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Review

MicroRNA as a Biomarker for Diagnostic, Prognostic, and Therapeutic Purpose in Urinary Tract Cancer

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Abstract: The incidence of urologic cancers, including kidney, upper tract urothelial, and bladder malignancies, is increasing globally, with a high percentage of cases showing metastasis upon diagnosis and low five-year survival rates. MicroRNA (miRNA), a small non-coding RNA, was found to regulate the expression of oncogenes and tumor suppressor genes in several tumors, including cancers of the urinary system. In the current review, we comprehensively discuss the recently reported up-or down-regulated miRNAs as well as their possible targets and regulated pathways involved in the development, progression, and metastasis of urinary tract cancers. These miRNAs represent potential therapeutic targets and diagnostic/prognostic biomarkers that may help in efficient and early diagnosis in addition to better treatment outcomes.

Keywords: miRNA; renal-cell carcinoma; urinary bladder cancer; upper tract urothelial carcinoma; diagnosis; prognosis; therapeutic targets

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1. Introduction

Cancers of the urinary system involving the kidney, bladder, and upper urinary tract are showing an increase in their incidence globally [1]. For instance, kidney cancer was the seventh on the list of the most common malignancies, accounting for 3.3% of all cancers globally [2]. Renal-cell carcinoma (RCC) represents around 95% of all kidney cancers [3], with clear-cell renal-cell carcinoma (ccRCC), arising from proximal tubules, encompassing about 75% of all cases [4]. Due to a high incidence rate and the considerable number of patients showing metastatic disease upon diagnosis [5], the economic burden of RCC reached approximately USD 556 million in the United States and USD 1.6 billion collectively in certain countries [5]. The urinary tract, starting from the renal collecting tubules and renal calyces, then the ureter and bladder up to the urethra, is lined with specialized epithelium termed as "urothelium" or "transitional epithelium", which possesses the same embryogenic origin. Urothelium undergoes malignant transformation, resulting in the development of different cancers of the urinary tract. Transitional cell carcinomas or urothelial carcinomas (UC) account for approximately 90% of these cancers; other rare types include squamous cell carcinoma and adenocarcinoma [6]. Most UCs originate from the urinary bladder causing urinary bladder cancer (UBC); whereas, upper tract urothelial carcinoma (UTUC), arising from renal pelvis and ureters, constitutes around 5–10% of all UCs [7]. Globally, UBC is the 9th most common cancer with more than 430,000 cases per year [8], and it ranks as the 13th most common cause of death among cancers [8].

UBC is also a male predominance disease, being the 7th most common cancer in men worldwide [9].

microRNA (miRNA) is a short, non-coding RNA molecule discovered in 1993 by Ambros and Ruvkun groups in *Caenorhabditis elegans* [10–12]. The biogenesis of miRNAs involves several steps of pre-miRNA transcription in addition to post-transcriptional modifications by several regulatory enzymes such as Drosha and Dicer [13]. miRNAs regulate protein synthesis via inhibiting the transcription and translation of messenger (m)RNA, therefore influencing various biological processes such as cell proliferation, migration, and apoptosis in addition to the negative feedback regulation of protein-coding genes [14,15]. miRNAs bind to the 3′ untranslated region of mRNA, resulting in its degradation or blocking of its translation [13]. In addition, some miRNAs were found to up-regulate genes via enhancing of the expression their miRNAs either directly, which is dependent on the mRNA sequence, binding sites and associated binding proteins, or indirectly through miRNA-mediated suppression of repressive miRNAs [13]. Regarding cancer biology, miRNAs were found to regulate the expression of oncogenes and tumor suppressor genes. Thus, it plays a pivotal role in the pathogenesis, progression, and metastasis of various malignancies [16–22]. miRNA could act as an oncogenic miRNA (oncomiR) or tumor suppressor miRNA depending on the target genes. Therefore, oncomiRs were shown to be up-regulated in malignant cells; however, tumor suppressor miRNAs were reported to be down-regulated [23]. Along with targeting oncogenes or tumor suppressor genes, recent evidence supports a potential involvement of miRNAs in a cell-to-cell communication approach [24,25], influencing a variety of biological processes at the receiving sites [26]. This feature is attained via the circulating miRNAs released from the primary site in either free form or stalked in membrane-bound vesicles, e.g., exosomes [27]. In the last two decades, scientific research has suggested miRNAs as possible diagnostic/prognostic biomarkers and therapeutic targets in cancer management [28]. As a result, researchers and clinicians are currently examining the potential role of miRNAs in the diagnosis and management of various malignancies. In this review, we focus on the recent findings on miRNAs which were shown to possess diagnostic, prognostic, and therapeutic potential in cancers of the urinary tract.

2. miRNAs in Kidney Cancer

Among early studies aimed at profiling the expression levels of miRNAs in RCC, Nakada et al. reported significant alterations of ~40 miRNAs in ccRCC when compared with chromophobe renal-cell carcinomas (chRCC) and normal kidneys [29]. Among these miRNAs, miR-141 and miR-200c were markedly down-regulated. miR-141 and miR-200c are commonly known to target *ZFHX1B* mRNA. Therefore, down-regulation of miR-141 and miR-200c in RCC results in up-regulation of *ZFHX1B*, leading to suppression of CDH1/E-cadherin transcription and enhancing levels of vimentin, thus potentially augmenting epithelial-mesenchymal transition (EMT) [30]. EMT is a crucial process for tumor invasion and metastasis that is usually mediated by reduced expression of E-cadherin and loss of cell adhesion [31].

In the last few years, several studies have investigated the expression levels of various miRNAs and their biological functions in RCC (Table 1). These miRNAs were found to regulate interlacing networks of pathways, resulting in up- and/or down-regulation of oncogenes or tumor suppressor genes controlling tumor development, progression, and metastasis (Figure 1). Interestingly, some of these miRNAs showed a different pattern of expression when compared with other cancers. For instance, in contrast with prostatic cancer, where miR-34 is overexpressed, miR-34a was found to be down-regulated in RCC [32–34]. Moreover, distinct miRNA profiling was detected in different subtypes of kidney cancer, indicating a significant diagnostic and prognostic value [35]. For example, miRNAs such as miR-200b could be used to distinguish tumors with high histopathological similarities, such as oncocytomas and chromophobe RCCs. On the other hand, a panel of five miRNAs was consistently observed in at least three genitourinary organ tumors [33].

These miRNAs, comprising miR-136, miR-154, miR-337, miR-377, and miR-411, were identified to be down-regulated in ccRCC, human epithelial ovarian cancer, and UBC, suggesting potential applications of these miRNAs in identifying various tumors and selectively confirming the diagnosis of histological subtypes.

Table 1. miRNAs acting as oncomiRs or tumor suppressor genes in addition to their biological roles and possible targets in kidney cancer. miRNAs are arranged numerically based on being most relevant and frequently attributed in the literature.

	miRNA	Samples	Target Genes/Function	Type	Level	Year	Ref.
1.	miR-21	RCC cell line (ACHN)	Promoted cell proliferation and differentiation and decreased apoptosis via regulating *MTOR-STAT3* signaling pathway	oncomiR	↑	2016	[36]
2.	miR-34a	FFPE kidney tissue samples from patients with primary RCC	*TP53INP2*, *Tp53*, *DFFA*	oncomiR	↑	2017	[37]
3.	miR-429	Cell lines (786-O, A498)	Inhibited cell proliferation, migration and invasion via down-regulating *Sp1*	TS	↓	2016	[38]
4.	miR-155-5p and miR-210-3p	Tumor tissue from patients with newly diagnosed and histologically confirmed ccRCC	Associated with a high risk of ccRCC recurrence by regulating inflammation-related pathways and IL-2 signaling events mediated by PI3Ks as well as BCR signaling	oncomiR	↑	2018	[39]
5.	miR-106b	RCC tissues and Cell lines (786-O and ACHN)	Enhanced cell migration and proliferation and suppressed apoptosis via targeting p21/WAF1/Cip1 pathway and *TWIST1*	oncomiR	↑	2016	[40]
6.	miR-206	ccRCC and corresponding non-cancerous tissues	Inhibited cell proliferation by inducing cell cycle arrest via targeting cell cycle-related gene *CDK4*, *CDK9* and *CCND1*	TS	↓	2016	[41]
7.	miR-22	Cell lines (786-O and A498)	Suppressed cell proliferation, migration and invasion by regulating *PTEN*	TS	↓	2016	[42]
8.	miR-30a-5p	ccRCC and adjacent normal tissue samples and 769-P cells	Prevented cellular proliferation and invasion in vitro and in vivo via targeting *ZEB2* and suppressing EMT	TS	↓	2017	[43]
9.	miR-21 and miR-221	Paired samples of primary ccRCC and adjacent non-tumorous tissue	Promoted cell cycle progression and facilitated cell proliferation via targeting p53 and p57	oncomiR	↑	2016	[44]
10.	miR-508	ccRCC tissues and paired adjacent normal tissues Papillary RCC cell lines (Caki-2, ACHN) and ccRCC cell lines (786-O, A498)	Decreased cell proliferation and invasion via targeting *ZEB1*	TS	↓	2019	[45]
11.	miR-384	RCC and normal tissues. RCC cell lines (769-P, 786-O, A498, SN12-PM6)	Suppressed cell proliferation, migration and cell cycle via targeting *RAB23*	TS	↓	2018	[46]

Table 1. *Cont.*

	miRNA	Samples	Target Genes/Function	Type	Level	Year	Ref.
12.	miR-10a	RCC tissues in addition to cell lines (A498 and 786-O)	Inhibited cell invasion and EMT via targeting *BDNF*	TS	↓	2021	[47]
13.	miR-10a-5p	Cell lines (786-O, A498)	Inhibited cell migration and invasion via targeting *SKA1*	TS	↓	2017	[48]
14.	miR-532-5p and miR-532-3p	RCC tissues and cell lines (786-O and A498)	Attenuated proliferation, migration and invasion by targeting *AQP9*	TS	↓	2019	[49]
15.	miR-101-5p and miR-101-3p	cRCC tissues and cell lines (786-0 and A498)	Induced cell cycle arrest and apoptosis via targeting *DONSON*	TS	↓	2020	[50]
16.	miR-149-5p and miR-149-3p	Tumor tissues from patients with ccRCC	Inhibited cell migration and invasion via targeting *FOXM1*	TS	↓	2017	[51]
17.	miR-19a and miR-19b	Paired tumor and adjacent normal kidney tissues and cell lines (786-O, Caki-1, Caki-2, A498, SN12pm6, ACHN)	Promoted cell migration, proliferation and invasion via targeting *RHOB*	oncomiR	↑	2018	[52]
18.	miR-451a	Tumor and normal tissues from RCC patients and cell lines (786-O, A498)	Inhibited cell migration and invasion via targeting *PMM2*	TS	↓	2018	[53]
19.	miR-27	Xenograft animal model and RCC cell line (786-O)	Suppressed cell proliferation, migration and invasion via targeting *EGFR* and induced cell apoptosis	TS	↓	2016	[54]
20.	miR-20b-5p	RCC tissues and cell lines (293T)	- Inhibited cell proliferation and migration - promoted cellular apoptosis via regulating *PTEN*, *BRCA1* and *p21*	TS	↓	2016	[55]
21.	miR-18a	Cell lines (ACHN, OSRC-2, HK-2, Caki-1, 786-O and A498)	Enhanced migration and invasion via regulating *HIF1A/PVT1* pathway	oncomiR	↑	2020	[56]
22.	miR-106a-5p	RCC tissues and cell lines (OSRC-2, 786-O, ACHN, Ketr-3)	Decreased cell metastasis, migration, invasion via targeting *PAK5*	TS	↓	2017	[57]
23.	miR-543	ccRCC tissues and adjacent non-cancerous tissues	Promoted cell proliferation and invasion via targeting *KLF6* and p21	oncomiR	↑	2018	[58]
24.	miR-200c	Metastatic ccRCC tissues	Suppressed cell growth and promoted apoptosis. Inhibited EMT by targeting *ZEB1* and *ZEB2*	TS	↓	2019	[59]
25.	miR-200a	RCC cell lines (786-O)	Suppressed cell growth, arrested cell cycle, and enhanced cell apoptosis by targeting *SIRT1*	TS	↓	2017	[60]
26.	miR-200a-3p	Cell lines (786-O, ACHN)	Inhibited cell proliferation by inducing apoptosis via down-regulating *SPAG9*	TS	↓	2016	[61]

Table 1. *Cont.*

	miRNA	Samples	Target Genes/Function	Type	Level	Year	Ref.
27.	miR-30e-3p	Cell lines (A498 and 786O)	Inhibited cell invasion and migration via targeting *SNAI1*	TS	↓	2017	[62]
28.	miR-101	RCC tissues from patients before and following sunitinib treatment	Down-regulation of miR-101 was associated with resistance to sunitinib. Inhibited cell migration and invasion via targeting *UHRF1*	TS	↓	2016	[63]

TS: tumor suppressor miRNA, RCC: renal-cell carcinoma, EMT: Epithelial-mesenchymal transition, BDNF; Brain-derived neurotrophic factor, TWIST1: Twist Family BHLH Transcription Factor 1, ZEB: Zinc Finger E-Box Binding Homeobox, AQP9: Aquaporin 9, UHRF1: Ubiquitin-like with PHD and ring finger domains 1, IL: interleukin, PI3K: phosphoinositide 3-kinase, BCR: B cell-receptor, SNAI1: Snail Family Transcriptional Repressor 1, FOXM1: Forkhead box protein M1, KLF6: Krüppel-like factor 6, CDK: cyclin-dependent kinase, CCND1: Cyclin D1, PTEN: phosphatase and tensin homolog, RHOB: Ras Homolog Family Member B, DONSON: DNA Replication Fork Stabilization Factor, TP53INP2: Tumor Protein P53 Inducible Nuclear Protein 2, DFFA: DNA Fragmentation Factor Subunit Alpha, EGFR: epidermal growth factor receptor, SIRT1: Sirtuin 1, BRCA1: Breast cancer type 1, HIF1A: Hypoxia-Inducible Factor 1 Subunit Alpha, PVT1: plasmacytoma variant translocation 1, PAK5: P21 (RAC1) Activated Kinase 5, MTOR: mammalian target of rapamycin, STAT3: Signal Transducer And Activator Of Transcription 3, PMM2: phosphomannomutase 2, RAB23: Ras-related protein Rab-23, SPAG9: Sperm Associated Antigen 9, SKA1: Spindle and kinetochore-associated protein 1.

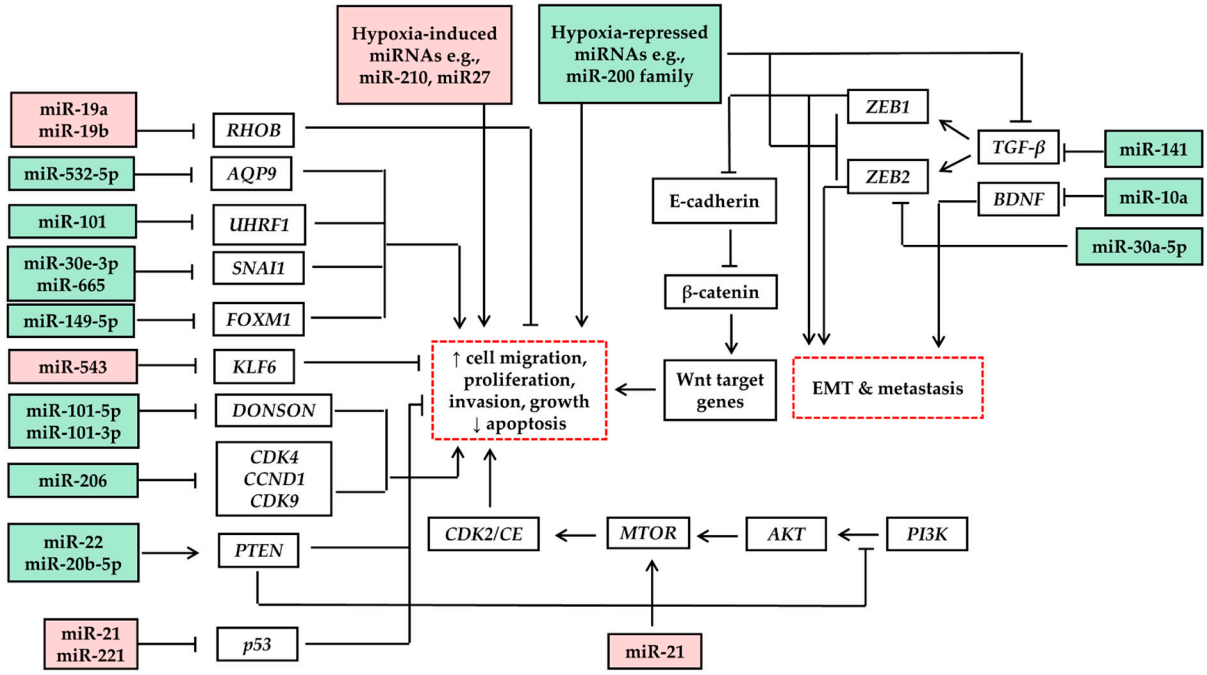

Figure 1. miRNAs up-regulated (red-colored) and down-regulated (green-colored) in renal-cell carcinoma and their target genes and regulated pathways. EMT: Epithelial-mesenchymal transition, TGF-β: transforming growth factor-beta, BDNF; Brain-derived neurotrophic factor, ZEB: Zinc Finger E-Box Binding Homeobox, PI3K: phosphoinositide 3-kinase, AKT: AKT Serine/Threonine Kinase 3, MTOR: mammalian target of rapamycin, CDK: cyclin-dependent kinase, RHOB: Ras Homolog Family Member B, AQP9: Aquaporin 9, UHRF1: Ubiquitin-like with PHD and ring finger domains 1, SNAI1: Snail Family Transcriptional Repressor 1, FOXM1: Forkhead box protein M1, KLF6: Krüppel-like factor 6, DONSON: DNA Replication Fork Stabilization Factor, CCND1: Cyclin D1, PTEN: phosphatase and tensin homolog.

RCC is well-recognized for cancer-associated hypoxia and enhanced angiogenesis. miRNA regulation through both processes has been well studied. For instance, hypoxia-regulated miRNAs, including miR-210, were remarkably up-regulated in RCC. miRNA profiling in RCC was broadly linked to angiogenesis, a pivotal biological process for tumor growth and progression. Researchers reported that hypoxic growth factors enhanced the expression of miR-296 in vascular endothelial cells [64]. MiR-296 has been shown to target the hepatocyte growth factor-regulated tyrosine kinase substrate (HRS), inhibiting

the degradation of angiogenic growth factor receptors such as *VEGFR2* and *PDGFR*-β, therefore enhancing angiogenesis [64].

Likewise, up-regulation of miR-29b was detected in RCC, where it was associated with high levels of von Hippel-Lindau (VHL) tumor suppressor protein [65]. miR-29b targets TPA-inducible sequence 11-B (*TIS11B*), which is a negative regulator of vascular endothelial growth factor (*VEGF*), thus enhancing new blood vessel formation. Others investigated VHL-regulated miRNAs, where miRNA expression in RCC was reported to be either hypoxia-inducible factors (HIFs)-dependent or HIF-independent [66]. miR-210, miR-155, let-7i, and members of the miR-17-92 cluster, are involved in the hypoxic pattern of gene expression [66]. Among them, miR-210 was distinctly up-regulated and its levels correlated inversely with the patient survival rate. miR-210 was suggested to target iron-sulfur cluster assembly (*ISCU1/2*), which codes for a protein that enhances the assembly of iron-sulfur clusters and prosthetic groups that are critical for electron transport and mitochondrial oxidation-reduction reactions, thus repressing mitochondrial respiration, thereby facilitating tumor cell adaptation to hypoxia and intensely influencing cell survival and function [67]. Other miRNAs such as miR-23b act as oncomiRs in renal cancer by targeting proline oxidase (*POX*), a potent mitochondrial tumor suppressor that inhibits proliferation and promotes apoptosis via the generation of reactive oxygen species (ROS), in addition to blocking HIF signaling [68].

Nearly one third of RCC cases are initially diagnosed with metastases, and about half of patients diagnosed with localized stage disease showed metastasis subsequent to complete resection of the primary tumor [69,70]. Although several therapeutic agents have been approved for treatment of metastatic stage [71], the determination of prognosis is extremely critical for choosing and initiating the proper plan of systemic treatments. Therefore, identifying prognostic biomarkers is usually the first step, shedding light on potential biological pathways of cancer development as well as developing efficacy-based criteria for that therapeutic intervention [72,73]. Despite the long-term use of the scoring system in the prognostication of renal cancer [74,75], it still lacks sensitive and specific genomic biomarkers that might reflect the underlying stage-specific tumor biology associated with disease development and progression [76,77]. These molecular prognostic biomarkers reflect genetic aberrations and thus promote the prediction of survival outcomes [78–80]. In the case of metastatic RCC, blood and urine miRNAs may represent non-invasive prognostic biomarkers since they remain considerably stable and intact via binding to lipoproteins, or being inside circulating membrane microvesicles, e.g., exosomes [81,82]. The feasibility of exosome sampling opened the door towards clinical applications involving diagnosis, prognosis, tumor assessment and therapies [83]. Recently reported studies demonstrated the possible use of free and exosomal serum and urinary miRNAs as diagnostic biomarkers with high sensitivity and specificity (Table 2). Similarly, levels of these miRNAs in blood or urine indicated a prognostic value. For instance, miRNAs in 44 metastatic RCCs were evaluated for survival analysis. Among them, researchers identified six miRNAs that were associated with overall survival (OS), including miR-let-7i-5p, miR-26a-1-3p and miR-615-3p [84]. miR-let-7i-5p with the clinical factor-based scoring was found to improve survival prediction from an area under the curve of 0.58 to an average of 0.64 during a 48-month follow-up [84]. Likewise, the suggested model managed to define a high-risk group with a median survival of 14 months and a low-risk group of 39 months. Despite the current promising potential, the miRNA-based prognostic determination still requires further validation.

Table 2. miRNAs and their diagnostic potentials in renal cell carcinoma.

miRNA	Samples	Level	Sensitivity	Specificity	Ref.
miR-144-3p	Plasma	↑	87.10%	83.00%	[85]
miR-210	Plasma	↑	82.50%	80.00%	[86]
miR-221and miR-222	Plasma	↑	72.50%	33.30%	[87]
miR-122-5p and miR-206	Serum	↑	57.10%	83.80%	[88]
miR-210	Serum	↑	70.00%	62.20%	[89]
miR-1233	Serum	↑	81.00%	76.00%	[89]
miR-30c-5p	Urine	↓	68.57%	100.0%	[90]
let-7	Urine	↑	71.00%	81.00%	[91]
miR-34b-5p and miR-1183	Urine	↑	69.00%	65.00%	[92]
miR-126-3p and miR-34b-5p	Urine	↑	82.80%	65.00%	[92]
miR-126-3p and miR-126-5p	Urine	↑	72.40%	70.00%	[92]
miR-150-5p and miR-126-3p	Urine	↑	72.40%	80.00%	[92]
miR-150 and 5p and miR-1183	Urine	↑	86.20%	55.00%	[92]
miR-210	Urine	↑	57.80%	80.00%	[93]
miR-486-5p and miR-126-3p	Urine	↑	72.40%	60.00%	[92]

3. miRNAs in Upper Tract Urothelial Carcinoma

UTUC is considered an uncommon genitourinary malignancy with an incidence rate of 1–2 cases per 100,000 individuals per year [94]. However, the majority of UTUC patients are diagnosed at an advanced stage, leading to poor prognoses and high mortality rates. Severe hematuria and/or renal obstruction are common signs of the disease. The diagnosis is confirmed by imaging, urine cytology, and biopsy. Subsequent to diagnosis, grading and staging of the tumor determine the treatment options. For example, in low-risk patients, nephron-sparing segmental ureterectomy and endoscopic ablation are commonly used [95,96]. However, in advanced cases, radical nephroureterectomy with an ipsilateral bladder cuff is the standard. Currently, recurrence-free survival (RFS) and OS are predicted using tumor grading based on histopathological findings and muscle invasion [94]. Yet, there is still room for improvement. A group of researchers reported that the currently established pathological staging and histological grading are inadequate to effectively predict tumor behavior [97]. The potential use of molecular biomarkers in addition to the well-characterized histopathological classification is crucial for risk stratification. The correct and early diagnosis is pivotal for determining the appropriate approach for treatment. Therefore, molecular biomarkers that can complement and enhance the current strategies for UTUC detection are being investigated to reduce morbidity and mortality rates. Examining wide-range miRNA expression patterns in tissue samples from cases with UTUC characterized a list of 26 miRNAs differentially expressed between patients with progressing and non-progressing UTUC [97]. Others have investigated the circulating miRNAs and their role as molecular biomarkers in the diagnosis and prognosis of UTUC. Interestingly, in UTUC patients, there was a remarkable increase in the serum levels of a few circulating miRNAs that could distinguish UTUC from controls, including miR-664a-3p, miR-423-5p, miR-33b-3p, miR-26a-5p, miR-16-5p, and let-7c [98].

miRNA profiling of formalin-fixed paraffin-embedded (FFPE) tissue sections from RCC, UTUC, and healthy cases demonstrated several miRNAs that were significantly dysregulated in cancerous vs. normal tissue. Surprisingly, clusters of miRNAs distinguished UTUC from RCC and classified various RCC subtypes [99]. Next-generation sequencing of UTUC, and normal tissue from 22 patients revealed that miR-30a-5p was markedly down-regulated in UTUC [100]. In vitro up-regulation of miR-30a-5p inhibited cell proliferation, migration and EMT in cultured UTUC cells. Mechanistically, miR-30a-5p was found to up-regulate claudin-5 in UTUC cells in the tight junction pathway. Therefore, they represent a potential therapeutic strategy for UTUC treatment via genetic delivery [100]. Balkan endemic nephropathy (BEN) was found to be strongly associated with UTUC. miRNA profiling of UTUC tissues from patients with BEN and without BEN reported several miRNAs that were differentially expressed in both tissues, suggesting these miRNAs as potential

diagnostic biomarkers [101]. Aristolochic acid (AA), a carcinogenic and nephrotoxic compound commonly isolated from Aristolochiaceae, was shown to be associated with UTUC pathogenesis, with the underlying mechanism still undetermined. Profiling of miRNAs in AA-induced UTUC and non-AA-induced UTUC tissues revealed 29 miRNAs that were differentially expressed. These miRNAs were suggested to target several genes, such as *AKT3*, *PSEN1*, *FGFR3* and *VEGFA*, which regulate tumor progression and growth [102]. Notably, most recent miRNAs studies in UTUC focused on examining miRNAs as diagnostic and/or prognostic biomarkers, with few of these reports investigating the biological pathways involved (Table 3).

Table 3. miRNAs and their diagnostic and/or prognostic values in upper tract urothelial carcinoma.

miRNA	Samples	Level	Diagnostic/Prognostic Value	Ref.
miR-31 and miR-149	FFPE UTUC tissues	↑	- Independently associated with high tumor progression, recurrence, stage and cancer-specific survival - Differentiated two groups with a significantly different probability of tumor progression (HR: 4.78) and death (HR: 2.76)	[103]
miR-29b-2-5p, miR-18a-5p, miR-223-3p and miR-199a-5p	Radical nephroureterectomy specimens from patients with UTUC	↑	Identified high-grade UTUC with a sensitivity of 83% and specificity of 85%	[97]
miR-10b-5p, miR-26a-5p-5p, miR-31-5p and miR-146b-5p			Predicted ≥ pT2 disease with a sensitivity of 64% and specificity of 96%	
miR-30a-5p	UTUC tissues and adjacent normal tissues and cell line (BFTC-909)	↓	Suppressed cell proliferation, migration and EMT	[100]
miR-3144-5p, miR-193b-3p, miR-587, miR-3117-3p, miR-769-5p and miR-617	UTUC, ccRCC, papRCC and chRCC tissues	↑	Differentiate between UTUC and other tumors (ccRCC, papRCC and chRCC)	[99]
miR-210	UTUC and adjacent normal tissues	↑	- Up-regulated in high-stage and high-grade tumors - Overexpression of HIF-1α correlated positively with miR-210 expression	[104]
miR-145-5p	UTUC tissues and paired adjacent normal tissues	↓	Inhibited cell migration and invasion by targeting *MMP2*, N-cadherin, *FAK* and *MMP7*	[105]
miR-17-92	FFPE UTUC tissues	↑	Associated with high-stage tumor	[106]

UTUC: Upper Tract Urothelial Carcinoma, ccRCC: clear-cell renal-cell carcinoma, papRCC: papillary renal-cell carcinoma, chRCC: chromophobe renal-cell carcinoma, EMT: Epithelial-mesenchymal transition, HIF1A: Hypoxia-Inducible Factor 1 Subunit Alpha, MMP: matrix metalloproteinase, FAK: Focal adhesion kinase.

4. miRNAs in Urinary Bladder Cancer

miRNA profiling in UBC began two decades ago, with several studies examining differential miRNA expression in the disease. Gottardo et al. reported a significant overexpression of several miRNAs in cancerous tissue, including miR-223, miR-221, miR-185, miR-203, miR-23a, and miR-205 [107]. Others showed altered expression of various miRNAs, including a reduction in the level of miR-145, and up-regulation of miR-21 [108]. Recently, several studies investigated the expression levels of various miRNAs and their biological functions in UBC (Table 4). These miRNAs regulate the expression of oncogenes or tumor suppressor genes involved in tumor development, progression, and metasta-

sis (Figure 2). For example, functional analysis of miR-129 revealed targeting of *SOX4* transcription factor and *GALNT1*, resulting in apoptosis evasion [108]. Interestingly, in normal urothelium tissue from patients with UBC, several miRNAs showed altered expression compared to samples from disease-free controls. Moreover, specific miRNAs were differentially expressed in a phenotype-specific manner in a way that could predict disease progression. A group of researchers reported a phenotype-specific expression of miRNAs such as miR-21/205 in various types of UBC [109], which collectively with other similar studies helped in understanding the tumor biology. Additionally, miRNA profiling significantly contributed to differentiating UBC with regard to grading. Low- and high-grade UBC were shown to have distinctive molecular pathways [110], in which miRNA alterations were noticed. For instance, low- and high-grade UBC had few miRNA signatures in common such as miR-211, miR-518e, miR-133b and miR-204, with several distinct miRNAs that were differentially expressed [111]. High-grade UBC was associated with up-regulation of miRNA-21 that suppresses p53. However, in low-grade UBC, many miRNAs were down-regulated, such as miRNAs-99a/100, which was correlated with up-regulation of *FGFR3* [111]. miRNAs' down-regulation was mainly attributed to promoter hypermethylation [51]. In contrast, high-grade non-invasive and invasive UBC shared many miRNA alterations, indicating the critical role of these miRNAs in tumor progression and behavior change [110,112].

Table 4. miRNAs acting as oncomiRs or tumor suppressor genes in addition to their biological roles and possible targets in urinary bladder cancer. miRNAs are arranged numerically based on being most relevant and frequently attributed in the literature.

	miRNA	Samples	Target Genes/Function	Type	Level	Year	Ref.
1.	miR-145-5p	UBC tissues and cell lines (T24 and 5637)	Inhibited cell proliferation and migration via targeting *TAGLN2*	TS	↓	2018	[113]
2.	miR-99a	UBC and paired adjacent non-cancerous tissues	Inhibited invasion via targeting *ST5*, *MTOR*, *FGFR3* and *IGF-1*	TS	↓	2017	[114]
3.	miR-497	- UBC and adjacent normal tissues - Cell lines (T24 and BIU-87)	Inhibited cell migration, invasiveness and metastasis via reducing vimentin and α-smooth muscle actin	TS	↓	2017	[115]
4.	miR-124-3p	UBC tissues and cell lines	Suppressed cell proliferation and migration, and promoted cell apoptosis via targeting *AURKA*	TS	↓	2017	[116]
		Clinical specimens from UBC patients and bladder cancer cell lines	Suppressed cell migration and invasion via targeting *ITGA3* and its downstream FAK/PI3K/AKT and FAK/Src pathways	TS	↓	2019	[117]
5.	miR-130b	UBC tissues and cell lines	Promoted cell proliferation and invasion via targeting *VGLL4*	oncomiR	↑	2018	[118]
6.	miR-186	UBC tissues and blood/urine samples	- Inhibited invasion and metastasis via targeting *VEGF-C* - miR-186 was reduced in tumor tissues, blood and urine	TS	↓	2017	[119]
7.	miR-135a	UBC and adjacent normal tissues	Enhanced cell proliferation, migration, invasion and tumor growth via targeting *GSK3β* and E-cadherin in addition to activating Wnt/β-catenin signaling pathway	oncomiR	↑	2018	[120]
8.	miR-1-3p	UBC tissues with adjacent normal tissues	Suppressed cell proliferation and invasion and promoted apoptosis via targeting *CCL2*	TS	↓	2017	[121]

Table 4. *Cont.*

	miRNA	Samples	Target Genes/Function	Type	Level	Year	Ref.
9.	miR-373	UBC and adjacent healthy tissues and blood samples	- Promoted cell proliferation, migration and invasion via up-regulation of *EGFR* - Serum miR-373 can accurately predict UBC	oncomiR	↑	2018	[122]
10.	miR-125b-5p	Cell lines (T24, RT4, J82, 5637, SV-HUC-1) and UBC tissues	- Low miR-125b-5p expression correlated with shorter 5-year survival time - Inhibited cell viability and migration and induced cell apoptosis by targeting *HK2* through suppressing PI3K/AKT pathway	TS	↓	2020	[123]
11.	miR-328-3p	Tumor tissues from patients with UBC	- Suppressed cell proliferation, migration and invasion by targeting *ITGA5* - Inhibited EMT and PI3K/AKT pathway	TS	↓	2019	[124]
12.	miR-154	- Cell lines (J82, T24 UM-UC-3, SV-HUC-1) - UBC and paired adjacent non-cancerous bladder tissues	- Low expression of miR-154 was associated with poor survival outcomes - Inhibited cell proliferation, migration, and invasion in cultured cancer cells as well as cell growth in xenograft model via targeting *ATG7*	TS	↓	2018	[125]
13.	miR-665	UBC cell lines	Reversed EMT progression and inhibited cell migration via targeting *SMAD3* and *SNAI1*	TS	↓	2021	[126]
14.	miR-532-5p	UBC tissues and cell lines	Inhibited cell proliferation and invasion by targeting *HMGB3* and regulation of nuclear expression of β-catenin as well as activation of Wnt/β-catenin signaling pathway	TS	↓	2019	[127]
15.	miR-153	UBC tissues and cell lines	- Low miR-153 expression was associated with advanced tumor stage and poor OS - miR-153 inhibited cancer growth via promoting cell apoptosis and suppressing migration, invasion, and EMT via targeting *IDO1* and IL6/STAT3/VEGF signaling	TS	↓	2019	[128]
16.	miR-300	Paired UBC and adjacent non-tumorous bladder mucosal tissues as well as cell lines (T24, UM-UC3, SV-HUC-1)	Inhibited cell migration via targeting *SP1* and regulating the SP1/MMP9 pathway	TS	↓	2018	[129]

TS: tumor suppressor miRNA, UBC: urinary bladder cancer, EMT: Epithelial-mesenchymal transition, HMGB3: high-mobility group protein B3, EGFR: epidermal growth factor receptor, IDO1: Indoleamine 2,3-Dioxygenase 1, STAT3: Signal Transducer and Activator of Transcription 3, VEGF: vascular endothelial growth factor, AURKA: Aurora Kinase A, ITGA: Integrin Subunit Alpha, PI3K: phosphoinositide 3-kinase, AKT3: AKT Serine/Threonine Kinase 3, VGLL4: Vestigial Like Family Member 4, TAGLN2: Transgelin 2, MMP9: Matrix Metallopeptidase 9, ATG7: Autophagy Related 7, ST5: tumorigenicity 5, FGFR3: fibroblast growth factor receptor 3, IGF-1: insulin-like growth factor 1, MTOR: mammalian target of rapamycin, HK2: Hexokinase 2, SNAI1: Snail Family Transcriptional Repressor 1, GSK-3β: Glycogen synthase kinase-3β, CCL2: C-C Motif Chemokine Ligand 2.

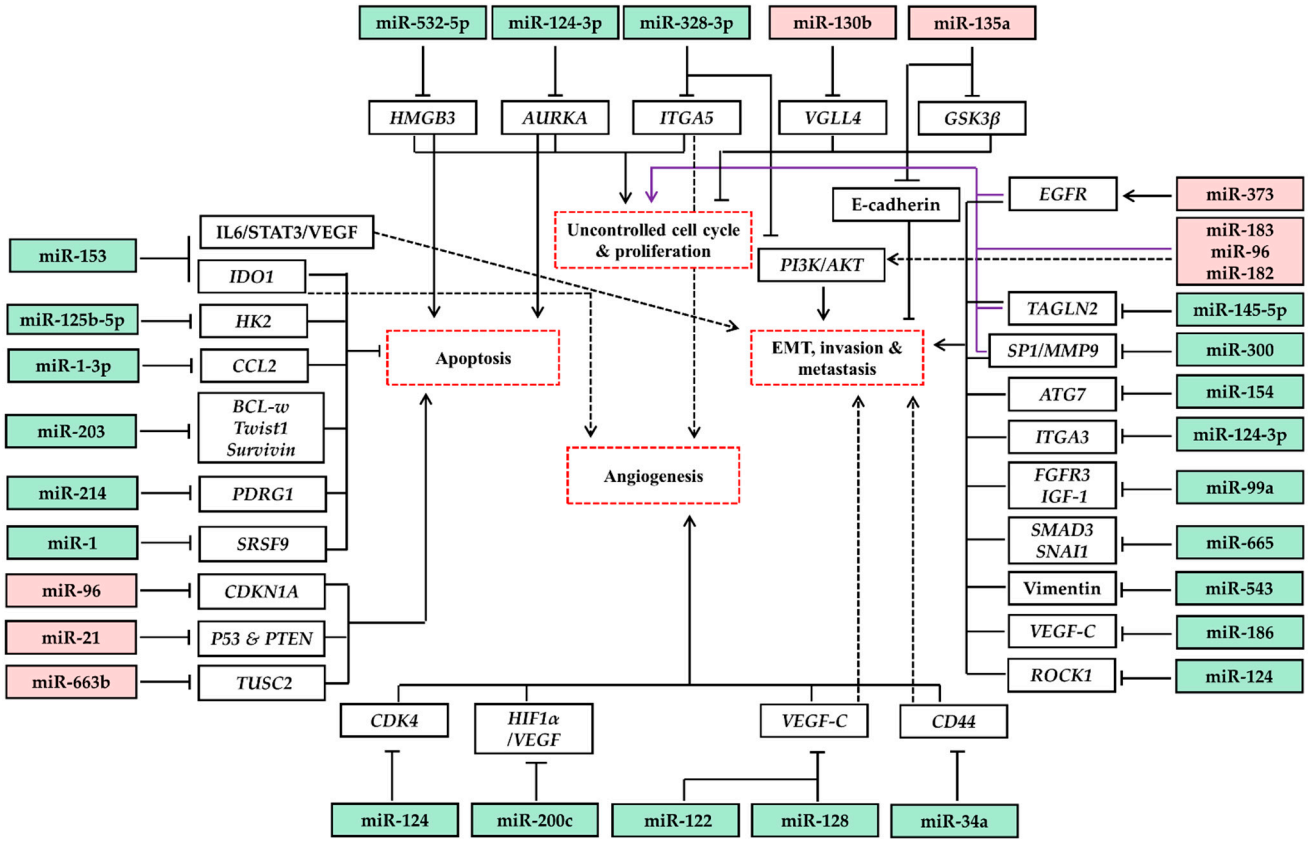

Figure 2. miRNAs up-regulated (red-colored) and down-regulated (green-colored) in urinary bladder cancer and their target genes. EMT: Epithelial-mesenchymal transition, EGFR: epidermal growth factor receptor, TAGLN2: Transgelin-2, MMP: matrix metaloprotenas, ATG7: Autophagy Related 7, ITGA: Integrin Subunit Alpha, FGFR: fibroblast growth factor receptor, IGF-1: insulin growth factor-1, SNAI1: Snail Family Transcriptional Repressor 1, VEGF: vascular endothelial growth factor, ROCK1: Rho Associated Coiled-Coil Containing Protein Kinase 1, HIF1A: Hypoxia-Inducible Factor 1 Subunit Alpha, CDK: cyclin-dependent kinase, STAT3: Signal Transducer And Activator Of Transcription 3, IDO: indoleamine 2,3-dioxygenase, HK2: hexokinase 2, CCL2: C-C Motif Chemokine Ligand 2 TWIST1: twist Family BHLH Transcription Factor 1, PDRG1: P53 And DNA Damage Regulated 1, SRSF9: serine/arginine-rich splicing factor 9, PTEN: phosphatase and tensin homolog, CDKN1A: Cyclin-Dependent Kinase Inhibitor 1A, TUSC2: Tumor Suppressor 2, Mitochondrial Calcium Regulator.

Regarding the mechanistic contribution of miRNAs to UBC development and progression, a group of researchers demonstrated a critical role for the miR-200 family via targeting *ERRF-1* [130], which regulates epidermal growth factor receptor (*EGFR*) and acts as an independent mediator of EMT. Therefore, the down-regulation of miR-200 enhances EMT and cellular migration. The loss of miR-200 was suggested to be induced by hypermethylation of its promoter as well as a correlated increase in the expression of the *TWIST1* transcription factor [131]. Likewise, the overexpression of *ZEB1* in UBC cases, concurrently with low levels of miR-200, promoted EMT via suppressing E-cadherin [132]. Collectively, *TWIST1* could silence miR-200 family members along with up-regulation of *ZEB1*, which in turn represses E-cadherin and directly targets miRs-141/200, constituting a feedback loop [133].

Several miRNAs are involved in the avoidance of apoptosis. miR-133b and miR-203 were shown to target *BCL2*, a family of proteins that can inhibit the intrinsic pathway of apoptosis, thus promoting cell survival. On the other hand, miR-195, miR-203, and miR-497 regulated *BIRC5* (survivin), a suppressor of apoptosis protein family [108]. Unlike miR-129, which directly targets genes involved in apoptosis protein transcription and expression, miR-1 has been shown to increase apoptosis by increasing caspase 3 and 7 activity by targeting SRSF9, an apoptosis inhibitor [134]. Notably, miR-1 was significantly down-regulated in UBC samples and cultured cells [134].

Cell cycle regulatory gene expression is controlled via a network of miRNAs contributing to cell survival and apoptosis escape. Among these genes, *CCNE1/2*, *CDC25A*, and *PKMYT1* were revealed to be directly regulated by miR-144-5p and miR-449a [135]. *CDK4* and *CDK6* are likewise regulated by miR-124-3p, miR-29c, and miR-449a [135]. *FSCN1* and *LASP1* genes code for protein essential for filopodia and lamellipodia involved in mediating dynamics of actin filaments during EMT. *FSCN1* was found to be regulated by miR-133a and miR-145 [136], whereas miR-1/133a and miR-218 control the expression of *LASP1* [137]. Other miRNAs regulate the expression of matrix metalloproteinases (MMPs), endopeptidases that facilitate tumor invasion and metastasis via degrading extracellular matrix proteins and cell surface receptors, in addition to the release of apoptotic ligands (e.g., FAS). In UBC, reduced expression of miR-200b directly regulates *MMP16*, which activates other MMPs (such as *MMP-2* and *MMP-9*) and growth factors to facilitate cell migration [138]. It is also worth mentioning that differential miRNA expression in the serum and urine of UBC patients was reported in several clinical trials, suggesting their potential role as diagnostic biomarkers (Table 5).

Table 5. miRNAs and their diagnostic potentials in urinary bladder cancer.

miRNA	Samples	Level	Sensitivity	Specificity	Ref.
miR-422a-3p, miR-486-3p, miR-103a-3p and miR-27a-3p	Serum	↑	90.0%	70.0%	[139]
miR-6724-5p, miR-1185-1-3p and miR-6831-5p	Serum	↑	95.0%	87.0%	[140]
miR-6087, miR-3960 and miR-1343-5p	Serum	↓			
RNA ratio: miR-126/miR-152	Urine	–	72.0%	82.0%	[141]
miR-21-5p	Urine	↑	75.0%	95.8%	[142]
mir-21, miR-93, miR-200c and miR-940	Urine	↑	88.0%	78.0%	[143]
miR-652, miR-199a-3p, miR-140-5p, miR-93 and miR-142-5p	Urine	↑	87%	100%	[144]
RNA ratio: miR-6124/miR-4511	Urine	–	>90.0%	–	[145]
miR-99a and miR-125b	Urine	↓	81.4%	87.0%	[146]
miR16, miR200c, miR205, miR21, miR221 and miR34a	Urine	↑	88.0%	48.0%	[147]

–: Unknown/Not applicable.

5. Drug Targets and miRNA-Based Therapeutic Strategies

Being involved in the development and progression of cancers of the urinary system, miRNAs potentially represent future therapeutic targets. Current research is deploying two main strategies to use miRNAs in cancer management: (1) replacement of down-regulated tumor suppressor miRNAs and (2) inhibition of up-regulated oncomiRs. However, these applications are facing several challenges, including validating delivery systems, selective cellular uptake by target cells, miRNA stability, off-target effects, and possible adverse reactions [148,149]. Several ongoing approaches to target OncomiRs are under investigation. These involve, for example, antisense miRNA inhibitors (also known as antagomirs), which bind specifically to the sense miRNA, leading to its degradation or deactivation [150]. To maintain the stability of antagomirs, locked nucleic acids are commonly attached to a phosphorothioate backbone [151,152]. Other strategies comprise miRNA sponges and MASK (miRNA-masking antisense oligonucleotides), which function via binding of complementary oligonucleotides to the possible binding sites of oncomiRs on mRNA [153, 154]. On the other hand, many miRNAs that are down-regulated in urologic cancers could have potential antitumor effects on growth and tumorigenesis. Consequently, clinicians and researchers are identifying and characterizing these tumor suppressor miRNAs and observing their biological roles. Techniques employed in restoring the activity of these miRNAs involve miRNA mimics as well as carriers, e.g., viral vectors and non-viral vectors, including inorganic compounds and lipid-based carriers [155,156].

6. Conclusions

As a result of the progressively increasing incidence of urinary tract cancers, scientists and clinicians are researching potential approaches and strategies to enhance the diag-

nosis and management of these malignancies. The ability of miRNAs to modulate gene expression empowers them to alter tumor development and progression. Fortunately, the currently available literature indicates that miRNAs can be used as powerful tools, i.e., being used as diagnostic and/or prognostic markers in addition to therapeutic targets in urologic cancers. In this review, we discussed, using the available literature, the expression levels of various miRNAs in urinary tract cancers. Notably, most studies reported in this review examined levels of miRNAs in tumor tissues that were removed surgically before applying any treatment. Investigating serum or urinary miRNA level in patients undergoing, and subsequent to chemo- or radiotherapy, may provide an insight into the prognostic values of these molecules. Despite the immensity of clinical studies as well as both in vivo and in vitro experiments characterizing miRNA expression in kidney, upper tract, and bladder cancers, we still have not established many of their biological functions and possible targets. Therefore, further research identifying the role of these miRNAs in cancer development and their regulated pathways is recommended. Similarly, additional studies promoting miRNA delivery strategies and applications are still required to be used in clinical trials and future cancer therapies.

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