**REVIEW ARTICLE** | renal cancer

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# Noncoding RNAs and Its Implication as Biomarkers in Renal Cell Carcinoma: A Systematic Analysis

Shiv Verma[1,2], Sanjay Gupta[1,2,3,4,5]

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**Abstract** Renal cell carcinoma (RCC) is one of the most devastating disease with higher mortality rates. It comprises several subtypes exhibiting distinct histological features and clinical staging. Despite recent advancement in understanding the biology of RCC success in treatment rates remains dismal. This may be partly due to lack of specific biomarkers for early detection/prognosis and poor clinical outcome. Noncoding protein transcripts in the genome play important role in the initiation, evolution and progression of cancer. With the advancement in genomic analysis techniques, especially next-generation sequencing, a large number of new transcripts have been discovered, leading to better understanding of coding and noncoding RNAs. In the present review, we summarize recent advancement on renal cancer associated noncoding RNAs which includes long noncoding RNAs, microRNAs, and circular RNAs for their involvement in RCC along with their clinical implication as prognostic and diagnosis biomarkers.

**Key words** renal cell carcinoma, noncoding RNAs, biomarkers, diagnosis, prognosis

1. Department of Urology, Case Western Reserve University, School of Medicine, Cleveland, OH, USA.
2. The Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA.
3. Department of Nutrition, Case Western Reserve University, Cleveland, OH, USA.
4. Department of Urology, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH, USA.
5. Division of General Medical Sciences, Case Comprehensive Cancer Center, Cleveland, OH, USA.
Correspondence: Sanjay Gupta (Department of Urology, The James and Eilleen Dicke Research Laboratory, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, Ohio 44106, USA; E-mail: sanjay.gupta@case.edu).

## Introduction

Renal cell carcinoma (RCC) is one of the most devastating cancer in adults, like other malignant diseases, its prognosis and diagnosis in early stage is still difficult [1]. Conventionally, it was considered that nearly all RCC and associated diseases are resistant to chemotherapy and radiation treatment [2, 3]. At present, the most common treatment of renal cancer is still radiation therapy for the late-stage disease; unfortunately, the response rate is less than 20% [4]. Metastatic renal cell carcinoma has a very poor prognosis, therefore better understanding of the epigenetics/genomics and its association with the pathogenesis of renal cancer might reveal new opportunities for the discovery of effective cancer biomarkers and therapeutic targets.

Recent development in encoding of the human genome and the Encyclopedia of DNA Elements (ENCODE) project has discovered that most of the human genome is transcribed into RNAs that do not encode proteins [5]. Moreover, the large database genomic information such as The Cancer Genome Atlas (TCGA), and the International Cancer Genome Consortium (ICGC), revealed that dysregulation in genome either due to mutation or copy number changes related to cancer overlap with noncoding DNA elements or noncoding RNA genes [6]. The outcome of above mentioned projects reformed the perception of noncoding (nc) RNAs from 'junk' transcriptional products to functional regulatory molecules [7]. This underlines the fact that junk DNA/RNA is indeed not a wasteland anymore. In fact, genes only comprise 2% of human genome or encoded proteins and the remaining noncoding portions of the genome transcription products are noncoding RNAs which differ in biogenesis and function. Nearly 80% of the human genome comprehends regulatory elements as well as ncRNA genes [8]. With the advancement in genomic analysis techniques, especially next-generation RNA sequencing (whole genome/exosome), a large number of new transcripts have been discovered, leading to better understanding of coding and noncoding RNAs. These include the discovery of long noncoding RNA (lncRNA), microRNAs (miRNAs), circular RNAs (circRNAs) playing a critical role in post-transcriptional gene regulation adding new dimensions to the development of novel diagnostic and treatment tools.

The present review summarize renal cancer-associated noncoding RNAs which includes lncRNAs, miRNAs, and circRNAs their involvement in tumor suppression or tumor promotion along with their clinical implication as prognostic and diagnostic biomarkers. In context to its implication as biomarker we have used 3 independent sets of GEO database viz. expression profiles of miRNAs in clear cell renal cell carcinomas (ccRCCs) and the matched normal kidney tissues (NCTs) by using a miRNAs microarray platform which comprise a total of 851 human miRNAs.

## Long noncoding RNA and its mechanistic role in renal cancer

The widely discovered lncRNA is a novel heterogeneous class of noncoding RNA [9] with more than 200 nucleotides [10]. Since the discovery of lncRNAs, it was obvious that it played an important role in regulating gene expression including chromatin and histone modifications, transcription and post-transcriptional processing [11-13]. It also interacts with RNA binding proteins, and act as co-activator of transcription factors, and inhibit the transcription process [14]. In addition to above, lncRNAs can modulate gene expression at post-transcriptional level or during splicing process of pre-mRNA, which could be linked with cancer [15, 16].

LncRNAs are defined by length ( > 200nt) which commonly originate from intergenic regions and are transcribed by RNA polymerase II. Applied next-generation sequencing have provided accumulating evidence of lncRNA deregulation in human cancers. In context to its regulatory mechanism, lncRNA is involved in 3 major physiological roles including transcriptional regulation, post-transcriptional regulation and chromatin remodeling (**Figure 1A**). Moreover, the mechanistic role of lncRNAs was decipher earlier in breast cancer where notable increase in lncRNAs-HOTAIR promotes invasion of breast carcinoma cells [17]. The above investigation represents a role model of lncRNAs and its regulatory function in renal cancer. Biological roles of lncRNAs include chromatin modeling where 5´domain of lncRNAs-HOTAIR interacts with Polycomb Repressive Complex 2 (PRC2) complex subunits viz. Enhancer of Zeste Homologue 2 (EZH2) and Suppressor of Zeste 12 (SUZ12) leading to alteration in the histone H3 lysine-27 trimethylation resulting in epigenetic modification of genes thereby increasing cancer invasiveness and progression [17, 18] (**Figure 1B & C**). Other mechanism(s) also exist, in particular, lncRNAs and its regulatory role in renal cancer. For instance, the role of lncRNA-SARCC and its function as a tumor suppress or in regulating androgen receptor in renal cell carcinoma is demonstrated by repressing AR activity through physical interaction (**Figure 1C**). LncRNA-SARCC binds and destabilize AR protein inhibiting AR function leading

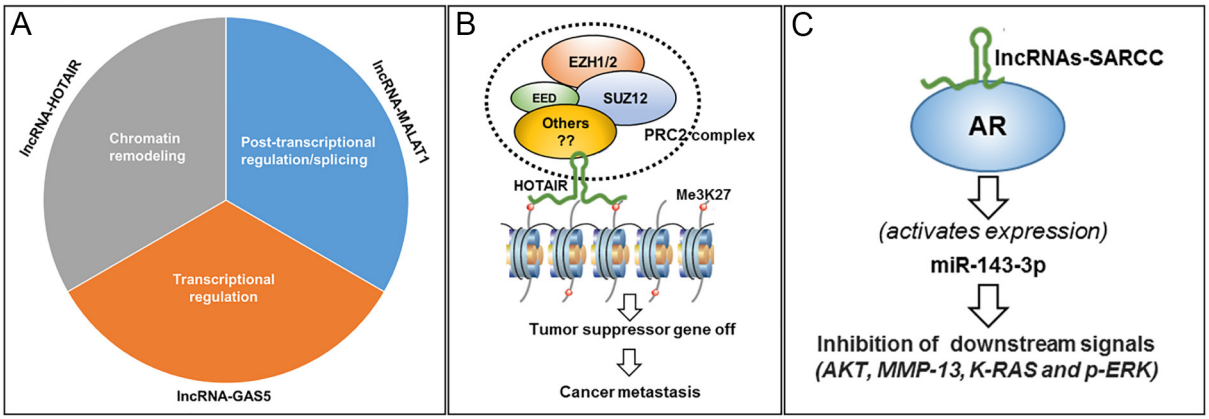


**Figure 1. Schematic representation of lncRNAs and their mechanistic regulatory role in cancer. A: Regulatory role of some select lncRNA; B: Presentation of lncRNAs HOTAIR binding with PRC2 complex and modulating the regulation of histone. This event leads to turn-off the tumor suppressor gene thereby increasing cancer metastasis; C: During hypoxia, lncRNAs-SARCC binds to androgen receptor (AR) and deactivates AR and modulate post-transcription. Consequently, HIF2A (hypoxia responsive element) binds to the promoter region on lncRNAs-SARCC and results in the upregulation of cMYC increasing cell proliferation.**

**Table 1. List of lncRNA proposed as prognostic biomarker and therapeutic target in renal cancer.**

| LncRNA name | Population cohort | Clinical utility | Reference |
|---|---|---|---|
| CADM1-AS1 | China | Prognostic biomarker | [28] |
| CCAT1 | China | Therapeutic target | [57] |
| COL18A1-AS1 | China | Prognostic biomarker | [58] |
| DNM1P35 | China | Prognostic biomarker | [59] |
| DRAIC | USA | Prognostic biomarker | [33] |
| DUXAP8 | China | Prognostic biomarker | [35] |
| EGOT | China | Prognostic biomarker | [60] |
| EPB41L4A-AS2 | China | Prognostic biomarker | [34] |
| FENDRR | China | Therapeutic target | [61] |
| FILNC1 | China | Prognostic biomarker | [62] |
| H19 | China | Prognostic biomarker | [63] |
| LINC00152 | China | Prognostic biomarker | [64] |
| lnc-ZNF180-2 | Germany | Prognostic biomarker | [31] |
| LUCAT1 | China | Biomarker/Therapeutic target | [65] |
| MALAT1 | China | Diagnosis and prognosis | [21] |
| MIR155HG | China | Prognostic biomarker | [59] |
| NBAT-1 | China | Biomarker/Therapeutic target | [29] |
| NEAT1 | China | Prognostic biomarker | [66] |
| NONHSAT123350 | China | Therapeutic target | [32] |
| OTUD6B-AS1 | China | Therapeutic target | [67] |
| PIK3CD-AS1 | China | Prognostic biomarker | [49] |
| PVT1 | China | Diagnosis and prognosis | [68] |
| RCCRT1 | China | Biomarker/Therapeutic target | [23] |
| ROR | China | Therapeutic target | [69] |
| SARCC | China | Therapeutic target | [70] |
| SLC25A5-AS1 | China | Prognostic biomarker | [19] |
| SLINKY | Japan | Prognostic biomarker | [71] |
| TREML3P | China | Prognostic biomarker | [49] |
| TUG1 | China | Prognostic biomarker | [72] |
| UCA1 | China | Prognostic biomarker | [73] |
| XIST | China | Therapeutic target | [74] |
| PANDAR | China | Prognostic biomarker | [75] |
| SRLR | China | Biomarker/Therapeutic target | [76] |

**Table 1. List of lncRNA proposed as prognostic biomarker and therapeutic target in renal cancer (*Continued*).**

| LncRNA name | Population cohort | Clinical utility | Reference |
|---|---|---|---|
| Z38 | China | Diagnostic biomarker | [77] |
| CASC2 | China | Diagnostic biomarker | [78] |
| SPRY4-IT1 | China | Prognostic/Therapeutic target | [24] |
| SDPR-AS | China | Biomarker/Therapeutic target | [79] |
| HOTTIP | China | Therapeutic target | [80] |

to transcriptionally activate miR-143-3p expression, consequently inhibiting the downstream signal including AKT, MMP-13, K-RAS and P-ERK (**Figure 1C**).

**Long noncoding RNAs as biomarker in renal cell carcinoma**

Identification for potential biomarkers in RCC, we downloaded expression profiles of lncRNAs, miRNAs, and mRNAs from The Cancer Genome Atlas (TCGA) database. The results of survival and regression analysis indicated 6 differentially expressed lncRNAs (DElncRNAs) named as COL18A1-AS1, WT1-AS, LINC00443, TCL6, AL356356.1 and SLC25A5-AS1 which significantly correlate with the clinical traits of RCC patients and might serve as biomarker(s) in RCC [19]. Another class of gene named as "alpha gene" or MALAT1 located on chromosome 11q13 reported to be up-regulated in several human cancers including lung, breast, pancreas, liver, colon, uterus, cervix and prostate [20]. Expression of MALAT1 in human RCC tissue was associated with reduced patient survival. Silencing of MALAT1 decreased RCC cell proliferation, invasion and also induced apoptosis in these cancer cells [21]. Mechanistic investigations showed that MALAT1 was transcriptionally activated by c-Fos and that it interacts with EZH2 in RCC [21]. Overexpression of MALAT1 confers oncogenic potential in RCC and may serve as a novel biomarker for renal cancer [21, 22]. Several other lncRNAs were identified who's dysfunction lead to the renal cancer cell proliferation, invasion and migration. In particular, increased expression of RCCRT1 [23], SPRY4-IT1 [24], H19 [25], and MALAT1 [21, 26], HOTTIP [27] were associated with poor prognosis. Whereas decrease expression of CADM1-AS1 [28], NBAT-1 [29, 30], lnc-ZNF180-2 [31], NONHSAT123350 [32], downregulate RNA in androgen independent cells (DRAIC) [33], and EPB41L4A-AS2 [34] were related to poor prognosis (**Table 1**). The newly discovered pseudogene-derived lncRNA named DUXAP8, a 2107-bp RNA, was markedly upregulated in RCC [35]. Deciphering the molecular and biological mechanism(s) suggested that lncRNA DUXAP8 enhanced RCC progression through downregulating miR-126, which opens new prognostic approach for the treatment of RCC[35]. These findings emphasize clinical implication of lncRNAs in early diagnostic/prognostic biomarker in renal cancer.

**MiRNA in renal cancer**

Another class of noncoding RNAs is categorized as small RNA or microRNAs (miRNAs). This particular class of noncoding RNA is 20-23 base pair nucleotide long, and functionally suppresses the expression of gene by binding to the 3' or 5' UTR region [36]. MiRNAs may target many different genes based on the presence of complementary mRNA targets for miRNA seed sequences. Several experimental studies reveal the fact that dysregulation of miRNAs may be linked to cancer cell proliferation and/or tumor progression. Conventionally, it was perceived that increased/decreased expression of miRNAs function as tumor suppressors modulating the expression of genes/transcription factors. The mechanisms underlying the dysregulation of miRNAs varies in cancer which includes changes in the transcriptional regulation of miRNAs by tumor-related protein viz. HIFα, c-myc, EZH2, Notch1, and mutation in DICER, a protein involved in miRNA processing [37].

The noncoding RNA profile array of clear cell (cc) RCC was downloaded from GEO database (GSE116251 platform ID-GPL25243) and data was reanalyzed using R and GEO2R script. The expression of 800 miRNAs were assessed in paired tumor and normal tissues from a discovery cohort of 18 ccRCC patients *via* Nanostring assay platform. Analysis of miRNA expression profiles of 36 samples revealed a subset of 3 miRNAs with log2 fold change (log2FC), which include has-miR-1246, has-miR-592, has-miR-21-5p, and has-miR-155-5p (**Additional file 1: Table S1**). In terms of downregulated miRNA, the expression of miR-200c-3p was -2.3 fold down in the above mentioned dataset. Moreover, dichotomized analysis linked the expression of 2 miRNAs, miR-155-5p and miR-210-3p with ccRCC recurrence [38].

Another set of miRNA expression profile (GSE95385, platform ID-GPL16770) in clear cell papillary renal cell carcinoma compared to normal adjacent tissue, identified 14 miRNAs (**Additional file 2: Table S2**), which showed upregulated

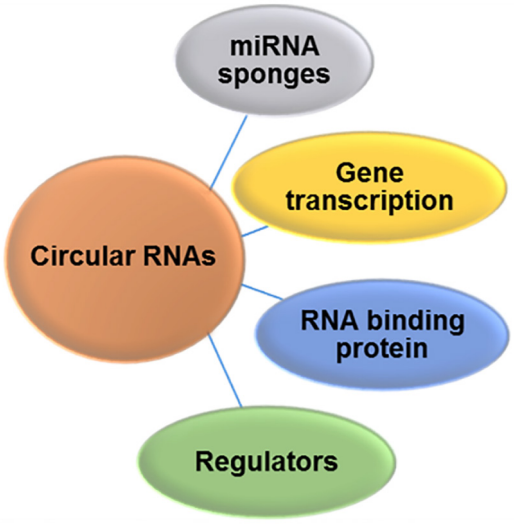


**Figure 2. Functional role of circular RNA in gene regulation. Circular RNA serve as regulator in gene expression by competing with mRNA production in pre-miRNA splicing, and as miRNA sponges, interacting with RNA binding proteins and gene regulators.**

expression greater than log2 fold 1.5. Among them the expression of hsa-miR-204, miR-192, miR194, was 5.3, 3.65 and 3.61 log2 fold higher and the expression of miR-210, miR-21, miR-34a and miR122 exhibited downregulation at -4.2, -2.4, -2.75, and -2.64 log2 fold, respectively (**Table 2**).

In another array dataset (GSE71302, platform ID-GPL10850) of ncRNA profiling, the expression profile of miRNAs in human ccRCCs, compared with normal kidney tissues (NCTs) identified a total of 851 miRNAs. In results, 22 miRNAs high log2FC ( > 2.0), among them the expression of hsa-miR-141, and hsa-miR-200c was significantly downregulated in ccRCC specimens [39]. On the other hand, 13 miRNAs showed increased level of expression in ccRCC specimens, among them the expression of hsa-miR-122, hsa-miR-210, and hsa-miR-224 (**Table 2**), the other 11 hsa-miRNAs are listed in the **Additional file 3: Table S3**. The above mentioned dataset were pooled and reanalyzed (using log2FC filter) largest to smallest, 31 miRNAs were upregulated and differentially expressed ( > log2FC, 2 to 6) in RCC patient's samples. Among them, the expression of hsa-miR-141 showed highest level of expression (6.70, log2FC), followed by hsa-miR-200c (4.9, log2FC), has-miR-138 (4.51, log2FC) and hsa-miR-210 (4.26, log2FC), respectively.

## MiRNAs as biomarker in renal cancer

Previously, we have documented the role of miRNA as prognostic/diagnostic biomarker in prostate cancer [40]. Here we review the role of miRNA as prognostic biomarker in RCC which is examined by metadata analysis. The above mentioned metadata analysis from 3 independent cohorts in renal cancer, demonstrate that miR-210 was upregulated (logFC 4.25/GSE95385; log2FC 4.4/GSE71302) in ccRCC despite different array platforms (GPL16770/GPL10850). The high expression of miR-210 in renal cancer further supported in RCC patients samples when compared with normal tissue controls, miR-210 was overexpressed over 10-fold higher in the ccRCCs ($N = 32$, $P < 0.001$, Mann–Whitney test), 2.8-fold in the papillary tumors ($N = 9$, $P < 0.05$, Mann–Whitney test). This set of information including metadata analysis in independent cohorts suggest miR-210 as prognostic biomarker in ccRCC. With respect to miRNA: mRNA target interaction, it was revealed that miR-210 binds to the 3′ UTR region of hypoxia-inducible factors (HIFs) and modulate gene expression of HIF1and HIF2 at the post-transcriptional level [41]. The experimentally validated in vivo study showed high expression of miR-210 association with improved clinico-pathological prognostic factors.

## Circular RNAs in renal cancer

A new class of noncoding RNAs referred as circular RNA provides new optimism in the field of cancer research. CircRNAs generated during the process of splicing of pre-mRNA from the coding/noncoding genomic region or both, with a majority comprising of exonic RNAs. CircRNA skip the process of canonical splicing and is formed by non-sequential back-splicing of pre-messenger RNA (pre-mRNA) transcripts [42]. Functionally, circRNAs acts as miRNA sponge combining with RNA binding proteins (RBPs) and is operational as a transcription factor and translation of proteins. Another novel role of circRNA is to compete with endogenous RNA. Together circRNA with miRNAs can influence the stability of target gene inhibitors and in regulating gene expression at

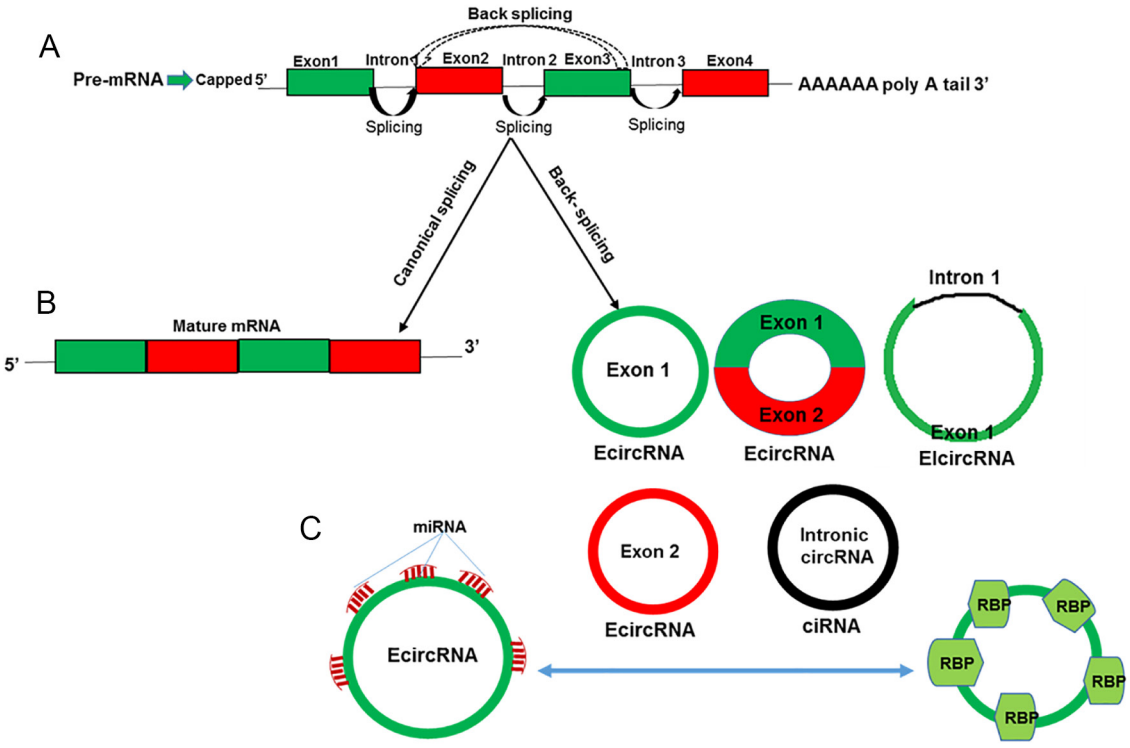


**Figure 3. Mechanism by which circular RNAs play important roles as miRNA sponges, gene transcription and gene regulators, RNA-binding protein (RBP) sponges and protein/peptide translators. A: Schematic representation of circular RNA biogenesis: Canonical pre-mRNA splicing yielded mature mRNA; B: Pre-mRNA undergoes the process called back-splicing and circularization, which resulted in the formation of intronic circRNAs, exonic circRNAs and exonic-intron circRNAs; C: Functional role of circRNA acting as miRNA sponges by competing for miRNA binding sites, diminishing the effect of miRNA-mediated regulatory activities by binding to RBPs.**

**Table 2. List of miRNAs and its expression associated with renal cancer.**

| MicroRNA | Expression | Target gene | Gene full name |
|---|---|---|---|
| miR-100 | Down | RBX1 | Ring-box 1, E3 ubiquitin protein ligase |
| miR-10b | Down | BDNF | Brain-derived neurotrophic factor |
| miR-125b | Down | RP1-228P16.5 | Uncharacterized protein |
| miR-26a+ | Down | POLR3G | RNA polymerase III (DNA directed) polypeptide G (32kD) |
| miR-133b | Down | LHFP | Lipoma HMGIC fusion partner |
| miR-135b | Down | ZNF302 | Zinc finger protein 302 |
| miR-136 | Down | MEX3C | Mex-3 RNA binding family member C |
| miR-141 | Down | ZNF385D | Zinc finger protein 385D |
| miR-149 | Down | LRIG2 | Leucine-rich repeats and immunoglobulin-like domains 2 |
| miR-154 | Down | E2F5 | E2F transcription factor 5, p130-binding |
| miR-199a | Down | KLHL3 | Kelch-like family member 3 |
| miR-200a* | Down | ZEB1 | Zinc finger E-box binding homeobox 1 |
| miR-200b | Down | ZEB1 | Zinc finger E-box binding homeobox 1 |
| miR-200c | Down | ZEB1 | Zinc finger E-box binding homeobox 1 |
| miR-211 | Down | AP1S2 | Adaptor-related protein complex 1, sigma 2 subunit |
| miR-30a-3p | Down | DST | Dystonin |
| miR-337 | Down | RAP2B | RAP2B, member of RAS oncogene family |
| miR-377 | Down | SLC6A19 | Solute carrier family 6 (neutral amino acid transporter), member 19 |
| miR-411 | Down | ATP6V1G1 | ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G1 |
| miR-429 | Down | ZEB1 | Zinc finger E-box binding homeobox 1 |
| miR-507 | Down | ZNF681 | Zinc finger protein 681 |
| miR-510 | Down | CMC2 | COX assembly mitochondrial protein 2 homolog (S. cerevisiae) |
| miR-514 | Down | GMFB | Glia maturation factor, beta |
| miR-142-3p | Up | HSBP1 | Heat shock factor binding protein 1 |
| miR-155 | Up | H3F3A | H3 histone, family 3A |
| miR-185 | Up | PRRT2 | Proline-rich transmembrane protein 2 |
| miR-21 | Up | FGF18 | Fibroblast growth factor 18 |
| miR-224 | Up | INIP | INTS3 and NABP interacting protein |
| miR-34a | Up | MDM4 | Mdm4 p53 binding protein homolog (mouse) |
| miR-34b | Up | FDX1 | Ferredoxin 1 |
| MiR-708 | Up | ATP6V1G1 | ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G1 |
| miR-1285 | Up | MRPL44 | Mitochondrial ribosomal protein L44 |
| miR-221 | Up | CDKN1B | Cyclin-dependent kinase inhibitor 1B (p27, Kip1) |

**Table 2. List of miRNAs and its expression associated with renal cancer (*Continued*).**

| MicroRNA | Expression | Target gene | Gene full name |
|---|---|---|---|
| miR-21 | Up | FGF18 | Fibroblast growth factor 18 |
| miR-183 | Up | UBE2G1 | Ubiquitin-conjugating enzyme E2G 1 |
| miR-135a | Down | c-MYC | MYC binding protein |
| miR-218 | Down | TUB | Tubby bipartite transcription factor |
| miR-205 | Up | Src family | Src family |
| miR-203 | Down | FGF2 | Fibroblast growth factor 2 |
| miR-210 | Up | FGF1R | Fibroblast growth factor receptor-like 1 |

transcriptional level [43, 44].

Circular RNAs are endogenous non-coding RNA, and the role of circRNA was pivotal in terms of regulating diverse cellular process, which includes gene transcription, RNA binding protein and acts as regulators and miRNAs sponge (**Figure 2**). In terms of biogenesis, circRNAs are generated by a spliceosome mediated pre-mRNA back splicing, fundamentally different than regular canonical (linear) splicing (**Figure 3A**). Regarding their biogenesis from different genomic regions (exon/intron) circRNA can be categorized into four types including i) exonic circular RNA (EcircRNAs), ii) circular intronic RNA (ciRNAs), iii) exon-intron circular RNAs (EIciRNAs), and iv) intergenic circular RNAs (**Figure 3B**). CircRNAs has better ability to bind with miRNAs and thus called as "super sponge" [45-47]. The mechanism of regulation of circRNA is similar like miRNAs as it blocks the binding of miRNAs and directly binds to the miRNAs indirectly regulating gene expression [43]. The mechanistic undermined function of cirRNA is that it plays as regulator of gene expression by competing with mRNA production in pre-miRNA splicing. Moreover, circular RNAs can serves as mRNA traps, another form of alternate splicing, and remove the start codons from mature mRNAs to reduce protein translation in cancer.

Remarkably, interaction between circRNA and miRNAs has already been observed to perform a significant role in a variety of human cancers. However, the current knowledge about the involvement of circRNAs in cancer development and progression is limited, and the role of circRNAs as miRNA sponge has been proposed as the most frequent mechanism of circRNA activity in tumor cells (**Figure 3C**). CircRNA act like miRNA sponge by competing for miRNA binding sites (**Figure 3C**), and reduce the effect of miRNA-mediated regulatory activities such as post-transcriptional repression. In fact, overexpression of miRNA sponge acting circRNAs increases the expression, whereas silencing of these circRNAs decreases the expression of miRNA targets. The "super sponge" mechanism ruled among the other proposed mechanism, indeed circRNAs serves as miRNA sponge with suggested potential role as competitive endogenous RNAs competing for miRNA-binding sites, thus affecting miRNA activities. CircRNA (circHIPK3) was observed to sponge 9 miRNAs with 18 potential binding sites and in particular regulates cell growth by sponging multiple miR-124 and inhibiting miR-124 activity in malignant tumors [48].

Several circRNAs have been identified so far with reference to renal cancer. Recently, it was shown that expression of circRNA, H long terminal repeat-associating protein 2 (HHLA2) was increased in renal cancer tissues compared with normal renal tissue both at the transcriptional and protein level [49]. Another, novel circRNA, circPCNXL2 was significantly upregulated in renal cancer. Indeed high abundance of circPCNXL2 was directly linked with poor survival rate of RCC patients [50]. Knockdown of circPCNXL2 has shown to reduceRCC cell proliferation in invitro and in vivo studies. Mechanistically, circPCNXL2 acts as miRNA sponge of miR-153 and modulate the expression of ZEB2 target gene, and thus increase cancer cell proliferation and invasion. Xiong et al. identified a new circRNA (circRNA ZNF609) whose expression is significantly increased in RCC. CircRNA ZNF609 acts as miRNA sponge of miRNA-138-5p and modulate the expression of forkhead box P4 (FOXP4), ultimately influencing renal cancer cell proliferation. Another circular RNA (circATP2B1) also influences renal cancer cell proliferation via miR-204-3p, and increases the expression of fibronectin 1 (FN1) [51]. Wang et al. identified a new circular RNA (circHIAT1) that was downregulated in ccRCC tissues [25]. Functionally, CircHIAT1 acts as miRNA sponge of miR-195-5p/29a-3p/29c-3p and regulates the expression of CDC42. Activation of androgen receptor suppressed circHIAT1 expression resulting in decreased CDC42 expression and enhanced ccRCC cell migration and invasion [25].

**Circular RNAs as biomarker in renal cancer**

Emerging evidences deciphered the role of circRNA in cancer having potential to serve as biomarker and therapeutic target in cancer. In context to biomarker, circRNAs stably expressed in saliva, blood, and exosomes, which satisfy the criteria as cancer biomarkers [52]. Also because circRNA has no open linear tail like other ncRNA and therefore are insensitive to exonuclease. Thus circRNAs are enriched and stable in exosomes also referred as exo-circRNAs [53], and exosome secretion may represent one of the mechanisms for the removal of circular RNAs. Quantifying and analyzing circRNAs by RT-PCR and in-situ hybridization is more sensitive compared to protein by an antigen-antibody reaction. For example, it was shown that expression of circular RNA-HHLA2 was increased in ccRCC tissues, compared with normal renal tissues at both transcriptional and protein level and suggested the role of HHLA2 as prognostic biomarker in RCC [54]. Also circular RNA (Hsa_circ_0001451) might be involved in renal tumor progression and suggested its role as prognostic biomarker, however the experimental validation has not been conducted, hence needs further investigation. Another class of circRNA (circATP2B1) also influenced the progression of ccRCC. Mechanistically, circATP2B1 acts as miRNA sponge of miR-204-3p and influence the expression of estrogen receptor beta (ERβ), together they influence RCC progression, suggesting circRNA ATP2B1 as prognostic biomarker for renal disease [51]. The

**Table 3. Clinical trials on miRNA in renal cancer.**

| noncoding RNA | Clinical trial ID | Description | Status |
|---|---|---|---|
| miRNA | NCT00743054 | The study examines RCC related miRNA and the target genes of related miRNA and the relationship between RCC related miRNA, pathological types, tumor stage and prognosis. The purpose of this study is to investigate the role of miRNA as novel biomarker(s) in the formation of RCC. | Completed |
| miRNA | NCT00806650 | The study intends to develop a blood test for anti-IMP3 antibody and microRNA in serum and tissue samples to diagnose RCC and provide effective treatment options to patients. | Completed |
| miRNA | NCT01829971 | Phase I, open-label, multicenter, dose-escalation study investigates the safety, pharmacokinetics and pharmacodynamics of the microRNA, MRX34 in patients with unresectable primary liver cancer or advanced or metastatic kidney cancer. | Terminated |

expression of circPCNXL2 was significantly increased in RCC patients, indeed the higher expression corresponds to poor survival of ccRCC patients [50]. Quantitative expression analysis of A-498, AXHN, ACHN, OS-RC-2, 769-P and G-401 as numerous renal cell lines showed increased expression of circ-ZNF609 [55].

## Clinical implication of noncoding RNA and renal cancer

It is clear from the above information that several research groups have identified ncRNA and proposed as prognostic/diagnostic biomarker in renal cancer. However, the lab to clinic data is not very striking. Using the web portal (https://clinicaltrials.gov) with key words "Renal Cancer" and "Noncoding RNA/miRNAs/lncRNAs" and "Circular RNA" to search the clinical impact of ncRNA exhibited a small list of clinical trials particularly with miRNA in renal cancer (**Table 3**). Moreover, the direct clinical implication of ncRNA against renal cancer is not documented so far. As mentioned above, targeting exosome cargos may express high diagnostic and/or prognostic potential. The current information presented here emphasize the role of ncRNAs as prognostic marker in renal cancer. Indeed, the role of circRNA was inevitable in terms of its existence in exosomes. In 2015, Lerner et al. first identified circRNA in exosomes from the RNA-Seq data (genome wide) enriched in exosomes compared to parental cells [56]. Clinical trials implementing exosome research is needed in future on RCC.

## Conclusions and future direction

Emerging evidence suggests that ncRNAs are a group of sensitive and specific novel noninvasive biomarkers for the prediction of pathological grade, metastasis/recurrence, and survival having significant impact on our understanding of the pathogenesis of RCC. At the same time, ncRNAs have shown to have potential as a tool for early diagnosis and prognosis for RCC. Noncoding RNAs contribute to RCC development at various stages and it is evident that these molecules can target signaling pathways related to RCC pathogenesis. However, dysregulation of the ncRNAs can be either a cause or an effect of carcinogenesis which needs further investigation. Additionally, mechanistic studies this far has provided the rationale of using ncRNAs as potential therapeutic targets in cancer. The bioinformatics and systems biology methods will be useful to investigate the functional roles of ncRNAs in renal cancer cell types to reveal its regulatory mechanism(s). This cell-type specific integrative network analysis will be valuable in understanding ncRNA function(s) in biological and cellular processes, and their specific regulatory roles in RCC.

Advancement in technology and investigations on ncRNAs have drawn increasing attention. The functions of lncRNA in pathogenesis, miRNA in regulation of gene expression and circRNAs as miRNA sponges and transcriptional regulators are increasingly recognized for their roles in biogenesis and functional mechanisms. These findings elucidate the physiological and pathological processes of a number of ncRNAs which may be considered as novel diagnostic biomarkers and potential therapeutic targets in cancer, however further research is needed to elucidate specific molecular mechanisms and pathways connections in relation to RCC. Additional studies are required to accurately identify the mechanisms by which miRNAs affect RCC. Summarizing recent knowledge, ncRNAs represent a new group of molecules having potential for development as tumor biomarkers that may improve the diagnostic, prognostic and even predictive abilities, and finally RCC patient management.

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## Ethical policy

No research involving experimentation on human or animal subjects was conducted.

## Author contributions

SV prepared the draft, collected data from the open source/public domain and performed analysis. SG conceived the manuscript outline, provided input and critical revisions on the manuscript.

**Competing interests**

The authors declare no conflict of interest with the work.

**Ethical statement**

Both authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

**Additional files**

Additional file 1: Table S1. GSE116251 list of microRNA expression profile in clear cell renal cell carcinoma (RCC) tissues, analyzed by GEO2R. The adjusted p value was calculated along with t-test (Moderated t-statistic (only available when two groups of Samples are defined) and B-statistic or log-odds that the gene is differentially expressed (only available when two groups of Samples are defined). The expression values were represented in the form of Log2-fold change between two experimental conditions.

Additional file 2: Table S2. GSE95385 list of microRNA expression profile in clear cell papillary renal cell carcinoma compared to normal adjacent tissue analyzed by GEO2R. The adjusted p value was calculated, along with t-test (Moderated t-statistic (only available when two groups of Samples are defined) and B-statistic or log-odds that the gene is differentially expressed (only available when two groups of Samples are defined). The expression values were represented in the form of Log2-fold change between two experimental conditions.

Additional file 3: Table S3. GSE71302 list of miRNAs in clear cell renal cell carcinomas (ccRCCs) and in matched normal kidney tissues (NCTs), analyzed by GEO2R. The adjusted p value was calculated, along with t-test (Moderated t-statistic (only available when two groups of Samples are defined) and B-statistic or log-odds that the gene is differentially expressed (only available when two groups of Samples are defined). The expression values were represented in the form of Log2-fold change between two experimental conditions.

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