MIRNA EXPRESSION IN BLADDER CANCER AND THEIR POTENTIAL ROLE IN CLINICAL PRACTICE

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Abstract

To date more than 3000 miRNA sequences have been described in humans and registered at miRBase since their discovery. However, the functions of only a few of these miRNAs have been experimentally determined using deep sequencing technology. Aberrant miRNA expression has been associated with differentiation, invasion and metastasis in several cancers. In this context, recent reports have suggested that miRNAs play important roles in the regulation of target genes by binding to complementary regions of messenger transcripts to repress their translation or regulate degradation. In addition, the expression profiles of certain miRNAs can function biologically as oncogenes and tumour suppressor genes.

In this review, we summarize the relationship between miRNAs expression and Bladder Cancer (BC). A comprehensive review of the literature has shown a differential expression between malignant and normal tissues, and that miRNAs could be the driving molecules of the BC progression. Similarly, the expression levels of miRNAs in urine and blood samples of BC patients have been demonstrated to be different from healthy people, a finding that might have diagnostic value.

In conclusion, the understanding of miRNAs mechanisms and cell distribution provides new opportunities for diagnosis, prognostic, disease monitoring and personalized therapy of BC patients.

Key-words: Bladder cancer; miRNA; Biomarker; Diagnosis; Prognosis

1. Introduction

1.1 Bladder Cancer

Bladder cancer (BC) is the most common cancer of the urinary system with an estimated 76,510 new cases in the United States in 2016 and is associated with significant morbidity and mortality [1]. The high rate of recurrence and the long term follow-up, with invasive and uncomfortable cystoscopic evaluations, makes BC one of the most expensive cancers [2]. The etiology of bladder tumorogenesis is not clearly and it is thought to result from an interaction between genetic and environmental factors.

Histologically, more than 95% of bladder cancers originate from the urothelial epithelium, which can be classified into different categories with distinct clinical behavior: 1) Non-muscle invasive BC (NMIBC) is the most common type of BC (75%) and is characterized by a high-recurrence probability (30-50%). This group is very heterogeneus and presentswith differences in disease behavior, aggressiveness, and prognosis between low-grade Ta (tumors confined to the mucosa) and high-grade T1 (tumor confined to the submucosa) [2]. 2) Muscle-invasive bladder cancer (MIBC) (stage T2 to 4) represents the remaining 25% of cases; remain and about 7% of them are actually metastatic at diagnosis. (AUTHOR: The highlighted sentence is vague and must be re-phrasedDONE). Therefore, this group is the major contributors to BC-related mortality [3]. Genetically, there may be at least two separate pathways leading to BC. On the one hand, papillary low-grade tumors (NMIBC) are commonly associated with FGFR3 mutation or chromosome 9 loss and by contrast, MIBC and high-grade differentiation are associated with p53 mutation or loss of RB1 [4].

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1.2 microRNAs

microRNAs (miRNAs) comprise a new class of small, non-coding endogenous RNAs (18 to 25 nucleotides long) that regulate the gene expression through complementary binding to the 3' untranslated region (UTR) of their target. The miRNAs function includes the regulation of numerous processes, such as apoptosis, cellular proliferation, invasion and differentiation [5]. Since ~~being discovered~~its discovery in 1993, as a mechanism of post-transcriptional gene regulation, a~~n elevated~~ number of miRNAs have been recognized in mammals [6]. Based on computer models, over 3000 miRNAs have been identified and sequenced in humans ~~and also ;~~ nowadays it is known that around 30% of the transcriptome is regulated by miRNAs [7] . Interestingly, the miRNAs play a key rol~~es~~ in cancer, a disease extremely diverse and complex that results from alterations at various molecular levels. Thus, the studies on miRNA in cancer are complicated by the genetic diversity of tumors and by th~~e~~at fact that ~~most often~~ many different miRNAs are found deregulated in the same tumor [8]. miRNAs circulate in a highly stable cell-free form in various body fluids, including serum, plasma and urine [9] . T~~hose~~ M~~m~~icroRNAs may enter the circulation by 2 major pathways:

1) ~~passive~~Passive leakage from ~~broken~~ injured cells that occur~~s~~ at the time of tissue damage such as ~~or~~ cellular apoptosis, ~~therefore, miRNAs may leak into circulation from injured cells~~ 2) active secretion via cell-derived microvesicles (MVs) has also been reported. MVs are small vesicles that can be detected under both normal and pathological conditions~~ in almost all cell types~~. Generally, they include microparticles and exosomes (small secreted

extracellular vesicles that contain miRNA, mRNA and proteins) that are secreted by normal and cancer cells. ~~Therefore, P~~patients with cancer seems to have increased numbers of exosomes in the blood. The vesicles can be isolated from cell culture medium as well as from bodily fluids by differential centrifugation [10] (Figure 1).

1.3 miRNAs and Bladder Cancer. Where are we?

A number of studies have demonstrated that ~~the~~ miRNAs are aberrantly expressed ~~aberrantly~~ in various types of malignancies including BC; thus new methodologies~~y~~ ha~~s~~ve been developed to quantify the expression of miRNAs [11, 12]. The expression of miRNAs is different ~~also altered~~ between tumors and normal tissues, therefore, the abnormal expression of miRNAs may be important for tumor initiation, progression and metastasis. Consequently, the identification of target genes associated with aberrantly expressed miRNAs might elucidate the role~~s~~ of miRNAs in cancer biology [13]. Studies based on miRNA~~s~~ have discovered several downregulated or~~and~~ upregulated miRNAs in BC [14]. These studies have demonstrated that overexpresed miRNAs can act as oncogenes by repressing tumor suppressor genes and ~~by~~ on the contrary, underexpressed miRNAs can function as tumor suppressors by negatively regulating oncogenes [13-15]. Recent findings have shown that miR-1, miR-26a, miR-133a/b, miR-143, miR-145, and miR-195 were downregulated in BC tissue compared with normal bladder tissue, suggesting that these miRNAs function as tumour suppressors, whereas upregulated miRNAs, such as miR-183, miR-96, miR17-5p and miR-20a have an oncogenic function [13]. Reportedly, miR-145 is the most frequently downregulated miRNA in BC and has been shown to significantly inhibit proliferation, migration and invasion [13,

16]. The downregulated miRNAs in BC and their target genes are listed in Table~~s~~ 1a. ~~Previous~~ Earlier studies have demonstrated differences and variations in the number of miRNAs detected~~,~~. ~~t~~This fact could be due to differences in technological platforms and the type and size of the sample ~~size used~~. Moreover, inconsistent results for the same miRNA have been detected, such as miR-222 that is down-regulated in bladder cancer tissue whereas that in cell lines is up-regulated and associated with PPP2R2A/AKT/mTOR pathway [17, 18]. Similarly, downregulation of miR-125b may regulate G1/S transition through the E2F3–Cyclin A2 signaling pathway [19, 20]. However, other studies show that upregulation of miR-125b inhibit~~s~~e proliferation, motility and increase~~d~~ apoptosis by suppressing SIRT7 and MALATA1 [21]. By contrast, of the miRNAs that are upregulated in BC (Table 1b) miR-130b, miR-221, miR-223, miR-137, miR-18a, miR-20a, miR-21, miR-96, miR-200c, miR-205, miR-203, miR-210, miR-~~182 have~~182 have been reported to be oncogenic markers. A set of two o more miRNAs constitute a miRNAs clusters, which are located in close proximity in the same genomic region, are transcribed coordinately and have similar functions regulating the same targets [20]. Research studies indicate~~s~~ that miRNAs clusters are frequently d~~e~~ys~~s~~regulated in several types of cancer. A series of miRNA~~s~~ clusters have been identified in BC. First, the miRNA-1/133a cluster is a frequent event in BC and acts as a tumor suppressor through targeting of several oncogenes involved in specific pathways of BC [22, 23] .Another miRNA cluster studied in BC is miRNA-143/145~~;~~, ~~desregulation~~deregulation of this cluster has been reported as an event in migration that regulates plasminogen activator inhibitor-1 [16, 20, 24]. In addiction, the miRNA-195/497 cluster is well known ~~and acts~~and acts as

tumor suppressor thusand providinges new information on its potential as therapeutic target [22]. Other downregulated miRNAs clusters found in BC are miR-206/133b, Let-7c/99a, miR-23b/27b and upregulated miR-183/96/182, which are important for tumor biology [16, 22, 25, 26]

2. miRNAs as biomarkers for BC

2.1 Biomarkers and diagnosis

Urine cytology is currently the standard of non-invasive procedure for early diagnosis and follow-up from patients with BC; unfortunately, the use of this tecnique is limited by its low sensitivity [27]. Therefore, the introduction of simple, noninvasive, sufficiently sensitive and specific method for detection and monitoring of patients is needed. [2]. In this waysense, the most recentof the studies are focused focusing on the diagnostic utility of expression/ profiling of miRNAs have been conducted on secretory samples.

2.1.1 Urine

Recent approaches studies have demonstrated the importance of miRNAs in urine sediment, which reflect the levels of intracellular expression, whereas, miRNAs in supernatant are cell- free and originate mainly from MVs secreted into to extracellular space [28]. Figure 1

A number of studies have identified specific microRNAs as potential diagnostic markers for bladder cancer, such as miR-126, miR-182 and miR-199a which are over-expressed in urine from patients with BC and can be used to detect CB BC with high specificity and sensibility [29, 30]. In another study, the combination of miRs-135*b*/15b/1224-*3p,* with a 94.1% of sensitivity and 51% of specificity, proved useful to detect BC disease [31]. Urinary levels of miR-106b

also showed a considerable diagnostic accuracy~~,~~ with ~~values of~~ sensitivity ~~about~~ of 76.8% and 72.4% of specificity, thus allowing to differentiate between patients with BCa and controls [32]. Results of the study carried out by *Puerta-Gil et al*. showed that miR-143, miR-452 and miR-222 in urine provided high accuracy~~ies~~ for bladder cancer diagnosis [33]. miR 96 and miR 183 are other miRNAs detected and highly expressed in urine which provide high accuracy~~ies~~ for bladder cancer diagnosis and also are significantly correlated with tumor stage and grade [34]. In addition, in another study the combination of miR-125b and miR-126 showed a very high diagnostic accuracy to detect BC patients, with a sensitivity of 100% and a specificity of 100% [35]. Finally, miR-187, miR-18a*, miR-25, miR-142-3p, miR-140-5p and miR-204 have been studied and show potential to discriminate and classify correctly patients with BC in urine [36].

Aberrant expression of miRNA-200c and miRNA-141 has been found in urine sediment from patients with BC [5]. Other findings have shown that urinary levels miR-200a also can be detectable and useful in the diagnosis of BC [37] nevertheless, urinary levels of miR-200 family, miR-155, miR-192, and miR-205 are ~~depressed~~ lower in patients with bladder cancer, therefore, these miRNAs have potential to be useful as noninvasive markers for BC [37]. The methylation of the regulative DNA sequences of miR-152, miR-10a and miR-200b could serve as epigenetic BC biomarkers but future studies in urine sediment should be carried out to ~~know~~ clarify their diagnostic performance [38]. Moreover, ~~the result of~~ other study revealed that the expression levels of miR-152 in urine could provide information on the recurrence risk of NMIBC [39].

2.1.2 Serum

Serum miRNAs play an important role in diagnosing BC although the reported results on miRNAs concentration in plasma and serum remainare still contradictory and a number aspects, such as hemolysis, need to be considered [40] (Figure 2).

A recent study found, using a microarray analysis found, elevated levels of miR-505, miR-363 and miR-663b and decreased levels of miR-99a, miR-194, miR-100, miR-497 and miR-1 in plasma of pacients with BC [41]. The same study has demostrated the diagnostic performance of miRNAs in according to different BC stage and grade, in particular, such as miR-497 and miR-663b which presents a high sensitivity and specificity, and could be promising novel circulating biomarkers toin clinically detection of BC [41]. Results on miRNA concentration in serum are contradictory and, therefore since there is certain a variability in reported data nce of microRNA expression profile in circulation. Some miRNAs such as miR-378, miR-942, miR-106a-5p, miR-142-3p and miR-374a have been identified as upregulated in serum, but these results need further validation studiesy using by larger series.e samples [42].

3. Biomarkers and tumour prognosis

In recent years, the investigation of miRNA expression profiles has increased and several studies have demonstrated the potential of miRNAs tofor provideing additional prognostic information. A variety of miRNAs have already been described in the literature, such as miR-141, miR-199a-3p, miR-205, and miR-214, which are significantly differentially expressed between NMIBC and MIBC [17]. Results from another study has reported, on the one hand that epigenetic silencing of miR-200 and miR-205 by hypermethylation could be a useful prognostic biomarker for BC and, on the other hand, that the expression

of miR-200c is significantly correlated to disease progression in T1 tumors [43]. The expression levels of miR-199b-5p is associated almost exclusively with papillary growth and NMIBC [44].

In terms of pathological stage and grade, miR-205 is able to discriminate between low-grade papillary urothelial carcinoma and high-grade papillary urothelial carcinoma, whereas miR-145 distinguishes high-grade papillary urothelial carcinoma from infiltrating carcinoma [12].

A recent study ~~carried out~~ on miRNAs profiles showed that four miRNAs (let-7c, miR-125b-1, miR-193a, and miR-99a) were significantly associated with the progression and aggressiveness of MIBC [45]. Increased expression of miR-146b and miR-9 is~~are~~ seen~~present~~ in MIBC and furthermore miR-9, miR-182 and miR-200b is significantly associated with both recurrence-free and overall survival [46]. However, downregulation of miR-143/145 contribute to BC recurrence as useful prognostic markers for non-muscle-invasive bladder tumours and provides a prediction of oncologic outcome [47].

Other reseach teams have also demostrated that decreased expression of miR-10a-5p play a role in the progression of Ta tumors indicating that this microRNA could be important for prognostication in this group of patients [48, 49]. Lastly~~By last~~, another miRNA ~~studied, and~~ that could serve as a promising biological marker, is miR-141 which contributes to the progression of BC [50, 51].

4. Can miRNAs predict treatment response?

About 30% of patients with BC have invasion into the detrusor musculature and are treated surgically by partial or total cystectomy~~ies~~. A significant proportion of post-cystectomy patients have a fatal outcome following development of

metastatic disease ~~dissemination~~. The main regimens of chemotherap~~y~~eutic in patients with locally advanced or metastatic disease are MVAC (Methotrexate, vinblastine, doxorubicin, and cisplatin) and GC (gemcitabine and cisplatin) [3]. Although many patients with metastatic disease respond to the treatment (30-50%), a significant number of patients are either resistant or develop resistance to chemotherapy over time. Early discrimination between likely responders and non-responders would greatly improve selection of patients to chemotherapy and thereby benefit both groups [3, 52]. The expression profiles of downregulated miRNAs may provide information about chemotherapy sensitivity or chemotherapy response. Among these are miR-27a, miR-296-5p, miR-642, and miR-886-3p. ~~On the one hand~~For instance, lower ~~decrease~~ levels of ~~ ~~miR-~~138 increases~~138 increases the cisplatin sensitivity and ~~on the other hand~~, ~~increase~~ higher levels of miR-27a and miR-642 increase cisplatin sensitivity [53]. Previous researchs have been especially focused on miR-143/145 and miR-183/96/182 clusters, whose function has been also extensively studied in BC. One study based on interrogating ~~to know~~ if T24 BC cells respond to treatment with cisplatin and paclitaxel by modulating the expression levels of these miRNAs showed that both of them, cisplatin and paclitaxel, decreased the viability of T24 cells. Additionally, the expression levels of miR-143 is down-regulated and miR-145, miR-183, miR-96, and miR-182 are up-regulated, demonstrating case-specific variations after recovery period [54].

Several reports have shown that miR-193a-3p is the most studied miRNA in the context of BC chemoresistance [55, 56]. Specifically, a study carried out using an RNA-seq-based omic analysis showed that miR-193a-3p is an important

instrumental toin activateing BC chemoresistance by inhibition ING5 gene expression [57]. Other studiesreseachs team have reported that miR-199a* in BC may have a tumor suppressive function in BC through the a mechanism underlying transcriptional repression of KRT7 [58] and miR-199a-5p (downregulated in BC) plays an important role in chemoresistance by targeting the endoplasmic reticulum chaperone and signaling regulator GRP78 [59].

Also, miR-34a is a downstream effector of p53-Rb signaling and has several targetseveral targets such as Cdk6 (control of Rb phosphorylation) and E2F3, which are associated with cell cycle and cell survival pathways. The transfection of cell lines with pre-miR-34a followed by cisplatin treatment shows a dramatic reduction in clonogenic potential and induction of senescence compared to treatment with cisplatin alone. Therefore, miR-34a could be a useful predictor of response to chemotherapy in patients with BC [60]. Recently, miR-150 has been suggested as a promising marker whose function is is is to modulate cisplatin chemosensitivity and promoting invasiveness of MIBC cells via targeting PDCD4 [61].

5. Therapeutic potential of miRNAs in bladder cancer

During the last decade, the therapeutic potential of miRNAs in cancer has been demonstrated in several studies. The miRNA-based therapies are based on two main approaches, 1) miRNA antagonists therapy (anti-miR or antagomiR), which inhibit endogenous miRNAs. This therapy is based in the introduction of a highly chemically-modified miRNA passenger strand, and 2) miRNA mimics (miRNA replacement therapy), which is used to restore a loss of function. The re-introduction of the miRNAs leads to a re-activation of pathways that are required for normal celular welfare and block those that drive the disease [62].

In this sense, new therapies are being investigated to improve overall survival from patients with BC and thus, several miRNAs are now under investigation to be possible~~s~~ candidates in futures targeted therapies. Reportedly, ~~Acording with the studies available in the literature,~~ the miR-192 is a important candidate. O~~e~~verexpression of this miRNA decrease significantly cellular ~~the~~ proliferation and induce the apoptotic death in BC cells through to ~~a~~ increase of p21, p27, and Bax levels, and a decrease of cyclin D1, Bcl-2, and Mcl-1 levels [63] . In another study, the authors oberved that the suppression of miR-138, a miRNA associated with cancer metastasis, may promote ZEB2-mediated cancer invasion and metastasis in BC cells [64]. In addition, the study of miR-3713 (a novel target for treating BC) contribute to the understanding of molecular regulation of MMP9 [65].

miRNAs also can be transfected into BC cell lines using plasmid or virus vectors such as miR-100 (with tumor supression function), which transfected in BC cells exhibit~~e~~ a significant growth inhibition using an intravesical orthotopic model. Similarly, the miRNAs miR-10b and miR-15 (both of them with oncogenic function) transfected in BC xenograft~~s~~ model~~s~~ exhibit a significant growth in comparison with controls [20]. Likewise, other intravesical orthotopic BC model is the intravesical injection of miR-145 using cationic liposomes (Lipofectamine RNAiMAX, Thermo Fisher Scientific, Waltham, MA, USA) [20]. Restoring of miR-34a expression by epigenetic therapy and/or delivery of miR-34a mimics may be a promising therapeutic strategy. The therapeutic efficacy of this miRNA is correlated with a reduced proliferation and enhanced apoptotic activity [66].

Finally, other miRNAs currently in development in the area of BC disease include miR-582-5p and miR-582-3p (downregulated in invasive BC) which have potential of ~~for~~ being used as therapeutic target against the continued threat of progression to muscle-invasion and metastasis [67].

In general, all aforementioned miRNA are promising candidates that could be used for clinical applications in the near future.

Conclusion

In recent years, a large number of studies on miRNAs signalling have been carried out in bladder cancer. These studies have shown that miRNAs regulate the expression of their target genes and generally act ~~as~~ as oncogenes or tumor suppressor~~s~~ genes. These genes play an important role~~s~~ in the development, tumor stratification and progression of bladder cancer. On the other hand, urinary and serum levels of miRNAs are clinically useful for bladder cancer diagnostics. Nevertheless, future studies using larger patient cohorts are necessary before their implementation in ~~the~~ clinical practice.

Conflicts of Interest

The authors declare no conflict of interests.

Figure 1: The bladder wall and bladder cancer development according to pT categories based on the TNM (Tumour-Node-Metastasis) system. Extracellular secretions of miRNAs differentially produce ~~form~~ the exosomes and micro-vesicles seen in blood and the urine.

Figure 2: Impact of miRNAs in bladder cancer based on their role as prognostic or diagnostic tools, or as markers for treatment.

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Table 1. Human miRNAs downregulated in bladder cancer

microRNA	Cytogenetic location	microRNA desregulation	Family	Specimen	Biological function	Aislated or Clustered	Target	Refs
miR-1	20q13.33	Down-regulated	miR-1-1 miR-1-2	Bladder Tissue Cell lines	Proliferation Apoptosis Motility Invasion	miR-1	UCA1	[68]
						miR-1/133a	PNP PTMA	[69]
							LASP1	[23]
							TAGLN2	[70]
miR-133b	6p12.2	Down-regulated	miR-133a-1 miR-133a-2 miR-133b	Bladder Tissue Cell lines	Proliferation Apoptosis Migration Invasion	miR-133b	BCL-W Akt-1	[71, 72]
						miR-206/133b	EGFR	[22, 25]
Let-7c	21q21.1	Down-regulated	Let-7c	Bladder Tissue	Proliferation Migration Invasion	Let-7c/99a	FGFR3	[16, 20, 22]
miR-143	5q32	Down-regulated	miR-143	Bladder Tissue	Proliferation Apoptosis Migration	miR-143/145	ESCN1 PAK1 IGF-IR	[16]
							PAI-1	[24]
miR-145-5p	5q32	Down-regulated	miR-145-5p	Bladder Tissue	Proliferation Differentiation	miR-145-5p	EMT NGAL MMP-9	[73]
miR-214-3p	1q24.3	Down-regulated	miR-214-3p	Bladder Tissue	Proliferation Differentiation	miR-214-3p	EMT NGAL MMP-9	[73]
miR-139-5p	11q13.4	Down-regulated	miR-139	Bladder Tissue Cell lines	Migration Invasion	miR-139-5p miR-139-3p	MMP11	[74]
miR-490-3p	7q33	Down-regulated	miR-490-3p miR-490-3p	Bladder Tissue	Proliferation Apoptosis	miR-490-3p	c-*FOS*	[75]
miR-204	9q21.12	Down-regulated	miR-204	Bladder Tissue	Apoptosis	miR-204	TRPM3 MCL-1 BCL-2	[46]
miR-125b	11q24.1	Down-regulated	miR-125b-1 miR-125b-2 miR-125b-5p	Bladder Tissue Cell lines	Regulation cell cycle Proliferation Motility Apoptosis	miR-125b	E2F3-Cyclin A2	[19]
		Up-regulated					SIRT7 MALAT1	[21]
miR-126	9q34.3	Down-regulated	miR-126	Cell lines	Proliferation Invasion	miR-126	PIK3R2	[76]
miR-140-5p	16q22.1	Down-regulated	miR-140-5p	Cell lines	Migration Invasion	miR-140-5p	TP63 LEPREL1	[77]
miR-144	17q11.2	Down-regulated	miR-144-5p miR-144-3p	Bladder Tissue	Proliferation	miR-451a miR-144-3p miR-144-5p	CCNE1 CCNE2 CDC25A PKMYT1	[78]
miR-150	19q13.33	Down-regulated	miR-150	Cell lines	Invasion	miR-150	PDCD4	[61]
miR-218	4p15.21	Down-regulated	miR-218-1 miR-218-2	Bladder Tissue	Proliferation Invasion Migration Apoptosis	miR-218	BMI-1 PTEN	[79]
miR-195	17p13.1	Down-regulated	miR-195	Cell lines	Proliferation Migration Invasion Metastasis	miR-195 miR-195-5p	CDC42 STAT3	[80]
							GLUT3	[81]
							CDK4	[82]
						miR-195/497	BIRC5 WNT7A	[22]
miR-100	11q24.1	Down-regulated	miR-100 miR-100-5p	Bladder Tissue Cell lines	Proliferation Motility	miR-100	mTOR	[83]

miR-30a	6q13	Down-regulated	miR-30a miR-30c	Bladder Tissue Cell lines	Migration Invasion	miR-30a	NOTCH1	[20, 84]
miR-23b	9q22.32	Down-regulated	miR-23a miR-23b	Bladder Tissue	Migration Invasion	miR-23b/27b	EGFR cMET	[85]
						miR-24-1	FOXM1	[86]
miR-26a	3p22.2	Down-regulated	miR-26a miR-26a-5p	Bladder Tissue Cell lines	Proliferation Motility Migrasion Invasion	miR-26a miR-26a-5p	HMGA1 PLOD2	[87] [88]
miR-26b	2q35	Down-regulated	miR-26b-5p	Bladder Tissue Cell lines	Migrasion Invasion	miR-26b-5p	PLOD2	[88]
miR-129	7q32.1	Down-regulated	miR-129-1 miR-129-2	Bladder Tissue Cell lines	Apoptosis	miR-129	SOX4 GALNT1	[89]
miR-15	13q14.2	Down-regulated	miR-15a, miR-15b miR-16-1, miR-16-2, miR-195, miR-497	Bladder Tissue Cell lines	Proliferation Apoptosis	miR-15a/16	BCL2	[90]
						miR-16	CCND1	[91]

Table 2. Human miRNAs upregulated in bladder cancer

microRNA	Cytogenetic location	microRNA desregulation	Family	Specimen	Biological function	Aislated or Clustered	Target	Refs
miR-130b	22	Up-regulation	miR-130b	Bladder Tissue Cell lines	Migration Invasion Progression	miR-130b	FAK Akt PTEN	[92]
miR-221	Xp11.3	Up-regulation	miR-221	Cell lines	Survival Migration Invasion Metastasis	miR-221	STMN1	[93]
miR-222	Xp11.3	Up-regulation	miR-222	Cell lines	Proliferation Migration Invasion	miR-222	PPP2R2A/AKT/mTOR	[18, 94]
		Down-regulation		Bladder tissue			Diagnosis	[17]
miR-223	Xq12	Up-regulation	miR-223	Bladder Tissue	Migration Invation	miR-223	MEF2C ZCCHC14 UE2A SPRED1 PSACS	[95]
miR-137	1p21.3	Up-regulation	miR-137	Bladder Tissue Cell lines	Proliferation Invasion	miR-137	PAQR3	[96]
miR-18a	13q31.3	Up-regulation	miR-18a	Cell lines	Proliferation	miR-18a miR-17/92	Dicer CTGF IGF1 CCND2 HIF1A	[97]
miR-19		Up-regulation	miR-19a miR-19b	Bladder Tissue Cell Lines	Prolifertion	miR-19a	PTEN	[98]
miR-20a	12q31.3	Up-regulation	miR-20a	Bladder Tissue	Proliferation Migration Invasion	miR-20a	Not date	[13]
miR-21	17q23.2	Up-regulation	miR-21	Bladder Tissue Cell lines	Invasion Apoptosis	miR-21	VEGF-C Maspin	[99]
miR-96	7q32.2	Up-regulation	miR-96	Bladder tissue Cell lines	Proliferaron Apoptosis	miR-96	CDKN1A	[100]
							FOXO1	[101]
miR-200	1p36.33	Up-regulation	miR-200a miR-200b miR-200c miR-141 miR-429	Bladder tissue Cell lines	Invasion Metastasis	miR-200 family	TWIST1	[43]
							EMT	[16]
miR-429	1p36.33	Up-regulation	miR-429	Cell lines	Migration Invasion	miR-429	ZEB1 B-catenin E-cadherin MMP-2	[102]
miR-205	1q32.2	Up-regulation	miR-205	Cell Lines	Proliferation Migration Invasion	miR-205	TWIST1	[43]
							CCNJ	[103]
miR-203	14q32	Up-regulation	miR-203	Bladder Tissue	Apoptosis	miR-203	Bcl-w Survivin	[104]
miR-210	11p15.5	Up-regulation	miR-210	Cell lines	Migration Apoptosis	miR-210	Not Data	[26]
miR-183	7q32.2	Up-regulation	miR-183	Cell lines	Migration Apoptosis	miR-183/96/182	Not Data	[26]
miR-182	7q32.2	Up-regulation	miR-182	Cell lines	Proliferation Migration Invasion	miR-182-5p	RECK Smad4	[105]
miR-106b-3p	7q22.1	Up-regulation	miR-106b	Bladder Tissue	Apoptosis	miR-106b	E2F	[106] [107]

Table 3. miRNA associated with BC diagnosis and prognosis

microRNA	Biological function	Sample type	Refs
miR-126	Diagnosis	Urine	[29]
miR-182	Diagnosis	Urine	[29, 108]
miR-199a	Diagnosis	Urine	[29]
miRs-135b/15b/1224-3p	Diagnosis	Urine	[31]
miR-106b	Diagnosis	Urine	[32]
miR-143	Diagnosis	Urine	[33]
miR-452	Diagnosis	Urine	[33]
miR-222	Diagnosis	Urine	[33]
miR-96	Diagnosis	Urine	[34]
miR-183	Diagnosis	Urine	[34]
miR-125b /miR-126	Diagnosis	Urine	[35]
miR-187	Diagnosis	Urine	[36]
miR-18a	Diagnosis	Urine	[36]
miR-25	Diagnosis	Urine	[36]
miR-142-3p	Diagnosis	Urine	[36]
miR-140-5p	Diagnosis	Urine	[36]
miR-204	Diagnosis	Urine	[36]
miR-200a	Diagnosis	Urine	[37]
miRNA-200c	Diagnosis	Urine sediment	[5]
miRNA-141	Diagnosis	Urine sediment	[5]
miR-200 famliy	Diagnosis	Urine sediment	[37]
miR-155	Diagnosis	Urine sediment	[37]
miR-205	Diagnosis	Urine sediment	[37]
miR-192	Diagnosis	Urine sediment	[37]
miR-497	Diagnosis	Serum	[41]
miR-663b	Diagnosis	Serum	[41]
miR-505	Diagnosis	Serum	[41]
miR-363	Diagnosis	Serum	[41]
miR-99a	Diagnosis	Serum	[41]
miR-194	Diagnosis	Serum	[41]
miR-100	Diagnosis	Serum	[41]
miR-1	Diagnosis	Serum	[41]
miR-152	Diagnosis	Serum	[39]
miR-378	Diagnosis	Serum	[42]
miR-942	Diagnosis	Serum	[42]
miR-106-5p	Diagnosis	Serum	[42]
miR-142-3p	Diagnosis	Serum	[42]
miR-374	Diagnosis	Serum	[42]
miR-9	Prognosis	Tissue	[46]
miR-182	Prognosis	Tissue	[46]
miR-200b	Prognosis	Tissue	[46]
miR-146-b	Prognosis	Tissue	[46]
miR-199b-5p	Prognosis	Tissue	[44, 59]
miR-200 family	Prognosis	Tissue	[43]
miR-205	Prognosis	Tissue	[43]
Let-7c	Prognosis	Tissue	[45]
miR-125b-1	Prognosis	Tissue	[45]
miR-193a	Prognosis	Tissue	[45]
miR-99a	Prognosis	Tissue	[45]
miR-145	Prognosis	Tissue	[12]
miR-143/145	Prognosis	Tissue	[47]
miR-10a-5p	Prognosis	Tissue	[48, 49]
miR-141	Prognosis	Tissue	[50, 51]