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A Review of Recent Research on the Role of MicroRNAs in Renal Cancer

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Renal cell carcinoma (RCC) is a most common type of urologic neoplasms; it accounts for 3% of malignant tumors, with high rates of relapse and mortality. The most common types of renal cancer are clear cell carcinoma (ccRCC), papillary renal cell carcinoma (pRCC), and chromophobe renal carcinoma (chRCC), which account for 90%, 6-15%, and 2-5%, respectively, of all renal malignancies. Although surgical resection, chemotherapy, and radiotherapy are the most common treatment method for those diseases, their effects remain dissatisfactory. Furthermore, recent research shows that the treatment efficacy of checkpoint inhibitors in advanced RCC patients is widely variable. Hence, patients urgently need a new molecular biomarker for early diagnosis and evaluating the prognosis of RCC. MicroRNAs (miRNAs) belong to a family of short, non-coding RNAs that are highly conserved, have long half-life evolution, and post-transcriptionally regulate gene expression; they have been predicted to play crucial roles in tumor metastasis, invasion, angiogenesis, proliferation, apoptosis, epithelial-mesenchymal transition, differentiation, metabolism, cancer occurrence, and treatment resistance. Although some previous papers demonstrated that miRNAs play vital roles in renal cancer, such as pathogenesis, diagnosis, and prognosis, the roles of miRNAs in kidney cancer are still unclear. Therefore, we reviewed studies indexed in PubMed from 2017 to 2020, and found several studies suggesting that there are more than 82 miRNAs involved in renal cancers. The present review describes the current status of miRNAs in RCC and their roles in progression, diagnosis, therapy targeting, and prognosis of RCC.

Keywords: Review • Diagnosis • Kidney Neoplasms • MicroRNAs • Prognosis

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Background

Renal cell carcinoma (RCC) is a typical malignant kidney lesion which represents 3% of all malignant tumors and has a high rate of relapse and a mortality rate of over 40%. In the last 20 years, there has been an annual increase of 2% in RCC incidence both worldwide and in Europe, leading to approximately 99 200 new RCC cases and 39 100 kidney cancer-related deaths within the European Union (EU) in 2018 [1]. Clear cell renal cell carcinoma (ccRCC) is the most common renal malignancy and accounts for approximately 90% of all kidney malignancy. Other subtypes, including papillary RCC (pRCC) and chromophobe RCC (chRCC), account for 6-15% and 2-5% of renal cancer cases, respectively [2]. Although modern ultrasound and CT technologies enable the diagnosis of kidney tumors in the early stages, imaging diagnosis does not allow precise differentiation between benign and malignant tumors [3]. Furthermore, laparoscopy and robotic surgery procedures have been developed, and biologic response modifiers have been applied in patients with metastatic RCC. However, the prognosis of terminal cancer cases remains poor, with a 5-year survival rate of 5-10% [4]. Tumor recurrence is mainly due to RCC resistance to chemotherapy and radiotherapy, and 5-10% of ccRCC cases extend into the renal vein or the inferior vena cava (IVC) [5]. Although anti-PD-L1 therapy can improve the overall survival (OS) of RCC patients, a recent study demonstrate that the treatment efficacy of checkpoint inhibitors is widely variable in advanced RCC patients [6]. Therefore, a novel molecular biomarker that can be used for early diagnosis and evaluating the prognosis of RCC, and even serve as a novel therapeutic target, is urgently needed.

MicroRNAs(miRNAs) are a family of short, non-coding RNAs that are highly conserved and have a long half-life, and they have been predicted to regulate numerous protein-coding genes. Mature miRNAs exist as 20-24 nucleotide miRNA duplexes comprising an miRNA guide strand and its complementary passenger strand [7]. The miRNA guide strand is subsequently integrated into the RNA-induced silencing complex (RISC), through which it carries out its regulatory function on target mRNAs. The miRNA-loaded RISC suppresses gene expression by interacting with complementary sequences in the 3' untranslated regions (3'-UTRs) and coding sequences of mRNAs, inducing translational repression [8]. A recent study newly identified ubiquitin ligases as a new type of regulator of target-directed microRNA degradation that can function independently of the trimming and tailing processes, implying that controlling the microRNA decay pathway will become a strategy for treating diseases and cancers [9].

Accumulating evidence has revealed that miRNAs derived from guide strands are pivotal regulators of all hallmarks of cancer, including cell growth and cell cycle control, apoptosis, invasion, and metastasis [10]. Although some previous studies

have illustrated the role of miRNAs in renal cancer, their functions remain unclear [11]. Indeed, a recent study posits that some miRNAs generated from passenger strands, such as miR-144-5p, miR-145-3p, and miR-199a-3p, also induce antitumor effects via their targeting of oncogenes in several cancers [12]. The aim of the present review was to describe miRNAs profile in RCC and their roles in the progression, diagnosis, therapeutic targeting, and prognostication of RCC.

miRNAs Act as Tumor Suppressors in Renal Cancer

RAS/MAPK Signaling Pathway

Accumulated evidence has confirmed that the Ras-Raf-MEK-ERK signaling pathway plays a vital role in the development of cancer [13]. For instance, astrocyte-elevated gene-1 (AEG-1), a downstream gene of Ha-ras, is highly expressed in RCC cells and increases cell growth and invasion, while its effect can be reversed by miR-384 [14]. Another study demonstrated that p21-activated kinase 5 (PAK5), a downstream target of Rho GTPases, is upregulated in renal cancer, and impairs the repression of RCC metastasis induced by miR-106a-5p [15]. Kirsten rat sarcoma viral oncogene (KRAS) and Rho-associated protein kinase 1 (Rock1), which are RAS GTPases, are highly expressed in RCC cells and facilitate tumor progression, whereas these effects can be suppressed by miR-199a and miR-532-5p, respectively. Furthermore, miR-532-5p represses tumor growth and inhibits the expression of P-ERK and ETS1 *in vivo*, and ETS1 act as an oncogene gene in multiple cancers [16,17] (**Table 1**).

The protein level of phosphorylation ERK(p-ERK), which is associated with the MAPK signaling pathway, can be increased by CCL18/LAMA4 and reduced by miR-622/200b in RCC. In addition, high CCL18 and LAMA4 expression in kidney cancer facilitates tumor progression, while its effect can be reversed by miR-622, and C-C motif chemokine 18(CCL18) and laminin subunit alpha-4 (LAMA4) play key roles in tumor progression [18,19]. Furthermore, overexpression of miR-363 impairs tumor growth and decreases the expression of p-ERK, N-cadherin, vimentin, and ZEB1 in ccRCC [20]. Likewise, SKA1 increases the levels of p-ERK1/2 and p-AKT, enhances tumor development, and also decreases the effect of tyrosine kinase inhibitor (TKI) treatment in renal cancer, whereas these effects can be reversed by miR-10a-5p, and spindle and kinetochore-associated protein 1 (SKA1) has been reported to be an oncogene in multiple cancers [21] (**Figure 1**).

PI3K/AKT/mTOR Signaling Pathway

The PI3K/Akt/mTOR signaling pathway is frequently dysregulated in renal cancer [22]. Forkhead box protein M1(FOXM1)

Table 1. miRNAs act as tumor suppressors in renal cancer. A summary of miRNAs name, specimen types, targeted messenger RNAs, functions, and clinical application is provided.

MicroRNA	Specimen	Biological function	Clinical application	Target	Pathways	Ref.
miR-122-5p and miR-206	In serum		liquid biopsy			[3]
miR-144-5p	In vitro	Suppress cell proliferation, migration and invasion	DFS	SDC3		[12]
miR-384	In vitro	Inhibit cell proliferation, colony formation and invasion		AEG-1	RAS signaling pathway	[14]
miR-106a-5p	In vitro and in vivo	Inhibit tumor metastasis	Diagnosis, potential therapeutic target	PAK5	RAS signaling pathway	[15]
miR-532-5p	In vitro and in vivo	Inhibit tumor growth and decrease expression of KRAS, NAP1L1, P-ERK and ETS1		KRAS, NAP1L1 and ETS1	MAPK signaling pathway	[16]
miR-199a	In vitro	Suppress cell proliferation, migration and invasion		ROCK1	RAS signaling pathway	[17]
miR-622	In vitro	Suppress cell migration and invasion and decrease levels of P-ERK		CCL18	MAPK signaling pathway	[18]
miR-200b	In vitro and in vivo	Inhibit tumor metastasis and decrease levels of P-ERK		LAMA4	MAPK signaling pathway	[19]
miR-363	In vitro and in vivo	Suppress cell proliferation, migration and invasion, decrease level of STAT3, JAK2, VEGF, p-STAT3/JAK2/ERK, PDGF-A/B, N-cadherin, vimentin and ZEB1		GHR, S1PR1	MAPK/VEGF signaling pathway	[20, 38]
miR-10a-5p	In vitro	Suppresses cell proliferation, migration and invasion, reduce p-ERK1/2, AKT, FAK and SRC	Potential therapeutic target	SKA1	MAPK and AKT signaling pathway	[21]
miR-149	In vitro	Inhibit cell migration, invasion and proliferation		FOXM1	PI3K/AKT signaling pathway	[23]
miR-320a	In vitro and in vivo	Reduce tumor growth	OS, diagnosis	FoxM1	PI3K/AKT signaling pathway	[24]
miR-338-3p	In vitro	Increase cell proliferation and invasion		p-AKT and PI3K	PI3K/AKT signaling pathway	[25]
miR-15a	In vitro	Inhibit cell proliferation, invasion and induce apoptosis, decrease expression of P13K, p-AKT, mTOR, cyclin D1, cyclin E, Bax, c-Myc and MMP3		eIF4E	P13K/AKT/mTOR signaling pathway	[26]
miR-488	In vitro and in vivo	Reduce tumor growth and decrease expression of N-cadherin, vimentin, p-AKT, p-mTOR, and P13K	Potential therapeutic target	HMGNS	P13K/AKT/mTOR signaling pathway	[27]

Table 1 continued. miRNAs act as tumor suppressors in renal cancer. A summary of miRNAs name, specimen types, targeted messenger RNAs, functions, and clinical application is provided.

MicroRNA	Specimen	Biological function	Clinical application	Target	Pathways	Ref.
miR-520c-3p/ 372-3p/373-3p	In vitro and in vivo	Decrease tumor growth, metastasis and increase the expression of E-cadherin and PTEN		SPOP	PI3K/AKT signaling pathway	[28]
miR-203	In vitro and in vivo	Decrease tumor growth, metastasis and increase the expression of E-cadherin, PTEN, p21 and p27			PI3K/AKT signaling pathway	[29]
miR-148a	In vitro and in vivo	Reduce tumor growth and decrease p-Akt/mTOR, improve sensitivity to TRAIL and cisplatin	Potential therapeutic target	AKT2 and Rab14	AKT signaling pathway	[30, 31]
miR-766-3p	In vitro and in vivo	Reduce tumor growth and decrease P-AKT and P-ERK	OS	SF2	AKT and MAPK signaling pathway	[32]
miR-375	In vitro	Inhibits cell proliferation, migration and invasion, while induce cell apoptosis		PDK1		[33]
miR-100	In vitro	Inhibit cell invasion, migration and increase autophagy, reduce expression of mTOR, MMP-2 and MMP-9, whereas improve level of LC3 and LC3-II/LC3-I		NOX4	mTOR signaling pathway	[34]
miR-205-5p	In vitro and in vivo	Repress tumor growth, inhibit expression of p-PI3K/Akt/-mTOR, increase sensitivity of cell to sunitinib, paclitaxel, 5-FU and oxaliplatin	OS, potential therapeutic target	VEGFA	VEGFA and PI3k/AKT signaling pathway	[36]
miR-299	In vitro and in vivo	Suppress tumor growth and inhibit expression of vimentin and N-cadherin		VEGF	VEGF signaling pathway	[37]
miR-218	In vitro and in vivo	Decreases the expression of VEGFA, p-PI3K/p-Akt/p-mTOR diminish tumor angiogenesis	OS	GAB2	VEGFA and PI3k/AKT/mTOR signaling pathway	[39]
miR-125a-3p	In vitro	Inhibit the expression of VEGF and tube numbers formed by HUVECs	OS, DFS	VEGF	VEGF signaling pathway	[122]
miR-148b-3p	in vitro and in vivo	Suppress tumor growth, tube formation of HUVECs and inhibit expression of HIF-1a, VEGF-A, PDGF-BB, and PDGF-D		FGF2	VEGF signaling pathway	[41]
miR-486-5p	in vitro	Inhibit cell proliferation and induce apoptosis, decrease apoptosis resistance induced by CCL2		TAK1	TGF- β signaling pathway	[43]

Table 1 continued. miRNAs act as tumor suppressors in renal cancer. A summary of miRNAs name, specimen types, targeted messenger RNAs, functions, and clinical application is provided.

MicroRNA	Specimen	Biological function	Clinical application	Target	Pathways	Ref.
miR-328	In vitro	Inhibit cell proliferation		ITGA5	TGF- β signaling pathway	[44]
miR-186	In vitro	Inhibit cell proliferation, invasion and induce apoptosis, decrease level of p-IkBa and p-p65		SENP1	NF- κ B signaling pathway	[46]
miR-765	In vitro	Suppress tumor growth and inhibit expression of VEGFA and Ki67 and eliminate lipids accumulation		PLP2	Metabolic related mechanism	[48]
miR-409-3p	In vitro	Decrease cell extracellular acidification rate, ATP production and increased oxygen consumption rate		PDK1	Metabolic related mechanism	[50]
miR-497-5p	In vitro	Inhibit cell proliferation, migration and increase apoptosis	OS	PD-L1	Immunity related mechanism	[51]
miR-216a	In vitro and in vivo	Reduce tumor growth		TLR4	Immunity related mechanism	[52]
miR-211-5p	In vitro and in vivo	Decrease tumor growth and metastasis	DFS, potential therapeutic target	SNAI1	EMT program	[58]
miR-124/203	In vitro	Inhibit cell proliferation and migration		ZEB2	EMT program	[59]
miR-101-5p	In vitro	Inhibit cell proliferation, invasion and induce apoptosis		slug	EMT program	[60]
miR-490-3p	In vitro and in vivo	Inhibit tumor growth and metastasis, decrease VM formation		TR4		[61]
miR-32-5p	In vitro and in vivo	Inhibit tumor metastasis and repress expression of TR4, HGF and p-Met		TR4		[62]
miR-451a	In vitro	Suppresses cell migration and invasion		PMM2		[121]
miR-200a-3p	In vitro and in vivo	Suppress tumor growth		CBL		[54]
miR-182-5p	In vitro and in vivo	Inhibit tumor growth and metastasis, increase expression of P53				[56]
miR-376b-3p	In rcc tissues		PFS, diagnosis			[101]
miR-9-5p	In rcc tissues		Diagnosis			[102]
miR-10a-5p/10b-5p/106a-5p/142-5p	In rcc tissues		Diagnosis			[107]

Table 1 continued. miRNAs act as tumor suppressors in renal cancer. A summary of miRNAs name, specimen types, targeted messenger RNAs, functions, and clinical application is provided.

MicroRNA	Specimen	Biological function	Clinical application	Target	Pathways	Ref.
miR-1208	In vitro	Inhibits cell proliferation and promote apoptosis, sensitizes cisplatin-induced apoptosis and TRAIL-induced apoptosis	Potential therapeutic target	TBCK		[111]
miR-99a-3p	In vitro	Inhibit cell proliferation and facilitate apoptosis, induce S phase arrest and increase sunitinib sensitivity	Potential therapeutic target	RRM2		[112]
miR-126	In vitro	Decrease cell migration and lactate production, inhibit expression of p-mTOR, and sensitize the cancer cells to cisplatin or X-ray treatment	Potential therapeutic target	SERPINE1	mTOR signaling pathway	[113]
miR-378a-5p	In vitro	Inhibit cell proliferation, migration, invasion and promote apoptosis	OS			[119]
miR-31-5p	In vitro	Suppress cell proliferation, migration and invasion	OS	CDK1		[120]
miR-22/24/99a/ 194/214/ 335/339/708			Biomarker			[6]

miRNAs – microRNAs; DFS – disease-free survival; SDC3 – syndecan-3; AEG – 1-astrocyte-elevated gene-1; RAS – rat sarcoma; PAK5 – p21-activated kinase 5; KRAS – Kirsten rat sarcoma viral oncogene; p-ERK – phosphorylate extracellular signal regulated kinase; ETS1 – E26 transformation-specific-1; MAPK – mitogen-activated protein kinases; ROCK1 – Rho-associated coiled-coil-forming protein kinase 1; CCL18/2 – C-C motif chemokine 18/2; LAMA4 – laminin subunit alpha-4; STAT3 – signal transducer and activator of transcription 3; JAK2 – Janus kinases 2; VEGF – vascular endothelial growth factor; PDGF – platelet-derived growth factor; ZEB1 – zinc finger E-box binding homeobox 1; GHR – growth hormone receptor; S1PR1 – sphingosine-1-phosphate receptor 1; AKT – protein kinase B; FAK – focal adhesion kinase; SKA1 – spindle and kinetochore-associated protein 1; FOXM1 – forkhead box M1; OS – overall survival; PI3K – phosphatidylinositol 3-kinase; mTOR – mammalian target of rapamycin; MMP3 – matrix metalloproteinase-3; eIF4E – eukaryotic initiation factor 4E; HMGN5 – high-mobility group nucleosome binding domain 5; PTEN – phosphatase and tensin homolog deleted on chromosome 10; SPOP – speckle-type POZ protein; TRAIL – tumor necrosis factor-related apoptosis inducing ligand; Rab14 – ras-related protein 14; SF2 – splicing factor 2; PDK1 – phosphoinositide-dependent kinase 1; NOX4 – NADPH oxidase 4; LC3 – microtubule-associated protein 1 light chain 3; GAB2 – GRB2-associated binding protein 2; HUVECs – human umbilical vein endothelial cells; FGF2 – fibroblast growth factor 2; TAK1 – TGF-beta-activated kinase 1; ITGA5 – integrin alpha5; SENP1 – sentrin specific peptidase1; PLP2 – proteolipid protein 2; PD-L1 – programmed death ligand 1; TLR4 – toll-like receptor 4; SNAI1 – snail family transcriptional repressor 1; TR4 – testicular nuclear receptor 4; VM – vasculogenic mimicry; HGF – hepatocyte growth factor; PMM2 – phosphomannomutase 2; CBL – casitas B-lineage lymphoma; PFS – progression-free survival; TBCK – TBC1-domain-containing kinase; RRM2 – ribonucleotide reductase regulatory subunit m2; SLC7A5 – solute carrier family 7 member 5; HIF1a/2a – hypoxia inducible factor 1a/2a; SERPINE1 – serine protease inhibitor clade E member 1.

belongs to the Forkhead box family, which is a downstream target of the PI3K/Akt pathway. FOXM1 is highly expressed in RCC and enhances tumor development, and these effects can be reversed by miR-149 and miR-320a [23,24]. The expression of PI3K and Akt can be downregulated by miR-338-3p, miR-15a, and miR-488 or upregulated by KIFC (Kinesin family member C1), eIF4E (eukaryotic initiation factor 4E), and HMGN5 (High-mobility group nucleosome binding domain 5) in RCC. In addition, overexpression of miR-338-3p, miR-15a, and miR-488 leads to repression of renal cancer progression induced by KIFC1, eIF4E, and HMGN5, respectively. KIFC1, eIF4E,

and HMGN5 have been reported to act as oncogenes in various cancers [25-27]. Moreover, the expression of PTEN, which is a master regulator of the PI3K/Akt pathway, could be augmented by miR-520/372/373 and miR-203 or diminished by SPOP in RCC. Overexpression of miR-520/372/373 results in attenuated renal tumor development by impairing SPOP, and speckle-type POZ protein (SPOP) has been reported to act as an oncogene in renal cancer [28,29] (**Table 1**).

AKT2 belongs to the Akt family, is highly expressed in RCC, and abolishes the inhibition of cell growth and mobility induced by

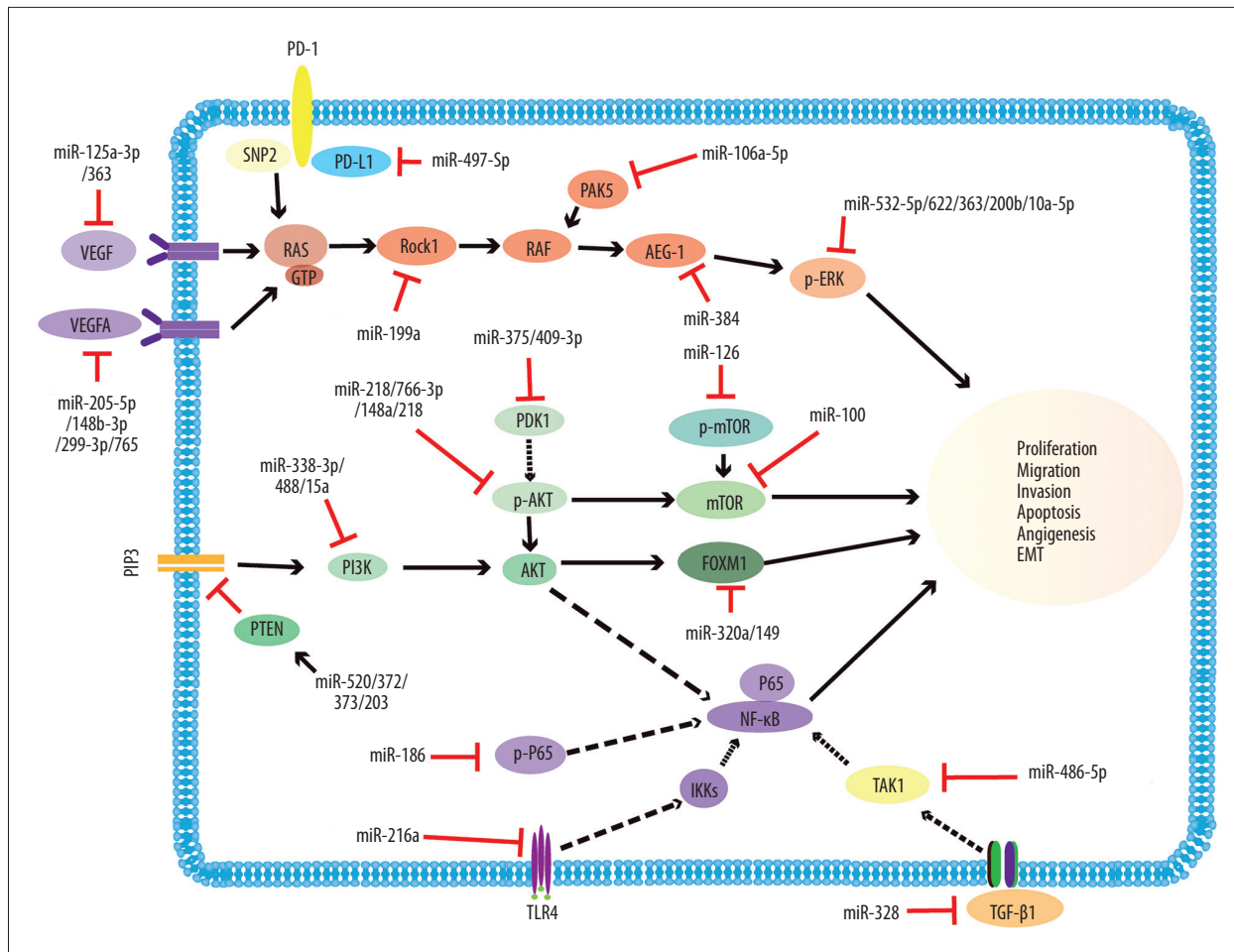


Figure 1. Representative diagram of miRNAs acting as tumor suppressors, and their associated signaling pathways in renal cancer. The drawing mainly illustrates that miR-125a-3p/363 and miR-205-5p/148b-3p/299-3p/765 inhibit the VEGF and VEGFA signaling pathways through decreasing the expression of VEGF and VEGFA, respectively. miR-199a, miR-106a-5p, miR-384, and miR-532-5p/622/363/200b/10a-5p restrain RAS/MAPK signaling pathways by decreasing the levels of Rock1, PAK5, AEG-1, and p-ERK, respectively. Furthermore, miR-338-3p/488/15a, miR-218/766-3p/148a/218, miR-375/409-3p, miR-126, miR-100, and miR-320a/149 influence the PI3k/AKT/mTOR signaling pathways by decreasing the levels of PI3k, p-AKT, PDK1, p-mTOR, mTOR, and FOXM1, respectively. In contrast, miR-520/372/373/203 increases the expression of PTEN and exerts the same effect. miR-328 and miR-486-5p inhibit the TGF- β signaling pathways through decreasing the expression of TGF- β 1 and TAK1, respectively. miR-186 and miR-216a influence NF- κ B signaling pathways by decreasing the levels of p-p65 and TLR4, respectively. In addition, miR-497-5p targets PD-L1, thus influencing immunity-related mechanisms. VEGF – vascular endothelial growth factor; Rock1 – Rho-associated coiled-coil-forming protein kinase; PAK5 – p21-activated kinase 5; AEG-1 – AEG-1-astrocyte-elevated gene-1; p-ERK – phosphorylate extracellular signal regulated kinase; PI3k – phosphatidylinositol 3-kinase; p-AKT – p-protein kinase B; PDK1 – phosphoinositide-dependent kinase 1; mTOR – mammalian target of rapamycin; FOXM1 – forkhead box M1; PTEN – phosphatase and tensin homolog deleted on chromosome 10; TGF- β 1 – transforming growth factor- β 1; TAK1 – TGF-beta-activated kinase 1; PLP2 – proteolipid protein 2; INF; TLR4 – toll-like receptor 4; PD-L1 – programmed death ligand 1.

miR-148a. In addition, miR-148a decreases the p-Akt and mTOR levels in renal cancer and boosts the expression of TRAIL (tumor necrosis factor-related apoptosis inducing ligand) and increases the drug sensitivity of RCC cells to cisplatin by regulating Rab14, Rab14 (Rab14 GTPase) as a member of the RAS oncogene family [30,31]. Additionally, the expression of P-Akt and P-ERK can be improved by splicing factor 2 (SF2) and reduced

by miR-766-3p in RCC. Overexpression of miR-766-3p leads to suppression of tumor growth by regulating SF2, and SF2 belongs to the splicing factor family and promotes carcinoma formation [32]. Furthermore, PDK1 (phosphoinositide-dependent kinase 1), an important molecule in the Akt pathway, is also highly expressed in kidney cancer cells and increases cell proliferation, while its effect can be reversed by miR-375 [33].

Interestingly, miR-100 attenuates the expression of mTOR and NOX4, and augments the levels of LC3 and LC3-II/LC3-I in RCC, consequently impairing the aggressiveness of RCC cells and improving autophagy. NOX4 (NADPH Oxidase 4) and LC3 (microtubule-associated protein 1 light chain 3) act as vital regulators of autophagy [34] (**Figure 1**).

VEGF Signaling Pathway

Vascular endothelial growth factor (VEGF), a cytokine secreted by tumor cells, plays a pivotal role in tumor development [35]. For example, VEGFA is highly expressed in RCC and enhances tumor progression, while this effect can be reversed by miR-205-5p and miR-299-3p. miR-205-5p increases the sensitivity of RCC cells to sunitinib, paclitaxel, 5-FU, and oxaliplatin by downregulating the levels of VEGFA and p-PI3K/p-Akt/p-mTOR [36,37]. Another study showed that the expression of VEGF is upregulated by GHR, which boosts tumor mobility of RCC cells, whereas these effects can be reversed by miR-363, and GHRH was verified to be positively correlated with the proliferation of renal cell carcinoma [38]. Similarly, miR-218 not only decreases the expression of VEGFA and p-PI3K/p-Akt/p-mTOR and restrains the migration ability of HUVECs (human umbilical vein endothelial cells), but also diminishes tumor angiogenesis in RCC by downregulating GRB2-associated binding protein 2 (GAB2). GAB2 is an important member of the Gabs family and acts as an oncogene in multiple cancers [39]. Previous evidence has shown that FGF (fibroblast growth factor) and VEGF play equal roles in angioblast induction and migration during vascular development [40]. Indeed, FGF2 augments the tube formation and invasion of HUVECs in RCC, but its effect can be reversed by miR-148b-3p. In addition miR-148b-3p impairs the expression of VEGF-A and platelet-derived growth factor-BB/D (PDGF-BB/D) in RCC, and PDGF-BB/D act as pro-angiogenic actors in multiple cancers [41] (**Table 1**).

TGF- β /NF- κ B signaling pathway

The Transforming growth factor- β (TGF β) and nuclear factor kappa B (NF- κ B) pathways play pivotal roles in renal disease [42]. Indeed, TAK1 is highly expressed in RCC and increases tumor progression, while its effect can be reversed by miR-486-5p, and TGF-beta-activated protein kinase 1 (TAK1) is a critical regulator of the TGF-beta pathway [43]. Another study showed that TGF- β 1 promotes tumor development by inhibiting miR-328, thus enhancing the expression of integrin α 5 (ITGA5). miR-328 reduces cell proliferation of RCC cells by downregulating ITGA5, and ITGA5 belongs to the integrin family [44]. Interestingly, SNIP1 (Smad nuclear interacting protein 1) can negatively regulate the transcription of the NF- κ B signaling pathways [45]. Indeed, the expression of p-IkBa and p-p65, which are components of the NF- κ B signaling pathways, can be boosted by SENP1 and impaired by miR-186 in renal cancer.

In addition, miR-186 suppresses RCC cell progression by targeting SENP1 in vitro [46] (**Figure 1**).

Metabolism/Immunity-Related Mechanism

Metabolic changes in the tumor micro-environment, inhibit the antitumor immunity by producing immunosuppressive metabolites [47]. For example, PLP2 high expression in ccRCC promotes tumor growth and mobility, and increases the expression of VEGFA and enhances lipid accumulation, while this effect can be reversed by miR-765. PLP2 is a novel member of the Cd-up-regulated genes and has been reported to act as an oncogene in breast cancer [48]. Previous research has shown that RCC cells, like multiple other types of cancers cells, have aberrant HIF stabilization and are dependent on aerobic glycolysis for ATP production [49]. Indeed, PDK1 high expression in ccRCC cells boosts ECAR (extracellular acidification rate) under hypoxic conditions, improves ATP production, and diminishes the oxygen consumption rate (OCR) of tumor cells, whereas these effects can be reversed by miR-409-3p [50]. Tumor immune escape is a common topic of research and is a hallmark of cancer. For instance, PD-L1, a ligand of PD-1 (Programmed death 1), is overexpressed in renal cancer and facilitates tumor progression, but its effect can be reversed by miR-497-5p [51]. Furthermore, Toll-like receptors (TLRs) mediate the innate immune response, which has been shown to participate in tumor development; for example, miR-216a suppresses RCC growth in vitro and in vivo by targeting TLR4 [52] (**Table 1**).

Other Mechanisms

Depending on its specific substrate, an E3 ligase can either promote or inhibit cancer development. For example, Cbl, a RING finger E3 ubiquitin ligase, has been identified as a critical regulator of cancer metastasis [53], and is overexpressed in RCC, which boosts tumor progression by downregulating miR-200a-3p [54]. E3 ubiquitin ligases usually retain an p53 inactive state in multiple cancers [55], whereas miR-182-5p causes cell cycle arrest at the G2/M phase, thus repressing ccRCC progression by upregulating p53 [56]. The abnormal activation of transcription factors promotes the proliferation and differentiation of tumor cells [57]. For instance, snail family transcriptional repressor 1 (SNAIL1), zinc finger E-box binding homeobox 2 (ZEB2), and slug, as transcription factors related to EMT, are highly expressed in RCC and increase tumor development, while their effects can be reversed by miR-211-5p, miR-124/miR-203, and miR-101-5p, respectively [58-60]. Another study showed that testicular nuclear receptor 4 (TR4) promotes vasculogenic mimicry (VM) formation and metastasis of ccRCC and augments the expression of vimentin, whereas these effects can be reversed by miR-490-3p and miR-32-5p, respectively [61,62]. TR4 is a transcriptional factor and is positively associated with the progression of prostate cancer [63] (**Table 1**).

miRNAs Act as Oncogenes in Renal Cancer

mTOR/Metabolic Pathway

Mammalian target of rapamycin (mTOR) is a protein kinase regulating cell growth and metabolism in various cancers [64]. miR-92b-3p decreases the protein expression of TSC complex subunit 1 (TSC1) and increases the phosphorylation of p70S6 kinase, which is downstream of TSC1, consequently activating the mTOR pathway and promoting ccRCC progression. TSC1 is an inhibitor of mTORC1 [65]. Another study demonstrated that overexpression of miR-501-5p increases cell autophagy through activating p-mTOR, leading to p53 degradation in renal cancer, thus facilitating tumor progression of RCC [66]. Recent research suggests that IMPA2 (inositol monophosphatase 2) leads to decreasing p-mTORC1 levels in ccRCC cells, and thus could be a biomarker for guiding the use of mTOR inhibitors to combat metastatic ccRCC in clinical practice [67]. Indeed, IMPA2 under-expression in ccRCC diminishes the expression of N-cadherin and Slug, and sabotages tumor metastasis by downregulating miR-25-3p [68]. Dysregulated cellular energetics is one of the hallmarks of RCC and of multiple cancers [47]. For example, up-regulation of the pentose phosphate pathway (PPP) is a key feature of the dysregulated metabolism of RCC cells, but G6PD is a rate-limiting enzyme of the PPP, and its inhibition attenuates the survival of RCC cells. Furthermore, upregulation of miR-146a-5p increases the expression of G6PD and transketolase (TKT), facilitating proliferation of RCC cells [69] (Table 2).

PI3K/AKT Signaling Pathway

The PI3K/Akt pathway is commonly mutated and highly activated in RCC, representing a tumorigenic characteristic [70]. The expression of p-PI3K and p-Akt is upregulated by miR-193a-3p and miR-224 and downregulated by ST3GalIV in RCC. miR-193a-3p and miR-224 promote tumor progression by targeting ST3GalIV (alpha-2,3-SialyltransferaseIV). ST3GalIV can catalyze the synthesis of α -2,3-sialic acid on the cell surface, which is closely related to tumor metastasis potential [71]. Another study demonstrated that the level of p-PTEN was improved by FRK (Fyn-related kinase) because it is a substrate of FRK, but this effect can be impaired by miR-19 in ccRCC. In addition, miR-19 overexpression facilitates cell proliferation of renal cancer by modifying FRK and PTEN [72]. FOXO3 belongs to the Forkhead box family, which is downstream of the PI3K-Akt signaling pathway; it shows high expression in ccRCC and is negatively regulated by miR-122. Overexpression of miR-122 promotes tumor development and increases the expression of E-cadherin in kidney cancer [73]. Intriguingly, BTG3 (B-cell translocation gene 3) diminishes p-Akt levels and acts as a tumor suppressor in prostate cancer cells [74]. Indeed, BTG3 inhibits RCC cell proliferation by negatively mediating miR-142-5p [75] (Figure 2).

TGF- β /Wnt Signaling Pathway

TGF- β and Wnt regulate numerous developmental events and participate in the development of numerous cancers [76]. For example, SMAD family member 4 (SMAD4) is a critical component of TGF- β signaling and low expression in RCC, and suppresses tumor metastasis in vitro, while its effect can be reversed by miR-452-5p. In addition, miR-452-5p impairs sensitivity of renal cancer cells in TKI treatment by regulating SMAD4 [77]. BMPR1B (bone morphogenetic protein receptor type 1B) is a member of the TGF- β superfamily, and participates in the progression of numerous cancers [78]. Similarly, miR-1274a increases cell proliferation and decreases apoptosis of ccRCC by downregulating BMPR1B [79]. Previous evidence has verified that Dickkopf1 (DKK1) and DKK3 belong to the extracellular Wnt inhibitor family and act as tumor suppressors in renal cancer [80,81]. Likewise, miR-543 and miR-125b facilitate tumor growth through negatively regulating DKK1 and DKK3, respectively, in RCC. In addition, overexpression of miR-125b leads to decreasing sensitivity to doxorubicin and sunitinib in renal cancer cells [82,83] (Figure 2).

NF- κ B signaling pathway

The protein levels of NF- κ B (p65) and TRAF6 are decreased by miR-146b-5p in renal cancer. In addition, miR-146b-5p increases tumor growth by regulating TRAF6 (TNF receptor associated factor 6) and impairs the serum level of IFN- γ . TRAF6 is a signal transducer in the NF- κ B pathway, and IFN- γ has been applied to treat patients with ovarian cancer [84]. Interestingly, KLF6 reduces the localization of p65 and inhibits cancer progression in glioblastoma [85]. Likewise, overexpression KLF6 increases the level of p21 and represses tumor progression in ccRCC, while its effect can be reversed by miR-543 [86], and p21 has been confirmed inactivate the NF- κ B pathway in prostate cancer [87]. Previous evidence suggested that TNF induced cell apoptosis and necroptosis by deactivating the NF- κ B pathway [88]. In contrast, miR-381-3p inhibits TNF-induced apoptosis and necroptosis through downregulating caspase-8, caspase-3, and RIPK3 (receptor-interacting protein kinase 1) in renal cancer, whereas it has no effect on TNF-induced NF- κ B activation, thus facilitating tumor progression and implying a poor outcome for papillary RCC patients; these findings suggest that the NF κ B pathway has different functions in different cells. RIPK3 is a key regulatory protein for programmed cell necroptosis [89] (Figure 2).

RAS/MAPK Signaling Pathway

The expression of KRAS can be attenuated by solute carrier family 4 (SLC4A4) and increased by miR-223-3p in ccRCC. In addition, SLC4A4 restrains ccRCC cell progression by targeting KRAS, whereas its effect can be reversed by miR-223-3p.

Table 2. miRNAs act as oncogenes in renal cancer. A summary of miRNAs name, specimen types, targeted messenger RNAs, functions and clinical application is provided.

MicroRNA	Specimen	biological Function	clinical application	Target	Pathways	Refs.
miR-154-5p	In vitro	Promote cell proliferation, migration, invasion and inhibit apoptosis	OS			[2]
miR-92b-3p	In vitro	Promote cell proliferation, migration and invasion, decrease expression of TSC1 and enhance p-p70S6 kinase	OS	TSC1	mTOR signaling pathway	[65]
miR-501-5p	In vitro and in vivo	Increase cell autophagy, growth, migration and activate mTOR kinase			mTOR signaling pathway	[66]
miR-25-3p	In vitro	Enhance cell migration and increase expression of N-cadherin and Slug	OS	IMPA2		[68]
miR-146a-5p	In vitro	Increase cell proliferation and improve expression of G6PD and TKT			Metabolic related mechanism	[69]
miR-193a-3p and -224	In vitro	Promote cell proliferation, invasion, migration and inhibit apoptosis, improve expression of PI3k and p-Akt		ST3GalIV	PI3K/Akt signaling pathway	[71]
miR-19	In vitro	Enhance cell proliferation and inhibit expression of FRK and PTEN		FRK and PTEN	PI3K/Akt signaling pathway	[72]
miR-122	In vitro and in vivo	Promote tumor growth, enhance expression of ZEB1 and ZEB2, p-Erk1/2 and p38	PFS	FOXO3 and occludin	PI3K/Akt, MAPK signaling pathway	[73, 91]
miR-142-5p	In vitro	Increase cell proliferation and migration		BTG3		[75]
miR-452-5p	In vitro and in vivo	Enhance tumor metastasis	OS, target	SMAD4	TGF- β signaling pathway	[77]
miR-1274a	In vitro	Promote cell proliferation and inhibit apoptosis		BMPR1B		[79]
miR-543	In vitro and in vivo	Facilitate tumor growth, metastasis and increase expression β -catenin and p-GSK-3 β , while inhibit expression of p21		DKK1, KLF6	Wnt signaling pathway	[82, 86]
miR-125b	In vitro and in vivo	Promote tumor growth and metastasis, inhibit sensitivity of cells to doxorubicin and sunitinib		DKK3	Wnt signaling pathway	[83]
miR-146b-5p	In vitro and in vivo	Inhibit expression of p65 and TRAF6		TRAF6	NF- κ B signaling pathway	[84]
miR-381-3p	In vitro	Inhibit TNF-induced cell apoptosis and necroptosis	OS	RIPK3		[89]
miR-223-3p	In vitro	Promote cell proliferation, migration, invasion and increase expression of KRAS	OS	SLC4A4	RAS signaling pathway	[90]

Table 2 continued. miRNAs act as oncogenes in renal cancer. A summary of miRNAs name, specimen types, targeted messenger RNAs, functions and clinical applicants is provided.

MicroRNA	Specimen	biological Function	clinical application	Target	Pathways	Refs.
miR-21	In vitro and in serum	Increase cell proliferation, invasion, migration and reduce apoptosis, decrease expression of p53 and p21, Bax, cyclin E2, VEGFA and p-c-Jun	Diagnosis, target	PTEN, PDCD4	PI3K/AKT and NF-κB signaling pathway	[8,93,94]
miR-204-5p	In urine/mice/RCC tissues		Liquid biopsy			[96]
miR-301a-3p and -1293	In plasma		Liquid biopsy			[97]
miR-19b-3p	In vitro and in exosomes	Enhance cell migration and invasion, while impair expression of E-cadherin and PTEN	Diagnosis			[99]
miR-130b/18a/223	In RCC tissues		Diagnosis			[108]
miR-15a/182/138/200c/16/210/34a/155	In RCC tissues		Diagnosis			[104]
miR-3199-2/1293	In RCC tissues		Diagnosis			[105]
miR-21/142/150/155	In RCC tissues		Diagnosis			[106]
miR-489-3p/630	In vitro	Promote cell proliferation and chemoresistance to oxaliplatin		OCT2		[110]
miR-720	In vitro and in vivo	Promote tumor growth	OS, diagnosis	E-cadherin and αE-catenin		[118]
miR-23a-3p	In vitro	Promote cell proliferation, migration and invasion, while inhibit apoptosis	OS	PNRC2		[117]
miR-572	In vitro	Promote cell proliferation, migration, invasion and inhibit cell apoptosis	OS			[4]
miR-221-5p	In vitro	Promote cell proliferation, migration, invasion and inhibit apoptosis	OS			[114]
miR-566	In vitro	Promote cell proliferation, migration, invasion and inhibit apoptosis	OS			[115]
miR-663a	In vitro	Promote cell proliferation, invasion, migration and inhibit apoptosis	OS			[116]
miR-155-5p/210-3p	In RCC tissues		Biomarker of recurrence			[123]

OS – overall survival; TSC1 – tuberous sclerosis complex subunit 1; mTOR – mammalian target of rapamycin; IMPA2 – myo-inositol monophosphatase 2; G6PD – glucose-6-phosphate dehydrogenase; TKT – transketolase; ST3GalIV – alpha-2,3-sialyltransferase IV; PI3K – phosphatidylinositol 3-kinase; AKT – protein kinase B; FRK – fyn-related kinase; PTEN – phosphatase and tensin homolog deleted on chromosome 10; ZEB1 – zinc finger E-box binding homeobox 1; Erk – extracellular signal regulated kinase; PFS – progression-free survival; FOXO3 – forkhead box O3; BTG3 – B-cell translocation gene 3; TGF-β – transforming growth factor-β; SMAD4 – SMAD family member 4; BMPR1B – bone morphogenetic protein receptor type 1B; DKK1/3 – Dickkopf1/3; KLF6 – Kruppel-like factor 6; TRAF6 – TNF receptor associated factor 6; RIPK3 – receptor-interacting protein kinase 1; SLC4A4 – solute carrier family 4; PDCD4 – programmed cell death 4; VEGFA – vascular endothelial growth factor A; OCT2 – octamer binding transcription factor 2; pncr2 – proline-rich nuclear receptor co-activator 2.

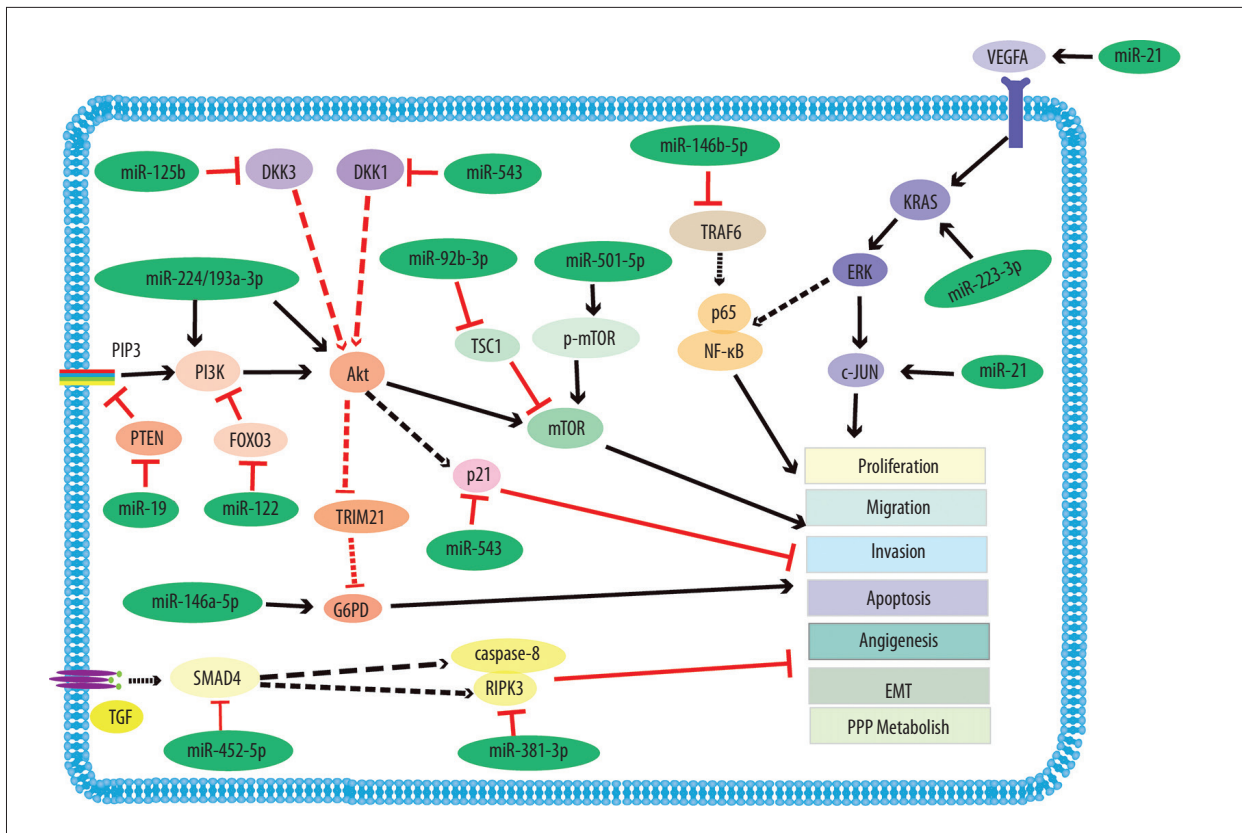


Figure 2. Representative diagram of miRNAs acting as oncogenes and their correlation with signaling pathways in renal cancer. The picture mainly demonstrates that miR-224/193a-3p and miR-501-5p improve PI3K/AKT and mTOR signaling pathway through increasing the level of PI3K, AKT, and p-mTOR, respectively. On the contrary, miR-19, miR-122, and miR-92b-3p inhibit the expression of PTEN, and FOXO3 and TSC1 exert the same effect. miR-21 and miR-223-3p facilitate the VEGF and RAS/MAPK signaling pathway by augmenting the levels of VEGFA/c-jun and KRAS, respectively. Moreover, miR-125b and miR-543 increase the Wnt signaling pathway by decreasing the expression of DKK3 and DKK1, respectively. miR-452-5p activates the TGF-β signaling pathway by decreasing the expression of SMAD4. In addition, miR-146a-5p and miR-146b-5p target G6PD and TRAF6, and thus are involved in PPP metabolism and inflammation mechanism, respectively. PI3k – phosphatidylinositol 3-kinase; p-AKT – p-protein kinase B; mTOR – mammalian target of rapamycin; PTEN – phosphatase and tensin homolog deleted on chromosome 10; FOXO3 – forkhead box O3; TSC1 – tuberous sclerosis complex subunit 1; VEGFA – vascular endothelial growth factor A; KRAS – Kirsten rat sarcoma viral oncogene; DKK1/3 – Dickkopf1/3; SMAD4 – SMAD family member 4; G6PD – glucose-6-phosphate dehydrogenase; TRAF6 – TNF receptor associated factor 6.

SLC4A4 has been reported to inhibit the development of ccRCC [90]. Another study showed that the level of p-Erk1/2 and cell migration can be reduced by occludin and enhanced by miR-122 in ccRCC, consequently promoting tumor progression. Occludin has been reported to act as a tumor suppressor in ccRCC [91]. Furthermore, the levels of p-c-Jun, which is part of the MAPK pathway, and VEGFA can be increased by miR-21 or diminished by programmed cell death 4 (PDCD4) in RCC. In addition, PDCD4 reduces the number of tubes and tube junctions of HMEC-1 cells and impairs RCC cell mobility, while its effect can be reversed by miR-21. PDCD4 act as a tumor suppressor in RCC [92, 93]. Additionally, miR-21 boosts cell proliferation and decreases the levels of p53, p21, cyclin E2, and Bax, which inhibits the p53 pathway to facilitate the progression of renal cancer [94] (Figure 2).

miRNAs Act as Biomarkers for the Diagnosis of RCC

Liquid Biopsies

Liquid biopsy is an important research area and has been used in multiple cancers, including renal cancer [95]. For instance, in PRCC-TFE3 Tg mice and translational RCC (tRCC) patients, miR-204-5p levels are significantly increased in urinary exosomes samples taken before and after tumor development; thus, miR-204-5p can be used as a marker to diagnose patients with Xp11 tRCC at an early stage [96]. Another study found ccRCC patients have a high level of plasma miR-1293 and a low level of plasma miR-301a-3p after surgery, and miR-301a-3p and miR-1293 are derived from extracellular vesicles.

In other words, these miRNAs can serve as markers of the effect of surgical resection [97]. In addition, miR-92a-1-5p, miR-149-3p, and miR-424-3p in plasma exosomes can be used to distinguish RCC patients from healthy patients, with sensitivities of 87.5%, 75%, and 75%, and specificities of 77.3%, 72.7%, and 81.8%, respectively [98]. Furthermore, the levels of serum miR-122-5p and miR-206 are significantly reduced in ccRCC patients. The level of miR-122-5p is correlated with RCC metastasis and grade, and the level of miR-206 is correlated with pT-stage and metastasis [3]. Intriguingly, miRNAs exist in both cancer exosomes and CSC (cancer stem cells). For example, the expression of miR-19b-3p in CSC (cancer stem cells) exosomes is significantly higher than that in renal cancer exosomes. Overexpression of miR-19b-3p impairs the expression of PTEN in ccRCC cells, promoting tumor cell metastasis [99] (Table 2).

Assessment of the treatment effect

Sunitinib is routinely used as first-line therapy for RCC, although 10-20% of advanced RCC patients are inherently refractory to sunitinib therapy [100]. Recent research demonstrated that miR-376b-3p enables the prediction of the response to Sunitinib therapy and the identification of patients who are likely to experience a long-term response (progression-free survival >12 months), with a sensitivity of 83% and specificity of 67%. The expression of miR-9-5p is also a marker of the effect of sunitinib treatment in RCC [101,102]. Nivolumab significantly improved the median OS benefit of patients with RCC, which led to regulatory approval in both the EU and the USA, but biomarkers to identify patient subgroups for immune-checkpoint treatment are not yet available [103]. A recent study demonstrated the expression of miRNAs, including miR-22/24/99a/194/214/335/339/708, in peripheral lymphocytes can be increased by anti-PD-1 treatment, implying that these miRNAs can be used to predict which patients are likely to have a long-lasting response to nivolumab treatment [6] (Table 1).

Differentiating Subtype

Although distinction of renal cancer subtypes depends on biopsy in clinical practice, some research demonstrates that miRNAs can also exert the same effect. For instance, miRNAs can distinguish TC-RCC (tubulocystic renal cell carcinoma) from CCPRCC (clear cell papillary renal cell carcinoma) and PRCC (papillary renal cell carcinoma), including miR-15a/182/138/200c/16, which are overexpressed, while miR-210/34a/155 are underexpressed in TC-RCC. Likewise, miR-3199-2 and miR-1293 can be used to distinguish patients with PRCC or other types of RCC from healthy patients [104,105]. Furthermore, miR-21 and miR-142 are significantly upregulated in ccRCC and sarcomatoid RCC, whereas miR-150 is overexpressed in chromophobe

tumors. In contrast, miR-155 is downregulated in oncocytoma compared with all RCC subtypes [106] (Table 2).

Discrimination Between Benign and Malignant in RCC

Similarly, some evidence shows that miRNAs can be used to discriminate malignant tissues from adjacent non-tumor tissues in kidney cancer. For instance, the expression of miR-10a-5p, miR-10b-5p, miR-106a-5p, and miR-142-5p is decreased in RCC nephrectomy specimens and has a sensitivity of 91.7% and specificity of 94% for distinguishing cancer from benign tissues [107]. Another report suggested that miR-130b, miR-18a, and miR-223 can distinguish patients with ccRCC from healthy controls, with a sensitivity of 83.1% and a specificity of 82.5% [108].

Target of Therapy

Accumulating evidence suggests that miRNAs levels correlate well with the effects of chemotherapy and radiotherapy in renal cancer changes [5]. Topotecan inhibits the function of mature miR-21, improves chemosensitivity and therapeutic response in renal cancer, and increases the expression of PDCD4 and PTEN by negatively mediating miR-21 [8]. Repression of octamer binding transcription factor 2 (OCT2) has been verified to drive oxaliplatin resistance in RCC [109]. Indeed, overexpression of miR-489-3p and miR-630 in cells and exosomes of ccRCC promotes tumor growth, and boosts chemoresistance to oxaliplatin by targeting OCT2 [110]. In contrast, the apoptosis of kidney cancer cells induced by cisplatin and TRAIL can be enhanced by miR-1208 via activation of the caspase pathway, thus impairing RCC cell growth, while these effects can be reversed by TBCK (TBC1 domain containing kinase). TBCK has been verified to affect mTOR signaling pathway transduction [111]. Furthermore, miR-99a-3p suppresses RCC development and facilitates TKI treatment by modifying RRM2 (ribonucleotide reductase regulatory subunit M2). RRM2 acts as an oncogene in gastric adenocarcinoma and breast cancer [112]. In addition, migration and lactate production of cells, and the expression of p-mTOR, can be interfered with by miR-126 in RCC. In addition, miR-126 augments the sensitivity of renal cancer cells to cisplatin and X-ray treatment [113] (Figure 1).

Prognosis

Although the outcome of patients with renal cancer depends on TNM stage, accumulating evidence shows that miRNAs can also predict outcome in RCC patients. For instance, miR-221-5p enables the evaluation of the OS of RCC patients, with a specificity and sensitivity of 44% and 63%, respectively [114]. Another study showed that patients with high expression

of miR-154-5p/566/663a/572/23a-3p/720 had poor OS because these miRNAs act as oncogenes and promote RCC progression [2,4,115-118]. On the contrary, miR-378a-5p/31-5p/451a/125a-3p act as tumor suppressors and inhibit RCC development; thus, RCC patients with overexpression of miR-378a-5p/31-5p/451a/125a-3p have better OS than those with low expression of these miRNAs [119-122]. Also, miR-144-5p, which is derived from the passenger strands, suppresses RCC development by modifying syndecan-3(SDC3). SDC3 has been reported to act as an oncogene in prostate cancer. In addition, RCC patients with high expression of miR-144-5p have better disease-free survival (DFS) than those with low expression of miR-144-5p [12]. miRNAs also can predict the relapse of renal cancer patients; for example, patients with high levels of miR-155-5p have a 2.64-fold increased risk of ccRCC recurrence (95% CI, 1.49 to 4.70; $P=0.0009$), and a similar result was found for miR-210-3p (HR, 1.80; 95% CI, 1.04 to 3.12; $P=0.036$) [123] (Table 1).

Conclusions

MicroRNAs are a class of short non-coding RNAs with highly conserved evolution that regulate genes expression through directly degrading or inhibiting the translation of mRNA [7].

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Conflict of Interests

None.

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