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Review Article

# MicroRNAs as Clinical Markers for Diagnosis and Therapeutic Targets in Bladder Cancer

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**Abstract**

This review investigated the evidence regarding the expression of microRNAs (miRNAs) and their role in various biological processes, such as proliferation, apoptosis, angiogenesis, metastasis, epithelial-mesenchymal transition (EMT), and treatment, as well as the potential clinical application of miRNAs as indicators for diagnosing and monitoring treatment approaches for bladder cancer (BC). We searched the studies in English conducted on animal/cell line/human specimens from the PubMed and Google Scholar databases up to 2024. Bladder cancer is one of the most common genitourinary malignancies. Early detection of cancer is vital for improving BC prognosis. There is no doubt that miRNAs are essential for the growth and function of many types of cells. They can modulate various biological processes and influence the pathological phenotypes, including bladder carcinoma. Abnormal synthesis or dysregulated signaling pathways related to miRNAs may be a significant mechanism and a compelling explanation for their aberrant expression and function in bladder neoplasia. Aberrant expression of miRNAs is associated with tumor pathological stages and grades, survival, recurrence, angiogenesis, and metastasis. In addition, miRNA expression can lead to tumor formation or progression by altering the expression or regulation of oncogenes and tumor suppressor genes. Therefore, they will have a profound impact on bladder carcinoma progression. MiRNAs are important markers for better understanding tumor biology. Considering the multifaceted role of miRNAs in different diseases and cancers, a more accurate analysis of miRNA gene expression profiles and multiple properties of miRNAs is essential. Therefore, ongoing research and technological advances will certainly reveal the hidden secrets of this process.

**Keywords:** Urinary bladder neoplasms, Biomarkers, MicroRNAs, Oncogenes, Genes, Tumor suppressor

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## Introduction

Bladder cancer (BC) accounts for 3% of all reported malignancy cases and is more prevalent in developed countries (1). Currently, urothelial bladder cancers are classified into two categories: non-muscle-invasive bladder cancers (NMIBCs) and muscle-invasive bladder cancers (MIBCs). It is noteworthy that about 70% of newly diagnosed cases are NMIBCs. The expected 5-year survival rate for NMIBCs by performing treatment is high. However, about 10–20% of NMIBCs progress to invasion. The probability of relapse at one year ranged from 15% to 61%, while the rate of progression at one year ranged from less than 1% to 17%. Evidence indicated a poor prognosis in subjects with high-risk NMIBC and tumor progression along with tolerance of relapse. The muscle-invasive kind of the disease is correlated with a poor 5-year recurrence-free survival rate (2-5).

Inflammation (6,7) and smoking (a serious public health concern) (8) are associated with a high risk of bladder carcinoma. Despite all the advances in timely diagnosis and treatment of the disease, the effective control of the disease has not yet been achieved, likely due to treatment resistance and the existence of considerable heterogeneity in the clinical behaviors of tumors. However, the difference in treatment outcomes of patients with bladder carcinoma is considered to be one of the major challenges. Meanwhile, cancer stem cells, a collection of undifferentiated cells with stem cell-like characteristics, (9) have been identified as the main cause of the high recurrence and even resistance to conventional treatments (like chemotherapy). Therefore, there is an urgent need for new treatment approaches. As a result, it is important to identify more reliable prognostic

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markers for treating different types of cancer.

Numerous miRNA-related studies have displayed the physiological role of miRNAs in the regulation of signaling pathways such as proliferation, differentiation, apoptosis, and metastasis, as well as in the pathogenesis of various types of cancers, resulting in the advanced alteration of normal cells into malignant cells (10-12). Abnormal expression of miRNAs may occur through multiple mechanisms such as gene deletion or amplification (13,14), incorrect synthesis of miRNAs (15), aberrant regulation of gene transcription or processing (16,17), and epigenetic processes (18).

The present study provides a brief overview of the role of miRNAs in controlling the expression levels of genes involved in the development and progression of the tumor, as well as the role of their expression levels in the diagnosis, prognosis, and treatment of bladder neoplasia.

## MiRNAs Synthesis

In the first step of miRNA synthesis, RNA polymerase II (mainly) transcribes the genomic DNA and produces a primary microRNA (pri-miRNA) transcript that is 5'-capped and 3'-polyadenylated. After the transcription by the polymerase II enzyme, Drosha (a member of the ribonuclease III family) processes the pri-miRNA in the nucleus, which consists of several thousand nucleotides in length and a specific stem-loop structure. Drosha and DGCR8 (microprocessor complex) generate a 70-nucleotide hairpin called the precursor microRNA (pre-miRNA) with a bump (2 nucleotides) at the 3′-end (19-23). Then, the pre-miRNA is transported out of the nucleus through interaction with Exportin-5 (a Ran GTP-dependent dsRNA-binding protein). After leaving the nucleus, the pre-miRNA is cleaved by Dicer/TRBP. The result of the cleavage is the creation of a duplex miRNA (double-stranded RNA). After duplex unwinding, a single-stranded mature miRNA is incorporated into RNA-induced silencing complex (RISC). Then, gene silencing occurs through mRNA cleavage/degradation or inhibiting the translation of target mRNAs (Figure 1) (24-30).

## MiRNAs as Oncogenes, Tumor Suppressors, and Non-Invasive Biomarkers in Cancer

MiRNAs are non-coding RNAs targeting specific mRNAs involved in various biological processes. Several miRNAs can act as tumor suppressors and/or oncogenes. The utility of miRNAs as biomarkers in various malignancies is rapidly growing. The let-7 family of miRNAs is evolutionarily conserved across species and plays critical roles in different biological processes, including growth, differentiation, proliferation, self-renewal, various diseases, and cancer. Therefore, let-7 expression needs to be strictly regulated. As a result, let-7 regulators can be effective for therapeutic advances. One study reported a relationship between decreased let-7 expression levels and undifferentiated and invasive cancer cells, including gynecological cancers (31,32). Toraih et al showed overexpression of miR-34a, along with the up-regulation of MET oncogene/E2F transcription factor 3 (E2F3) and the down-regulation of tumor protein p53-inducible nuclear protein 2 (TP53INP2)/SRY-box transcription factor 2 (SOX2) in renal cell carcinoma (33). The results of this study indicated that miR-34a can play a significant role in carcinogenesis (33). Meanwhile, researchers reported miR-21 overexpression in various malignancies. MiR-21 can exert its anti-apoptotic effects through Fas ligand inhibition (34,35). Tristetraprolin (TTP) can cause metastasis/EMT in collaboration with the oncogenic Ras signaling pathway.

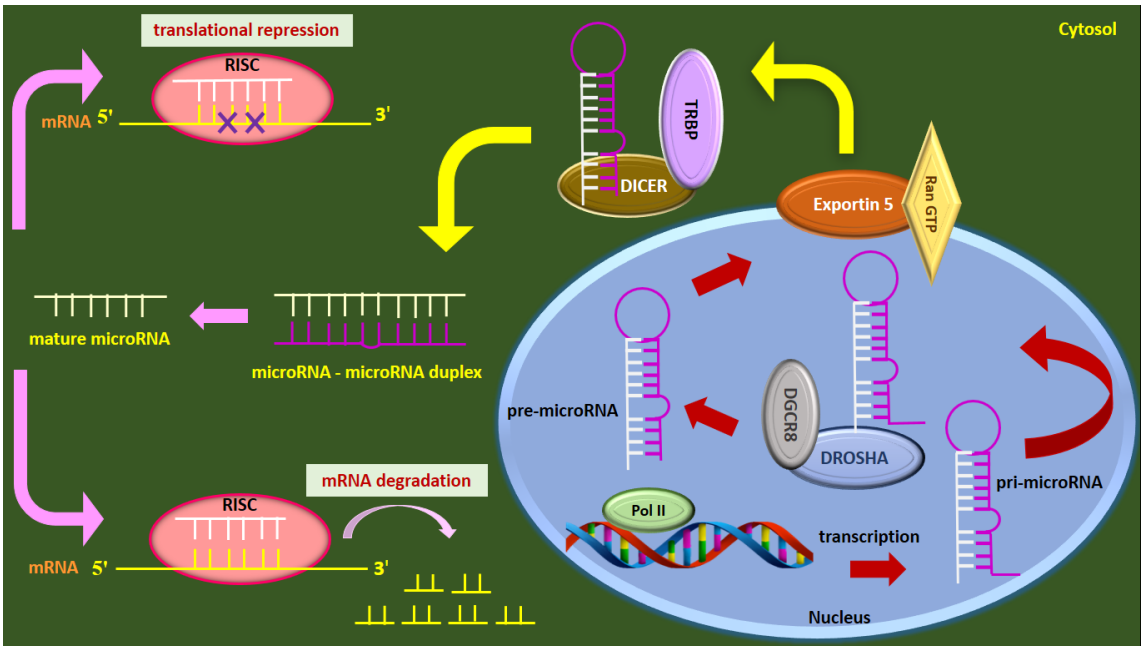



**Figure 1.** The Synthesis of MicroRNA. The biological processes of microRNA synthesis include microRNA gene transcription, primary transcript (pri-miRNA) production, pri-miRNA cleavage, precursor miRNA (pre-miRNA) production, pre-miRNA importation from the nucleus into the cytoplasm, miRNA-miRNA duplex forming, the incorporation of the mature miRNA into the RNA-induced silencing complex (RISC), mRNA-miRNA binding, mRNA cleavage/degradation or translation repression. *Note.* TRBP: Transactivation response element RNA-binding protein; Pol II: RNA polymerase

The up-regulation of MiR-29a prevents the expression of TTP (36). Lee et al have stated that the high expression of miR-7 increases the radio-sensitivity of malignant cells through targeting epidermal growth factor receptor (EGFR) and its downstream targets, suggesting that it may be an effective target in miRNA-based cancer therapy (37).

A study of 391 cases with advanced non–small cell lung cancer (NSCLC) indicated that 35 miRNAs had high expression. Additionally, 17 of the 35 miRNAs were significantly associated with patient survival. In addition, it was observed that miR-16 overexpression was related to good survival. In a previous study, serum miRNAs were identified as predictors of survival in advanced NSCLC (38). Khan et al have indicated the overexpression of miR-122-5p, miR-192-5p, and miR-215-5p and lower expression of miR-320b and miR-30b-5p in pancreatic ductal adenocarcinoma patients; in other words, these miRNAs can differentiate pancreatic ductal adenocarcinoma patients from chronic pancreatitis patients and normal control subjects and can act as non-aggressive indicators for the diagnosis of pancreatic ductal adenocarcinoma at early stages (39). Moreover, these miRNAs (miR-17, miR-20a, miR-20b, and miR-106a) can be non-invasive indicators for predicting the risk of prostate neoplasia after radical prostatectomy. These miRNAs can also detect the pathological stage of the tumor. In addition, an association between their overexpression with a shorter time to relapse in the TCGA dataset and the creation of an aggressive phenotype (in vitro) was reported (40). In another study, Kashyap et al pointed out the importance of various cell-free miRNAs as non-invasive indicators for the classification, early detection, and anticipation and monitoring of breast cancer cell metastasis (41).

Some researchers have examined the levels of several miRNAs in the urine of subjects with cancer. For example, the findings of a study showed that some specific miRNAs, including miR-34a-5p, miR-92a-1-5p, miR-143-3p, miR-196a-5p, and miR-501-3p, in urinary exosomes might act as non-aggressive indicators for prostate carcinoma; especially, miR-196a-5p and miR-501-3p are favorable and hopeful indicators (42). In another study, the importance of urinary miRNAs such as let7-i, miR-424, miR-423, and miR-660 as particular indicators and non-invasive markers that can differentiate breast cancer subjects from normal individuals was demonstrated (sensitivity: 98.6% and specificity: 100%) (43). Recently, miR-21, miR-200, and miR-145 have been introduced as possible oncogenes in BC. Their expression was high in the urine of high-grade and low-grade bladder carcinoma subjects and in bladder neoplasia tissues and may act as early non-invasive diagnostic markers and beneficial targets for BC therapy (44). In brief, the expression patterns of miRNAs may be reliable markers in the prognosis and prediction of cancer treatment outcomes.

## MiRNAs Mechanism in Bladder Carcinoma

Scientists have determined the stages of cancer progression in which several mutated genes are involved. These genetic changes are responsible for the essential phenotypic characteristics of malignancy, tumor progression, uncontrolled cell proliferation, and tissue heterogeneity (45). Neoplastic cells target proto-oncogenes and tumor suppressor genes. Proto-oncogenes are critical regulators of biological processes. Changes in these genes can appear in cancer cells as active oncogenes. Therefore, oncogenes cause normal cells to transform into cancer cells, and tumor suppressor genes prevent cancer from progressing (46). The up-regulation/down-regulation of miRNAs may affect genes involved in biological processes, which lead to uncontrolled cell proliferation, invasion, angiogenesis, and metastasis of tumors (47). In the following, we will discuss the role of miRNAs as oncogenes or tumor suppressors in BC progression.

## The Role of MiRNAs in Proliferation and Apoptosis of Bladder Neoplasia

In cancer, cells evade natural growth and proliferation. Tumor cells respond to apoptosis induction aberrantly, which leads to excessive cellular proliferation. Documents confirm the role of overexpression of inhibitors of apoptosis proteins (IAP family) in apoptosis suppression in cancer (48).

Many miRNAs are involved in cancer cell proliferation and apoptosis pathways in bladder neoplasia. High expression of miR-96 can enhance cell proliferation and invasion in bladder neoplasia by targeting cyclin-dependent kinase inhibitor 1A (CDKN1A) (49). A study indicated that overexpression of miR-19a was related to more aggressive phenotype in the cancerous tissues and plasma obtained from individuals with bladder carcinoma through targeting phosphatase and tensin homolog (PTEN) (50). On the contrary, the finding of a study indicated that the overexpression of miR-145-5p can inhibit cell proliferation in bladder neoplasia by targeting transgelin-2 (TAGLN2) (51). Mir-608 often has a low expression level in human BC tissues; the up-regulation of miR-608 suppresses both the proliferation and carcinogenesis of bladder tumor cells through stimulating the G1 phase arrest by protein kinase B (AKT)/forkhead box O3a (FOXO3a) signaling pathways and Flotillin-1 (FLOT1) inhibition (52). SMAD3 is a direct target of miR-5581-3p. Increased expression of miR-5581-3p can notably inhibit the proliferation/migration in BC (in vitro/in vivo) by targeting SMAD3 (53).

Guo et al showed that miR-144 overexpression affects enhancer of zeste homologue 2 (EZH2) expression and leads to the inhibition of cell proliferation by inactivating the Wnt/β-catenin signaling pathway. They suggested that miR-144 may be a beneficial therapeutic option for bladder neoplasia (54). In addition, miR-34a can have a significant role in regulating tumor cell proliferation/invasion in BC by targeting hepatocyte nuclear factor 4 gamma (HNF4G). Therefore, the miR-34a/HNF4G axis is a critical pathway in suppressing malignancy (55). The results of two studies showed the anti-tumor effects of miR-138-5p/miR-497 (56,57). These miRNAs repressed the proliferation of BC cells by inhibiting baculoviral IAP repeat containing 5

(BIRC5; also known as survivin)/E2F3 levels in bladder transitional cell carcinoma, respectively. According to the evidence, they can act as diagnostic tools and prognostic biomarkers for BC therapeutic approaches (56,57).

Apoptosis is a crucial response to environmental changes to maintain the natural homeostasis of the body. Matsushita et al found that miR-144-5p directly regulates genes involved in the cell cycle (e.g., CCNE1/2); the overexpression of CCNE1 or CCNE2 may be associated with shorter overall survival (58). MiR-449a levels were found to be low in human BC tissues; therefore, it can act as a tumor inhibitor by targeting cyclin-dependent kinase 6 (CDK-6)/cell division cycle 25A (CDC25A) (59). Oncogene E2F3 had high expression in high-grade BC. Regulating G1/S transition can be exerted by miR-125b via the cyclin A2/E2F3 signaling pathway. Therefore, miR-125b down-regulation may lead to the development of BC in patients (60). According to the results of the study conducted by Inoguchi et al, miR-24-1 overexpression leads to the down-regulation of oncogenic forkhead box protein M1 (FOXM1) levels in BC cells. The miR-24-1/FOXM1 axis may provide a comprehensive understanding of the molecular processes involved in bladder carcinoma (61).

Several miRNAs can target Bcl-2-like protein 2 (BCL2L2; Bcl-w)/BIRC5 to regulate apoptosis. A study reported decreased miR-133b levels and increased Akt1/BCL2L2 levels in BC tissues, regulation of the proliferation and apoptosis of T24 cells by targeting Akt1/BCL2L2 levels by miR-133b, and a strong association between miR-133b expression level and the pathological grade of bladder carcinoma (62). In addition, miR-203 can be a prognostic marker in BC patients treated with cisplatin-based chemotherapy by inducing apoptosis via targeting both BCL2L2/BIRC5 (63). Down-regulation of Mir-195 and miR-497 can cause advanced BC by their direct binding to some specific positions in the 3′-UTR of BRIC5 and Wnt family member 7A (WNT7A) mRNAs, respectively. Moreover, miR-195 overexpression can arrest G1 phase in T24 cells by affecting cyclin-dependent kinase 4 (CDK-4) (64,65). According to Yoshino et al, miR-1 can induce apoptosis via its binding in 3′-UTR of serine/arginine-rich splicing factor 9 (SRSF9) in bladder cancer, thereby suppressing oncogenic SRSF9/SRp30c (66). Meanwhile, an inverse association was found between miR-124-3p and endothelin receptor type B (EDNRB) levels in bladder neoplastic tissues/cell lines; in other words, miR-124-3p may be a crucial tumor inhibitor that can effectively induce apoptosis (Figure 2) (67).

## The Role of MiRNAs in Angiogenesis of Bladder Neoplasia

Angiogenesis is a necessary stage and characteristic of tumor progression by forming new blood vessels. Genes such as vascular endothelial growth factor A (VEGF-A), ANGPT-1, and ANGPT-2 are related to angiogenesis in tumor cells (68). Moreover, hypoxia-inducible factor-1α (HIF-1α) and its downstream targets are significant in the development and progression of the tumor. In this line,

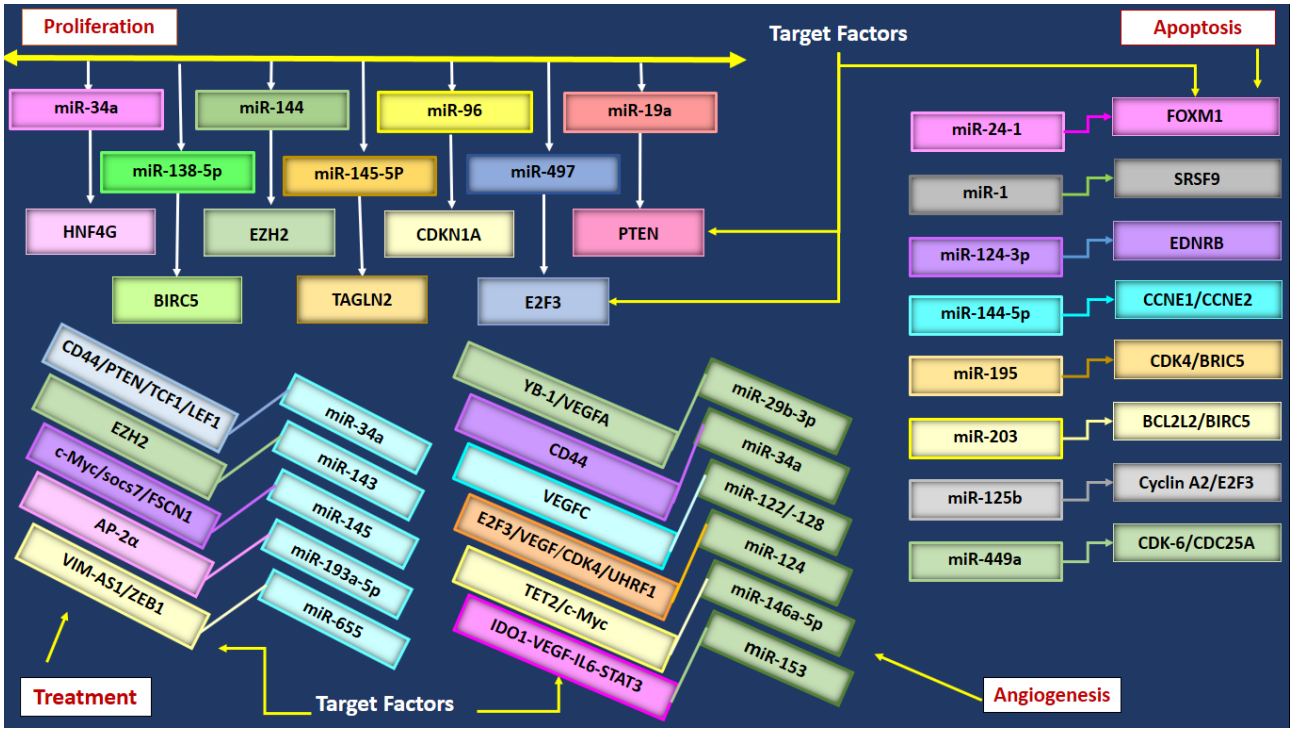



**Figure 2.** Schematic representation of microRNAs participating in cancer cell proliferation, apoptosis, angiogenesis, and treatment, along with their target factors in bladder carcinoma. *Note.* AKT1: Protein kinase B 1; AP-2α: Activating protein 2α; BCL2L2: B cell lymphoma-2-like 2; BIRC5: Baculoviral IAP repeat containing 5; CCNE1/2: *Cyclin E1/2*; CDC25A: Cell division cycle 25A; CDK4: Cyclin-dependent kinase 4; CDK6: Cyclin-dependent kinase 6; CDKN1A: Cyclin-dependent kinase inhibitor 1A; EDNRB: Endothelin receptor type B; E2F3: E2F transcription factor 3; EZH2: Enhancer of zeste homologue 2; FOXM1: Forkhead box protein M1; FSCN1: Fascin actin-bundling protein 1; HNF4G: Hepatocyte nuclear factor 4 gamma; LEF1: Lymphoid enhancer-binding factor 1; PTEN: Phosphatase and tensin homolog; SOCS7: Suppressor of cytokine signaling 7; SRSF9: Serine and arginine-rich splicing factor 9; TAGLN2: Transgelin-2; TCF1: T cell factor 1; TET2: Tet methylcytosine dioxygenase 2; UHRF1: Ubiquitin like with PHD and ring finger domains 1; VEGFA/C: Vascular endothelial growth factor A/C; VIM-AS1, VIM antisense RNA 1; YB-1: Y-box binding protein 1; ZEB1: Zinc finger E-box binding homeobox 1

HIF-1α inhibitors can be an efficient option in tumor treatment (69).

MiRNAs can regulate the expression of factors involved in angiogenesis. MiR-200c can inhibit angiogenesis by targeting the HIF-1α/VEGF A/Akt2/mammalian target of rapamycin (mTOR) axis in bladder neoplasia cells (70). The findings of a study exhibited that up-regulation of miR-124 expression was correlated with inhibiting cell proliferation, suppressing angiogenesis, and decreasing CDK-4 (as the direct target of miR-124)/Ki-67/E2F3/VEGF levels (71). In this line, Wang et al indicated that the upregulation of miR-124 inhibited the expression level of ubiquitin-like with PHD and RING finger domains 1 (UHRF1), which led to the reduction of aggressive phenotypes in-vitro/in-vivo (72). Another study suggested that miR-122/miR-128 can suppress bladder tumor growth and angiogenesis through reducing VEGFC levels (73,74). In addition, the miRNA-34a/CD44 axis can be beneficial in anti-metastatic/anti-angiogenic therapeutic methods of bladder carcinoma (75). One study showed that Y-box binding protein 1 (YB-1) can induce angiogenesis (76). Angiogenesis is inhibited through overexpression of miR-29b-3p by targeting the YB-1/VEGFA axis in bladder neoplasia (76), and conversely, increased level of miR-146a-5p is associated with angiogenesis. A recent study indicated that the urinary levels of miR-146a-5p were higher in subjects with high-grade bladder neoplasia compared to those with low-grade bladder neoplasia. Meanwhile, extracellular vesicles treated with miR-146a-5p and obtained from high-grade BC led to Tet methylcytosine dioxygenase 2 (TET2) inhibition and increased levels of c-Myc (Figure 2) (77).

## The Role of MiRNAs in Metastasis and EMT of Bladder Neoplasia

Metastasis is a crucial step in tumor progression and a big problem in cancer treatment. Mir-34a can suppress angiogenesis and metastasis in bladder transitional cell carcinoma by directly targeting CD44. Accordingly, Yu et al reported that miR-34a expression can regulate the EMT in BC (75). Declined levels of miR-153 are associated with the pathological stage of the tumor and a lower overall survival rate; however, miR-153 can exert its antitumor effects via the suppression of proliferation/EMT/migration/invasion of bladder neoplastic cells in vitro, tumor cell xenograft growth in vivo, and the blockage of tryptophan metabolism by targeting indoleamine 2,3-dioxygenase 1 (IDO1) levels and VEGF/interleukin 6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling pathway (78). The overexpression of MiR-138 and miR-101 can suppress metastasis through zinc finger E-box binding homeobox 2 (ZEB2) and frizzled class receptor 4 (FZD4), respectively. Besides, the down-regulation of miR-101 expression is significantly related to tumor pathological stage and weak prognosis in bladder carcinoma (79,80). Yao et al indicated the inhibition of miR-186-mediated metastasis by affecting NSBP1(HMGN5), N-cadherin, Vimentin (mesenchymal markers), and E-cadherin (epithelial marker) levels (81). Meanwhile, the up-regulation of miR-1-3p/miR-194 blocks the invasion by repressing C-C motif chemokine ligand 2 (CCL2) and RAP2B (belongs to the Ras-related protein family) expression in BC cells, respectively (82,83). Moreover, the up-regulation of miR-451 can suppress invasion and migration through c-Myc in BC (84). On the other hand, miR-10b overexpression can enhance metastasis of bladder cancer cells through kruppel-like factor 4 (KLF4)/homeobox D10 (HOXD10) both in vitro and in vivo. HOXD10/KLF4 can affect matrix metalloproteinases 14 (MMP14)/E-cadherin expression levels, respectively (85).

The epithelial–mesenchymal transition (EMT) is the alteration of features of epithelial cells to motile and invasive mesenchymal cells, which can cause tumor progression. As a result, cancer cells migrate from primary sites to distant sites. The levels of some transcription factors (e.g., Snail, Twist, zinc finger E-box binding homeobox 1 (ZEB1), and ZEB2) can be influential in establishing BC malignant parameters (86-89). The EMT can act as a downstream target of miRNAs/transcription factors in bladder carcinoma and trigger enhanced migration/metastasis of bladder carcinoma cells. Targeting EMT is crucial in blocking invasive BC cells. Therefore, miRNAs can have a pivotal role in EMT regulation. For example, one study showed that the miR-200 family expression levels can affect EGFR-therapy sensitivity and the EMT process in BC cells and are sufficient to reverse the biology of mesenchymal cell lines (especially miR-200c/-b) via regulating their direct targets, such as ZEB1/ZEB2/ERBB receptor feedback inhibitor 1 (ERRFI-1) (90). Meanwhile, Huang et al showed that sulforaphane (SFN), one of the isothiocyanates, can repress invasion and reverse EMT by targeting miR-200c/ZEB1 levels in BC cells (91). In another study, high expression of miR-451 was correlated with the TNM stage and the degree of differentiation in BC tissues (92). According to the authors, miR-451 can block the EMT by maintaining tumor cells in epithelial phenotype, thereby preventing tumor cell migration/invasion in BC (92). MiR-22 can exert its effects through the mitogen-activated protein kinase 1 (MAPK1). It can repress cell proliferation by targeting MAPK1 and block cell motility by affecting the MAPK1/Snail axis. There is also an interaction among Vimentin, Slug, and MAPK1 in BC cells. MAPK1-mediated Slug levels can enhance Vimentin expression, and Vimentin levels induce MAPK. However, miR-22 can inhibit EMT in BC by blocking the Snail/MAPK1/Slug/Vimentin axis (93). High LINC01410 (lncRNA1410) expression can lead to an aggressive phenotype. The oncogenic effects of LINC01410 target miR-4319/Snail1 levels in BC (94). ZEB1 can stimulate migration and invasion in vitro; it is a direct target of miR-23b in BC. The up-regulation of MiR-23b can reduce ZEB1 expression to suppress the EMT (88,95). On the contrary, VIM antisense RNA 1 (VIM-AS1) abrogates miR-655-associated repression of ZEB1 and potentiates the EMT in BC (96). However, gambogic acid (GA) can enhance miR-205-5p expression and simultaneously inhibit ZEB1 expression, thereby reducing the cisplatin-based chemotherapy resistance of

BC cells through the EMT pathway inhibition (97). Similar to ZEB1, ZEB2 can stimulate invasion and migration. The inhibitory effects of miR-374b-5p and miR-454-3p can affect invasion/migration by targeting ZEB2 in BC (98). In addition, miR-328-3p (99) and miR-15 (100) suppress the EMT via phosphoinositide 3-kinase (PI3K)/Akt down-expression by targeting integrin α5 (ITGA5) and B cell-specific moloney murine leukemia virus integration site 1 (BMI1) levels, respectively, resulting in decreased invasion in BC. Moreover, miR-3619-5p can block Wnt signaling by inhibiting the levels of β-catenin/cyclin-dependent kinase 2 (CDK-2) and activating p21, resulting in decreased EMT/invasion in BC (101). On the contrary, Wnt7a can enhance β-catenin expression to trigger the EMT, and miR-370-3p can directly prevent Wnt7a-mediated EMT in BC cells (102).

MMPs can play an important role in cancerous cell invasion and metastasis. Caspase recruitment domain-containing membrane-associated guanylate kinase 3 (CARMA3 (helps the progression of BC cells; it can affect the levels of c-Myc/MMP2/MMP9. CARMA3 can reduce E-cadherin levels and increase β-catenin levels (103). In this notion, Yonemori et al have also exhibited that decreased levels of miR-139-5p and miR-139-3p can induce invasion/migration through affecting the MMP11 gene in bladder neoplastic cells (104). Transforming growth factor-β1 (TGF-β1) can induce the EMT and MMP16 levels by reducing the expression of miR-200b, which leads to bladder carcinoma cell migration (105). Meanwhile, the TGF-β1/suppressor of mothers against decapentaplegic homolog 2 (SMAD2) signaling is a crucial signaling pathway of EMT, and miR-132 can exert its inhibitory effects on the promoted EMT by targeting the TGF-β1/SMAD2 axis in BC (106). A recent study reported that miR-665 up-regulation can reduce the levels of SMAD3/Snail and block the EMT in BC cells (Figure 3) (107). Indeed, to combat tumor cell migration/invasion, combination therapy is needed to target different miRNAs.

## The Role of MiRNAs in the Treatment of Bladder Neoplasia

Mir-34a/CD44/PTEN axis can be a therapeutic option for BC. The pro-apoptotic effects of MiR-34a can be triggered by regulating CD44 (75) and PTEN expression (108). In this regard, Xiaobing et al have shown that miR-34a determines the chemo-sensitivity of BIU87/ADR by targeting the T cell factor 1 (TCF1)/lymphoid enhancer-binding factor 1 (LEF1) axis (109). Xiong et al have found that the miR-655/VIM-AS1/ZEB1 axis might be a perfect option to ameliorate BC metastasis through EMT (96). In addition, miR-143/miR-21/miR-155/miR-222/miR-214 can be biomarkers for early diagnosis, recurrence, risk stratification, and even beneficial remedial approaches for treating bladder neoplasia patients (110). However, the low expression of miR-143 can be due to the high expression of EZH2; the EZH2/miR-143 axis may be efficient for BC patients (111). Transfection of 253J B-V cells with miR-145 induced apoptosis, repressed migration, reduced levels of c-Myc/β-catenin/catenin δ-1/suppressor of cytokine signaling 7 (socs7)/E-cadherin/fascin actin-bundling protein 1 (FSCN1), but increased PI3K/Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways (in vitro). In addition, miR-145-treated mice indicated 76% cell growth suppression and survival rate elevation (in vivo). Therefore, intravesical administration of miR-145 may be a reliable and effective method in treating human bladder neoplasia (112). Regarding drug resistance, Zhou et al have shown that miR-193a-5p has

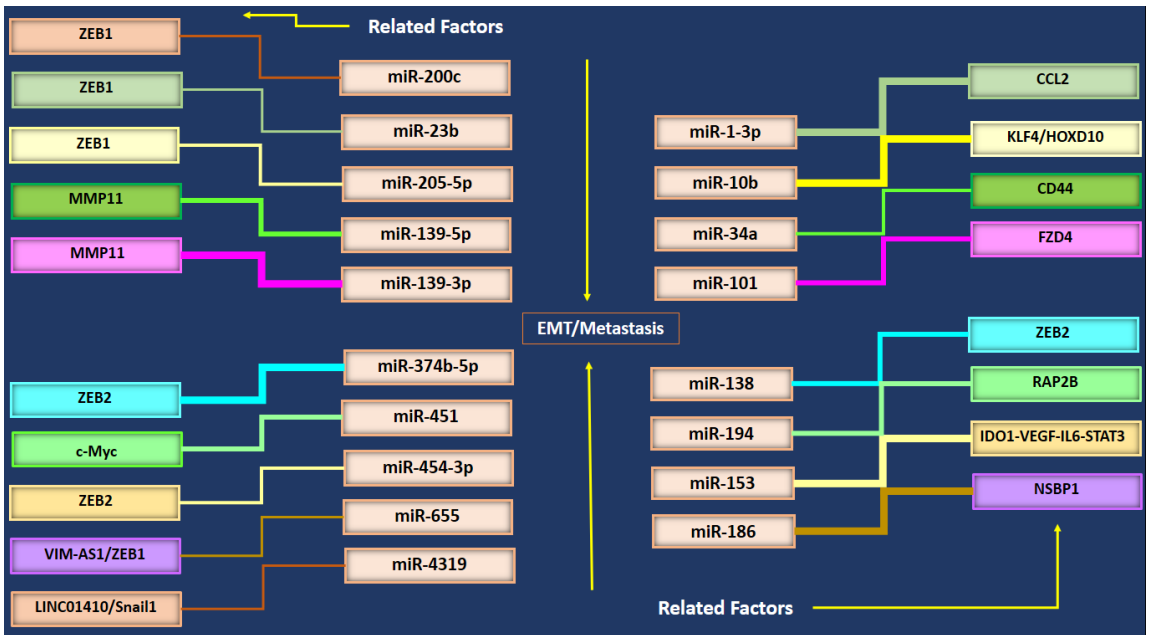



**Figure 3.** Schematic representation of microRNAs participating in metastasis/EMT, along with their related factors in bladder carcinoma. *Note.* CCL2: C-C motif chemokine ligand 2; FZD4: Frizzled class receptor 4; HOXD10: Homeobox D10; IDO1: Indoleamine 2,3-dioxygenase 1; IL-6: Interleukin-6; KLF4: Kruppel-like factor 4; MMP11: Matrix metalloprotease 11; NSBP1: Nucleosomal binding protein 1; RAP2B: Member of RAS oncogene family; STAT3: Signal transducer and activator of transcription 3; VEGF: Vascular endothelial growth factor; VIM-AS1: VIM antisense RNA-1; ZEB1/2: Zinc finger E-box binding homeobox 1/2

a high expression in bladder neoplastic cells. It targets the levels of activating protein 2α (AP-2α; a prognostic indicator of chemotherapy) and binds to the coding region of AP-2α, causing resistance to cisplatin (Figure 2) (113). Figure 4 presents a schematic representation of some miRNAs and their signaling pathways in bladder neoplasia.

## The Role of MiRNAs in the Diagnosis of NMIBC and MIBC

One study showed that cell-free miR-155 levels were elevated in the urine of individuals with NMIBC compared to the normal group and related to the grade/stage of NMIBC; therefore, according to authors, it could be a marker for NMIBC detection, the progression of NMIBC, and recurrence (114). Another study reported that let-7c, miR-345, miR-204, miR-148a, miR-135a, and miR-135b could also accurately distinguish BC cases from healthy cases, high-grade NMIBC subjects, NMIBC patients from MIBC subjects, and low-grade BC cases from high-grade BC cases using urine samples (independent of stage and grade) (115). Moreover, the levels of miR-26b-5p/miR-144-5p/miR-374-5p in blood samples, miR-618/miR-1255b-5p levels in the urine samples (116), and the levels of miR-138-5p/miR-146b-5p/miR-155-5p/miR-200a-3p in tumor tissues were significantly associated with aggressive bladder tumors. In addition, higher expression of miR-155-5p and miR-146b-5p in urinary extracellular vesicles was observed in MIBC patients (117). The value and importance of urinary miRNAs in identifying patients with malignancies, such as bladder carcinoma, as biomarkers are assuredly much higher than expensive, invasive, and time-consuming methods. Meanwhile, another challenge in health and patient management is the high recurrence rate of NMIBC after treatment. Therefore, finding minimally invasive diagnostic biomarkers and their application can effectively manage patient health.

In the study by Blanca et al, low expression and high expression of miR-138 were associated with tumor recurrence and longer recurrence-free survival, respectively. In addition, there was an association between lower miR-100 levels and cancer-specific overall survival/lengthy progression-free survival. The findings of this study showed miR-100/miR-138 as prognostic indicators in NMIBC (118). Jiang et al showed that high expression of miR-152 and low expression of miR-3187-3p were associated with poorer recurrence-free survival in NMIBC subjects, and serum miR-152 expression was also a marker of tumor relapse risk (119). Moreover, miR-26b-5p levels in tumor tissue were associated with tumor recurrence and progression in NMIBC. According to the authors, miR-26b-5p could serve as a prognostic marker for NMIBC recurrence (120). Yang et al evaluated miR-10a-5p expression levels in both tissue and plasma (121). They showed an association between miR-10a-5p level in human BC tissues and advanced clinicopathological features, indicating the high efficiency of the serum levels of miR-10a-5p in distinguishing BC individuals from healthy individuals before surgery and even in distinguishing NMIBC patients from MIBC (121). MiR-222 can be a suitable and non-invasive tool for distinguishing MIBC

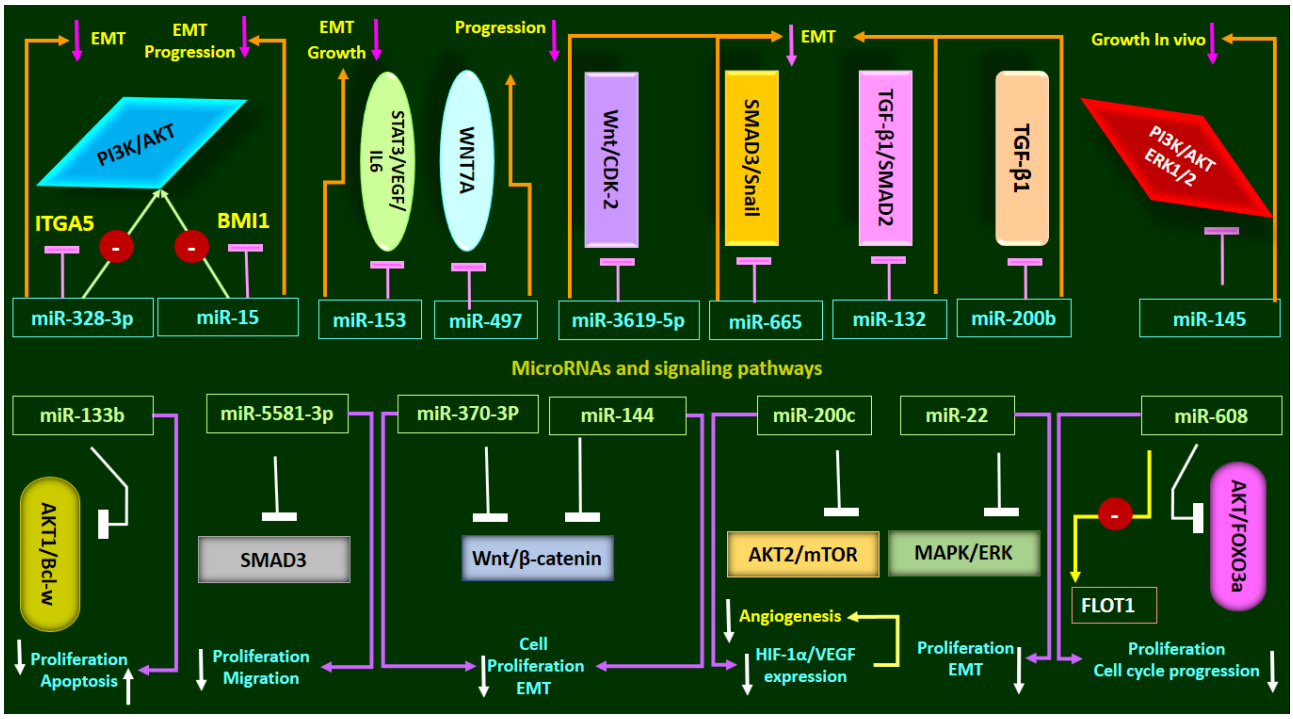



**Figure 4.** Schematic representation of some microRNAs and their signaling pathways in bladder neoplasia. *Note.* AKT1/2: Protein kinase B 1/2; BIRC5: Baculoviral IAP Repeat Containing 5; BMI1: B cell-specific moloney murine leukemia virus integration site 1; CDK2/4: Cyclin-dependent kinase 2/4; EMT: Epithelial-mesenchymal transition; ERK1/2: Extracellular signal-regulated kinase 1/2; FLOT1: Flotillin-1; FOXO3a: Forkhead box O3a; HIF-1α: Hypoxia-inducible factor-1α; ITGA5: Integrin α5; MAPK: Mitogen-activated protein kinase 1; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase; SMAD2/3: Suppressor of mothers against decapentaplegic homolog 2/3; TGF- β1: Transforming growth factor-β1; VEGF: Vascular endothelial growth factor A; WNT7A: Wnt Family Member 7A
→: Activation/up-regulation; ┤: Inhibition/down-regulation; –: Inhibition; +: Activation; ↑: Increase; ↓: Decrease

from NMIBC. The study exhibited high expression of miR-222 in subjects with BC compared to healthy subjects, higher expression in patients with MIBC than in NMIBC patients, and a link between miR-222 level and tumor stage/distant metastasis/weak prognosis in BC (122). However, miR-143 may be an efficient biomarker for early detection of bladder tumors (AUC = 0.88). Interestingly, together with miR-100, the diagnostic power was higher (AUC = 0.95) (123). A recently published study reported that declined miR-145 core promoter methylation profiling in pre-treatment cell-free DNA was significantly correlated with an increased risk of poor overall survival and tumor short-term progression after treatment. It is suggested that miR-145 core promoter methylation in pre-treatment cell-free DNA can be an independent and low-invasive tool for prognosis, risk stratification, and prediction of MIBC patients' treatment outcomes (124). Table 1 indicates the target genes and biological roles of several miRNAs involved in BC.

## Conclusion

MiRNAs are non-coding RNAs targeting specific mRNAs involved in various biological processes. The field of miRNA-associated research has notably progressed over the past decade. In this regard, many studies have investigated the role of miRNAs in different types of human cancers,

**Table 1.** Some MicroRNAs and Their Target Genes in Bladder Neoplasia

| MicroRNA | MicroRNA type | Target | Function | Reference |
|---|---|---|---|---|
| miR-23b/-27b cluster | Tumor suppressor | EGFR/c-Met | Proliferation/Migration/Invasion | (125) |
| Mir-27a | Tumor suppressor | RUNX1<br>SLC7A11 | Drug-based chemotherapy | (126)<br>(127) |
| Mir-27b | Tumor suppressor | engrailed-2 | Proliferation/Invasion/Apoptosis | (128) |
| Mir-29c | Tumor suppressor | CDK6 | Proliferation/Cellular growth/<br>Migration/Invasion/Cell cycle | (129) |
| Mir-30a | Tumor suppressor | NOTCH1 | Proliferation/Migration/Invasion/Cell cycle | (130) |
| Mir-34a | Tumor suppressor | NOTCH1 | Migration/Invasion | (131) |
| Mir-99a | Tumor suppressor | FGFR3 | Proliferation/Migration/Invasion | (132) |
| Mir-100 | Tumor suppressor | mTOR | Proliferation/Cell cycle/Metastasis/ Tumorigenesis | (133) |
| Mir-124-3p | Tumor suppressor | AURKA | Proliferation/Migration/Apoptosis | (134) |
| Mir-133a/b | Tumor suppressor | EGFR | Proliferation/Migration/Invasion | (135) |
| Mir-143 | Tumor suppressor | IGF-1R | Proliferation/Drug-based chemotherapy | (136) |
| Mir-199a-5p | Tumor suppressor | CCR7 | Migration/Invasion/Metastasis | (137) |
| MiR-200c | Tumor suppressor | BMI-1/E2F3<br>ZEB1 | Proliferation/Migration/Invasion/EMT Migration/Invasion | (138)<br>(139) |
| miR-205-3p | Tumor suppressor | Glyoxalase 1 | Occurrence/Proliferation/Metastasis | (140) |
| Mir-214 | Tumor suppressor | netrin-1 | Proliferation/Migration/Apoptosis/Drug-based chemotherapy | (141) |
| Mir-320a | Tumor suppressor | ITGB3 | Invasion | (142) |
| Mir-320c | Tumor suppressor | CDK6 | Proliferation/Migration/Invasion/Cell cycle | (143) |
| Mir-323a-3p | Tumor suppressor | MET/SMAD3/SNAIL | EMT | (144) |
| Mir-409-3P | Tumor suppressor | c-Met | Migration/Invasion | (133,145) |
| Mir-433 | Tumor suppressor | c-Met/CREB1 | Proliferation/Migration/Invasion/EMT | (146) |
| Mir-574-3p | Tumor suppressor | MESDC1 | Proliferation/Migration/Invasion/Apoptosis | (147) |
| Mir-576-3p | Tumor suppressor | Cyclin D1 | Proliferation/Cell cycle | (148) |
| Mir-590-3p | Tumor suppressor | TFAM | Proliferation/Migration/Tumorogenesis | (149) |
| Mir-613 | Tumor suppressor | SphK1 | Proliferation/Migration/Invasion/EMT | (150) |
| miR-1307-5p | Tumor suppressor | MDM4/Hippo pathway | Cell growth/Proliferation/Cell cycle/Apoptosis | (151) |
| Mir-19a | Oncogene | RhoB | Invasion/EMT | (152) |
| Mir-21 | Oncogene | PTEN/p53 | Proliferation/Migration | (153) |
| Mir-92b | Oncogene | DAB2IP | Migration/Invasion/EMT | (154) |
| Mir-150 | Oncogene | PDCD4 | Invasive/Drug-based chemotherapy | (155) |
| Mir-155 | Oncogene | DMTF1 | Cell growth/Cell cycle | (156) |
| Mir-182-5p | Oncogene | RECK/SMAD4 | Proliferation/Migration/Invasion | (157) |
| Mir-221 | Oncogene | STMN1<br>TRAIL | EMT<br>poptosis | (158)<br>(159) |
| Mir-373 | Oncogene | EGFR | Proliferation/Migration/Invasion | (160) |
| Mir-492 | Oncogene | GJB4 | Proliferation/Metastasis | (161) |
| Mir-708 | Oncogene | CASP2 | Cell growth/Apoptosis/Carcinogenesis | (162) |

including bladder carcinoma. The discovery of miRNAs has raised our understanding of human malignancies. The results of studies by researchers show the potential effectiveness of using miRNAs as diagnostic, prognostic, and therapy biomarkers in BC. Various factors can affect the expression of oncogenes or tumor suppressors. If their expression changes, carcinogenesis occurs. There is an association between changes in different biological properties of tumors and the impaired regulation of the expression levels of miRNAs. The dysregulated expression of miRNAs can target vital cellular processes. As a result, altered processes can lead to the development and progression of BC. MiRNAs are present in blood and urine and can be extracted from individuals repeatedly and non-invasively.

Considering the aberrant expression of miRNAs and their effects on cancer cells, as well as the existence of challenges like resistance to chemotherapy drugs, tumor biology, the high rate of proliferation of cancer cells, and metastasis to other parts of the body, it is essential to find more effective treatment strategies for reducing proliferation, invasion, and prolonging the survival of patients.

Dysregulated expression of miRNAs affects their upstream/downstream signaling pathways and ultimately causes a profound effect on the progression of cancers such as BC. MiRNAs have a massive set of targets and may play a carcinogenic role by changing their peculiar targets and functioning. Therefore, it is crucial to recognize the potential targets of miRNAs and develop secure procedures for providing miRNA-based therapies to manage cancer. As a result, targeting miRNA-related signaling pathways, their upstream/downstream targets, the other molecules involved in both synthesis and regulation of their expression, and combination therapy may be recognized as effective treatments for bladder neoplasia. Combination treatment is a favorable strategy for attaining better therapeutic results in patients with progressed tumors.

Overall, to better understand the functional mechanism and clinical utility of miRNAs and their target genes as a viable and handy therapeutic method for bladder carcinoma treatment, more comprehensive and rigorously designed clinical trials are necessary in the future. The results of these studies will surely guarantee miRNA-based therapies. Therefore, miRNA-based therapeutics are promising tools to manage bladder carcinoma.

Since a single miRNA can be efficient in the pathogenesis of several types of cancer, designing a novel nanocarrier-based platform with no side effects on normal cells is a vital step toward treating malignancies (163), including bladder carcinoma (164). More studies will reveal the potential of nanotechnology-mediated systems to target miRNAs for treating BC, especially when combined with other therapies. To utilize the extraordinary potential of nanoparticles while protecting human health, it is essential to consider biochemical toxicity, long-term biosafety/efficacy of nanoparticles in healthcare, and the mode of administration/dosage of miRNA-loaded carriers.

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**Competing Interests**

The authors declare that they have no conflict of interests

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