Review Article

The current status of miRNA in urinary bladder cancer: A minireview and strength, weakness, opportunity, and threat analysis

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ABSTRACT

MicroRNAs, small noncoding RNA molecules, are critical in modulating gene expression and contribute substantially to the initiation and progression of urinary bladder cancer (UBCa), a major malignancy affecting people globally. UBCa is known for its high recurrence rates and significant heterogeneity. The stability of miRNAs in body fluids such as urine and blood are excellent potential noninvasive markers for early detection, monitoring treatment progress, and predicting outcomes of patients with UBCa. In addition, miRNAs could also improve the effectiveness of immunotherapy and support the development of personalized treatment strategies. Despite their significant potential, challenges such as variability in the expression of miRNAs and shortcomings in their delivery systems must be carefully addressed. This strength, weakness, opportunity, and threat (SWOT) analysis highlights the crucial role of miRNAs in UBCa and explores their potential in advancing precision oncology.

INTRODUCTION

Urinary bladder cancer (UBCa) ranks as the tenth most frequently diagnosed cancer globally and is more prevalent in men than in women.[1] Roughly 70%–75% of the recently diagnosed individuals are have nonmuscle invasive bladder cancer (NMIBC), whereas 25% of the patients present as MIBC or with metastatic disease.[2] Early detection of UBCa is crucial for improving the chances of survival. However, diagnosing the bladder cancer with conventional methods is challenging. Although urinary cytology is noninvasive; it often lacks sufficient accuracy, whereas cystoscopy is invasive albeit reliable. Therefore, there is an unmet need of more accurate and less invasive diagnostic tools for the detection of UBCa.[3] MiRNAs show unique expression patterns in cancerous tissues compared to the normal tissues and the expression varies across the different types of cancers. This unique expression profile makes miRNAs a promising tools for the diagnosis and treatment of cancers. Studies have revealed that miRNAs take part in various cell activities such as apoptosis, cell development, proliferation, and differentiation. MiRNAs are small RNA molecules, 18–22 nucleotides in length, that do not encode proteins but play a key role in regulating the gene expression.[4,5] They inhibit gene activity by binding partially to the 3′ untranslated regions of the target messenger RNAs.[6] In UBCa, miRNAs are derived from various cellular sources within the tumor environment, including tumor, immune, and stromal cells. Once released, miRNAs circulate in bodily fluids such as urine, blood, cerebrospinal fluid, and saliva, often encased in protective exosomes or bound to proteins, which shield them from enzymatic degradation.[7] Recent research shows that miRNAs have the potential

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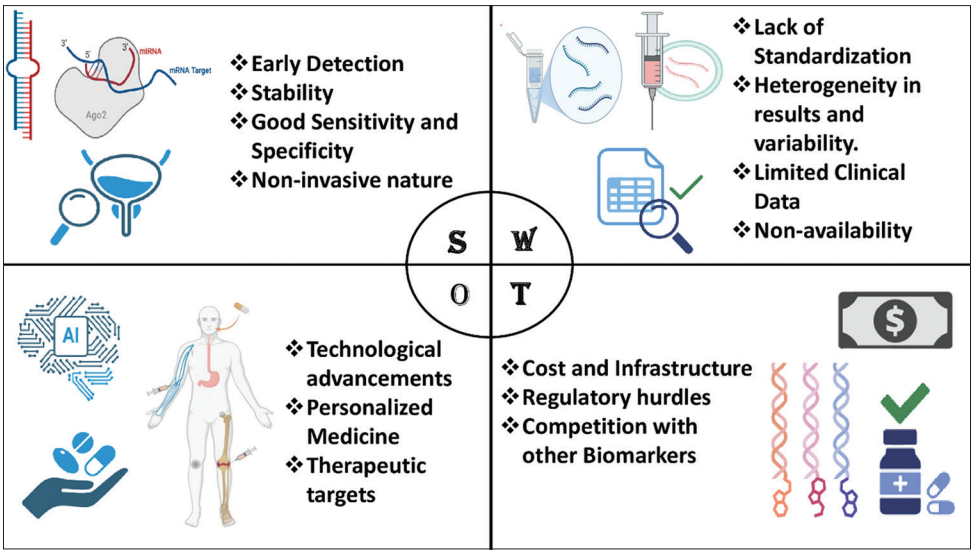

Figure 1: Strength, weakness, opportunity, and threat analysis of miRNA in urinary bladder cancer: strategies from laboratory to clinical application: the strength section emphasizes early detection potential and the stability of targeted therapy. The weaknesses section addresses the technical complexities, potential hazards, and limited clinical data. Opportunities are highlighted, noting the increasing medical needs and expanding market demand for miRNA. Finally, the threats section identifies regulatory challenges, market acceptance issues, competition, and high costs associated with miRNA as significant hurdles to be overcome in the development of miRNA

to revolutionize the diagnosis and treatment of UBCa. Noninvasive biomarkers such as urinary exosomal miRNAs and a seven-miRNA serum panel (miR-141, miR-145, miR-221, miR-222, miR-181a, miR-23b, and miR-375) offer high accuracy (AUC = 0.98) for the diagnosis of UBCa. MiRNAs are also being explored as therapeutic targets to modulate cancer progression, with trials ongoing to assess their efficacy. This seven-miRNA panel has been identified as a predictor of response to the treatment, enabling personalized therapies. These advancements provide novel insights into the disease mechanism and pave the way for less invasive, personalized treatments. Alterations in the miRNA levels following procedures like transurethral resection of bladder tumor (TURBT) further demonstrate their dynamic role. TURBT has been associated with an increase in the circulating tumor cells and the release of tumor-derived molecules, including miRNAs, into the bloodstream or urine, potentially influencing their levels. These changes underscore the multifaceted utility of miRNAs in the diagnosis and therapeutic monitoring, paving the way for further innovations.[3,8,9] MiRNA and cytology offer unique strengths and limitations in the diagnosis of bladder cancer. Cytology is a traditional method that is highly specific (90%–95%) but has low sensitivity (30%–40%) for low-grade tumors. miRNAs, as molecular biomarkers, provide higher sensitivity and specificity across the tumor grades, with a 7-miRNA panel showing sensitivity of up to 96.1% and specificity of around 91%. While cytology is accessible and affordable, it often misses early or low-grade tumors. MiRNAs, detectable in the biofluids, offer noninvasive earlier detection but require advanced technology and standardized protocols. Overall, miRNAs show promise in surpassing the cytology in precision diagnostics.[10] A strength, weakness, opportunity, and threat (SWOT) analysis further explores their future potential [Figure 1].

STRENGTHS

Noninvasive nature

Cystoscopy, the standard method for diagnosing and monitoring UBCa, is an essential and effective procedure. However, repeated cystoscopies negatively affects the patient's adherence to the follow-up schedule. MiRNA testing offers a promising noninvasive alternative or can be an adjunct to cystoscopy for the detection of UBCa, providing a convenient noninvasive approach to complement the traditional methods.

Studies indicate that miRNA profiling detects the primary UBCa as well as the recurrences, which is crucial for the effective management of the disease. Cell-free miRNAs, grouped in panels including markers such as miR-16-5p, miR-21, and miR-200, have shown high accuracy in detecting NMIBC.[5,11-14] These panels could complement or even replace cystoscopy, particularly for the early detection and follow-up. Shifting to noninvasive urine-based miRNA testing may also reduce the healthcare costs and improve the patient's comfort, paving the way for more accessible and patient-friendly UBCa diagnostics.[15] Early detection of the UBCa is crucial for improving the patient's outcomes, and several tests are currently used in the clinical practice.[3] One significant challenge in the screening of UBCa is that while it is valuable, conventional techniques such as cystoscopy and urine cytology have specific diagnostic roles.[16] For instance, urine cytology, though less invasive, has a specificity of 90%–100% and sensitivity of 40%–60%, with high specificity observed particularly in detecting the

high-risk disease. There is a need for less invasive and more efficient diagnostic methods for UBCa.

Specific miRNAs, bound to proteins like Argonaute 2, as part of the RNA-induced silencing complex, are shielded from RNase degradation, which provides stability and allows them to persist in harsh environments. This stability makes them promising biomarkers for noninvasive diagnosis.[17] Several studies have investigated the potential of circulating miRNAs, particularly in urine, as biomarkers for UBCa. MiRNAs in urine have shown promise for detecting early-stage UBCa and monitoring the recurrence, positioning them as a valuable target for liquid biopsy. This research highlights the potential of urine-based miRNA testing as a less invasive and more efficient alternative compared with the traditional diagnostic methods in UBCa and other cancers.[11,18]

Stability

MiRNAs are stable in biofluids such as urine and blood, making them a promising biomarker. Research indicates that miRNAs can endure extreme conditions, such as high temperatures and prolonged storage, while maintaining their integrity. Exosomal miRNAs exhibit significant resistance to thermal degradation and proteolytic enzymes, which aids in their extraction from the urine for analysis. This stability enables the collection of urine samples without the need of immediate processing, making miRNAs an ideal choice for noninvasive testing. Research has identified specific miRNAs that remain stable under various collection and storage conditions, highlighting their potential as a reliable biomarker for the early detection and monitoring of the bladder cancer.[19,20]

Sensitivity and specificity

Integrating miRNAs into diagnostic panels significantly improves the specificity and sensitivity, complementing the traditional methods such as urine cytology for the detection of UBCa. Urine cytology is a valuable diagnostic tool; however, it often has limited sensitivity, especially for low-grade tumors, which can result in false-negatives. In contrast, miRNA panels offer a more effective method for the detection of molecular alterations linked to cancer, enhancing the likelihood of identifying the disease at an earlier stage. According to the studies, specific miRNA panels, including miR-21, miR-200c, and miR-155, demonstrated improved sensitivity and specificity for distinguishing patients with UBCa from the healthy controls, with the miR-21 panel achieving an 80% sensitivity and 85% specificity. At the same time, the combination of miR-200c and miR-155 also showed significant diagnostic potential.[17]

WEAKNESS

Lack of standardization

The lack of standardization in the protocols for collecting, storing, and analyzing miRNAs presents a significant challenge in their clinical application as biomarkers for UBCa. This variability can lead to inconsistent results across different studies, hampering the reliability and comparability of the findings. Issues in sample handling, processing techniques, and analytical methods have been noted, indicating the need for established guidelines to ensure reproducibility and accuracy of miRNA-based diagnostics.[3]

Accuracy and variability

Although miRNAs hold the potential as novel biomarkers for UBCa, their diagnostic accuracy can be affected by various factors, including biological variability, the presence of coexisting conditions, and inconsistencies in methods of assay such as quantitative polymerase chain reaction (PCR), next-generation sequencing (NGS), and microarray analysis.[21-23] Individual differences in miRNA expression can create challenges in determining clear cutoff values for the diagnosis. Furthermore, the interaction of miRNAs with other molecular components in the urine can further complicate interpretation, highlighting the need for further research to improve their diagnostic reliability and precision.

The adjunct and systemic therapies for UBCa, such as immunotherapy, chemotherapy, and targeted therapies, may impact the expression of miRNA, but the data are not robust.[24] Intravesical treatments such as chemotherapy and immunotherapy are widely used for the management of UBCa, and research into their impact on the expression of miRNA expression is still emerging. Mitra *et al*. recently identified urine-based microRNA signatures that can predict how patients with NMIBC will respond to intravesical BCG therapy. Through variance filtering and the use of random forest models, a 233-features classifier achieved 81% sensitivity and 64% specificity in the discovery set and 78% sensitivity with 53% specificity in the validation set. Based on the 35 features, a more concise classifier demonstrated improved performance in the discovery set (85% sensitivity and 68% specificity) and produced similar results in the validation set (78% sensitivity and 46% specificity).[25] In a study by Adibzadeh Sereshgi *et al*., intravesical BCG modulates immunorelated miRNAs such as miR142-3p and miR155, which regulate inflammatory mediators and immune pathways.[26] The effects of intravesical mitomycin-C on the miRNA expressions, like the miR-31, hold a significant potential in monitoring the treatment response and improving clinical outcomes. Although the evidence of miRNA's role in patients with bladder cancer on intravesical treatment is at a naïve stage and remains unexplored extensively, further large-scale studies are required to establish a change in the miRNA levels during intravesical therapies to establish its place as a prognostic urinary biomarker.[27] Regarding the therapeutic effect of miRNA, a study on the intravesical miR-145 administration demonstrated its therapeutic potential. It induced apoptosis, suppressed cell migration, and inhibited

tumor growth by 76% in mice, significantly prolonging survival. This highlights that miRNA modulation is a promising therapeutic approach.[28] However, the effect of intravesical treatment on miRNA expression has not been widely studied; and it presents a promising area for further investigation.

OPPORTUNITIES

Technological and combination biomarkers' advancements

Advancements in the testing for bladder cancer have benefited from cutting-edge technologies.[29] Bioinformatics tools facilitate large-scale dataset analysis to uncover biological pathways and validate biomarkers, while quantitative reverse transcription (qRT)-PCR offers high sensitivity and specificity in measuring the miRNA levels.[30,31] Machine learning further enhances the predictive modeling by integrating miRNA data with clinical characteristics for improved stratification and diagnostic accuracy. Combinatorial biomarker studies, such as combining miRNA profiles with circulating tumor DNA (ctDNA), provide complementary tumor and genetic information for the early diagnosis. Integrating clinical factors such as the age and smoking history with metabolomic, and miRNA profiling reveals disease-related metabolic changes.[32] Exploring immune-related biomarkers alongside miRNAs offers insights into the tumor microenvironment. Together, these approaches enable robust detection techniques, improved patient outcomes, and personalized treatment plans.

NGS enables detailed profiling of the miRNA expression patterns, aiding in identifying miRNAs that are linked to cancer development and treatment response.[33] Regarding the turnaround time, the quantitative PCR (qPCR) and NGS provide faster results compared with the traditional methods like cystoscopy. qPCR can deliver results within hours, while NGS, though slightly slower, offer a more detailed and comprehensive dataset. qPCR-based assays are typically more economical, but NGS can be more cost-effective for large-scale analyses due to its extensive data output. Interpretation varies across the methods, with qPCR, NGS, and microarray analysis differing in sensitivity, specificity, and scalability. While qPCR is widely used for its simplicity and reliability, NGS stands out for its ability to perform in-depth analyses and to identify novel biomarkers, albeit requiring specialized equipment and expertise.

Therapeutic targets

Micro-RNAs are biomarkers for UBCa that have substantial therapeutic promise in addition to being used for the diagnosis. MiRNAs are potential targets for therapeutic interventions because they are regulatory molecules that affect tumor behavior and play an essential role in the gene expression.[34] Altering the amount of certain miRNAs may change the course of the disease because they are linked to several cancer processes, such as metastasis, apoptosis, and proliferation.[35] Furthermore, miRNAs can function as markers of therapeutic response, assisting in customization of the treatment according to the unique characteristics of each patient and boosting the efficacy of the currently used treatments. The development of miRNA-based therapies, such as miRNA mimics or inhibitors, may become novel approaches for the treatment of UBCa as the research progresses.[36,37]

Personalized medicine

Early detection of UBCa with miRNA presents a transformative opportunity for personalized medicine. By identifying specific miRNA profiles associated with different stages or subtypes of the disease, clinicians can tailor treatment strategies to individual patients.[38] This targeted approach enables the selection of the most effective therapies while minimizing the exposure to ineffective or overly aggressive treatments. Furthermore, early detection allows for close monitoring of the disease progression, facilitating timely intervention and improving the overall outcomes. Personalized treatment plans, informed by biomarker analysis, can enhance patient's quality of life, reduce healthcare costs, and contribute to more efficient use of resources within the healthcare system.[21] Integrating early detection methods into the clinical practice ultimately empowers the patients and fosters a more precise and practical approach to the management of UBCa.[38,39]

THREATS

Competition with other biomarkers

Numerous alternative biomarkers, including proteins (ctDNA) and other noncoding RNAs, are under investigation or have established roles in clinical practice. These biomarkers may offer advantages such as the ease of detection, established protocols, or superior specificity and sensitivity. In addition, the competitive landscape is continually evolving, with ongoing research identifying novel biomarkers that may outperform miRNAs in diagnostic accuracy or predictive value. As a result, to secure a foothold for miRNA-based diagnostics in the clinical market, it is necessary to consistently demonstrate their efficacy and reliability compared to these competing biomarkers. This competitive pressure demands rigorous validation of miRNAs and innovative strategies to showcase their unique advantages to acquire the market for bladder cancer diagnosis.[40,41]

Regulatory hurdles

The pathway to regulatory approval is often lengthy and requires extensive preclinical and clinical validation to demonstrate the safety and efficacy of any new diagnostic tool. Regulatory bodies, such as the Food and Drug Administration (FDA) and Emergency Medical Assistance (EMA), typically demand evidence of clinical

utility, which can be challenging for miRNA-based diagnostics due to the need for standardization in the detection methods and the interpretation of the results. The relatively novel nature of the miRNA research can complicate the regulatory landscape because the scientific community is still exploring and validating miRNAs as biomarkers for clinical applications. Regulatory bodies such as the FDA and EMA rely on established evidence and guidelines for approving new diagnostic and therapeutic tools. Since miRNA-based diagnostics are a recent development, there may be a lack of standardized protocols, comprehensive validation studies, and clear guidelines for their use. In addition, the molecular mechanisms underlying miRNA-based diagnostics are not yet fully understood, making it challenging for the regulators to evaluate their safety, efficacy, and clinical utility. This uncertainty can result in extended approval timelines and more stringent scrutiny. This uncertainty can lead to longer review times and increased costs for the developers seeking the approval. This can also lead to logistical and financial challenges, further delaying their entry into the market. These regulatory and operational hurdles may hinder innovation and slow the progress of miRNA-based diagnostics.[42]

Cost and infrastructure

Additional barriers include the need for standard laboratory facilities and trained personnel for handling and analyzing miRNA samples. Many healthcare institutions may not stick to the necessary infrastructure and safety provisions to implement these advanced diagnostic techniques, leading to disparities in access to the cutting-edge diagnostics across different regions and populations. High costs associated with sophisticated detection methods, such as the NGS or advanced PCR techniques, can limit the availability and accessibility, particularly in the resource-constrained healthcare settings. In addition, the cost-effectiveness of miRNA-based diagnostics compared to the existing methods remains crucial. Suppose these new tests do not demonstrate clear economic benefits or improvements in the patient outcomes; in that case, healthcare providers may be reluctant to invest in their adoption, particularly in environments where cost management is a priority.

Challenges in translating miRNA research to clinical practice in bladder cancer

The gap between laboratory research and the clinical application of miRNAs in UBCa presents a significant challenge. Despite extensive identification of the potential miRNA biomarkers, integrating these findings into standard clinical practice remains challenging. Key challenges in the clinical application of miRNA panels include the lack of standardized protocols, the need for validation across diverse populations, and integrating these panels into the existing diagnostic systems. Several studies have reported promising validation scores for miRNA panels in UBCa. For instance, Sapre *et al*. identified a urinary miRNA signature with an AUC of 0.98 for early-stage detection. These findings highlight the diagnostic potential of miRNA panels, but further validation in diverse populations is necessary before they can be widely implemented in the clinical practice.[11] Unless these challenges are addressed, the practical use of miRNAs as a diagnostic tool will not reach its full potential.

CONCLUSION

miRNAs are promising noninvasive biomarkers for UBCa diagnosis, prognosis, and monitoring. However, substantial challenges must be addressed before they can be integrated into the clinical practice. A SWOT analysis can provide valuable insights into the strengths and limitations of the current research, as well as future directions and external factors that may influence the successful implementation of miRNA-based diagnostics. This analysis will help prioritize areas for future research, such as the standardization of miRNA measurement techniques, validation in larger patient cohorts, and integration with other biomarker modalities to improve the diagnostic accuracy.

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