investigations are concentrating on ncRNAs [85–87]. The functions of ncRNA-encoding peptides and proteins have prospective applications in cancers, with some potential challenges [88].

3. Characteristics and Functions of lncRNAs

Relying on the genetic position concerning neighboring protein-coding genomes, IncRNAs have been classified into five categories (Figure 2) [89,90]. The first category is the sense IncRNAs, which interact with protein coding gene. The specific genes on the sense strand are transcribed from the sense strand of the genome concerning protein-coding genes, such as COLDAIR [9,91]. The second group of IncRNAs is the antisense IncRNAs, which are transcribed from the antisense strand of the genome, such as IncRNA ANRIL. These IncRNAs interact with one and sometimes most exons of the protein-coding genome upon its reverse strand [9,91]. The third category is the bidirectional IncRNAs; for example, the IncRNA-enhancing eNOS (endothelial nitric oxide synthase) expression (LEENE) and IncRNA HCCL5, in this category the IncRNA and a protein-coding gene are located on the opposite sides of the genome and are derived from different directions of protein-coding genes [9,17,91]. The fourth intronic IncRNAs are generated entirely within the introns of the protein-coding genes, with no exons overlapping [9,91]. The fifth group of intergenic IncRNAs is found nearby almost no protein-coding genes [9,17,91–94].

LncRNAs can also be classified according to their targeting mechanisms, including signal, decoy, and scaffolds [9,95]. The lncRNA signal can control cell-specific expression in response to numerous stimuli [9,96]. Some IncRNAs function as decoys to negatively regulate target expression, acting as a molecular basin to dilute the cellular level of protein or other miRNAs [95,97]. Some lncRNAs act as scaffolds to a prearranged telomerase complex by accumulating modular binding sites for telomeric regulatory proteins [17,95]. Many investigations have found that IncRNAs mainly interact with miRNAs to execute their biological functions as competing endogenous RNAs (ceRNAs) [28,98,99]. In turn, miRNAs may directly interact with IncRNAs to silence their expressions. Various lncRNAs are difficult to classify in specific classifications [20,28,49,98,99].

The amount of illustrated lncRNAs has changed dramatically in recent years due to sequencing technologies. More than 50,000 lncRNAs have been described, with almost 58,000 lncRNA transcripts assembled in the Encyclopaedia of DNA Elements (ENCODE), and Project Consortium (GENCODE release 36), with 27,919 lncRNAs of humans and the elevated 50 ending in the Functional Annotation of Mammalian Genome (FANTOM5) [25]. There may be more than 15,000 lncRNAs in the human genome. Their expression is highly regulated by transcription factors and methylated lysines, such as mRNAs [100]. A more specific definition of lncRNA is an RNA molecule that cannot code for proteins and has a length of 200 bp to 100 kbp [9,54]. LncRNAs can have an open reading frame of more than 100 amino acids [101]. Polypeptides with fewer than 100 amino acids can be useful in species and are not considered byproducts of authoritative proteins [101]. RNA polymerase II transcribes the largest portion of lncRNAs, which is most often capped and polyadenylated [102], unlike mRNAs, which are highly conserved between humans and rodents [103].

LncRNAs have species- and tissue-specific expression patterns, which may relate to their key roles [73,103]. The three fundamental levels of IncRNA structure and sequence composition are primary, secondary, and tertiary [104]. The structural properties of IncRNAs assist researchers to improve their understanding of the chemical mechanisms that enable lncRNAs to perform their roles. Secondary structures of IncRNAs typically include duplexes, internal loops, junctions, and bulges, which can serve as protein-binding sites and
are important components of operational lncRNAs, such as Watson-Crick complementary base pairing and stability of unpaired locations [105,106]. Terminal differentiation-induced noncoding RNA is conserved at its 5’ ends across vertebrates other than mice [107], but the 3’ end indicates the difference in sequence in vertebrates [73,108]. The triple helix at the 3’ ends of lncRNAs can stabilize the poly (A) tail-lacking lncRNAs. It also contributes to the structure of lncRNAs by providing interactive interfaces and preserving lncRNA stabilization [29,109].

LncRNAs have been found to play important roles not only in the normal biological functions of cells but also in the pathophysiological behaviors of various illnesses. Particularly tumors, through chromosome alteration, splicing, transcription factor activation, mRNA fragmentation, and other mechanisms (Figure 3) [25,29,110–116]. LncRNAs are considered to have significant regulative functions in pathogenesis with respect to the development of various human diseases. Proliferation, apoptosis, differentiation, and tumor growth are only a few examples that describe the functions of lncRNAs [117–119]. LncRNAs are sometimes expressed abnormally in tumors [120]. They can function as oncogenes or tumor suppressor drivers [88,110,112]. Compared to protein-coding genes, lncRNA modifications are particular to tumors. This particularity provides lncRNAs with important diagnostic biomarkers [99,121–125]. In HCC, some lncRNAs play important controlling roles in the growth and metastasis of HCC [126–128] by halting the cell cycle, preventing cell death, and enhancing DNA injury repair. LncRNAs can perform significant functions with respect to chemo- and radio resistance of tumors [129], which could be used to identify possible targets and explore novel strategies for chemo- and radiotherapy in HCC [20,28,130].

Figure 3. The functions of lncRNAs. LncRNAs perform a key function in gene regulation via a variety of processes, including transcriptional regulation, post-transcriptional regulation, and other mechanisms.
4. Cancer-Associated lncRNAs

In comparison to healthy controls, most lncRNAs are found in patients with malignant tumors [25,49]. Due to high expression levels of lncRNAs in tumors, lncRNAs can be found in body fluids such as blood, saliva, and plasma, suggesting that circulating lncRNAs may be employed as non-invasive tools for diagnosis of various cancers, including HCC [25,49,131,132].

A number of mechanisms involving genetic, as well as environmental, changes are involved in transforming normal cells into cancer cells, with which they share some common characteristics [133–135]. To alter the cell physiology and regulate cancerous development, healthy cells must introduce new capabilities. Biochemical capabilities that are gained during the multiphase production of human tumors are considered the hallmarks of cancer [135]. Maintaining proliferative signaling, escaping progression suppressors, avoiding apoptosis, initiating angiogenesis, and inducing invasion and metastasis are all examples of such alterations [136]. LncRNAs are related to nearly all cancer hallmarks [90,137].

The manipulation of diverse mechanisms is responsible for the effect of such lncRNAs in cancer hallmarks [71,135,138].

A strong relationship between tumors and lncRNAs has been identified [139]. Differential expression of lncRNAs in nearby normal and tumor tissues, as well as in normal and malignant cell lines, makes lncRNAs potential cancer biomarkers [67,125,139]. Because lncRNAs can change cell growth by modifying expressions of genes, dysregulated expressions of lncRNAs may contribute to cancer pathophysiology [74]. In such situations, the changes within lncRNAs are linked to cancer. LncRNAs can be used as potential therapeutic biomarkers [140–146]. Cancer-causing and anticancer lncRNAs are two types of lncRNAs in tumors (Table 1). Due to their ability to interact with molecules of DNA, protein, and RNA, as well as the ability to alter many cancer hallmarks, lncRNAs play important roles in tumor progression [73,138,141,142].

More than 8000 lncRNAs have been discovered in cancer cells [151,152]. Owing to their considerable quantity and specificity of expression, such lncRNAs are effective biomarkers and strong therapeutic targets (Table 1).

### Table 1. Biological functions of lncRNAs in cancers.

| LncRNAs                | Target Pathways/ Mechanisms                                                                 | Biological Functions in Cancers                                                                 | Type of Cancer          | Reference |
|------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------|-----------|
| LncRNA 00665 SNHG20 UCA1 VCAN-AS1 LINC01559 SNHG4 TTN-AS1 LINC00673 RAIN PVT1 FOXD2-AS1 LINC0052 | miR-224-5p/VMA21 miR-345-5p/RACGAP1 miR-148a/ROCK1 miR-206 p53 YAP ZIC5 miR-515-5p/MARK4/Hippo RUNX2 Smad3/miR-140-5p miR-185-5p miR-608/EGFR | Promoting proliferation, invasion, and migration of cancer cells | Melanoma [146] |          |
| ADAMTS9-AS2 ENST00000489676 OSER1-AS1 TCONS-00020456 | Smad2/PKCa CDH3 MIR-922 miR-372-3p/Rah23 | Suppression of proliferation and invasion of cancer cells | Glioblastoma cancer [164] Esophageal cancer [165] Thyroid cancer [166] Hepatocellular carcinoma [167] |          |
| HOXA-AS3 UCA1, H19 | HOXA3 FUS/MDM2 5-fluorouracil | Prognosis and efficacy | NSCL cancer [168] Glioblastoma cancer [169] Rectal cancer [170] |          |
| SNHG12 HOTAIR SNHG11 | | Potential biomarkers | Pan-cancer [171] Breast cancer [172] Colorectal cancer [173] |          |
5. LncRNAs in HCC

LncRNAs perform important functions with respect to the induction and development of HCC [69], with increased expression levels of 27 kinds of lncRNAs. Actin filamentin-1 antisense RNA (AFAP-AS1), zinc finger E-box binding homeobox 1-antisense 1 (ZEB-1-AS1), and HOX transcript antisense intergenic RNA (HOTAIR) are correlated with poor prognosis of HCC, whereas reduced expressions of 18 lncRNAs, including growth arrest-specific transcript 5 (GAS5), XIST, and maternally expressed gene 3 (MEG3), are correlated with an even worse prognosis of HCC [28]. By inducing the invasion and initiation of metastatic spread of HCC cells, IncRNA SNHG8 (small nucleolar RNA host gene 8), LINC00052, IncRNA W42 [67], LINC01225, PITFNA antisense RNA 1 (PITFNA-AS1), and ZEB1-AS1 exhibit oncogenic characteristics [120,174,175]. IncRNA-hPVT1, AFAP1-AS1, XIST, HOXA cluster antisense RNA 2 (HOXA-AS2), HOST2, and cervical carcinoma high-expressed IncRNA 1 (CCHE1) are examples of lncRNAs that can cause and promote cell proliferation, suppressing apoptosis of HCC cells [28,176]. IncRNA SNHG17 is considerably upregulated in tissues and cell lines of HCC and associated with large tumor size, poor differentiation, and the presence of vascular invasion [177]. The IncRNA TUG1-miR328-3p-SRSF9 mRNA axis works as a unique ceRNA regulator axis related to HCC malignancies [178]. LINC01194 is upregulated in the HCC cell line and controls the proliferation and migration of HCC cells by interacting with the miR-655-3p/SMAD5 axis, which provides new biomarkers for HCC diagnosis and treatment [179]. The increasing appearance of lncRNAs in HCC is assumed to be oncogenic, and lncRNAs with low expression in HCC are considered to be tumor-suppressor lncRNAs [28,99]. Those characteristics may be effective as potential therapeutic targets for HCC, especially for patients who may have already developed resistance to chemotherapeutic drugs [28,30–32,180]. The functions of lncRNAs in HCC are to promote cancer cell growth and invasion, repress cancer cell growth and invasion, estimate prognosis and efficacy, and act as potential biomarkers (Table 2).

Table 2. Biological functions of lncRNAs in hepatocellular carcinoma (HCC).

| LncRNAs     | Target Pathways/Mechanisms | Biological Functions in HCC                  | Reference   |
|-------------|---------------------------|---------------------------------------------|-------------|
| LncRNA CYTOR| miR-125b/SEMA4C           | Promoting proliferation, invasion, and migration of cancer cells | [181]       |
| DNAJC3-AS1  | miR-27b                   |                                             |             |
| LncRNA SNHG8| miR-542-3p and miR-4701-5p|                                             |             |
| MCM3AP-AS1  | miR-194-5p/FOXA1 axis     |                                             |             |
| RNA LINC00908| Sox-4                    |                                             |             |
| SNHG15      | miR-490-3p/histone deacetylase 2 axis |                 |             |
| G1HCG       | miR-200b/a/429 PPAR gamma |                                             |             |
| ANRIL       | EZH2 protein Target gene DNA |                                           |             |
| TUG1        | EZH2 protein Target gene DNA |                                           |             |
| UFC1        | β-catenin mRNA HuR protein |                                             |             |
| MALAT1      | miR-143-3p                |                                             |             |
| ICR         | ICAM-1 mRNA               |                                             |             |
| ZFAS1       | miR-150                   |                                             |             |
| MV1H        | PGK1 protein              |                                             |             |
| CASC9       | HNRNPL protein            |                                             |             |
| LncCAMTA1   | CAMTA1                    |                                             |             |
| Ftx         | PPAR gamma                |                                             |             |
| ATB         | Autophagy-related protein  |                                             |             |
| PDPK2P      | PDK1/AKT/Caspase 3        |                                             |             |
| HOXD-AS1    | SOX4                      |                                             |             |
| HIS         | ERK&AKT/GSK-3b            |                                             |             |
| HOTAIR      | OGF, miR-122, SETD2       |                                             |             |
| LINC0161    | Activate ROCK2, miR-90-3p |                                             |             |
| DLGAP1-AS1  | miR-26a/b-5p/IL-6/JAK2/STAT3|                                            |             |
| 91H         | IGF2                      |                                             |             |
| MYLK-AS1    | miR-424-5p/E2F7 & activating VEGFR-2 |               |             |
| Linc-ROR    | DEPDCl                    |                                             |             |
| HULC        | HULC/miR-383-5p/VAMP2     |                                             |             |

Table 2. Biological functions of lncRNAs in hepatocellular carcinoma (HCC).
The biosynthesis of lncRNAs is similar to that of protein-coding transcripts. Epigenetic modification, transcription complex recruitment, and RNA processing are all important activities that influence lncRNA production. Aberrant lncRNA biosynthesis is related to the pathogenesis of various diseases, including HCC. In comparison to non-cancerous liver tissues, high-throughput techniques such as RNA sequencing and microarray have characterized distinct lncRNA expression patterns within HCC tissues, demonstrating that lncRNA production is dysregulated throughout HCC progression [189,239]. Aberrant biogenesis activities include epigenetic activation of tumor suppression. LncRNA transcriptional repression through certain tumor-suppressive transcription factors, special processing patterns that associate lncRNAs with oncogenic activities and the binding of lncRNAs with miRNAs affect lncRNA stability [195].

5.1. Regulation and Modification of Chromatin by lncRNAs

Increasing evidence has shown that lncRNAs can perform a variety of functions, including epigenetic modifications in HCC [240,241] (Figure 4a). Methylation of histone and DNA is an essential epigenetic modulation that regulates gene expressions [24,242–244]. Inappropriate chromatin alterations of lncRNA genes, such as methylation of DNA histone modification, have generally been described throughout HCC development [245, which

| LncRNAs            | Target Pathways/Mechanisms          | Biological Functions in HCC                      | Reference |
|--------------------|-------------------------------------|--------------------------------------------------|-----------|
| LINC00238          | miR-522/SFRP2/DKK1                  | Suppression of proliferation, invasion, and migration | [213]     |
| TEMT20-A51         | TMEM220/β-catenin                   | Suppression of HCC progression                   | [214]     |
| NBR2               | JNK/ERK                            |                                                   | [215]     |
| IncRNA W5          | GA8                                |                                                   | [216]     |
| GAS8-A51           | miR-10a-5p/NCOR2                    |                                                   | [217]     |
| MIR22HG            | microRNA-575                        |                                                   | [218]     |
| MIR31HG            | miR182/ANGPTL1                      |                                                   | [219]     |
| GAS5               | miR-423-5p                          |                                                   | [220]     |
| FENDRR             | miR301a-5p/FOX1L                     |                                                   | [221]     |
| EPB41L4A-A52       | ENO1                               |                                                   | [222]     |
| TCONS_00006195     | LATS1                              |                                                   | [223]     |
| Uc.134             | MMP2 and 9                         |                                                   | [224]     |
| SVUGP2             | PABPC4 Ubiquitination               |                                                   | [225]     |
| RP11-286H15.1      | Vimentin protein                    |                                                   | [226]     |
| LncRNA-Dreh        | miR-52b                            |                                                   | [227]     |
|                   |                                     |                                                   |           |
| LINC00221          | IncRNA–miRNA–mRNA                   | Prognosis and efficacy                           | [49]      |
| LOC554202          | miR-485-5p/BSG                       |                                                   | [229]     |
| LncRNA DDX11-A51   | miR-195-5p/MACC1                    |                                                   | [230]     |
| RP11-464I1.1       | HNRNPA2B1/NF-KB                     |                                                   | [231]     |
| miR503HG           | Caspase-8/LSH1/H3K9me3              |                                                   | [232]     |
| MALAT1, HOTAIR,    |                                     |                                                   | [82]      |
| MDG                | miR-195/EYA1 axis                   |                                                   | [233]     |
| HOTAIR             |                                     |                                                   |           |
| CTC-297N7.9,       |                                     |                                                   |           |
| CTD-2139B15.2,     |                                     |                                                   |           |
| RP11-589N15.2,     |                                     |                                                   |           |
| RP11-345N15.5, and |                                     |                                                   |           |
| RP11-479G22.8      |                                     |                                                   |           |
| LINC00511          |                                     |                                                   |           |
|                   |                                     |                                                   |           |
| IncRNA W42         | miR-448/ROCK1                       | Potential biomarkers                              | [67]      |
| PTTPNA-A51         |                                     |                                                   | [120]     |
| PVT1, uc002mbe 2 e |                                     |                                                   |           |
| UCA1               |                                     |                                                   |           |
| RP11-486O12.2,     |                                     |                                                   | [234]     |
| RP11-273G15.2,     |                                     |                                                   | [235]     |
| 863K10.7 and       |                                     |                                                   | [236]     |
| LINC01093          |                                     |                                                   | [237]     |
| LRBI               |                                     |                                                   | [238]     |
| ELM01-A51          |                                     |                                                   |           |

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can cause a reduction in repressive lncRNAs of HCC and an increase in cancer-promoting lncRNAs related to HCC [195]. Linc-GALH (Gankyrin-associated LincRNA in HCC), with respect to judgment of HCC metastasis, can promote DNMT1 (DNA methyltransferase1) degradation by enthuising ubiquitination and appearance of Gankyrin (PSMD10) and decreasing HCC methylation [246]. EMT (epithelial-mesenchymal transition) is thought to be essential for tumor metastasis and relapse [247]. The up regulation of linc00441 increases H3K27 acetylation [248]. In contrast, abundantly expressed linc00441 induces DNA methyltransferases 3 alpha (DNMT3A) to methylation, deactivating the neighborhood RB1 gene to induce HCC cell proliferation [195,248]. Significantly increasing lncRNAs has been demonstrated to show their interaction with epigenetic regulator enhancer of zest homolog 2 (EZH2) to stimulate gene expression, influencing HCC metastasis [195].

Figure 4. The roles of lncRNAs in HCC. (a) Regulation and modification of chromatin. (b) Transcriptional activation. (c) Interaction with mRNAs. (d) Sponging of microRNAs. (e) Protein binding and modification. (f) Other mechanisms and pathways of lncRNAs.

5.2. Transcriptional Regulation and Activation

LncRNAs can regulate transcription by binding to promoters of nearby or distinct genes to recruit transcription factors to further regulate transcriptional activation [95] (Figure 4b). LncMAPK6, a mitogen-activated protein kinase 6 (MAPK6) lncRNA, has been abundantly expressed in association with liver tumor development [249]. Its interaction with RNA polymerase II recruits MAPK6 promoter, thus activating MAPK6 transcription [249]. YAP, c-Myc, and catenin are the oncogenic transcription factors that are highly
expressed in HCC [250]. These transcription factors enable lncRNAs to be involved in necroptosis and cell cycle arrest in HCC, demonstrating that lncRNA transcription is critical throughout HCC [195,251].

5.3. Interaction with mRNAs

Certain lncRNAs affect the stabilization and translating procedures of mRNAs (Figure 4c). Through intermodulation with lncRNA-mRNA, lncRNAs activated by transforming growth factor-β (lncRNA-ATB) regulate and maximize mRNA of interleukin-11, encouraging the proliferation of circulated HCC cells in distant parts of the body [252]. Only a few primary lncRNA transcripts are affected by the exon-insertion scenario. During the formation of HCC, such process modules can play an oncogenic role. The splicing factor muscle blind-like 3 (MBNL3) was found to be overexpressed throughout the fetal liver in HCC tissues that were lacking in adults, causing LncRNA PXN-AS1 (PXN antisense RNA 1) exon 4 inclusions. Due to the splicing alteration, the lncRNA PXN-AS1 is able to interact with PXN mRNA in HCC [253]. HCC progression and metastatic spread are inhibited through LncRNA LINC01093 specific to the liver, which also acts as protein scaffolding on the way to induce insulin-like growth factor mRNA binding protein1 (IGF2BP1) and to further promote the degradation of Glioma-associated oncogene homologue 1 (GLI1) mRNA [254].

5.4. Sponge of MicroRNAs

LncRNAs can function as miRNA sponges, reducing deficit miRNA activity (Figure 4d). LncRNAs have been used as an extra layer of post-transcriptional regulation of gene expression [234,255]. Numerous lncRNAs have been implicated in controlling the expression of genes by interfering with miRNAs and prohibiting particular miRNAs from binding with the target mRNAs [256–259]. The HCC-associated lncRNA (HCAL) stimulates HCC metastasis by binding miR-196a, miR-196b, and miR-15a [260]. LncRNAMALAT1 (metastasis-associated lung adenocarcinoma transcription 1) can promotes migration and invasion of HCC via sponging of miR-204 [261]. In patients with HCC, a sufficient proportion of lncRNA HOXD-AS1 (HOXD cluster antisense RNA 1) expression is related to the high tumor nod [200,262]. HOXD-AS1 conservatively binds with miR-130a-3p, which can inhibit SOX4 (sex-determining region Y-related high-mobility group box transcription factor 4) to miRNA intermediated destruction, stimulating the expression of EZH2 and MMP2 to promote HCC metastasis [200]. HOXD-AS1 can also regulate the expression of Rho GTPase-activating protein 11A through highly competitive interaction with miR-19a, resulting in HCC tumor growth [262]. LncRNA HULC (highly upregulated in liver cancer) enhances HCC progression and metastasis by increasing epithelial–mesenchymal transition (EMT) progression in the miR-200a-3p/ZEB1 signaling pathway [263]. LncRNA MALAT1 enhances HCC development by sponging miR-143-3p to control ZEB1 expression [190]. MiR-34a has been reported to bind specifically with lncRNA-UFC1, causing its half-life to be reduced, thus preventing HCC growth mediated by lncRNA-UFC1 [189]. Because miRNAs are downregulated generally during HCC production, oncogenic lncRNAs are likely to be reactivated, leading to abnormal lncRNA expression profiles [195].

5.5. Protein Binding and/or Modification

Except for binding with miRNAs, lncRNAs are subject to biochemical processes that include protein modification (Figure 4e). Many reports have suggested that lncRNAs perform roles in protein phosphorylation modulation [264,265]. LncRNA TSLNC8 (tumor-suppressive lncRNA on chromosome 8p12) inhibits phosphorylation of STAT3 (signal transducer and activator of transcription 3) in HCC by inactivating the IL-6/STAT3 signaling pathway [264,265]. RNA-binding proteins (RBPs) have been discovered to manipulate lncRNA stabilization via physical interaction [266]. IGF2BP1/3 (insulin-like growth factor 2 mRNA-binding protein 1/3) is an RBP that binds and remains stable with long intergenic non-protein coding RNA 1138 (LINC01138) on its 220-1560-nt fragment, which is
essential for HCC invasion progression [266]. Furthermore, lncRNA UFC1 can interact with another RBP, called human antigen R (HuR), via its fragment (1102-1613-nt), which is required for HCC [189]. These findings indicate that RBP-controlled lncRNA decay occurs to compensate for unusual lncRNA biogenesis in HCC.

Some reports have shown that lncRNA HNF1A-AS1 (HNF1A antisense RNA 1) prevents HCC invasion and spread by directly attaching to the C terminal of SHP-1 (SH2-containing protein tyrosine phosphatase 1), thereby stimulating phosphatase [267]. The effect of lncRNAs on the expression of genes by modification of protein is not restricted to target protein phosphorylation. In HCC, LINC01138 can exert oncogenesis behavior by interfering with arginine methyltransferases 5 (PRMT5), strengthening the stability of protein by stopping ubiquitin degradation [266]. LncRNA miR503HG comes into contact mostly with heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1) and represses metastatic tumor repression by controlling the ubiquitination status of hnRNPA2B1 [231]. By hindering CUL4A (cullin4A) intermediated ubiquitination and degradation of LATS1 (long-acting thyroid stimulator 1) within the cytoplasm, lncRNA uc.134 can disrupt HCC invasion and metastasis [224]. In particular, lncRNAs affect protein acetylation, which is an essential post-translational modification of protein control degradation [268]. Histone deacetylase 3 (HDAC3) governs lncRNA-LET (low expression in the tumor), which may be implicated in hypoxia-induced cell death [268]. LncRNA-LET inhibits Nuclear Factor 90 (NF90) protein degradation but is essential for hypoxia-induced cellular penetration [268]. LncRNAs can have a variety of effects on the formation of HCC.

5.6. Other Mechanisms and Pathways of lncRNAs in HCC

LncRNAs have significant effects on transcriptional, as well as post-transcriptional, regulation, relying on their subcellular localization [25]. Trans-acting nuclear lncRNAs control gene transcription epigenetically by interacting with tissue-specific chromatin modifications, such as histone-modifying complexes and DNA methyltransferases [269] (Figure 4f). Certain lncRNAs manage to sustain nuclear architecture through the scaffolding structure of the DNA-RNA-protein framework at unique sites [270,271]. Due to the genomic similarity toward their targets, the cis-acting lncRNAs may become capable of controlling gene expression inside the locus with an allele-specific method [270,271].

In cancer, lncRNAs are involved in tumor proliferation and metastasis signaling pathways [272]. The crucial mediator throughout the development of cancer is significant in HCC development and progression [273,274]. According to increasing prevalence, triggering of the catenin cascade can play a vital role in HCC [275]. Several lncRNAs play key roles in the stimulation and repression of the catenin pathway in HCC [271]. Overexpression of long intergenic non-protein-coding RNA 00210 (LINC00210) in liver tumor tissues interferes with catenin beta-interacting protein 1 (CTNNB1) to block the inhibitory function of CTNNB1P1 in catenin stimulation and enhance the association of catenin and TCF/LEF (T-cell factor/lymphoid enhancer factor family) complex, thereby triggering catenin signaling and liver tumor growth [276]. Some other pathways seem to be lncRNA-activated through TGF (lncRNA-ATB), further inducing EMT and aggression via highly competitive binding of the miR-200 family but also modulating ZEB1 and ZEB2 [277]. In HCC, lncRNA-HEIH (HCC upregulated EZH2-associated lncRNA), in combination with enhancer of zeste homolog 2 (EZH2), performs very significant roles in G0/G1 arrest, usually requiring suppression of the EZH2 target gene [44]. Higher URHC, upregulated in HCC, can induce cell proliferation and prevent cell death by suppressing the sterile alpha motif and leucine zipper-containing kinase AZK (also known as ZAK (zipper-containing kinase) [278]. Two single nucleotide polymorphisms, rs7763881 within HULC and rs619586 within MALAT1, exist in 1344 HBV-persistent drivers and 1300 HBV-positive HCC patients [279]. Interactions of lncRNAs with some other significant signaling pathways participating in HCC metastasis and growth have been identified [280,281]. Through upregulation of PTTG1 (pituitary tumor-transforming gene 1) to trigger the PI3K/AKT signaling pathway, lncRNA PTTG3P (pituitary tumor-transforming 3 pseudo gene) enhances HCC development, as well as
tumor growth [282]. HCC metastasis-promoting linc-GALH is known to be implicated in the regulation of the AKT signaling pathway [246,283]. Linc00974 also encourages the growth and migration in HCC by interfering in KRT19 (Keratin 19) [284]. LncRNA uc.134 stimulates hippo kinase signaling by preventing CUL4A from moving to the cytoplasm from the nucleus [224]. These findings illustrate that lncRNAs can function as mediating variables of the oncogenesis signaling pathways such, as Hippo kinase, Wnt, JAK/STAT, and PI3K/AKT. Although it is still unknown how lncRNAs affect HCC development, the relationship between lncRNAs and signaling pathways has paved the way for both the identification of innovative diagnostics and therapy in HCC [244,285].

6. Importance of Gene Expression Regulation in HCC Progression

HCC onset and development can be assessed using global genomic research due to genetic alterations that alter the expression of thousands of cancer-related genes. Hepatocarcinogenesis and the molecular pathways that underpin complicated clinical features have been studied using HCC gene regulation analysis [286,287]. The development of phenotypic expression gene profiling could revolutionize how HCC is identified and treated [286,287]. Complementary DNA microarrays for analysis of global gene expression, single-nucleotide polymorphism genotyping for identification of mutations that significantly alter gene expression and abnormal protein activities, chromosome instability mapping, and DNA–protein interactions are all widely accepted genomic data analysis technologies. In addition, several functional groups are used to develop new HCC serum diagnostic markers and therapy targets [287]. Although cancer cells disrupt EMT, it is a straightforward physiological activity that involves development and wound repair. In HCC, EMT effectors, such as fibronectin, cadherins, integrins, and vimentin, have been found to be altered, allowing for a much more mesenchymal phenotype [39,288–290]. In HCC, transcription factors that promote EMT, such as slug, twist, Snail, and Zeb, are upregulated [39,288–290]. Furthermore, the majority of studies on miRNAs, exosomes, lncRNAs, and regulatory cellular processes have been associated with EMT and found to be important in the advancement of HCC [39,288–290]. During primary HCC, the hypoxic microenvironment is significantly related to cancer development and angiogenesis [291]. Cancer cells interact with the aberrant microenvironment, ECM, cytokines, and chemokines and elevate the growth factors, resulting in enhanced angiogenesis [292,293]. Hepatic cells play a significant role in hepatocarcinogenesis, and the transformation of all such cells can result in cancer stem cells (CSCs) with various intrinsic factors (genetics and autoimmune diseases) and various extrinsic factors (HBV, HCV, alcohol, and AFBI), accounting for about 70–90% of the conversion of tiny hepatocyte-like progenitor cells into cancer cells [294]. Several potential surface markers of liver CSCs, such as epithelial cell adhesion molecule (EpCAM) [295], CD90 [296], CD133 [297], CD44 [298], and CD13 [299], have been identified. However, an improved understanding as to how molecular categorization and mutational confirmations influence HCC progression is required before it can be used as a targeted therapy in a medical context [296].

7. LncRNAs as Diagnostic and Therapeutic Markers in HCC

In HCC patients who are diagnosed later in the disease process, curative medications are no longer valuable [265]. Currently, ultrasound imaging and alpha-fetoprotein (AFP) analysis are used to diagnose HCC. Ultrasound scanning and testing are recommended in high-risk populations, and patients who undergo increasingly regular imaging have been associated with improved prognosis [300]. Nevertheless, with 47% sensitivity, surveillance imaging is insufficient to detect early-stage HCC [301]. The commonly used HCC biomarker AFP (alpha-fetoprotein) seems to have a sensitivity of 52.9%, as well as a specificity of 93.3%, which can be strengthened when combined with ultrasound imaging [302]. In the absence of HCC, some variables, including HCV infection, have also been reported to increase AFP levels [303]. However, neither ultrasound imaging nor AFP analysis reduces HCC patient mortality [304]. In early HCC, surgical procedures, including resection and liver
transplantation, remain the only therapeutic choices, whereas late-stage HCC is essentially untreatable. To develop the diagnosis and treatment of HCC, new biomarkers and targeted therapies are critically required [305]. Metastasis seems to be a significant factor affecting long-term survival in patients with severe HCC [306].

7.1. LncRNAs as a Potential Biomarker of HCC

Patients with HCC who are diagnosed early have an increased chance of survival. Because of their tissue specificity, lncRNAs are intriguing as biomarkers [265]. It would be more appropriate to use circulating lncRNAs throughout the body fluid instead of some in malignant tissues as non-invasive markers for cancer diagnosis and surveillance [265]. However, most lncRNAs have been shown to exhibit uneven expression levels in some cancers and non-cancerous illnesses, such as cirrhosis and liver damage, resulting in diminished consistency [307]. As a result, combining lncRNAs with other chemicals, such as the well-known HCC biomarker AFP, makes a successful HCC diagnosis considerably more likely. Multiple lncRNAs, for example, UCA1 and WRAP53, in combination with AFP, ensure up to 100 percent responsiveness [307]. Similarly, combining two lncRNAs, PVT1 and uc002mbe.2, along with AFP, has been shown to serve well in the diagnosis of HCC relative to AFP alone [195,308].

As reported, lncRNA ZFAS1 (zinc finger antisense 1) is a new serum diagnostic marker for the detection of HCC [309]. The extracellular vesicle long RNAs (exLRs), which were found only in blood samples of 104 patients with HCC, can effectively distinguish HCC from non-tumor controls [310]. Consequently, a combination of serum exosomal ENSG00000258332.1 and LINC00635 with AFP is a reliable tool for HCC diagnosis [311]. LncRNA associated with micro vascular invasion in HCC (LncRNA MVIH) up regulation has been found to significantly predict persistent relapse in initial HCC patients, indicating that MVIH might be a useful marker for the early detection and individual care assessment of HCC patients [244,312,313]. The combination of XLOC014172, LINC00152, and RP11-160H22.5 could differentiate HCC patients from hepatitis patients [314]. Furthermore, the lncRNA gene polymorphism is important for HCC diagnosis [315].

7.2. LncRNAs as Promising Therapeutic Potentials for HCC

In addition to their potential use as diagnostic biomarkers, lncRNAs have important therapeutic techniques for new treatments of HCC [195]. The base-pairing paradigm RNA-targeting methods are simpler to implement than protein-targeting approaches. Antisense oligonucleotides (ASOs) and RNAi are the most widespread oncogenic lncRNA-targeting techniques for the treatment of HCC [316–319]. The infusion of ASOs, such as MALAT1, inhibits tumor growth in HCC-bearing nude mice [265,276,320]. ASO-mediated linc00210 absence inhibits HCC cell self-renewal and aggression, but knockout of lncRNA CASC9 (cancer susceptibility candidate 9) by RNAi decreases cancer progression in HCC [194,276]. Using precisely constructed siRNAs against lncRNAs is a technique for influencing lncRNA efficiency. The use of artificial lncRNA has been proposed to specifically target many miRNAs and may be a useful approach for resolving Sorafenib resistance in the HCC medication [321].

Discovery of more operative treatments is imperative. Recent findings have shown that a combination of atezolizumab and bevacizumab results in antitumor activity in patients with unresectable HCC [322]. *Taraxacum officinale* (L.) Weber ex F.H. Wigg, a perennial member of the Compositae family, has antitumor properties in HCC cells and has long been conventionally used as Chinese herbal medicine for liver, breast and gallbladder, hepatitis, as well as digestive, diseases [323]. According to the US Food and Drug Administration, the medication for HCC first-line therapies are bevacizumab in combination with atezolizumab, Sorafenib, and Lenvatinib; the second-line therapies include cabozantinib, pembrolizumab, ramucirumab, and regorafenib, in addition to other agents, such as bevacizumab, nivolumab, and nivolumab in combination with ipilimumab [324].
Among first-line treatments, atezolizumab in combination with bevacizumab has the highest overall survival (OS) value, although lenvatinib has the highest objective response rate (ORR) value. Among second-line treatments, cabozantinib has the highest progression-free survival (PFS) value, as well as ORR value, compared to placebo [325]. Sorafenib, the RTK-targeting drug, is perhaps the most commonly used effective medication for the treatment of HCC. LncRNA-targeting methods have certain benefits over protein-targeting approaches for the treatment of HCC [326].

Recent advancements in molecular cell biology have significantly contributed to our awareness of the molecular mechanisms of tumor genesis and its development, which, in turn, offers prospects for finding of new molecularly targeted agents to prevent molecular irregularities as promising cancer treatments [135]. Molecularly targeted treatment generally includes TKIs (tyrosine kinase inhibitors), as well as monoclonal antibodies. Five targeted therapies have been approved for treatment of progressed HCC. Among these five therapies, four are small-molecule kinase inhibitors, and the one is a monoclonal antibody against VEGFR2 (vascular endothelial growth factor receptor) [327]. In addition to the mentioned appropriate targeted therapies, various targeted therapies are in clinical trials.

Knocking out oncogenic lncRNAs and injection tumor-suppressor lncRNA may be acceptable strategies for HCC treatment. As reported, lncRNA PRAL, a tumor suppressor that acts by stabilizing p53, dramatically prevents HCC development in tumor-bearing mice [239]. ASOs and RNAi function depending on a variety of factors, such as the subcellular positioning of the target lncRNAs. ASOs perform better than RNAi in nuclei, but RNAi performs better than ASOs when it targets cytoplasmic lncRNAs [328], which may be why RNaseH is primarily found in the nucleus, although RISC is primarily found in the cytoplasm [329,330].

8. Future Prospects and Conclusions

Cancer-related lncRNAs are slowly but steadily becoming the most widely discussed themes, even in RNA biology, as well as oncology. According to the existing data, abnormal transcription and processing activities may result in up regulation of the tumor-promoting lncRNAs that mostly interact with DNA, RNA, and proteins. As a consequence, lncRNAs can control expression, function, and some similar characteristics of their partner binding sites, causing various cancerous phenotypes, including recurrent proliferation, irregular metabolism, and tumor growth. All of these contribute to HCC carcinogenesis and development. Given their critical functions, a subclass of lncRNAs found in body fluid may be used as HCC biomarkers, either alone or in association with other metabolites to increase specificity.

As a result, altering lncRNA expression could be a new diagnostic and treatment technique for HCC [195]. According to the US food and Drug Administration, tyrosine kinase inhibitors Sorafenib and Lenvatinib have been proven as first-line treatments, and now, bevacizumab, in combination with atezolizumab, Sorafenib, and Lenvatinib, is considered the first-line treatment for accelerated HCC [324,331].

Some lncRNAs linked to inflammatory signaling pathways, such as the IL-6/STAT3 and NF-B pathways, have been discovered. However, the exact regulatory systems that govern development from inflammation to neoplasia remain unknown. The liver is responsible for lipid metabolism and is the primary location for endogenous cholesterol metabolism. Abnormalities in these metabolic pathways promote HCC etiology, as indicated by the increased risk of HCC in patients with diabetes, extreme obesity, and hepatic steatosis [265]. Whereas significant progress has been made, the activities of lncRNAs remain unknown. LncRNAs are often questioned based on the lack of functional analyses that may be attributed to the lower sequence conservation in comparison to protein-coding genes [332]. LncRNAs prefer to sustain highly preserved secondary structures [333]. The important problem at present is thoroughly attempting to understand the main aspects of lncRNAs, such as their structures, functions, expressions, and related mechanisms. Improved statistical techniques for lncRNA biological activities can assist in identifying their
significance with respect to various cancers. This knowledge may open the way for lncRNAs as potential prognostic markers and possibly even targeted therapies. In particular, strategies to target lncRNAs, including the use of siRNAs to initiate lncRNA deterioration and CRISPR/Cas9-mediated editing of the gene, must be regarded and improved. It is difficult to determine how to get the perfect molecules into appropriate cells [334]. RNA-seq is used to determine the differential expression of lncRNAs amongst tumor and non-tumor cells in an effort to explain active lncRNAs in HCC. Activities of lncRNAs are not always reflected in their variable expression patterns. Various genetic strategies are needed to illustrate lncRNA activities, which appears to be a challenging task, given thousands of lncRNAs that can only be identified simultaneously. The CRISPR sequencing technique is used to investigate the roles of protein-coding genes and lncRNAs related to screening phenotypes, proliferation, and drug resistance [335–337]. CRISPR analysis not only allows for identification of new functional lncRNAs that affect phenotypes of concern but makes it easier to create lncRNA-based potential therapies for a variety of human diseases [25].

9. Conclusions

Translating lncRNA studies into potential treatments is complex. LncRNA-based identification strategies are slowly emerging. The involvement of lncRNAs in regulation is related to the development of HCC. There are many unanswered questions at present. Future studies should concentrate on the functions and molecular pathways of lncRNAs in stimulating HCC development rather than just the concise recognition of differentially regulated and expressed lncRNAs. The main objective of gaining an improved appreciation of lncRNAs in HCC is to find new targeted therapies and biomarkers for HCC.

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Abbreviations

HCC hepatocellular carcinoma
lncRNAs long noncoding RNAs
snRNAs small nuclear RNAs
ncRNAs noncoding RNAs
siRNAs small interfering RNA
mRNAs messenger RNAs
tRNAs transport RNAs
rRNAs ribosomal RNAs
ceRNAs competing endogenous RNAs
DNMT1 DNA methyltransferase1
MAPK6 lncMAPK6, mitogen-activated protein kinase 6
HULC highly upregulated in liver cancer
LATS1 long-acting thyroid stimulator 1
HDAC3 histone deacetylase 3
EMT epithelial-mesenchymal transformation
URHC upregulated in HCC
PTTG3P pituitary tumor-transforming 3 pseudo gene
AFP alpha-fetoprotein
ASOs antisense oligonucleotides
MALAT1 metastasis-associated in lung adenocarcinoma transcript
TINCR terminal differentiation-induced noncoding RNA

References
1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424. [CrossRef] [PubMed]
2. Fitzmaurice, C.; Akinyemiju, T.F.; Al Lami, F.H.; Alam, T.; Alizadeh-Navaei, R.; Allen, C.; Yonemoto, N. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, a Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2018, 4, 1553–1568. [PubMed]
3. Ferlay, J.; Foucher, E.; Tieulent, J.; Rosso, S.; Coebergh, J.W.; Comber, H.; Forman, D.; Bray, F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur. J. Cancer 2013, 49, 1374–1403. [CrossRef]
4. Ferlay, J.; Foucher, E.; Tieulent, J.; Rosso, S.; Coebergh, J.W.; Comber, H.; Forman, D.; Bray, F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers. Eur. J. Cancer 2018, 103, 356–387. [CrossRef] [PubMed]
5. Döbrössy, L. Cancer mortality in central-eastern Europe: Facts behind the figures. Lancet Oncol. 2002, 3, 374–381. [CrossRef]
6. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics. CA Cancer J. Clin. 2021, 71, 7–33. [CrossRef]
7. Bhan, A.; Soleimani, M.; Mandal, S.S. Long noncoding RNA and cancer: A new paradigm. Cancer Res. 2017, 77, 3965–3981. [CrossRef]
8. Glassman, M.L.; de Groot, N.; Hochberg, A. Relaxation of imprinting in carcinogenesis. Cancer Genet. Cytogenet. 1996, 89, 69–73. [PubMed]
9. Nandwani, A.; Rathore, S.; Datta, M. LncRNAs in cancer: Regulatory and therapeutic implications. Cancer Lett. 2021, 501, 162–171. [CrossRef]
10. Chen, W.; Sauer, A.M.G.; Chen, M.S., Jr.; Kagawa-Singer, M.; Jemal, A.; Siegel, R.L. Cancer statistics in China. CA Cancer J. Clin. 2016, 66, 115–132. [CrossRef]
11. Torre, L.A.; Siegel, R.L.; Ward, E.M.; Jemal, A. Global cancer incidence and mortality rates and trends—An update. Cancer Epidemiol. Biomark. Prev. 2016, 25, 16–27. [CrossRef]
12. Gotwals, P.; Cameron, S.; Cipolletta, D.; Cremasco, V.; Crystal, A.; Hewes, B.; Mueller, B. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat. Rev. Cancer 2017, 17, 286–301. [CrossRef] [PubMed]
13. Baudino, A.T. Targeted cancer therapy: The next generation of cancer treatment. Curr. Drug Discov. Technol. 2015, 12, 3–20. [CrossRef] [PubMed]
14. Da, C.M.; Gong, C.Y.; Nan, W.; Zhou, K.S.; Zuo-Long, W.U.; Zhang, H.H. The role of long non-coding RNA MIAT in cancers. Biomed. Pharmacother. 2020, 129, 110359. [CrossRef]
15. Siegel, R.L.; Miller, K.D.; Fedewa, S.A.; Ahnen, D.J.; Mester, R.G.; Barzi, A.; Jemal, A. Colorectal cancer statistics. CA Cancer J. Clin. 2017, 67, 177–193. [CrossRef] [PubMed]
16. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef]
17. Han, X.; Yao, Y.; Li, J.; Li, Z.; Han, X. Role of LncRNAs in the Epithelial-Mesenchymal Transition in Hepatocellular Carcinoma. Front. Oncol. 2021, 11, 2014. [CrossRef]
18. Han, L.-L.; Lv, Y.; Guo, H.; Ruan, Z.-P.; Nan, K.-J. Implications of biomarkers in human hepatocellular carcinoma pathogenesis and therapy. World J. Gastroenterol. 2014, 20, 10249. [CrossRef]
19. El-Serag, H.B.; Rudolph, K.L. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology 2007, 132, 2557–2576. [CrossRef]
20. Zhang, X.; Zhu, Y. Research Progress on regulating LncRNAs of hepatocellular carcinoma stem cells. OncoTargets Ther. 2021, 14, 917. [CrossRef] [PubMed]
21. Singhal, A.G.; El-Serag, H.B. Hepatocellular carcinoma from epidemiology to prevention: Translating knowledge into practice. J. Clin. Gastroenterol. 2015, 13, 2140–2141. [CrossRef] [PubMed]
22. McGlynn, K.A.; Petrick, J.L.; London, W.T. Global epidemiology of hepatocellular carcinoma: An emphasis on demographic and regional variability. Clin. Liver Dis. 2015, 19, 223–238. [CrossRef] [PubMed]
23. Ledda, C.; Loreto, C.; Zammit, C.; Marconi, A.; Fago, L.; Materia, S.; Constanzo, V.; Fuccio, G.; Palmucci, S.; Ferrante, M.; et al. Non-infective occupational risk factors for hepatocellular carcinoma: A review. Mol. Med. Rep. 2017, 15, 511–533. [CrossRef] [PubMed]
24. Nagaraju, G.P.; Dariya, B.; Kasa, P.; Peela, S.; El-Rayes, B.F. Epigenetics in hepatocellular carcinoma. In Seminars in Cancer Biology; Elsevier: Amsterdam, The Netherlands, 2021.
25. Wong, L.-S.; Wong, C.-M. Decoding the Roles of Long Noncoding RNAs in Hepatocellular Carcinoma. *Int. J. Mol. Sci.* 2021, 22, 3137. [CrossRef] [PubMed]

26. Liu, P.; Wen, D.Y.; Li, Q.; He, Y.; Yang, H.; Chen, G. Genome-wide analysis of prognostic IncRNAs, miRNAs, and mRNAs forming a competing endogenous RNA network in hepatocellular carcinoma. *Cell. Physiol. Biochem.* 2018, 48, 1953–1967. [CrossRef] [PubMed]

27. Longo, D.; Villanueva, A. Hepatocellular Carcinoma. *N. Engl. J. Med.* 2019, 380, 1450–1462.

28. Kim, Y.-A.; Park, K.-K.; Lee, S.-J. lncRNAs act as a link between chronic liver disease and hepatocellular carcinoma. *Int. J. Mol. Sci.* 2020, 21, 2883. [CrossRef]

29. Li, C.; Chen, J.; Zhang, K.; Feng, B.; Wang, R.; Chen, L. Progress and prospects of long noncoding RNAs (lncRNAs) in hepatocellular carcinoma. *Cell. Physiol. Biochem.* 2016, 36, 423–36. [CrossRef] [PubMed]

30. Brunetti, O.; Gnoli, A.; Licchetta, A.; Longo, V.; Calabrese, A.; Argentiero, A.; Delcuratoro, S.; Solimando, A.; Gardini, A.; Silvestris, A. Predictive and prognostic factors in HCC patients treated with sorafenib. *Medicina* 2019, 55, 707. [CrossRef]

31. Hu, X.; Jiang, J.; Xu, Q.; Ni, C.; Yang, L.; Huang, D. A systematic review of long noncoding RNAs in hepatocellular carcinoma: Molecular mechanism and clinical implications. *BioMed Res. Int.* 2018, 2018, 8126208. [CrossRef]

32. Ghidini, M.; Braconi, C. Non-coding RNAs in primary liver cancer. *Front. Med.* 2015, 2, 36. [CrossRef] [PubMed]

33. Wang, J.; Chu, E.S.H.; Chen, H.Y.; Man, K.; Go, M.Y.Y.; Huang, X.R.; Lan, H.Y.; Sung, J.J.Y.; Yu, J. microRNA-29b prevents liver fibrosis by attenuating hepatic stellate cell activation and inducing apoptosis through targeting PI3K/AKT pathway. *Oncotarget* 2015, 6, 7325. [CrossRef] [PubMed]

34. Wang, X.; Hu, F.; Hu, X.; Chen, W.; Huang, Y.; Yu, X. Proteomic identification of potential *Clonorchis sinensis* excretory/secretory products capable of binding and activating human hepatic stellate cells. *Parasitol. Res.* 2014, 113, 3063–3071. [CrossRef] [PubMed]

35. Intini, C.; Hodgkinson, T.; Casey, S.M.; Gleeson, J.P.; O’Brien, F.J. Highly Porous Type II Collagen-Containing Scaffolds for Enhanced Cartilage Repair with Reduced Hypertrophic Cartilage Formation. *Bioengineering* 2022, 9, 232. [CrossRef] [PubMed]

36. Peng, H.; Wan, L.Y.; Liang, J.J.; Zhang, Y.Q.; Ai, W.B.; Wu, J.F. The roles of IncRNA in hepatic fibrosis. *Cell. Physiol. Biochem.* 2018, 8, 63. [CrossRef] [PubMed]

37. Piscaglia, F; Svegliati-Baroni, G.; Barchetti, A.; Pecorelli, A.; Marinelli, S.; Tirielli, C.; Bellentani, S.; HCC-NAFLD Italian Study Group. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. *Hepatology* 2016, 63, 827–838. [CrossRef]

38. Juhring, F.; Hamdane, N.; Crouchet, E.; Li, S.; El Saghire, H.; Mukherji, A.; Fujiwara, N.; Oudot, M.A.; Thumann, C.; Saviano, A.; et al. Targeting clinical epigenetic reprogramming for chemoprevention of metabolic and viral hepatocellular carcinoma. *Gut* 2021, 70, 157–169. [CrossRef]

39. Ogunwobi, O.O.; Harricharran, T.; Huaman, J.; Galuza, A.; Odumuwagun, O.; Tan, Y.; Ma, G.X.; Nguyen, M.T. Mechanisms of hepatocellular carcinoma progression. *World J. Gastroenterol.* 2019, 25, 2279–2293. [CrossRef]

40. Okrah, K.; Tarighat, S.; Liu, B.; Koeppen, H.; Wagle, M.C.; Cheng, G.; Sun, C.; Dey, A.; Chang, M.T.; Sumiyoshi, T.; et al. Transcriptomic analysis of hepatocellular carcinoma reveals molecular features of disease progression and tumor immune biology. *NPJ Precis. Oncol.* 2018, 2, 25. [CrossRef] [PubMed]

41. Safcak, D.; Draziova, S.; Gazda, J.; Andrasina, I.; Adamcova-Selcanova, S.; Barila, R.; Mego, M.; Rac, M.; Skladany, L.; Zigrai, M.; et al. Nonalcoholic Fatty Liver Disease-Related Hepatocellular Carcinoma: Clinical Patterns, Outcomes, and Prognostic Factors for Overall Survival—A Retrospective Analysis of a Slovak Cohort. *J. Clin. Med.* 2021, 10, 3186. [CrossRef] [PubMed]

42. Geh, D.; Derek, M.; Manas, H.; Reeves, L. Hepatocellular carcinoma in non-alcoholic fatty liver disease—A review of an emerging challenge facing clinicians. *Hepatobiliary Surg. Nutr.* 2021, 10, 59. [CrossRef] [PubMed]

43. Vesque, A.D.; Decraecker, M.; Blanc, J.-F. Profile of Cabozantinib for the Treatment of Hepatocellular Carcinoma: Patient Selection and Special Considerations. *J. Hepatocell. Carcinoma* 2020, 7, 91. [CrossRef]

44. Yang, F.U.; 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. *NPJ Precis. Oncol.* 2018, 2, 25. [CrossRef] [PubMed]

45. Kudo, M. Systemic therapy for hepatocellular carcinoma: 2017 update. *Oncology* 2017, 93 (Suppl. S1), 135–146. [CrossRef]

46. Li, D.; Liu, X.; Zhou, J.; Hu, J.; Zhang, D.; Liu, J.; Qiao, Y.; Zhan, Q. Long noncoding RNA HULC modulates the phosphorylation of YB-1 through serving as a scaffold of extracellular signal-regulated kinase and YB-1 to enhance hepatocarcinogenesis. *Hepatology* 2017, 65, 1612–1627. [CrossRef]

47. Ghanem, I.; Riveiro, M.E.; Paradis, V.; Faivre, S.; de Parga, P.M.V.; Raymond, E. Insights on the CXCL12-CXCR4 axis in hepatocellular carcinoma. *Am. J. Transl. Res.* 2014, 6, 340.

48. Villanueva, A.; Minguet, B.; Forner, A.; Reig, M.; Llovet, J.M. Hepatocellular carcinoma: Novel molecular approaches for diagnosis, prognosis, and therapy. *Arnu. Rev. Med.* 2010, 61, 317–328. [CrossRef]

49. Feng, Y.; Dramani Maman, S.T.; Zhu, X.; Liu, X.; Bongolo, C.C.; Liang, C.; Tu, J. Clinical value and potential mechanisms of LINC00221 in hepatocellular carcinoma based on integrated analysis. *Epigenomics* 2021, 13, 299–317. [CrossRef]

50. Hu, X.; Chen, R.; Wei, Q.; Xu, X. The Landscape of Alpha Fetoprotein in Hepatocellular Carcinoma: Where Are We? *Int. J. Biol. Sci.* 2022, 18, 536–551. [CrossRef] [PubMed]

51. Bao, H.; Su, H. Long noncoding RNAs act as novel biomarkers for hepatocellular carcinoma: Progress and prospects. *Biomed. Res. Int.* 2017, 2017, 6049480. [CrossRef] [PubMed]
52. Wu, J.-L.; Su, T.-H.; Chen, P.-J.; Chen, Y.-R. Acute-phase serum amyloid A for early detection of hepatocellular carcinoma in cirrhotic patients with low AFP level. *Sci. Rep.* 2022, 12, 5799. [CrossRef] [PubMed]

53. Shi, Y. Mechanistic insights into precursor messenger RNA splicing by the spliceosome. *Nat. Rev. Mol. Cell Biol.* 2017, 18, 655. [CrossRef] [PubMed]

54. Goodall, G.J.; Wickramasinghe, V.O. RNA in cancer. *Nat. Rev. Cancer* 2021, 21, 22–36. [CrossRef]

55. Vo, J.N.; Cieslik, M.; Zhang, Y.; Shukla, S.; Xiao, L.; Zhang, Y.; Wu, Y.-M.; Dhnanasekaran, S.M.; Engelke, C.G.; Cao, X.; et al. The landscape of circular RNA in cancer. *Cell* 2019, 176, 869–881.e13. [CrossRef] [PubMed]

56. Gruber, A.J.; Zavolan, M. Alternative cleavage and polyadenylation in health and disease. *Nat. Rev. Genet.* 2019, 20, 599–614. [CrossRef] [PubMed]

57. Dvinge, H.; Guenthoer, J.; Porter, P.L.; Bradley, R.K. RNA components of the spliceosome regulate tissue-and cancer-specific alternative splicing. *Genome Res.* 2019, 29, 1591–1604. [CrossRef]

58. Ramos-Rodriguez, D.H.; Pashneh-Tala, S.; Bains, A.K.; Moorehead, R.D.; Kassos, N.; Kelly, A.L.; Paterson, T.E.; Orozco-Diaz, C.A.; Gill, A.A.; Asencio, I.O. Demonstrating the Potential of Using Bio-Based Sustainable Polyester Blends for Bone Tissue Engineering Applications. *Bioengineering* 2022, 9, 163. [CrossRef] [PubMed]

59. Ning, J.; Sun, K.; Fan, X.; Jia, K.; Wang, X.; Ma, C.; Wei, L. Necroptosis-related IncRNAs and Hepatocellular Carcinoma Undoubtedly Secret. *Res. Sq.* 2022, 25. [CrossRef] [PubMed]

60. Amaral, P.P.; Leonardi, T.; Han, N.; Vire, E.; Gascoigne, D.K.; Arias-Carrasco, R.; Büscher, M.; Pandolfini, L.; Zhang, A.; Pluchino, S.; et al. Genomic positional conservation identifies topological anchor point RNAs linked to developmental loci. *Genome Biol.* 2018, 19. [CrossRef] [PubMed]

61. Anastasiadou, E.; Jacob, L.S.; Slack, F.J. Non-coding RNA networks in cancer. *Nat. Rev. Cancer* 2018, 18, 5–18. [CrossRef] [PubMed]

62. Fernandez-Ruiz, J. A new role for IncRNAs in atherosclerosis. *Nat. Rev. Cardiol.* 2018, 15, 195. [CrossRef] [PubMed]

63. Wong, C.-M.; Tsang, F.H.-C.; Shukla, S.; Xiao, L.; Zhang, Y.; Wu, Y.-M.; Dhnanasekaran, S.M.; Engelke, C.G.; Cao, X.; et al. The landscape of circular RNA in cancer. *Cell* 2019, 176, 869–881.e13. [CrossRef] [PubMed]

64. Lei, G.L.; Niu, Y.; Cheng, S.J.; Li, Y.Y.; Bai, Z.F.; Yu, L.X.; Hong, Z.X.; Liu, H.; Liu, H.H.; Yan, J.; et al. Upregulation of long non-coding RNA W42 promotes tumor development by binding with DBN1 in hepatocellular carcinoma. *World J. Gastroenterol.* 2021, 27, 2586. [CrossRef]

65. Li, Y.; Guo, D.; Lu, G.; Chowdhury, A.T.M.M.; Zhang, D.; Ren, M.; Chen, Y.; Wang, R.; He, S. LncRNA SNAI3-AS1 contributes to colon cancer progression through the miR-150-5p/VEGFA axis. *Ann. Oncol.* 2018, 29, v52–v53. [CrossRef]

66. Zhang, J.; Han, X.; Jiang, L.; Han, Z.; Wang, Z. LncRNA CERNA2 is an independent predictor for clinical prognosis and is related to tumor development in gastric cancer. *Int. J. Clin. Exp. Pathol.* 2018, 11, 5783. [CrossRef] [PubMed]

67. Le, G.L.; Niu, Y.; Cheng, S.J.; Li, Y.Y.; Bai, Z.F.; Yu, L.X.; Hong, Z.X.; Liu, H.; Liu, H.H.; Yan, J.; et al. Upregulation of long noncoding RNA W42 promotes tumor development by binding with DBN1 in hepatocellular carcinoma. *World J. Gastroenterol.* 2021, 27, 2586. [CrossRef]

68. Lei, G.L.; Niu, Y.; Cheng, S.J.; Li, Y.Y.; Bai, Z.F.; Yu, L.X.; Hong, Z.X.; Liu, H.; Liu, H.H.; Yan, J.; et al. Upregulation of long noncoding RNA W42 promotes tumor development by binding with DBN1 in hepatocellular carcinoma. *World J. Gastroenterol.* 2021, 27, 2586. [CrossRef]

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

70. Hu, W.; Alvarez-Dominguez, J.R.; Lodish, H.F. Regulation of mammalian cell differentiation by long non-coding RNAs. *EMBO Rep.* 2012, 13, 971–983. [CrossRef] [PubMed]

71. Garcia, L.; Zambalde, E.; Mathias, C.; Barazetti, J.; Gradia, D.; Oliveira, J. IncRNAs in Hallmarks of Cancer and Clinical Applications. In *Non-Coding RNAs; IntechOpen*: London, UK, 2019.

72. Guttmann, M.; Rinn, J.L. Modular regulatory principles of large non-coding RNAs. *Nature* 2012, 482, 339–346. [CrossRef] [PubMed]

73. Taniue, K.; Akimitsu, N. The functions and unique features of lncrnas in cancer development and tumorigenesis. *Int. J. Mol. Sci.* 2021, 22, 632. [CrossRef] [PubMed]

74. Parasramka, M.A.; Maji, S.; Matsuda, A.; Yan, I.K.; Patel, T. Long non-coding RNAs as novel targets for therapy in hepatocellular carcinoma. *Pharmacol. Ther.* 2016, 161, 67–78. [CrossRef] [PubMed]

75. Xiao, Z.; Shen, J.; Zhang, L.; Li, M.; Hu, W.; Cho, C. Therapeutic targeting of noncoding RNAs in hepatocellular carcinoma: Recent progress and future prospects. *Oncol. Lett.* 2018, 15, 3395–3402. [CrossRef] [PubMed]

76. Chen, S.; Zhang, Y.; Ding, X.; Li, W. Identification of IncRNA/circRNA-miRNA-mRNA ceRNA Network as Biomarkers for Hepatocellular Carcinoma. *Front. Genet.* 2022, 538. [CrossRef] [PubMed]

77. Han, T.-S.; Hur, K.; Cho, H.-S.; Ban, H.S. Epigenetic associations between IncRNA/circRNA and miRNA in hepatocellular carcinoma. *Cancers* 2020, 12, 2622. [CrossRef] [PubMed]

78. Meng, H.; Niu, R.; Huang, C.; Li, J. Circular RNA as a Novel Biomarker and Therapeutic Target for HCC. *Cells* 2022, 11, 1948. [CrossRef] [PubMed]

79. Sato, K.; Glaser, S.; Francis, H.; Alpini, G. Concise review: Functional roles and therapeutic potentials of long non-coding RNAs in cholangiopathies. *Front. Med.* 2020, 7, 48. [CrossRef] [PubMed]
80. Jopling, C.L.; Yi, M.; Lancaster, A.M.; Lemon, S.M.; Sarnow, P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science* 2005, 309, 1577–1581. [CrossRef]

81. Kitabayashi, J.; Shirasaki, T.; Shimakami, T.; Nishiyama, T.; Welsch, C.; Funaki, M.; Murai, K.; Sumiyadorj, A.; Takatori, H.; Kitamura, K.; et al. Upregulation of the long non-coding RNA HULC by hepatitis C virus and its regulation of viral replication. *J. Infect. Dis.* 2020. [CrossRef]

82. Wang, D.; Chen, F.; Zeng, T.; Tang, Q.; Chen, B.; Chen, L.; Dong, Y.; Li, X. Comprehensive biological function analysis of IncRNAs in hepatocellular carcinoma. *Genes Dis.* 2020, 8, 157–167. [CrossRef]

83. Khalil, A.M.; Guttman, M.; Huarte, M.; Garber, M.; Raj, A.; Morales, D.R.; 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]

84. Bhan, A.; Mandal, S.S. LncRNA HOTAIR: A master regulator of chromatin dynamics and cancer. *Biochim. Biophys. Acta Rev. Cancer* 2015, 1856, 151–164. [CrossRef]

85. Zheng, J.; Lin, Z.; Dong, P.; Lu, Z.; Gao, S.; Chen, X.; Wu, C.; Yu, F. Activation of hepatic stellate cells is suppressed by microRNA-150. *Int. J. Mol. Med.* 2013, 32, 17–24. [CrossRef] [PubMed]

86. Zheng, J.; Dong, P.; Gao, S.; Wang, N.; Yu, F. High expression of serum miR-17-5p associated with poor prognosis in patients with hepatic carcinoma. *Hepatogastroenterology* 2013, 60, 549–552. [PubMed]

87. Zheng, J.; Wu, C.; Lin, Z.; Guo, Y.; Shi, L.; Dong, P.; Lu, Z.; Gao, S.; Liao, Y.; Chen, B.; et al. Curcumin up-regulates phosphatase and tensin homologue deleted on chromosome 10 through micro RNA-mediated control of DNA methylation—A novel mechanism suppressing liver fibrosis. *FEBS J.* 2014, 281, 88–103. [CrossRef]

88. Zhou, B.; Yang, H.; Bao, Y.-L.; Yang, S.-M.; Liu, J.; Xiao, Y.-F. Translation of noncoding RNAs and cancer. *Cancer Lett.* 2021, 497, 89–99. [CrossRef]

89. Zhang, L.-G.; Zhou, X.-K.; Zhou, R.-J.; Lv, H.-Z.; Li, W.-P. Long non-coding RNA LINC00673 promotes hepatocellular carcinoma progression and metastasis through negatively regulating miR-205. *Am. J. Cancer Res.* 2017, 7, 2536. [PubMed]

90. de Oliveira, J.C.; Oliveira, L.C.; Mathias, C.; Pedroso, G.A.; Lemos, D.S.; Salviano-Silva, A.; Jucocki, T.S.; Lobo-Alves, S.C.; Zambalde, E.P.; Cipolla, G.A.; et al. Long non-coding RNAs in cancer: Another layer of complexity. *J. Gene Med.* 2019, 21, e3065. [PubMed]

91. ZZhang, T.; Hu, H.; Yan, G.; Wu, T.; Liu, S.; Chen, W.; Ning, Y.; Lu, Z. Long non-coding RNA and breast cancer. *Technol. Cancer Res. Treat.* 2019, 18, 1533033819843889.

92. Ponting, C.P.; Oliver, P.L.; Reik, W. Evolution and functions of long noncoding RNAs. *Cell* 2009, 136, 629–641. [CrossRef]

93. He, Y.; Meng, X.-M.; Huang, C.; Wu, B.-M.; Zhang, L.; Lv, X.-W.; Li, J. Long noncoding RNAs: Novel insights into hepatocellular carcinoma. *Cancer Lett.* 2014, 344, 20–27. [CrossRef] [PubMed]

94. Derrien, T.; Johnson, R.; Bussotti, G.; Tanzer, A.; Djebali, S.; Ilbouz, E.; 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]

95. Wang, K.C.; Chang, H.Y. Molecular mechanisms of long noncoding RNAs. *Mol. Cell* 2011, 43, 904–914. [CrossRef] [PubMed]

96. Pandey, R.R.; Mondal, T.; Mohammad, F.; Enroth, S.; Redrup, L.; Komorowski, J.; Nagano, T.; Mancini-DiNardo, D.; Kanduri, C. Kcnq1ot1 antisense noncoding RNA mediates lineage-specific transcriptional silencing through chromatin-level regulation. *Mol. Cell* 2008, 32, 232–246. [CrossRef] [PubMed]

97. Hung, T.; Wang, Y.; Lin, M.P.; Koegel, A.; Fan, X.-M. Long non-coding RNAs: Spatial amplifiers that control nuclear structure and gene expression. *Nat. Rev. Mol. Cell Biol.* 2016, 17, 756–770. [CrossRef]

98. Liz, J.; Esteller, M. IncRNAs and microRNAs with a role in cancer development. *Biochim. Biophys. Acta Gene Regul. Mech.* 2016, 1859, 169–176. [CrossRef] [PubMed]

99. Niu, Z.-S.; Niu, X.-J.; Wang, W.-H. Long non-coding RNAs in hepatocellular carcinoma: Potential roles and clinical implications. *World J. Gastroenterol.* 2017, 23, 5860. [CrossRef] [PubMed]

100. O’Brien, A.; Zhou, T.; Tan, C.; Alpini, G.; Glaser, S. Role of Non-Coding RNAs in the Progression of Liver Cancer: Evidence from Experimental Models. *Cancers* 2019, 11, 1652. [CrossRef] [PubMed]

101. Yu, F.-J.; Zheng, J.-J.; Dong, P.-H.; Fan, X.-M. Long non-coding RNAs: Spatial amplifiers that control nuclear structure and gene expression. *Nat. Rev. Mol. Cell Biol.* 2016, 17, 756–770. [CrossRef]

102. Ng, D.; 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. *Mol. Cell* 2010, 39, 925–938. [CrossRef] [PubMed]
107. Kretz, M.; Siprashvili, Z.; Chu, C.; Webster, D.; Zehnder, A.; Qu, K.; Lee, C.S.; Flockhart, R.J.; Groff, A.F.; Chow, J.; et al. Control of somatic tissue differentiation by the long non-coding RNA TINCR. Nature 2013, 493, 231–235. [CrossRef]

108. Ransohoff, J.D.; Wei, Y.; Khavari, P.A. The functions and unique features of long intergenic non-coding RNA. Nat. Rev. Mol. Cell Biol. 2018, 19, 143–157. [CrossRef]

109. Jayaraj, G.G.; Pandey, S.; Scaria, V.; Maiti, S. Potential G-quadruplexes in the human long non-coding transcriptome. RNA Biol. 2012, 9, 81–89. [CrossRef] [PubMed]

110. Li, P.; Zhang, G.; Li, J.; Yang, R.; Chen, S.; Wu, S.; Zhang, F.; Bai, Y.; Zhao, H.; Wang, Y.; et al. Long noncoding RNA RGMB-AS1 indicates a poor prognosis and modulates cell proliferation, migration and invasion in lung adenocarcinoma. PLoS ONE 2016, 11, e0150790. [CrossRef]

111. Wilk, R.; Hu, J.; Blotsky, D.; Krause, H.M. Diverse and pervasive subcellular distributions for both coding and long noncoding RNAs. Genes Dev. 2016, 30, 594–609. [PubMed]

112. Chen, K.; Zhao, B.S.; He, C. Nucleic acid modifications in regulation of gene expression. Cell Chem. Biol. 2016, 23, 74–85. [CrossRef] [PubMed]

113. Wang, J.; Sun, J.; Wang, J.; Song, Y.; Gao, P.; Shi, J.; Chen, P.; Wang, Z. Long noncoding RNAs in gastric cancer: Functions and clinical applications. OncoTargets Ther. 2016, 9, 681. [CrossRef] [PubMed]

114. Wang, J.; Xu, A.; Zhang, J.; He, X.; Pan, Y.; Cheng, G.; Qin, C.; Hua, L.; Wang, Z. Prognostic significance of long non-coding RNA MALAT-1 in various human carcinomas: A meta-analysis. Genet. Mol. Res. 2016, 15, 15017433.

115. Sun, L.; Guo, Y.; He, P.; Xu, Z.; Zhang, X.; Wang, H.; Tang, T.; Zhou, W.; Xu, P.; Xie, P. Genome-wide profiling of long noncoding RNA expression patterns and CeRNA analysis in mouse cortical neurons infected with different strains of borna disease virus. Genes Dis. 2019, 6, 147–158. [PubMed]

116. Rinn, J.L.; Chang, H.Y. Genome regulation by long noncoding RNAs. Annu. Rev. Biochem. 2012, 81, 145–166. [PubMed]

117. Isin, M.; Dala, Y.N. LncRNAs and neoplasia. Clin. Chim. Acta 2015, 444, 280–288.

118. Serves, J.T.; Johnsson, P.; Grandé, D. An emerging role for long non-coding RNAs in cancer metastasis. Front. Genet. 2014, 5, 234. [PubMed]

119. Harries, L.W. Long non-coding RNAs and human disease. Biochem. Soc. Trans. 2012, 40, 902–906. [PubMed]

120. Wang, Q.-f.; Wang, Q.-l.; Cao, M.-b. LncRNA PITPNA-AS1 as a potential diagnostic marker and therapeutic target promotes tumor growth and invasion in gastric cancer. Biomed. Pharmacother. 2019, 118, 109249. [CrossRef] [PubMed]

121. Kretz, M.; Siprashvili, Z.; Chu, C.; Webster, D.; Zehnder, A.; Qu, K.; Lee, C.S.; Flockhart, R.J.; Groff, A.F.; Chow, J.; et al. Control of somatic tissue differentiation by the long non-coding RNA TINCR. Nature 2013, 493, 231–235. [CrossRef]

122. 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, 30, 594–609. [CrossRef]

123. Zheng, Q.-X.; Wang, J.; Gu, X.-Y.; Huang, C.-H.; Chen, C.; Hong, M.; Chen, Z. TTN-AS1 as a potential diagnostic and prognostic biomarker for multiple cancers. Biomed. Pharmacother. 2021, 135, 111169. [CrossRef] [PubMed]

124. Jin, T. LncRNA DRAIR is a novel prognostic and diagnostic biomarker for gastric cancer. Mamm. Genome 2021, 32, 503–507. [PubMed]

125. Maier, I.M.; Maier, A.C. miRNAs and lncRNAs: Potential non-invasive biomarkers for endometriosis. Biomedicines 2021, 9, 20210021. [PubMed]

126. Mercer, T.R.; Dinger, M.E.; Mattick, J.S. Long non-coding RNAs. Annu. Rev. Genet. 2013, 47, 587–607. [CrossRef]

127. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer: The next generation. Cell 2011, 144, 646–674. [CrossRef] [PubMed]

128. Nagy, Á.; Munkácsey, G.; Györfi, B. Pancancer survival analysis of cancer hallmark genes. Sci. Rep. 2021, 11, 6047. [CrossRef] [PubMed]

129. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. Cell 2000, 100, 57–70. [CrossRef]

130. Huang, H.; Chen, J.; Ding, C.; Jin, X.; Jia, Z.; Peng, J. Lnc RNA NR 2F1-AS 1 regulates hepatocellular carcinoma oxaliplatin resistance by targeting ABCC 1 via miR-363. J. Cell. Mol. Med. 2018, 22, 3238–3245. [CrossRef]

131. El-Ashmawy, N.E.; Hussien, F.Z.; El-Feky, O.A.; Hamouda, S.M.; Al-Ashmawy, G.M. Serum LncRNA-ATB and FAM83H-AS1 as potential biomarkers for breast cancer. Diagnostics 2018, 8, 250. [CrossRef]

132. Maier, I.M.; Maier, A.C. miRNAs and lncRNAs: Potential non-invasive biomarkers for endometriosis. Biomedicines 2021, 9, 20210021. [PubMed]

133. Ransohoff, J.D.; Wei, Y.; Khavari, P.A. The functions and unique features of long intergenic non-coding RNA. Nat. Rev. Mol. Cell Biol. 2018, 19, 143–157. [CrossRef]

134. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer: The next generation. Cell 2011, 144, 646–674. [CrossRef] [PubMed]

135. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. Cell 2000, 100, 57–70. [CrossRef]
137. Menyhért, O.; Hrami-Papp, H.; Sukumar, S.; Schäfer, R.; Magnani, L.; de Barrios, O.; Győrffy, B. Guidelines for the selection of functional assays to evaluate the hallmarks of cancer. *Biochem. Biophys. Acta Rev. Cancer* 2016, 1866, 300–319. [CrossRef]

138. Chen, Y.; Zitello, E.; Gao, R.; Deng, Y. The function of lncRNAs and their role in the prediction, diagnosis, and prognosis of lung cancer. *Clin. Transl. Med.* 2021, 11, e367. [CrossRef]

139. Zhang, R.; Xia, L.Q.; Lu, W.W.; Zhang, J.; Zhu, J.S. LncRNAs and cancer. *Oncol. Lett.* 2016, 12, 1233–1239. [CrossRef]

140. Ahmad, S.; Abbas, M.; Ullah, M.F.; Aziz, M.H.; Beylerli, O.; Alam, M.A.; Syed, M.A.; Uddin, S.; Ahmad, A. Long non-coding RNAs regulated NF-κB signaling in cancer metastasis: Micromanaging by not so small non-coding RNAs. In *Seminars in Cancer Biology; Elsevier*: Amsterdam, The Netherlands, 2021.

141. Tanne, A.; Muniz, L.R.; Puzio-Kuter, A.; Leonova, K.I.; Gudkov, A.V.; Ting, D.T.; Monasson, R.; Cocco, S.; Levine, A.J.; Bhardwaj, N.; et al. Distinguishing the immunostimulatory properties of noncoding RNAs expressed in cancer cells. *Proc. Natl. Acad. Sci. USA* 2015, 112, 15154–15159. [CrossRef] [PubMed]

142. Rooney, M.S.; Shukla, S.A.; Wu, C.J.; Getz, G.; Hacohen, N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell* 2015, 160, 48–61. [CrossRef]

143. Pan, L.; Liang, W.; Gu, J.; Wang, N.; Huang, Z.; Shi, H.; Chen, J.; Fu, M.; Zhang, P.; Xiao, X.; et al. Long noncoding RNA DANCR is activated by SALL4 and promotes the proliferation and invasion of gastric cancer cells. *Oncotarget* 2018, 9, 1915. [CrossRef]

144. Li, S.; Li, J.; Chen, C.; Zhang, R.; Wang, K. Pan-cancer analysis of long non-coding RNA NEAT1 in various cancers. *Genes Dis.* 2018, 5, 27–35. [CrossRef] [PubMed]

145. Zhou, D.; Ren, K.; Wang, M.; Wang, J.; Li, E.; Hou, C.; Su, Y.; Jin, Y.; Zou, Q.; Zhou, P.; et al. Long non-coding RNA H19 inhibits cell viability, migration, and invasion via miR-345-5p/RACGAP1-mediated mitochondrial fission. *Mol. Oncol.* 2021, 15, 543. [CrossRef] [PubMed]

146. Wang, X.; Wang, Y.; Lin, F.; Xu, M.; Zhao, X. Long non-coding RNA LINC00665 promotes melanoma cell growth and migration via regulating the miR-224-5p/VMA21 axis. *Exp. Dermatol.* 2020, 31, 64–73. [CrossRef] [PubMed]

147. He, R.-Z.; Luo, D.-X.; Mo, Y.-Y. Emerging roles of lncRNAs in the post-transcriptional regulation in cancer. *Genes Dis.* 2019, 6, 6–15. [CrossRef] [PubMed]

148. Liang, W.Q.; Zeng, D.; Chen, C.F.; Sun, S.M.; Lu, X.F.; Peng, C.Y.; Lin, H.Y. Long noncoding RNA H19 is a critical oncogenic driver and contributes to epithelial-mesenchymal transition in papillary thyroid Carcinoma. *Cancer Manag. Res.* 2019, 11, 2059. [CrossRef]

149. Wang, P.; Liu, G.; Xu, W.; Liu, H.; Bu, Q.; Sun, D. Long noncoding RNA H19 inhibits cell viability, migration, and invasion via downregulation of IRS-1 in thyroid cancer cells. *Technol. Cancer Res. Treat.* 2017, 16, 1102–1112. [CrossRef]

150. Wu, Z.R.; Yan, L.; Liu, Y.T.; Cao, L.; Guo, Y.H.; Zhang, Y.; Yao, H.; Cai, L.; Shang, H.B.; Rui, W.W.; et al. Inhibition of mTORC1 by IncRNA H19 via disrupting 4E-BP1/Raptor interaction in pituitary tumours. *Nat. Commun.* 2018, 9, 4624. [CrossRef]

151. Gao, H.; Hao, G.; Sun, Y.; Li, L.; Wang, Y. Long noncoding RNA H19 mediated the chemosensitivity of breast cancer cells via Wnt pathway and EMT process. *Oncotargets Ther.* 2018, 11, 8001. [CrossRef]

152. Lou, C.; Zhao, J.; Gu, Y.; Li, Q.; Tang, S.; Wu, Y.; Tang, J.; Zhang, C.; Li, Z.; Zhang, Y. LINC01559 accelerates pancreatic cancer cell proliferation and migration through YAP-mediated pathway. *J. Cell. Physiol.* 2020, 235, 4388–4398. [CrossRef]

153. Wang, Z.Y.; Duan, Y.; Wang, P. SP1-mediated upregulation of IncRNA SNHG4 functions as a ceRNA for miR-377 to facilitate progression of breast cancer cells via regulating the miR-224-5p/VMA21 axis. *Exp. Dermatol.* 2020, 31, 64–73. [CrossRef] [PubMed]

154. Wang, Z.; Jiang, F.; Xiong, Y.; Cheng, X.; Qiu, Z.; Song, R. LncRNA TTN-AS1 sponges miR-376a-3p to promote colorectal cancer progression. *Oncotarget* 2018, 9, 8001. [CrossRef] [PubMed]

155. Feng, L.; Li, J.; Li, F.; Li, H.; Bei, S.; Zhang, X.; Yang, Z. Long noncoding RNA VCAN-AS1 contributes to the progression of gastric cancer via regulating p53 expression. *J. Cell. Physiol.* 2020, 235, 3928–3938. [CrossRef] [PubMed]

156. Lou, C.; Zhao, J.; Gu, Y.; Li, Q.; Tang, S.; Wu, Y.; Tang, J.; Zhang, C.; Li, Z.; Zhang, Y. LINC01559 accelerates pancreatic cancer cell proliferation and migration through YAP-mediated pathway. *J. Cell. Physiol.* 2020, 235, 3928–3938. [CrossRef] [PubMed]

157. Wang, Y.; Jiang, F.; Xiong, Y.; Cheng, X.; Qiu, Z.; Song, R. LncRNA TTN-AS1 sponges miR-376a-3p to promote colorectal cancer progression via upregulating KLF15. *Life Sci.* 2020, 244, 116936. [CrossRef] [PubMed]

158. Qiao, K.; Ning, S.; Wan, L.; Wu, H.; Wang, Q.; Zhang, X.; Xu, S.; Pang, D. LINC00673 is activated by YY1 and promotes the proliferation of breast cancer cells via the miR-515-5p/MARK4/ Hippo signaling pathway. *J. Exp. Clin. Cancer Res.* 2019, 38, 418. [CrossRef] [PubMed]

159. Rossi, T.; Pistoni, M.; Sancisi, V.; Gobbi, G.; Torricelli, F.; Donati, B.; Ribisi, S.; Gugnoni, M.; Ciarrocchi, A. RAIN is a novel Enhancer-associated lncRNA that controls RUNX2 expression and promotes breast and thyroid cancer. *Mol. Cancer* 2020, 19, 140–152. [CrossRef]

160. Chang, Q.-Q.; Chen, C.-Y.; Chen, Z.; Chang, S. LncRNA PVT1 promotes proliferation and invasion through enhancing Smad3 expression by sponging miR-140-5p in cervical cancer. *Radiol. Oncol.* 2019, 53, 443. [CrossRef] [PubMed]

161. Chang, Q.-Q.; Chen, C.-Y.; Chen, Z.; Chang, S. LncRNA PVT1 promotes proliferation and invasion through enhancing Smad3 expression by sponging miR-140-5p in cervical cancer. *Radiol. Oncol.* 2019, 53, 443. [CrossRef] [PubMed]

162. Li, H.; Han, Q.; Chen, Y.; Chen, X.; Ma, R.; Chang, Q.; Yin, D. Upregulation of the long non-coding RNA FOXD2-AS1 is correlated with tumor progression and metastasis in papillary thyroid cancer. *Am. J. Transl. Res.* 2019, 11, 5457.
163. Ouyang, T.; Zhang, Y.; Tang, S.; Wang, Y. Long non-coding RNA LINC00052 regulates miR-608/EGFR axis to promote progression of head and neck squamous cell Carcinoma. Exp. Mol. Pathol. 2019, 111, 104321. [CrossRef] [PubMed]

164. Tang, C.; Wang, Y.; Zhang, L.; Wang, J.; Wang, W.; Han, X.; Mu, C.; Gao, D. Identification of novel LncRNA targeting Smad2/PKCa signal pathway to negatively regulate malignant progression of glioblastoma. J. Cell. Physiol. 2020, 235, 3835–3848. [CrossRef] [PubMed]

165. Liu, D.; Wu, K.; Yang, Y.; Zhu, D.; Zhang, C.; Zhao, S. Long noncoding RNA ADAMTS9-AS2 suppresses the progression of esophageal cancer by mediating CDH3 promoter methylation. Mol. Carcinog. 2020, 59, 32–44. [CrossRef] [PubMed]

166. Wang, W.; Xia, S.; Zhan, W. The long non-coding RNA ENST00000489676 influences papillary thyroid cancer cell proliferation and invasion through regulating MiR-922. J. Cancer 2019, 10, 5434. [CrossRef] [PubMed]

167. Fan, J.; Zhang, J.; Huang, S.; Li, P. LncRNA OSER1-AS1 acts as a ceRNA to promote tumorigenesis in hepatocellular carcinoma by regulating miR-372-3p/Rab23 axis. Biochem. Biophys. Res. Commun. 2020, 521, 196–203. [CrossRef] [PubMed]

168. Lin, S.; Zhang, R.; An, L.; Li, Z.; Fang, C.; Pan, B.; Chen, W.; Xu, G.; Han, W. LncRNA HOXA-AS3 confers cisplatin resistance by interacting with HOXA3 in non-small-cell lung cancer cells. Oncogenesis 2019, 8, 60. [CrossRef] [PubMed]

169. Yan, Y.; Xu, Z.; Chen, X.; Wang, X.; Zeng, S.; Zhao, Z.; Qian, L.; Li, Z.; Wei, J.; Huo, L.; et al. Novel function of LncRNA ADAMTS9-AS2 in promoting temozolomide resistance in glioblastoma via upregulating the FUS/MDM2 ubiquitination axis. Front. Cell Dev. Biol. 2019, 7, 217.

170. Yokoyama, Y.; Sakatani, T.; Wada, R.; Ishino, K.; Kudo, M.; Koizumi, M.; Yamada, T.; Yoshida, H.; Naito, Z. In vitro and in vivo studies on the association of long non-coding RNAs H19 and uterine cervical cancer associated 1 with the susceptibility to 5-fluorouracil in rectal cancer. Int. J. Oncol. 2019, 55, 1361–1371. [CrossRef]

171. Tamang, S.; Acharya, V.; Roy, D.; Sharma, R.; Aryaa, A.; Sharma, U.; Khandelwal, A.; Prakash, H.; Vasquez, K.M.; Jain, A. SNHG12: An LncRNA as a potential therapeutic target and biomarker for human cancer. Front. Oncol. 2019, 9, 901. [CrossRef]

172. Avazpour, N.; Hajjari, M.; Birgani, M.T. HOTAIR: A promising long non-coding RNA with potential role in breast invasive carcinoma. Front. Genet. 2017, 8, 170. [CrossRef]

173. Xu, W.; Zhou, G.; Wang, H.; Liu, Y.; Chen, B.; Chen, W.; Lin, C.; Wu, S.; Gong, X.; Xu, M. Circulating IncRNA SNHG11 as a novel biomarker for early diagnosis and prognosis of colorectal cancer. Int. J. Cancer 2020, 146, 2901–2912. [CrossRef]

174. Li, T.; Xie, J.; Chen, S.; 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]

175. Tong, H.; He, S.; Li, K.; Zhang, K.; Jin, H.; Shi, J.; Cheng, Y.; Wang, L.; Liu, P. IncRNA SNHG8 Promotes Liver Cancer Proliferation and Metastasis by Sponging miR-542-3p and miR-4701-5p. Res. Sq. 2021, 25. [CrossRef]

176. Wang, F.; Yuan, J.-H.; Wang, S.-B.; Yang, F.; Yuan, S.-X.; Ye, C.; Yang, N.; Zhou, W.-P.; Li, W.-L.; Sun, S.-H. Oncofetal long noncoding RNA PVT1 promotes proliferation and stem cell-like property of hepatocellular carcinoma cells by stabilizing NOP2. Hepatology 2014, 60, 1278–1289. [CrossRef] [PubMed]

177. Luo, Y.; Lin, J.; Zhang, J.; Song, Z.; Zheng, D.; Chen, F.; Zhuang, X.; Li, A.; Liu, X. LncRNA SNHG17 contributes to proliferation, migration, and poor prognosis of hepatocellular carcinoma. Can. J. Gastroenterol. Hepatol. 2021; 11, 9990338.

178. Liu, Y.; Yao, X.; Ma, Z.; Chen, W.; Guo, X.; Yu, L.; Deng, X.; Jiang, F.; Li, T.; Lin, N.; et al. Aberrant regulation of LncRNA TUG1-microRNA-328-3p-SRSF9 mRNA Axis in hepatocellular carcinoma: A promising target for prognosis and therapy. Mol. Cancer 2022, 21, 36. [CrossRef]

179. Liu, Y.; Liu, J.; Cui, J.; Zhong, R.; Sun, G. Role of IncRNA LINC01194 in hepatocellular carcinoma via the miR-655-3p/SMAD family member 5 axis. Bioengineered 2022, 13, 1115–1125. [CrossRef] [PubMed]

180. Pennisi, G.; Celsa, C.; Giammanno, A.; Spatola, F.; Petta, S. The burden of hepatocellular carcinoma in non-alcoholic fatty liver disease: Screening issue and future perspectives. Int. J. Mol. Sci. 2019, 20, 5613. [CrossRef] [PubMed]

181. Tian, Q.; Yan, X.; Yang, L.; Liu, Z.; Yuan, Z.; Zhang, Y. IncRNA CYTOR promotes cell proliferation and tumor growth via miR-125b/SEMA4C axis in hepatocellular carcinoma. Oncol. Lett. 2021, 22, 796. [CrossRef]

182. Fu, C.; Li, J.; Li, P.; Cheng, D. LncRNA DNAJC3-AS1 Promotes Hepatocellular Carcinoma (HCC) Progression via Sponging Premature miR-27b. Cancer Manag. Res. 2021, 13, 8575. [CrossRef]

183. Wang, Y.; Yang, L.; Chen, T.; Liu, X.; Guo, Y.; Zhu, Q.; Tong, X.; Yang, W.; Xu, Q.; Huang, D.; et al. A novel IncRNA MCM3AP-AS1 promotes the growth of hepatocellular carcinoma by targeting miR-194-5p/FOXA1 axis. Mol. Cancer 2019, 18, 28. [CrossRef]

184. Hu, X.; Li, Q.; Zhang, J. The long noncoding RNA LINC00908 facilitates hepatocellular carcinoma progression via interaction with Sox-4. Cancer Manag. Res. 2019, 11, 8789. [CrossRef]

185. Dai, W.; Dai, J.L.; Tang, M.H.; Ye, M.S.; Fang, S. IncRNA-SNHG15 accelerates the development of hepatocellular carcinoma by targeting miR-490-3p/histone deacetylase 2 axis. World J. Gastroenterol. 2019, 25, 5789. [CrossRef] [PubMed]

186. Sui, C.-J.; Zhou, Y.-M.; Chen, W.-F.; Dai, B.-H.; Lu, J.-J.; Zhang, M.-F.; Yang, J.-M. Long non-coding RNA GIHCG promotes hepatocellular carcinoma progression through epigenetically regulating miR-200b/a/429. J. Mol. Med. 2016, 94, 1281–1296. [CrossRef] [PubMed]

187. Huang, M.D.; Chen, W.M.; Qi, F.Z.; Xia, R.; Sun, M.; Xu, T.P.; Yin, L.; Zhang, E.B.; De, W.; Shu, Y.Q. Long non-coding RNA ANRIL is upregulated in hepatocellular carcinoma and regulates cell apoptosis by epigenetic silencing of KLF2. J. Hematol. Oncol. 2015, 8, 50. [CrossRef]
191. 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 hepatocellular carcinoma progression. *Cell. Biochem.* 2017, 118, 4836–4843. [CrossRef] [PubMed]

192. Li, T.; Xie, J.; Shen, C.; Cheng, D.; Shi, Y.; Wu, Z.; Deng, X.; Chen, H.; Shen, B.; Peng, C.; et al. Amplification of long noncoding RNA ZFAS1 promotes metastasis in hepatocellular carcinoma. *Cancer Res.* 2015, 75, 3181–3191. [CrossRef]

193. Yuan, S.-X.; Yang, F.; Yang, Y., Tao, Q.-F.; Zhang, J.; Huang, G.; Wang, R.-Y.; Yang, S.; Huo, X.-S.; Zhang, L.; 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]

194. Klingenberg, M.; Gross, M.; Goyal, A.; Polycarpou-Schwarz, M.; Miersch, T.; Ernst, A.S.; Leupold, J.; Patil, N.; Warnken, U.; Allgayer, H.; et al. The IncRNA CASC9 and RNA binding protein HNRNPL form a complex and co-regulate genes linked to AKT signaling. *Hepatology* 2018, 68, 1817–1832. [CrossRef]

195. Huang, Z.; Zhou, J.; Peng, Y.; He, W.; Huang, C. The role of long noncoding RNAs in hepatocellular carcinoma. *Cancer Res.* 2020, 19, 77. [CrossRef] [PubMed]

196. Ding, L.-J.; Li, Y.; Wang, S.-D.; Wang, X.-S.; Fang, F.; Wang, W.-Y.; Lv, P.; Zhao, D.-H.; Wei, F.; Qi, L. Long noncoding RNA LncRNA HOTAIR promotes human liver cancer stem cell malignant proliferation and metastasis via regulating miR-590-3p/ROCK axis in hepatocellular carcinoma. *Oncol. Lett.* 2017, 16, 1617. [CrossRef] [PubMed]

197. Li, X.; Zhao, Q.; Qi, J.; Wang, W.; Zhang, D.; Li, Z.; Qin, C. IncRNA Ftx promotes aerobic glycolysis and tumor progression through the PPARγ pathway in hepatocellular carcinoma. *Int. J. Oncol.* 2018, 53, 551–566. [CrossRef] [PubMed]

198. Wang, C.Z.; Yan, G.X.; Dong, D.S.; Xin, H.; Liu, Z.Y. LncRNA-ATB promotes autophagy by activating Yes-associated protein and inducing autophagy-related protein 5 expression in hepatocellular carcinoma. *World J. Gastroenterol.* 2019, 25, 5310. [CrossRef]

199. Pan, W.; Li, W.; Zhao, J.; Huang, Z.; Zhao, J.; Chen, S.; Wang, C.; Xue, Y.; Huang, F.; Fang, Q.; et al. Inc RNA-PD PK 2P promotes hepatocellular carcinoma progression through the PDK 1/ AKT/Caspase 3 pathway. *Mol. Oncol.* 2019, 13, 2246–2258. [CrossRef]

200. Wang, H.; HUO, X.; Yang, X.R.; He, J.; Cheng, L.; Wang, N.; Deng, X.; Jin, H.; Wang, N.; Wang, C.; et al. STAT3-mediated upregulation of IncRNA HOXD-AS1 as a ceRNA facilitates liver cancer metastasis by regulating SOX4. *Mol. Cancer* 2017, 16, 136. [CrossRef]

201. Chen, Z.; Yu, W.; Zhou, Q.; Zhang, J.; Jiang, H.; Hao, D.; Wang, J.; Zhou, Z.; He, C.; Xiao, Z. A novel IncRNA IHS promotes tumor proliferation and metastasis in HCC by regulating the ERK-and AKT/GSK-3β-signaling pathways. *Mol. Ther. Nucleic Acids* 2019, 16, 707–720. [CrossRef]

202. Wu, Y.; Xiong, Q.; Li, S.; Yang, X.; Ge, F. Integrated proteomic and transcriptomic analysis reveals long noncoding RNA HOX transcript antisense intergenic RNA (HOTAIR) promotes hepatocellular carcinoma cell proliferation by regulating opioid growth factor receptor (OGFr). *Mol. Cell. Proteom.* 2018, 17, 146–159. [CrossRef]

203. Cheng, D.; Deng, J.; Zhang, B.; He, X.; Meng, Z.; Li, G.; Ye, H.; Zheng, S.; Wei, L.; Deng, X.; et al. LncRNA HOTAIR epigenetically suppresses miR-122 expression in hepatocellular carcinoma via DNA methylation. *EBioMedicine* 2018, 36, 159–170. [CrossRef]

204. Yao, Y.; Li, J.; Wang, L. Large intergenic non-coding RNA HOTAIR is an indicator of poor prognosis and a therapeutic target in human cancers. *Int. J. Mol. Sci.* 2014, 15, 18985–18999. [CrossRef] [PubMed]

205. Wu, L.; Zhang, L.; Zheng, S. Role of the long non-coding RNA HOTAIR in hepatocellular Carcinoma. *Oncol. Lett.* 2017, 14, 1233–1239. [CrossRef] [PubMed]

206. Li, H.; An, J.; Wu, M.; Zheng, Q.; Gui, X.; Li, T.; Pu, H.; Lu, D. LncRNA HOTAIR promotes human liver cancer stem cell malignant growth through downregulation of SETD2. *Oncotarget* 2015, 6, 27847. [CrossRef] [PubMed]

207. You, L.-N.; Tai, Q.-W.; Xu, L.; Hao, Y.; Guo, W.-J.; Zhang, Q.; Tong, Q.; Zhang, H.; Huang, W.-K. Exosomal LIN00161 promotes angiogenesis and metastasis via regulating miR-590-3p/ROCK axis in hepatocellular carcinoma. *Cancer Gene Ther.* 2021, 28, 719–736. [CrossRef]

208. Lin, Y.; Jian, Z.; Jin, H.; Wei, X.; Zou, X.; Guan, R.; Huang, J. Long non-coding RNA DLGAP1-AS1 facilitates tumorigenesis and epithelial–mesenchymal transition in hepatocellular carcinoma via the feedback loop of miR-26a/b-5p/IL-6/JAK2/STAT3 and Wnt/β-catenin pathway. *Cell Death Dis.* 2020, 11, 1–17. [CrossRef] [PubMed]

209. Yi, T.; Wang, T.; Shi, Y.; Peng, X.; Tang, S.; Zhong, L.; Chen, Y.; Li, Y.; He, K.; Wang, M.; et al. Long noncoding RNA 91H overexpression contributes to the growth and metastasis of HCC by epigenetically positively regulating IGF2 expression. *Liver Int.* 2020, 40, 456–467. [CrossRef]
210. Teng, F.; Zhang, J.-X.; Chang, Q.-M.; Wu, X.-B.; Tang, W.-G.; Wang, J.-F.; Feng, J.-F.; Zhang, Z.-P.; Hu, Z.-Q. LncRNA MYLK-AS1 facilitates tumor progression and angiogenesis by targeting miR-424-5p/E2F7 axis and activating VEGFR-2 signaling pathway in hepatocellular carcinoma. *J. Exp. Clin. Cancer Res.* 2020, 39, 1–18.

211. Tian, C.; Abudoureyimu, M.; Lin, X.; Chu, X.; Wang, R. Linc-ROR facilitates progression and angiogenesis of hepatocellular carcinoma by modulating DEPDC1 expression. *Cell Death Dis.* 2021, 12, 1047. [CrossRef]

212. Li, P.; Li, Y.; Ma, L. Long noncoding RNA highly upregulated in liver cancer promotes the progression of hepatocellular carcinoma and attenuates the chemosensitivity of oxaliplatin by regulating miR-383-5p/vesicle-associated membrane protein-2 axis. *Pharmaco. Res. Perspect.* 2021, 9, e00815. [CrossRef]

213. Qian, H.; Wu, Q.; Wu, J.H.; Tian, X.Y.; Xu, W.; Hao, C.Y. Long noncoding LINC00238 restrains Hepatocellular Carcinoma Malignant Phenotype via Sponging miR-322. *Res. Sq.* 2021, 21. [CrossRef]

214. Liu, Y.; Liu, R.; Zhao, J.; Zeng, Z.; Shi, Z.; Lu, Q.; Guo, J.; Li, L.; Yao, Y.; Liu, X.; et al. LncRNA TMEM220-AS1 suppresses hepatocellular carcinoma cell proliferation and invasion by regulating the TMEM220/β-catenin axis. *J. Cancer* 2021, 12, 6805. [CrossRef]

215. Sheng, J.-Q.; Wang, M.-R.; Fang, D.; Liu, L.; Huang, W.-J.; Tian, D.-A.; He, X.-X.; Li, P.-Y. LncRNA NBR2 inhibits tumorigenesis by regulating autophagy in hepatocellular carcinoma. *Biomed. Pharmacother.* 2021, 133, 111023. [CrossRef]

216. Lei, G.-L.; Fan, H.-X.; Wang, C.; Niu, Y.; Li, T.-L.; Yu, L.-X.; Hong, Z.-X.; Yan, J.; Wang, X.-L.; Zhang, S.-G.; et al. Long non-coding ribonucleic acid W5 inhibits progression and predicts favorable prognosis in hepatocellular carcinoma. *World J. Gastroenterol.* 2022, 27, 55. [CrossRef]

217. Tian, C.; Abudoureyimu, M.; Lin, X.; Chu, X.; Wang, R. LncRNA MYLK-AS1 facilitates progression and angiogenesis of hepatocellular carcinoma by modulating DEPDC1 expression. *Cell Death Dis.* 2021, 12, 1047. [CrossRef]

218. Wu, Y.; Zhou, Y.; Huan, L.; Xu, L.; Shen, M.; Huang, S.; Liang, L. LncRNA MIR22HG inhibits growth, migration and invasion through regulating the miR-10a-5p/NCOR2 axis in hepatocellular carcinoma cells. *Cancer Sci.* 2019, 110, 973–984. [CrossRef] [PubMed]

219. Pan, W.; Zhang, N.; Liu, W.; Liu, J.; Zhou, L.; Liu, Y.; Yang, M. The long noncoding RNA GAS8-AS1 suppresses hepatocarcinogenesis by epigenetically activating the tumor suppressor GAS8. *J. Biol. Chem.* 2018, 293, 17154–17165. [CrossRef]

220. Wang, Y.-G.; Wang, T.; Shi, M.; Zhai, B. Long noncoding RNA EPB41L4A-AS2 inhibits hepatocellular carcinoma development by sponging miR-301a-5p and targeting FOXL1. *Exp. Clin. Cancer Res.* 2018, 37, 214. [CrossRef] [PubMed]

221. Chen, F.; Li, Y.; Li, M.; Wang, L. Long noncoding RNA GAS5 inhibits metastasis by targeting miR-182/ANGPTL1 in hepatocellular carcinoma. *Am. J. Cancer Res.* 2019, 9, 108. [PubMed]

222. Yu, Z.; Zhao, H.; Feng, X.; Li, H.; Qiu, C.; Yi, X.; Tang, H.; Zhang, J. Long non-coding RNA FENDRR acts as a miR-423-5p sponge to suppress the Treg-mediated immune escape of hepatocellular Carcinoma cells. *J. Cancer* 2019, 10, 516–529. [CrossRef]

223. Wu, Y.; Zhou, Y.; Huan, L.; Xu, L.; Shen, M.; Huang, S.; Liang, L. LncRNA MIR22HG inhibits growth, migration and invasion through regulating the miR-10a-5p/NCOR2 axis in hepatocellular carcinoma cells. *Cancer Sci.* 2019, 110, 973–984. [CrossRef] [PubMed]

224. Hu, J.; Song, C.; Duan, B.; Zhang, X.; Li, D.; Zhu, L.; Gao, H. LncRNA-SVUGP2 suppresses progression of hepatocellular carcinoma via the miR-195-5p/MACC1 pathway. *Ann. Hepatol.* 2020, 19, 100258. [CrossRef]

225. Hu, J.; Song, C.; Duan, B.; Zhang, X.; Li, D.; Zhu, L.; Gao, H. LncRNA-SVUGP2 suppresses progression of hepatocellular carcinoma via the miR-195-5p/MACC1 pathway. *Ann. Hepatol.* 2020, 19, 100258. [CrossRef]

226. Huang, J.-F.; Guo, Y.-J.; Zhao, C.-X.; Yuan, S.-X.; Wang, Y.; Tang, G.-N.; Zhou, W.-P.; Sun, S.-H. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma progression and predicts favorable prognosis in hepatocellular carcinoma. *J. Cancer* 2021, 12, 38. [CrossRef]

227. Hu, J.; Song, C.; Duan, B.; Zhang, X.; Li, D.; Zhu, L.; Gao, H. LncRNA-SVUGP2 suppresses progression of hepatocellular carcinoma. *Oncotarget* 2017, 8, 97835. [CrossRef]

228. Jiang, X.; Wang, G.; Liu, Y.; Mei, C.; Yao, Y.; Wu, X.; Chen, X.; Ma, W.; Li, K.; Zhang, Z.; et al. A novel long non-coding RNA RP11-286H15.1 represses hepatocellular carcinoma progression by promoting ubiquitination of PABPC4. *Cancer Lett.* 2021, 499, 109–121. [CrossRef]

229. Wang, Y.; Guo, Y.-J.; Zhao, C.-X.; Yuan, S.-X.; Wang, Y.; Tang, G.-N.; Zhou, W.-P.; Sun, S.-H. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma progression by targeting intermediate filament protein vimentin. *Hepatology*. 2013, 57, 1882–1892. [CrossRef]

230. Huang, L.-K.; Yang, Y.T.; Ma, X.; Han, B.; Wang, Z.S.; Zhao, Q.Y.; Wu, L.Q.; Qu, Z.Q. MicroRNA-92b promotes hepatocellular Carcinoma progression by targeting Smad7 and is mediated by long non-coding RNA XIST. *J. Cancer* 2021, 12, 2203. [CrossRef]

231. Wang, Y.; Guo, Y.-J.; Zhao, C.-X.; Yuan, S.-X.; Wang, Y.; Tang, G.-N.; Zhou, W.-P.; Sun, S.-H. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma progression by targeting intermediate filament protein vimentin. *Hepatology*. 2013, 57, 1882–1892. [CrossRef]

232. Wang, Y.; Guo, Y.-J.; Zhao, C.-X.; Yuan, S.-X.; Wang, Y.; Tang, G.-N.; Zhou, W.-P.; Sun, S.-H. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma progression by targeting intermediate filament protein vimentin. *Hepatology*. 2013, 57, 1882–1892. [CrossRef]

233. Wang, Y.; Guo, Y.-J.; Zhao, C.-X.; Yuan, S.-X.; Wang, Y.; Tang, G.-N.; Zhou, W.-P.; Sun, S.-H. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Dreh) inhibits hepatocellular carcinoma progression by targeting intermediate filament protein vimentin. *Hepatology*. 2013, 57, 1882–1892. [CrossRef]
233. Hu, W.Y.; Wei, H.Y.; Li, K.M.; Wang, R.B.; Xu, X.Q.; Feng, R. LINC00511 as a ceRNA promotes cell malignant behaviors and correlates with prognosis of hepatocellular carcinoma patients by modulating miR-195/EYA1 axis. *Biomed. Pharmacother.* **2020**, *121*, 109642. [CrossRef] [PubMed]

234. Yu, J.; Han, J.; Zhang, J.; Li, G.; Liu, H.; Cui, X.; Xu, Y.; Li, T.; Liu, J.; Wang, C. The long noncoding RNAs PVT1 and uc002mbe in sera provide a new supplementary method for hepatocellular carcinoma diagnosis. *Medicine* **2016**, *95*, e4436. [CrossRef] [PubMed]

235. 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. *Int. J. Med. Res.* **2018**, *46*, 348–356. [CrossRef] [PubMed]

236. Li, G.; Shi, H.; Wang, X.; Wang, B.; Qu, Q.; Geng, H.; Sun, H. Identification of diagnostic long non-coding RNA biomarkers in patients with hepatocellular carcinoma. *Mo. Med. Rep.* **2019**, *20*, 1121–1130. [CrossRef] [PubMed]

237. Wang, Z.; Hu, R.; Pang, J.; Zhang, G.; Yan, W.; Li, Z. Serum long noncoding RNA LRBI as a potential biomarker for predicting the diagnosis and therapeutic target and prognostic biomarker for hepatocellular carcinoma. *Oncol. Lett.* **2018**, *16*, 1593–1601. [CrossRef]

238. Luo, T.; Chen, M.; Zhao, Y.; Wang, D.; Liu, J.; Chen, J.; Luo, H.; Li, L. Macrophage-associated IncRNA ELM01-AS1: A novel therapeutic target and prognostic biomarker for hepatocellular carcinoma. *Oncotargets Ther.* **2019**, *12*, 6203. [CrossRef] [PubMed]

239. Zhou, C.-C.; Yang, F.; Yuan, S.-X.; Ma, J.-Z.; Liu, F.; Yuan, J.-H.; Bi, F.-R.; Lin, K.-Y.; Yin, J.-H.; Cao, G.-W.; et al. Systemic genome screening identifies the outcome associated focal loss of long noncoding RNA PRAL in hepatocellular carcinoma. *Hepatology* **2016**, *63*, 850–863. [CrossRef]

240. Wang, Z.; Yang, B.; Zhang, M.; Guo, W.; Wu, Z.; Wang, Y.; Jia, L.; Li, S.; Caesar-Johnson, S.J.; Demchok, J.A.; et al. IncRNA epigenetic landscape analysis identifies EPI1C as an oncogenic IncRNA that interacts with MYC and promotes cell-cycle progression in cancer. *Cancer Cell* **2018**, *33*, 706–720.e9. [CrossRef]

241. Xing, Z.; Lin, A.; Li, C.; Liang, K.; Wang, S.; Liu, Y.; Park, P.K.; Qin, L.; Wei, Y.; Hawke, D.H.; et al. IncRNA directly cooperates epigenetic regulation downstream of chemokine signals. *Cell* **2014**, *159*, 1110–1125. [CrossRef]

242. Chiappinelli, K.B.; Strissel, P.L.; Desrichard, A.; Li, H.; Henke, C.; Akman, B.; Hein, A.; Rote, N.S.; Cope, L.M.; Snyder, A.; et al. Inhibiting DNA methylation causes an interferon response in cancer via dsRNA including endogenous retroviruses. *Cell* **2015**, *162*, 974–986. [CrossRef]

243. Guccione, E.; Bassi, C.; Casadio, F.; Martinato, F.; Cesaroni, M.; Schuchlautz, H.; Lüscher, B.; Amati, B. Methylation of histone H3R2 by PRMT6 and H3K4 by an MLL complex are mutually exclusive. *Nature* **2007**, *449*, 933–937. [CrossRef]

244. Chen, X.; Tang, F.-R.; Artuso, F.; Cai, W.-Q.; Ma, Z.; Yang, J.; Sethi, G. The emerging role of long non-coding RNAs in the metastasis of hepatocellular carcinoma. *Biomolecules* **2020**, *10*, 66. [CrossRef]

245. Yuan, S.-X.; Zhang, J.; Xu, Q.-G.; Yang, Y.; Zhou, W.-P. Long noncoding RNA, the methylation of genomic elements and their emerging crosstalk in hepatocellular carcinoma. *Cancer Lett.* **2016**, *379*, 239–244. [CrossRef]

246. Xu, X.; Lou, Y.; Tang, J.; Teng, Y.; Zhang, Z.; Yin, Y.; Zhuo, H.; Tan, Z. The long non-coding RNA Linc-GALH promotes hepatocellular carcinoma metastasis via epigenetically regulating Gankylin. *Cell Death Dis.* **2019**, *10*, 1–13. [CrossRef]

247. Nebel, S.; Lux, M.; Kuth, S.; Bider, F.; Dietrich, W.; Egger, D.; Boccaccini, A.R.; Kasper, C. Alginate Core–Shell Capsules for 3D Cultivation of Adipose-Derived Mesenchymal Stem Cells. *Bioengineering* **2022**, *9*, 66. [CrossRef] [PubMed]

248. Tang, J.; Xie, Y.; Xu, X.; Yin, Y.; Jiang, R.; Deng, L.; Tan, Z.; Gargarapu, 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]

249. Chen, Z.; Gao, Y.; Yao, L.; Liu, Y.; Huang, L.; Yan, Z.; Zhao, W.; Zhu, P.; Weng, H. LincFZD6 initiates Wnt/β-catenin and liver TIC self-renewal through BRG1-mediated FZD6 transcriptional activation. *Oncogene* **2018**, *37*, 3098–3112. [CrossRef] [PubMed]

250. Zheng, G.X.; Do, B.T.; Webster, D.E.; Khavarì, P.A.; Chang, H.Y. Dicer-microRNA-Myc circuit promotes transcription of hundreds of long noncoding RNA LINC01093 suppresses HCC progression by interaction with IGF2BP1 to facilitate decay of GLI1 mRNA. *Cancer Lett.* **2019**, *450*, 98–109. [CrossRef]

251. Tran, D.D.H.; Kessler, C.; Niehus, S.; Mahnkopf, M.; Koch, A.; Tamura, T. Myc target gene, long intergenic noncoding RNA, the methylation of genomic elements and their emerging crosstalk in hepatocellular carcinoma. *Cell Death Dis.* **2016**, *7*, 572–585. [CrossRef]

252. Li, W.; Kang, Y. A new Lnc in metastasis: Long noncoding RNA mediates the prometastatic functions of TGF-β. *Cancer Cell* **2014**, *25*, 557–559. [CrossRef]

253. Yuan, J.H.; Liu, X.N.; Wang, T.T.; Pan, W.; Tao, Q.F.; Zhou, W.P.; Wang, F.; Sun, S.H. The MBNL3 splicing factor promotes hepatocellular carcinoma by increasing PXN expression through the alternative splicing of IncRNA-PXN-AS1. *Nat. Cell Biol.* **2017**, *19*, 820–832. [CrossRef] [PubMed]

254. He, J.; Zuo, Q.; Hu, B.; Jin, H.; Wang, C.; Cheng, Z.; Deng, X.; Yang, C.; Ruan, H.; Yu, C.; et al. A novel, liver-specific long noncoding RNA LINC01093 suppresses HCC progression by interaction with IGF2BP1 to facilitate decay of GLI1 mRNA. *Cancer Lett.* **2019**, *450*, 98–109. [CrossRef]

255. Moore, J.B., IV; Uchida, S. Functional characterization of long noncoding RNAs. *Curr. Opin. Cardiol.* **2020**, *35*, 199–206. [CrossRef] [PubMed]

256. Salmena, L.; Poliseno, L.; Tay, Y.; Kats, L.; Pandolﬁ, P.P. A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? *Cell* **2011**, *146*, 353–358. [CrossRef] [PubMed]

257. Yoon, J.-H.; Abdelmohsen, K.; Gorospe, M. Functional interactions among microRNAs and long noncoding RNAs. In *Seminars in Cell & Developmental Biology*; Elsevier: Amsterdam, The Netherlands, 2014.
Bioengineering 2022, 9, 406

258. Cesana, M.; Cacchiarelli, D.; Legnini, I.; Santini, T.; Sthandier, O.; Chinappi, M.; Tramontano, A.; Bozzoni, I. A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell 2011, 147, 358–369. [CrossRef] [PubMed]

259. Uchida, S.; Kauppinen, S. Long non-coding RNAs in liver cancer and nonalcoholic steatohepatitis. Non-Coding RNA 2020, 6, 34.

260. Xie, C.-R.; Wang, F.; Zhang, S.; Wang, F.-Q.; Zheng, S.; Li, Z.; Lv, J.; Qi, H.-Q.; Fang, Q.-L.; Wang, X.-M.; et al. Long noncoding RNA HULC facilitates the growth and metastasis of hepatocellular carcinoma by acting as a ceRNA of LAPT4MB. Mol. Ther. Nucleic Acids 2017, 9, 440–451. [CrossRef]

261. Ho, 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. Tumor Biol. 2017, 39, 1010428317718135. [CrossRef]

262. Lu, S.; Zhou, J.; Sun, Y.; Li, N.; Miao, M.; Jiao, B.; Chen, H. The noncoding RNA HOXD-AS1 is a critical regulator of the metastasis and apoptosis phenotype in human hepatocellular carcinoma. Mol. Cancer 2017, 16, 125. [CrossRef] [PubMed]

263. 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. [CrossRef] [PubMed]

264. Yang, F.; Huo, X.-S.; Yuan, S.-X.; Zhang, L.; Zhou, W.-P.; Wang, F.; Sun, S.-H. Repression of the long noncoding RNA-LET by histone deacetylase 3 contributes to hypoxia-mediated metastasis. Mol. Cell 2013, 49, 1083–1096. [CrossRef] [PubMed]

265. Cesana, M.; Cacchiarelli, D.; Legnini, I.; Santini, T.; Sthandier, O.; Chinappi, M.; Tramontano, A.; Bozzoni, I. A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell 2011, 147, 358–369. [CrossRef] [PubMed]

266. Li, Z.; Zhang, J.; Liu, X.; Li, S.; Wang, Q.; Li, S.; Chen, D.; Hu, Z.; Yu, T.; Ding, J.; Li, J.; et al. The LINC01138 drives malignancies via LncRNA HNF1A-AS1 reverses the malignancy of hepatocellular carcinoma by enhancing the phosphatase activity of SHP-1. Mol. Cancer 2018, 17, 63. [CrossRef] [PubMed]

267. Ding, C.H.; Yin, C.; Chen, S.J.; Wen, L.Z.; Ding, K.; Lei, S.J.; Liu, J.P.; Wang, J.; Chen, K.X.; Jiang, H.L.; et al. The LINC01138 drives malignancies via LncRNA HNF1A-AS1 reverses the malignancy of hepatocellular carcinoma by enhancing the phosphatase activity of SHP-1. Mol. Cancer 2018, 17, 63. [CrossRef] [PubMed]

268. Yang, F.; Huo, X.-S.; Yuan, S.-X.; Zhang, L.; Zhou, W.-P.; Wang, F.; Sun, S.-H. Repression of the long noncoding RNA-LET by histone deacetylase 3 contributes to hypoxia-mediated metastasis. Mol. Cell 2013, 49, 1083–1096. [CrossRef] [PubMed]

269. Tao, G.-Z.; Lehwald, N.; Jang, K.Y.; Baek, J.; Xu, B.; Omary, M.B.; Sylvester, K.G. Wnt/β-catenin signaling protects mouse liver against oxidative stress-induced apoptosis through the inhibition of forkhead transcription factor FoxO. J. Biol. Chem. 2013, 288, 17214–17224. [CrossRef] [PubMed]

270. Chen, X.; Xu, C.; Liu, Y. Involvement of ERK1/2 signaling in proliferation of eight liver cell types during hepatic regeneration in rats. Genet. Mol. Res. 2013, 12, 665–677. [CrossRef]

271. Xu, D.; Yang, F.; Yuan, J.-H.; Zhang, L.; Bi, H.-S.; Zhou, C.-C.; Liu, F.; Wang, F.; Sun, S.-H. Long noncoding RNAs associated with liver regeneration 1 accelerates hepatocyte proliferation during liver regeneration by activation Wnt/β-Catenin signaling. Hepatol. 2018, 1, 148, 1294–1310. [CrossRef] [PubMed]

272. Schmitt, A.M.; Chang, H.Y. Long noncoding RNAs in cancer pathways. Cancer Cell 2016, 29, 452–463. [CrossRef]

273. Clevers, H. Wnt/β-catenin signaling in development and disease. Cell 2006, 127, 469–480. [CrossRef]

274. Clevers, H.; Nusse, R. Wnt/β-catenin signaling and disease. Cell 2012, 149, 1192–1205. [CrossRef]

275. Monga, S.P. β-catenin signaling and roles in liver homeostasis, injury, and tumorigenesis. Gastroenterology 2015, 148, 1294–1310. [CrossRef] [PubMed]

276. Xie, C.; Li, S.-Y.; Fang, J.-H.; Zhu, Y.; Yang, J.-E. Functional long non-coding RNAs in hepatocellular carcinoma. Cancer Lett. 2020, 500, 288–291. [CrossRef]

277. Li, Z.; Zhang, J.; Li, X.; Li, S.; Wang, Q.; Chen, D.; Hu, Z.; Yu, T.; Ding, J.; Li, J.; et al. The LINC01138 drives malignancies via activating arginine methyltransferase 5 in hepatocellular carcinoma. Nat. Commun. 2018, 9, 1572. [CrossRef] [PubMed]

278. Xu, W.-H.; Zhang, J.-B.; Dang, Z.; Li, X.; Zhou, T.; Liu, J.; Wang, D.-S.; Song, W.-J.; Dou, K.-F. Long non-coding RNA UHRIC regulates cell proliferation and apoptosis via ZAK through the ERK/MAPK signaling pathway in hepatocellular carcinoma. Int. J. Biol. Sci. 2014, 10, 664. [CrossRef]

279. Zhang, L.; Yang, F.U.; 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]

280. Dai, X.; Ahrn, K.S.; Kim, C.; Siveen, K.S.; Ong, T.H.; Shammugam, M.K.; Li, F.; Shi, J.; Kumar, A.P.; Wang, L.Z.; et al. Ascorclorin, an isoprenoid antibiotic inhibits growth and invasion of hepatocellular carcinoma by targeting STAT3 signaling cascade through the induction of PIAS3. Mol. Oncol. 2015, 9, 818–833. [CrossRef] [PubMed]

281. Rajendran, P.; Li, F.; Shammugam, M.K.; Vali, S.; Abbasi, T.; Kapoor, S.; Ahrn, K.S.; Kumar, A.P.; Sethi, G. Honokiol inhibits signal transducer and activator of transcription-3 signaling, proliferation, and survival of hepatocellular carcinoma cells via the protein tyrosine phosphatase SHP-1. J. Cell. Physiol. 2012, 227, 2184–2195. [CrossRef] [PubMed]

282. Huang, J.-L.; Cao, S.-W.; Ou, Q.-S.; Yang, B.; Zheng, S.-H.; Tang, J.; Chen, J.; Hu, Y.-W.; Zheng, L.; Wang, Q. The long non-coding RNA PTIG3P promotes cell growth and metastasis via up-regulating PTG1 and activating PI3K/AKT signaling in hepatocellular carcinoma. Mol. Cancer 2018, 17, 93. [CrossRef]
Bioengineering 2022, 9, 406

283. Zhao, X.; Liu, Y.; Yu, S. Long noncoding RNA AWPPH promotes hepatocellular carcinoma progression through YBX1 and serves as a prognostic biomarker. *Biochim. Biophys. Acta Mol. Basis Dis.* 2017, 1863, 1805–1816. [CrossRef]

284. Tang, J.; Zhou, H.; Zhang, X.; Jiang, R.; Ji, J.; Deng, L.; Qian, X.; Zhang, F.; Sun, B. A novel biomarker Linc00974 interacting with KRT19 promotes proliferation and metastasis in hepatocellular carcinoma. *Cell Death Dis.* 2014, 5, e1549. [CrossRef]

285. Zhi, Y.; Huang, S.; Lina, Z. Suppressor of Cytokine Signaling 6 in cancer development and therapy: Deciphering its emerging and suppressive roles. *Cytokine Growth Factor Rev.* 2022, 64, 21–32.

286. Zhang, L.-H.; Ji, J.-F. Molecular profiling of hepatocellular carcinomas by cDNA microarray. *World J. Gastroenterol.* 2005, 11, 463. [CrossRef] [PubMed]

287. Aravalli, R.N.; Steer, C.J.; Cressman, E.N. Molecular mechanisms of hepatocellular carcinoma. *Hepatology* 2008, 48, 2047–2063. [CrossRef]

288. Ogunwobi, O.O.; Puszyk, W.; Dong, H.-J.; Liu, C. Epigenetic upregulation of HGF and c-Met drives metastasis in hepatocellular carcinoma. *PLoS ONE* 2013, 8, e63765. [CrossRef]

289. Long, L.; Xiang, H.; Liu, J.; Zhang, Z.; Sun, L. ZEB1 mediates doxorubicin (Dox) resistance and mesenchymal characteristics of hepatocarcinoma cells. *Exp. Mol. Pathiol.* 2019, 106, 116–122. [CrossRef] [PubMed]

290. Qu, W.; Wen, X.; Su, K.; Gou, W. MiR-552 promotes the proliferation, migration and EMT of hepatocellular carcinoma cells by inhibiting AJAP1 expression. *J. Cell Mol. Med.* 2019, 23, 1541–1552. [CrossRef] [PubMed]

291. Lu, Y.J.; Lin, N.A.N.; Chen, Z.; Xu, R. Hypoxia-induced secretion of platelet-derived growth factor-BB by hepatocellular carcinoma cells increases activated hepatic stellate cell proliferation, migration and expression of vascular endothelial growth factor-A. *Mol. Med. Rep.* 2015, 11, 691–697. [CrossRef] [PubMed]

292. Galié, M.; Sorrentino, C.; Montani, M.; Micossi, L.; Di Carlo, E.; D’Antuono, T.; Calderan, L.; Marzola, P.; Benati, D.; Mergio, F.; et al. Mammary carcinoma shows highly tumourigenic and invasive reactive stromal cells. *Carcinogenesis* 2005, 26, 1868–1878. [CrossRef] [PubMed]

293. Hernandez–Gea, V.; Toffanin, S.; Friedman, S.L.; Llovet, J.M. Role of the microenvironment in the pathogenesis and treatment of hepatocellular Carcinoma. *Gastroenterology* 2014, 144, 512–527. [CrossRef]

294. Wu, S.; E Powers, S.; Zhu, W.; Hannun, Y.A. Substantial contribution of extrinsic risk factors to cancer development. *Nature* 2016, 529, 43–47. [CrossRef]

295. Yamashita, T.; Ji, J.; Budhu, A.; Forgues, M.; Yang, W.; Wang, H.Y.; Jia, H.; Ye, Q.; Qin, L.X.; Wauthier, E.; et al. EpCAM-positive hepatocellular carcinoma cells are tumour-initiating cells with stem/progenitor cell features. *Gastroenterology* 2009, 136, 1012–1024.e4. [CrossRef]

296. Yang, Z.F.; Ho, D.W.; Ng, M.N.; Lau, C.K.; Yu, W.C.; Wu, C.-S.; et al. Mammary carcinoma provides highly tumourigenic and invasive reactive stromal cells. *Carcinogenesis* 2005, 26, 1868–1878. [CrossRef] [PubMed]

297. Ma, S.; Chan, K.-W.; Hu, L.; Lee, T.K.-W.; Wo, J.Y.-H.; Ng, I.O.-L.; Zheng, B.-J.; Guan, X.-Y. Identification and characterization of cancer stem/progenitor cells are highly enriched in CD133+ CD44+ tumorigenic liver cancer stem/progenitor cells. *Gastroenterology* 2007, 132, 2542–2556. [CrossRef] [PubMed]

298. Zhu, Z.; Hao, X.; Yan, M.; Yao, M.; Ge, C.; Gu, J.; Li, J. Cancer stem/progenitor cells are highly enriched in CD133+ CD44+ population in hepatocellular carcinoma. *Int. J. Cancer* 2010, 126, 2067–2078. [CrossRef] [PubMed]

299. Haraguchi, N.; Ishii, H.; Mimori, K.; Tanaka, F.; Ohkuma, M.; Kim, H.M.; Akitaka, H.; Takiuchi, D.; Hatano, H.; Nagano, H.; et al. CD13 is a therapeutic target in human liver cancer stem cells. *Cancer Cell* 2008, 13, 153–166. [CrossRef]

300. Ma, S.; Chan, K.-W.; Hu, L.; Lee, T.K.-W.; Wu, J.Y.-H.; Ng, I.O.-L.; Zheng, B.-J.; Guan, X.-Y. Identification and characterization of tumorigenic liver cancer stem/progenitor cells. *Carcinogenesis* 2007, 132, 2542–2556. [CrossRef] [PubMed]

301. Zhu, Z.; Hao, X.; Yan, M.; Yao, M.; Ge, C.; Gu, J.; Li, J. Cancer stem/progenitor cells are highly enriched in CD133+ CD44+ population in hepatocellular carcinoma. *Int. J. Cancer* 2010, 126, 2067–2078. [CrossRef] [PubMed]

302. Chang, T.-S.; Wu, Y.-C.; Tung, S.-Y.; Wei, K.-L.; Hsieh, Y.-Y.; Huang, H.-C.; Chen, W.-M.; Shen, C.-H.; Lu, C.-H.; Wu, C.-S.; et al. Alpha-fetoprotein measurement benefits hepatocellular carcinoma surveillance in patients with cirrhosis. *Am. J. Gastroenterol.* 2015, 110, 836–844. [CrossRef] [PubMed]

303. Biseeglie, A.M.; Sterling, R.K.; Chung, R.T.; Everhart, J.E.; Dienstag, J.L.; Bonkovsky, H.L.; Wright, E.C.; Everson, G.T.; Lindsay, K.L.; Lok, A.S.; et al. Serum alpha-fetoprotein levels in patients with advanced hepatitis C: Results from the HALT-C. *J. Clin. Investig.* 2013, 126, 3326–3339. [CrossRef] [PubMed]

304. Moon, A.M.; Weiss, N.S.; Beste, L.A.; Su, F.; Ho, S.B.; Jin, G.-Y.; Lowy, E.; Berry, K.; Ioannou, G.N. No association between screening for hepatocellular and reduced cancer-related mortality in patients with cirrhosis. *Gastroenterology* 2018, 155, 1128–1139.e6. [CrossRef]

305. Xu, C.; Xu, Z.; Zhang, Y.; Evert, M.; Calvisi, D.F.; Chen, X. β-Catenin signaling in hepatocellular carcinoma. *J. Clin. Investig.* 2022, 132, e154515. [CrossRef]

306. Li, J.; Yang, X.; Huang, L.; Zhu, X.; Qiu, M.; Yan, J.; Yan, Y.; Wei, S. Treatment Strategy for Post-hepatectomy Recurrent Hepatocellular Carcinoma Within the Milan Criteria: Repeat Resection, Local Ablative Therapy or Transarterial Chemoembolization? *Indian J. Surg.* 2022, 84, 1–6. [CrossRef]

307. Kamel, M.M.; Mathboli, M.; Sallam, M.; Montasser, I.F.; Saad, A.S.; El-Tawidi, A.H. Investigation of long noncoding RNAs expression profile as potential serum biomarkers in patients with hepatocellular carcinoma. *Transl. Res.* 2016, 168, 134–145. [CrossRef]
308. Kodidela, S.; Behera, A.; Reddy, A.B.M. Risk factors and clinical aspects associated with hepatocellular carcinoma: Role of long non-coding RNAs. In *Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 341–356.

309. Luo, P.; Liang, C.; Zhang, X.; Liu, X.; Wang, Y.; Wu, M.; Feng, X.; Tu, J. Identification of long non-coding RNA ZFAS1 as a novel biomarker for diagnosis of HCC. *Biosci. Rep.* 2018, 38, 31. [CrossRef]

310. Li, Y.; Zhao, J.; Yu, S.; Wang, Z.; He, X.; Su, Y.; Guo, T.; Sheng, H.; Chen, J.; Zheng, Q.; et al. Extracellular vesicles long RNA sequencing reveals abundant mRNA, circRNA, and lncRNA in human blood as potential biomarkers for cancer diagnosis. *Clin. Chem.* 2019, 65, 798–808. [CrossRef] [PubMed]

311. Xu, H.; Chen, Y.; Dong, X.; Wang, X. Serum exosomal long noncoding RNAs ENSG00000258332. 1 and LINC00635 for the diagnosis and prognosis of hepatocellular carcinoma. *Cancer Epidemiol. Biomark. Prev.* 2018, 27, 710–716. [CrossRef]

312. Sasaki, R.; Kanda, T.; Yokosuka, O.; Kato, N.; Matsuoka, S.; Moriyama, M. Exosomes and hepatocellular carcinoma: From bench to bedside. *Int. J. Mol. Sci.* 2019, 20, 1406. [CrossRef] [PubMed]

313. Zhang, C.; Ji, Q.; Yang, Y.; Li, Q.; Wang, Z. Exosome: Function and role in cancer metastasis and drug resistance. *Technol. Cancer Res. Treat.* 2018, 17, 153303818763450. [CrossRef] [PubMed]

314. Yuan, W.; Sun, Y.; Liu, L.; Zhou, B.; Wang, S.; Gu, D. Circulating LncRNAs serve as diagnostic markers for hepatocellular carcinoma. *Cell. Physiol. Biochem.* 2017, 44, 125–132. [CrossRef]

315. Wu, E.-R.; Hsieh, M.-J.; Chiang, W.-L.; Hsieh, K.-C.; Yang, S.-F.; Su, S.-C. Association of IncRNA CCAT2 and CASC8 gene polymorphisms with hepatocellular carcinoma. *Int. J. Environ. Res.* 2019, 26, 1833. [CrossRef] [PubMed]

316. Tonus, C.; Cloquette, K.; Ectors, F.; Piret, J.; Gillet, L.; Antoine, N.; Desmecht, D.; Vanderplasschen, A.; Waroux, O.; Grobet, L. Long term-cultured and cryopreserved primordial germ cells from various chicken breeds retain high proliferative potential and gonadal colonisation competency. *Reprod. Fertil. Dev.* Dec. 2016, 28, 628–639. [CrossRef] [PubMed]

317. Hong, D.; Kurzrock, R.; Kim, Y.; Woessner, R.; Younes, A.; Nemunaitis, J.; Fowler, N.; Zhou, T.; Schmidt, J.; Mo, J.; et al. AZD9150, a next-generation antitumor oligonucleotide inhibitor of STAT3 with early evidence of clinical activity in lymphoma and lung cancer. *Sci. Transl. Med.* 2015, 7, 314ra183. [CrossRef] [PubMed]

318. Arun, G.; Diermeier, S.; Akerman, M.; Chang, K.-C.; Wilkinson, J.E.; Hearn, S.; Kim, Y.; MacLeod, A.R.; Krainer, A.R.; Norton, L.; et al. Differentiation of mammary tumors and reduction in metastasis upon Malat1 IncRNA loss. *Genes Dev.* 2016, 30, 34–51. [CrossRef] [PubMed]

319. Espósito, R.; Bosch, N.; Lanzós, A.; Polidori, T.; Pulido-Quetglas, C.; Johnson, R. Hacking the cancer genome: Profiling therapeutically actionable long non-coding RNAs using CRISPR-Cas9 screening. *Cancer Cell* 2019, 33, 545–557. [CrossRef] [PubMed]

320. Huang, M.; Wang, H.; Hu, X.; Cao, X. IncRNA MALAT1 binds chromatin remodelling subunit BRG1 to epigenetically promote inflammation-related hepatocellular carcinoma progression. *Oncoimmunology* 2019, 8, e1518628. [CrossRef] [PubMed]

321. 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. [CrossRef] [PubMed]

322. Finn, R.S.; Qin, S.; Ikeda, M.; Galle, P.R.; Ducrues, M.; Kim, T-Y.; Kudo, M.; Breder, V.; Merle, P.; Kaseb, A.O.; et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N. Engl. J. Med.* 2020, 382, 1894–1905. [CrossRef] [PubMed]

323. Ren, F.; Zhang, Y.; Qin, S.; Shang, J.; Wang, Y.; Wei, P.; Guo, J.; Jia, H.; Zhao, T. Taraxasterol prompted the anti-tumor effect in mice burden hepatocellular carcinoma by regulating T lymphocytes. *Cell Death Discov.* 2022, 8, 264. [CrossRef] [PubMed]

324. Su, G.L. AGA Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma. *Gastroenterology* 2022, 162, 920–934. [CrossRef]

325. Park, R.; da Silva, I.L.; Nissaisorakorn, V.; Riano, I.; Williamson, S.; Sun, W.; Saeed, A. Comparison of Efficacy of Systemic Therapies in Advanced Hepatocellular Carcinoma: Updated Systematic Review and Frequentist Network Meta-Analysis of Randomized Controlled Trials. *J. Hepatocell Carcinoma* 2021, 8, 145–154. [CrossRef]

326. Marron, T.U.; Fiel, M.I.; Hamon, P.; Fiaschi, N.; Kim, E.; Ward, S.C.; Zhao, Z.; Kim, J.; Kennedy, P.; Gunasekaran, G.; et al. Neoadjuvant cemiplimab for resectable hepatocellular carcinoma: A single-arm, open-label, phase 2 trial. *Lancet Gastroenterol. Hepatol.* 2022, 7, 219–229. [CrossRef]

327. Zhang, H.; Zhang, W.; Jiang, L.; Chen, Y. Recent advances in systemic therapy for hepatocellular carcinoma. *Biomark. Res.* 2022, 10, 3. [CrossRef] [PubMed]

328. Lennox, K.A.; Behlke, M.A. Cellular localization of long non-coding RNAs affects silencing by RNAi more than by antisense oligonucleotides. *Nucleic Acids Res.* 2016, 44, 863–877. [CrossRef] [PubMed]

329. Peng, Y.; Croce, C.M. The role of MicroRNAs in human cancer. *Signal Transduct. Target. Ther.* 2016, 1, 1–9. [CrossRef]

330. Wheeler, T.M.; Leger, A.J.; Pandey, S.K.; MacLeod, A.R.; Nakamori, M.; Cheng, S.H.; Wentworth, B.M.; Bennett, C.F.; Thornton, C.A. Targeting nuclear RNA for in vivo correction of myotonic dystrophy. *Nature* 2012, 488, 111–115. [CrossRef] [PubMed]

331. Li, D.; Sedano, S.; Allen, R.; Gong, J.; Cho, M.; Sharma, S. Current treatment landscape for advanced hepatocellular carcinoma: Patient outcomes and the impact on quality of life. *Cancers* 2019, 11, 841. [CrossRef] [PubMed]

332. Necsulea, A.; Soumillon, M.; Warnefors, M.; Liechti, A.; Daish, T.; Zeller, U.; Baker, J.C.; Grützner, F.; Kaessmann, H. The evolution of lncRNA repertoires and expression patterns in tetrapods. *Nature* 2014, 505, 635–640. [CrossRef]

333. Juan, V.; Crain, C.; Wilson, C. Evidence for evolutionarily conserved secondary structure in the H19 tumor suppressor RNA. *Nucleic Acids Res.* 2000, 28, 1221–1227. [CrossRef]
334. Zhou, L.; Zhu, Y.; Sun, D.; Zhang, Q. Emerging roles of long non-coding RNAs in the tumor microenvironment. *Int. J. Biol. Sci.* **2020**, *16*, 2094. [CrossRef]

335. Wei, L.; Lee, D.; Law, C.-T.; Zhang, M.S.; Shen, J.; Chin, D.W.-C.; Zhang, A.; Tsang, F.H.-C.; Wong, C.L.-S.; Ng, I.O.-L.; et al. Genome-wide CRISPR/Cas9 library screening identified PHGDH as a critical driver for Sorafenib resistance in HCC. *Nat. Commun.* **2019**, *10*, 4681. [CrossRef]

336. Bester, A.C.; Lee, J.D.; Chavez, A.; Lee, Y.-R.; Nachmani, D.; Vora, S.; Victor, J.; Sauvageau, M.; Monteleone, E.; Rinn, J.J.; et al. An integrated genome-wide CRISPRa approach to functionalize lncRNAs in drug resistance. *Cell* **2018**, *173*, 649–664.e20. [CrossRef]

337. Liu, S.J.; Horlbeck, M.A.; Weissman, J.S.; Lim, D.A. Genome-Scale Perturbation of Long Noncoding RNA Expression Using CRISPR Interference. In *Functional Analysis of Long Non-Coding RNAs*; Springer: New York, NY, USA, 2021; pp. 323–338.