Medical Oncology (2020) 37:118
https://doi.org/10.1007/s12032-020-01435-0

REVIEW ARTICLE

MicroRNAs and target molecules in bladder cancer

Payam Kheirmand Parizi[1,2] · Fereshteh Yarahmadi[3] · Hoseins Movahedi Tabar[4] · Zohreh Hosseini[5] · Abdolazim Sarli[6] · Nadia Kia[7] · Alireza Tafazoli[8,9] · Seyed-Alireza Esmaeili[10,11]

Received: 29 July 2020 / Accepted: 27 October 2020

Abstract

Bladder cancer (BC) is considered as one of the most common malignant tumors in humans with complex pathogenesis including gene expression variation, protein degradation, and changes in signaling pathways. Many studies on involved miRNAs in BC have demonstrated that they could be used as potential biomarkers in the prognosis, response to treatment, and screening before the cancerous phenotype onset. MicroRNAs (miRNAs) regulate many cellular processes through their different effects on special targets along with modifying signaling pathways, apoptosis, cell growth, and differentiation. The diverse expression of miRNAs in cancerous tissues could mediate procedures leading to the oncogenic or suppressor behavior of certain genes in cancer cells. Since a specific miRNA may have multiple targets, an mRNA could also be regulated by multiple miRNAs which further demonstrates the actual role of miRNAs in cancer. In addition, miRNAs can be utilized as biomarkers in some cancers that cannot be screened in the early stages. Hence, finding blood, urine, or tissue miRNA biomarkers by novel or routine gene expression method could be an essential step in the prognosis and control of cancer. In the present review, we have thoroughly evaluated the recent findings on different miRNAs in BC which can provide comprehensive information on better understanding the role of diverse miRNAs and better decision making regarding the new approaches in the diagnosis, prognosis, prevention, and treatment of BC.

Keywords miRNA · Bladder cancer · Cancer · Biomarker

Introduction

Bladder cancer (BC) is the most common urological malignancy and a major tumor in the urinary tract with a high risk of mortality [1]. In 2018, approximately 80,000 new cancers/year were diagnosed in the United States and about 17,000 patients/year died due to BC. The incidence and mortality rate of bladder cancer in men is four times higher than women. In addition, global cancer statistics have stated that bladder cancer causes 130,000 deaths annually [2]. Despite the advances made in many therapeutic approaches such as surgery, chemotherapy, and immunotherapy, the rate of

✉ Seyed-Alireza Esmaeili
Imunoman2009@gmail.com

1 Cellular, Molecular and Genetics Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

2 Genome Medical Genetics Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

3 School of Medicine, Hamedan University of Medical Sciences, Hamedan, Iran

4 School of Medicine, Semnan University of Medical Science, Semnan, Iran

5 Faculty of Veterinary Medicine, Shahid Chamran University, Ahvaz, Iran

6 Department of Medical Genetic, Faculty of Medical Science, Tarbiat Modares University, Tehran, Iran

7 Agostino Gemelli University Hospital, Torvergata University of Medical Sciences, Rome, Italy

8 Department of Analysis and Bioanalysis of Medicines, Faculty of Pharmacy With the Division of Laboratory Medicine, Medical University of Bialystok, Bialystok, Poland

9 Clinical Research Center, Medical University of Bialystok, Bialystok, Poland

10 Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

11 Immunology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Published online: 20 November 2020

relapse and progression remains within 5 years, the risk of metastasis is high and the prognosis is poor [3–5]. Recently, emerging biophysical methods have accelerated the process of identifying the mechanisms involved in the development of bladder cancer at the molecular level. Moreover, several studies have already shown and approved the correlation between microRNAs (miRNA/miR) and the pathogenesis of cancer, including bladder cancer [6, 7]. MicroRNAs are evolving between distinct species, and to date 38,589, miRNA molecules have been identified in 271 species [8]. A map of microRNA genes includes approximately 1% of the genome of different species, yet each of them has hundreds of target genes and about 30% of the encoding genes are regulated by microRNAs [9]. The miRNA biogenesis in mammals involves multiple stages which are summarized in Fig. 1.

miRNA clusters are small endogenous non-coding RNAs comprised of about 19–24 nucleotides that regulate the target genes after transcription [10–12]. miRNAs play a key role in the growth, differentiation, metastasis, and apoptosis of tumor cells [13]. Studies have shown that miRNAs are involved in the development of several types of cancer including hepatic, gastric, and bladder cancer and gliomas in which miRNAs act as central regulators to gene expression [14, 15]. Regarding the importance of microRNAs in the pathogenesis and control of bladder cancer, further studies are anticipated focusing on the controlling role of microRNAs in carcinogenesis and the progression of bladder cancer.

Cellular function of microRNAs

The primary role of miRNAs is the suppression of mRNAs and affecting the translation pathway. miRNAs can fully bond to their target on the mRNA and cut in a paired area with 10–11 nucleotides. This incision causes the mRNA endonucleotide to become more susceptible to exo-nucleotide attacks. In most cases of animal cells, miRNAs are incompletely bonded to the targets; thus, miRNA increases through accelerating the removal of the poly-A tail. Along with de-adenylating, the protein bonded poly-A tail loses its function which accelerates the removal of the 5′cap; the

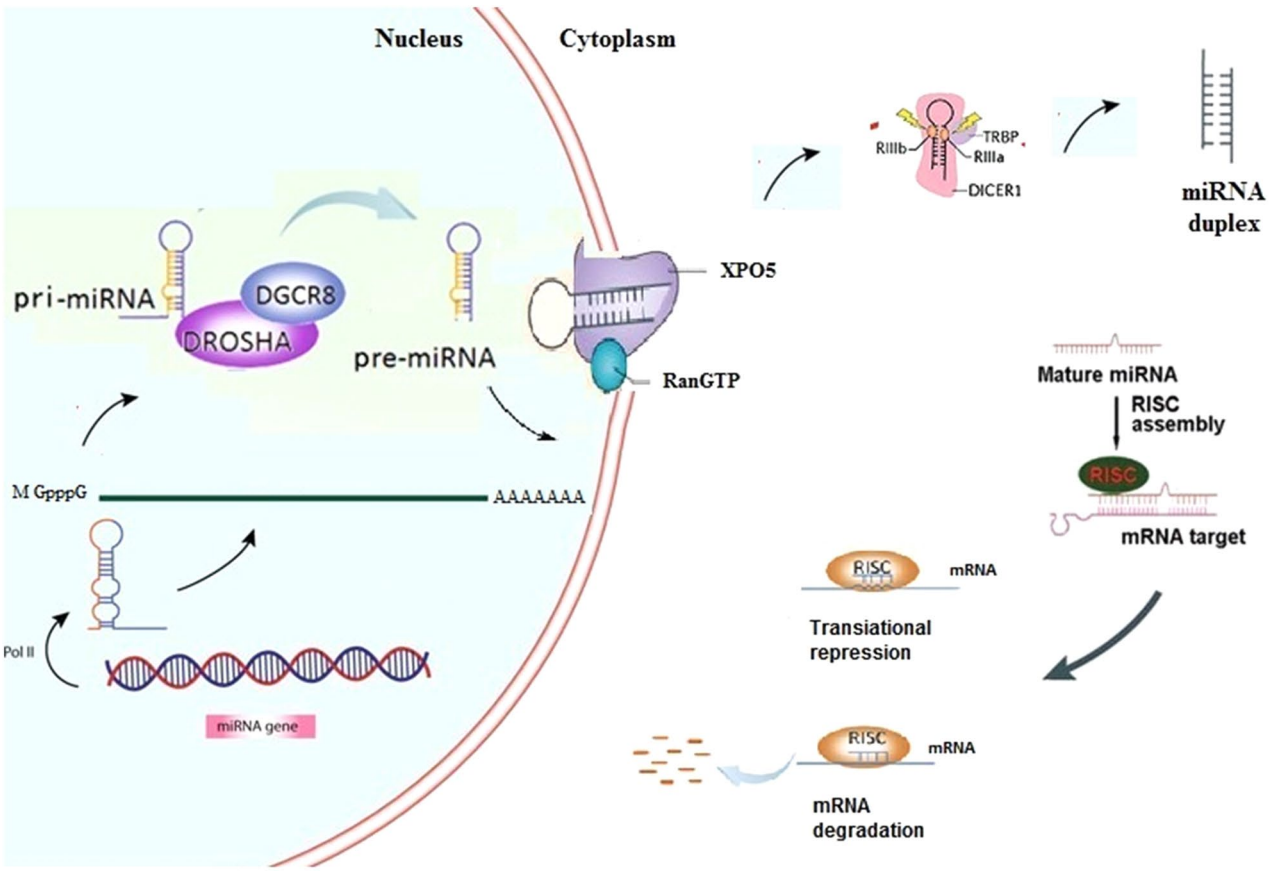

Fig. 1 The schematic pattern of the different steps of miRNAs production in the nucleus and cytoplasm. First, in the nucleus, Pri-miRNAs are produced by RNA Polymerase II and then processed to pre-miRNAs by Drosha endonuclease. Second, in the cytoplasm the transferred pre-miRNAs convert to mature microRNAs trough the Dicer enzyme. Then mature microRNAs are transferred to the RISC complex and bind to their complementary sequences in the target mRNA to inhibit translation or degradation

mRNA is thus exposed to digest exo-nucleotides from the end of 5′. Moreover, it has been indicated that under certain conditions, miRNAs can stimulate translation, but the mechanism has not yet been precisely determined [9, 16].

Role of microRNAs in cancer

Given that microRNAs play a major role in cell proliferation, apoptosis, cell development, and cell differentiation, they are also noticeably detectable in the shift or control of cancers. Cancers affect so many well-known microRNAs, and in human chromosomes, many miRNAs were found to be connected to carcinogens. Approximately 52.5% of human genes are located in the chromosomal locus that is involved in human cancers [17]. For the first time, the importance of miRNA in cancer was diagnosed with chronic lymphocytic leukemia (CLL) [18]. miRNAs have two different roles in a pre-cancerous condition; In the first role, the high expression of one miRNA for any reason decreases the expression of the target gene resulting in a suppressor role; as an example, miR-21 decreases PECD1 and PTEN leading to reduced apoptosis and increased cellular growth [19]. In the second role, the low expression of one miRNA, for any reason, increases the target gene expression which acts as an oncogene, such as let-7 which increases the amount of RAS leading to increased cell proliferation [20, 21].

Pharmacogenomics of miRNAs in bladder cancer (diverse response to drug therapy)

Common medicines in bladder cancer have shown different responses in patients. Due to some cases of drug resistance and toxicity in affected individuals, alternative dosage/prescription utilization has been recommended for various patients with bladder malignancies. Pharmacogenomic studies have indicated that part of the differences in cancer treatment results arise from the interaction between drugs and miRNAs with specific types of polymorphism in their pre/mature sequences or related genes, generally known as miRSNPs. For example, rs1045385 A > C in AP-2α gene is associated with increased cisplatin sensitivity through direct interaction between miR-200 families and their target site in bladder cancer patients [22]. Such drug – miR interactions, could be considered as the inhibitor or stimulator of cancer-related miRNAs in cells, causing different trends of cell proliferation and/or apoptosis in cancer development. However, applying this approach requires the background knowledge of the potential altered genotype landscape of miRNAs and related target genes in different people and also advanced technologies for dealing with targeting miRNA activities inside cells, both in general and particular directions. Untargeted sequencing platforms like Sanger and RNA-Seq are employed for miRNA identification and profiling in different individuals [23]. Examples of miRNA targeting drugs include the usage of Bevacizumab and some of intercalator medicines resulting in DROSHA, DICER, AGO2, etc. level alteration as the general modification of miRNA expression. Drugs with potential effect on bladder cancer normally involve miRNAs like Tretinoin and 5-Fluorouracil as miR-200 expression modifier and miR-96 expression inhibitor [24–26]. Furthermore, the variants in miRNAs, miRNA target genes, drug metabolizing enzyme genes, and drug transporter genes will affect the treatment safety and efficacy in different bladder cancer patients. Moreover, miRNA pharmacogenetics and miRNA drug-dedicated databases could be utilized in finding drugs with a certain impact on specific types of miRNAs (Pharmaco-miR and SM2miR) [27, 28].

Molecular targets of microRNAs in bladder cancer

Studies have shown that miR expression is associated with bladder cancer besides regulating different tumoral pathways. miR studies in different stages and grades of bladder cancer have been performed and compared with each other [29]. These studies have reported and approved the different expressions and functions of distinct miRs on target molecules. As a result, it is possible to say that there is a complex network of emerging interactions demonstrating the new factors in gene modulation in the pathogenesis of bladder cancer [30]. Various studies have shown that the irregular expression of miRNAs can act as an oncogenic miRNA (onco-miRNAs) or suppressor miRNA (TS-miRNAs) in bladder cancer [31]. Since miRNA can play a role in the onset, survival, and invasion of the tumor, many researchers have focused on the miRNAs' targeting genes expressed in bladder cancer compared to bladder epithelium [32].

MiR-1 acts as a tumor suppressor by controlling oncogenic TAGLN2 (Transgelin peptide) in BC. MiR-1 transfection along with TAGLN2 knockdown can lead to reduction in bladder cancer cell survival and induction of apoptosis. Other studies have also shown that the loss of HuR/HOTAIR (HOX Transcript Antisense RNA) in bladder cancer prevents cell proliferation, migration, invasion, and apoptosis stimulation. HOTAIR is known to be a potential target for miR-1 in BC cells [30, 32–34]. In miR-9 studies on bladder cancer, CDH-1 (Cadherin 1), GSK-3β (Glycogen synthase kinase 3), and LASS2 (Longevity assurance homolog 2) have been more important. MiR-9 can target the CDH-1 gene and alter the expression of E-cadherin which facilitates tumor metastasis; MiR-9 inhibition can enhance the expression of GSK-3β, inhibit bladder cancer proliferation, and facilitate

apoptosis. In addition, miR-9 promotes BC chemoresistance by targeting LASS2 [34–36].

MiR-16 also plays a main role in bladder cancer by targeting CCND1 and COX-2. Elevated levels of COX-2 expression could promote cancer cell growth and the invasion of bladder cancer cells. Therefore, the administration of COX-2 inhibitors is a selective approach in the treatment of bladder cancer. Stimulating the expression of miR-16 leads to decreased COX-2 expression levels. Moreover, Cyclin D1 has a regulatory role in cell proliferation, and the non-coding microRNAs function is related to modulation of cyclin D1. Several studies have shown that miR-16 can target bladder cancer cell lines by targeting Cyclin D1. These data suggest that miR-16 plays an important role in regulating the proliferation of bladder cancer cells and acts as a tumor suppressor [32, 36–39]. Various studies on MiR-24 have shown that the function of MiR-24-1-FOXM1 axis is related to the proliferation of cancer cells in BC, and downstream signaling could cause unknown molecular mechanisms in BC oncogenesis. MiR-24 affects the downregulation of CARMA3 leading to the inhibition of cell invasion, proliferation, and EMT in bladder cancer cells. MiR-24-3p improves bladder cancer through the inhibition of DEDD [32, 40].

Nevertheless, miR-101, as an important MircroRNA in bladder cancer, also has different target molecules. Several studies have shown that the reduction of miR-101 concentration is associated with bladder cancer progression; in fact, miR-101 can inhibit the invasion and migration of BC cells through FZD4 targeting. Another target molecule for miR-101 is EZH2 (Enhancer of Zeste Homolog 2) which causes the gene to be muted through H3 (histone 3) in K27 (lysine 27). The high expression of EZH2 in cancer is related with the downregulation of miR-101 that promotes cell proliferation and shift from the G-phase to S-phase in bladder cancer cells. MiR-101 could also suppress VEGF-C expression and increase cell invasion and migration. MiR-101 is a novel suppressor of T24 cell invasion and migration due to its negative modulation effect on c-Met. COX-2 expression is modulated by the miR-101 function, whereas on the other hand, bladder cell resistance to cisplatin is modulated through targeting COX-2 expression. Expression of miR-101 in BC by targeting the products of the FGFR3 gene affects cell proliferation, differentiation and apoptosis. In addition, miR-101 could directly target c-FOS and decrease the invasion and proliferation of BC cells [41–48].

Considering the role of miR-129 in bladder cancer, it could suppress SOX4 and GALNT1 as a tumor suppressor. SOX4 is an important regulator of bladder cancer stem cells and can be used as a biomarker in the aggressive form of bladder cancer. MiR-129 potentially targets MDM4 genes, the main negative regulator of p53, which affects its signaling. MiR-129 also has an effect on PKC that promotes stimulation of NF-κB activation and leads to cellular resistance to apoptosis, thus increasing the tumorigenicity of bladder cancer. MiR-129 could also affect Protein Receptor 2 (Grb2) as an adapter, which is widely expressed in many tissues and is essential for the development of embryos and multicellular functions. Amplification of Grb2 protein plays an important role in the carcinogenesis of human bladder cancer. A novel study showed that transfection of miR-129 precursor in the T24 and SW780 bladder carcinoma cells significantly prevents growth and apoptosis induction [49–56].

MiR-145, as a tumor-suppressive factor, enables the direct regulation of oncogenic FSCN-1 in BC. MiR-145 indirectly regulates the pathway of Akt with targeting integrase linkage kinase (ILK); it is synergistically inhibited by cell growth in bladder cancer cells. In addition, miR-145 suppresses bladder cancer cells through targeting PAK1. Replacement of miR-145 can be an effective method for inhibiting PAK1 growth and treating tumors in bladder cancer. Excessive expression of SOCS proteins in various cells can inhibit signaling by a wide variety of cytokines. MiR-145 contributes to an increase in IFN-β cells via the SOCS7 injection leading to the transfer of the STAT3 nucleus, while SOCS7 stimulates the growth of bladder cancer cells via stimulating the PI3K/Akt signaling pathway. Insulin-growth factor receptor (IGF-IR) is a proto-oncogene with mitogenesis and antiapoptotic activity. MiR-145 stimulates cell apoptosis and prevents cell proliferation and migration by suppressing IGF-IR expression. It can also inhibit the onset of bladder cancer by affecting the IGF-IR signaling. MiR-145 silences KLF4 in bladder cancer cells and disrupts the Warburg effect by suppressing the path of KLF4 / PTBP1 /PKMs and inhibiting cell growth. In addition, miR-145 plays an important role in BC cells by adjusting UHRF1, which its expression may be regarded as a prognostic marker for the survival of patients with BC. MiR-145 is a new, strong, and direct target gene for HIF which can increase apoptosis in NMI BC cells. STAT3 expression and activation status are related to the human BC cells' response to miR-145 and its growth by modulating FOXO1 expression. Identifying the new molecular pathways and goals set by the miR-145 / UHRF1 axis may lead to a better understanding of progression and aggression in BC [57–66].

MiRNA-34a also acts as a tumor suppressor gene in various types of cancer. In bladder cancer, miR-34a prevents cancer cells proliferation, migration, and invasion through several pathways. MiR-34a, as a tumor suppressor in bladder cancer, directly targets CD44, which can effectively prevent related metastasis. MiR-34a can prevent the survival, colonization, and invasion of tumor cells by reducing the expression of HNF4G. MiR-34a also affects Notch1 signaling, which inhibits cell migration and invasion. The renewal of miR-34a expression in cancer cells caused by aging is at least partly due to the targeting of CDK6. The higher concentration of miR-34a results in excessive expression

of GOLPH3, a target gene for miR-34a, and the miR-34a/GOLPH3 axis plays an important role in cancer stem-like cells (CSCs), which considered as a therapeutic approach in the treatment of drug-resistant UBC (urothelial bladder cancer). MiR-34a directly regulates the TCF1/LEF1 axis, which is involved in bladder cancer metastasis and chemoresistance; the modulation of miR-34a and TCF1/LEF1 axis may serve as a new strategy for treating drug-resistant BC with increased chemical sensitivity. In another study, miR-34a, as a suppressor for miRNA, affected the miR-34a/TCF1/LEF1 axis and played a major role in the survival of BC cells. Therefore, the miR-34a/TCF1/LEF1 axis is a suitable candidate for treating drug-resistant BC through special targeting and increased chemosensitivity [67–70]. The role of other microRNAs in bladder cancer and their main functions are addressed in Table 1.

Use of microRNA in bio-fluid to screen bladder cancer

The special properties and sensitivity of miRNAs as biological markers could be applied in cancer screening and diagnosis. For example, recent technology has developed a method for detecting miRNAs in the urine aimed at earlier screening of bladder cancer. Therefore, the clinical diagnosis and bladder cancer prediction through body fluids such as urine and blood can be a major step in this respect [78]. Body fluids, as a source of miRNAs and miRNAs, are very important for the early diagnosis of bladder cancer. Any change in the level of miRNAs in urine and blood further proves their role as novel biochemical markers for bladder cancer diagnosis [79]. In 2010, Hank et al. published the first report on miRNAs in urine specimens, as a diagnostic marker for bladder cancer. Therefore today, the existence of miRNAs in biological fluids is considered as an important biological marker with a high sensitivity and specificity [80]. Regarding the various challenges ahead, more accurate and sensitive technological methodology is still required to focus on detecting circulating miRNAs as vital biomarkers in the diagnosis, categorization, and treatment of bladder cancer [78].

MicroRNAs in blood, urine, and tissues

Herein, we have investigated the studies focusing on variations in general microRNAs or specific microRNAs expression [81]. The latest and most important microRNAs expression variations in bladder cancer and the differences of altered microRNAs in biological samples along with the target molecules of the microRNAs are presented in Table 2. Accordingly, it can be concluded that the profiles of cancer-related microRNAs expression in tumor samples, urine, and blood samples of bladder cancer patients are significantly different compared to healthy individuals.

miRNA expression differs among blood, urine, and tissue samples, whereas most studies on bladder cancer are mainly based on tissue samples [81]. In this paper, for the first time, we have studied the main role of each miRNA separately in blood, urine, and cancerous tissue; these roles could be useful as a prognostic, diagnostic, or therapeutic tool in bladder cancer (Table 2).

microRNAs as diagnostic, prognostic, and therapeutic markers in bladder cancer

Screening

miRNAs in biological samples can provide valuable information regarding the oncogenesis of bladder cancer. Therefore, the usage of miRNA-based screening methods will gradually become a standardized approach in clinical diagnosis as an integral part of medical research. The development of new methods in recent years, enabling the measurement of small numbers of miRNAs, has provided a potential that could be used in screening for biomarkers.

Diagnosis

The diagnosis and follow-up of bladder cancer in affected patients depend on urine cytology and cystoscopy. Urine cytology with a high specificity (90–95%) is a reliable method for the diagnosis of bladder cancer. Many studies have shown that miRNAs are a new class of cancer diagnostic markers, with a mean sensitivity and specificity of about 70 and 80%, respectively, indicating that microRNAs can serve as useful diagnostic markers.

Prognosis

Some miRNAs could potentially be considered as biological markers in the prognosis of bladder cancer. Many studies have shown the role of microRNAs as prognostic markers, and different miRNAs have a role in the prognosis of bladder cancer; miR-200, miR-145, and miR-214 are all important prognostic parameters for this type of cancer.

Treatment

In the recent years, many studies have shown that microRNAs are affected during the development of bladder cancer and have suggested that some of them could be used as a potential therapeutic target for BC. Their results have shown that miRNAs targeting plays a significant role in the proliferation, migration, apoptosis, and invasion of bladder

Table 1 Expression of different microRNAs in bladder cancer and the mechanism of their effect

miRNA	Locus	Target	Target gene cellular function	miR Type	Mechanism of action	Annotation	Target validation in clinical BCs	Ext Notes	References
27a	19p13	*RUNX1* (runt-related transcription factor 1)	Transcription factor	TS	Novel target of miR-27a/ regulation of chemosensitivity in bladder cancer	Metabolic	NO	Highest sensitivity of 90% in blood sample	[32]
		SLC7A11 (solute carrier family 7 member 11)	Cysteine/glutamate exchanger		Changes the expression of microRNA-27a	Transporter	NO	Highest specificity of 90% in blood sample	
29c	1q32	*CDK6* (cell division protein kinase 6)	Cyclin-dependent protein kinase	TS	–Downregulation of DNA methyl transferase –Upregulation of demethylation genes –Overexpression of miR-29c inhibited the proliferation, migration, and affected G1 phase arrest	Cell cycle	YES		[32]
128	2q21	*VEGF-C*	RAS regulator, growth factor	TS	–Regulation of growth, invasion, apoptosis, stem cell properties, and differentiation of some tumor cells –VEGF-C is a direct target of miR-128 in BC cells	VEGF signaling	YES		[71]
138	3p21	*ZEB-2* (zinc finger E-box-binding homeobox 2)	Transcription repression	TS	–ZEB1 and ZEB-2 are essential for maintaining the mesenchymal cell phenotype and for EMT induction –ZEB-2 levels have significantly increased in comparison with normal bladder cells/tissue –BC metastases seem to contain low miR-138 levels	EMT	YES	The role of preventing metastatic bladder cancer	[72]

Table 1 (continued)

miRNA	Locus	Target	Target gene cellular function	miR Type	Mechanism of action	Annotation	Target validation in clinical BCs	Ext Notes	References
186	1p31	*HMGN5* (high mobility group nucleosome-binding domain 5)	Nucleosome, transcription activation	TS	–MiR-186 inhibits invasion and cell proliferation by suppressing NSBP1 expression –NSBP1 involves miR-186 suppressed EMT which decreases the mesenchymal markers expression (vimentin and N-cadherin) and epithelial marker (E-cadherin) expression induction	EMT	YES	MiR-186 suppresses NSBP1 by directly targeting NSBP1 UTR (3′-untranslated region) and (HMGN5) expression in human BC cells	[73]
214	1q24	*PDRG1* (P53 and DNA damage-regulated 1)	Oncogene, DNA damage-regulated gene	TS	–PDRG1 is a target gene for miR-214 –MiR-214 can directly regulate the oncogene PDRG1 protein and its tumor-suppressing effects in bladder cancer	Unknown			[74]
203	14q32	*BCL2L2* (Bcl-2-like protein 2)	Apoptosis	TS	MiR-203 expression can increase susceptibility to cisplatin by promoting apoptosis trough targeting of Bcl2	Apoptosis	YES		[32, 75–77]
		Twist1	Transcription factor 1		MiR-203 negatively targets Twist1 and acts as a tumor suppressor microRNA in BC	EMT	YES		

TS tumor suppressor, *EMT* epithelial-mesenchymal transition

Table 2 Comparison of microRNAs expression in different samples of bladder cancer patients

miRNAs	Sample types			Main role	Target of microRNA	References
	Urine	Tissue	Blood			
MiR-1	Down	Down	Down	Molecular mechanisms of cancer development	*PTMA*, *PNP*, *SRSF9/SRp30c*, *LASP1*, and *TAGLN1*	[6, 81–83]
MiR-7-5p		Down		Requires further investigation	*Gli3*	[84]
MiR-9		Up		Therapeutic target	*CBX7*, *CERS2*, *LASS2*	[81, 85]
MiR-10a		Up		Potential as biomarkers in pathogenesis	*ARSJ*, *CADM2*, *SOBP*, *BDNF*, and *FIGN*	[6, 81, 86]
MiR-10b	Up	Up		Therapeutic approach to block BC cell metastasis	*KLF4*, *HOXD10*	[87, 88]
MiR-15a	Up Down	Up		Contradictory results and needs further investigation	*FGF2*, *SCL11A2*, *PLAG1*, *ZBTB34*, and *MGATA4*	[81, 86]
MiR-16	Up	Up		Important regulator in the BC mechanism	*CCND1*	[89–91]
MiR-18a		Up	Up	Prognostic factor	*NEDD9*, *PHC3*, *INADL*, *TMEM170B*, and *HCFC2*	[86, 92]
MiR-19a		Up	Up	Diagnostic and therapeutic roles	*PTEN*	[81, 93, 94]
MiR-20a		Up		Diagnosis of NMIBC at early stages	*FGD4*, *PKD2*, *MAP3K2*, *ZNFX1*, and *PDCD1LG2*	[95, 96]
MiR-21	Down	Down	Down	Prognostic factor / therapeutic target	*ZNF367*, *GPR64*, *YOD1*, *PHF14*, and *PLEKHA1*	[81, 96–98]
MiR-25	Up	Down	Down	Diagnosis	*CD69*, *FNIP1*, *SCL12A5*, *MAN2A1*, and *ACTC1*	[6, 99, 100]
MiR-26a		Down		Important role in the molecular etiology of bladder cancer and application in bladder cancer therapy	*KLHDC5*, *TET2*, *STRADB*, *CHORDC1*, and *FAM98A*	[101, 102]
MiR-26b-5p		Down	Up	Good prognostic marker	*PDCD10*	[103, 104]
MiR-27b	Down	Down		Mechanisms of BC oncogenesis and metastasis	*DROSHA*, *EGFR* *MET*	[105, 106]
MiR-29a	Down	Down		Requires further investigation	*ATAD2B, COL3A1*, *ELN*, *HBP1*, and *COL4A4*	[81, 86]
MiR-29c	Up	Down		Requires further investigation	*CDK6*, *PI3K-AKT*	[81, 88]
MiR-30a		Down	Down	Therapeutic strategy	*NOTCH1*	[107, 108]
MiR-31		Down		Prognostic predictor and can serve as a potential therapeutic target	*FGFR3*, *integrin α5*	[109, 110]
MiR-34a		Down	Down	Important role in the molecular etiology of bladder cancer	*CD44*, *HNF4G*, *NOTCH1*	[81, 111, 112]
MiR-93	Up	Up		New therapeutic target	*CROT*, *FGD4*, *LATS2*, *TGFBR2*, *LASS2* and *ZKSCAN1*	[81, 113]
MiR-96	Up	Up		Partly contributes to aggressive malignancy	*IRS1*, and *MAP4K1*, *CDKN1A*	[113–115]
MiR-99a	Down	Down	Down	Therapeutic target	*FGFR3*	[81, 116]
MiR-100	Down	Down	Down	Diagnosis	*FGFR3*, *MTOR*	[106, 117]
MiR-101		Down		Diagnostic and prognostic	*EZH2*, *COX-2*, *MET*, *VEGF-C*, *FGFR3*, *PLCG*	[46]
MiR-122		Down	Down	therapeutic marker	*VEGF-C*	[118]
MiR-124		Down		Therapeutic candidate for BC	*CAV1*, *CDK-4*	[119, 120]
MiR-125a	Down	Down		Therapeutic role	*RAF1*, *KRAS*, *FGFR3 CDKN2A*, *TP53*	[81, 121, 122]
MiR-125b	Down	Down		Diagnostic markers with good discriminating power, high sensitivity, and high specificity	*E2F3*, *MMP13*, *SPHK1*	[81, 116, 123]
MiR-126	Up	Down		Requires further investigation	*ADAM9*	[80, 81, 124]
MiR-133a	Down	Down		Molecular mechanisms	*PTMA*, *PNP*, *LASP1*, *KRT7*, *FSCN-1*, *TAGLN1*, and *GSTP1*	[82, 83, 86, 116]

Table 2 (continued)

miRNAs	Sample types			Main role	Target of microRNA	References
	Urine	Tissue	Blood			
MiR-135a		Up		Diagnostic and therapeutic target	*PHLPP2* and *FOXO1*	[125]
MiR-141	Down	Up		Potential to diagnose invasive bladder tumors	*ZFR*, *RANBP6*, *ZEB-2*, *ABL2*, and *ARPC5*	[82, 126, 127]
MiR-143	Down	Down	Down	Therapeutic strategies	*PAI-1*, *IGF-1R*	[81, 128]
MiR-145	Down	Down		Therapeutic strategies	*PKC*, *FGFR3*, *CBFB*, *CLINT1 FSCN-1*, *ILK*, *PAK1*, *PPP3CA* *SERPIN1*, *SOCS7*, *IGF-1R*	[6, 81, 129, 130]
MiR-152	Down	Down	Down	Therapeutic modality and early biomarker for BC	*DNMT1*	[81, 131]
MiR-182	Up	Up		Screening	*RGS17*, *MITF*, *MFAP3*, CTTN, and *TMEM20*	[6, 80, 82, 132]
MiR-183	Up	Up		Screening	*ABAT*, *AKAP12*, *PIGX*, *PFN2*, and *PTPN4*	[81, 132–134]
MiR-186		Down		Novel therapeutic approach	*HMGN5*	[73]
MiR-195		Down		Therapeutic	*CDK-4*, *RAF1*, *MAP2K1/2*, *MAPK1*, *SOS1/2*, *GRB2*, *FGFR3*, *BIRC5*, *CDC42*, *GLUT3*, *WNT7A*	[86, 135]
MiR-204	Down	Down		Inhibition of cancer progression	*SLC37A3*, *PHOX2B*, *AP1S2*, *RAB22A*, and *HGSNAT*	[81, 136]
MiR-203	Down	Up		Mechanism related to BC pathogenesis and therapy	*BCL2L2*, *BIRC5*, *Twist1*	[6, 77]
MiR-210	Up	Up	Up	Screening, prediction, and monitoring of BC	*VEGF*	[81, 137]
MiR-214	Down	Down		Early diagnosis and prognosis	*PDRG1*	[6, 138]
MiR-218		Down		Diagnostic and therapeutic strategies for the treatment of BC	*LASP1*, *BMI-1*, *Glut1*	[139–141]
MiR-320a		Down	Down	Therapeutic strategy	*LPPR1*, *KITLG*, *DNER*, *PBX3*, and *IRF6*, *ITGB3*	[81, 142]
MiR-370		Down		Prevents tumor growth	*SLD5*	[143]
MiR-424	Down	Down		Molecular predictor and therapeutic target	*EGFR*	[100, 144]
MiR-429	Down	Up		Requires further investigation	*CDKN2B*	[81]
MiR-451		Down		Therapeutic strategy	*c-Myc*	[145]
MiR-497		Down	Down	Diagnosis	*BIRC5*, *WNT7A*	[6, 146]
MiR-574-3p		Down	Up	Requires further investigation	*MESDC1*	[81, 147]

cancer cells, and therefore, miRNAs can serve as novel targets in bladder cancer treatment.

The most comprehensive list of miRNAs and their target molecules that have been explicitly expressed in bladder cancer are displayed in Table 2. These molecules can be used as potential biomarkers in the diagnosis, prognosis, and development of new treatment strategies for bladder cancer.

Among all microRNAs, only miR-1, miR-99a, miR-100, and miR-143 have shown reduced expression in all tissues, blood, and urine samples. In contrast, only miR-21 and miR-210 levels have demonstrated increased expression in all three samples. However, in order to generalize these results, further studies on blood and urine samples of bladder cancer patients are required.

Expression of microRNAs, regulation in bladder cancer, target genes, and proposed mechanisms

The downregulation and upregulation of miRNAs have been reported in different studies. Furthermore, it has been shown that miRNAs regulate the expression of the target genes [31]. Downregulation of some miRNAs and their effect on certain targets have also been investigated in bladder cancer; they include miR-1, miR-99a, miR-100, miR-143, and the miR-200 family. The upregulation of some miRNAs in bladder cancer such as miR-21 and miR-210 was also identified. These miRNAs play a role in several cellular processes such as cell cycle growth, apoptosis, cell death programs, and signaling pathways in the downstream of cancer cells.

To date, numerous miRNAs have been recognized that are responsible in the progression and metastasis of bladder cancer cells. In the current study, we have investigated several specific cases and the role of microRNAs [32]. Studies have shown that the expression of miR-143 in bladder cancer is low and this low expression regulates the expression of RAS in this type of cancer. Some miRNAs such as miR-133a, miR-30-3p, and miR-199a are involved in the regulation of bladder cancer growth by regulating CRT7 activity [148–152].

miRNAs which affect the physiological activity of the cell (migration, invasion, proliferation, and survival) as a tumor suppressor include miR-106a, miR-223, and miR-613, respectively, which induce their effects by regulating MAPKs, NCOA1, and SPHK1. In addition, oncogenes such as miR-130, miR-200c, and miR-556, which imply their effect by regulating PTEN, RECK, and DAB2IP, respectively, play an important role in bladder cancer [153–155]. MiR-124-3p decreases the migration and progression of bladder cancer cells by targeting Rho-linked protein kinase 1 (ROCK1). Moreover, miR-124 has suppressive effects on cellular growth and angiogenesis of bladder cancer by targeting ubiquitin-like, containing PHD and UHRF1 [156, 157]. Furthermore, miR-124 inhibits the growth of bladder cancer by its direct effect on Cyclin D Kinase (CDK-4) [120]. MiR-409-3p, through targeting c-Met, decreases cell migration and progression in bladder cancer, [158] and miR-150-5p, as a tumor promoter, acts by reducing the chemical properties and increasing invasion in bladder cancer by targeting PDCD4 [159, 160].

Regarding previous studies, the downregulation of MIC-1 expression is significantly induced or enhanced in bladder cancer. This microRNA directly regulates the expression of the transgelin-2 protein (located on q21—1q25/exon 7) [59, 161]. In recent years, the new MS-LC method has been used to extract the transgelin protein from bladder tumoral tissue indicating that transgelin is a useful biomarker for the diagnosis and evaluation of metastatic lymph nodes in patients affected by bladder cancer. A sevenfold increase in the expression of transgelin was reported in the BC tissue compared to the control group; immunohistochemistry studies also indicated a positive association between TAGLN 2 expression and tumor grade in clinical samples of bladder cancer [162]. It has been reported that MIC-1 in bladder cancer acts via suppressing TAGLN 2 [83].

Recently, two microRNAs, 145 and 133a, have been identified with a tumor suppressor role in bladder cancer. MicroRNA-133a, like mic-1, involves the regulation of transgelin and miR-145 plays a vital role in the regulation of the FSCN-1 protein. Actin-binding proteins play a crucial role in the integrity of intercellular connections and increase their motions. The high expression of this gene may have a part in bladder cancer metastasis by increasing cellular movements; it is believed that the Fscn-1 gene probably has an oncogenic role in the development of bladder cancer [163]. Therefore, considering the direct inhibitory role of FSCN-1 in BC through viral vectors of microRNA, it can be expected to inhibit this type of cancer. In addition, miR-145 influences the PAK1 gene expression in bladder cancer which itself contributes to the progression and invasion of BC [129]. Mir-143 has also been evaluated in various studies revealing an interaction between 3′ UTR in the RAS-K gene and miR-143. RAS is considered an oncogene in tumors, and RAS gene regulation is done by using miR-143. These findings indicate that miR-143 may have a regulatory role on the level of RAS following translation [117, 164]. Furthermore, miR-195 has a suppressor role in different malignant tumors including bladder cancer, but its precise function has not yet been fully understood. Incremental regulation of miR-195 with repressing cdc42 and possibly through the activation of the Stat3 pathway inhibits cancerous cell proliferation in bladder cancer. In addition, increased cdc42 level can reduce the inhibitory effect of miR-195; therefore, miR-195, through direct targeting of the cdc42/stat3 pathway, reduces bladder cancer cells proliferation [135, 165].

Several studies have been conducted on different types of microRNAs used in the prognosis and treatment of bladder cancer. Accordingly, Table 3 presents a comprehensive database of the approved microRNAs and their mechanism in bladder cancer. In summary, these information could be used to diagnose the different microRNAs in order to better understand the pathophysiology of BC leading to its better control and treatment.

Conclusion

In conclusion, with respect to the aforementioned comprehensive information on the role and function of microRNAs in bladder cancer, the integrated analysis of BC is recommended for better treatment results. In the present study, the latest and most complete changes in miRNAs expression in bladder cancer were thoroughly reviewed. The contradictory results proved the need for more precise and systematic tests for this purpose. Our findings also provide useful information on the role and impact of miRNAs in bladder cancer for future studies, developing better strategies for the prognosis, diagnosis, and more promising treatments outcomes in bladder cancer. Better understanding of the mechanisms of action, signaling cascades and target molecules will allow us to develop effective drugs in the treatment and prevention of disease. In addition, early detection of miRNAs enables us to develop new screening and laboratory tests for healthy individuals.

Table 3 Types of microRNA that are used in the prognosis and treatment of bladder cancer

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-187-5P		Oncogene	–Reduces the risk of recurrence in patients with low expression of miR-187-5P –Increases cell proliferation –Decreases apoptosis	Affects 5637 and UM-UC-3 cells	[166]
MiR-9	*GSK-3β*	Oncogene	–Suppressing the expression of GSK-3β –Facilitating the pathogenesis of bladder cancer –Decreases apoptosis	Other target CDH-1 CBX7, CERS2	[35]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-411	*MLLT11*	TS	–Suppresses the expression of MLLT11 –Induces the expression of p21 –Triggers the G2/M stage cell arrest (inhibition of BC tumor growth)	ZnT1 could regulate cellular signaling, migration, and cell growth. ZnT1 can regulate MMP2 and cyclin D1 expression. Therefore, miR-411 can inhibit cell proliferation by inhibiting cyclin D1 levels and inhibiting cellular invasion and metastasis by inhibiting the MMP2 expression	[167, 168]
	ZnT1		–Low expression in bladder cancer which is negatively correlated with ZnT1 expression –MiR-411 affects the progression and growth rate of bladder cancer cells with the effect of ZnT1		

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-145	*N-Cadherin*	TS	MiRNA-145 by regulating N-Cadherin inhibits the migration and invasion of cancer stem cells	–Could be used as a biologically diagnostic and predictive marker –Could be used as a therapeutic goal for treating BC	[169]
MiR-96	*HERG1*	Oncogene	–Increases invasion and proliferation of cancer cells -Decreases apoptosis	–Could be used as a therapeutic goal for treating BC	[170]
MiR-183-5p	-	Oncogene	–High expression in bladder cancer tissues –Involved in bladder cancer development	Helps the progression of cancer by affecting the epithelial-to-mesenchymal pathway	[133]
MiR-186	*VEGF-C*	TS	MiR-186 through its effect on VEGF-C regulates the progression and metastasis of bladder cancer	Downregulated level of both mRNA and VEGF-C protein in tumor tissue, blood, and urine of bladder cancer patients	[171]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-612	*Malic enzyme 1* (*ME1*)	TS	MiR-612 directly affects ME1 expression and leads to a decrease in cell growth, migration, and progression	–ME1 is a NADP + cytosolic enzyme that is responsible for producing NADPH, fatty acid biosynthesis, and lipogenesis in cells and tissues –Could be used as a therapeutic goal for treating BC	[172]
MiR-497	*E2F3*	TS	MiR-497 can inhibit the invasion, progression, proliferation and migration of bladder cancer cells by targeting E2F3	–Increased expression of miR-497 significantly reduces the number of T24 and BIU-87 invasive cells. –Expression of miR-497 increases the levels of E-cadherin protein and mRNA while active levels of wining and α-smooth muscles are reduced –Could be used as a biologically diagnostic and predictive marker	[173, 174]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-539	*IGF-1R*	TS	The miR-539 directly manages the growth factor 1 (IGF-1R) receptor besides inhibiting proliferation and cellular invasion in bladder cancer	–miR-539/IGF-1R could be used as a potential target for the treatment of bladder cancer	[175]
MiR-379-5p	*MDM2*	TS	–Low expression in bladder cancer tissues and cell lines –Affects MDM2 and regulates the proliferation, migration and invasion of cancer cells	–miR-379-5p/MDM2 could be used as a potential target for the treatment of bladder cancer	[176]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-154	*RUNX2* *RSF1*	TS	–MiR-154 significantly overexpresses RSF1 and RUNX2 and inhibits the invasion and migration of cancer cells	–The miR-154-RSF1/RUNX2 interaction in bladder cancer could be used as a potential target for the treatment of bladder cancer –To date, several miRNAs, including miR-520b, miR-375, miR-7, and miR-217, have been proved to inhibit cell growth and survival through targeting ATG7 in tumor cells	[177, 178]
	ATG7		–Decreases the expression of ATG7 and plays a suppressor role in proliferation		
MiR-21	*PPP2R2A*	Oncogene	MiR-21 through PPP2R2A induces the growth of stem cells	I.V. MKAD-21 inhibitor effectively reduces tumor growth by the PPP2R2A-ERK network	[179]
MiR-135a	*Cdr1*	?	Cdr1 directly bounds to miR-135a and shows anti-oncogenic functions	Overexpression of Cdr decreases the proliferation, invasion, and migration of bladder cancer cells both in vitro and in vivo	[180]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-22-3p	*NET1*	?	By targeting NET1 and MiR-22-3p reduces BC chemical resistance	Could be used as a biologically diagnostic and predictive marker	[181]
MiR-200	*XIST*	TS	MiR-200c by reduction in the expression of XIST inhibits cell clone formation, self-renewal ability, EMT, and growth of bladder cancer cells	–Targeting XIST could be used as a potential strategy for the treatment of bladder cancer	[182]
MiR-223-5p	*ANLN*	?	MiR-223-5p directly regulates the ANLN gene in BC cells, and up-expression of ANLN leads to poor prognosis in patients with BC	–	[183, 184]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-130b	*VGLL4*	?	miR-130b by targeting VGLL4 shows its role in BC. Suppression of VGLL4 results in the migration, proliferation, and invasion of BC cells	The miR-130b could be used as a potential strategy for the clinical treatment in BC	[185]
MiR-22	*MAPK1*	TS	miR-22 by inhibiting the MAPK1/Slug/vimentin loop could suppress the epithelial-mesenchymal transition (EMT) of bladder cancer cells	MAPK1/Slug/vimentin loop could be used in the treatment of bladder cancer	[186]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-146b	*BDNF*	?	Positive correlation between MiR-146b and BDNF VAL-66MET polymorphism is associated with a risk of bladder cancer	MiR-146b could be used as a diagnostic marker	[187]
MiR-126	*KRAS*	TS	–miR-126 negatively regulates KRAS –Overexpression of KRAS increases cell efficiency, migration and invasion, and active signaling pathways of PI3K/AKT and mTOR	MiR-126 could be used as a prognostic marker or a therapeutic goal for bladder cancer	[188]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-149-3p	*S100A4*	TS	-miR-149-3p has anti-metastatic effects -Overexpression of miR-149-3p by reduction in S100A4 expression in BC cells inhibits its proliferation, migration, and invasion	S100A4 in metastatic tumor cells has high level expression and promotes growth, migration, and invasion of the cells	[189]
MiR-145-5p	*TAGLN2*	TS	MiR-145-5p through regulating TAGLN2 expression modulates cell proliferation, differentiation, migration, and apoptosis	MiR-145-5p / TAGLN2 axis could be used as a therapeutic goal for bladder cancer	[190]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-125a-5p	*FUT4*	TS	MiR-125a-5p as a tumor suppressor in bladder cancer acts by targeting FUT4 and inhibiting the progression of bladder cancer	FUT4 acts as an oncogen in bladder cancer with induction of cell migration, proliferation, and invasion	[122]
MiR-124	*STAT3* *Caveolin 1*	TS	MiR-124 can suppress bladder cancer tumors by targeting STAT3 MiR-124 has a suppressive role in the proliferation, migration, and invasion of bladder cancer cells by targeting CAV1	STAT3 is considered an oncogene, and increased activity of STAT3 is directly associated with the growth and survival of BC tumors	[119, 191]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-3619-5p	*β-catenin CDK2 p21*	TS	MiR-3619 expression inhibits its cell growth, invasion, and metastasis	-P21, CDK2, and β-catenin are direct downstream targets of miR-3619 -Could be used as a new therapeutic target for the treatment of bladder cancer	[1]
MiR-374a	*WNT5A*	TS	MiR-374a reduces the expression of WNT5A and leads to decreased invasion and metastasis,	-WNT5A is an oncogene in bladder cancer that increases invasion in both T24 and J28 - miR-374a may be a new therapeutic target	[192]
Micro-RNA-1247	*RAB36*	TS	–MiR-1247 expression was significantly downregulated in bladder cancer tissues and cell lines –MiR-1247 expression and RAB36 are directly associated with bladder cancer and metastasis	MiR-146b could be used as a diagnostic marker	[193]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MicroRNA-206	*YRDC*	TS	MiR-206 by decreasing YRDC expression inhibits proliferation, progression, colony formation, and G0/G1 cell cycle arrest	MiR-206 could be used as a new target for the treatment of bladder cancer by targeting YRDC	[194]
MiR-137	*PAQR3*	TS or Oncogene	–Increased expression in bladder cancer cells and tissues –MiR-137 expression by targeting PAQR3 promoted cell proliferation, progression, and migration in bladder cancer	MiR-137/PAQR3 axis could be used to find a therapeutic strategy for the treatment of bladder cancer	[195]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-758-3	*NOTCH2*	TS	MiR-758-3p suppresses NOTCH2, which can suppress migration and invasion of bladder cancer cells	MiR-758-3 may be a new therapeutic target	[196]
MiR-335	*CRKL*	TS	MiR-335 by suppressing CRKL can suppress proliferation and migration of bladder cancer cells	–Low expression in bladder cancer	[197]
Micro-RNA-223	*WDR62*	Onco or TS	Micro-RNA-223 regulates the expression of WDR62	–Knockdown of WDR62 significantly reduces tumor growth and induces apoptosis in BC	[198]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MicroRNA-338-3p	*ETS1*	TS	MiR-338-3p could decrease the development of bladder cancer proliferation, invasion, and EMT by modulation of ETS1 expression	Further study is required	[199]
MiR-3622a	*LASS2*	Onco	MiR-3622a by down-regulating LASS2 stimulates proliferation and invasion of bladder cancer cells	Further study is required	[200]
MicroRNA-663b	*TUSC2*	?	MiR-663b by targeting TUSC2 modulates survival and apoptosis in bladder cancer cells	Could be used as a new therapeutic target for the treatment of bladder cancer	[201]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MiR-506	*RWDD4*	TS	MiR-506 could suppress the invasive properties of bladder cancer cells by targeting RWDD4	Could be used as a new therapeutic target for the treatment of bladder cancer	[202]
Micro-RNA-132	*TGFβ1/Smad2 signaling pathway*	?	MiR-132 may play an important role in the metastasis of bladder cancer cells through the TGFβ1/Smad2 signaling pathway	Further study is required	[203]
Micro-RNA-153	*IDO-1*	TS	MiR-153 targets IDO-1 expression and has anti-tumor activity in BC	Further study is required	[204]

Table 3 (continued)

MicroRNA	Target	Notes on target gene	Mechanism of action	Notes	References
MicroRNA-328-3p	*ITGA5*	TS	MiR-328-3p suppresses cell migration, proliferation, and progression of bladder cancer by targeting ITGA5	MiR-328-3p inhibits EMT, activation of PI3K/AKT pathway, and tumor growth of bladder cancer	[205]
MicroRNA-621	*TRIM29*	TS	MiR-621 inhibits the proliferation and metastasis of bladder cancer cells by targeting TRIM29	The miR-621/TRIM29 axis acts through the Wnt/β-catenin signaling pathway –MicroRNA-621 could be used as a diagnostic marker	[206]
MicroRNA-3648	*TCF21*	Onco	MiR-3648 inhibits the expression of TCF21, which leads to a decreased KISS1 expression, migration, and invasion of bladder cancer cells	MicroRNA-3648 could be used as a therapeutic marker	[207]

*TS: tumor suppressor

Acknowledgments The authors appreciate the cooperation of Mashhad University of Medical Sciences. This article was conducted within the projects, which have received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie Grant Agreement No. 754432 and the Polish Ministry of Science and Higher Education, from financial resources for science in 2018-2023 granted for the implementation of an international co-financed project.

Author contributions PKP, FY, HMT, ZH, and AS participated in data collection and manuscript writing. NK and AT participated as the grammatical editor. S-AE designed and drafted the article. All authors have fully read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing financial and non-financial interests.

References

1. Zhang Q, Miao S, Han X, Li C, Zhang M, Cui K, et al. MicroRNA-3619-5p suppresses bladder carcinoma progression by directly targeting β-catenin and CDK2 and activating p21. Cell Death Dis. 2018;9(10):960.
2. Wu Z, Huang W, Wang X, Wang T, Chen Y, Chen B, et al. Circular RNA CEP128 acts as a sponge of miR-145-5p in promoting the bladder cancer progression via regulating SOX11. Mol Med. 2018;24(1):40.
3. Bi J, Liu H, Cai Z, Dong W, Jiang N, Yang M, et al. Circ-BPTF promotes bladder cancer progression and recurrence through the miR-31-5p/RAB27A axis. Aging (Albany NY). 2018;10(8):1964.
4. Lin Y-L, Xie P-G, Ma J-G. Aberrant methylation of CDH13 is a potential biomarker for predicting the recurrence and progression of non-muscle-invasive bladder cancer. Med Sci Monit Int Med J Exp Clin Res. 2014;20:1572.
5. Zhang L, Feng C, Zhou Y, Zhou Q. Dysregulated genes targeted by microRNAs and metabolic pathways in bladder cancer revealed by bioinformatics methods. Oncol Lett. 2018;15(6):9617–24.
6. Li X, Chen J, Hu X, Huang Y, Li Z, Zhou L, et al. Comparative mRNA and microRNA expression profiling of three genitourinary cancers reveals common hallmarks and cancer-specific molecular events. PLoS ONE. 2011;6(7):e22570.
7. Guo A-Y, Sun J, Jia P, Zhao Z. A novel microRNA and transcription factor mediated regulatory network in schizophrenia. BMC Syst Biol. 2010;4(1):10.
8. Wu K, He J, Pu W, Peng Y. The role of Exportin-5 in microRNA biogenesis and cancer. Genom Proteomics Bioinform. 2018;16(2):120–6.
9. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004;116(2):281–97.
10. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120(1):15–20.
11. Moghaddam AS, Afshari JT, Esmaeili S-A, Saburi E, Joneidi Z, Momtazi-Borojeni AA. Cardioprotective microRNAs: lessons from stem cell-derived exosomal microRNAs to treat cardiovascular disease. Atherosclerosis. 2019;285:1–9.
12. Vahidi Z, Samadi M, Mahmoudi M, RezaieYazdi Z, Sahebari M, Tabasi N, et al. *Lactobacillus rhamnosus* and *Lactobacillus delbrueckii* ameliorate the expression of miR-155 and miR-181a in SLE patients. J Funct Foods. 2018;48:228–33.
13. Yu X, Li Z, Shen J, Wu WK, Liang J, Weng X, et al. MicroRNA-10b promotes nucleus pulposus cell proliferation through RhoC-Akt pathway by targeting HOXD10 in intervetebral disc degeneration. PLoS ONE. 2013;8(12):e83080.
14. Zhang X, Hu S, Zhang X, Wang L, Zhang X, Yan B, et al. MicroRNA-7 arrests cell cycle in G1 phase by directly targeting CCNE1 in human hepatocellular carcinoma cells. Biochem Biophys Res Commun. 2014;443(3):1078–84.
15. Huber RM, Rajski M, Sivasankaran B, Moncayo G, Hemmings BA, Merlo A. Deltex-1 activates mitotic signaling and proliferation and increases the clonogenic and invasive potential of U373 and LN18 glioblastoma cells and correlates with patient survival. PLoS ONE. 2013;8(2):e57793.
16. Khvorova A, Reynolds A, Jayasena SD. Functional siRNAs and miRNAs exhibit strand bias. Cell. 2003;115(2):209–16.
17. Miska EA. How microRNAs control cell division, differentiation and death. Curr Opin Genet Dev. 2005;15(5):563–8.
18. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci. 2002;99(24):15524–9.
19. Si M, Zhu S, Wu H, Lu Z, Wu F, Mo Y. miR-21-mediated tumor growth. Oncogene. 2007;26(19):2799.
20. Ibarra I, Erlich Y, Muthuswamy SK, Sachidanandam R, Hannon GJ. A role for microRNAs in maintenance of mouse mammary epithelial progenitor cells. Genes Dev. 2007;21(24):3238–43.
21. Akao Y, Nakagawa Y, Naoe T. let-7 microRNA functions as a potential growth suppressor in human colon cancer cells. Biol Pharm Bull. 2006;29(5):903–6.
22. Li M-P, Hu Y-D, Hu X-L, Zhang Y-J, Yang Y-L, Jiang C, et al. MiRNAs and miRNA polymorphisms modify drug response. Int J Environ Res Public Health. 2016;13(11):1096.
23. Kang W, Friedländer MR. Computational prediction of miRNA genes from small RNA sequencing data. Front Bioeng Biotechnol . 2015;3:7.
24. Schmidt MF. Drug target miRNAs: chances and challenges. Trends Biotechnol. 2014;32(11):578–85.
25. Vincenzi B, Zoccoli A, Schiavon G, Iuliani M, Pantano F, Dell'Aquila E, et al. Dicer and Drosha expression and response to Bevacizumab-based therapy in advanced colorectal cancer patients. Eur J Cancer. 2013;49(6):1501–8.
26. Maiti M, Nauwelaerts K, Herdewijn P. Pre-microRNA binding aminoglycosides and antitumor drugs as inhibitors of Dicer catalyzed microRNA processing. Bioorg Med Chem Lett. 2012;22(4):1709–11.
27. Rukov JL, Wilentzik R, Jaffe I, Vinther J, Shomron N. PharmacomiR: linking microRNAs and drug effects. Brief Bioinform. 2014;15(4):648–59.
28. Liu X, Wang S, Meng F, Wang J, Zhang Y, Dai E, et al. SM2miR: a database of the experimentally validated small molecules' effects on microRNA expression. Bioinformatics. 2013;29(3):409–11.
29. Wu X-R. Urothelial tumorigenesis: a tale of divergent pathways. Nat Rev Cancer. 2005;5(9):713.
30. Guancial EA, Bellmunt J, Yeh S, Rosenberg JE, Berman DM, editors. The evolving understanding of microRNA in bladder cancer. Urologic oncology: seminars and original investigations; 2014: Elsevier.
31. Matullo G, Naccarati A, Pardini B. Micro RNA expression profiling in bladder cancer: the challenge of next-generation sequencing in tissues and biofluids. Int J Cancer. 2016;138(10):2334–45.
32. Enokida H, Yoshino H, Matsushita R, Nakagawa M. The role of microRNAs in bladder cancer. Investig Clin Urol. 2016;57(Suppl 1):S60–76.
33. Yamasaki T, Yoshino H, Enokida H, Hidaka H, Chiyomaru T, Nohata N, et al. Novel molecular targets regulated by tumor

suppressors microRNA-1 and microRNA-133a in bladder cancer. Int J Oncol. 2012;40(6):1821–30.
34. Yu D, Zhang C, Gui J. RNA-binding protein HuR promotes bladder cancer progression by competitively binding to the long noncoding HOTAIR with miR-1. OncoTargets Ther. 2017;10:2609.
35. Dong Z, Zhang D, Wang S, Lin Z. Target inhibition on GSK-3β by miR-9 to modulate proliferation and apoptosis of bladder cancer cells. Eur Rev Med Pharmacol Sci. 2018;22(10):3018–26.
36. Xie Y, Ma X, Chen L, Li H, Gu L, Gao Y, et al. MicroRNAs with prognostic significance in bladder cancer: a systematic review and meta-analysis. Sci Rep. 2017;7(1):1–12.
37. Smakman N, Schaap N, Snijckers CM, Rinkes IHB, Kranenburg O. NS-398, a selective cyclooxygenase-2 inhibitor, reduces experimental bladder carcinoma outgrowth by inhibiting tumor cell proliferation. Urology. 2005;66(2):434–40.
38. Zuo W, Wang Z-Z, Xue J. Artesunate induces apoptosis of bladder cancer cells by miR-16 regulation of COX-2 expression. Int J Mol Sci. 2014;15(8):14298–312.
39. Greenhough A, Smartt HJ, Moore AE, Roberts HR, Williams AC, Paraskeva C, et al. The COX-2/PGE 2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. Carcinogenesis. 2009;30(3):377–86.
40. Yu G, Jia Z, Dou Z. miR-24-3p regulates bladder cancer cell proliferation, migration, invasion and autophagy by targeting DEDD. Oncol Rep. 2017;37(2):1123–31.
41. Chen L, Long Y, Han Z, Yuan Z, Liu W, Yang F, et al. MicroRNA-101 inhibits cell migration and invasion in bladder cancer via targeting FZD4. Exp Therap Med. 2019;17(2):1476–85.
42. Lei Y, Li B, Tong S, Qi L, Hu X, Cui Y, et al. miR-101 suppresses vascular endothelial growth factor C that inhibits migration and invasion and enhances cisplatin chemosensitivity of bladder cancer cells. PLoS ONE. 2015;10(2):e0117809.
43. Bu Q, Fang Y, Cao Y, Chen Q, Liu Y. Enforced expression of miR-101 enhances cisplatin sensitivity in human bladder cancer cells by modulating the cyclooxygenase-2 pathway. Mol Med Rep. 2014;10(4):2203–9.
44. Hu Z, Lin Y, Chen H, Mao Y, Wu J, Zhu Y, et al. MicroRNA-101 suppresses motility of bladder cancer cells by targeting c-Met. Biochem Biophys Res Commun. 2013;435(1):82–7.
45. Zabolotneva AA, Zhavoronkov A, Garazha AV, Roumiantsev SA, Buzdin AA. Characteristic patterns of microRNA expression in human bladder cancer. Front Genet. 2013;3:310.
46. Zhang H, Qi F, Cao Y, Chen M, Zu X. Down-regulated microRNA-101 in bladder transitional cell carcinoma is associated with poor prognosis. Med Sci Monitor Int Med J Exp Clin Res. 2014;20:812.
47. Friedman JM, Liang G, Liu C-C, Wolff EM, Tsai YC, Ye W, et al. The putative tumor suppressor microRNA-101 modulates the cancer epigenome by repressing the polycomb group protein EZH2. Can Res. 2009;69(6):2623–9.
48. Long Y, Wu Z, Yang X, Chen L, Han Z, Zhang Y, et al. MicroRNA-101 inhibits the proliferation and invasion of bladder cancer cells via targeting c-FOS. Mol Med Rep. 2016;14(3):2651–6.
49. Dyrskjøt L, Ostenfeld MS, Bramsen JB, Silahtaroglu AN, Lamy P, Ramanathan R, et al. Genomic profiling of microRNAs in bladder cancer: miR-129 is associated with poor outcome and promotes cell death in vitro. Can Res. 2009;69(11):4851–60.
50. Shen H, Blijlevens M, Yang N, Frangou C, Wilson KE, Xu B, et al. Sox4 expression confers bladder cancer stem cell properties and predicts for poor patient outcome. Int J Biol Sci. 2015;11(12):1363.
51. Liu W, Peng Y, Tobin DJ. A new 12-gene diagnostic biomarker signature of melanoma revealed by integrated microarray analysis. PeerJ. 2013;1:e49.
52. Kong C, Zhu Y, Liu D, Yu M, Li S, Li Z, et al. Role of protein kinase C-alpha in superficial bladder carcinoma recurrence. Urology. 2005;65(6):1228–32.
53. Watanabe T, Shinohara N, Moriya K, Sazawa A, Kobayashi Y, Ogiso Y, et al. Significance of the Grb2 and son of sevenless (Sos) proteins in human bladder cancer cell lines. IUBMB Life. 2000;49(4):317–20.
54. Jang IK, Cronshaw DG, Xie L-K, Fang G, Zhang J, Oh H, et al. Growth-factor receptor-bound protein-2 (Grb2) signaling in B cells controls lymphoid follicle organization and germinal center reaction. Proc Natl Acad Sci. 2011;108(19):7926–31.
55. Li Q, Lozano G. Molecular pathways: targeting Mdm2 and Mdm4 in cancer therapy. Clin Cancer Res. 2013;19(1):34–41.
56. Veerla S, Lindgren D, Kvist A, Frigyesi A, Staaf J, Persson H, et al. MiRNA expression in urothelial carcinomas: important roles of miR-10a, miR-222, miR-125b, miR-7 and miR-452 for tumor stage and metastasis, and frequent homozygous losses of miR-31. Int J Cancer. 2009;124(9):2236–42.
57. Fukuda T, Ochi H, Sunamura S, Haiden A, Bando W, Inose H, et al. MicroRNA-145 regulates osteoblastic differentiation by targeting the transcription factor Cbfb. FEBS Lett. 2015;589(21):3302–8.
58. Ostenfeld MS, Bramsen JB, Lamy P, Villadsen SB, Fristrup N, Sørensen KD, et al. miR-145 induces caspase-dependent and-independent cell death in urothelial cancer cell lines with targeting of an expression signature present in Ta bladder tumors. Oncogene. 2010;29(7):1073.
59. Chiyomaru T, Enokida H, Tatarano S, Kawahara K, Uchida Y, Nishiyama K, et al. miR-145 and miR-133a function as tumour suppressors and directly regulate FSCN1 expression in bladder cancer. Br J Cancer. 2010;102(5):883–91.
60. Cui SY, Wang R, Chen LB. Micro RNA-145: a potent tumour suppressor that regulates multiple cellular pathways. J Cell Mol Med. 2014;18(10):1913–26.
61. Villadsen S, Bramsen JB, Ostenfeld M, Wiklund E, Fristrup N, Gao S, et al. The miR-143/-145 cluster regulates plasminogen activator inhibitor-1 in bladder cancer. Br J Cancer. 2012;106(2):366.
62. Noguchi S, Yamada N, Kumazaki M, Yasui Y, Iwasaki J, Naito S, et al. socs7, a target gene of microRNA-145, regulates interferon-β induction through STAT3 nuclear translocation in bladder cancer cells. Cell Death Dis. 2013;4(2):e482-e.
63. Zhu Z, Xu T, Wang L, Wang X, Zhong S, Xu C, et al. MicroRNA-145 directly targets the insulin-like growth factor receptor I in human bladder cancer cells. FEBS Lett. 2014;588(17):3180–5.
64. Minami K, Taniguchi K, Sugito N, Kuranaga Y, Inamoto T, Takahara K, et al. MiR-145 negatively regulates Warburg effect by silencing KLF4 and PTBP1 in bladder cancer cells. Oncotarget. 2017;8(20):33064.
65. Takai T, Yoshikawa Y, Inamoto T, Minami K, Taniguchi K, Sugito N, et al. A novel combination RNAi toward Warburg effect by replacement with miR-145 and silencing of PTBP1 induces apoptotic cell death in bladder cancer cells. Int J Mol Sci. 2017;18(1):179.
66. Matsushita R, Yoshino H, Enokida H, Goto Y, Miyamoto K, Yonemori M, et al. Regulation of UHRF1 by dual-strand tumor-suppressor microRNA-145 (miR-145-5p and miR-145-3p): inhibition of bladder cancer cell aggressiveness. Oncotarget. 2016;7(19):28460.
67. Zhang Q, Zhuang J, Deng Y, Yang L, Cao W, Chen W, et al. miR34a/GOLPH3 Axis abrogates urothelial bladder cancer chemoresistance via reduced cancer stemness. Theranostics. 2017;7(19):4777.
68. Sun H, Tian J, Xian W, Xie T, Yang X. miR-34a inhibits proliferation and invasion of bladder cancer cells by targeting orphan nuclear receptor HNF4G. Disease markers. 2015;2015.

69. Zhang C, Yao Z, Zhu M, Ma X, Shi T, Li H, et al. Inhibitory effects of microRNA-34a on cell migration and invasion of invasive urothelial bladder carcinoma by targeting Notch1. J Huazhong Univ Sci Technol [Medical Sciences]. 2012;32(3):375–82.
70. Lodygin D, Tarasov V, Epanchintsev A, Berking C, Knyazeva T, Körner H, et al. Inactivation of miR-34a by aberrant CpG methylation in multiple types of cancer. Cell Cycle. 2008;7(16):2591–600.
71. Zhou X, Qi L, Tong S, Cui Y, Chen J, Huang T, et al. miR-128 downregulation promotes growth and metastasis of bladder cancer cells and involves VEGF-C upregulation. Oncol Lett. 2015;10(5):3183–90.
72. Sun D-K, Wang J-M, Zhang P, Wang Y-Q. MicroRNA-138 regulates metastatic potential of bladder cancer through ZEB2. Cell Physiol Biochem. 2015;37(6):2366–74.
73. Yao K, He L, Gan Y, Zeng Q, Dai Y, Tan J. MiR-186 suppresses the growth and metastasis of bladder cancer by targeting NSBP1. Diagnostic pathology. 2015;10(1):146.
74. Wang J, Zhang X, Wang L, Yang Y, Dong Z, Wang H, et al. MicroRNA-214 suppresses oncogenesis and exerts impact on prognosis by targeting PDRG1 in bladder cancer. PLoS ONE. 2015;10(2):e0118086.
75. Xu D, Wang Q, An Y, Xu L. miR-203 regulates the proliferation, apoptosis and cell cycle progression of pancreatic cancer cells by targeting Survivin. Mol Med Rep. 2013;8(2):379–84.
76. Zhang X, Zhang Y, Liu X, Fang A, Li P, Li Z, et al. MicroRNA-203 is a prognostic indicator in bladder cancer and enhances chemosensitivity to cisplatin via apoptosis by targeting Bcl-w and survivin. PLoS ONE. 2015;10(11):e0143441.
77. Shen J, Zhang J, Xiao M, Yang J, Zhang N. miR-203 suppresses bladder cancer cell growth and targets Twist1. Oncol Res Featur Preclin Clin Cancer Therapeut. 2018;26(8):1155–65.
78. Liu X, Liu X, Wu Y, Wu Q, Wang Q, Yang Z, et al. MicroRNAs in biofluids are novel tools for bladder cancer screening. Oncotarget. 2017;8(19):32370.
79. Netto GJ. Molecular biomarkers in urothelial carcinoma of the bladder: are we there yet? Nat Rev Urol. 2012;9(1):41.
80. Hanke M, Hoefig K, Merz H, Feller AC, Kausch I, Jocham D et al., editors. A robust methodology to study urine microRNA as tumor marker: microRNA-126 and microRNA-182 are related to urinary bladder cancer. Urologic oncology: seminars and original investigations; 2010: Elsevier.
81. Dong F, Xu T, Shen Y, Zhong S, Chen S, Ding Q, et al. Dysregulation of miRNAs in bladder cancer: altered expression with aberrant biogenesis procedure. Oncotarget. 2017;8(16):27547.
82. Han Y, Chen J, Zhao X, Liang C, Wang Y, Sun L, et al. MicroRNA expression signatures of bladder cancer revealed by deep sequencing. PLoS ONE. 2011;6(3):e18286.
83. Yoshino H, Chiyomaru T, Enokida H, Kawakami K, Tatarano S, Nishiyama K, et al. The tumour-suppressive function of miR-1 and miR-133a targeting TAGLN2 in bladder cancer. Br J Cancer. 2011;104(5):808.
84. Li J, Qiu M, An Y, Huang J, Gong C. miR-7-5p acts as a tumor suppressor in bladder cancer by regulating the hedgehog pathway factor Gli3. Biochem Biophys Res Commun. 2018;503(3):2101–7.
85. Xie D, Shang C, Zhang H, Guo Y, Tong X. Up-regulation of miR-9 target CBX7 to regulate invasion ability of bladder transitional cell carcinoma. Med Sci Monitor Int Med J Exp Clin Res. 2015;21:225.
86. Gulìa C, Baldassarra S, Signore F, Rigon G, Pizzuti V, Gaffi M, et al. Role of non-coding RNAs in the etiology of bladder cancer. Genes. 2017;8(11):339.
87. Xiao H, Li H, Yu G, Xiao W, Hu J, Tang K, et al. MicroRNA-10b promotes migration and invasion through KLF4 and HOXD10 in human bladder cancer. Oncol Rep. 2014;31(4):1832–8.
88. Eissa S, Matboli M, Hegazy MG, Kotb YM, Essawy NO. Evaluation of urinary microRNA panel in bladder cancer diagnosis: relation to bilharziasis. Translat Res. 2015;165(6):731–9.
89. Jiang Q-Q, Liu B, Yuan T. MicroRNA-16 inhibits bladder cancer proliferation by targeting Cyclin D1. Asian Pac J Cancer Prev. 2013;14(7):4127–30.
90. Güllü Amuran G, Peker Eyuboglu I, Tinay I, Akkiprik M. New insights in bladder cancer diagnosis: urinary miRNAs and proteins. Med Sci . 2018;6(4):113.
91. Kent M, Zwingenberger A, Westropp J, Barrett L, Ghosh P, Vinall RL. MiRNA profiling of dogs with transitional cell carcinoma of the bladder using blood and urine samples. AACR; 2016.
92. Zhou L, Li Z, Pan X, Lai Y, Quan J, Zhao L, et al. Identification of miR-18a-5p as an oncogene and prognostic biomarker in RCC. Am J Translat Res. 2018;10(6):1874.
93. Feng Y, Liu J, Kang Y, He Y, Liang B, Yang P, et al. miR-19a acts as an oncogenic microRNA and is up-regulated in bladder cancer. J Exp Clin Cancer Res. 2014;33(1):67.
94. Jiang X, Du L, Duan W, Wang R, Yan K, Wang L, et al. Serum microRNA expression signatures as novel noninvasive biomarkers for prediction and prognosis of muscle-invasive bladder cancer. Oncotarget. 2016;7(24):36733.
95. Huang X, Zhao H, Qian X, Qiu J. MiR-20a in cell-free urine as a potential diagnostic biomarker for non-muscle invasive bladder cancer: a Chinese population-based study. Int J Clin Exp Med. 2018;11:209–16.
96. Mitash N, Agnihotri S, Tiwari S, Agrawal V, Mandhani A. MicroRNA-21 could be a molecular marker to predict the recurrence of nonmuscle invasive bladder cancer. IJU J Urol Soc India. 2017;33(4):283.
97. De Long J, Sullivan TB, Humphrey J, Logvinenko T, Summerhayes KA, Kozinn S, et al. A non-invasive miRNA based assay to detect bladder cancer in cell-free urine. Am J Translat Res. 2015;7(11):2500.
98. Zhang HH, Qi F, Cao YH, Zu XB, Chen MF. Expression and clinical significance of microRNA-21, maspin and vascular endothelial growth factor-C in bladder cancer. Oncol Lett . 2015;10(4):2610–6.
99. Adam L, Wszolek MF, Liu C-G, Jing W, Diao L, Zien A et al., editors. Plasma microRNA profiles for bladder cancer detection. Urologic oncology: seminars and original investigations; 2013: Elsevier.
100. Mengual L, Lozano JJ, Ingelmo-Torres M, Gazquez C, Ribal MJ, Alcaraz A. Using microRNA profiling in urine samples to develop a non-invasive test for bladder cancer. Int J Cancer. 2013;133(11):2631–41.
101. Lin Y, Chen H, Hu Z, Mao Y, Xu X, Zhu Y, et al. miR-26a inhibits proliferation and motility in bladder cancer by targeting HMGA1. FEBS Lett. 2013;587(15):2467–73.
102. Wang G, Zhang H, He H, Tong W, Wang B, Liao G, et al. Up-regulation of microRNA in bladder tumor tissue is not common. Int Urol Nephrol. 2010;42(1):95–102.
103. Miyamoto K, Seki N, Matsushita R, Yonemori M, Yoshino H, Nakagawa M, et al. Tumour-suppressive miRNA-26a-5p and miR-26b-5p inhibit cell aggressiveness by regulating PLOD2 in bladder cancer. Br J Cancer. 2016;115(3):354.
104. Tölle A, Jung M, Rabenhorst S, Kilic E, Jung K, Weikert S. Identification of microRNAs in blood and urine as tumour markers for the detection of urinary bladder cancer. Oncol Rep. 2013;30(4):1949–56.
105. Chiyomaru T, Seki N, Inoguchi S, Ishihara T, Mataki H, Matsushita R, et al. Dual regulation of receptor tyrosine kinase genes

EGFR and c-Met by the tumor-suppressive microRNA-23b/27b cluster in bladder cancer. Int J Oncol. 2015;46(2):487–96.
106. Miah S, Dudziec E, Drayton R, Zlotta A, Morgan S, Rosario D, et al. An evaluation of urinary microRNA reveals a high sensitivity for bladder cancer. Br J Cancer. 2012;107(1):123.
107. Chung Y-H, Li S-C, Kao Y-H, Luo H-L, Cheng Y-T, Lin P-R, et al. MiR-30a-5p inhibits epithelial-to-mesenchymal transition and upregulates expression of tight junction protein claudin-5 in human upper tract urothelial carcinoma cells. Int J Mol Sci. 2017;18(8):1826.
108. Jiang X, Du L, Wang L, Li J, Liu Y, Zheng G, et al. Serum microRNA expression signatures identified from genome-wide microRNA profiling serve as novel noninvasive biomarkers for diagnosis and recurrence of bladder cancer. Int J Cancer. 2015;136(4):854–62.
109. Xu T, Qin L, Zhu Z, Wang X, Liu Y, Fan Y, et al. MicroRNA-31 functions as a tumor suppressor and increases sensitivity to mitomycin-C in urothelial bladder cancer by targeting integrin α5. Oncotarget. 2016;7(19):27445.
110. Tian Z, Cao S, Li C, Xu M, Wei H, Yang H, et al. LncRNA PVT1 regulates growth, migration, and invasion of bladder cancer by miR-31/CDK1. J Cell Physiol. 2019;234(4):4799–811.
111. Wang W, Li T, Han G, Li Y, Shi L-H, Li H. Expression and role of miR-34a in bladder cancer. 2013.
112. Liu J, Wang H, Wang Y, Li Z, Pan Y, Liu Q, et al. Repression of the miR-93-enhanced sensitivity of bladder carcinoma to chemotherapy involves the regulation of LASS2. OncoTargets Ther. 2016;9:1813.
113. He C, Zhang Q, Gu R, Lou Y, Liu W. miR-96 regulates migration and invasion of bladder cancer through epithelial-mesenchymal transition in response to transforming growth factor-β1. J Cell Biochem. 2018;119(9):7807–17.
114. Guo Y, Liu H, Zhang H, Shang C, Song Y. miR-96 regulates FOXO1-mediated cell apoptosis in bladder cancer. Oncol Lett. 2012;4(3):561–5.
115. Wu Z, Liu K, Wang Y, Xu Z, Meng J, Gu S. Upregulation of microRNA-96 and its oncogenic functions by targeting CDKN1A in bladder cancer. Cancer Cell Int. 2015;15(1):107.
116. Zhang D-Z, Lau K-M, Chan ES, Wang G, Szeto C-C, Wong K, et al. Cell-free urinary microRNA-99a and microRNA-125b are diagnostic markers for the non-invasive screening of bladder cancer. PLoS ONE. 2014;9(7):e100793.
117. Motawi TK, Rizk SM, Ibrahim TM, Ibrahim IAR. Circulating microRNAs, miR-92a, miR-100 and miR-143, as non-invasive biomarkers for bladder cancer diagnosis. Cell Biochem Funct. 2016;34(3):142–8.
118. Wang Y, Xing Q-F, Liu X-Q, Guo Z-J, Li C-Y, Sun G. MiR-122 targets VEGFC in bladder cancer to inhibit tumor growth and angiogenesis. Am J Translat Res. 2016;8(7):3056.
119. Zhou W, He L, Dai Y, Zhang Y, Wang J, Liu B. MicroRNA-124 inhibits cell proliferation, invasion and migration by targeting CAV1 in bladder cancer. Exp Ther Med. 2018;16(4):2811–20.
120. Zhang T, Wang J, Zhai X, Li H, Li C, Chang J. MiR-124 retards bladder cancer growth by directly targeting CDK4. Acta Biochim Biophys Sin. 2014;46(12):1072–9.
121. Snowdon J, Boag S, Feilotter H, Izard J, Siemens DR. A pilot study of urinary microRNA as a biomarker for urothelial cancer. Can Urol Assoc J. 2013;7(1–2):28.
122. Zhang Y, Zhang D, Lv J, Wang S, Zhang Q. MiR-125a-5p suppresses bladder cancer progression through targeting FUT4. Biomed Pharmacother. 2018;108:1039–47.
123. Huang L, Luo J, Cai Q, Pan Q, Zeng H, Guo Z, et al. MicroRNA-125b suppresses the development of bladder cancer by targeting E2F3. Int J Cancer. 2011;128(8):1758–69.
124. Jia A, Castillo-Martin M, Bonal D, Sánchez-Carbayo M, Silva J, Cordon-Cardo C. MicroRNA-126 inhibits invasion in bladder cancer via regulation of ADAM9. Br J Cancer. 2014;110(12):2945.
125. Mao XP, Zhang LS, Huang B, Zhou SY, Liao J, Chen LW, et al. Mir-135a enhances cellular proliferation through post-transcriptionally regulating PHLPP2 and FOXO1 in human bladder cancer. J Translat Med. 2015;13(1):86.
126. Wang G, Chan ES-Y, Kwan BC-H, Li PK-T, Yip SK-H, Szeto C-C et al. Expression of microRNAs in the urine of patients with bladder cancer. Clin Genitourinary Cancer. 2012;10(2):106–13.
127. Mahdavinezhad A, Mousavi-Bahar SH, Poorolajal J, Yadegarazari R, Jafari M, Shabab N, et al. Evaluation of miR-141, miR-200c, miR-30b expression and clinicopathological features of bladder cancer. Int J Mol Cell Med. 2015;4(1):32.
128. Wang H, Li Q, Niu X, Wang G, Zheng S, Fu G, et al. miR-143 inhibits bladder cancer cell proliferation and enhances their sensitivity to gemcitabine by repressing IGF-1R signaling. Oncol Lett. 2017;13(1):435–40.
129. Kou B, Gao Y, Du C, Shi Q, Xu S, Wang C-Q et al., editors. miR-145 inhibits invasion of bladder cancer cells by targeting PAK1. Urologic oncology: seminars and original investigations; 2014: Elsevier.
130. Yun SJ, Jeong P, Kim W-T, Kim TH, Lee Y-S, Song PH, et al. Cell-free microRNAs in urine as diagnostic and prognostic biomarkers of bladder cancer. Int J Oncol. 2012;41(5):1871–8.
131. Zhang H, Qi D, Li J, Peng T, Yang L, Yuan J, et al. A novel regulatory circuit of miR-152 and DNMT1 in human bladder cancer. Oncol Rep. 2018;40(3):1803–12.
132. Wei S, Bing Z, Yao Y, Master SR, Gupta P. Higher expression of miR-182 in cytology specimens of high-grade urothelial cell carcinoma: a potential diagnostic marker. Acta Cytol. 2015;59(1):109–12.
133. Gao J-M, Huang L-Z, Huang Z-G, He R-Q. Clinical value and potential pathways of miR-183-5p in bladder cancer: a study based on miRNA-seq data and bioinformatics analysis. Oncol Lett. 2018;15(4):5056–70.
134. Xu H, Chen H, Zhang Q, Zhang X, Wang J. Significance of microRNA-183 family expression in cancer diagnosis: a meta-analysis. Int J Clin Exp Med. 2016;9(8):15296–305.
135. Zhao C, Qi L, Chen M, Liu L, Yan W, Tong S, et al. microRNA-195 inhibits cell proliferation in bladder cancer via inhibition of cell division control protein 42 homolog/signal transducer and activator of transcription-3 signaling. Exp Ther Med. 2015;10(3):1103–8.
136. Thomas I, Hwang S, Lin J-F, Lin Y-C, Chen H-E, Chou K-Y, et al. miR-204 acts as a tumor suppressor in human bladder cancer cell T24 by targeting antiapoptotic BCL2. Urol Sci. 2016;27(2):101–8.
137. Yang Y, Qu A, Liu J, Wang R, Liu Y, Li G, et al. Serum miR-210 contributes to tumor detection, stage prediction and dynamic surveillance in patients with bladder cancer. PLoS ONE. 2015;10(8):e0135168.
138. Wang J, Zhang X, Wang L, Dong Z, Du L, Yang Y, et al. Down-regulation of urinary cell-free microRNA-214 as a diagnostic and prognostic biomarker in bladder cancer. J Surg Oncol. 2015;111(8):992–9.
139. Cheng Y, Yang X, Deng X, Zhang X, Li P, Tao J, et al. MicroRNA-218 inhibits bladder cancer cell proliferation, migration, and invasion by targeting BMI-1. Tumor Biol. 2015;36(10):8015–23.
140. Tatarano S, Chiyomaru T, Kawakami K, Enokida H, Yoshino H, Hidaka H et al. miR-218 on the genomic loss region of chromosome 4p15. 31 functions as a tumor suppressor in bladder cancer. Int J Oncol. 2011;39(1):13–21.
141. Li P, Yang X, Cheng Y, Zhang X, Yang C, Deng X, et al. MicroRNA-218 increases the sensitivity of bladder cancer to cisplatin by targeting Glut1. Cell Physiol Biochem. 2017;41(3):921–32.

142. Shang C, Zhang H, Guo Y, Hong Y, Liu Y, Xue Y. MiR-320a down-regulation mediates bladder carcinoma invasion by targeting ITGB3. Mol Biol Rep. 2014;41(4):2521–7.
143. Yamane K, Naito H, Wakabayashi T, Yoshida H, Muramatsu F, Iba T, et al. Regulation of SLD5 gene expression by miR-370 during acute growth of cancer cells. Sci Rep. 2016;6:30941.
144. Wu C-T, Lin W-Y, Chang Y-H, Lin P-Y, Chen W-C, Chen M-F. DNMT1-dependent suppression of microRNA424 regulates tumor progression in human bladder cancer. Oncotarget. 2015;6(27):24119.
145. Zeng T, Peng L, Chao C, Fu B, Wang G, Wang Y, et al. miR-451 inhibits invasion and proliferation of bladder cancer by regulating EMT. Int J Clin Exp Pathol. 2014;7(11):7653.
146. Du M, Shi D, Yuan L, Li P, Chu H, Qin C, et al. Circulating miR-497 and miR-663b in plasma are potential novel biomarkers for bladder cancer. Sci Rep. 2015;5:10437.
147. Tatarano S, Chiyomaru T, Kawakami K, Enokida H, Yoshino H, Hidaka H, et al. Novel oncogenic function of mesoderm development candidate 1 and its regulation by MiR-574-3p in bladder cancer cell lines. Int J Oncol. 2012;40(4):951–9.
148. Li W, Liu J, Zou D, Cai X, Wang J, Wang J, et al. Exploration of bladder cancer molecular mechanisms based on miRNA-mRNA regulatory network. Oncol Rep. 2017;37(3):1461–8.
149. Pignot G, Cizeron-Clairac G, Vacher S, Susini A, Tozlu S, Vieillefond A, et al. microRNA expression profile in a large series of bladder tumors: identification of a 3-miRNA signature associated with aggressiveness of muscle-invasive bladder cancer. Int J Cancer. 2013;132(11):2479–91.
150. Yang X, Cheng Y, Li P, Tao J, Deng X, Zhang X, et al. A lentiviral sponge for miRNA-21 diminishes aerobic glycolysis in bladder cancer T24 cells via the PTEN/PI3K/AKT/mTOR axis. Tumor Biol. 2015;36(1):383–91.
151. Zhao X, He W, Li J, Huang S, Wan X, Luo H, et al. MiRNA-125b inhibits proliferation and migration by targeting SphK1 in bladder cancer. Am J Translat Res. 2015;7(11):2346.
152. Zhao X, Li J, Huang S, Wan X, Luo H, Wu D. MiRNA-29c regulates cell growth and invasion by targeting CDK6 in bladder cancer. Am J Translat Res. 2015;7(8):1382.
153. Egawa H, Jingushi K, Hirono T, Ueda Y, Kitae K, Nakata W, et al. The miR-130 family promotes cell migration and invasion in bladder cancer through FAK and Akt phosphorylation by regulating PTEN. Sci Rep. 2016;6:20574.
154. Cheng Y, Zhang X, Li P, Yang C, Tang J, Deng X, et al. MiR-200c promotes bladder cancer cell migration and invasion by directly targeting RECK. OncoTargets Ther . 2016;9:5091.
155. Feng C, Sun P, Hu J, Feng H, Li M, Liu G, et al. miRNA-556-3p promotes human bladder cancer proliferation, migration and invasion by negatively regulating DAB2IP expression. Int J Oncol. 2017;50(6):2101–12.
156. Xu X, Li S, Lin Y, Chen H, Hu Z, Mao Y, et al. MicroRNA-124-3p inhibits cell migration and invasion in bladder cancer cells by targeting ROCK1. J Translat Med. 2013;11(1):276.
157. Wang X, Wu Q, Xu B, Wang P, Fan W, Cai Y, et al. miR-124 exerts tumor suppressive functions on the cell proliferation, motility and angiogenesis of bladder cancer by fine-tuning UHRF 1. FEBS J. 2015;282(22):4376–88.
158. Xu X, Chen H, Lin Y, Hu Z, Mao Y, Wu J, et al. MicroRNA-409-3p inhibits migration and invasion of bladder cancer cells via targeting c-Met. Mol Cells. 2013;36(1):62–8.
159. Lei Y, Hu X, Li B, Peng M, Tong S, Zu X, et al. miR-150 modulates cisplatin chemosensitivity and invasiveness of muscle-invasive bladder cancer cells via targeting PDCD4 in vitro. Med Sci Monitor Int Med J Exp Clin Res. 2014;20:1850.
160. Zhang D-Q, Zhou C-K, Jiang X-W, Chen J, Shi B-K. Increased expression of miR-222 is associated with poor prognosis in bladder cancer. World J Surg Oncol. 2014;12(1):241.
161. Uchida Y, Chiyomaru T, Enokida H, Kawakami K, Tatarano S, Kawahara K et al., editors. MiR-133a induces apoptosis through direct regulation of GSTP1 in bladder cancer cell lines. Urologic oncology: seminars and original investigations; 2013: Elsevier.
162. Chen C-L, Chung T, Wu C-C, Ng K-F, Yu J-S, Tsai C-H, et al. Comparative tissue proteomics of microdissected specimens reveals novel candidate biomarkers of bladder cancer. Mol Cell Proteomics. 2015;14(9):2466–78.
163. Catto JW, Alcaraz A, Bjartell AS, White RDV, Evans CP, Fussel S, et al. MicroRNA in prostate, bladder, and kidney cancer: a systematic review. Eur Urol. 2011;59(5):671–81.
164. Truta A, Popon TAH, Saraci G, Ghervan L, Pop IV. Novel non invasive diagnostic strategies in bladder cancer. Clujul Medical. 2016;89(2):187.
165. Lin Y, Wu J, Chen H, Mao Y, Liu Y, Mao Q, et al. Cyclin-dependent kinase 4 is a novel target in micoRNA-195-mediated cell cycle arrest in bladder cancer cells. FEBS Lett. 2012;586(4):442–7.
166. Li Z, Lin C, Zhao L, Zhou L, Pan X, Quan J, et al. Oncogene miR-187-5p is associated with cellular proliferation, migration, invasion, apoptosis and an increased risk of recurrence in bladder cancer. Biomed Pharmacother. 2018;105:461–9.
167. Jin H, Sun W, Zhang Y, Yan H, Liufu H, Wang S, et al. MicroRNA-411 downregulation enhances tumor growth by upregulating MLLT11 expression in human bladder cancer. Mol Therapy-Nucleic Acids. 2018;11:312–22.
168. Liu Y, Liu T, Jin H, Yin L, Yu H, Bi J. Mir-411 suppresses the development of bladder cancer by regulating ZnT1. OncoTargets Ther . 2018;11:8695.
169. Zhang XF, Zhang XQ, Chang ZX, Wu CC, Guo H. microRNA-145 modulates migration and invasion of bladder cancer cells by targeting N-cadherin. Mol Med Rep. 2018;17(6):8450–6.
170. Xu T, Du XW, Hu JB, Zhu YF, Wu HL, Dai GP, et al. Anticancer effect of miR-96 inhibitor in bladder cancer cell lines. Oncol Lett. 2018;15(3):3814–9.
171. He X, Ping J, Wen D. MicroRNA-186 regulates the invasion and metastasis of bladder cancer via vascular endothelial growth factor C. Exp Therap Med. 2017;14(4):3253–8.
172. Liu M, Chen Y, Huang B, Mao S, Cai K, Wang L, et al. Tumor-suppressing effects of microRNA-612 in bladder cancer cells by targeting malic enzyme 1 expression. Int J Oncol. 2018;52(6):1923–33.
173. Wei Z, Hu X, Liu J, Zhu W, Zhan X, Sun S. MicroRNA-497 upregulation inhibits cell invasion and metastasis in T24 and BIU-87 bladder cancer cells. Mol Med Rep. 2017;16(2):2055–60.
174. Zhang Y, Zhang Z, Li Z, Gong D, Zhan B, Man X, et al. MicroRNA-497 inhibits the proliferation, migration and invasion of human bladder transitional cell carcinoma cells by targeting E2F3. Oncol Rep. 2016;36(3):1293–300.
175. Liao G, Chen F, Zhong J, Jiang X. MicroRNA-539 inhibits the proliferation and invasion of bladder cancer cells by regulating IGF-1R. Mol Med Rep. 2018;17(4):4917–24.
176. Wu D, Niu X, Tao J, Li P, Lu Q, Xu A, et al. MicroRNA-379-5p plays a tumor-suppressive role in human bladder cancer growth and metastasis by directly targeting MDM2. Oncol Rep. 2017;37(6):3502–8.
177. Zhao X, Ji Z, Xie Y, Liu G, Li H. MicroRNA-154 as a prognostic factor in bladder cancer inhibits cellular malignancy by targeting RSF1 and RUNX2. Oncol Rep. 2017;38(5):2727–34.
178. Zhang J, Mao S, Wang L, Zhang W, Zhang Z, Guo Y, et al. MicroRNA-154 functions as a tumor suppressor in bladder cancer by directly targeting ATG7. Oncol Rep. 2019;41(2):819–28.
179. Koutsioumpa M, Chen H-W, O'Brien N, Koinis F, Mahurkar-Joshi S, Vorvis C, et al. MKAD-21 suppresses the oncogenic activity of the miR-21/PPP2R2A/ERK molecular network in bladder cancer. Mol Cancer Ther. 2018;17(7):1430–40.

180. Li P, Yang X, Yuan W, Yang C, Zhang X, Han J, et al. CircRNA-Cdr1as exerts anti-oncogenic functions in bladder cancer by sponging MicroRNA-135a. Cell Physiol Biochem. 2018;46(4):1606–16.
181. Xiao J, Niu S, Zhu J, Lv L, Deng H, Pan D, et al. miR-22-3p enhances multi-chemoresistance by targeting NET1 in bladder cancer cells. Oncol Rep. 2018;39(6):2731–40.
182. Xu R, Zhu X, Chen F, Huang C, Ai K, Wu H, et al. LncRNA XIST/miR-200c regulates the stemness properties and tumourigenicity of human bladder cancer stem cell-like cells. Cancer Cell Int. 2018;18(1):41.
183. Sugawara S, Yamada Y, Arai T, Okato A, Idichi T, Kato M, et al. Dual strands of the miR-223 duplex (miR-223-5p and miR-223-3p) inhibit cancer cell aggressiveness: targeted genes are involved in bladder cancer pathogenesis. J Hum Genet. 2018;63(5):657.
184. Zeng S, Yu X, Ma C, Song R, Zhang Z, Zi X, et al. Transcriptome sequencing identifies ANLN as a promising prognostic biomarker in bladder urothelial carcinoma. Sci Rep. 2017;7(1):3151.
185. Liu X, Kong C, Zhang Z. miR-130b promotes bladder cancer cell proliferation, migration and invasion by targeting VGLL4. Oncol Rep. 2018;39(5):2324–32.
186. Xu M, Li J, Wang X, Meng S, Shen J, Wang S, et al. MiR-22 suppresses epithelial–mesenchymal transition in bladder cancer by inhibiting Snail and MAPK1/Slug/vimentin feedback loop. Cell Death Dis . 2018;9(2):209.
187. Li C, Zeng X, Liu Z, Li F, Wang K, Wu B. BDNF VAL-66MET polymorphism elevates the risk of bladder cancer via MiRNA-146b in micro-vehicles. Cell Physiol Biochem. 2018;45(1):366–77.
188. Zhai X, Xu W. Long noncoding RNA ATB promotes proliferation, migration, and invasion in bladder cancer by suppressing MicroRNA-126. Oncol Res Featur Preclin Clin Cancer Therapeut. 2018;26(7):1063–72.
189. Yang D, Du G, Xu A, Xi X, Li D. Expression of miR-149-3p inhibits proliferation, migration, and invasion of bladder cancer by targeting S100A4. Am J Cancer Res. 2017;7(11):2209.
190. Zhang H, Jiang M, Liu Q, Han Z, Zhao Y, Ji S. miR-145-5p inhibits the proliferation and migration of bladder cancer cells by targeting TAGLN2. Oncol Lett. 2018;16(5):6355–60.
191. Wang S, Wu G, Han Y, Song P, Chen J, Wu Y, et al. miR-124 regulates STAT3-mediated cell proliferation, migration and apoptosis in bladder cancer. Oncol Lett. 2018;16(5):5875–81.
192. Chen X, Jia C, Jia C, Jin X, Gu X. MicroRNA-374a inhibits aggressive tumor biological behavior in bladder carcinoma by suppressing Wnt/β-catenin signaling. Cell Physiol Biochem. 2018;48(2):815–26.
193. Zhu Y, Liang S, Pan H, Cheng Z, Rui X. Inhibition of miR-1247 on cell proliferation and invasion in bladder cancer through its downstream target of RAB36. J Biosci. 2018;43(2):365–73.
194. Huang B, Zhai W, Hu G, Huang C, Xie T, Zhang J, et al. MicroRNA-206 acts as a tumor suppressor in bladder cancer via targeting YRDC. Am J Translat Res. 2016;8(11):4705.
195. Xiu Y, Liu Z, Xia S, Jin C, Yin H, Zhao W, et al. MicroRNA-137 upregulation increases bladder cancer cell proliferation and invasion by targeting PAQR3. PLoS ONE. 2014;9(10):e109734.
196. Wu X, Chen B, Shi H, Zhou J, Zhou F, Cao J, et al. miR-758-3p suppresses human bladder cancer cell proliferation, migration and invasion by targeting NOTCH2. Exp Therapeut Med. 2019;17(5):4273–8.
197. Liu X, Chen D, Li X. MiR-335 suppresses cell proliferation and migration by upregulating CRKL in bladder cancer. Eur Rev Med Pharmacol Sci. 2019;23(6):2399–408.
198. Sugita S, Yoshino H, Yonemori M, Miyamoto K, Matsushita R, Sakaguchi T, et al. Tumor-suppressive microRNA-223 targets WDR62 directly in bladder cancer. Int J Oncol. 2019;54(6):2222–36.
199. Zhang L, Yan R, Zhang S, Zhang H, Ruan X, Cao Z, et al. MicroRNA-338-3p inhibits the progression of bladder cancer through regulating ETS1 expression. Eur Rev Med Pharmacol Sci. 2019;23(5):1986–95.
200. Fu S, Luan T, Jiang C, Huang Y, Li N, Wang H, et al. miR-3622a promotes proliferation and invasion of bladder cancer cells by downregulating LASS2. Gene. 2019;701:23–31.
201. Chen J, Song B, Kong G. MicroRNA-663b downregulation inhibits proliferation and induces apoptosis in bladder cancer cells by targeting TUSC2. Mol Med Rep. 2019;19(5):3896–902.
202. Hou Y. MiR-506 inhibits cell proliferation, invasion, migration and epithelial-to-mesenchymal transition through targeting RWDD4 in human bladder cancer. Oncol Lett. 2019;17(1):73–8.
203. Wei XC, Lv ZH. MicroRNA-132 inhibits migration, invasion and epithelial-mesenchymal transition via TGFβ1/Smad2 signaling pathway in human bladder cancer. OncoTargets Ther. 2019;12:5937.
204. Zhang W, Shi D, Zhang J, Zhang Z, Guo Y, Wu Y, et al. MicroRNA-153 decreases tryptophan catabolism and inhibits angiogenesis in bladder cancer by targeting indoleamine 2, 3-dioxygenase 1. Front Oncol . 2019;9:619.
205. Yan T, Ye X. MicroRNA-328-3p inhibits the tumorigenesis of bladder cancer through targeting ITGA5 and inactivating PI3K/AKT pathway. Eur Rev Med Pharmacol Sci. 2019;23(12):5139–48.
206. Tian H, Wang X, Lu J, Tian W, Chen P. MicroRNA-621 inhibits cell proliferation and metastasis in bladder cancer by suppressing Wnt/β-catenin signaling. Chemico–biological interactions. 2019.
207. Sun W, Li S, Yu Y, Jin H, Xie Q, Hua X, et al. MicroRNA-3648 is upregulated to suppress TCF21, resulting in promotion of invasion and metastasis of human bladder cancer. Mol Ther Nucleic Acids. 2019;16:519–30.