The Diagnostic and Prognostic Significance of MicroRNA-21 in Non-muscle Invasive Bladder Tumors

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Abstract

Bladder cancer (BC) is one of the commonly diagnosed urological cancers that causes human death, ranked as the seventh most common cancer worldwide. To date, no reliable diagnostic tool has been defined to recognize non-muscle invasive bladder tumors other than cystoscopy. For this reason, scientists have focused on finding new non-invasive biomarkers that can be used to diagnose BC with higher specificity and sensitivity. The purpose of this study was to evaluate the diagnostic role and prognostic significance of microRNA-21 (miR-21) in non-muscle invasive bladder tumors. In this review, the overall diagnostic performance of miR-21 was discussed on non-invasive BC based on a literature search of PubMed and Cochrane Library. Although findings are insufficient, promising results have been reported regarding circulating miR-21 as a biomarker for BC prospective studies with larger numbers of participants are needed.

Keywords: Non-muscle invasive bladder tumor, microRNA-21, diagnostic marker

Introduction

Bladder cancer (BC) is one of the urological cancers that causes the most deaths worldwide. It is the seventh most commonly diagnosed cancer (1). In 2016, more than 76,000 newly diagnosed cases of BC were reported in the United States and more than 16,000 of those resulted in death (2). BC is 3-4 times more common in men than in women (3). There are geographic variations in the incidence of BC and smoking has an important role in its etiology (4).

BC is classified into two main groups, non-muscle invasive BC (NMIBC) and muscle-invasive BC (MIBC), based on its pathologic and clinical features (5). Approximately 70% of cases are NMIBC at initial diagnosis, and the 5-year survival rate after endoscopic resection of these tumors is around 80% (6,7,8). In 50-70% of NMIBC cases, recurrence is observed in the first two years, while 10-20% of cases progress to MIBC, in which the chance of 5-year survival decreases to 56% (9,10). Although it does not require life-long follow-up, patients diagnosed with BC face invasive procedures like cystoscopy, as well as associated complications such as infections and trauma, due to the frequency of recurrence in the first two years. Progression to MIBC is detected in 20-30% of patients with high-risk superficial BC treated with transurethral resection (TUR) followed by intravesical Bacillus Calmette-Guérin (BCG) therapy (11). Early detection of progression is important because the mortality rate is as high as 44% in MIBC, which can progress rapidly and metastasize despite the availability of effective treatment strategies (8,9,12,13). Although various diagnostic tools and biological markers have been developed to predict the recurrence and progression of NMIBC, most have been shown to have inadequate efficacy and accuracy due to the heterogeneous nature of BC (14,15,16). BC is diagnosed by cystoscopy and urine cytology as well as tumor markers like nuclear matrix protein-22 (NMP-22) and bladder tumor antigen (BTA). The most sensitive of these diagnostic methods is the combination of cystoscopy and urine cytology (17,18). Although cystoscopy is regarded as the gold standard method for the diagnosis of BC, its main disadvantages are that it is invasive, causes patient discomfort, and must be performed by a urologist (19). While urine cytology is a non-invasive method, it is generally more successful in the diagnosis of high-grade and high-stage BCs compared to low-grade tumors (20). NMP-22 and BTA are currently used as urinary biomarkers and are simple, rapid, and non-invasive tests for BC screening. NMP-22 and BTA have specificity of 47-100% and 29-83% and sensitivity of 55-98% and 56-86%, respectively, and therefore they cannot be recommended as ideal diagnostic methods (21,22,23). Non-invasive biomarkers with higher sensitivity and specificity are needed to enable earlier detection of BC. For this reason, new biomarkers should be identified that can be used alone or in combination with parameters affecting BC prognosis in order to identify patients with poor prognosis in advance. MicroRNAs (miRNA) are single-stranded, non-coding RNA gene products, usually 22 nucleotides in length, that are involved in the regulation of gene expression (24). Recent studies suggest that abnormal miRNA structures are associated with the development, progression, and prognosis of various human

cancers (25,26). Non-invasive biomarkers for the diagnosis of BC can be developed from urinary or circulating miRNAs (27,28,29,30,31,32,33,34).

In this study, we address the diagnostic value and prognostic significance of miRNA-21 in NMIBC.

Discussion

MicroRNA molecules are single-stranded, non-coding gene products 22 nucleotides in length whose roles in human disease are being investigated (35). These molecules post-transcriptionally regulate gene expression by binding to the 3'-UTR region of target mRNAs, resulting in the degradation or translational inhibition of the target mRNA (36). After these molecules that regulate gene expression and various biological processes were first identified in 1993, they were later reported to also affect proliferation, apoptosis, metabolism, and immune mechanisms. The up- or down-regulation of miRNA has been established as a biomarker in numerous cancer types and, accordingly, is thought to have potential utility in the diagnosis or prognosis of various cancers of colorectal (37), breast (38), lung (39), and ovarian (40) origin (25,26,41,42). It has been shown that bladder tumors, like other known solid tumors, also contain hypoxic regions and that excessive release of hypoxia-inducible markers is associated with poor prognosis (43). In 2015, Blick et al. (44) demonstrated that miRNA-210, miRNA-193b, miRNA-145, miRNA-125-3p, miRNA-708, and miRNA-517 were associated with hypoxia in BC cells. The same study demonstrated the functional significance of hypoxia-induced miRNAs and showed that miRNA-145 controlled BC cell apoptosis. miRNA-21 was shown to have a p53-mediated anti-apoptotic effect by specifically targeting programmed cell death mRNAs (45,46). A study conducted by Liu et al. (47) in 2011 showed that the overexpression of miRNA-21 in a prostate cancer cell line increased the release of hypoxia-induced factor 1alpha (HIF-1a) and vascular endothelial growth factor.

miRNA studies on the diagnosis and prognosis of BC showed that these molecules can be obtained from urine (27-34). Although the patient's age and sex or the presence of hematuria may adversely affect the biomarker quality of miRNA, detection of miRNA in urine should be considered an important finding in terms of BC. In recent years, studies have been published on the prognostic significance of different miRNA molecules in patients with BC. In 2016, Zhang et al. (48) reported that miRNA-155 analysis in cell-free urine samples of NMIBC patients had diagnostic value with 85.8% sensitivity. In another study investigating the role of miRNA-203 in predicting treatment response in patients planned to start cisplatin-based chemotherapy for BC, it was reported that low miRNA-203 level predicted progression and poor prognosis while overexpression of miRNA-203 may increase the sensitivity to cisplatin by directly stimulating apoptosis (49). It was also reported that miRNA-214 down-regulates oncogenic P53 and DNA damage-regulated gene 1 and that this is a determining factor in BC prognosis (50). In 2010, Kiemeney et al. (51) expanded their earlier study on Dutch and Icelandic populations to include some European countries, increasing the number of patients to 4,739 and the number of controls to 45,549, and examined the relationship between DNA variants and BC using the 20 best known markers. In this study, they demonstrated that the T allele of rs798766 on 4p16.3 was associated with low-grade and noninvasive BC (51).

miRNA-21, which is considered an oncogene, is frequently upregulated in BC patients and supports tumor cell proliferation and metastasis by interfering with tumor suppressor checkpoints (52,53). Although it is believed that miRNA-21 may have utility as a diagnostic and prognostic biomarker because of its increased release in certain cancers, there are conflicting reports concerning its diagnostic power and prognostic value. One of these was a meta-analysis by Wang et al. (54) in which a total of 528 studies were reviewed and the results of 17 studies that met the study criteria were used to evaluate the relationship between miRNA-21 levels and survival in patients with cancer. Eleven of these studies focused on the diagnostic value of miRNA-21 and 9 studies evaluated prognosis, and plasma miRNA-21 was determined to have sensitivity and specificity of 75.7% and 79.3%, respectively, when used as a diagnostic biomarker. Because coagulation could affect miRNA-21 expression, serum miRNA-21 measurements were also evaluated but no difference was found in terms of sensitivity and specificity (54). A limitation of this meta-analysis was that it did not include studies investigating the relationship between miRNA-21 and BC. In a study examining the relationship between bile duct cancers and miRNA-21, Kishimoto et al. (55) reported its negative predictive value (NPV) as 76.6%. Kotb et al. (56) reported this rate as 90% for prostate cancer. In a study investigating response to preoperative chemoradiotherapy in locally advanced rectal cancers, the NPV for miRNA-21 was found to be 42.8% (57). While it is not surprising that the NPV of miRNA-21 varied for different cancer types in these studies, there is currently no ongoing or completed study showing the NPV of miRNA-21 in BC. In a 2015 study by Zhang et al. (58), TUR was performed on 53 patients with BC who had not received neoadjuvant therapy and RNA was extracted from the specimens. They formed a control group by obtaining healthy bladder tissue from patients who underwent TUR-prostatectomy (TUR-P) due to benign prostate hyperplasia. Patient characteristics such as age, tumor grade, tumor number, stage, and size, recurrence rates, and lymph node involvement were recorded. They determined that miRNA-21 expression was upregulated in BC tissues compared to normal bladder tissues. Upregulation of miRNA-21 was associated with tumor stage, grade, and lymph node metastasis, but not with patient sex, age, tumor size, number of tumors, or recurrence. However, the authors cited the small patient number as a limitation of the study and acknowledged that more extensive studies are needed (59).

Mitash et al. (60) conducted another study with a limited number of cases and short follow-up period, in which they reported that increased miRNA-21 expression was associated with recurrence in NMIBC and that miRNA-21 level was negatively correlated with time to recurrence. It has long been known that high-grade T1 NMIBC is prone to recurrence. The epithelial-mesenchymal transition (EMT) promotes tumor cell proliferation, invasion, and migration, thereby increasing tumor aggressiveness. Histopathologic findings of vimentin

upregulation and e-cadherin down-regulation, which are indirect indicators of EMT (61), plus miRNA-21 overexpression also indicates the tumor will undergo an aggressive transformation (62,63). In a study investigating the critical role of miRNA-21 in cell proliferation, apoptosis, and chemosensitivity in addition to its oncogenic role in BC, it was reported that this molecule will facilitate the differential diagnosis between NMIBC and MIBC. With that study, the authors reported for the first time that increased miRNA-21 level conferred chemoresistance against doxorubicin, an agent used in the treatment of BC, through different mechanisms by stimulating down-regulation in the T24 cell line and that it carried the potential for developing treatment strategies for BC in the future (64).

Conclusion

The results of the few studies demonstrating the importance of miRNA-21 in monitoring BC and predicting prognosis are promising despite some limitations. Extensive prospective studies with larger patient numbers are needed to determine the utility of miRNA-21 as a biomarker.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Consept: N.A.M., Ö.Ç., Design: N.A.M., Ö.Ç., Data Collection and Processing: Ö.Ç., Analysis and Interpretation: N.A.M., Ö.Ç., Literature Search: Ö.Ç., Writing: Ö.Ç.

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