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Review Article

Long Non-Coding RNAs: A Double-Edged Sword in Renal Cell Carcinoma Carcinogenesis

[1,2]Tian Liu and [1,2]Hui Zhao

[1]Clinical Experimental Center, Xi'an International Medical Center Hospital, No. 777 Xitai Road Xi'an, Shaanxi 710100, China
[2]Xi'an Engineering Technology Research Center for Cardiovascular Active Peptides, No. 777 Xitai Road Xi'an, Shaanxi 710100, China

Abstract

Renal cell carcinoma (RCC) is a malignant tumor that results in high mortality and a huge economic burden worldwide. Owing to the paucity of therapy options, it still has a poor prognosis. Therefore, it is of great importance to find an effective strategy for the treatment of RCC. Long Non-Coding RNAs (lncRNAs) emerge as a pivotal regulator of diverse cancers in many biological processes, including proliferation metastasis, apoptosis and metabolism by tethering with DNA, RNA or protein. Recently, a strong body of investigations revealed that lncRNAs play a critical role in carcinogenesis and cancer progression. Hence, this review provides a synopsis of the molecular mechanisms and clinical implications of lncRNAs in the progression of RCC and found that lncRNAs have the potential to be used clinically in RCC in the future.

Key words: Renal cell carcinoma, long non-coding RNA, diagnosis, prognosis, therapy

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Corresponding Author: Hui Zhao, Clinical Experimental Center, Xi'an International Medical Center Hospital, No. 777 Xitai Road Xi'an, Shaanxi 710100, China
Tel: +029-68302970

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Renal cell carcinoma (RCC), which comprises 90% of kidney cancers, was ranked sixth for mortality worldwide and accounts for 2% of human malignancies[1-4]. The RCC occurs more frequently in the elderly and in men, which resulted in more than 140000 deaths yearly[5,6]. Von hippel-lindau (VHL) gene, BRCA1-associated protein 1 (BAP1), polybromo-1 (PBRM1) and SET domain-containing 2 (SETD2) mutations are the key drivers in the development of RCC and many risk factors may contribute to RCC, including smoking, hypertension obesity and chronic kidney disease[7,8]. The RCC mainly contains 3 subtypes: Clear cell RCC (ccRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC) and ccRCC is most frequent followed by pRCC and chRCC[9,10]. Currently, most patients with RCC are diagnosed at advanced stages due to the high ratio of relapse and metastasis. In addition, RCC exhibited high chemoresistance and radioresistance, which brings large obstacles to the therapy of RCC[11,12]. Thus, it is of urgent importance to explore the precise molecular mechanism of RCC for early diagnosis and treatment.

Only about 1-2% of the total RNA could be translated into protein, while more than 90% of RNA, namely Non-coding RNAs (ncRNAs), is thought to have no capacity to encode protein[13,14]. Owing to lacking sufficient knowledge, ncRNAs were initially viewed as transcriptional noise and attracted little attention. However, upon further study, ncRNAs were confirmed to play an essential role in multiple human diseases[15-17]. The ncRNAs longer than 200 nucleotides are called Long Non-coding RNAs (lncRNAs) that have been associated with various functions[18]. In the last decade, accumulating evidence has shown that several lncRNAs have emerged as pivotal regulators in multiple biological processes, such as cell growth and differentiation, tumorigenesis and inflammation[19,20]. Until now, lncRNAs found to be dysregulated in multiple cancers. A growing number of studies revealed that lncRNAs play an essential role in promoting the tumorigenesis and progression of human cancers, including RCC and served as regulators in many cellular behaviours, including proliferation, invasion, migration, as well as apoptosis[21,22]. Emerging evidence also indicated that aberrant expression lncRNAs are significantly associated with the diagnosis and prognosis of RCC[23,24]. Furthermore, they may have the potential to be therapeutic targets for RCC. In this review, we summarized the roles of lncRNAs in tumor initiation and progression of RCC and highlighted the possible utilization of lncRNAs for the diagnosis and therapy in RCC.

Molecular mechanisms of lncRNAs: In the past few decades, researchers have conducted considerable work and in-depth studies to clarify the molecular mechanisms of lncRNAs. A strong body of evidence indicated that lncRNAs regulate gene expression mainly at three levels namely epigenetic, transcriptional and post-transcriptional regulation. (a) Epigenetic level: Transcription process can be regulated by recruiting chromatin remodelling/modification complexes to specific sites and affect the chromosome structure, histone modification and DNA methylation (b) Transcriptional level: Affecting the process of gene transcription by binding with RNA polymerase II, pre-initiation complex and transcription factors and (c) Post-transcriptional level: Regulating mRNA processing in multiple aspects such as mRNA selective splicing, degradation or translation[24,25].

Additionally, lncRNAs can sequester miRNA away from their target mRNA via interacting with miRNAs by acting as competing endogenous RNA (ceRNA) or RNA sponges. lncRNAs and mRNAs can interact by competing for miRNA binding, thus affecting their respective expression levels[26]. Relevant studies also showed that lncRNAs can bind to specific RNA or DNA sequences by base-pairing interactions and fold into advanced structures that regulate their interaction with proteins[27]. Moreover, lncRNAs could exert functions in both cytoplasm and nucleus via various mechanisms including the regulation of chromosome architecture and genomic regions, interaction with chromatin modification complexes, transcriptional enhancers activation, nuclear domains conformation, the transcriptional machinery interference and nuclear bodies' structural formation and maintenance (Fig. 1)[28]. Collectively, increasing evidence demonstrated that lncRNAs exert an irreplaceable role in different diseases. The regulatory mechanisms of lncRNAs still need further investigation and conformation to enable them as novel targets for the diagnosis and treatment of diseases in the clinic.

lncRNAs in RCC: Recently, lncRNAs were confirmed as new players in human cancers. Accumulating evidence has demonstrated that lncRNAs are dysregulated and affect the progression of many malignant tumors, including RCC[19]. Many studies indicated that lncRNAs might be potential biomarkers of diagnosis and prognosis, targets for molecular targeted therapy and serve as new budding stars in RCC. Here, we illuminated the functions and mechanisms of some lncRNAs in the development of RCC to provide a good understanding of their roles in RCC.

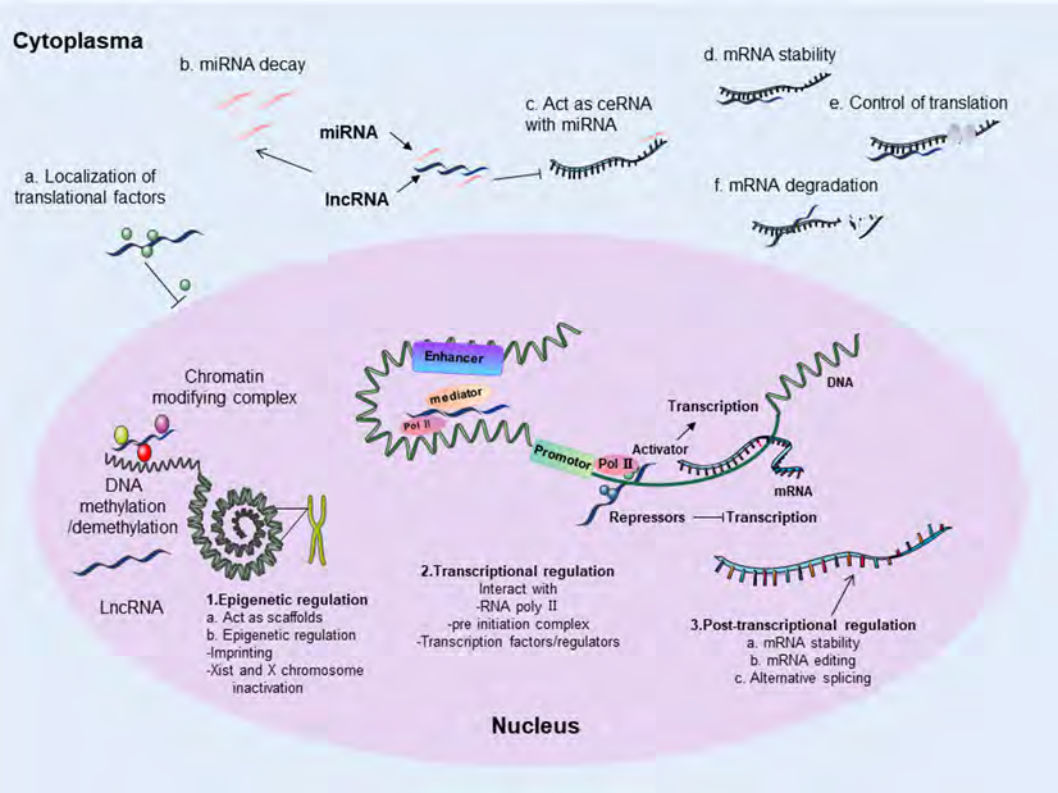

Fig. 1: Molecular mechanisms of long non-coding RNAs

lncRNAs regulate gene expression in three ways, namely epigenetic regulation, transcriptional regulation and post-transcriptional regulation[28]

lncRNAs as oncogenes in RCC

MALAT: With more than 8000 nucleotides, the Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) is located on chromosome 11q13 and was confirmed to serve as a critical participant in multiple cancers[29]. Significantly, MALAT1 was upregulated in the RCC tissues and cells (A-498 and 786-O cells) compared to normal renal tissues[30,31]. The MALAT1 promoted the proliferation and migration of Caki-1 cells by targeting miR-22-3p via the phosphatidylinositide 3-kinase/protein kinase B (PI3K/Akt) signalling pathway. Similarly, overexpression of MALAT1 can promote the progression of RCC by the regulation of miR-203/baculoviral inhibitor of apoptosis repeat containing 5 (BIRC5) axis[30,32]. Other related studies indicated that MALAT1 deficiency inhibited the proliferation, invasion and migration of RCC cells by sponging miR-429 or targeting miR-200s/zinc finger E-box binding homeobox 2 (ZEB2) axis[33,34]. Moreover, MALAT1 was confirmed to interact with miR-205 and was activated by the c-Fos that interacted with the enhancer of zeste homolog 2 (EZH2), which is a PRC2 subunit. Knockdown of MALAT1 blocked epithelial-mesenchymal transition (EMT) in the progression of RCC, as indicated by the upregulation of E-cadherin and reduction of β-catenin via EZH2[31]. Of note, knockdown of MALAT1 can also suppress sunitinib chemoresistance by downregulating miR-362-3p-mediated RasGAP SH3-domain-Binding Protein1 (G3BP1) expression, indicating that MALAT1 might serve as a therapeutic target for sunitinib-resistance RCC[35]. In conclusion, these findings indicated the in-depth role of MALAT1 in RCC carcinogenesis, suggesting a detailed mechanism in RCC progression (Fig. 2).

HOTAIR: The HOX Antisense intergenic RNA (HOTAIR), which is located on chromosome 12q13.13 with 2158 nucleotides and 6 exons, represents an important oncogene in various human cancers and is presented as a potential prognostic biomarker[36,37]. Notably, HOTAIR was upregulated in RCC cell lines (ACHN and Caki-1 cells) and tissues. Overexpression of miR-203 or HOTAIR inhibition repressed the proliferation, invasion and migration while promoting apoptosis of ACHN and Caki-1 cells. In contrast, HOTAIR deficiency inhibited the expression of E-cadherin, claudin, phosphatase and tensin homolog (PTEN), p21 and p27, indicating that HOTAIR suppression inhibited EMT and tumor metastasis[38]. Moreover, HOTAIR promoted the progression of RCC by sponging

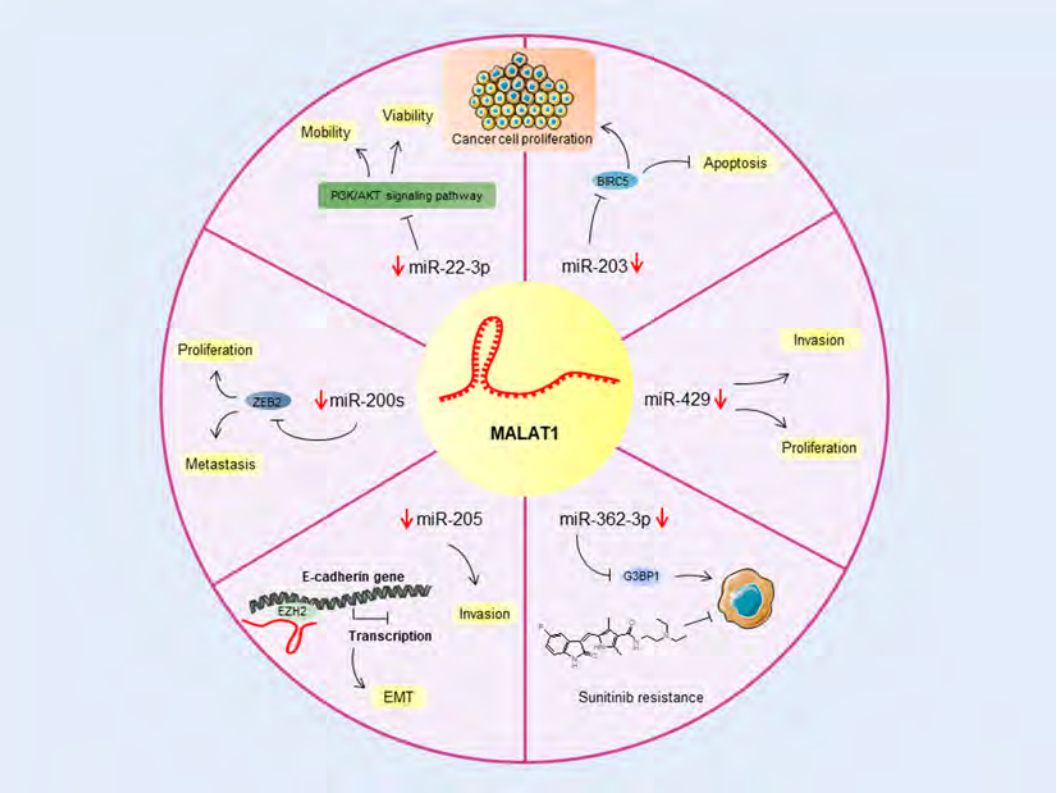

Fig. 2: lncRNA MALAT1 is an essential oncogene in the progression of renal cell carcinoma

lncRNA MALAT1 can affect the many processes of RCC, including cell proliferation, invasion, motility, viability, apoptosis and sunitinib resistance through targeting various pathways[30,32-35]

miR-124 through α-2, 8-sialyltransferase 4. Knockdown of HOTAIR, a target of miR-217, inhibited tumorigenesis by downregulating the expression of Hypoxia-Inducible Factor-1α (HIF-1α) and anexelekto (AXL). Particularly, overexpression of HOTTIP had a significantly shorter overall survival (OS) and disease-free survival (DFS), suggesting that HOTTIP may serve as a prognostic predictor of RCC[39,40]. In addition, knockdown of HOTAIR by siRNA can also inhibit the proliferation, migration and invasion of A-498 and OS-RC-2 cells with a cell cycle arrest in the G0/G1 phase and with the reduced number of cells in the G2/M phase. Meanwhile, HOTAIR deficiency promoted the expression of p53, p21 and p16 at both mRNA and protein levels, whereas, downregulated the level of EZH2 protein with lower recruitment and binding abilities[41]. These studies indicated that HOTAIR was involved in the tumorigenesis of RCC and exhibited oncogenic properties, providing a novel therapeutic target for the treatment of RCC.

UCA1: The Urothelial carcinoma associated 1 (UCA1), which is located on chromosome 19, serves as an oncogene in many tumors and was firstly discovered in bladder cancer[42,43]. The expression of UCA1 was significantly upregulated in RCC tissues and cells (769-P, 786-O, ACHN, A498 and Caki2 cells). It has been shown to promote the proliferation and invasion of RCC cells, whereas, inhibited cell apoptosis by acting as a ceRNA of miR-129 to upregulate the level of SRY-box transcription factor 4 (SOX4) in RCC[44]. Furthermore, lncRNA UCA1 has been found to play a carcinogenic role in RCC. The expression of UCA1 promoted cell proliferation by inhibiting the expression of miR-495 and p21 in 786-O and ACHN cells. Overexpression of UCA1 was intimately associated with the advanced tumor-node-metastasis (TNM) stage and led to a shorter OS time[45]. These findings demonstrated that overexpression of UCA1 contributes to the progression and promotion of RCC and may serve as a potential molecular predictor for poor prognosis in RCC patients.

TUG1: With 4 exons, the Taurine Upregulated Gene 1 (TUG1) is located on chromosome 22q12 and exerts important regulatory functions in multiple types of human cancers[46-48]. In RCC tissues and cells (ACHN and OS-RC-2 cells), TUG1 was significantly increased. A new study implied that knockdown of TUG1 inhibited RCC formation by sponging miR-299-3P via

downregulating Vascular Endothelial Growth Factor (VEGF) expression[49]. The expression of TUG1 can promote the proliferation, migration and invasion of RCC 786-O cells while inhibiting cell apoptosis by downregulating miR-196a. Meanwhile, TUG1 can promote the progression of RCC by regulating miR-9/yes-associated protein (YAP) axis[50-52]. In addition, TUG1 inhibited apoptosis and autophagy, whilst promoting the proliferation of RCC 786-0 and A498 cells by upregulating flotillin 1 (FLOT1) expression via sponging miR-31-5p[53].

CYTOR: The Cytoskeleton Regulator (CYTOR), which consists of 828 bp, is located on chromosome 2p11.2. The CYTOR was firstly discovered in hepatic carcinoma and acts as a critical oncogene in various human cancers[54]. The CYTOR deficiency retarded the proliferation of RCC 786-O and Caki-1 cells while facilitating cell apoptosis by repressing miR-136-5p to regulate methionine adenosyltransferase (MAT) 2B. The MAT2B was demonstrated to affect RCC progression by interacting with Bcl2-associated athanogene 3 (BAG3), In addition, knockdown of CYTOR significantly inhibited the tumor growth in 786-O xenograft nude mice. Thus, CYTOR may act as a potential therapeutic target for RCC[55].

AFAP1-AS1: Located on chromosome 4p16.1, the actin filament-associated protein 1-antisense RNA 1 (AFAP1-AS1) consists of 6810 nucleotides that are involved in many malignant tumors[56]. The upregulation of AFAP1-AS1 was observed in RCC tissues and cell lines (786-O, Caki-1, ACHN and A498 cells). In RCC patients, overexpression of AFAP1-AS1 had a poorer OS and was closely related to the TNM stage and lymph node metastasis of RCC patients. Knockdown of AFAP1-AS1 inhibited the proliferation, invasion, migration and EMT in Caki-1 and ACHN cells and inhibited tumor growth via PTEN/AKT signalling[57]. These results demonstrated that AFAP1-AS1 exhibits oncogenic properties and provides a potential therapeutic target for targeted interventional therapy of RCC.

HOTTIP: The HOXA Transcript at the Distal Tip (HOTTIP), which is located on the chromosomal locus 7p15.2, is transcribed from the HOXA cluster[58]. Upregulation of HOTTIP has been shown to play a critical role in various human cancers via epigenetic modifications, lncRNA-miRNA and lncRNA-protein interactions[59]. The HOTTIP deficiency inhibited the proliferation, migration and invasion by promoting autophagy through the PI3K/Akt/Atg13 signalling pathway and induced apoptosis by epigenetically downregulating large tumor suppressor 2 (LATS2) via interacting with EZH2 and Lysine-Specific Demethylase 1 (LSD1) in RCC ACHN and OSRC-2 cells. Moreover, HOTTIP overexpression led to larger tumor size and advanced TNM stage[60,61]. In addition, by acting as a ceRNA of miR-615, HOTTIP can increase the expression of IGF-2, leading to the promotion of RCC malignancy. Overexpression of HOTTIP had significant statistical relevance to the undesirable OS and DFS in RCC[62].

H19: The lncRNA H19, which is expressed during embryonic progression and then is inhibited after birth, is transcribed from H19/Insulin-like Growth Factor 2 (IGF2) that is located on chromosome 11p15.5[63]. The lncRNA H19 was over-expressed in RCC tissues and cells (768-O, ACHN and Caki-1 cells). Upregulation of lncRNA H19 inhibited the expression of miR-29a-3p by targeting E2F transcription factor 1 (E2F1) and led to a shorter OS[64,65]. In addition, knockdown of lncRNA H19 repressed the migration and invasion of RCC 786-O cells, whereas E2F1 overexpression reversed these effects[65]. Moreover, lncRNA H19 was significantly associated with the susceptibility and mortality of RCC[66]. These studies indicated that lncRNA H19 may be a genetic predictor for the prognosis of RCC and exert its function by regulating the miR-29a-3p/E2F1 axis.

LINC00641: Located on chromosome 14q11.2, the long intergenic non-coding RNA 00641 (LINC00641) is usually at a low level in a normal state and acts as both an oncogene and tumor suppressor in different types of cancers[67,68]. It was reported that LINC00641 was upregulated in RCC tissues and cell lines (GRC-1, 786-O, SN12-PM6, A498 and ACHN cells). The proliferation and invasion were inhibited, while apoptosis was promoted in RCC A498 and ACHN cells when LINC00641 was knocked down. Moreover, LINC00641 deficiency suppressed tumorigenesis in the xenograft tumor model. Mechanistically, LINC00641 affected the progression of RCC via sponging miR-340-5p[68]. In addition, overexpression of LINC00641 was closed associated with TNM stage and poor prognosis[68].

PCED1B-AS1: The lncRNA PC-Esterase Domain Containing 1B Antisense RNA 1 (PCED1B-AS1) is implicated in multiple human malignant tumors, including hepatocellular carcinoma, glioblastoma and pancreatic cancer[69-71]. In a recent study, the significant upregulation of PCED1B-AS1 was observed in RCC tissues compared to adjacent normal renal tissue[72]. Knockdown of PCED1B-AS1 by siRNA promoted the migration, proliferation and EMT of A498 and Caki-1 cells by regulating the miR-484/zinc finger E-box-binding homeobox 1 (ZEB1) axis. In addition, PCED1B-AS1 might be a potential

prognostic diagnostic marker and high expression of PCED1B-AS1 resulted in a shorter OS time, higher tumor stage and Fuhrman grade in RCC patients[72]. These findings demonstrated that overexpression of PCED1B-AS1 contributes to the promotion and progression of RCC.

SNHG1: Small nucleolar RNA host gene 1 (SNHG1) is a newly identified lncRNA, which is located at 11q12.3 with 11 exons[73]. The expression of SNHG1 was increased in RCC tissues and cell lines (ACHN, A498 and Caki 1)[74]. Knockdown of SNHG1 retarded proliferation and invasion of RCC Caki 1 cells by promoting the expression of miR 103a through targeting HMGA2[74]. Furthermore, SNHG1 knockdown inhibited the immune escape ability of RCC A498 and 786-O cells by targeting miR 129 3p to downregulate STAT3 and PD L1. SNHG1 deficiency can also suppress EMT in RCC and RCC patients with high SNHG1 levels had a shorter OS than those with low SNHG1 levels[75,76].

SNHG5: With six exons, the small nucleolar RNA host gene 5 (SNHG5), which is localized on chromosome 6q14.3 and consists of 524 bp, was firstly identified at a chromosomal translocation breakpoint[77]. The SNHG5 was recently confirmed as an aberrantly upregulated lncRNA in RCC tissues. High expression of SNHG5 was positively associated with TNM stage, tumor size, lymphatic invasion and distant metastasis[78]. On the one hand, knockdown of SNHG5 significantly inhibited the proliferation, invasion and migration of ACHN cells by acting as a ceRNA for miR-205-5p via targeting ZEB1 in RCC cells. On the other hand, overexpression of SNHG5 promoted tumorigenesis and metastasis *in vivo*[78]. Additionally, lncRNA SNHG5 deficiency inhibited the invasion and induced apoptosis in 786-O cells by promoting the expression of miR-363-3p. Inhibition of twist, a direct target of miR-363-3p, inhibited tumor metastasis and promoted apoptosis of 786-O cells by decreasing matrix metalloproteinase-9 (MMP-9) and MMP-2 at protein level[79].

MIR4435-2HG: The lncRNA MIR4435-2 host gene (MIR4435-2HG) is located on chromosome 2q13 and was proved as carcinogenic lncRNA in a broad range of tumors[80]. Of note, MIR4435-2HG was found to be increased in RCC tissues and 769-P cells[81]. The MIR4435-2HG boosted the proliferation and invasion of 769-P cells by inhibiting the expression of miR-513a-5p that directly targeted Kruppel-like factor 6 (KLF6). Reciprocally, *in vivo* experiment further demonstrated that knockdown of MIR4435-2HG led to smaller tumor size and less tumor formation and these effects can be reversed by KLF6 overexpression[81].

SNHG12: The Small nucleolar host gene 12 (SNHG12), which is located at chromosome 1p35.3, was discovered to be dysregulated in a series of cancers as a newly discovered lncRNA[82,83]. Recently, the level of SNHG12 was confirmed to be notably upregulated in the tissues of RCC patients and cell lines (A498 and 786-O cells)[84]. Overexpression of SNHG12 was associated with TNM stage, lymph node and distant metastases and resulted in a poor prognosis. In addition, SNHG12 prompted cell viability and invasion, whereas inhibited the apoptosis of RCC cells by decreasing the expression of miR-200c-5p by targeting collagen type XI α1 chain (COL11A1)[84]. These results indicated that SNHG12 exerts its oncogenic role through miR-200c-5p/COL11A1 axis.

CASC19: The long non-coding RNA cancer susceptibility 19 (CASC19) is located on the 8q24 region of the chromosome and is an important participant in the development of human cancers, such as gastric cancer, nasopharyngeal carcinoma and non-small cell lung cancer[85,86]. Recently, overexpression of CASC19 was observed in RCC tissues and cell lines (786-O and A498 cells)[86]. High expression of CASC19 resulted in larger tumor sizes, advanced TNM stage and a poor prognosis. Knockdown of CASC19 attenuated the proliferation, migration and invasion of RCC cells by sponging miR-532 via regulating ETS proto-oncogene 1 (ETS1) expression, indicating that CASC19 affecting the progression through miR-532/ETS1 Axis. In addition, further *in vivo* studies showed that interference of CASC19 inhibited tumor growth in A498 xenograft nude mice[86]. Collectively, these results indicated that CASC19/miR-532/ETS1 pathway might be used to monitor prognosis and provides potential therapeutic targets for the clinical management of RCC (Table 1).

lncRNAs as tumor suppressors in RCC

MEG3: The Maternally Expressed Gene 3 (MEG3) is located on chromosome 14q32.3 and is also known as Gene trap locus 2 (Gtl2)[87]. It was reported that the expression of MEG3 is downregulated in various cancers, including RCC and acts as a tumor suppressor[88,89]. The MEG3 promoted cell apoptosis via inhibiting miR-7 while inhibiting the proliferation, invasion and migration of A-498 cells by upregulating the expression of RAS like family 11 member B (RASL11B), which is the target of miR-7. Moreover, MEG3 induced the G0/G1 cell cycle arrest in RCC A-498 cells[89]. This study demonstrated that MEG3 exert an anti-cancer function in RCC by regulating miR-7/RASL11B signalling.

Table 1: Oncogenic lncRNAs in RCC

lncRNAs	Changes	Cell lines	Location	Targets/signaling	Functions	Mechanisms	References
MALAT1	Up	A-498 and 786-O	Chromosome 11q13	miR-203, BIRC5, miR-205, miR-22-3p, PI3K/Akt signaling, miR-429, miR-200s ZEB2 miR-362-3p, G3BP1	Oncogene	Proliferation, invasion, migration, EMT and sunitinib chemoresistance	Li *et al.*[30], Hirata *et al.*[31], Zhang *et al.*[32], Jiang *et al.*[33] and Wang *et al.*[35]
HOTAIR	Up	ACHN and Caki-1	Chromosome 12q13.13	miR-203, PTEN, P21, P27 miR-124, HIF-1 α, AXL, p53, p21, p16 and EZH2	Oncogene	Proliferation, invasion migration and apoptosis, EMT metastasis	Dasgupta *et al.*[38], Pan *et al.*[39], Hong *et al.*[40] and Wu *et al.*[41]
UCA1	Up	769P, 786O, ACHN, A498 and Caki2	Chromosome 19	miR-129, SOX4, miR-495, p21	Oncogene	Proliferation, invasion and apoptosis	Liu *et al.*[44] and Lu *et al.*[45]
TUG1	Up	ACHN and OS-RC-2	Chromosome 22q12	miR-299-3p, VEGF, miR-196a, miR-9, YAP, miR-31-5p, FLOT1	Oncogene	Proliferation, migration, invasion, apoptosis and autophagy	Li *et al.*[49], Liu *et al.*[50], Yang *et al.*[51], Zhang *et al.*[52] and Lv *et al.*[53]
CYTOR	Up	Caki-1, A498, ACHN and 7860	Chromosome 2p11.2	miR-136-5p, MAT2B, BAG3	Oncogene	Proliferation and apoptosis	Wang *et al.*[55]
AFAP1-AS1	Up	786-O and Caki-1	chromosome 4p16.1	PTEN/AKT	Oncogene	Proliferation, invasion, migration and EMT	Mu *et al.*[57]
HOTTIP	Up	786-O, ACHN and OSRC-2	Chromosome 7p15.2	PI3K/Akt/Atg13, LATS2, EZH2, LSD1, miR-615, IGF-2	Oncogene	Proliferation, invasion, migration, apoptosis and autophagy	Su *et al.*[60], Peng *et al.*[61] and Wang *et al.*[62]
H19	Up	768-O, ACHN and Caki-1	Chromosome 11p15.5	miR-29a-3p, E2F1	Oncogene	Migration and invasion	Wang *et al.*[64], He *et al.*[65] and Cao *et al.*[66]
LINC00641	Up	ACHN, 786-O, Caki-1 and Caki-2	Chromosome 2p11.2	miR-340-5p	Oncogene	Proliferation, invasion and apoptosis	Zhang *et al.*[68]
PCED1B-AS1	Up	A498 and Caki-1	Chromosome 12	miR-484/ZEB1,	Oncogene	Proliferation, migration and EMT	Qin *et al.*[72]
SNHG1	Up	ACHN, A498 and Caki 1	Chromosome 11q12.3	miR-103a, HMGA2, miR-129-3p, STAT3, PD-L1	Oncogene	Proliferation, invasion, immune escape and EMT	Ye *et al.*[74] and Tian *et al.*[75]
SNHG5	Up	ACHN	Chromosome 6q14.3	miRNA-205-5p, ZEB1, miR-363-3p/twist, MMP-9, MMP-2	Oncogene	Proliferation, invasion, migration, apoptosis and metastasis	Xiang *et al.*[78] and Li *et al.*[79]
MIR4435-2HG	Up	769-P	Chromosome 2q13	miR-513a-5p/KLF6	Oncogene	Proliferation and invasion	Zhu *et al.*[81]
SNHG12	Up	A498, 768-O	Chromosome 1p35.3	miR-200c-5p/COL 11A1	Oncogene	Viability, invasion and apoptosis	Xu *et al.*[84]
CASC19	Up	786-O and A498	Chromosome 8q24	miR-532/ETS1	Oncogene	Proliferation, migration and invasion	Luo *et al.*[86]

Table 2: Tumour suppressive lncRNAs in RCC

lncRNAs	Changes	Cell lines	Location	Targets/signaling	Functions	Mechanisms	References
MEG3	Down	A-498 and 786-O	Chromosome 14q32.3	miR-7/RASL11B	Tumour suppressor	Proliferation, invasion and migration	Ghafouri-Fard *et al.*[88] and He *et al.*[89]
LINC01510	Down	786-O and Caki-2	Chromosome 7	β-catenin	Tumour suppressor	Proliferation and invasion	Ma *et al.*[90]
LINC01939	Down	ACHN and CAKI-1	Chromosome 2	miR-154, Wnt/β catenin	Tumour suppressor	Proliferation, migration and apoptosis	Zhang *et al.*[92]
ZNF710-AS1-202	Down	ACHN and 786-O	-	ZNF710	Tumour suppressor	Proliferation, survival and apoptosis	Li *et al.*[93]
ASB16-AS1	Down	786-O	Chromosome 17q21	miR-185-5p/miR-214-3p-LARP1	Tumour suppressor	Proliferation, migration, invasion, EMT and metastasis	Li *et al.*[94]

LINC01510: In malignant RCC tissues, the expression of the LINC01510 was observed to be decreased[90]. Overexpression of LINC01510 declined the level of cyclin D1 (CCND1), cyclin E1 (CCNE1) and matrix metalloproteinases (MMPs) to affect the cell cycle and invasion of RCC 786-O and Caki-2 cells. In addition, ectopic expression of LINC01510 suppressed proliferation of RCC 786-O cells and attenuated the ability of invasion by boosting the expression of β-catenin, indicating that LINC01510 exerted tumor suppressive effect on RCC cell lines through Wnt/β-catenin signalling pathway[90].

LINC01939: The long intergenic non-coding RNA 1939 (LINC01939) is a novel lncRNA and was first confirmed to be downregulated in gastric cancer and involved in cancer progression[91]. Recently, the latest study indicated that LINC01939 possessed decreased expression in RCC tissues[92]. Upregulation of LINC01939 inhibited the proliferation and migration, as well as induced the apoptosis of ACHN and CAKI-1 cells by decreasing the level of miR-154 with the bluntness of Wnt/β catenin and Notch[92].

ZNF710-AS1-202: The ZNF710-AS1-202 is a newly-found lncRNA, which was first unveiled to be a tumor suppressor in RCC and was significantly declined in RCC tissues[93]. The expression of ZNF710-AS1-202 was associated with pathological grade, tumor size, local invasion and TNM stage. Moreover, RCC patients with high levels of ZNF710-AS1-202 had longer OS time and DFS than those with low ZNF710-AS1-202 levels, as measured by cancer genome atlas (TCGA) analysis[93]. The increase in ZNF710-AS1-202 promoted the proliferation and survival, as well as inhibited apoptosis of ACHN and 786-O cells by decreasing the expression of ZNF710 mRNA and increasing the expression of ZNF710 protein[93].

ASB16-AS1: The lncRNA ASB16 antisense RNA 1 (ASB16-AS1) is a 2275-bp-long lncRNA encoded on chromosome 17q21 and was downregulated in RCC tissues compared to non-tumorous renal tissue[94]. The ASB16-AS1 deficiency promoted the proliferation, migration and invasion, inhibited EMT phenotype in 786-O cells and enhanced tumor growth and metastasis in 786-O xenograft mice by decreasing La-related protein 1 (LARP1) expression via sponging miR-185-5p and miR-214-3p. Moreover, low-level expression of ASB16-AS1 was associated with larger tumors and advanced tumor stage[94]. These findings suggested that ASB16-AS1 exerts its tumor-suppressive function in the progression of RCC through miR-185-5p/miR-214-3p-LARP1 pathway (Table 2).

lncRNAs act as diagnostic biomarkers in RCC: At the present stage, many RCC patients are diagnosed at the late stage when effective treatments cannot be applied. Approximately, one-third of RCC patients have been detected with metastatic RCC[11]. Therefore, potential novel biomarkers are needed to improve the early diagnosing rate of RCC. Evaluating the circulating level of lncRNAs in bodily fluids would be more practical and convenient than those in tissues for tumor diagnosis. Nowadays, more and more studies indicated that serum lncRNAs might be new diagnostic biomarkers in RCC. For example, the serum gradually increased during hepatocarcinogenesis (GIHCG) was significantly increased in RCC patients and can distinguish RCC patients from healthy controls with an AUC of 0.920 in the testing set[95]. Similarly, another study indicated that serum C-X-C motif chemokine ligand 2 (CXCL2) level was markedly higher than that in healthy subjects. Further ROC curve analysis showed that serum CXCL2 might be a potential diagnostic predictor for RCC and the AUC value was 0.868[96]. In addition, the level of LINC00887 was also increased in the serum of RCC patients compared with healthy volunteers with an AUC of 0.803[97]. These findings demonstrated that the signature of serum lncRNAs has the potential to be biomarkers for the early diagnosis of RCC patients. However, the low specificity or sensitivity of these serum diagnostic biomarkers and the small sample size for RCC screening have limited their clinical practicability. To date, there is no recognized lncRNA for the diagnosis of RCC. Consequently, further in-depth exploration of the clinical diagnostic value of lncRNA is necessary in the future study.

Promise and challenges of lncRNAs therapy in RCC: The lncRNAs have served as prospective candidates for RCC therapy and many studies performed in RCC cell lines and RCC cell xenograft mice model have revealed the potential targeting lncRNAs to affect the progression of RCC, which provides a strong basis for the treatment of RCC. However, lncRNAs in RCC are yet in their infancy and there is no sufficient evidence to confirm the effects of lncRNAs in RCC patients. For example, the level of lncRNA activated in RCC with sunitinib resistance (lncARSR) in plasma and tumor tissues was positively correlated with the drug resistance of RCC patients during sunitinib therapy[98,99], but the sample size was small and still warrants further investigation. In addition, several critical issues need to be solved before lncRNAs can be used for RCC therapy. Firstly, whether the therapeutic capabilities of lncRNAs in animal models hold for humans remains obscure as lncRNAs are highly conserved among different species, thus limiting the exploration of the mechanism of lncRNAs in RCC[100]. Secondly, multiple studies have demonstrated that lncRNAs exert their regulatory functions in various biological processes by acting as ceRNAs. However, compared with highly expressed miRNAs, the expression level of most lncRNAs is low in both cytoplasm and nucleus. The sponge function is arduous to exert because miRNAs harbour only one putative binding site for each lncRNA.

CONCLUSION

Over the past few decades, an increasing number of lncRNAs have been confirmed to play essential roles in the pathogenesis of RCC. The lncRNAs can inhibit the proliferation, invasion and migration and induce the apoptosis of RCC cell lines by acting on various molecular targets. Moreover, the expressions of many lncRNAs are closely associated with the clinic's pathological characteristics and prognosis. Emerging studies have defined lncRNAs as novel biomarkers of diagnosis and prognosis and potential therapeutic targets for RCC. Nevertheless, what we have done is far from enough. The clinical utilities of lncRNAs remain unclear and there is still a large obstacle before lncRNAs can be used clinically for the treatment of RCC. Therefore, the precise molecular mechanisms of lncRNAs in RCC are still worth further exploration. Although many challenges remain to be addressed, we anticipate that lncRNAs have a broader prospect as a viable candidate therapeutic targets in RCC.

SIGNIFICANCE STATEMENT

Renal cell carcinoma (RCC) is ranked sixth of all cancer deaths for morbidity and mortality worldwide. Owing to the paucity of effective diagnostic and treatment options, it is necessary to find and develop new strategies for the treatment of lung cancer. Long Non-Coding RNAs (lncRNAs) act as a critical regulatory factor of diverse cancers in many cellular regulatory processes, including proliferation metastasis, apoptosis and metabolism. In the past few decades, an increasing number of investigations indicated that lncRNAs play an important role in the pathogenesis and development of various cancers. The current review discusses the molecular mechanisms and clinical implications of lncRNAs in the progression of RCC and found that lncRNAs may be novel therapeutic targets for RCC.

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