4

The Role of MicroRNA in the Metastatic Phenotype of Bladder Cancer

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Abstract: Bladder cancer is among the most common cancers globally, with significant mortality associated with more advanced disease. Early detection and diagnostic accuracy are thus fundamental to the clinical pathway for managing bladder cancer. MicroRNA (miRNA) are small, non-coding segments of RNA that regulate gene expression and have been implicated in the process of carcinogenesis. Dysregulation and aberrant expression of miRNAs have been shown to have both oncogenic and tumor suppressive effects. A vast number of miRNAs, across the entire field of cancer biology, have already been identified and characterized, and many of these have been associated with bladder cancer. These miRNAs have furthered our understanding of the genetic profile of bladder cancer, and ultimately, may be utilized in the detection, prognosis, and treatment of this disease. This chapter focuses on the role of miRNA in the pathogenesis of metastatic

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bladder cancer and overviews many of the miRNA thought to be associated with bladder cancer. Additionally, this chapter explores the clinical utilities of miRNAs in bladder cancer to serve as biomarkers and guide individualized treatment.

Keywords: metastamirs in bladder cancer; metastatic bladder cancer; microRNA in metastatic bladder cancer; miRNAs as prognostic indicators in bladder cancer; therapeutic utility of miRNAs in bladder cancer

INTRODUCTION

There is an ongoing paradigm shift in cancer treatment. The clinical pathways for treating cancer have grown increasingly individualized and the treatments themselves increasingly targeted. Central to these advances is a better understanding of the genetics and the biomolecular mechanisms of different cancers. In practice, characterizing the distinct oncologic profiles of specific tumors has allowed for more personalized therapies. Elucidating the factors that contribute to tumor promotion and suppression is paramount to constructing and understanding these profiles. One of these factors, microRNA (miRNA) is thought to play a major role in gene expression and in the development of cancer.

MiRNAs are small, non-coding segments of RNA approximately 19–22 nucleotides in length. MiRNA regulate messenger RNA (mRNA) in a post-transcriptional, or pre-translational, fashion (1, 2). Approximately 30% of all human genes and 60% of mRNA are regulated by miRNA (3). While miRNAs are evidently responsible for supporting normal human biological functioning, aberrant expression of these non-coding RNA segments may contribute to the pathogenesis of cancer and other diseases (4). Dysregulation of miRNA can trigger both tumor promotion and suppression via a multitude of biomolecular processes and pathways. Alterations to these pathways may significantly impact cancer phenotype, including cell migration and invasion, epithelial-to-mesenchymal transition (EMT) and angiogenesis—all factors that can contribute to metastatic potential (5). MiRNAs that are associated with the promotion or suppression of metastatic potential, when differentially expressed, are known as "metastamiRs" (6). The role of metastamiRs in the detection, prognosis and treatment of cancer continues to be investigated.

In addition to regulating gene expression at the cellular level, miRNAs are often exported from the cell and act as signaling molecules (7). MiRNA is widespread in the human body in both tissue and fluids, and it is relatively stable. The availability and stability of miRNA in easily accessible specimens, such as urine and blood, largely enables the feasibility of miRNA research (8). Basic research into identifying miRNA, their targets, and their downstream oncologic effects, as well as translational research into how these findings can be applied clinically, is ongoing. MiRNA as a non-invasive biomarker presents multiple uses, from detecting cancer to predicting and monitoring treatment response (8–10). Furthermore, the prospective use of miRNAs in personalizing care by identifying individual chemosensitivities to various chemotherapeutic agents, based on the specific genetics of individual tumors, would change the landscape of cancer management (11–13). The clinical utility of miRNA would be particularly welcome in the realm

of bladder cancer—a cancer that traditionally requires multiple invasive procedures to diagnose as well as to surveille, with early detection and accurate staging vital for long-term survival. This chapter will explore the current knowledge base surrounding miRNA in bladder cancer metastasis and the proposed clinical applications of miRNA in this disease.

THE ROLE OF MICRORNAS IN THE METASTATIC PHENOTYPE OF BLADDER CANCER

Bladder cancer is the 10th most common cancer in the world and accounts for 3% of cancer diagnoses globally. In more developed regions of the world, such as Western Europe and the US, bladder cancer is particularly prevalent. In the US, bladder cancer is the 6th most common cancer and represents 4.6% of all cancer diagnoses, clearly outpacing global averages (14). In 2022, approximately 81,000 new cases of bladder cancer will be diagnosed and 17,000 people will die from the disease in the US (15). Ninety percent (90%) of bladder cancer cases are urothelial in origin (UCC or TCC) with additional variants (such as squamous cell carcinoma and adenocarcinoma) being very rare and associated with a worse prognosis. While the overall 5-year survival rate for bladder cancer in the US is 77%, for metastatic bladder cancer the survival rate is about 5% (14). Thus, early detection and diagnosis is vital in addressing bladder cancer before progression to more advanced disease states. Herein we discuss the potential role of miRNAs in revolutionizing how bladder cancer is detected, staged, monitored, and treated.

METASTAMIRS IN BLADDER CANCER

There has been extensive research into the role of miRNAs in bladder cancer, and numerous metastamiRs have been implicated in its progression. Metastasis-promoting miRNAs in bladder cancer downregulate tumor suppressors like PTEN and facilitate increased expression of oncogenes such as the MMP family to facilitate increased cell migration and invasion. Conversely, metastasis-suppressing miRNAs in bladder cancer downregulate genes such as TGFβ1 and E2F3 to inhibit cellular proliferation, migration, and invasion. Tables 1 and 2 provide a summary of specific metastamiRs in bladder cancer and their identified targets and functions (16–94). These tables are far from an all-inclusive list, as the body of research is extraordinarily vast and can be discordant. For example, several studies have reported that miR-200c promotes cell migration and invasion; however, alternate studies posit that downregulation of miR-200c leads to increased cell migration, invasion, and is associated with lung metastases (16–22). While these contradictory findings may be a result of differing methodology or perhaps differences due to tissue origin in the respective studies, the definitive function of miR-200c remains unclear and requires further investigation. Nevertheless, these studies continue to highlight the diverse and multifaceted nature of bladder cancer and how dysregulation of seemingly opposite pathways can still lead to metastasis.

TABLE 1 **Summary of metastasis-promoting miRNAs involved in bladder cancer with impacted pathways, targets, and resulting oncologic outcome**

miRNA	Target/Regulator	Function	Reference
miR-10b	KLF4, HOXD10	Promotes cell migration and invasion	(23)
miR-21	PTEN	Promotes invasion and migration via upregulation of PI3K/AKT and AKT/STAG3 pathways. Enhances resistance to doxorubicin	(24, 25)
miR-92b	DAB2IP	Promotes cell migration, invasion and EMT	(26)
miR-129-5p	SOX4	Promotes cell migration and invasion	(27)
miR-137	PAQR3	Promotes cell migration and invasion	(28)
miR-146b	ETS2, MMP2, AUF1	Promotes cell invasion	(29)
miR-182-5p	RECK, Smad4	Promotes cell migration and invasion	(30)
miR-200a	PTEN, Dicer/cJun, MMP-2	Promotes cell invasion by downregulating Dicer and its respective downstream targets, leading to MMP-2 upregulation	(31)
miR-492	GJB4	Promotes cell migration and invasion	(32)
miR-495	PTEN	Promotes cell invasion	(33)
miR-516a	MMP9, PHLPP2, SMURF1	Promotes cell migration and invasion via AKT/FOXO3A/SMURF1 pathway and inhibition of MMP-9 degradation	(34)
miR-556-3p	DAB2IP	Promotes cell proliferation and colony formation via upregulation of Ras-ERK pathways, cell migration and invasion	(35)
miR-3622a	LASS2	Promotes cell invasion	(36)
miR-3648	TCF21, KISS1	Promotes cell migration and invasion	(37)
miR-4295	BTG1	Promotes cell proliferation and migration	(38)

Diagnostic and therapeutic utility of miRNAs in bladder cancer

Diagnosis of bladder cancer utilizes urine cytology and cystoscopic biopsies of bladder tissue. Further biopsies are occasionally needed for staging and differentiation between muscle invasive (MIBC) and non-muscle invasive bladder cancer (NMIBC) as well as to detect response to intravesical treatment and recurrence. These diagnostic procedures are not without risk, as patients undergoing bladder biopsies require induction with general anesthesia, and the surgeries themselves can cause bleeding, urinary tract infections (UTI), as well as damage to the prostate, bladder, or urethra. Given the physical risks of these procedures, the emotional toll on patients, and the financial burden of diagnosis, an alternative, less invasive diagnostic test utilizing miRNAs would rectify several of these existing issues.

TABLE 2 **Summary of metastasis-suppressing miRNAs involved in BC with impacted pathways, targets, and resulting oncologic outcome**

miRNA	Target/Regulator	Function	Reference
miR-15	BMI1	Inhibits cell migration and invasion.	(39)
miR-22	E2F3, Snail, MAPK	Inhibits cell migration, invasion and EMT.	(40, 41)
miR-24	CARMA3	Inhibits cell invasion and EMT.	(42)
miR-26a-5p, -26b-5p	PLOD2	Inhibits cell migration and invasion.	(43)
miR-34a-5p	TCF1, LEF1, DNMT3B, MMP-2	Inhibits cell migration and invasion. Enhances epirubicin sensitivity.	(44–46)
miR-101	FZD4, c-FOS, VEGF-C	Inhibits cell migration and invasion. Increases cisplatin sensitivity.	(47–50)
miR-124-3p	ITGA3	Inhibits cell migration, invasion, and EMT via downregulation of FAK/PI3K/AKT pathway.	(51)
miR-125b-5p	SIRT7, MALAT1, MMP13, HK2	Inhibits proliferation, cell migration, and invasion via the PI3K/AKT pathway. Promotes apoptosis.	(52–54)
miR-132	TGFβ1	Inhibits cell migration, invasion and EMT via TGFβ1/SMAD2 pathway.	(55)
miR-138	ZEB2	Inhibits cell migration and invasion.	(56)
miR-140-3p	FOXQ1	Inhibits cell invasion.	(57)
miR-145	N-cadherin, MMP9	Inhibits cell migration and invasion.	(58)
miR-146a-3p	PTTG1	Inhibits cell migration and invasion.	(59)
miR-154	ATG7	Inhibits cell migration and invasion.	(60)
miR-186	VEGF-C	Inhibits cell migration, invasion, angiogenesis.	(61)
miR-194-5p	E2F3	Inhibits cell migration and invasion.	(62)
miR-199a-5p	CCR7, MMP9	Inhibits cell migration, invasion, EMT.	(63)
miR-200b	TGF-β1	Inhibits cell migration and invasion. Enhances cisplatin sensitivity.	(64, 65)
miR-203a	SIX4	Inhibits cell migration, invasion and EMT.	(66)
miR-204	ROBO4	Inhibits cell migration and invasion.	(67)
miR-210-3p	FGFRL1	Inhibits cell invasion.	(68)
miR-223	WDR62	Inhibits cell migration and invasion.	(69)
miR-300	SP1/MMP9 pathway	Inhibits cell migration.	(70)
miR-325-3p	MT3	Inhibits cell migration, invasion, and EMT.	(71)

Table continued on following page

TABLE 2 **Summary of metastasis-suppressing miRNAs involved in BC with impacted pathways, targets, and resulting oncologic outcome (Continued)**

miR-338-3p	ETS1	Inhibits cell proliferation, metastasis and EMT.	(72)
miR-370	SOX12	Inhibits cell migration and invasion.	(73)
miR-372/373	CUL4B	Inhibits cell migration and invasion via downregulation of PI3K/AKT pathway.	(74)
miR-375-3p	FZD8	Inhibits cell migration.	(75)
miR-379-5p	MDM2	Inhibits cell migration and invasion.	(76)
miR-381-3p	BMI1, Rho/ROCK, CCNA2, MET	Inhibits cell invasion, migration and EMT.	(77, 78)
miR-429	MMP2, E-cadherin	Inhibits cell migration, invasion, and EMT via E-cadherin upregulation.	(79, 80)
miR-485-5p	HMGA2	Inhibits cell invasion and metastatic potential. Inhibits cancer cell adhesion and EMT.	(81, 82)
miR-486-5p	ROCK, CD44, MMP9	Inhibits cell migration. Enhances cisplatin sensitivity.	(83)
miR-497	Vimentin, α-SMA, E-cadherin, E2F3	Inhibits cell migration, invasion, and EMT by downregulating vimentin and α-SMA and upregulating E-cadherin.	(84, 85)
miR-502-5p	CCND1, NOP14, DNMT3B	Inhibits cell migration.	(86)
miR-539	IGF-1R	Inhibits cell proliferation and invasion.	(87)
miR-612	ME1	Inhibits cell migration, invasion, and EMT.	(88)
miR-613	SphK1	Inhibits cell migration, invasion, and EMT.	(89)
miR-621	TRIM29, Wnt/β-catenin	Inhibits cell proliferation and metastatic potential by downregulation of the Wnt/β-catenin pathway.	(90)
miR-1182	hTERT	Inhibits cell proliferation and invasion. Enhances cisplatin sensitivity.	(91)
miR-1280	ROCK1	Inhibits cell proliferation, migration and invasion.	(92)
miR-3619-5p	β-catenin, CDK2	Inhibits cell migration, invasion, and reduces metastatic potential by upregulating p21.	(93)
miR-4324	RACGAP1	Inhibits cell colony formation, migration, invasion and EMT. Enhances doxorubicin sensitivity.	(94)

miRNAs as diagnostic biomarkers

A urine-based diagnostic test utilizing miRNAs as biomarkers for bladder cancer would be an ideal clinical tool, given the ease and non-invasive nature of specimen collection. Several pilot studies have investigated the feasibility of detecting miRNAs in urine to diagnose bladder cancer (95–100), and a meta-analysis found that urine-based miRNA assays were more sensitive than urine cytology in diagnosis of bladder cancer (101). Implementing a urine-based miRNA test in the pathway of bladder cancer management could prove invaluable if it lessens the burden of repetitive invasive testing as required in NMIBC. Furthermore, tissue-based miRNA profiles may have a role in bladder cancer diagnostics as well. Patients often require repeat resections to ensure the presence of muscle in the specimen—the differentiator between NMIBC and MIBC. To this end, a tissue-based miRNA test could preclude the need for repeat resection if the presence of specific miRNAs in the initial specimen can predict muscle invasion (20) or risk of recurrence.

Utilizing miRNAs to screen and assess treatment response in bladder cancer

Treatment algorithms differ between NMIBC and MIBC. While bladder tumor resections, intravesical chemotherapy, and immunotherapy are mainstay treatments for NMIBC, surgical removal of the bladder via radical cystectomy and urinary diversion, often after neoadjuvant cisplatin-based chemotherapy, is the standard of care for MIBC (102–103). However, roughly 60% of all patients subjected to neoadjuvant chemotherapy fail to have an adequate response to systemic treatment and still have invasive disease upon cystectomy (104). Thus, a large percentage of patients with MIBC receiving neoadjuvant chemotherapy are subjected to the morbid side-effects of these chemotherapeutic agents, while not benefiting from any considerable response. Furthermore, completion of systemic therapy in this population serves to delay definitive management via surgery.

Utilizing a biomarker to identify patients who are likely to respond to chemotherapy prior to its initiation could transform the utility of neoadjuvant treatment by both minimizing unnecessary chemotherapy exposure and expediting surgery for those who are unlikely to respond. Current research suggests miRNAs may be particularly suited for this purpose. For example, miR-101, -1182, -200b and -486-5p are all implicated in tumor suppression and have been associated with cisplatin sensitivity (47, 48–50, 65, 83, 91). As such, these miRNAs could potentially be utilized to screen patients as likely responders to cisplatin-based neoadjuvant chemotherapy and would thus allow for the more appropriate provision of systemic chemotherapeutics. Furthermore, miRNAs could be used in this capacity to not just dictate the utility of cisplatin-based therapy but may also identify other chemotherapeutic options for those deemed unlikely to respond to cisplatin, thus personalizing treatment and optimizing the likelihood of response.

miRNAs as prognostic indicators in bladder cancer

While there are no current prognostic calculators for bladder cancer that utilize miRNA, there is potential for miRNAs to act in this realm. Xie et al. identified five miRNAs in a systematic review and meta-analysis that could potentially be useful in prognostics, citing high levels of miR-21 and miR-222 and low levels of miR-214 were associated with low overall survival. Furthermore, they detailed high levels of miR-143 and miR-155 were associated with poor progression-free survival (105). More recently, Yin et al. proposed a 21-signature miRNA profile to determine prognosis in BC patients (106).

MiRNAs may specifically be useful in addressing the need for a prognostic indicator for risk of disease progression. This would be particularly helpful in those who have low stage/grade disease and therefore are—based on conventional indicators—stratified as having a low risk of progression. That is, those with low stage disease who are determined to be at high risk of progression would benefit from more frequent clinical surveillance, thus providing earlier detection of disease progression, and allowing for better therapeutic options and outcomes.

UPPER TRACT UROTHELIAL CARCINOMA

Upper tract urothelial carcinoma (UTUC) refers to urothelial cancer of the renal collecting system, including the renal pelvis and the ureter. While the role of miRNAs in UTUC is far less elucidated than in UCC (bladder cancer), several studies have identified miRNAs that are dysregulated in UTUC. A serum miRNA analysis by Tao et al. found significantly different expression patterns of 13 miRNAs between UTUC patients and cancer-free patients (107). Another study by Hsu et al. identified miR-145-5p as downregulated in UTUC tissue, and a modulator of cell migration and invasion through its regulation of ARF6 (108). Furthermore, rescue of miR-145-5p expression yielded a suppression of EMT markers through its correlation with an increase in E-cadherin levels and a decrease in MMP7 and N-cadherin (108). EMT was also noted to be inhibited by miR-30a-5p in a study comparing UTUC tissue to adjacent normal tissue after nephroureterectomy for UTUC (109). In addition, Browne et al. identified several miRNAs that were associated with an invasive phenotype in UTUC, including miRs-10b-5p, -26a-5p, -31-5p, and -146b-5p (110). Lastly, Ke et al. found that miR-210 was overexpressed in UTUC compared to benign urothelium and proposed miR-210 involvement in promoting UTUC carcinogenesis and tumor progression (111).

While there is a paucity of literature regarding the role of miRNAs in UTUC in comparison to that of bladder cancer, several miRNAs have been identified with potential for therapeutic and diagnostic targeting. While further research is necessary, these miRNAs show promise in bladder cancer and UTUC alike to both further advance and refine the clinical management of these malignancies.

CONCLUSION

The clinical pathways and algorithms used for diagnosing and treating cancer are in the midst of a seismic shift and continue to rapidly evolve. An emphasis on individualized care—targeted therapy—is at the forefront of these changes. The ability to increasingly characterize a tumor based on its genetics has opened the door for improved diagnosis, prognostication, and treatment. While there are many factors found in the genetic profile of a cell that may aid its transformation into a cancer, abundant research across the spectrum of cancer biology has explored miRNA and how these short, non-coding RNA segments regulate gene expression. The potential clinical applications of miRNA are vast. MiRNAs as biomarkers could revolutionize how cancer is detected, monitored, and treated. For example, reliable urine miRNA biomarkers in bladder cancer could negate the need for the multiple invasive procedures. Further, establishing a miRNA profile for a specific tumor may elucidate its chemosensitivities, and in turn, enable personalized, targeted chemotherapy. Bladder cancer is particularly deadly in its advanced and metastatic stages and using the genetics of a tumor to refine therapeutic options could greatly alleviate the mortality burden. MiRNA research, for bladder cancer and beyond, holds great promise.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this chapter.

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