Review

Long Non-Coding RNA Emergence During Renal Cell Carcinoma Tumorigenesis

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Key Words

Long non-coding RNAs • LncRNAs • Kidney cancer • Renal cell carcinoma • Tumorigenesis

Abstract

Renal cell carcinoma (RCC) is the most common kidney cancer diagnosed across the globe and has steadily increased in incidence in recent decades. Techniques for diagnosing or treating RCC are limited, and confined mostly to later stages of the disease. Almost all RCC pathological types are resistant to chemotherapeutics and radiation therapy. To this effect, new markers for diagnosis and target therapy are urgently needed. Advanced genome sequencing technologies have revealed long non-coding RNAs (lncRNAs) as a novel marker, transcribed throughout the human genome. The emergence of lncRNAs is an aberrant expression and is involved in the tumorigenesis of RCC. lncRNAs drive cancer phenotypes through their interaction with other cellular macromolecules including DNA, protein, and RNA. Recent research on lncRNA molecular mechanisms has revealed new markers to functionally annotate these cancers' associated transcripts, making them targets for effective diagnosis and therapeutic intervention in the fight against cancer. In this review, we first highlight the common mechanisms that underlie aberrant lncRNA expression in RCC. We go on to discuss the potential translational application of lncRNA research in the diagnosis, prognosis, and treatment of RCC.

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Introduction

Cancer is a major public health problem and the leading cause of death in the world's population [1]. According to the National Central Cancer Registry of China (NCCR), the incidence of renal carcinoma (RC) ranks first among malignant tumors related to urologic cancer; the incidence of renal cell carcinoma (RCC) ranks second among malignant tumors of the urinary system, just behind bladder cancer. RCC, in short, is one of the major cancers threatening human health across the globe. There are about 63,920 newly diagnosed cases each year [2]. Roughly one-third of RCC patients receive their diagnosis in the late phase of the

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disease, at which point surgical treatment is no longer feasible. Almost all RCC pathological types are resistant to chemotherapeutics and radiation therapy. Immunotherapy, at present, is the most common treatment for the late-phase disease; unfortunately, the response rate is less than 20% [3]. Better understanding of the molecular pathogenesis of RCC may reveal new opportunities for the discovery of effective cancer biomarkers and therapeutic targets.

Long non-coding RNAs (lncRNAs) have a sequence length of above 200bp and are located in nuclear or cytosolic fractions [4, 5]. An extensive landscape of functional mutations within the non-coding genome are revealed via genome-wide cancer mutation analyses, which have profound effects on the expression of long non-coding RNAs (lncRNAs). There is mounting evidence to indicate that lncRNAs can regulate gene expression at various levels, such as through chromatin modification, transcription, and post-transcription processing [6-8]. lncRNAs can drive many important cancer phenotypes by interacting with other macromolecules including DNA, protein, and RNA. Several biological processes such as transcription, translation, cellular differentiation, gene expression regulation, cell cycle, chromatin modification, and nuclear cytoplasmic trafficking can also be regulated by lncRNAs [9-11].

lncRNAs are known to play a pleiotropic role in human diseases [12]. There has been a dramatic increase in research on lncRNAs in regards to tumor initiation, promotion, and progression, making them one of the hottest topics today in the field of tumor and RNA biology.

However, there has been relatively little research on the role of lncRNAs in RCC specifically. A number of lncRNAs have emerged alongside studies related to the biological functions of lncRNAs in human cancers such breast cancer [13], prostate cancer [14], melanoma [15], and RCC [16]. Aberrant lncRNA expression is involved in the recurrence, metastasis, and prognosis of RCC [17-19]. The function and mechanism of lncRNAs are the most obscure and least understood elements of the extant research in terms of RCC. Better and more comprehensive understanding of lncRNAs as they affect RCC may reveal useful information on the pervasive genomic transcription in RCC tumorigenesis and metastasis. Researchers have already confirmed the importance of lncRNA biologic processes in RCC progression, and genome sequencing technologies and databases including complementary expression and other information on lncRNAs have become available to support further study [20, 21].

In this review, we mainly focus on lncRNAs identified in human RCC tissues with special emphasis on those that are significantly associated with tumorigenesis and metastasis. Below, we first describe the roles and molecular mechanisms that underlie lncRNAs involved in RCC including lncRNA TUG1 [22], H19 [23], MEG3 [24], KCQN10T1 [17], MALAT1 [25], HOTAIR [26], and others. We then discuss the potential clinical application of lncRNAs in RCC diagnosis and treatment. The major challenges and future perspectives of ongoing lncRNA research related to RCC are also discussed. Finally, we propose that lncRNAs play an informative role in the initiation, promotion, and progression of RCC, thus serving as an effective biomarker of the disease.

Overview of lncRNA

Origins of lncRNA

lncRNAs were originally thought to be expression noise, which comprises the majority of the human transcripts resulting from low RNA polymerase fidelity [27]. The GENCODE annotation project established the most complete human lncRNA annotation to date, and indicated that lncRNAs are generated through pathways similar to those of protein-coding genes [28]. About 70-90% of the human genome is pervasively transcribed and has vases that are identifiable in primary transcripts; protein-coding human genes account for less than 2% of human genome sequences [29, 30]. There are many non-protein-coding transcripts including small interference RNAs (siRNAs), microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs) [30]. Most transcripts which are not protein-

coding in sequence are related to lncRNAs [31]. lncRNAs are ubiquitous in all vertebrate species. Their genome sequence, rather than protein-coding genes, covers a major fraction of the human genome. These lncRNAs are located in nuclear or cytosolic fractions, may or may not be polyadenylated, and are mostly transcribed from part of either strand within a protein-coding locus [32]. lncRNA was discovered earlier than miRNA, although miRNAs have attracted more research attention over the last two decades. The first lncRNA H19 was discovered in 1990 by Brannan et al [33], and the second lncRNA X-inactive-specific transcript (XIST) was discovered in 1991 by Brown et al. [34].

Functional long non-coding RNAs appear through various evolutionary scenarios [35]. The first scenario is the metamorphosis of the protein-coding gene into a non-coding RNA sequence. Frame disruptions are acquired by a protein-coding gene and transformed into a functional long non-coding RNA which incorporates certain previous coding sequences. The lncRNA *Xist* originates from the metamorphosis of a previous protein-coding gene while acquiring a transposable element sequence [36, 37]. In the second scenario, during the rearrangement of a chromosome, two well-separated untranscribed sequence regions are juxtaposed and give rise to multi-exon non-coding RNAs. Non-coding RNA (supported by ESTs BM537447, C0597044, and DN744681) in canines undergoes this lineage-specific change. The duplication of a non-coding gene by retrotransposition can also generate either a functional non-coding retrogene or a nonfunctional non-coding retropseudogene [38]. Further, neighboring repeats within a non-coding RNA can create tandem duplication events. lncRNAs may also emerge after the insertion of a transposable element, to form functional non-coding RNA [39, 40].

lncRNAs are more conserved than introns or random intergenic regions but less conserved than protein-coding genes [41, 42]. Evolutionary conservation is commonly used in describing the functional significance of newly discovered genes. Current researchers accept that lncRNAs are conserved in four dimensions: sequence, structure, function, and expression from syntenic loci. Two recently described knockout mouse models for the lncRNAs MALAT1 and HOTAIR highlight the multifaceted levels of conservation. These models also suggest that lncRNA sequence conservation does not always correspond to the function in other species [43].

lncRNA classifications

lncRNA classification is of fundamental importance for lncRNA research and can assist with in-depth investigations on newly discovered lncRNAs, new hypotheses based on different features of lncRNAs, and exploration of the functional mechanisms of lncRNAs [44]. Here, we summarize a few key lncRNA classifications characterized by four key features: genomic location and context, effect on DNA sequences, functioning, and targeting mechanisms.

lncRNAs can be classified into (1) sense or (2) antisense categories when overlapping one or more exons of another transcript on the same strand or opposite strand, respectively; they may also be (3) bidirectional, where a neighboring coding transcript on the opposite strand is initiated in close

Fig. 1. Overview of five broad classifications of lncRNAs. (A) Sense; (B) Intronic; (C) Bidirectional; (D) Intergenic; (E) Antisense.

genomic proximity to its expression, or (4) intronic, i.e., derived completely from an intron of a second transcript (although these transcripts sometimes may represent pre-mRNA sequences). Finally, they may be (5) intergenic, or derived within the genomic interval between two genes (Fig. 1) [35, 44].

Other researchers have also classified lncRNAs according to their mode of action and functions [18, 45]. (1) Signal: lncRNAs may serve as molecular signaling mediators on signaling pathways to modulate a certain set of gene expressions. (2) Decoy: lncRNAs may function as molecular decoys which take proteins or RNAs away from specific locations. (3) Guide: lncRNAs can play a role as molecular guides, locating certain ribonucleoprotein complexes to a specific target site on the chromatin. (4) Scaffold: lncRNAs can support the assembly of protein complexes which link factors together in the proper complex formation to generate brand new functions.

Many studies suggest that defining lncRNAs solely on the basis of size without considering protein-coding capability is intellectually far from satisfying [35, 46]. In the past, lncRNA was widely defined as any RNA molecule longer than 200 nucleotides that is not translated into a protein. Currently, however, lncRNAs are strictly defined as RNA molecules which may function as primary or spliced transcripts and do not fit into small RNA or structure RNA categories (i.e., miRNAs, PIWI-interacting RNAs, transfer RNAs, spliceosomal RNAs), and with a length that is arbitrarily set (while not all lncRNAs are more than 200 nucleotides) [47]. A given lncRNA can contain ORFs longer than 100 amino acids (defined as “PCG”) and not necessarily synthesize polypeptides [48]. lncRNAs are still poorly recognized overall and worthy of further study in regards to fully precise definitions.

Dysregulation and molecular mechanism of lncRNAs in RCC

In this section, we review some of the recurring molecular mechanisms that govern the manner in which lncRNAs regulate RCC tumorigenesis. lncRNA functions are consistent with lncRNA cellular localizations: nuclear lncRNAs mainly perform chromatin interactions, transcriptional regulation, and RNA processing, while cytoplasmic lncRNAs can modulate mRNA stability or translation and influence cellular signaling cascades accordingly [49]. lncRNA can drive many important cancer phenotypes through their interaction with other cellular macromolecules including DNA, protein, and RNA (Fig. 2).

lncRNAs localizing to chromatin

lncRNA localizing to chromatin is a well-established mechanism known to mediate activities affecting neighboring intrachromosomal genes in cis or targeting genes in trans on different chromosomes [50-52]. In cis, lncRNA can recruit protein complexes to their site of transcription thus creating a locus-specific address; cells can then use this mechanism to repress or activate gene expression [53]. lncRNA are commonly known to regulate genes in

Fig. 2. lncRNA mechanisms rely on interaction with cellular macromolecules. (A) Chromatin interactions; (B) RNA interactions; (C) Protein interactions.

cis as enhancer-associated RNAs through transcriptional regulation [54-56], transcription factor trapping [57], chromatin looping [58], and gene methylation [59]. In trans, lncRNA can recruit protein complexes to chromatin loci away from their site of transcription [60]. lncRNA are also widely known to regulate distant genes by modulating transcription factor recruitment [61] and chromatin modification [62], and by serving as a scaffold for the assembly of multiple regulatory molecules at a single locus [63].

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1), also known as NEAT2 (nuclear-enriched abundant transcript 2), shows a high degree of conservativeness among several species and represents a ubiquitously expressed lncRNA [64]. A direct correlation between MALAT1 and EZH2, a subunit of PRC2, was recently established. After inactivation of MALAT1, the expression of EZH2, H3K27me3, and c-myc was observed to reduce in ccRCC in contrast to increased levels of E-cadherin. MALAT1 regulates this process in cis or trans, enabling allele-specific control of transcription. Further, MALAT1 is upregulated in ccRCC samples and in RCC cell lines compared to non-tumorous renal tissue or cells [65-67]. A knockdown of MALAT1 in RCC cell lines inhibits cell proliferation, migration, and invasion [67]. Further, the lncRNAs H19 and HOTAIR, are known to bind to PRC2 to induce gene silencing via H3K27 trimethylation in bladder cancer and breast cancer, respectively [68-70].

lncRNA interactions with protein

The interactions of lncRNAs with protein are commonly known to modulate protein function, regulate protein-protein interactions, and direct localization within cellular compartments. These interactions play key roles in determining lncRNA functional effects.

Recently, Zhai et al. identified a novel lncRNA, lncRNA ENST00000460407, which they named lncRNA-SARCC (lncRNA-Suppressing Androgen Receptor in Renal Cell Carcinoma) [71]. lncRNA-SARCC can interact with AR and decrease the stability of the AR protein. Specifically, lncRNA-SARCC suppresses AR and alters HIF-2a/c-myc signals under hypoxia. lncRNA-SARCC can be directly suppressed by HIF-2a via hypoxia responsive elements in the lncRNA promoter, forming a negative feedback loop between lncRNA-SARCC and HIF-2a that can modulate cell proliferation and migration for RCC under hypoxia.

lncRNA targets RNA (RNA targets of lncRNA actions)

lncRNA targets RNA throughout the modulation of mRNA stability, splicing, and translation. This is a newly emerging research topic in regards to the lncRNA mechanism. lncRNAs can function as molecular decoys to transport RNAs away from specific locations, as mentioned above [72]. lncRNAs have also been postulated to act as competing endogenous RNA (ceRNA) or "RNA sponges" which interact with miRNAs in a manner that can sequester these molecules and reduce their regulatory effect on target mRNA [73].

Qu et al. identified an lncRNA called lncARSR (lncRNA Activated in RCC with Sunitinib Resistance) [74]. lncARSR acts as a ceRNA for miR34 and miR-449 to promote AXL and c-MET expression leading to sunitinib resistance. Targeting lncARSR by LNA-based treatment restored the sunitinib responses in sunitinib-resistant RCC.

lncRNAs drivers of RCC phenotypes

Cancer consists of several phenotypes resulting from dysfunctional intrinsic cellular regulatory networks and intercellular communication which generate the tumor microenvironment [75, 76]. Intrinsic cellular signaling networks are regulated in RCC to sustain cell proliferation, impair differentiation, enhance viability, and promote motility. As lncRNAs have been primarily studied per the role of intracellular regulatory networks in RCC, our review focuses on the role of lncRNAs in these hallmarks of cancer. Indeed, each of the hallmarks described by Hanahan and Weinberg [75] is regulated by the activity of multiple lncRNAs.

Proliferation circuits

The HOX transcript antisense RNA (HOTAIR), an lncRNA, coordinates with chromatin-modifying enzymes to regulate gene silencing. lncRNA HOTAIR knockdown by RNA interference with siRNA significantly affects the G0/G1 phase cell cycle and weakens RCC cell proliferation [26], which is suppressed by miR-141 in an Ago2-dependent manner [77]. lncRNA SAS2 is also downregulated by miR-21 to increase the proliferation of RCC. Hypoxia mediates tumor progression in hypoxia inducible factor-2a (HIF-2a); interestingly, lncRNA-SARCC suppresses VHL-mutant RCC cell proliferation yet promotes VHL-normal RCC proliferation by modulating androgen receptor/HIF-2a/C-MYC axis under hypoxia [71]. High levels of lncRNA CRNDE expression promotes cell proliferation by activating Wnt/b-catenin signaling [78]. lncRNA BX357664 also regulates cell proliferation via the inhibition of TGF- β 1/p38/HSP27 signaling in RCC [79]. lncRNAs FTX, MALAT1, uc009by.1, and TUG1 can promote the proliferation of RCC cells, but their precise mechanisms merit further research [22, 80-82].

Viability circuits

lncRNAs are extensively involved in stem cell maintenance and differentiation circuits [83]. In RCC, a feed-forward loop between lncARSR and YAP activity promotes the viability of renal tumor-initiating cells [84]. Renal tumor-initiating cells contribute to tumorigenesis, and RCC progression. lncARSR attenuates the self-renewal, tumorigenicity of renal-initiating cells. Mechanistically, lncARSR binding to YAP facilitates YAP nuclear translocation, while YAP promotes lncARSR transcription.

Tumor-suppressor circuits

Several lncRNAs have been recently found to play important roles in modulating tumor-suppressor and growth-arrest pathways, such as lncRNA TRIM52-AS1, DRAIC/PCAT29, and GAS5 [16, 85, 86]. lncRNA CASC2 was downregulated in human RCC tissues and RCC cell lines (786-O and A498), and the downregulation of lncRNA CASC2 by miR-21 also increases the proliferation and migration of RCC cells. lncRNA CADM1-AS1 regulates cell proliferation, apoptosis and migration via CADM1 modulation.

Motility circuits

The overexpression of MALAT1 and evolutionarily conserved, abundant nuclear lncRNA have been found to predict a high risk of metastatic progression in patients with RCC [87]. lncRNA MALAT1 functions as a ceRNA to regulate ZEB2 expression by sponging miR-200s in ccRCC [67]. Multiple cancer-associated lncRNAs have been implicated in regulating cancer invasion and metastasis in RCC, including lncRNA TUG1, ATB, RCCRT1, and HOTAIR [22, 88, 89].

Diagnostic and therapeutic promise via lncRNAs

lncRNAs, as highly tissue-specific drivers of cancer phenotypes, have notable potential as diagnostic markers or therapeutic targets. For instance, the high expression of MALAT1 may be a biomarker for the early detection of lymph node metastasis or a predictor of poor survival in RCC patients [25, 90]. A 5-lncRNA signature including lncRNA-LET, PVT1, PANDAR, PTENP1, and lnc00963 can discriminate patients with clear cell RCC from healthy controls [91]. lncRNA TCL6, NBAT-1, SPRY4-IT1, RCCRT1, GAS5, and CADM1-AS1 have all been associated with poor prognosis in RCC patients [88, 92-96].

The development of RNA-targeting therapeutics represents a tremendous opportunity for modulating lncRNAs for anti-cancer therapy. Various therapeutic methods targeting lncRNAs have been developed and several pharmaceutical companies are actively developing lncRNA-targeting therapeutics [97, 98]. Small interfering RNAs (siRNAs), upon loading in the RISC complex in the cytoplasm, can efficiently deplete lncRNAs; antisense oligonucleotides

(ASOs) are chimeric RNA/DNA oligonucleotides that direct RNase H to cleave complementary target lncRNA and robustly deplete the transcripts [99]. Research has also shown that lncRNA cellular localization is critical in the screening of appropriate strategies for robust lncRNA modulation [100]. siRNA can efficiently deplete cytoplasmic lncRNAs, while ASOs can robustly deplete lncRNAs regardless of their localization. ASOs are already currently poised for use in lncRNA-targeted therapeutics [97].

Fig. 3. Expression of lncRNAs in RCC progression.

Emerging paradigms and future directions

lncRNAs represent a new layer of complexity in the molecular architecture of human disease. The nature of protein-coding genes has been studied extensively, but the nature of non-coding genes remains a mystery. There are still many unknowns clouding our understanding of lncRNA functions, though there have been remarkable advancements in our exploration of lncRNAs and their effects on human diseases. The extant research indeed suggests that lncRNAs play a significant role in cancer diagnosis and therapy. Understanding the precise molecular mechanism of lncRNAs in hallmarks of RCC is a crucial step forward in exploring new targets for RCC therapy [17, 19, 101].

lncRNA related to RCC is yet in its infancy, but we do now understand several important effects of lncRNAs in different states of RCC (Fig. 3). Notably, each of the hallmarks of RCC are regulated by multiple lncRNAs (Table 1). lncRNAs play an informative role in the initiation, promotion, and progression of RCC. MALAT1, for example, has been detected in the blood of RCC patients [102] and lncRNA ARSR are mediated chemotherapy-resistant in RCC [74].

There is much work yet to be done before the research discussed here can be effectively applied in the clinic, however. To facilitate this shift, it is necessary to innovate molecular tools to survey lncRNA interactions with other cellular macromolecules to identify and confirm lncRNA functions [103]. Databases centered around lncRNA information must be established and validated. We also must determine what mediates the different expressions lncRNAs in normal and cancerous tissues [104]. RCC is an immunotherapy effective disease [105], and research on whether lncRNAs can regulate the immune pathways of RCC is well merited. The epigenetic aberrations leading to variations in lncRNA expression should be carefully elucidated to determine the role of lncRNAs as drivers of tumorigenesis.

The research discussed in this review altogether indicates that lncRNAs are critical in RCC development and progression. lncRNAs may serve as effective drug targets in RCC therapy and may be better biomarkers for RCC diagnosis and prognosis than the markers

Table 1. lncRNAs in the tumorigenesis of RCC

Category	lncRNA	Upstream regulators	Downstream targets	Cellular Functions	References
Primary RCC	CADM1-AS1	miR-141	CADM1	Proliferation	96
	MEG3		Bcl-2, procaspase-9	Apoptosis	24
	HOTAIR		JMJD3, miR-217	Proliferation	26,77
	MALAT1		miR-200, HIF2A	Proliferation, migration	67
			AR, HIF2a, miR143-3p	proliferation, migration	71
		LncRNA-SARCC	MYC	Proliferation	91
	PVT1		Wnt/beta-catenin	Apoptosis	78
	CRNDE		TGF-beta1, p38	Proliferation	79
	BX357664		EZH2, miR-205	Invasion	66
	MALAT1		miR-34, miR-449, YAP	Stem cell-like, chemoresistance	84
Aggressive RCC	lncARSR				

currently in use in clinics across the globe. Although there are interesting potential clinical targets for lncRNAs, a better and more comprehensive understanding of their functions and mechanisms in RCC pathology is yet necessary.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81470989), and partly by the clinical research project key projects of the Second Affiliated Hospital, Third Military Medical University (2015YLC06). We would also like to thank Dr. Fan Yang for the constructive comments and for editing the manuscript. We are also grateful to the authors and publications that were not cited in this review due to space restrictions.

Disclosure Statement

No conflict of interests exists.

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