Molecular Therapy
Oncolytics
Original Article

Comprehensive analysis of lncRNAs as biomarkers for diagnosis, prognosis, and treatment response in clear cell renal cell carcinoma

Xiaoyu Chao,[1,5] Pei Wang,[1,5] Xiaoyu Ma,[1,5] Zhenfen Li,[2] Yubing Xia,[2] Ying Guo,[1] Linna Ge,[1] Linzhu Tian,[1] Hong Zheng,[1] Yaowu Du,[1] Jitian Li,[3] Zhanjie Zuo,[4] Longxiang Xie,[1] and Xiangqian Guo[1]

[1]Department of Preventive Medicine, Institute of Biomedical Informatics, Bioinformatics Center, Henan Provincial Engineering Center for Tumor Molecular Medicine, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China; [2]Kaifeng Tumor Hospital, Kaifeng 475004, China; [3]Laboratory of Molecular Biology, Henan Luoyang Orthopedic Hospital (Henan Provincial Orthopedic Hospital), Zhengzhou 450000, China; [4]Thoracic Cancer Treatment Center, Armed police Beijing Corps Hospital, Beijing 100027, China

Clear cell renal cell carcinoma (ccRCC) is the most common histological type of renal carcinoma and has a high recurrence rate and poor outcome. Accurate patient risk stratification based on genetic markers can help to identify the high-risk patient for early and further treatments and would promote patient survival. Long non-coding RNAs (lncRNAs) have attracted widespread attention as biomarkers for early diagnosis, treatment, and prognosis because of their high specificity and sensitivity. Here, we performed a systematic search in NCBI PubMed and found 44 lncRNAs as oncogenes, 18 lncRNAs as tumor suppressors, 199 lncRNAs as diagnostic biomarkers, 62 lncRNAs as prognostic biomarkers, and 3 lncRNAs as predictive biomarkers for ccRCC. We also comprehensively discuss the biological functions and molecular regulatory mechanisms of lncRNAs in ccRCC. Overall, the present study is a systemic analysis to assess the expression and clinical value of lncRNAs in ccRCC, and lncRNAs hold promise to be diagnostic, prognostic, and predictive biomarkers.

INTRODUCTION

Kidney cancer ranks as the 16th most common cause of cancer death worldwide, and there were 179,368 kidney cancer-related deaths and 431,288 new cases in 2020.[1] Clear cell renal cell carcinoma (ccRCC) accounts for 70%–80% of all kidney cancers.[2,3] Recent advances in imaging technology and increased use of screening modalities contribute to the detection of ccRCC at an early stage and promote the prognosis through partial nephrectomy. However, 30% of patients with this disease present metastasis at the time of diagnosis because of prior insipidity or absence of symptoms.[4] In addition, for ccRCC patients with metastasis or recurrence, the sensitivity to chemotherapy and radiotherapy is generally low, and the effect of targeted therapy including sunitinib, sorafenib, pazopanib, aldesleukin, and temsirolimus varies from person to person. The 5-year survival rate of metastatic ccRCC patients is just 8%–11.7%.[5,6] Hence, it is urgent for us to investigate the molecular mechanisms and identify new, sensitive, and reliable biomarkers for diagnosis and prediction of treatment response and prognosis in ccRCC, which can enhance the survival probability of patients.

Long non-coding RNAs (lncRNAs) are a type of non-coding RNA (ncRNA) >200 nucleotides in length and pervasively transcribed in the human genome, having high tissue specificity.[7–10] There were 9,640 lncRNA loci in the human genome according to a report by the ENCODE Project Consortium in 2012, and the number continues to increase.[8,11] lncRNAs play essential functions in virtually every aspect of cell biology, including cellular differentiation, proliferation, DNA damage response, dosage compensation, chromosomal imprinting, transcriptional regulation in *cis* or *trans*, nuclear domain organization, and so on.[12,13] Moreover, lncRNAs are emerging as new players in cancer and have regulatory functions in tumorigenesis, metastasis, and drug resistance with frequently abnormal expression.[14] The important function of lncRNAs in regulating gene expression is related to their complicated structures, because lncRNAs have a complex secondary and tertiary structure, which endows the abilities to bind protein, RNA, and/or DNA partners. Consequently, they possess several regulatory capacities.[15] Accordingly, dysregulated lncRNAs can contribute to various pathological events, including cancer initiation and progression.[16] For instance, HOTAIR overexpression promoted breast cancer metastasis as seen in *in vivo* assay by changing the cell expression profile, favoring metastasis.[17] Several lncRNAs were also found abnormally expressed in ccRCC

Received 23 March 2021; accepted 12 August 2021;
https://doi.org/10.1016/j.omto.2021.08.003.

[5]These authors contributed equally

Correspondence: Longxiang Xie, Department of Preventive Medicine, Institute of Biomedical Informatics, Bioinformatics Center, Henan Provincial Engineering Center for Tumor Molecular Medicine, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China.
E-mail: xielongxiang123@126.com
Correspondence: Xiangqian Guo, Department of Preventive Medicine, Institute of Biomedical Informatics, Bioinformatics Center, Henan Provincial Engineering Center for Tumor Molecular Medicine, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China.
E-mail: xqguo@henu.edu.cn

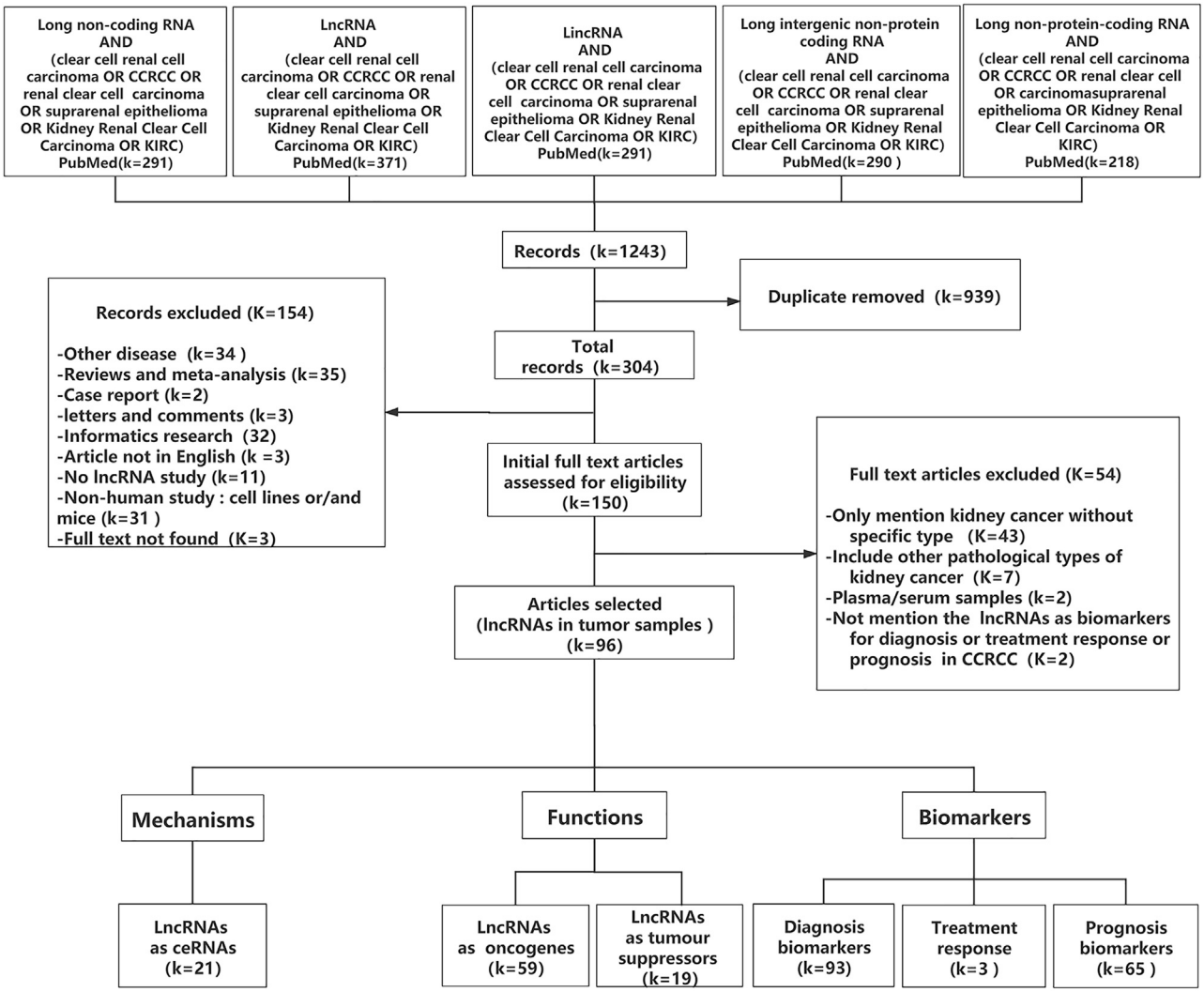

Figure 1. Flowchart diagram of study selection

k, number of records.

and were involved in initiation and progression of ccRCC.[18–22] Additionally, dysregulated lncRNAs may be used as novel diagnostic, prognostic, and predictive biomarkers in ccRCC.[23–25] Therefore, we systematically analyzed the potential roles of these dysregulated lncRNAs as diagnostic, treatment response predictive, and prognostic biomarkers, their functions, and their molecular mechanisms in ccRCC.

RESULTS

A flowchart showing the selection process of lncRNA identification, inclusion, and exclusion criteria is presented in Figure 1. In brief, the initial records were 1,243 studies in the NCBI PubMed database, and of these a total of 939 duplicate studies were excluded. Next, we excluded 154 records after reading the titles and abstracts according to the inclusion and exclusion criteria (Figure 1). Then, we read and checked carefully the full texts of the remaining 150 publications. Accordingly, 54 publications out of these were excluded on the basis of the exclusion criteria (Figure 1). In total, 96 publications were finally included in this systematic review. Among the 96 publications, 21 publications were about lncRNAs as competing endogenous RNAs (ceRNAs), 59 publications about oncogenes, 19 publications about tumor suppressors, 93 publications about diagnostic biomarkers, 65 publications about prognostic biomarkers, and 3 publications about therapeutic predictive biomarkers.

Regulatory mechanisms of lncRNAs in cancer

lncRNAs are subject to fine-tuned regulation, ranging from epigenetic to posttranscriptional regulation.[26,27] Genetic and epigenetic changes are mainly responsible for the abnormal expression of lncRNAs.[28,29] Studies have shown that small- and large-scale mutations affect

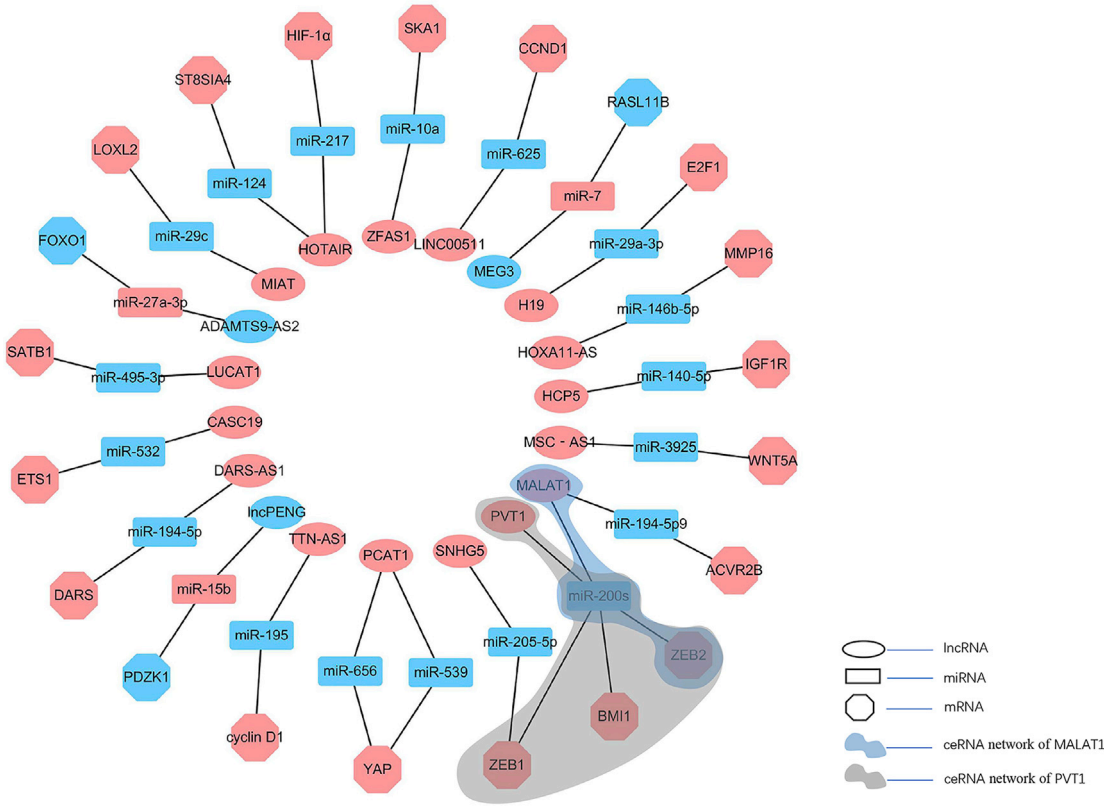

Figure 2. lncRNAs, miRNAs, and mRNAs form the ceRNA network
Light coral represents high expression, and blue represents low expression.

non-coding regions of the genome, including chromosomal translocations, copy number alterations, nucleotide expansions, and single-nucleotide polymorphisms (SNPs).[30] Dozens of lncRNAs abnormally expressed in cancers can also be regulated by specific oncogenic and tumor suppressor-related signals and regulatory factors such as Sp1, p53, and linc-p21.[31] In addition, lncRNAs can regulate protein, RNA, and/or DNA partners by forming a complicated network responsible for cancer initiation and development.[16] Therefore, the mechanisms for lncRNA regulation in ccRCC are complicated.

Among all the mechanisms, the ceRNA network is attracting increasing attention. In the ceRNA network, lncRNAs act as ceRNAs or natural microRNA (miRNA) sponges; they can bind to miRNAs through their miRNA binding sites (also referred to as miRNA response elements [MRE]), thereby de-repressing the target genes' mRNAs of the respective miRNAs. This indicates that these lncRNAs serve as posttranscriptional regulators of gene expression.[32] Accordingly, the ceRNA network in ccRCC is systematically summarized in Figure 2. There are 21 studies analyzing lncRNAs that function as ceRNAs by serving as sponges that bind and sequester away miRNAs in ccRCC. These studies reported that 19 lncRNAs, including LINC00511, ZFAS1, HOTAIR, MIAT, ADAMTS9-AS2, LUCAT1, MALAT1, HOXA11-AS, PVT1, H19, MEG3, CASC19, SNHG5, HCP5, lncPENG, PCAT1, MSC-AS1, TTN-AS1, and DARS-AS1 are involved in the ceRNA network in ccRCC (Figure 2).

Among these 19 lncRNAs, MALAT1, HOTAIR, and PCAT1 were reported to bind to two relevant miRNAs, respectively. MALAT1 functions as a ceRNA by binding miR-200s to regulate *ZEB2* expression and also sponges miR-194-5p9 to regulate *ACVR2B* expression.[33,34] Similarly, HOTAIR regulates *ST8SIA4* expression by binding to miR-124[20] and regulates *HIF-1α* expression by binding to miR-217.[18] PCAT1 sponges miR-539 and miR-656 for *YAP*, the same target.[35] From the intersection of the ceRNA network, two lncRNAs, MALAT1 and PVT1, are found to bind the same miRNA, miR-200s, in our ceRNA network (Figure 2). MALAT1 binds miR-200s to regulate *ZEB2* expression, whereas PVT1 binds miR-200s to regulate *ZEB1* and *BMT1* besides *ZEB2* (Figure 2).[22,33]

lncRNA functions in ccRCC

Fourteen hallmarks of cancer have been reported: evading growth suppressors, avoiding immune destruction, inducing angiogenesis, enabling replicative immortality, sustained proliferative signaling, resisting cell death, deregulating cellular epigenetics, activating invasion and metastasis, genome instability and mutation, tumor promoting inflammation, dedifferentiation and transdifferentiation, epigenetic

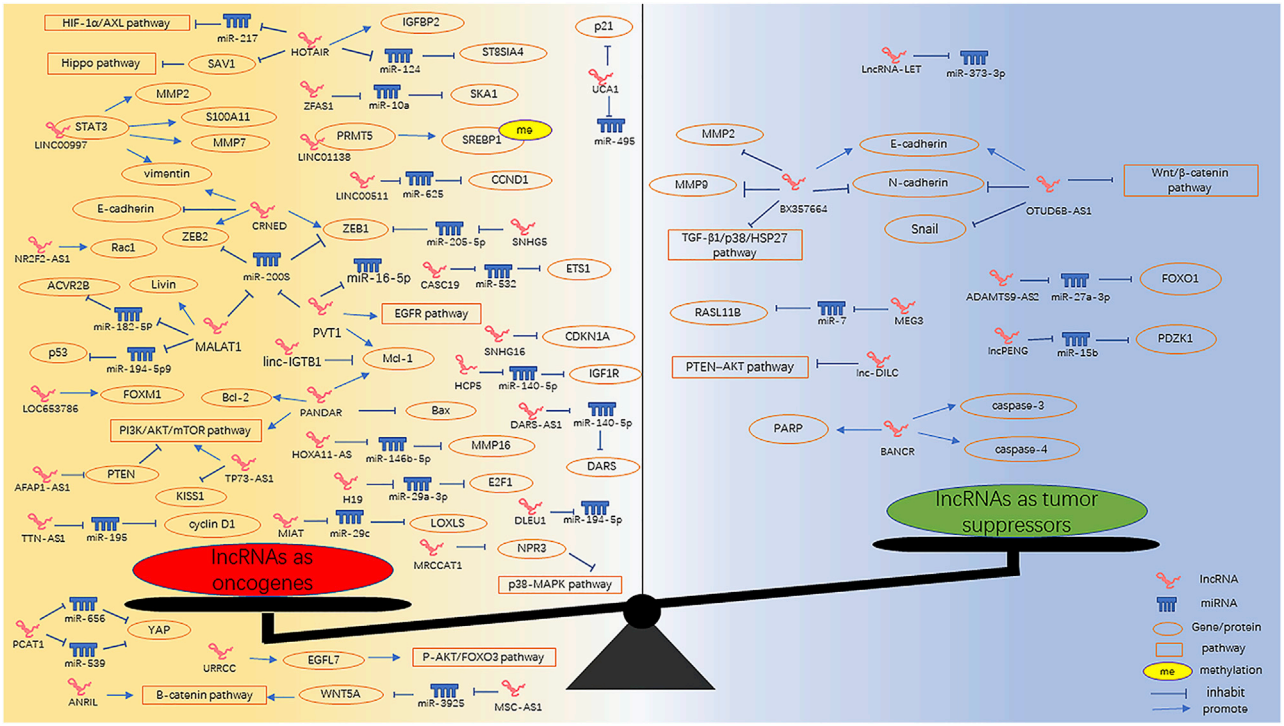

Figure 3. The molecular functions of lncRNAs in ccRCC progression

lncRNAs function as oncogenes or tumor suppressors just like an unbalanced balance. On the left of the balance (red), lncRNAs act as oncogenes and are overexpressed in ccRCC; on the contrary, on the right (green), lncRNAs act as tumor suppressors.

dysregulation, altered microbiome, and altered neuronal signaling.[36,37] More and more lncRNAs have been reported to play critical roles as tumor oncogenes or tumor suppressors, involved in the cancer hallmark process of initiation, growth, and metastasis in ccRCC (Figure 4; Table S1). The dysregulated lncRNAs involved in the above processes and their molecular mechanisms in ccRCC are summarized in Figure 3 and Figure 4.

lncRNAs as oncogenes in ccRCC

Forty-four lncRNAs with abnormal expression were reported as oncogenes in 59 publications and were related to cell cycle, proliferation, apoptosis, migration, invasion, metastasis or epithelial-mesenchymal transition (EMT) in ccRCC (Figure 4). Among them, MALAT1, PVT1, HOTAIR, and LUCAT1 were explored in more than 2 studies, and the corresponding reporting frequency of each lncRNA was 6,[22,33,34,38–40] 4,[21,22,41,42] 4,[18–20,43] and 3[23–25] studies.

MALAT1 was reported to be the most consistent oncogene. The upregulation of MALAT1 was correlated with tumor progression and poor prognosis in ccRCC. Xiao et al.[33] demonstrated that MALAT1 promotes ccRCC proliferation, migration, and metastasis through the MALAT1/miR-200s/*ZEB2* pathway by *in vitro* and *in vivo* studies. There was also a direct interaction between MALAT1 and Livin protein. MALAT1 regulated and increased Livin levels by enhancing the stability of the protein via MALAT1 protein interaction, which promoted cell proliferation and suppressed cell apoptosis.[38] In addition, other studies identified that MALAT1 plays important roles in promoting cell cycle, invasion, and EMT (Figures 3 and 4; Table S1).[38,39,44,45]

PVT1 was found upregulated in ccRCC, and its high expression was associated with a shorter overall survival time.[42] In addition, PVT1 expression was closely correlated with TNM stage, Fuhrman grade, lymph node metastasis, and tumor size. Ren et al.[21] reported that PVT1 promotes proliferation, invasion, and EMT of ccRCC through downregulation of miR-16-5p. Moreover, PVT1 can inhibit ccRCC cell apoptosis by upregulating *Mcl-1*.[41] Correspondingly, knockdown of PVT1 induced apoptosis and cell cycle arrest in ccRCC, which was associated with the epidermal growth factor receptor pathway (Figures 3 and 4; Table S1).[42]

It has been shown that HOTAIR promotes the development and progression of ccRCC. Hu et al.[19] found that increased expression of HOTAIR predicts a poor prognosis of ccRCC after surgery and HOTAIR can promote RCC cell proliferation and growth *in vitro* and *in vivo*. Hong et al.[18] demonstrated that HOTAIR facilitates ccRCC proliferation, migration, and the EMT process and inhibits apoptosis and that HOTAIR knockdown suppresses tumor growth. Furthermore, the migration of ccRCC cell was promoted by increased HOTAIR, which upregulated insulin growth factor–binding protein

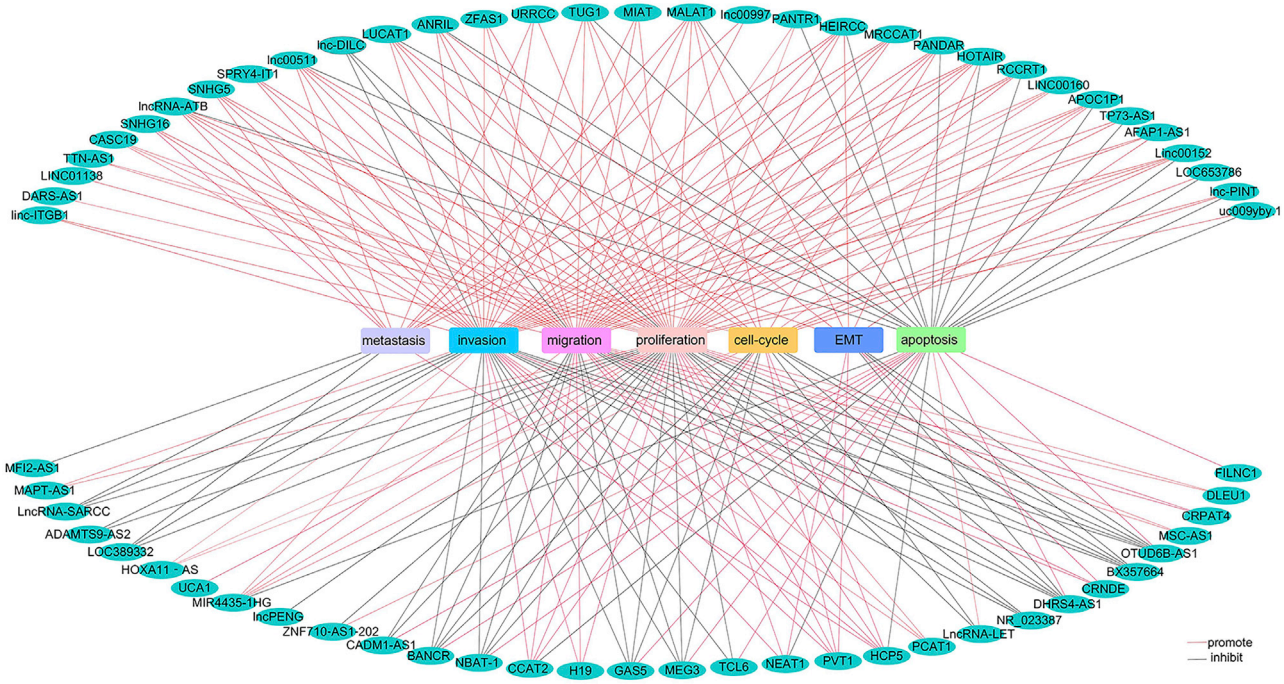

Figure 4. Network of aberrantly expressed lncRNAs in diverse cellular functions

2.[46] Pan et al.[20] found that HOTAIR promotes renal cell carcinoma malignancy through alpha-2,8-sialyltransferase 4 by sponging miRNA-124 (Figures 3 and 4; Table S1).

LUCAT1 expression was significantly upregulated in tumor tissues compared with matched adjacent non-tumor tissues, promoting renal cancer cell proliferation, and its expression level was also associated with cancer grade, pathological stage, and survival time.[24] Additionally, Wang et al.[23] reported that LUCAT1 promotes proliferation and invasion of ccRCC cells by negatively regulating miR-495-3p. Zheng et al.[25] showed that LUCAT1 promotes proliferation and invasion through the AKT/GSK-3β signaling pathway in ccRCC (Figures 3 and 4; Table S1).

lncRNAs as tumor suppressors in ccRCC

Apart from roles as oncogenic lncRNAs in ccRCC, some lncRNAs, as tumor suppressors, have been proven to have significant regulatory effects on inhibiting cell proliferation and invasion in ccRCC. There are 18 lncRNAs described as tumor suppressors in 19 publications (Figures 3 and 4). Among them, MEG3 was researched in more than 2 studies. MEG3 expression was significantly decreased in ccRCC tissues and cells, and upregulating MEG3 expression effectively inhibited proliferation, accelerated cell apoptosis, and induced the G0/G1 phase cell cycle by increasing the expression of RASL11B.[47] Similarly, BANCR, considered as a tumor inhibitor, was significantly decreased in ccRCC, and its low expression was associated with poor prognosis. Moreover, BANCR overexpression inhibited the proliferation, migration, and invasion capacity of ccRCC, meanwhile, apoptosis was increased and G1 cell cycle arrest was induced *in vitro*.[48] Other lncRNAs like GAS5, LOC389332, SARCC, and TCL6 were reported as tumor suppressors in ccRCC as well. However, they are not drawn or discussed in more detail here because of the lack of in-depth mechanisms in published articles.[49–52]

Clinical applications of lncRNAs in ccRCC

Characterization of lncRNAs in the initiation and progression of ccRCC would be definitely beneficial for cancer diagnosis and therapy. The discovery of sensitive and specific biomarkers for ccRCC will facilitate early detection and improve current clinical management of ccRCC.

Diagnostic biomarkers in ccRCC

The lncRNA expression in ccRCC was analyzed in 93 studies. A total of 199 differentially expressed lncRNAs between ccRCC and healthy controls are shown in Table S2.

There are 5 lncRNAs, including MALAT1, PVT1, HOTAIR, LUCAT1, and HEIRCC, recurrently reported to be upregulated in ccRCC in more than 2 papers (Table S2). MALAT1,[22,33,34,38–40,45] PVT1,[21,22,41,42,53] and HOTAIR[18–20,43] overexpression were reported in 7, 5, and 4 studies, respectively. In addition, there were 3 publications separately indicating that LUCAT1[23–25] and HEIRCC[25,54,55] were upregulated. On the other hand, MEG3 was downregulated significantly in 3 publications.[47,56,57] None of these lncRNAs has inconsistent results reported in 93 studies. Therefore, these significantly upregulated or downregulated lncRNAs have the potential to be developed as diagnostic biomarkers.

Prognostic biomarkers in ccRCC

Sixty-five studies analyzed the correlation between lncRNAs and prognosis of ccRCC patients. A total of 62 lncRNAs were significantly correlated with the prognosis of ccRCC patients (Table S3).

Among them, PVT1, MALAT1, and LUCAT1 had significant changes in more than 2 studies (Table S3). Increased expression of PVT1, LUCAT1 and MALAT1 were all associated with poor prognosis. PVT1 was the lncRNA most frequently studied as prognostic biomarker, and 5 publications indicated that high expression of PVT1 was associated with poor overall survival (OS) and disease-free survival (DFS).[21,22,41,42,53] LUCAT1 was also a poor prognostic factor, and higher expression of LUCAT1 was related to a poorer OS and DFS in 3 studies.[23–25] MALAT1 was an important prognostic biomarker in 3 studies. The expression of MALAT1 was significantly higher in ccRCC with poor prognosis.[34,39,45] The other 59 lncRNAs were also markedly correlated with the prognosis of ccRCC patients (Table S3).

Treatment response-predictive biomarkers in ccRCC

Three studies focused on the role of lncRNAs as biomarkers for predicting therapeutic response in ccRCC, and the results showed that 3 lncRNAs including ADAMTS9-AS2, GAS5 and SARCC, were predictive biomarkers for drug treatment. However, each lncRNA was only analyzed in one study, without replicated results (Table S4).

All 3 lncRNAs were found to be associated with a favorable response to therapy. They can serve as useful biomarkers for drug effectiveness. ADAMTS9-AS2 attenuated the susceptibility of ccRCC cells to chemotherapy drugs such as cisplatin.[58] GAS5 was found to sensitize renal cell carcinoma to sorafenib.[59] In addition, SARCC was a key mediator to influence sunitinib efficacy, and enhancing the expression of SARCC was a novel therapeutic approach to enhance sunitinib efficacy in ccRCC treatment.[60]

DISCUSSION

With the development of high-throughput sequencing technology and bioinformatics, lncRNA dysregulation has been found to be related to the initiation and progression of various types of cancers including ccRCC and is involved in multiple biological behaviors of cancer, including cell proliferation, apoptosis, migration, and metastasis.[61] Previous reviews and meta-analyses have reported the prognostic values of lncRNAs in multiple cancers, such as colorectal cancer, ovarian cancer, lung cancer, etc.[62,63] However, no one investigated ccRCC specifically. Therefore, we conducted this systematic analysis to highlight the values of lncRNAs in ccRCC. It should be pointed out that we excluded the papers reporting plasma/serum ncRNAs in ccRCCs for the following reasons. First, the studies reporting lncRNAs in plasma/serum samples are limited, not enough for a systematic discussion and analysis.[64,65] In addition, we were concerned that the expression of ncRNAs is not consistent or comparable between blood and tissue samples. Therefore, we only included the studies of lncRNAs in tissue samples of clear cell carcinoma of the kidney. We comprehensively clarified the association between lncRNA expression and molecular mechanisms, functions, and clinical applications in ccRCC. The ceRNA hypothesis particularly provides a new perspective in terms of studying tumor formation mechanisms and the developing cancer treatments. Therefore, we summarized the ceRNA network participating in ccRCC. In clinical application, we generalized abnormally expressed lncRNAs in ccRCC tissues as diagnosis, prognosis, and treatment response biomarkers.

To identify diagnostic lncRNAs for ccRCC, 93 papers were collected and analyzed. Most of these studies primordially analyzed lncRNA expression profiles by microarray and then validated the differentially expressed lncRNAs by qRT-PCR in ccRCC. As a result, a total of 6 lncRNAs, MALAT1,[22,33,34,38–40,45] PVT1,[21,22,41,42,53] HOTAIR,[18–20,43] LUCAT1,[23–25] HEIRCC,[25,54,55] and MEG3,[47,56,57] were reported to be expressed aberrantly in ccRCC in more than 2 studies with accordant results. Among them, MALAT1 and PVT1 were reported as significantly upregulated in more than 5 studies and may have great important significance for the diagnosis of ccRCC.

The prognosis for ccRCC patients is favorable when detected in the early stages, but is poor when diagnosed in the advanced stages.[4] To select promising prognosis biomarkers, 62 lncRNAs were identified from publications. Briefly, PVT1,[21,22,41,42,53] MALAT1,[34,39,45] and LUCAT1[23–25] were related to the patients' prognosis in 3 or more studies with concordant results. This implies that PVT1, MALAT1 and LUCAT1 can serve as potential prognostic biomarkers for ccRCC patients.

To identify treatment lncRNAs, 3 lncRNAs (ADAMTS9-AS2, LncRNA-SARCC, and GAS5) were recognized in 3 studies. LncRNA-SARCC, GAS5, and SARCC were found to be associated with treatment sensitivity of cisplatin, sorafenib, and sunitinib, respectively.[58–60] ADAMTS9-AS2 attenuated the chemosensitivity of ccRCC cells to cisplatin via the ADAMTS9-AS2/miR-27a-3p/*FOXO1* axis.[58] GAS5 overexpression conferred RCC cell resistance to sorafenib via the GAS5/miR-21/*SOX5* axis.[59] SARCC influenced sunitinib efficacy through binding and destabilizing androgen receptor (AR) protein, which led to transcriptional increase of miR-143-3p expression and thus inhibited ccRCC tumor progression.[60]

It has been shown that MALAT1 and PVT1 can act as diagnostic and prognostic biomarkers in ccRCC. MALAT1 is one of the first identified cancer-associated lncRNAs and has been found with poor prognosis in various cancers, such as lung cancer,[66–68] bladder cancer,[69,70] breast cancer,[71,72] and others.[73–75] In lung cancer, for instance, MALAT1 was upregulated and transcriptionally activated by Oct4 via enhancer binding to promote cell proliferation and motility and led to lung tumorigenesis and poor prognosis.[76] Similarly, in gastric cancer, MALAT1 levels were significantly higher in cases with distant metastasis than in cases without distant metastasis and healthy controls. In addition, high levels of plasma MALAT1 independently correlated to a poor prognosis for gastric cancer patients. Functional studies revealed that knockdown of MALAT1 could inhibit cell proliferation, cell cycle progression, migration, and invasion and

promote apoptosis in gastric cancer cells.[77] In this paper, MALAT1 was found to be upregulated in the cancer tissues in 7 independent studies of ccRCC and may be used as a potential diagnostic biomarker.[22,33,34,38–40,45] MALAT1 was also an important prognostic biomarker in 3 studies.[34,39,45] ccRCC patients with high MALAT1 expression had significantly shorter OS, and MALAT1 upregulation was correlated with big tumor size, advanced tumor stage, and lymph node metastasis in ccRCC patients.[34,39,45]

As for PVT1, previous studies found that it is upregulated in bladder cancer[78], cervical cancer[79], gastric cancer,[80,81] and other cancers.[82] Notably, PVT1 was the most studied prognostic biomarker for ccRCC in 5 studies,[21,22,41,42,53] and PVT1 was reported to be upregulated in ccRCC tissues.[21,22,41,42,53] It was demonstrated that ccRCC patients with higher expression of PVT1 have worse OS and DFS. In addition, high expression of PVT1 was significantly associated with larger tumor size, advanced TNM stage, and lymph node metastasis.[21,22,41,42,53] PVT1 can promote ccRCC cell proliferation, migration and invasion, and EMT, induce ccRCC cell cycle arrest, and inhibit apoptosis.[21,41,42,53]

In conclusion, this article summarized the potential carcinogenesis and ceRNA network of dysregulated lncRNAs in ccRCC, then reviewed their functions in tumorigenesis and progression, and finally discussed the potential roles of lncRNAs in diagnosis, prognosis, and treatment response in ccRCC.

MATERIALS AND METHODS

Paper search strategy

Studies for lncRNAs as diagnostic, prognostic, or predictive biomarkers of ccRCC were searched in PubMed until June 26, 2020. The search terms used for paper retrieval were as follows: ((“long non-coding RNA”) OR (“lncRNA”) OR (“lincRNA”) OR (“long intergenic non-protein coding RNA”) OR (“long non-protein-coding RNA”)) AND (“clear cell renal cell carcinoma OR ccRCC OR renal clear cell carcinoma OR suprarenal epithelioma OR kidney renal clear cell carcinoma OR KIRC”).

Eligibility criteria

Eligible studies should fulfill the following criteria: (1) a definitive diagnosis of ccRCC with the gold standard and (2) independent original studies that evaluated the expression of lncRNAs in ccRCC tumor tissue as diagnosis, prediction of treatment response, or prognosis biomarkers in patient populations. The exclusion criteria were as follows: (1) duplicate reports; (2) written in a language other than English; (3) non-human studies; (4) case reports, comments, letters, and reviews or meta-analyses; (5) other diseases; (6) not clear cell carcinoma of the kidney clearly; (7) not lncRNA studies; (8) studies did not assess the role of lncRNA in diagnosis, prognosis, and treatment response. All evaluations were independently performed by two individual researchers to ensure the accurate inclusion of studies. The discrepancies were resolved by discussion.

Data extraction

Two reviewers (X.C. and P.W.) independently extracted the data from the included studies by using a standardized table that included the following items: the names of differentially expressed lncRNAs, result of the abnormal expression (up or down), sample size, control group size, testing methods, survival outcome, regulatory mechanisms, functions in ccRCC, and the PMID number of the studies.

Cytoscape

Cytoscape is public software for integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework, and is applicable to any system of molecular components and interactions.[83] We used Cytoscape 3.7.2 to construct the frameworks of lncRNA cellular functions in ccRCC.

Abbreviations

ccRCC, clear cell renal cell carcinoma; lncRNA, long non-coding RNA; ceRNA, competing endogenous RNA; ncRNA, non-coding RNA; HOTAIR, HOX transcript antisense gene RNA; lincRNA, long intergenic non-coding RNA; SNP, single-nucleotide polymorphism; miRNA, microRNA; ZFAS1, ZNFX1 antisense RNA 1; MIAT, Myocardial infarction associated transcript; ADAMTS9-AS2, ADAMTS9 antisense RNA 2; LUCAT1, Lung cancer associated transcript 1; MALAT1, Metastasis associated lung adenocarcinoma transcript 1; HOXA11-AS, HOXA11 antisense RNA; PVT1, Plasmacytoma variant translocation 1; MEG3, Maternally expressed 3; CASC19, Cancer susceptibility 19; SNHG5, Small nucleolar RNA host gene 5; HCP5, HLA complex P5; PCAT1, Prostate cancer associated transcript 1; MSC-AS1, MSC antisense RNA 1; TTN-AS1, TTN antisense RNA 1; DARS-AS1, DARS1 antisense RNA 1; ZEB2, Zinc finger E-box binding homeobox 2; ACVR2B, activin A receptor type 2B; ST8SIA4, ST8 alpha-*N*-acetyl-neuraminide alpha-2,8-sialyltransferase 4; HIF-1α, hypoxia-inducible factor 1 subunit alpha; YAP, Yes1 associated transcriptional regulator; ZEB1, Zinc finger E-box binding homeobox 1; EMT, epithelial to mesenchymal transition; RASL11B, RAS like family 11 member B; BANCR, BRAF-activated non-protein coding RNA; GAS5, Growth arrest specific 5; TCL6, T cell leukemia/lymphoma 6; FOXO1, Forkhead box O1; SOX5, SRY-box transcription factor 5; OS, overall survival; DFS, disease-free survival.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.omto.2021.08.003.

ACKNOWLEDGMENTS

This work was supported by the Kaifeng Science and Technology Development Plan (Nos. 2003116, 2103005), National Natural Science Foundation of China (No. U2004136), supporting program for Central Plain Young Top Talents (ZYQR201912176), Graduate meritocracy program (SYL20060138), program for Innovative Talents of Science and Technology in Henan Province (No. 18HASTIT048), and supporting grants of Henan University (Nos. 2018YLJC01, 2019YLXKJC01,

2020YLZDYJ14). We also thank Professor Abualgasim Elgaili Abdalla for helping us to polish the English of this manuscript.

AUTHOR CONTRIBUTIONS

X.G. and L.X.: study concept and design. X.C., P.W., X.M., Z.L., Y.X., Y.G., L.G., L.T., H.Z., Y.D., J.L., and Z.Z.: acquisition of data. X.C., P.W., X.M., Z.L., Y.X., Y.G., L.G., L.T., H.Z., Y.D., J.L., and Z.Z.: analysis and interpretation of data. X.C., P.W., X.M., X.G., and LX: draft of the manuscript. L.X. and X.G,: critical revision of the manuscript for intellectual content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. .https://globocan.iarc.fr. (Accessed 2 March 2021).
2. Shuch, B., Amin, A., Armstrong, A.J., Eble, J.N., Ficarra, V., Lopez-Beltran, A., Martignoni, G., Rini, B.I., and Kutikov, A. (2015). Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. Eur. Urol. *67*, 85–97.
3. Jonasch, E., Gao, J., and Rathmell, W.K. (2014). Renal cell carcinoma. BMJ *349*, g4797.
4. Janzen, N.K., Kim, H.L., Figlin, R.A., and Belldegrun, A.S. (2003). Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol. Clin. North Am. *30*, 843–852.
5. Zhang, P., Ma, X., Song, E., Chen, W., Pang, H., Ni, D., Gao, Y., Fan, Y., Ding, Q., Zhang, Y., and Zhang, X. (2013). Tubulin cofactor A functions as a novel positive regulator of ccRCC progression, invasion and metastasis. Int. J. Cancer *133*, 2801–2811.
6. Courtney, K.D., Infante, J.R., Lam, E.T., Figlin, R.A., Rini, B.I., Brugarolas, J., Zojwalla, N.J., Lowe, A.M., Wang, K., Wallace, E.M., et al. (2018). Phase I Dose-Escalation Trial of PT2385, a First-in-Class Hypoxia-Inducible Factor-2α Antagonist in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma. J. Clin. Oncol. *36*, 867–874.
7. Cabili, M.N., Trapnell, C., Goff, L., Koziol, M., Tazon-Vega, B., Regev, A., and Rinn, J.L. (2011). Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev. *25*, 1915–1927.
8. Derrien, T., Johnson, R., Bussotti, G., Tanzer, A., Djebali, S., Tilgner, H., Guernec, G., Martin, D., Merkel, A., Knowles, D.G., et al. (2012). The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. *22*, 1775–1789.
9. Washietl, S., Kellis, M., and Garber, M. (2014). Evolutionary dynamics and tissue specificity of human long noncoding RNAs in six mammals. Genome Res. *24*, 616–628.
10. Ponting, C.P., Oliver, P.L., and Reik, W. (2009). Evolution and functions of long noncoding RNAs. Cell *136*, 629–641.
11. ENCODE Project Consortium (2012). An integrated encyclopedia of DNA elements in the human genome. Nature *489*, 57–74.
12. Kopp, F., and Mendell, J.T. (2018). Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell *172*, 393–407.
13. Mercer, T.R., Dinger, M.E., and Mattick, J.S. (2009). Long non-coding RNAs: insights into functions. Nat. Rev. Genet. *10*, 155–159.
14. Bartonicek, N., Maag, J.L., and Dinger, M.E. (2016). Long noncoding RNAs in cancer: mechanisms of action and technological advancements. Mol. Cancer *15*, 43.
15. Pauli, A., Rinn, J.L., and Schier, A.F. (2011). Non-coding RNAs as regulators of embryogenesis. Nat. Rev. Genet. *12*, 136–149.
16. Lin, C., and Yang, L. (2018). Long Noncoding RNA in Cancer: Wiring Signaling Circuitry. Trends Cell Biol. *28*, 287–301.
17. Gupta, R.A., Shah, N., Wang, K.C., Kim, J., Horlings, H.M., Wong, D.J., Tsai, M.-C., Hung, T., Argani, P., Rinn, J.L., et al. (2010). Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature *464*, 1071–1076.
18. Hong, Q., Li, O., Zheng, W., Xiao, W.Z., Zhang, L., Wu, D., Cai, G.Y., He, J.C., and Chen, X.M. (2017). LncRNA HOTAIR regulates HIF-1α/AXL signaling through inhibition of miR-217 in renal cell carcinoma. Cell Death Dis. *8*, e2772.
19. Hu, G., Dong, B., Zhang, J., Zhai, W., Xie, T., Huang, B., Huang, C., Yao, X., Zheng, J., Che, J., and Xu, Y.F. (2017). The long noncoding RNA HOTAIR activates the Hippo pathway by directly binding to SAV1 in renal cell carcinoma. Oncotarget *8*, 58654–58667.
20. Pan, Y., Wu, Y., Hu, J., Shan, Y., Ma, J., Ma, H., Qi, X., and Jia, L. (2018). Long non-coding RNA HOTAIR promotes renal cell carcinoma malignancy through alpha-2, 8-sialyltransferase 4 by sponging microRNA-124. Cell Prolif. *51*, e12507.
21. Ren, Y., Huang, W., Weng, G., Cui, P., Liang, H., and Li, Y. (2019). LncRNA PVT1 promotes proliferation, invasion and epithelial-mesenchymal transition of renal cell carcinoma cells through downregulation of miR-16-5p. OncoTargets Ther. *12*, 2563–2575.
22. Yang, T., Zhou, H., Liu, P., Yan, L., Yao, W., Chen, K., Zeng, J., Li, H., Hu, J., Xu, H., and Ye, Z. (2017). lncRNA PVT1 and its splicing variant function as competing endogenous RNA to regulate clear cell renal cell carcinoma progression. Oncotarget *8*, 85353–85367.
23. Wang, L.N., Zhu, X.Q., Song, X.S., and Xu, Y. (2018). Long noncoding RNA lung cancer associated transcript 1 promotes proliferation and invasion of clear cell renal cell carcinoma cells by negatively regulating miR-495-3p. J. Cell. Biochem. *119*, 7599–7609.
24. Xiao, H., Bao, L., Xiao, W., Ruan, H., Song, Z., Qu, Y., Chen, K., Zhang, X., and Yang, H. (2017). Long non-coding RNA Lucat1 is a poor prognostic factor and demonstrates malignant biological behavior in clear cell renal cell carcinoma. Oncotarget *8*, 113622–113634.
25. Zheng, Z., Zhao, F., Zhu, D., Han, J., Chen, H., Cai, Y., Chen, Z., and Xie, W. (2018). Long Non-Coding RNA LUCAT1 Promotes Proliferation and Invasion in Clear Cell Renal Cell Carcinoma Through AKT/GSK-3beta Signaling Pathway. Cell. Physiol. Biochem. *48*, 891–904.
26. Djebali, S., Davis, C.A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A., Tanzer, A., Lagarde, J., Lin, W., Schlesinger, F., et al. (2012). Landscape of transcription in human cells. Nature *489*, 101–108.
27. Dinger, M.E., Pang, K.C., Mercer, T.R., and Mattick, J.S. (2008). Differentiating protein-coding and noncoding RNA: challenges and ambiguities. PLoS Comput. Biol. *4*, e1000176.
28. Struhl, K. (2007). Transcriptional noise and the fidelity of initiation by RNA polymerase II. Nat. Struct. Mol. Biol. *14*, 103–105.
29. Akhade, V.S., Pal, D., and Kanduri, C. (2017). Long Noncoding RNA: Genome Organization and Mechanism of Action. In Long Non Coding RNA Biology, M.R.S. Rao, ed. (Singapore: Springer Singapore), pp. 47–74. https://doi.org/10.1007/978-981-10-5203-3_2.
30. Wapinski, O., and Chang, H.Y. (2011). Long noncoding RNAs and human disease. Trends Cell Biol. *21*, 354–361.
31. Cheng, Y., Imanirad, P., Jutooru, I., Hedrick, E., Jin, U.H., Rodrigues Hoffman, A., Leal de Araujo, J., Morpurgo, B., Golovko, A., and Safe, S. (2018). Role of metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) in pancreatic cancer. PLoS ONE *13*, e0192264.
32. Xu, J., Li, Y., Lu, J., Pan, T., Ding, N., Wang, Z., Shao, T., Zhang, J., Wang, L., and Li, X. (2015). The mRNA related ceRNA-ceRNA landscape and significance across 20 major cancer types. Nucleic Acids Res. *43*, 8169–8182.
33. Xiao, H., Tang, K., Liu, P., Chen, K., Hu, J., Zeng, J., Xiao, W., Yu, G., Yao, W., Zhou, H., et al. (2015). LncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging miR-200s in clear cell kidney carcinoma. Oncotarget *6*, 38005–38015.
34. Ye, Y., Zhang, F., Chen, Q., Huang, Z., and Li, M. (2019). LncRNA MALAT1 modified progression of clear cell kidney carcinoma (KIRC) by regulation of miR-194-5p/ACVR2B signaling. Mol. Carcinog. *58*, 279–292.

35. Wang, R., Zheng, B., Liu, H., and Wan, X. (2020). Long non-coding RNA PCAT1 drives clear cell renal cell carcinoma by upregulating YAP via sponging miR-656 and miR-539. Cell Cycle *19*, 1122–1131.

36. Senga, S.S., and Grose, R.P. (2021). Hallmarks of cancer-the new testament. Open Biol. *11*, 200358.

37. Hanahan, D., and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. Cell *144*, 646–674.

38. Chen, S., Ma, P., Zhao, Y., Li, B., Jiang, S., Xiong, H., Wang, Z., Wang, H., Jin, X., and Liu, C. (2017). Biological function and mechanism of MALAT-1 in renal cell carcinoma proliferation and apoptosis: role of the MALAT-1-Livin protein interaction. J. Physiol. Sci. *67*, 577–585.

39. Hirata, H., Hinoda, Y., Shahryari, V., Deng, G., Nakajima, K., Tabatabai, Z.L., Ishii, N., and Dahiya, R. (2015). Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205. Cancer Res. *75*, 1322–1331.

40. Kulkarni, P., Dasgupta, P., Bhat, N.S., Shahryari, V., Shiina, M., Hashimoto, Y., Majid, S., Deng, G., Saini, S., Tabatabai, Z.L., et al. (2018). Elevated miR-182-5p Associates with Renal Cancer Cell Mitotic Arrest through Diminished *MALAT-1* Expression. Mol. Cancer Res. *16*, 1750–1760.

41. Wu, Q., Yang, F., Yang, Z., Fang, Z., Fu, W., Chen, W., Liu, X., Zhao, J., Wang, Q., Hu, X., and Li, L. (2017). Long noncoding RNA PVT1 inhibits renal cancer cell apoptosis by up-regulating Mcl-1. Oncotarget *8*, 101865–101875.

42. Li, W., Zheng, Z., Chen, H., Cai, Y., and Xie, W. (2018). Knockdown of long non-coding RNA PVT1 induces apoptosis and cell cycle arrest in clear cell renal cell carcinoma through the epidermal growth factor receptor pathway. Oncol. Lett. *15*, 7855–7863.

43. Dasgupta, P., Kulkarni, P., Majid, S., Shahryari, V., Hashimoto, Y., Bhat, N.S., Shiina, M., Deng, G., Saini, S., Tabatabai, Z.L., et al. (2018). MicroRNA-203 Inhibits Long Noncoding RNA HOTAIR and Regulates Tumorigenesis through Epithelial-to-mesenchymal Transition Pathway in Renal Cell Carcinoma. Mol. Cancer Ther. *17*, 1061–1069.

44. Wang, G., Zhang, Z.J., Jian, W.G., Liu, P.H., Xue, W., Wang, T.D., Meng, Y.Y., Yuan, C., Li, H.M., Yu, Y.P., et al. (2019). Novel long noncoding RNA OTUD6B-AS1 indicates poor prognosis and inhibits clear cell renal cell carcinoma proliferation via the Wnt/β-catenin signaling pathway. Mol. Cancer *18*, 15.

45. Zhang, H.M., Yang, F.Q., Chen, S.J., Che, J., and Zheng, J.H. (2015). Upregulation of long non-coding RNA MALAT1 correlates with tumor progression and poor prognosis in clear cell renal cell carcinoma. Tumour Biol. *36*, 2947–2955.

46. Katayama, H., Tamai, K., Shibuya, R., Nakamura, M., Mochizuki, M., Yamaguchi, K., Kawamura, S., Tochigi, T., Sato, I., Okanishi, T., et al. (2017). Long non-coding RNA HOTAIR promotes cell migration by upregulating insulin growth factor-binding protein 2 in renal cell carcinoma. Sci. Rep. *7*, 12016.

47. He, H., Dai, J., Zhuo, R., Zhao, J., Wang, H., Sun, F., Zhu, Y., and Xu, D. (2018). Study on the mechanism behind lncRNA MEG3 affecting clear cell renal cell carcinoma by regulating miR-7/RASL11B signaling. J. Cell. Physiol. *233*, 9503–9515.

48. Xue, S., Jiang, S.Q., Li, Q.W., Wang, S., Li, J., Yang, S., Zhang, H.M., Xu, Y.F., Wang, L.S., and Zheng, J.H. (2018). Decreased expression of BRAF-activated long non-coding RNA is associated with the proliferation of clear cell renal cell carcinoma. BMC Urol. *18*, 79.

49. Yang, W., Zhang, K., Li, L., Ma, K., Hong, B., Gong, Y., and Gong, K. (2020). Discovery and validation of the prognostic value of the lncRNAs encoding snoRNAs in patients with clear cell renal cell carcinoma. Aging (Albany NY) *12*, 4424–4444.

50. Wen, J.F., Jiang, Y.Q., Li, C., Dai, X.K., Wu, T., and Yin, W.Z. (2020). LncRNA-SARCC sensitizes osteosarcoma to cisplatin through the miR-143-mediated glycolysis inhibition by targeting Hexokinase 2. Cancer Biomark. *28*, 231–246.

51. Chen, Z., Zhuang, Q., Cheng, K., Ming, Y., Zhao, Y., Ye, Q., and Zhang, S. (2020). Long non-coding RNA TCL6 enhances preferential toxicity of paclitaxel to renal cell carcinoma cells. J. Cancer *11*, 1383–1392.

52. Liu, H., Ye, T., Yang, X., Lv, P., Wu, X., Zhou, H., Zeng, J., Tang, K., and Ye, Z. (2020). A Panel of Four-lncRNA Signature as a Potential Biomarker for Predicting Survival in Clear Cell Renal Cell Carcinoma. J. Cancer *11*, 4274–4283.

53. Bao, X., Duan, J., Yan, Y., Ma, X., Zhang, Y., Wang, H., Ni, D., Wu, S., Peng, C., Fan, Y., et al. (2017). Upregulation of long noncoding RNA PVT1 predicts unfavorable prognosis in patients with clear cell renal cell carcinoma. Cancer Biomark. *21*, 55–63.

54. Xiong, J., Liu, Y., Luo, S., Jiang, L., Zeng, Y., Chen, Z., Shi, X., Lv, B., and Tang, W. (2017). High expression of the long non-coding RNA HEIRCC promotes Renal Cell Carcinoma metastasis by inducing epithelial-mesenchymal transition. Oncotarget *8*, 6555–6563.

55. Yu, G., Yao, W., Wang, J., Ma, X., Xiao, W., Li, H., Xia, D., Yang, Y., Deng, K., Xiao, H., et al. (2012). LncRNAs expression signatures of renal clear cell carcinoma revealed by microarray. PLoS ONE *7*, e42377.

56. Wang, M., Huang, T., Luo, G., Huang, C., Xiao, X.Y., Wang, L., Jiang, G.S., and Zeng, F.Q. (2015). Long non-coding RNA MEG3 induces renal cell carcinoma cells apoptosis by activating the mitochondrial pathway. J. Huazhong Univ. Sci. Technolog. Med. Sci. *35*, 541–545.

57. He, H., Wang, N., Yi, X., Tang, C., and Wang, D. (2017). Long non-coding RNA H19 regulates E2F1 expression by competitively sponging endogenous miR-29a-3p in clear cell renal cell carcinoma. Cell Biosci. *7*, 65.

58. Song, E.L., Xing, L., Wang, L., Song, W.T., Li, D.B., Wang, Y., Gu, Y.W., Liu, M.M., Ni, W.J., Zhang, P., et al. (2019). LncRNA ADAMTS9-AS2 inhibits cell proliferation and decreases chemoresistance in clear cell renal cell carcinoma via the miR-27a-3p/FOXO1 axis. Aging (Albany NY) *11*, 5705–5725.

59. Zhou, H., Tang, K., Liu, H., Zeng, J., Li, H., Yan, L., Hu, J., Guan, W., Chen, K., Xu, H., and Ye, Z. (2019). Regulatory Network of Two Tumor-Suppressive Noncoding RNAs Interferes with the Growth and Metastasis of Renal Cell Carcinoma. Mol. Ther. Nucleic Acids *16*, 554–565.

60. Zhai, W., Sun, Y., Guo, C., Hu, G., Wang, M., Zheng, J., Lin, W., Huang, Q., Li, G., Zheng, J., and Chang, C. (2017). LncRNA-SARCC suppresses renal cell carcinoma (RCC) progression via altering the androgen receptor(AR)/miRNA-143-3p signals. Cell Death Differ. *24*, 1502–1517.

61. Han, X., Sekino, Y., Babasaki, T., Goto, K., Inoue, S., Hayashi, T., Teishima, J., Sakamoto, N., Sentani, K., Oue, N., et al. (2020). Microtubule-associated protein tau (MAPT) is a promising independent prognostic marker and tumor suppressive protein in clear cell renal cell carcinoma. Urol. Oncol. *38*, 605.e9–605.e17.

62. Luo, P., Liu, X.F., Wang, Y.C., Li, N.D., Liao, S.J., Yu, M.X., Liang, C.Z., and Tu, J.C. (2017). Prognostic value of abnormally expressed lncRNAs in ovarian carcinoma: a systematic review and meta-analysis. Oncotarget *8*, 23927–23936.

63. Ma, W., Chen, X., Ding, L., Ma, J., Jing, W., Lan, T., Sattar, H., Wei, Y., Zhou, F., and Yuan, Y. (2017). The prognostic value of long noncoding RNAs in prostate cancer: a systematic review and meta-analysis. Oncotarget *8*, 57755–57765.

64. Wu, Y., Wang, Y.Q., Weng, W.W., Zhang, Q.Y., Yang, X.Q., Gan, H.L., Yang, Y.S., Zhang, P.P., Sun, M.H., Xu, M.D., and Wang, C.F. (2016). A serum-circulating long noncoding RNA signature can discriminate between patients with clear cell renal cell carcinoma and healthy controls. Oncogenesis *5*, e192.

65. Qu, L., Ding, J., Chen, C., Wu, Z.J., Liu, B., Gao, Y., Chen, W., Liu, F., Sun, W., Li, X.F., et al. (2016). Exosome-Transmitted lncARSR Promotes Sunitinib Resistance in Renal Cancer by Acting as a Competing Endogenous RNA. Cancer Cell *29*, 653–668.

66. Yao, Y., Fan, Y., Wu, J., Wan, H., Wang, J., Lam, S., Lam, W.L., Girard, L., Gazdar, A.F., Wu, Z., and Zhou, Q. (2012). Potential application of non-small cell lung cancer-associated autoantibodies to early cancer diagnosis. Biochem. Biophys. Res. Commun. *423*, 613–619.

67. Tano, K., Mizuno, R., Okada, T., Rakwal, R., Shibato, J., Masuo, Y., Ijiri, K., and Akimitsu, N. (2010). MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. FEBS Lett. *584*, 4575–4580.

68. Ji, P., Diederichs, S., Wang, W., Böing, S., Metzger, R., Schneider, P.M., Tidow, N., Brandt, B., Buerger, H., Bulk, E., et al. (2003). MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene *22*, 8031–8041.

69. Fan, Y., Shen, B., Tan, M., Mu, X., Qin, Y., Zhang, F., and Liu, Y. (2014). TGF-β-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. Clin. Cancer Res. *20*, 1531–1541.

70. Han, Y., Liu, Y., Nie, L., Gui, Y., and Cai, Z. (2013). Inducing cell proliferation inhibition, apoptosis, and motility reduction by silencing long noncoding ribonucleic acid

metastasis-associated lung adenocarcinoma transcript 1 in urothelial carcinoma of the bladder. Urology *81*, 209.e1–209.e7.

71. Paschoal, A.R., Maracaja-Coutinho, V., Setubal, J.C., Simões, Z.L.P., Verjovski-Almeida, S., and Durham, A.M. (2012). Non-coding transcription characterization and annotation: a guide and web resource for non-coding RNA databases. RNA Biol. *9*, 274–282.
72. Zhao, Z., Chen, C., Liu, Y., and Wu, C. (2014). 17β-Estradiol treatment inhibits breast cell proliferation, migration and invasion by decreasing MALAT-1 RNA level. Biochem. Biophys. Res. Commun. *445*, 388–393.
73. Lin, R., Maeda, S., Liu, C., Karin, M., and Edgington, T.S. (2007). A large noncoding RNA is a marker for murine hepatocellular carcinomas and a spectrum of human carcinomas. Oncogene *26*, 851–858.
74. Liu, N., Dai, Q., Zheng, G., He, C., Parisien, M., and Pan, T. (2015). N(6)-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature *518*, 560–564.
75. Okugawa, Y., Toiyama, Y., Hur, K., Toden, S., Saigusa, S., Tanaka, K., Inoue, Y., Mohri, Y., Kusunoki, M., Boland, C.R., and Goel, A. (2014). Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. Carcinogenesis *35*, 2731–2739.
76. Jen, J., Tang, Y.-A., Lu, Y.-H., Lin, C.-C., Lai, W.-W., and Wang, Y.-C. (2017). Oct4 transcriptionally regulates the expression of long non-coding RNAs NEAT1 and MALAT1 to promote lung cancer progression. Mol. Cancer *16*, 104.
77. Xia, H., Chen, Q., Chen, Y., Ge, X., Leng, W., Tang, Q., Ren, M., Chen, L., Yuan, D., Zhang, Y., et al. (2016). The lncRNA MALAT1 is a novel biomarker for gastric cancer metastasis. Oncotarget *7*, 56209–56218.
78. Tian, Z., Cao, S., Li, C., Xu, M., Wei, H., Yang, H., Sun, Q., Ren, Q., and Zhang, L. (2019). LncRNA PVT1 regulates growth, migration, and invasion of bladder cancer by miR-31/ CDK1. J. Cell. Physiol. *234*, 4799–4811.
79. Gao, Y.L., Zhao, Z.S., Zhang, M.Y., Han, L.J., Dong, Y.J., and Xu, B. (2017). Long Noncoding RNA PVT1 Facilitates Cervical Cancer Progression via Negative Regulating of miR-424. Oncol. Res. *25*, 1391–1398.
80. Huang, T., Liu, H.W., Chen, J.Q., Wang, S.H., Hao, L.Q., Liu, M., and Wang, B. (2017). The long noncoding RNA PVT1 functions as a competing endogenous RNA by sponging miR-186 in gastric cancer. Biomed. Pharmacother. *88*, 302–308.
81. Li, T., Meng, X.L., and Yang, W.Q. (2017). Long Noncoding RNA PVT1 Acts as a "Sponge" to Inhibit microRNA-152 in Gastric Cancer Cells. Dig. Dis. Sci. *62*, 3021–3028.
82. Derderian, C., Orunmuyi, A.T., Olapade-Olaopa, E.O., and Ogunwobi, O.O. (2019). PVT1 Signaling Is a Mediator of Cancer Progression. Front. Oncol. *9*, 502.
83. Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., Amin, N., Schwikowski, B., and Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. *13*, 2498–2504.