

Investigating the potential of microRNAs as biomarkers for bladder cancer diagnosis and prognosis

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Abstract:

Bladder cancer (BC) is a significant health concern, with high incidence and mortality rates, particularly among men. The molecular mechanisms underlying BC development and progression, including DNA damage response (DDR) and microRNAs (miRNAs) dysregulation, play crucial roles in tumorigenesis. This paper aims to explore the role of miRNAs in BC, focusing on their association with tumor formation, invasion, and response to chemotherapy and radiotherapy. The study categorizes miRNAs based on their impact on BC pathogenesis, highlighting both down-regulated tumor suppressor miRNAs and up-regulated miRNAs promoting tumor development. Additionally, the paper discusses the potential of miRNAs as biomarkers for predicting chemo-resistance and radio-resistance in BC patients, elucidating how miRNA expression profiles can influence treatment outcomes and patient survival. Furthermore, this article reviews the current modalities of cancer treatment, including chemotherapy, targeted therapies, and radiotherapy, emphasizing the importance of personalized medicine approaches. Overall, this review highlights the importance of miRNAs in BC pathophysiology and their potential as therapeutic targets or diagnostic tools in improving patient outcomes.

Keywords: Biomarker, Bladder cancer, Chemoresistance, miRNA

Introduction

Bladder cancer (BC) ranks as the sixth most frequently diagnosed and ninth most lethal neoplasm among males. It is more prevalent in men, with an incidence rate of 9.6 per 100,000 compared to 2.4 per 100,000 in women. According to GLOBOCAN data from 2018, an estimated 550,000 individuals were diagnosed with BC, with 22.80% females and

77.20% males. Additionally, BC accounted for 200,000 deaths, with 25.83% being females and 74.17% being males. These figures correspond to approximately 3% of all new cancer cases. Nations in Southern and Western Europe and North America have the highest rates of BC (1). Cancer develops due to the accumulation of mutations resulting from DNA damage or errors in DNA replication that remain uncorrected (2). The DNA damage

response (DDR) is a cellular mechanism that detects DNA damage, transmits signals and facilitates repair. The primary role of DDR is to arrest the cell cycle, allowing for DNA repair or inducing apoptosis if the damage is extensive. Defects in DNA repair contribute to mutation accumulation, consequently leading to cancer. Enhancing our understanding of the molecular underpinnings of tumors and advancements in diagnostic technologies can significantly improve the management of various cancers. Therefore, investigating epigenetic alterations, gene expression profiles of cancer cells, and employing strategies to correct or mitigate these changes are of great importance (3). Dysregulation of microRNAs (miRNAs) has been observed in nearly all cancer types, with several miRNAs found to regulate genes involved in DNA repair (4, 5). Notably, due to the widespread dysregulated expression patterns of miRNAs in cancer and their characteristics such as temporal and spatial specificity and sensitivity, miRNAs hold significant potential as a novel class of cancer biomarkers (6). The clinical management of cancer remains challenging in the 21st century, with treatment modalities encompassing radiotherapy, surgery, chemotherapy, immunotherapy, and hormonal therapy. Therefore, the objective of this study is to identify miRNAs implicated in tumor development and suppression, as well as those associated with radio- and chemoresistance, to establish them as biomarkers for this life-threatening condition.

miRNAs associated with BC

MicroRNAs (miRNAs) are a class of small regulatory RNAs, typically consisting of 19-25 nucleotides, that are derived from stem-loop regions of longer RNA transcripts. They are synthesized and processed in the nucleus before being released into

cytoplasm. In addition to their intracellular presence, miRNAs can also be detected in various body fluids, including free circulating miRNAs, miRNAs bound to ribonucleoprotein complexes, and miRNAs encapsulated within extracellular vesicles such as exosomes (7). The human genome encodes hundreds of different miRNAs, and their regulatory influence on a wide range of mRNA targets suggests their involvement in numerous developmental processes and diseases (8). Recent studies have highlighted the association of miRNAs with resistance to cancer therapeutic agents, which can arise from dysregulated DNA damage repair, altered drug efflux or influx, and aberrant autophagy in malignant cells (9). Given that miRNAs can be detected in urine-derived extracellular vesicles, where they are protected from degradation, profiling of extracellular vesicle miRNAs holds promise as a non-invasive diagnostic and prognostic tool for bladder cancer. In this study, we aim to categorize miRNAs associated with bladder cancer based on their role in tumor formation and invasion. Furthermore, we will further classify these miRNAs based on their specific mechanisms of action, although it is important to note that some overlap between mechanisms may exist.

Down-regulated miRNAs in BC

1. Tumor suppressor markers

Several miRNAs, including miR-1, miR-133a, miR-145, miR-195, and the miR-200 family, are commonly down-regulated in bladder cancer (BC). These miRNAs play critical roles in fundamental cellular processes such as epithelial-mesenchymal transition (EMT), cell cycle regulation, apoptosis, and various cancer signaling pathways. For instance, miR-1 acts as a tumor suppressor in BC by inducing apoptosis through the upregulation of

the apoptosis inhibitor SRSF9 (10).

Down-regulation of miR-195 and miR-497 in BC tissues has been associated with enhanced tumor progression and metastasis (11). Additionally, miR-145, which is frequently down-regulated in BC, is known to inhibit proliferation, migration, and invasion. It operates within the p53 regulatory network and suppresses tumors by down-regulating syndecan-1 and promoting cell-cell adhesion via E-cadherin, particularly in low-grade cancers rather than high-grade malignancies (12). Overexpression of miR-145 down-regulates syndecan-1, and suppresses tumors by enhancing cell-cell adhesion through E-cadherin expressed in low-grade rather than in high-grade cancers (13).

miR-34a acts as a tumor suppressor regulator in different types of cancer. In this regard, its down-regulation has been reported in patients with BC. Normally, miR-34a increases the expression of phosphatase and tensin homolog (PTEN) in BC cells and decreases cell migration and invasion (14, 15). MiRNA-143 is another marker that is down-regulated in BC. It plays a role in inhibiting the proliferation of vascular smooth muscle cells, maintaining the balance between smooth muscle cells and blood vessels, and tumor suppressor role in oral squamous cell carcinoma and promoting chemosensitivity (16-18).

Lower expression of miR-31, a well-identified miRNA as a tumor suppressor, in noninvasive urethral BC cases, correlates with a higher risk of cancer recurrence and progression, also suppressed through negative regulation of cell cycle and migration (19).

2. Cell proliferation and invasion markers

miR-124 directly targets the *STAT3* 3'untranslated region to inhibit *STAT3* expression. Knockdown of

STAT3 significantly promoted apoptosis and suppressed cell cycle progression, migration, proliferation, and colony formation. Overall, miR-124 may suppress BC tumorigenesis by targeting *STAT3* (20, 21). Overexpression of *Bcl-w* and *Akt1* targeted by miR-133b has been observed in BC tissue. Decreased expression of miR-133b in BC tissues is linked to high-grade BC since it inhibits cell proliferation and induces apoptosis (22).

Overexpression of miR-200c inhibits invasion, migration, and proliferation through down-regulation of *BMI-1*, *E2F3*, *ZEB1*, *ZEB2*, and *ERRFI-1*, suppresses angiogenesis by targeting *Akt2/mTOR*, controls the EMT process, and regulates *EGFR* expression (23-25).

Loss of expression of miR-141 and miR-200b increases invasion and migration of BC cell lines, up-regulating *MMP-2*, *MMP-9*, *vimentin*, and *N-cadherin* expression as well as down-regulating the expression of *E-cadherin* (26).

miR-124-3p is a proposed therapeutic target and prognostic biomarker for BC, which is down-regulated in both BC specimens and cell lines. It has been found that lower expression of this biomarker contributes to higher cell migration and invasion in BC, being mediated by targeting integrin $\alpha 3$ (*ITGA3*) through FAK/PI3K/AKT and FAK/Src signaling mechanism as well as EMT process (27). Down-regulation of both miR-139-5p and miR-139-3p in BC tissues contributes to tumor migration and invasion through direct targeting and higher expression of *MMP11* which leads to shorter survival of BC patients (28). Lower expression of miR-328-3p identified in BC tissues correlates with poor prognosis in these patients. The suppressing effect of miR-328-3p on cell proliferation, migration, and invasion in BC is mediated through *ITGA5* along with EMT inhibition and inactivation

of PI3K/AKT pathway (29).

A study on miRNA profiling in BC tissues showed the highest down-regulation for miR-145, while miR-21 was identified as the most up-regulated one. miR-129, miR-133b, and miR-518c have been proposed as predictors of cancer progression. Down-regulation of miRNA-129 is directly linked to down-regulation of its targets *GALNT1* and *SOX4*, inhibiting growth and inducing apoptosis (30). Lower expression of miR-490-5p in human BC tissue and cell lines significantly inhibits cell proliferation via G1-phase arrest through direct targeting of *c-Fos*. The related study has proposed that miR-490-5p is a tumor suppressor in BC cells (31). Zhang et al. demonstrated that down-regulation of miR-99a and miR-125b was directly correlated to the tumor grade (32).

Up-regulated miRNAs in BC

1. Tumor suppressor markers

Up-regulation of miR-24 inhibits proliferation, invasion, and EMT, and induces apoptosis of T24 and UMUC-3 cells by targeting CARMA3. Additionally, up-regulation of miR-24 decreases the protein levels of cyclin D1, CDK4, CDK6, p-Rb, and Bcl-2 (33). Overexpression of miR-31 inhibits proliferation, migration, and cell invasion. miR-31 expression reverses adhesion mediated drug (MMC) resistance via down-regulation of *ITGA5* and inactivating Akt and ERK pathways (19, 34).

Overexpression of miR-124 in vitro induces poor cell proliferation, migration, invasion, and angiogenesis by modulating *UHRF1* regulation. Induced by mimic transfection, overexpression of miR-124 was observed to inhibit cell viability, angiogenesis, and proliferation (21, 35). Overexpression of miR-15 inhibits the progression by targeting *BM11* oncogene and PI3K/AKT pathway (36).

Overexpression of miR-23b suppresses the onco-

gene *ZEB1* leading to suppression of cell proliferation and invasion, while inducing cell cycle arrest and apoptosis. A potential role has been suggested for this marker in the early detection and prognosis of BC. High expression of miR-23b is positively correlated with higher overall survival of BC patients (37).

Overexpression of miR-22 reverses MAPK and Snail-induced proliferation, migration, and invasion, thus playing an important role in EMT progression and the MAPK1/Slug/vimentin feedback loop (38). Overexpression of miR-34a exerts its anti-metastatic, anti-angiogenic, and pro-apoptotic roles in BC through CD44 inhibition, whereas the circulation and tissue level of miR-34a expression is reduced in patients with BC (39).

Overexpression of miR-128 has been identified to inhibit BC cell growth rate, proliferation, migration, and invasion and angiogenesis capacities (40).

High expression of miR-301b down-regulates *EGR1* in BC tissue, while decreased miR-103b suppresses proliferation, migration, and invasion and promotes EMT by increasing *EGR1* expression (41). Overexpression of miR-373 promotes proliferation, migration, and invasion by up-regulating *EGFR* in BC cells (42).

Higher expression of miR-135a in BC tissues than normal adjacent tissue is directly correlated to EMT, invasion, and migration of BC through activation of the Wnt/ β -catenin signaling pathway which results in down-regulation of *GSK3 β* . Moreover, high levels of miR-135a down-regulated tumor suppressor genes, *PHLPP2* and *FOXO1*, act as an onco-miR (43, 44).

2. Markers of tumor development

miR-708, as an oncogene, is up-regulated in BC tissue versus adjacent normal tissue. This

oncogene induces the carcinogenicity of BC by down-regulating the direct target, *Caspase-2*, as an apoptosis mediator (45).

The role of miR-132 in the metastasis of BC cells is mediated via TGF β 1/Smad2 signaling pathway. Its overexpression suppresses the expression of mesenchymal cell markers such as N-Cadherin, Zeb1, Snail, and Vimentin (46).

Generalized increased expression of miR-21 is observed in high-grade, recurrence, muscle-invasive BC (MIBC) compared with adjacent normal bladder urothelium by lower expression of *PTEN* (47).

Cancer treatment and targeted therapy

In general, the significance of the cancer problem has led to many researchers have been conducting new treatment approaches. In recent years, targeted cancer therapies have emerged as a prominent approach in the field of cancer treatment. These therapies employ pharmacological agents that specifically target and inhibit cancer cells' growth, tumorigenesis, and metastasis while promoting cell death. Referred to as biological therapies, targeted cancer therapies have gained significant recognition as a major modality in medical treatment. Their unique specificity holds the promise of improved efficacy and reduced adverse effects compared to alternative treatment options such as hormonal therapies and cytotoxic therapies (48, 49). One of the most attractive procedures is targeting the miRNAs (50).

1. Chemotherapy in BC patients

The first step in the treatment of BC is chemotherapy, which increases patient survival by suppressing cancer progression and also prevents recurrence (51). In the treatment of the disease, the simultaneous use of cystectomy and chemotherapy is a suitable option to increase patient survival (52).

Chemotherapy for bladder cancer typically involves a combination of various agents. The specific medications used can depend on the stage of the cancer, whether it is muscle-invasive or non-muscle-invasive, and other individual patient factors. Common combination regimens include: A regimen that includes Gemcitabine and Cisplatin (GC); a combination regimen of dose-dense methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (ddMVAC); a combination regimen of Cisplatin, methotrexate, and vinblastine (CMV); and a combination regimen of Gemcitabine and paclitaxel (GemTaxol). While, the medicines used in a combined regimen of chemo-radiation therapy are as follows: Cisplatin, Cisplatin plus fluorouracil (5-FU), and Mitomycin plus 5-FU (53).

The standard treatment approach for clinically localized muscle-invasive bladder cancer (MIBC) in patients with adequate renal function involves neoadjuvant systemic chemotherapy using a platinum-based regimen, followed by radical cystectomy and urinary diversion. It is recommended to perform regional lymph node dissection in conjunction with cystectomy (54). However, due to the need for urinary diversion following cystectomy, alternative bladder-sparing options have been explored, including external beam radiotherapy with or without chemotherapy, partial cystectomy, and maximal transurethral resection of the bladder tumor (TURBT) (55). Nevertheless, it is important to consider that the median age of diagnosis for bladder cancer (UBC) is 65 years, which is associated with poor prognoses and a high risk of recurrence and distant metastasis. Additionally, a significant proportion of advanced UBC patients are ineligible for standard cytotoxic chemotherapy due to comorbidities such as renal impairment. To address these limitations, ongoing research is focused

on investigating various molecular targeting agents as potential alternatives (56).

1.1. Chemo-sensitivity and Chemo-resistance

Despite many successes of chemotherapies in cancer patients, the effectiveness plus many side effects cause great physical and emotional strains on the patients undergoing chemotherapy. Evaluation of chemo-sensitivity before the start of treatment could help to choose the appropriate drug regimen. Chemo-resistance is the opposite of chemo-sensitivity; it is rare for cancers to be resistant to all medication that could be used to treat them. So, alternatives can be found if the chemo-resistance is predicted in advance (57). Chemo-resistance is a factor leading to disease recurrence and metastasis and is therefore a major obstacle to cancer treatment. Understanding the molecular mechanisms underlying chemo-resistance in bladder cancer involves various factors such as transporter pumps, oncogenes, tumor suppressor genes, mitochondrial alterations, DNA repair mechanisms, autophagy, epithelial-mesenchymal transition (EMT), cancer stemness, and exosomes (58, 59).

1.2. miRNAs and Chemotherapy Interaction

miRNAs play a significant role in the development of chemo-resistance in bladder cancer cells, particularly under conditions of multidrug resistance. They represent potential therapeutic targets due to their involvement in overcoming drug resistance, which is a critical challenge in clinical settings leading to tumor recurrence and metastasis (60). For instance, Mucin 4 enhances the chemo-resistance of bladder cancer cells to gemcitabine by modulating miRNAs such as 1290, 138, let-7i, and let-7b (61). Identifying the miRNAs involved in chemoresistance and their profiling in the patients with BC could have a potential role in the

treatment plan for these patients. To date, alterations in the expression of many of them have been reported in BC patients with chemo-resistance. They exert their effects through different pathways. Targeting these molecules in combination with an appropriate chemo or radiotherapy regimen can augment the therapeutic effects of the treatment. A comprehensive list of miRNAs in BC associated with chemotherapeutic resistance is presented in Table 1.

2. Radiation therapy

Radiation therapy plays a significant role in the curative treatment of cancer, accounting for approximately 40% of such treatments. Over the past century, continuous advancements in radiation treatment techniques, coupled with an increased understanding of the biological responses of cancer cells to radiation, have resulted in improved patient survival rates (91). Exposure to ionizing radiation (IR) causes double-strand breaks (DSBs) in the DNA of all cells. DSBs can also occur when DNA replication encounters lesions or repair intermediates. The processing and repair of DSBs can lead to genetic mutations, loss of heterozygosity, and chromosome rearrangements, which may ultimately result in cell death or the development of cancer. The type and energy of radiation are critical factors that influence the types of DNA damage induced, subsequently affecting cell survival and the repair mechanisms employed to address the damaged DNA (92). In the context of radiation therapy, tumor cells exhibit survival mechanisms. Two main DNA DSB repair processes, namely homologous recombination and non-homologous end-joining, are present in irradiated cells. However, there are still uncertainties regarding the primary sensing event and its dependence on the complexity,

Table 1: The microRNAs associated with chemotherapeutic resistance in bladder cancer

microRNA	Expression status	Drug	Result	Ref No
miR-21	Up	Doxorubicin	miR-21 could modulate chemosensitivity of T24 cells to doxorubicin	(62)
miR-22-3p	Up	Paclitaxel, Pirarubicin; Adriamycin, hydrochloride, Epirubicin, Hydroxy camptothecin, Cisplatin, and Gemcitabine	miR-22-3p promoted chemotherapy in bladder tumor cells by suppressing NET1.	(63)
miR-27a	Down	Paclitaxel, Adriamycin, Cisplatin	miR-27a/RUNX-1 pathway has a key function in chemo-resistance, MiR-27a deregulation induced cisplatin resistance in bladder cancer cells via up-regulating SLC7A11.	(64, 65)
miR-34a	Down	Cisplatin, Epirubicin, Gemcitabine	miR-34a sensitized tumor cells to cisplatin by targeting SIRT-1 and CDK6, miR-34a targets CD44 after cisplatin therapy, MiR-34a significantly reduced Epirubicin chemoresistance in bladder tumor cells through targeting TCF1 and LEF1, MiR34a regulation of GOLPH3 is active in bladder CSCs resistant to gemcitabine and cisplatin. Increased miR-34a expression significantly sensitized MIBC cells to cisplatin.	(66-69)
miR-34b-3p		Paclitaxel, Adriamycin, Epirubicin, Cisplatin, Pirarubicin	miR-34b-3p attenuated chemoresistance in bladder cancer by suppressing CCND2 and P2RY1.	(70)
miR-93	Down	Cisplatin	inhibiting miR-93 promoted cisplatin-induced apoptosis due to the accumulation of DNA damage	(71)
miR-98		Cisplatin, Doxorubicin	miR-98 promotes chemo-resistance through targeting LASS2.	(72)
miR-101	Down	Cisplatin	miR-101 regulates cisplatin sensitivity in bladder tumor cell lines via targeting the COX-2.	(73)
miR-101-3p		Cisplatin	miR-101-3p decreased cisplatin resistance in bladder urothelial carcinoma through repressing EZH2 and MRP1.	(74)
miR-129-5p		Gemcitabine	miR-129-5p inhibits resistance to gemcitabine in bladder cancer cells and promotes their apoptosis via targeting WNT5a	(75)
miR-133b		Cisplatin	MST1P2/miR-133b axis had an important role in cisplatin-resistance of bladder cancer through SIRT1/p53 pathway	(76)
miR-138	Up	Gemcitabine	miR-1290, 138, let-7i, and let-7b in imparting resistance to gemcitabine in UCB cell lines in part through the modulation of mucin-4	(61)
miR-143	Down	Gemcitabine	miR-143 Overexpression inhibited cell proliferation and promoted chemosensitivity.	(18)
miR-145	Up	Gemcitabine	lncRNA-LET/NF90/miR-145 promoted chemoresistance.	(77)
miR-150	Up	Cisplatin	miR-150 inhibition significantly enhanced chemosensitivity to cisplatin and suppressed the invasiveness of 5637 and T24 cells	(78)

Table 1. (Continued)

miR-193a-3p	Down	Pirarubicin, Paclitaxel, Adriamycin, Epirubicin Hydrochloride, and Cisplatin	miR-193a-3p regulated ING5 gene activates (DNA damage response pathway and inhibits multi-chemoresistance) and mediated HOX-C9 down-regulation which resulted in poorer sensitivity to chemotherapeutic drugs, PSEN1 was directly targeted by miR-193a-3p and executed its impact on the multi-chemo resistance, CEBPD/miR-193b-3p axis had key roles in cisplatin response, MiR-193a-3p induced multi-drug resistance in bladder cancer cells through down-regulating LOXL4, HIC2, SRSF2, and PLAU achieve their role in relaying miR-193a-3p's effect on chemoresistance in bladder cancer through regulation of Myc/Max, NF- κ B, DNA damage response, and NOTCH pathway. miR-193a-3p promotes both tumor growth and paclitaxel chemoresistance.	(79-81)
miR-193a-5p	Up	Cisplatin	miR-193a-5p induces cisplatin resistance by inhibiting AP-2 α expression	(82)
miR-196a-5p	Up	Cisplatin /gemcitabine	The reduced expression of miR-196a-5p enforced sensitivity to the growth inhibition effects of cisplatin/gemcitabine	(83)
miR-200	Up	EGFR-blocking agents	Expression of miR-200 is sufficient to restore EGFR dependency	(23)
miR-200b		Cisplatin	TNFSF10, ICAM1, and IGFBP3 were induced in the resistant cells as a result of miR-200b + cisplatin treatment	(84)
miR-203	Down	Cisplatin	The miR-203 overexpression increased the cytotoxic effects of cisplatin and decreased tumor cell viability through suppressing Survivin and BCL-w.	(85)
miR-214		Cisplatin	miR-214 decreased chemoresistance in bladder cancer tissues and cell lines by suppressing NTN1.	(86)
miR-218	Up	Cisplatin	miR-218 increases cisplatin resistance through GLUT1 targeting.	(87)
miR-222	Down	Cisplatin	miR-222 up-regulation decreased cisplatin-induced apoptosis in bladder tumor cells through modulation of PPP2R2A/Akt/mTOR pathway.	(88)
miR-294	Up	Cisplatin	miR-294 promoted the sensitivity of T24 cells to cisplatin.	(89)
miR-328-3p	Down	Puerarin	Puerarin impedes cell viability, migration, invasion, and glycolysis, and promotes apoptosis by regulating circ_0020394/miR-328-3p/NRBP1 axis.	(90)
miR-1290	Up	Gemcitabine	miR-1290, 138, let-7i, and let-7b in imparting resistance to gemcitabine in UCB cell lines in part through the modulation of mucin -4	(61)

Table 2: The microRNAs associated with radio-resistance in bladder cancer

microRNA	Regulation status	Radiotherapy	Result	Ref No.
miR-21		Radio-resistance		(104)
miR-1246	down	Radio sensitivity	miR-1246 irradiation by targeting the inhibition of p53 gene translation.	(105)

location, and timing of the DNA damage. Interactions and overlaps between different repair pathways play a crucial role in determining repair efficiency and determining the functional behavior of cells in response to unrepaired or improperly repaired DNA lesions (93). In the case of bladder cancer radiotherapy, two different fractionation schedules are commonly used. Treatment centers may choose to administer either 55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks to patients. Typically, synchronous chemotherapy is administered alongside radiotherapy (94).

2.1. Radio-sensitivity and Radio-resistance

There is a genetic foundation influencing cellular susceptibility to ionizing radiation, as evidenced (95). DNA repair pathways are pivotal in mitigating radiation-induced DNA damage and serve as potential therapeutic targets for sensitizing tumors to radiotherapy. However, exploiting the differential vulnerability between tumor and normal cells to selectively target tumor DNA repair while sparing normal tissues remains a significant challenge (96). Conversely, tumor recurrence and metastasis often stem from the acquisition of radio-resistance (RR) during fractionated irradiation (97). RR mechanisms are observed across various cancers such as head and neck, non-small cell lung, and bladder cancers (98, 99). RR cells exhibit resistance to apoptosis, reduced reactive oxygen species (ROS) production, enhanced DNA repair activation, and heightened migratory and invasive ca-

pabilities, prompting intense interest in deciphering their underlying biology and developing strategies to overcome this resistance (100).

2.2. microRNAs and Radiotherapy Interaction

MicroRNAs (miRNAs) have emerged as significant players in cellular responses to irradiation, with altered expression profiles suggesting their involvement in the DNA damage response (DDR) (101, 102).

Several radiation-responsive miRNAs, like the miR-15/16 family, let-7 family, miR-21, and miR-155, regulate multiple essential DDR proteins, underscoring their multifaceted roles (101, 103). Understanding these roles of miRNAs in radiotherapy (RT) can offer insights into managing treatment-related toxicity and potentially monitoring both professional and accidental radiation exposures (101). In BC patients, two miRNAs of miR-21 and miR-1246 have been identified that interact with radiotherapy, (Table 2) (104, 105). Altogether, there is a strong hope that miRNAs manipulation can regulate the therapeutic effects of radiotherapy and tumor resistance and would increase patients' survival in the future.

Discussion

MicroRNAs (miRNAs) are small non-coding RNAs that play pivotal roles in regulating gene expression post-transcriptionally by binding to the 3'-UTR region of target gene transcripts, thereby silencing or degrading them. They are integral in various biological processes in humans and are

crucial regulators of molecular mechanisms, including tumor cell invasion, metastasis, and the modulation of gene expression. Drug development is a complex and costly process fraught with numerous challenges and a high likelihood of failure. Developing miRNA-targeted drugs is particularly challenging due to limited experience, with studies still in early stages of exploration. Despite these obstacles, early clinical trials suggest promising potential for miRNAs in both diagnostics and therapeutics. miRNAs function as oncogenes or tumor suppressors and influence critical tumor-associated processes such as the cell cycle, cell proliferation, apoptosis, and metastasis. In summary, miRNAs represent a promising frontier in biomedical research, holding significant implications for understanding disease mechanisms and potentially offering novel avenues for therapeutic intervention in cancer and other diseases. Due to the progress of cancer worldwide, the emergence of early diagnostic methods with high sensitivity and specialized treatments can be an important factor in the prevention and timely treatment of patients. Knowing that the expression of miRNAs in tissue samples and biological fluids is variable and is also the most appropriate option for diagnosis and treatment of the disease, their identification in timely diagnosis, prognosis, and treatment is significant.

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