The roles of long non-coding RNAs in renal cell carcinoma (Review)

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Abstract. Long non-coding RNAs (lncRNAs) are involved in the gene expression regulation and usually play important roles in various human cancers, including the renal cell carcinoma (RCC). Dysregulation of certain lncRNAs are associated with the prognosis of patients with RCC. In the present review, several recently studied lncRNAs were discussed and their critical roles in proliferation, migration, invasion, apoptosis and drug resistance of renal cancer cells were revealed. The research on lncRNAs further increases our understanding on the development and progression of RCC. It is suggested that lncRNAs can be used as biomarkers or therapeutic targets for diagnosis or treatment of renal cancer.

Contents

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1. Introduction

Kidney cancer accounts for ~2% of all cancers, resulting in millions of deaths worldwide each year (1,2). In 2016, 62,700 people were initially diagnosed with kidney cancer, and 14,240 patients succumbed to this disease in the United States (3). Renal cell carcinoma (RCC) is the most common type of kidney cancer, and its incidence is increasing (4-6). A total of ~20% of patients with RCC are diagnosed with tumors in advanced stages, and 30% of patients with localized RCC suffer relapses and metastasis after surgical treatment (7,8). However, specific biomarkers for RCC are rarely reported. Therefore, the further investigation of the molecular mechanism of RCC is urgently needed.

Multiple factors, including DNA methylation, histone modification, genomic instability and gene mutations, are involved in the molecular mechanism of RCC (9,10). The dysregulation of protein-coding genes is known to promote tumorigenesis (11,12). In addition, noncoding RNAs have been proven to be involved in various cellular activities (13-15), and the aberrant expression of non-coding RNAs accelerates the formation and development of RCC (16,17).

Noncoding RNAs are RNAs that cannot be translated into proteins (18). Long non-coding RNAs (lncRNAs), microRNAs (miRNAs or miRs), circular RNAs and small nuclear RNAs are non-coding RNAs (19,20). The research on lncRNAs is a hot topic. Each lncRNA is >200 bp in length and lacks protein-coding ability (21). LncRNAs were once considered to be noises in transcriptional processes. However, previous studies have demonstrated that lncRNAs participate in various biological processes, such as cell proliferation, cell death, cell differentiation and cell cycle regulation (22-26). Moreover, lncRNAs are closely correlated with the occurrence of diseases, such as atherosclerosis, Parkinson's disease and cancers (27-29). In accordance with their roles in cancer progression, lncRNAs are classified as tumor suppressor genes, oncogenes, or both (30).

With the development of lncRNA biology, a growing number of functional lncRNAs in RCC progression have been identified. In patients with RCC, the dysregulation of lncRNAs can promote the progression of RCC, resulting in poor prognosis (31-33). RCC

tumorigenesis is a complex biological process that involves not only mutations in genetic networks but also epigenomic alterations that can trigger imbalances in cellular homeostasis and ultimately lead to abnormal cell growth. During the process of malignant transformation, cells and their microenvironment must acquire various biological properties that favor malignant cell growth. These biological properties include and are not limited to: proliferation, migration, apoptosis and metabolism of RCC cells (34-36). lncRNAs play an important regulatory role in each of these biological events in RCC patients (Fig. 1). Moreover, lncRNAs can activate the expression of encoding genes, miRs and oncogenes to promote the development of RCC cells (37,38). In the present review, the clinicopathological features, biological functions and molecular mechanisms of lncRNAs in RCC development were presented.

2. Features and functions of lncRNAs in carcinogenesis

On the basis of their different transcription sites, lncRNAs are classified into five categories: sense, antisense, bidirectional, intergenic and bidirectional lncRNAs (39). Moreover, their functions are determined by their transcription sites to certain extent. lncRNAs are involved in gene expression regulation at different stages in a variety of tumors. They can recruit chromatin-modifying complexes to promote gene transcriptional expression levels and function with transcription factors, proteins, miRNAs, or mRNAs to control post-transcriptional processes (40-43). They can act as scaffolds to absorb various regulatory molecules at a single locus (44). The number of lncRNAs participating in epigenetic regulation is increasing. lncRNA MALAT1 was revealed to upregulate the expression of EZH2 by binding with miR-205 and promote the apoptosis of acute lymphoblastic leukemia cells (32). In chemo-resistant, castration-resistant prostate cancer, lncRNA HOXD-AS1 utilized histone H3 lysine 4 trimethylation to absorb WDR5, thereby inhibiting PKL1 and AURKA expression (45). In gastric cancer cells, lncRNA FEZF1-AS1 suppressed P21 expression by binding with LSD1 (46).

lncRNAs also execute important roles in the development of cancers. Multiple studies have demonstrated that some cancer-promoting lncRNAs could promote the proliferation and migration and inhibit the apoptosis of cancer cells, such as gastric cancer cells (47,48). In addition, certain lncRNAs could promote cancer drug resistance and alter energy metabolism in cancer cells (49,50).

3. lncRNAs and RCC

Expression profile of lncRNAs in RCC. Microarray and RT-qPCR assays were previously used to determine the relative expression of lncRNAs in RCC. The relative expression levels of lncRNAs in RCC are shown in Table I.

lncRNAs are associated with the prognosis of patients with RCC. Numerous studies have shown that the aberrant expression of lncRNAs is closely associated with the pathological features and prognosis of patients with RCC. NEAT1 overexpression was significantly associated with the tumor size, histological grade, and lymph node metastasis of patients with RCC, thus worsening overall survival (51). He *et al* (35) found that the expression of lncRNA FTX in RCC tissues was 5-fold higher than that in adjacent normal tissues. The high expression of FTX was positively correlated with large tumor size, lymphatic metastasis and high TNM stage. Xiong *et al* (52) found that lncRNA ATB was obviously overexpressed in RCC tissues, and the augmented expression of ATB was closely associated with histological grade, tumor stage, lymph node metastasis and distant metastasis. lncRNA RCCRT1 was also elevated in RCC tissues. Correlations have been found between RCCRT1 expression and pathological features, including histological grade, distant metastasis and lymph node metastasis (53). Moreover, lncRNAs MALAT1, lnc-ZNF180-2, Linc00152, HOTAIR, and HEIRCC were upregulated in RCC tissues compared with normal kidney tissues (32,54-57). In patients with RCC, high MALAT-1 expression resulted in large tumor size, high tumor stage and lymph node metastasis (32). In patients with RCC, the decreased expression of lncRNA H19 caused high histological grade and tumor stage, as well as lymph node and distant metastasis (58). The correlations between clinicopathological features and the expression of other cancer-promoting lncRNAs are shown in Table I. Certain lncRNAs, including lncRNAs TCL6, CADM1-AS1, GAS5, and LOC389332, are downregulated in the progression of RCC (59-62). The expression of lncRNA TCL6 was negatively correlated with TNM stage, lymph node metastasis, and distant metastasis (59). The relationships between clinicopathological features and other tumor-suppressor lncRNAs are shown in Table I.

lncRNAs control the proliferation of RCC cells. Infinite proliferation is an important feature of cancer cells (63,64). RCC cells can proliferate with impunity when nutrition and space are enough. Moreover, RCC cells can compress their surrounding tissue during proliferation (65). lncRNAs play important roles in the proliferation of RCC cells. Oncogene lncRNAs can promote the proliferation of RCC cells, whereas tumor suppressors can inhibit proliferation. The relevant biological functions in which lncRNAs are involved are presented in Table II.

Zhang *et al* (32) and Chen *et al* (36) demonstrated that the knockdown of lncRNA MALAT-1 inhibited the proliferation of RCC cells.

Wu *et al* (55) showed that the amplification of lncRNA Linc00152 enhanced the proliferation of RCC cells. Wu *et al* (66) found that the inhibition of lncRNA HOTAIR suppressed the proliferation of RCC cells. Moreover, the percentage of G2/M phase cells was reduced significantly. Xiong *et al* (57) discovered that lncRNA HEIRCC promoted the proliferation of RCC cells. In addition, RCC cell proliferation was significantly downregulated when lncRNA ATB was suppressed (52). Cellular proliferation was inhibited when lncRNA FTX was knocked down in RCC cells (35). Ning *et al* (51) found that the knockdown of lncRNA NEAT1 weakened the proliferation of RCC cells. Furthermore, lncRNA UCA1 could strengthen the proliferation of RCC cells (67). Zhai *et al* (68) identified an interesting lncRNA, lncRNA SARCC, that was differentially expressed in the hypoxic environment depending on the expression of von Hippel-Lindau (VHL). The overexpression of lnRNA SARCC inhibited the proliferation of VHL-mutant RCC cells by decreasing the stability and expression of androgen

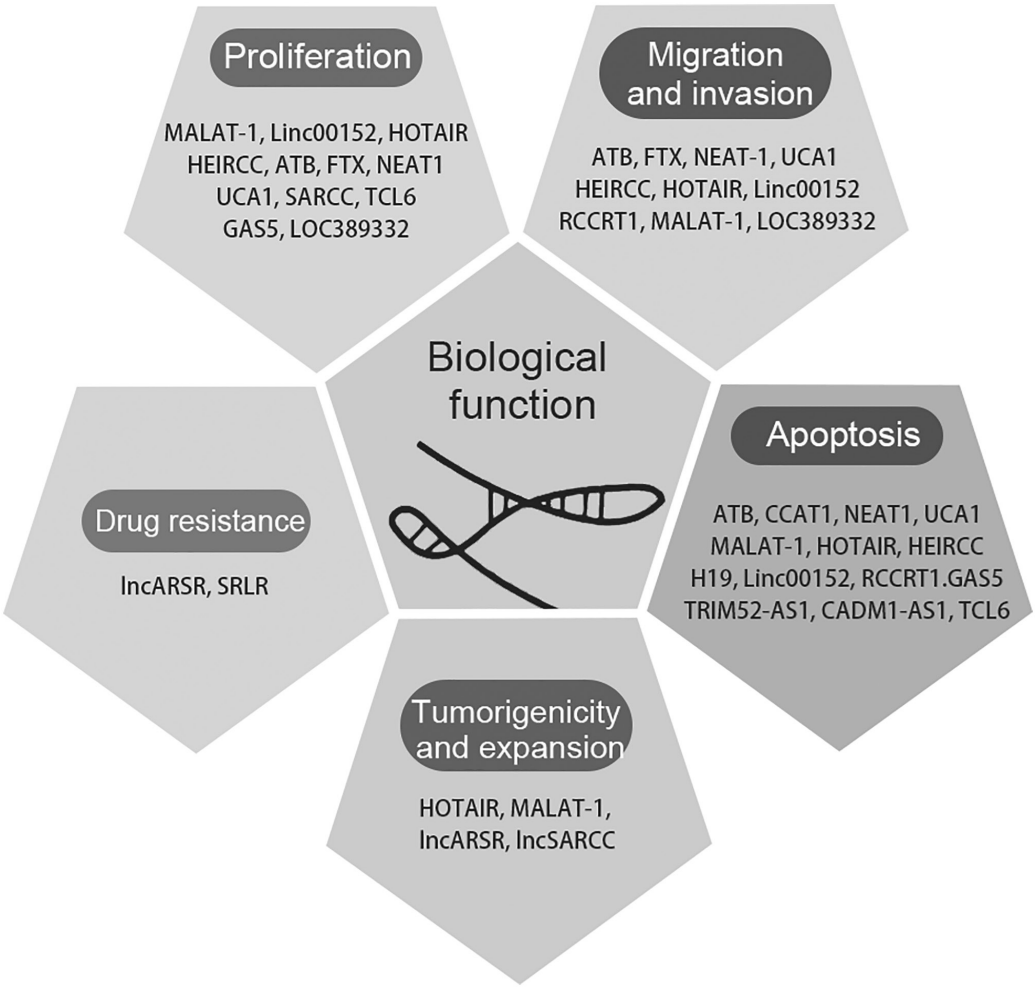

Figure 1. The involvement of long non-coding RNAs in renal cell carcinoma carcinogenesis.

receptor (AR) protein. The decreased expression of AR protein suppressed HIF-2α and C-MYC expression. C-MYC is the downstream effector of HIF-2α. Finally, Zhai *et al* (68) clearly demonstrated that the signals of lncRNA SARCC/AR/HIF-2α/C-MYC/p27/E2F1 were present in the absence of oxygen, thus opening up a new molecular pathway for RCC cancer progression under hypoxic conditions.

Tumor-suppressor lncRNAs can suppress the proliferation of RCC cells. The overexpression of lncRNA TCL6, GAS5, or LOC389332 can restrain RCC cell proliferation (48,50,51).

lncRNAs affect the migration and invasion of RCC cells. Metastasis is a massive problem for cancer therapy. The migration and invasion of cancer cells are the main reasons for tumor metastasis (69,70). Hence, a deep insight into RCC cell migration and invasion will contribute to the research on tumor metastasis. The relevant biological functions in which lncRNAs are involved are shown in Table II.

Xiong *et al* (52) revealed that the decreased expression of lncRNA ATB reduced the migration and invasion ability of RCC cells by repressing the epithelial-mesenchymal transition (EMT). He *et al* (35) demonstrated that the inhibition of lncRNA FTX weakened the migration and invasion of RCC cells. Ning *et al* (51) found that NEAT-1 accelerated EMT to enhance the invasiveness of RCC cells. RCC cell motility was significantly decreased when the cellular expression of lncRNA UCA1 was inhibited (67). The silencing of lncRNA HEIRCC suppressed RCC cell migration and invasion by inhibiting the EMT program (57). Chiyomaru *et al* (71), Xia *et al* (56) and Wu *et al* (66) demonstrated that the knockdown of lncRNA HOTAIR weakened the migration and invasion of RCC cells, whereas the overexpression of HOTAIR produced opposite results. The increased expression of Linc00152 promoted the invasion of RCC cells, whereas the deletion of Linc00152 resulted in contrasting results (55). RCC cells with decreased RCCRT1 expression showed attenuated migration ability (53). Finally, Xiao *et al* (72) and Zhang *et al* (32) reported that the deletion of lncRNA MALAT-1 inhibited cell migration and invasion. However, the amplification of the tumor-suppressor lncRNA LOC389332 suppressed the migration of RCC cells (55).

lncRNAs affect the apoptosis of RCC cells. The apoptosis of normal cells is promoted by complicated apoptotic mechanisms, and a series of genes and signaling pathways are activated (73,74). However, the apoptosis of cancer cells is not controlled by programmed cell death (75,76). The apoptosis of RCC cells is obviously suppressed and the expression of apoptosis-related genes is activated during the progression of RCC (77,78). With the improved understanding of lncRNAs,

Table I. Clinicopathological features and relative expression levels of genes associated with long non-coding RNAs in patients with RCC.

Gene	Clinicopathologic features	Relative expression levels in RCC	(Refs.)
MALAT1	Tumor size, tumor stage, lymph node metastasis, poor prognosis	High	(32)
CCAT1	None	High	(34)
FTX	Tumor size, lymphatic metastasis and higher TNM stage	High	(35)
NEAT1	Tumor size, histological grade, lymph node metastasis	High	(51)
ATB	Histological grade, tumor stage, lymph node metastasis, distance metastasis	High	(52)
RCCRT1	Histological grade, distant metastasis and lymph node metastasis	High	(53)
lnc-ZNF180-2	Tumor stage, poor prognosis	High	(50)
Linc00152	Poor prognosis	High	(54)
HOTAIR	Lymph nodes, poor prognosis	High	(56)
HEIRCC	Tumor stage, histological grade, lymph node metastasis, distant metastasis	High	(57)
H19	Histological grade, tumor stage, lymph nodes metastasis, distant metastasis	High	(58)
UCA1	None	High	(67)
TCL6	TNM stage, T classification, lymph node metastasis, distant metastasis	Low	(59)
CADM1-AS1	AJCC stage, poor prognosis	Low	(60)
GAS5	None	Low	(61)
LOC389332	Histological grade, lymph node metastasis, poor prognosis	Low	(62)

RCC, renal cell carcinoma; TNM, tumor node metastasis; AJCC, American Joint Commission on Cancer.

Table II. The biological function of long non-coding RNAs in patients in RCC.

Biological function	Related long non-coding RNAs	(Refs.)
Proliferation of RCC cells	MALAT-1, Linc00152, HOTAIR, HEIRCC, ATB, FTX, NEAT1,UCA1, SARCC, TCL6, GAS5, LOC389332	(32,35,36,48,50-52,55,57,66-68)
Migration and invasion of RCC cells	ATB, FTX, NEAT-1, UCA1, HEIRCC, HOTAIR, Linc00152, RCCRT1, MALAT-1, LOC389332	(32,35,51-53,55-57,66,67, 71,72)
Apoptosis of RCC cells	ATB, CCAT1, NEAT1, UCA1, MALAT-1, HOTAIR, HEIRCC, H19, Linc00152, RCCRT1, GAS5, TRIM52-AS1, CADM1-AS1, TCL6	(34,36,37,51-53,55,57-59, 60,61,67,71,81)
Tumorigenicity and expansion of RCC cells	HOTAIR, MALAT-1, lncARSR, lncSARCC	(66,72,86-88)
Drug resistance of RCC cells	lncARSR, SRLR	(38,89)

RCC, renal cell carcinoma.

certain apoptosis-related genes in RCC have been reported. The relevant biological functions in which lncRNAs are involved are shown in Table II.

Xiong *et al* (52) reported that the decreased expression of lncRNA ATB promoted the apoptosis of RCC cells, indicating that lncRNA ATB restrained apoptosis during

the development of RCC cells. Chen *et al* (34) detected the role of CCAT1 in cell apoptosis and found that CCAT1 knockdown led to an increase in apoptotic RCC cells, as well as caspases 3, 7, and 9. However, the antiapoptotic protein Bcl-2 was downregulated upon CCAT1 knockdown. CCAT1 exerted its anti-apoptosis effect by increasing the expression of Livin. Ning *et al* (51) confirmed that the deletion of lncRNA NEAT1 enhanced the apoptotic rate of RCC cells. Li *et al* (67) identified the negative effect of lncRNA UCA1 on RCC cell apoptosis. Hirata *et al* (37) and Chen *et al* (36) showed that the knockdown of lncRNA MALAT-1 obviously strengthened the apoptosis of RCC cells, whereas the enforced expression of MALAT inhibited cell apoptosis. Chiyomaru *et al* (71) discovered that the suppression of lncRNA HOTAIR increased apoptotic RCC cells by inhibiting the expression of miR-141. miR-141 is a member of the miR-200 family that acts as a tumor suppressor in the progression of cancers. The amplification of miR-141 promotes the apoptosis of cancer cells (79,80). Xiong *et al* (57) investigated the effect of lncRNA HEIRCC on RCC cell apoptosis and detected increased apoptosis when HEIRCC was knocked down. Moreover, lncRNAs H19, Linc00152, and RCCRT1 could inhibit the apoptosis of RCC cells (53,55,58).

The dysregulation of tumor-suppressor lncRNAs is associated with the progression of RCC. Qiao *et al* (61) found that the enforced expression of lncRNA GAS5 increased the percentage of early apoptotic cells and total apoptotic cells in RCC cells. Liu *et al* (81) identified that the attenuated expression of lncRNA TRIM52-AS1 facilitated RCC cell apoptosis. Yao *et al* (60) observed that the rate of apoptotic RCC cells was increased in the lncRNA CADM1-AS1 knockdown group compared with that in the negative control group. Su *et al* (59) demonstrated that the upregulation of lncRNA TCL6 enhanced the apoptosis of RCC cells.

lncRNAs are responsible for the tumorigenicity and expansion of RCC cells in vivo. Current studies have provided valuable novel insights into the lncRNA-induced tumorigenicity and expansion of RCC cells *in vivo* (82,83). The amplification of certain lncRNAs can facilitate tumor formation and expansion by enhancing angiogenesis and altering the intracellular environment (84,85). During carcinogenesis, carcinoma cell lines can grow out of control, stifling reef recovery. However, the impaired expression of carcinogenic lncRNAs, such as HOTAIR, MALAT-1, lncARSR, and lncSARCC, can reduce the size and weight of RCC tissues *in vivo* (66,72,86-88). The relevant biological functions in which lncRNAs are involved are shown in Table II.

Wu *et al* (66) injected RCC cells expressing low HOTAIR levels into mice. The growth rate and weight of tumors induced by the RCC cells were significantly lower than those in the negative control groups. Moreover, the knockdown of HOTAIR upregulated the expression levels of p53, p21 and p16 *in vivo*. Xiao *et al* (72) revealed that the inhibition of lncRNA MALAT-1 *in vivo* significantly reduced the tumor size and quality of RCC. Qu *et al* (87) identified that silencing lncRNAs weakened the tumorigenicity and metastasis of renal tumor-initiating cells by binding to the Yes-associated protein (YAP). Mechanistically, the 5' end of lncARSR binds to YAP to interrupt LATS1-mediated YAP phosphorylation. To sum up, the lncARSR-YAP axis functions as a promising therapeutic target in patients with RCC.

lncRNAs contribute to the drug resistance of RCC cells. Tumor drug treatments, such as chemotherapy and targeted therapy, have been widely used in cancer treatment. In renal cancer, drug treatment is known to gradually become insensitive. Although the mechanisms of tumor drug resistance have been studied and reported, no one could completely explain all the observations. Two recent works have highlighted the involvement of lncRNAs in the drug resistance of RCC cells. Qu *et al* (38) reported an uncharacterized lncRNA, lncARSR, to be highly expressed in sunitinib-resistant RCC cells and functionally required for the resistant phenotype. lncARSR acts as a ceRNA for miR-34 and miR-449, resulting in the upregulation of AXL/c-MET and the activation of STAT3, AKT and ERK signaling. It was also found that lncARSR could be used to predict the poor response of patients with RCC. Notably, this lncRNA could also be secreted from resistant cells through exosomes, thereby transforming sunitinib-sensitive cells into resistant cells. Xu *et al* (89) identified lncRNA SRLR, which was upregulated in intrinsically sorafenib-resistant RCC cells. The knockdown of lncRNA SRLR sensitized non-responsive RCC cells to sorafenib treatment. By contrast, the overexpression of lncRNA SRLR conferred sorafenib resistance to responsive RCC cells. The potential molecular mechanism of this lncRNA and was further studied and it was revealed that lncRNA SRLR directly bound to NF-κB, enhanced IL-6 transcription and led to the activation of STAT3 and the development of sorafenib tolerance. lncRNA SRLR functioned as not only a predictive marker for sorafenib resistance but also as a therapeutic target to enhance responses to sorafenib in patients with RCC. The relevant biological functions in which lncRNAs are involved are shown in Table II.

4. Conclusions

Renal caner is a fatal disease with aberrant gene expression (90,91). Although the treatments for renal cancer have been rapidly improved over the past few decades, the survival of patients with RCC has not been significantly improved (92,93). Recurrence and metastasis are the major reasons for RCC treatment failure (94-96). However, the clear molecular mechanisms of RCC initiation and progression remain largely mysterious.

Coding genes were once believed to act as the major regulators during the development of cancers (97-99). Protein-coding genes have been reported to account for ~1-2% of the human genome, and non-protein-coding genes constitute more than 90% of the human genome (100). With the development of whole-genome sequencing, lncRNAs have been reported be important regulators in the development of RCC, and a growing number of unknown lncRNAs have been identified. The dysregulation of certain lncRNAs is closely associated with the occurrence and clinicopathological features and prognosis of RCC (101,102). Further studies revealed that lncRNAs are involved in the proliferation, migration, apoptosis and drug resistance of RCC cells (38,103,104). Moreover, a series of molecular mechanisms

and signaling pathways have been reported. lncRNA SARCC inhibited the proliferation of VHL-mutant RCC cells by regulating the androgen receptor/HIF-2α/C-MYC axis (68). HOTAIR facilitated RCC cell migration by downregulating the expression of miR-141. miR-141 decreased the HOTAIR downstream target genes ABL2 and PCDH10 (71). lncRNA MALAT1 inhibited the apoptosis of RCC cells by increasing EZH2 and decreasing miR-205 expression. c-Fos acted as an upstream regulator in the MALAT1/EZH2/miR-205 axis (37). lncRNA ARSR promoted sunitinib resistance in RCC and could be used to predict the poor responses of patients with RCC. Moreover, lncRNA ARSR served as a ceRNA for miR-449 and miR-34 to enhance the expression of c-MET and AXL. In general, lncRNAs perform important roles in the development of RCC (38).

Although numerous studies on lncRNAs in RCC have been reported, no study on energy metabolism and internal environment regulation exists. Furthermore, the concentrations of lncRNAs in the sera of patients with RCC remain unclear. This situation greatly hinders the clinical application of lncRNAs. The number of follow-up patients is insufficient, and the follow-up time is still too short. Hence, additional detailed studies on the biological functions of lncRNAs in RCC are needed. Deeply understanding the content of lncRNAs in the human body and molecular mechanisms of lncRNAs in RCC may contribute to the application of lncRNAs in clinical work. Studies searching for lncRNA-related nucleic acids and proteins may be useful for investigating the post-transcriptional controls of lncRNAs and their regulatory networks in RCC. RNAi therapies targeting lncRNAs may also be used in advanced RCC animal models and even clinical trials. In conclusion, lncRNAs can serve as molecular biomarkers to predict the prognosis of patients with RCC and can be used as the therapeutic targets to fight against RCC in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZS, JA, GX and CG designed the present study. FZ and GX integrated and analyzed the data. HC wrote the manuscript. ZS edited and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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