MicroRNA Signature in Renal Cell Carcinoma

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Renal cell carcinoma (RCC) includes 2.2% of all diagnosed cancers and 1.8% of cancer-related mortalities. The available biomarkers or screening methods for RCC suffer from lack of sensitivity or high cost, necessitating identification of novel biomarkers that facilitate early diagnosis of this cancer especially in the susceptible individuals. MicroRNAs (miRNAs) have several advantageous properties that potentiate them as biomarkers for cancer detection. Expression profile of miRNAs has been assessed in biological samples from RCC patients. Circulatory or urinary levels of certain miRNAs have been proposed as markers for RCC diagnosis or follow-up. Moreover, expression profile of some miRNAs has been correlated with response to chemotherapy, immunotherapy or targeted therapeutic options such as sunitinib. In the current study, we summarize the results of studies that assessed the application of miRNAs as biomarkers, therapeutic targets or modulators of response to treatment modalities in RCC patients.

Keywords: miRNA, renal cell carcinoma, expression, cancer, biomarker

INTRODUCTION

Renal cell carcinoma (RCC) is the 15th most frequent cancer, based on the statistics provided by GLOBOCAN (1). This kind of cancer includes 2.2% of all diagnosed cancers and 1.8% of cancer-related mortalities (1). The incidence of this type of cancer is different in different regions. RCC is associated with numerous risk factors among them are smoking, obesity, and hypertension (2). The varied incident and mortality rates of RCC in different geographical regions necessitate enactment of regional screening programs and development of precise biomarkers (2). Among the screening methods for sporadic RCC, urine dipstick has yielded low level of accuracy impeding its clinical application (3). Moreover, none of the proposed serum and urine markers such as aquaporin 1, perilipin 2, and KIM1 had enough sensitivity or specificity to be applied in this regard (4). On the other hand, computed tomography and abdominal ultrasound suffer from high cost and low sensitivity for the identification of small tumors, respectively (2, 3). Therefore, development of effective non-invasive screening methods for RCC is a necessity. Recent investigations have potentiated microRNAs (miRNAs) as screening tools for several kinds of human malignancies (5). These transcripts contribute in the pathogenesis of human disorders. In this review, we clarify the main points of studies in RCC to judge the potential of miRNAs as biomarkers or therapeutic targets in this malignant condition.
miRNA Biogenesis and Function

miRNAs have sizes about 23 nucleotides and are present in different species. By acting as antisense transcripts, miRNAs post-transcriptionally decrease expression of their targets. Although the regulatory effects of each miRNA on the expression of its target gene is not great, the resultant interactive network between miRNAs, target genes and downstream effectors plays crucial impacts on the regulation of cellular functions (6). The majorities of these transcripts are transcribed from DNA templates into primary miRNAs and undergo a number of steps to be processed into the precursor and mature miRNAs, respectively (7). Two kinds of RNase III molecules, i.e., Drosha and Dicer proteins participate in the miRNA processing in the nuclear and cytoplasmic cellular compartments, respectively (7). The critical function of miRNAs in gene expression modulation is additionally highlighted by the point that an individual gene is concurrently regulated by several miRNAs, and each miRNA can modulate expression of several targets which have sequence complementarity with its seed region (8). About one-third of human genome and virtually all essential cell processes are expected to be regulated by miRNAs (9, 10). The role of miRNAs in the pathogenesis of human cancers has been vastly examined (11). These molecules have been reported to influence the main features of carcinogenic process such as sustained proliferative capacity, evasion from growth inhibitor signals, resistance to apoptosis, induction of invasive and metastatic programs, and enhancement of angiogenic processes (12). The importance of miRNAs in development of cancer has been firstly highlighted through the spotting miR-15a and miR-16-1 in a commonly deleted region in B-cell chronic lymphocytic leukemias (13). Subsequent investigations revealed other genomic alterations in a number miRNA coding genes in different cancers such as lung cancer (14), melanoma as well as ovarian and breast cancers (15). Moreover, well-known oncogenes such as c-Myc were shown to influence expression of oncogenic activates miRNAs including miR-17-92 (16) or inhibit expression of tumor suppressor miRNAs including miR-15a, miR-26, miR-29, miR-30, and let-7 (17). In RCC, quite a lot of investigation have measured expression profile of miRNAs in different biological samples to identify the pathogenic roles of these transcripts in the development of this type of cancer (18).

Dysregulated miRNAs in RCC

A number of studies have assessed differentially expressed miRNAs and their target genes in RCC samples and normal control. Using this approach, Li et al. have identified down-regulation of 521 genes and up-regulation of 473 genes in RCC samples. Protein-protein interaction network showed RHCG, RALYL, SLC4A1, UMOD, and CA9 as nodes with high degrees of interactions. The differentially expressed genes were enriched in cytokine and cytokine receptor pathway (19). Such approaches are useful in identification of biomarkers and therapeutic targets for RCC. Other studies have reported dysregulation of a number of miRNAs in RCC samples. Figure 1 shows a number of dysregulated miRNAs in RCC and their interaction with the PTEN tumor suppressor.

The following sections describe the function of these miRNAs.

Up-Regulated miRNAs in RCC

Numerous oncomiRs have been recognized in RCC. Gottardo et al. have described up-regulation of miR-28, miR-185, miR-27, and let-7f-2 in tissue samples obtained from RCC patients compared to normal kidney samples. Notably, these miRNAs were different from up-regulated miRNAs in bladder cancer samples in their cohort of patients, implying the presence of distinctive miRNA signature between these two cancers of the
urogenital system (20). Wulffken et al. have investigated miRNA signature in both tissue and serum specimens of patients with RCC. They reported over-expression of 109 circulatory miRNAs in cancer patients; among them were 36 miRNAs that were up-regulated in tissue samples as well. Additional verification steps indicated up-regulation of miR-1233 in another cohort of RCC patients. Notably, expression patterns of this miRNA in patients with angiomyolipoma or oncocyotoma was similar with RCC patients (21). miR-301a is another up-regulated miRNA in RCC cell lines and clinical samples. Over-expression of this miRNA has been associated with advanced stage and poor survival of RCC patients. Mechanistically, miR-301a has been displayed to target PTEN tumor suppressor (22). Two other oncomiRs, namely, miR-22 and miR-193a-3p also suppress expression of PTEN in RCC cells (23, 24). In addition, miR-1293 has been up-regulated in RCC cells enhancing viability of these cells their migratory potential and invasiveness. These effects are mediated through suppression of Hydrocyanic Oxidase 2 (25). Table 1 gives a summary of the roles of up-regulated miRNAs in RCC.

Down-Regulated miRNAs in RCC

In a high throughput approach, Nakada et al. have assessed miRNA signature in clear cell carcinomas (CCCs), and chromophobe RCC compared with normal kidney tissues. They reported down-regulation of 37 and 51 miRNAs in CCC and chromophobe RCC, respectively. As the number of up-regulated miRNAs in cancer tissues was significantly lower than the number of down-regulated ones, authors have deduced that expression of miRNAs have a tendency to be decreased in both histological types of RCC compared with normal renal samples. miR-141 and miR-200c were the most remarkably under-expressed miRNAs in CCC samples being down-regulated in all assessed samples of this type. In *silico* and functional studies indicated that decreased expression of miR-141 and miR-200c in CCCs may inhibit CDH1/E-cadherin expression through increasing ZFHX1B levels (66). Two other tumor suppressor miRNAs, namely, miR-30c-5p and miR-138-1 levels, have been down-regulated in RCC samples even in the early stage tumors. Its expression has been lower in RCC samples of Fuhrman grade G3 + G4 compared with G2 (67). Another commonly down-regulated miRNA in RCC is miR-362-3p. Forced up-regulation of miR-362-3p resulted in the attenuation of cell proliferation, induction of cell cycle arrest and reduction of motility. These effects are exerted through modulation of AKT/FOXO3 signaling. SP1 has been identified as a direct target of miR-362-3p (68). Besides, expression of miR-200b has been reduced in RCC samples. Forced over-expression of miR-200b in the RCC cell lines has inhibited their migration and invasiveness and reduced cancer metastasis in xenograft models. Laminin subunit alpha 4 (LAMA4) has been predicted as a direct target of miR-200b (69). Table 2 summarizes the data about down-regulated miRNAs in RCC.

Diagnostic/Prognostic Value of miRNAs in RCC

Diagnostic and prognostic values of several miRNAs have been appraised in tissue samples, urine, or peripheral blood of RCC patients. A previous meta-analysis of available literature about miRNA signature in RCC tissues and their matching non-cancerous tissues has shown elevated levels of miR-21 and miR-210, while decreased levels of miR-141, miR-200c, and miR-429. Altered expressions of these miRNAs have been related with poor cancer-specific survival after tumor excision. Expression profile of these miRNA has been shown to be a suitable prognostic and predictive method for appraisal of survival of RCC patients particularly those with CCC (121).

An important application of miRNAs in the diagnostic process of RCC has been provided by their presence in the circulation of patients and their potential in liquid biopsy. Tusong et al. have reported over-expression of miR-21 and miR-106a in the serum samples of RCC patients compared with normal control samples. Notably, serum levels of these miRNAs have been decreased in patients a month after surgery suggesting their appropriateness as biomarkers for RCC (122). Wang et al. have reported consistent down-regulation of miR-200a in serum samples of patients with this kind of cancer, particularly in patients with stage I disease. Notably, level of this miRNA was commonly decreased in urine specimens of patients as well (123). A comprehensive assessment of miRNA profile in plasma specimens of ccRCC patients and healthy subjects has revealed the correlation between circulating miRNA signature and ccRCC stage. miRNA profiles were remarkably different between stage III/IV sections and both controls and early stage samples. Plasma levels of miR-150 were considerably correlated with patients’ survival (124). A large-scale detection of formerly unannotated miRNA sequences in human renal specimens has led to identification of several miRNAs being dysregulated in ccRCC tumors and linked with poor survival of patients (125). Finally, experiments in a transgenic model of Xp11 RCC have shown higher amounts of miR-204-5p in urinary exosomes compared with control animals. Expression of this miRNA was also elevated in primary RCC cell lines created from transgenic mice indicating its role as a diagnostic marker for Xp11 tRCC (126).

Table 3 gives a brief record of studies which reported the diagnostic/prognostic role of miRNAs in RCC.

The Role of miRNAs in Determination of Response of RCC Patients to Treatment Modalities

Expression profile of a number of miRNAs correlates with response of RCC cells to chemotherapeutic agents. For instance, miR-381 has been shown to improve response of RCC cells to 5-fluorouracil through targeting WEE1 and enhancing activity of cyclin-dependent kinase 2 (128). Expression of miR-451 has been elevated in low multi-drug resistant (MDR) cell line compared with the high MDR cell line. This miRNA has been shown to target ATF-2 and suppress its expression. Up-regulation of miR-451 has increased drug resistance, while its silencing improved response to chemotherapeutic agents (118). In the clinical settings, serum levels of miR-183 have been shown to predict response of RCC patients to cytotoxic effects of natural killer cells (129), implying the importance of miRNAs in immunotherapeutic options. A genome-wide miRNA profiling in RCC patients who received sunitinib showed lower levels of miR-141 in tumor samples of
| miRNA | Samples | Targets/Regulators | Pathways | Roles | Ref |
|-------|---------|------------------|----------|-------|-----|
| miR-301a | 516 tumor samples and 71 ANTTs | PTEN | cell cycle G1/S transition | miR-301a regulates PTEN expression. | (22) |
| miR-429 | 28 pairs of tumor and ANTTs | CRKL | TGF-β, SOS1/MEK/ERK/ MMP2/MMP9 pathway | Has a role in migration and invasion | (26) |
| miR-92a-3p | 16 pairs of RCC tissues and ANTTs | FBXW7 | - | miR-92a-3p silencing suppressed cell proliferation and reduced colony number. | (27) |
| miR-1293 | PRCC (292 tumor tissues and 34 normal) and ccRCC (545 tumor tissues and 71 normal), from TCGA database | HAO2 | EMT | Has a role in cell viability, invasion, and migration | (25) |
| miR-210-3p | 21 paired ccRCC tissues and ANTTs and urine samples | - | f VHL/hypoxia 314 – VEGFR Wnt signaling | - | (28) |
| miR-671-5p | 90 primary ccRCC tissues and 90 ANTTs | APC | - | Has a role in invasion and migration | (29) |
| miR-935 | Twenty-five patient samples with ccRCC/ Cancer tissues and normal kidney tissues were frozen | IREB2 | - | Has a role in proliferation, migration and invasion | (30) |
| miR-592 | 114 paired ccRCC tissues and ANTTs and urine samples | SPRY2 | - | Has a role in proliferation, migration and invasion | (31) |
| miR-22 | 480 paired ccRCC tissues and ANTTs and urine samples | PTEN | - | Has a role in invasion | (23) |
| miR-720 | 30 paired cancer tissues and ANTTs | E-cadherin and E-catenin | - | Has a role in EMT and metastasis | (32) |
| miR-210-3p, miR-218, and miR-1233 | Plasma samples from 54 RCC patients and 50 healthy individuals | - | - | Patients with up-regulated miR-210, miR-221 and miR-1233 had higher risk of specific death by RCC. | (33) |
| miR-122 | 148 cancer tissues and 60 ANTTs | Dicer | miR-122/Dicer pathway | miR-122 induces EMT, migration and invasion in RCC. | (34) |
| miR-125b | 276 paired cancer tissues and ANTTs | - | - | miR-125b forecasts recurrence and outcome of ccRCC after surgical resection. | (35) |
| miR-378 and miR-210 | Serum samples from 195 RCC patient and 100 healthy controls | - | - | Combination of Mir-378 and Mir-210 Serum Levels serve as powerful non-invasive Detection in RCC. | (36) |
| miR-224 | 20 paired cancer tissues and ANTTs and serum sample from 108 ccRCC patients | - | - | miR-224 increased cell viability and invasion ability, reduced apoptosis. | (37) |
| miR-7 | 72 paired samples from cancer tissues and ANTTs | MEG3, RASL11B | - | miR-7 induces progression of ccRCC. | (38) |
| miR-203a | 40 paired cancer tissues and ANTTs | GSK-3β | Wnt/β-catenin pathway | miR-203a induces cell proliferation, migration, cell cycle, and suppresses apoptosis of RCC cells. | (39) |
| miR-155 | 20 paired cancer tissues and ANTTs | FOXO3a | - | miR-155 increased the proliferation, and inhibited apoptosis and cell cycle arrest. | (40) |
| miR-125b | 24 paired cancer tissues and ANTTs | - | - | miR-125b induced cell mobility and inhibited apoptosis. | (41) |
| miR-122 | 90 paired cancer tissues and ANTTs | Occludin | MAPK pathway | miR-122 enhanced cell proliferation, migration and invasion. | (42) |
| miR-221/222 | 57 paired cancer tissues and ANTTs | KDR | angiogenesis pathways | miR-221/222 enhances tumor cell proliferation. | (43) |
| miR-223-3p | 156 nephrectomy and 46 kidney biopsy specimens | - | - | Levels of miR-223-3p may be biomarker for ccRCC and it was correlated with cancer-specific survival. | (44) |
| miR-21, miR-155, and/or miR-142-5p | 59 normal kidney and 54 tumor specimens; and 38 paired cancer tissues and ANTTs | PTEN | P3K signaling pathway | Three-miRNA combination is as a potential predictor of renal cancer in patients. | (45) |
| miR-193a-3p | 30 paired cancer tissues and ANTTs | - | - | miR-193a-3p induces cell proliferation, cell migration and the cell cycle. | (24) |
| miR-99, miR-miR-200b,miR-106a, miR-106b | 56 paired cancer tissues and ANTTs | mTOR, VHL | - | These miRNAs increased the aggressiveness of RCC. | (47) |

(Continued)
poor responders compared with good responders (81). Therefore, miRNAs modulate response of RCC patients to a wide range of treatment modalities. Table 4 summarizes the impact of miRNAs in resistance to therapeutic modalities in RCC.

**DISCUSSION**

The oncogenic function of numerous miRNAs has been proved in RCC cells. These oncomiRs have been shown to enhance cell proliferation and invasive features of RCC cells whilst decreasing apoptosis. Notably some tumor suppressor genes such as PTEN, APC, and MEG3 have been identified as targets of oncomiRs such as miR-301a, miR-193a-3p, miR-22, miR-671-5p, and miR-7, indicating a possible mechanism for their participation in the pathogenesis of RCC. Instead, tumor suppressor miRNAs which are down-regulated in RCC cells have potential roles in the activation of apoptotic pathways and arrestment of cell cycle transition. A number of these miRNAs target EMT-associated genes such as ZEB1, Slug, HOTAIR, and HIF-1α. Thus, their down-regulation is associated with the enhancement of EMT program. miRNAs are regarded as potential markers of different malignancies including RCC. These transcripts regulate several cancer-related cellular functions such as apoptosis, survival, migration, and angiogenesis. Therefore, several miRNAs have similar functions and expression profiles in diverse cancers. Although aberrant expression of miRNAs in cancer patients is a useful tool for follow-up of patients, identification of tissue-specific pattern of their expression is necessary to differentiate between different cancers originating from a certain body system. In spite of extensive efforts for biomarker discovery, there is no consensus on miRNA panels that are specific for a certain type of cancer. A previous study has reported up-regulation of miR-28, miR-185, miR-27, and let-7f-2 in RCC samples, whereas
| miRNA          | Samples                                                                 | Targets/Regulators | Signaling Pathways                      | Roles                                                                 | Ref    |
|---------------|-------------------------------------------------------------------------|--------------------|-----------------------------------------|----------------------------------------------------------------------|--------|
| hsa-miR-30c-5p| 47 paired tumor samples and ANNTs                                       | -                  | -                                       | mr-30c-5p inhibits proliferation and tumor formation.               | (67)   |
| hsa-miR-138-1 | -                                                                       | -                  | -                                       | mr-138-1 might be associated with an unfavorable course of the disease. | (67)   |
| miR-363        | 77 adjacent normal renal tissues                                        | S1PR1              | ERK, including PDGF-A, PDGF-B, EMT     | miR-363 inhibited the proliferation, migration and invasive capacity of ccRCC cells. | (70)   |
| miR-362-3p     | Twenty-five paired of RCC tissues and ANNTs                             | SP1                | AKT/FOXO3                               | miR-362-3p inhibited the proliferation of RCC cells.                | (68)   |
| miR-214        | -                                                                       | LVIN               | -                                       | miR-214 reduces the cell proliferation and tumorigenesis.           | (71)   |
| miR-133b       | 60 paired cancerous tissues and ANNTs                                   | -                  | ERK                                     | miR-133b suppresses cell proliferation, migration and invasion, while inducing apoptosis. | (72)   |
| miR-206        | 60 paired cancer tissues and ANNTs                                       | CDK6               | -                                       | MR-206 effectively caused apoptosis and cell cycle arrest at G0/G1 phase. | (73)   |
| miR-143        | 67 paired ccRCC tissues and ANNTs                                       | ABL2               | -                                       | MR-143 decreases cells adhesion, migration and EMT.                  | (74)   |
| miR-124 and miR-203 | 34 paired ccRCC tissues and ANNTs                                     | ZEB2               | EMT                                     | miR-124 and miR-203 inhibit cell proliferation and migration.       | (75)   |
| miR-101-5p and miR-101-3p | 18 clinical ccRCC tissue samples/5 patients resistant to several tyrosine kinase inhibitor | DONSON             | G2/M checkpoint, EMT                   | Expression of miR-101-5p induced cell cycle arrest and apoptosis.  | (76)   |
| miR-765        | 36 ccRCC patient samples 18 non-ccRCC patient samples and 18 plasma samples (prooperative and operational day 7) | PLP2               | -                                       | Up-regulation of miR-765 inhibited cell proliferation and metastasis. | (77)   |
| miR-212-5p     | 32 pairs of ccRCC and ANNTs                                             | TBX15              | -                                       | mr-212-5p acted as a tumor suppressor gene in ccRCC.                | (78)   |
| miR-200 family | 23 paired ccRCC tissues and ANNTs and urine samples                     | -                  | -                                       | mr-200c affects the carcinogenic potential of malignant cells.      | (79)   |
| miR-135a-5p    | 96 paired cancer tissues and ANNTs                                       | -                  | -                                       | Expression of miRNA-135a-5p can identify renal carcinogenesis and metachronous metastasis in ccRCCs. | (80)   |
| miR-141        | 20 ccRCC tissues                                                        | ZEB2               | proliferative pathways                  | mr-141 expression in ccRCC decreased cell proliferation.           | (81)   |
| miR-124-3p, -30a-5p and -200c-3p | 87 matched ccRCC tissues                                                  | CAV1 and FLOT1     | -                                       | Up-regulation of all three miRNAs decreased migration and invasion in ccRCC cell lines. | (82)   |
| miR-148a       | 52 paired cancer tissues and ANNTs                                       | AKT2               | Akt pathway                             | Has a role in cell proliferation, colony formation, migration and invasion. | (83)   |
| miR-766-3p     | 75 tumor tissues and 40 normal tissues                                  | SF2                | SF2/P-AKT/P-ERK signaling pathway       | mr-766-3p suppresses cell-cycle progression.                        | (84)   |
| miR-30a-5p     | 40 paired cancer tissues and ANNTs                                       | ZEB2               | -                                       | mr-30a-5p inhibits cell growth, migration and invasion.             | (85)   |
| miR-129-3p     | 69 paired cancer tissues and ANNTs                                       | SOX4, and MMP-2/9  | -                                       | mrR129-3p inhibits migration and invasion in RCC.                  | (86)   |
| miR-99a        | 40 paired cancer tissues and ANNTs                                       | mTOR               | mTOR pathway                            | mr-99a inhibits tumorigenicity and tumor growth, and promotes G1-phase cell cycle arrest. | (87)   |
| miR-203        | 24 paired cancer tissues and ANNTs                                       | HOTAIR             | PTEN pathway                            | mr-203 up-regulation reduces cell proliferation, migration, and invasion and induces apoptosis and cell-cycle arrest. | (88)   |
| miR-145        | 15 paired cancer tissues and ANNTs                                       | ADAM17             | -                                       | mr-145 suppresses proliferation and promotes cell apoptosis in RCC. | (89)   |
| miR-22         | 68 paired cancer tissues and ANNTs                                       | PTEN               | Ras/mitogen-activated protein kinase pathway | mrR-22 inhibits cell proliferation, migration and invasion.        | (90)   |
| miR-217        | 86 paired cancer tissues and ANNTs                                       | HOTAIR, HIF-1α     | HIF-1α/AXL signaling                    | mr-217 reduces proliferation, migration, and EMT and increases apoptosis | (91)   |

(Continued)
| miRNA        | Samples                                                                 | Targets/Regulators            | Signaling Pathways                  | Roles                                                                                                                                                                                                 | Ref  |
|--------------|-------------------------------------------------------------------------|--------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| miR-122-5p   | Serum samples from 68 ccRCC, 47 BRT, and 28 healthy controls            | -                              | -                                   | Serum expression levels of miR-122-5p and miR-206 are biomarkers for patients with ccRCC.                                                                                                             | (92) |
| miR-199a-5p  | 9 paired cancer tissues and ANTTs                                      | TGFBR1 and JunB                | -                                   | miR-199a-5p reduces invasion of ccRCC cells.                                                                                                                                                    | (93) |
| miR-10b      | 9 paired cancer tissues and ANTTs                                      | -                              | -                                   | miR-10b inhibits cell proliferation, invasive ability and migration, and induces cell cycle arrest.                                                                                                  | (94) |
| miR-30c      | 32 paired cancer tissues and ANTTs                                     | Slug                           | -                                   | miR-30c suppresses EMT.                                                                                                                                                                           | (95) |
| miR-372      | 30 paired cancer tissues and ANTTs                                     | IGF 2BP 1                      | -                                   | miR-372 as a tumor suppressor inhibits tumor progression, cell proliferation, cell invasion.                                                                                                       | (96) |
| miR-186      | 20 paired cancer tissues and ANTTs                                     | SENP1                          | NF-κB signaling pathway             | miR-186 Suppresses cell Proliferation and invasion, and induces apoptosis.                                                                                                                          | (97) |
| miR-126      | 264 samples from primary ccRCC and 40 paired samples from ccRCC patients | EGFL7, PIK3CD, VEGF, and PIK3R2 | HIF-1, VEGF, mTOR, and PI3k-Akt signaling pathways | miR-126 reduced cell proliferation and migration in RCC cells.                                                                                                                                       | (98) |
| miR-10b      | 262 paired cancer tissues and ANTTs                                    | PDGFβ, ET3, GRB2, PIK3CA, PIK3R3, CRK, BCL2 and MDM2 | MAPK, Wnt and p53 signaling pathways | miR-10b has prognostic significance in ccRCC and its overexpression is associated with PDF and OS.                                                                                                  | (99) |
| miR-10a-5p, -miR-10b-5p | 156 nephrectomy and 46 kidney biopsy specimens | -                              | -                                   | Levels of miR-10a-5p, -10b-5p may be biomarkers for ccRCC and they were correlated with cancer-specific survival. miR-182-5p inhibits tumorigenicity and enhances apoptosis. | (44) |
| miR-182-5p   | 53 paired cancer tissues and ANTTs                                     | MALAT-1                        | apoptotic pathways                  | miR-182-5p inhibits tumorigenicity and enhances apoptosis.                                                                                                                                       | (99) |
| miR-144-3p   | 120 paired cancer tissues and ANTTs                                    | MAP3K8                         | MAP3K8 pathway                      | miR-144-3p suppresses EMT, viability and metastasis.                                                                                                                                             | (100)|
| MicroRNA:138 | 67 paired cancer tissues and ANTTs                                     | SOX4                           | -                                   | MR-138 inhibits EMT, tumor growth, cell proliferation, migration and invasion.                                                                                                               | (101)|
| miR-192 and miR-194 | 59 normal kidney and 54 tumor specimens; and 38 paired samples from cancer tissues and ANTTs | -                              | -                                   | Two-miRNA combination is a potential predictor of renal cancer in patients.                                                                                                                          | (45) |
| miR-124      | 30 paired cancer tissues and ANTTs                                     | HOTAIR                         | -                                   | miR-124 inhibits RCC cell proliferation and metastasis.                                                                                                                                         | (62) |
| miR-149-5p   | 16 paired cancer tissues and ANTTs                                     | FOXM1                          | -                                   | miR-149-5p suppresses Cell Migration and Inversion through Targeting FOXM1.                                                                                                                       | (102)|
| miR-194      | 234 paired cancer tissues and ANTTs                                    | HIF1A, MDM2,PIK3R2, MAPK1, IGF1R,BCL2, ITGB1, and CRK E-cadheri | HIF-hypoxia pathway, VEGF, mTOR, Wnt, TGF-beta, and MAPK signaling pathways | miR-194 is a biomarker for prognosis in ccRCC.                                                                                                                                                    | (103)|
| miR-429      | 187 paired cancer tissues and ANTTs                                    | ROCK1                          | -                                   | miR-429 inhibits cellular migration and cell motility.                                                                                                                                           | (104)|
| miR-199a     | 150 paired cancer tissues and ANTTs                                     | ROCK1                          | -                                   | MR-199a inhibits cell proliferation, migration and invasion.                                                                                                                                       | (105)|
| miR-106a-5p  | 30 paired cancer tissues and ANTTs                                     | PAK5                           | -                                   | miR-106a-5p inhibits RCC progression and metastasis via PAK5.                                                                                                                                       | (106)|
| miR-129-2    | 48 paired samples from cancer tissues and ANTTs                        | NKIRAS1 RARB2, CHL1 and RHOA  | -                                   | MR-129-2 suppresses ccRCC progression.                                                                                                                                                    | (50)  |
| miR-28-5p and miR-378 | Serum from 107 RCC patients and 107 controls                  | -                              | -                                   | These miRNAs may be diagnostic biomarker for RCC.                                                                                                                                                  | (51)  |
| miR-30a-5p   | 249 cancer tissues and 71 matched normal samples                      | GRP78                          | miR-30a-5p/GRP78 signaling pathway   | miR-30a-5p suppresses the cell growth and induces apoptosis in RCC.                                                                                                                                  | (107)|
| miR-28-5p    | 33 paired cancer tissues and ANTTs                                     | RAP1B                          | p38 and Erk1/2 pathways             | miR-28-5p suppresses the tumorigenesis, cell proliferation, cell migration, and invasion.                                                                                                            | (108)|
| miR-30e-3p   | 8 paired cancer tissues and ANTTs                                     | Snail1                         | -                                   | miR-30e-3p reduces cell invasion and migration.                                                                                                                                                    | (107)|
| miR-492      | 6 paired cancer tissues and ANTTs                                     | -                              | -                                   | miR-492 induces apoptosis and suppresses cell proliferation and invasion.                                                                                                                          | (109)|

(Continued)
TABLE 2 | Continued

| miRNA     | Samples                                      | Targets/Regulators | Signaling Pathways | Roles                                                                 | Ref |
|-----------|----------------------------------------------|--------------------|--------------------|----------------------------------------------------------------------|-----|
| miR-137   | 45 paired cancer tissues and ANTts           | RLIP76             | -                  | miR-137 inhibits cell growth and metastasis, and induces apoptosis.   | (110) |
| miR-144   | 40 paired cancer tissues and ANTts           | MTOR               | PI3K/AKT signaling pathway | miR-144 inhibits cell proliferation and cell viability and promotes cell cycle arrest. | (111) |
| miR-34a, miR-200c and miR-141 | paired serum samples from 30 patients | -                  | -                  | These miRNAs may be useful as diagnostic biomarkers.                      | (58) |
| miR-203   | 90 paired cancer tissues and ANTts           | FGF2               | -                  | miR-203 inhibits cell proliferation, migration and invasion of RCC via inhibiting of FGF2. | (112) |
| hsa-miR-101 | 15 paired cancer tissues and ANTts         | TIGAR              | -                  | hsa-miR-101 increases glycolysis and cell proliferation.               | (113) |
| miR-137   | 50 paired cancer tissues and ANTts           | PI3K, p-AKT        | PI3 K/AKT signaling pathway | miR-137 decreases cell proliferation, migration and invasion, and induces cell apoptosis. | (114) |
| miR-451   | 51 paired cancer tissues and ANTts           | PSMB8              | inflammation pathway | miR-451 promotes cell apoptosis and suppresses cell proliferation and growth of RCC. | (115) |
| miR-497   | 86 paired cancer tissues and ANTts           | -                  | -                  | miR-497 reduces cell proliferation, migration and invasion of RCC.       | (116) |
| miR-375   | 27 paired cancer tissues and ANTts           | YWHAZ              | -                  | miR-375 inhibits cell proliferation, migration, and invasion.           | (117) |
| miR-451   | -                                            | ATF-2              | -                  | miR-451 enhanced drug resistance and cell apoptosis, and reduced cell viability. | (118) |
| miR-381   | 60 paired cancer tissues and ANTts           | -                  | -                  | miR-381 enhances cell apoptosis, and inhibits cell proliferation and chemoresistance. | (119) |
| miR-124   | -                                            | FZD5, P-gp         | Wnt signaling pathway | miR-124 promotes cell apoptosis, and inhibits chemoresistance.           | (120) |

ANTTs, adjacent non-tumoral tissues.

expression of a different set of miRNAs including miR-223, miR-26b, miR-221, and miR-103-1 was increased in bladder cancer samples. Based on these results, authors suggested the potential of miRNAs in differentiating between these two types of cancers (20). However, others have reported over-expression of bladder cancer-related miRNAs such as miR-223 and miR-221 in RCC samples (33, 130) casting doubt on the possibility of identification of tissue-specific miRNA signature in different cancers. Studies which appraised the biomarker role of miRNAs in RCC suffer from small sample size, inclusion of samples from diverse clinical stages and histologic subclasses as well as benign kidney lesions and validation in independent samples. Possibly, the most important limitation of miRNAs as diagnostic markers is their inability for differentiation between malignancies with diverse origins. Based on this limitation, they cannot be used for primary diagnosis of cancer but for patients’ follow-up. Another possible application of miRNAs in the RCC patients rises from their importance in the determination of patients’ response to chemotherapy. Therefore, a prior identification of miRNA profile in the biopsy samples might facilitate selection of the most appropriate therapeutic regimen in a personalized manner. Moreover, targeted suppression of certain miRNAs is a possible modality to enhance response of patients to chemotherapy. miR-21 represents a promising candidate in this regard, since it has been shown to be over-expressed in RCC samples in independent studies and its silencing has enhance response to multiple anti-cancer drugs such as paclitaxel, 5-fluorouracil, oxaliplatin, and dovitinib. Yet, miRNA-based therapies face a number of challenges such as design of specific formulations to avoid off-target effects and low efficacy of delivery methods (131).

Comparison of miRNA levels in serum and tissue samples of RCC patients and healthy subjects has led to identification of several dysregulated miRNAs in serum samples. Yet, only a fraction of these miRNAs have been dysregulated in tissue samples, implying that a minor portion of circulating miRNAs have been originated from the tumor tissues (21). Therefore, future studies are needed to explore the source of circulating miRNAs in RCC patients. Based on the results of recent investigations, both serum and urine samples of patients with RCC might be used as sources for discovery of miRNA levels, facilitating conduction of non-invasive methods for RCC diagnosis.

miRNA signature can be used for classification of RCC subtypes. The miRNA-based classification system developed by Youssef et al. could discriminate different subtypes of RCC such as clear cell, papillary, oncocytoma, and chromophobe RCC with sensitivity values between 97% and 100% (132). Moreover, miR-15a has been shown to have distinct expression pattern between RCC and oncocytoma being up-regulated in the former, yet down-regulated in the latter. Expression of this miRNA was similarly up-regulated in chromophobe carcinoma, while in the papillary RCC samples miR-15a expression was not such over-expressed. Over-expression of miR-15a was also detectable in urine samples of RCC patients. However, miR-15a was almost
| Samples | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Reference |
|---------|-----------------|-------------|-------------|-----------------------|--------------------------|-----------------------------|-----------|
| 96 paired cancer tissues and ANTTs | 0.675 for miRNA-135a-5p | 45.5% | 81.1% | Patients with lower expression of miRNA-135a-5p have higher metachronous metastasis. | Tumor necrosis, pT stage, Fuhrman grade, vascular invasion and lower miRNA-135a-5p levels were correlated with metachronous metastasis. | - | (50) |
| 30 paired cancer tissues and ANTTs | 0.905 for miR-720 | 80% | 100% | Low expression of miR-720 indicated higher OS. | Higher level of miR-124-3p was associated with better OS. | - | (32) |
| 87 paired cancer tissues and ANTTs | - | - | - | Higher level of miR-200c-3p was associated with lower DFS and OS. | - | (82) |
| 75 tumor tissues and 40 normal tissues | - | - | - | Higher level of miR-124-3p was associated with better OS. Higher level of miR-200c-3p was associated with lower DFS and OS. | - | - |
| 30 paired cancer tissues and ANTTs | 0.905 for miR-720 | 80% | 100% | Low expression of miR-720 indicated higher OS. | Higher level of miR-766-3p levels were associated with better 5-year OS. | - | (32) |
| 87 paired cancer tissues and ANTTs | - | - | - | Higher level of miR-124-3p was associated with better OS. Higher level of miR-200c-3p was associated with lower DFS and OS. | - | (82) |
| Plasma samples from 54 RCC patients and 50 healthy individuals | 0.735 for miR-129-3p | 75.9 % | 62.1 % | miR-129-3p expression levels were associated with OS and DFS. | Patients with higher levels of miR-210 and miR-1233 display a significantly lower cancer-specific survival. | - | (98) |
| 148 ccRCC tissue samples along with 60 ANTTs | - | - | - | Patients with high miR-122 levels display a significantly lower metastasis-free survival rates than those with low miR-122 levels. | - | (33) |
| 276 paired cancer tissues and ANTTs | - | - | - | Patients with high miR-122 levels display a significantly lower metastasis-free survival rates than those with low miR-122 levels. | - | (33) |
| Serum samples from 196 RCC patient and 100 healthy persons | 0.85 for combination of miR-378 and miR-210 | 80% for combination of miR-378 and miR-210 | 78% for combination of miR-378 and miR-210 | Patients with high miR-122 expression had a poorer survival rate | High miR-122 level was associated with shorter RFS. | - | (34) |
| Serum samples from 68 ccRCC, 47 BRT, and 28 healthy controls | 0.733 for the combination of miR-122-5p and miR-206 | 60.9% for miR-210, 71.4% for miR-221, 39.1% for miR-1233 | 73.1% for miR-210, 65% for miR-221, 92.6% for miR-1233 | | High miR-122 level is a poor prognostic factor for metastasis | High miR-122 is an independent prognostic factor from gender, age, BMI, overall TNM, tumor size, grade and staging. Fuhrman grade, T stage and miR-125b levels are independent prognostic factors for RFS. | (35) |
| 40 paired cancer tissues and ANTTs | - | - | - | There were correlations between high serum miR-378 expression and clinical stage, and between miR-378 expression and DFS. | Increased miR-122-5p and miR-206 serum levels were associated with lower progression-free, cancer-specific, and OS. | - | (36) |
| | | | | miR-206 expression in serum has independent prognostic value in RCC. | High miR-203a level was associated with higher pathological stage and shorter OS after radical nephrectomy. | High miR-203a level in RCC tissues suggests risk of RCC recurrence. | (92) |

(Continued)
| Samples | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Reference |
|---------|-----------------|-------------|-------------|------------------------|--------------------------|-----------------------------|-----------|
| 264 paired samples from primary ccRCC and 20 paired samples from metastatic ccRCC | - | - | - | miR-126 positivity was correlated with significantly higher DFS and OS. | Higher miR-126 expression associated with higher DFS and OS. | - | (53) |
| 57 paired cancer tissues and ANTTs | - | - | - | miR-221 up-regulation was correlated with a poor PFS. | Patients with overexpressed miR-126 have higher DFS and OS. | - | (43) |
| 262 paired cancer tissues and ANTTs | - | - | - | Overexpression of miR-10a-5p and miR-10b-5p and down-regulation of miR-223-3p were significantly correlated with survival. | High grade, high stage, lower BMI, low miR-10a-5p, low miR-10b-5p, and high miR-223-3p expression were associated with survival. | - | (84) |
| 156 nephrectomy and 48 kidney biopsy specimens | 0.895 for combination of miR-10a-5p, miR-10b-5p, and miR-223-3p | 86.7% for combination of miR-10a-5p, miR-10b-5p, and miR-223-3p | 75% for combination of miR-10a-5p, miR-10b-5p, and miR-223-3p | 97% for miR-182-5p | Low expression of miR-144-3p was significantly correlated with poor survival in RCC patients. | Down-regulation of miR-182-5p was associated with an increase in Fuhrman grade. | (44) |
| 53 paired cancer tissues and ANTTs | 0.954 for miR-182-5p | - | - | - | - | - | (99) |
| 120 paired cancer tissues and ANTTs | - | - | - | - | - | - | (100) |
| 67 paired cancer tissues and ANTTs | - | - | - | - | - | - | (101) |
| 150 normal kidney and 54 tumor specimens; and 38 paired samples from cancer tissues and ANTTs | - | 80% for combination of miR-21 and miR-194 | 97.5% for combination of miR-21 and miR-194 | - | - | - | (45) |
| 234 paired cancer tissues and ANTTs | - | - | - | - | - | - | (49) |
| 137 paired cancer tissues and ANTTs | - | - | - | - | - | - | (49) |
| 123 paired cancer tissues and ANTTs | 0.799 for hsa-miR-27b, 0.793 for hsa-miR-23b and 0.800 for hsa-miR-628-5p | - | - | - | - | - | (49) |
| 284 (264 primary and 20 metastatic ccRCC) | - | - | - | Patients with higher miR-210 expression had significantly lower DFS and OS. | miR-210 was not an independent prognostic marker for survival. | - | (53) |

(Continued)
| Samples | Area under curve | Sensitivity | Specificity | Kaplan-Meier analysis | Univariate cox regression | Multivariate cox regression | Reference |
|---------|-----------------|-------------|-------------|-----------------------|--------------------------|---------------------------|-----------|
| paired cancer tissues and ANTTs | - | - | - | Down-regulation of miR-30a-5p and up-regulation of GRP78 were associated with shorter OS. | miR-30a-5p, TNM stage and grade, were independent prognostic factors for patients’ survival. | miR-30a-5p, TNM stage and grade were independent prognostic factors for patients’ survival. | (107) |
| 249 cancer tissues and 71 ANTTs | - | - | - | | | | |
| 45 paired cancer tissues and ANTTs | - | - | - | Up-regulation of miR-29b was significantly correlated with TNM stage and OS. | OS of ccRCC patients was correlated with miR-203 expression level, tumor stage, lymph node metastasis, and histological grade. | Level of miR-203, tumor stage, lymph node metastasis, and histological grade were independent prognostic factors for OS. | (112) |
| 90 paired cancer tissues and ANTTs | - | - | - | Low level of miR-203 was associated with shorter OS. | | | |
| 15 paired cancer tissues and ANTTs | - | - | - | Down-regulation of miR-210-3p and up-regulation of TWIST1 were correlated with poorer OS and DFS. | | | |
| Serum samples from 82 ccRCC patients and 80 healthy controls | 0.69 for miR-210 | 70% for miR-210 | 62.2% for miR-210 | | | | |
| 51 paired cancer tissues and ANTTs | - | - | - | Down-regulation of miR-451 was associated with poor survival. | Patients with higher miR-18a-5p expression had lower OS compared to patients with lower miR-18a-5p expression. | Down-regulation of miR-18a-5p was associated with better survival. | (115) |
| 42 paired cancer tissues and ANTTs | - | - | - | High expression of miR-18a-5p was associated with poor survival. | The OS of ccRCC patients was correlated with miR-497 expression, histological grade, tumor stage, and lymph node metastases. | miR-497 expression, tumor stage, histological grade, and lymph node metastases were correlated with OS. | (116) |
| 86 paired cancer tissues and ANTTs | - | - | - | Down-regulation of miR-497 was correlated with poor OS. | | | |
| 516 tumor samples and 71 ANTTs | - | - | - | Up-regulation of miR-301a was associated with poor OS. | miR-301a is an independent prognostic marker for RCC patients. | miR-301a is an independent prognostic marker for RCC patients. | (22) |
| 60 paired cancer tissues and ANTTs | - | - | - | Low expression of miR-206 was associated with poor OS. | | | |
| 67 paired ccRCC tissues and ANTTs | - | - | - | Low level of miR-143 was associated with poor OS. | | | |
| 18 clinical ccRCC tissue samples/5 patients with resistant to several tyrosine kinase inhibitor | - | - | - | Low expressions of miR-101-5p and miR-101-3p were correlated with high pathological grade, poor DFS and OS. | | | |
| PRCC (292 tumor tissues and 34 normal) and ccRCC (545 tumor | - | - | - | High expression of miR-1293 was associated with poor OS. | | | |

(Continued)
untraceable in oncocytoma, other tumors, and inflammatory disorders of the urinary tract (133). These results indicate the possibility of substitution of histopathological classification methods by molecular methods. The clinical implications of these findings should be confirmed in larger samples of patients.

Taken together, miRNAs participate in the pathogenesis of RCC and response of patients to diverse therapeutic modalities. Moreover, as they are traceable in circulation and urine samples of patients, they can be used as biomarkers for this kind of cancer. However, at the present time, there is no miRNA that can be widely applied as biomarker or treatment target in the clinical setting. This research filed lacks comprehensive assessment of miRNA profiles in large cohorts of RCC patients. Therefore, future studies with these features are expected to facilitate design of suitable diagnostic panels containing miRNAs.

AUTHOR CONTRIBUTIONS

MT and SG-F wrote the draft and revised it. ZS-F and WB designed the tables and study, and performed the data collection. All authors contributed to the article and approved the submitted version.

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