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Research Progress on the Expression of miRNA in the Diagnosis and Treatment of Bladder Urothelial Carcinoma

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Abstract: As one of the most common highly invasive tumors in the urinary system, bladder cancer has a high incidence rate and recurrence rate due to the lack of accurate biomarkers. MicroRNA (miRNA) is a non coding microRNA that regulates human gene expression and participates in cell growth cycle, development, proliferation, apoptosis, and differentiation. Studies have found that miRNA can affect the proliferation, invasion, metastasis and other malignant biological behaviors of bladder cancer through various ways, and may become a new biomarker in the early diagnosis, treatment and prognosis of bladder cancer. This article reviews the research progress of miRNA expression in the diagnosis and treatment of bladder cancer.

1. Introduction

Bladder cancer is a malignant tumor that occurs on the bladder mucosa. It is the most common malignant tumor in the urinary system and one of the top ten common tumors in the body. It occupies the first place in the incidence rate of urogenital tumors in China, while in the West its incidence rate is second only to prostate cancer, ranking second. Bladder cancer can occur at any age, even in children. Its incidence rate increases with age, and the high incidence age is 50-70 years old. The incidence rate of bladder cancer in men is 3-4 times higher than that in women. In 2004, according to the WHO Pathology and Genetics of Urinary System and Male Genital Organ Tumors, the pathological types of bladder cancer in the histological classification of urinary system tumors include bladder urothelial carcinoma, bladder squamous cell carcinoma, bladder adenocarcinoma, and other rare types include bladder clear cell carcinoma, bladder small cell carcinoma, and bladder carcinoid. The most common is bladder urothelial carcinoma, which accounts for more than 90% of the total number of bladder cancer patients. Timely and accurate early diagnosis and new treatment targets are of great significance for improving the cure rate of early bladder cancer, improving the quality of life of bladder cancer patients, and prolonging the survival time of patients, which depends on in-depth understanding of the potential mechanisms of bladder cancer occurrence, development, invasion and metastasis.

The exosomes secreted by cells, especially tumor cells, are rich in a large amount of miRNA. MicroRNA (miRNA) is a type of endogenous small RNA with a length of approximately 20-24 nucleotides, which regulates the expression of protein coding genes through specific sequences by inhibiting RNA translation or cleavage. With the continuous progress of high-throughput sequencing technology, more and more abnormal miRNAs are detected between bladder cancer patients and healthy volunteers, or between bladder cancer tumor tissue and matched peripheral tissue [1]. The expression and biological significance of miRNA in bladder cancer have attracted extensive attention.

2. Expression of miRNA in diagnosis of bladder cancer

For painless gross hematuria over the age of 40, the possibility of urinary system tumors should be considered. Based on the patient's past and family history, combined with symptoms and physical examination, make a preliminary judgment and further conduct relevant examinations. The examination methods include urine routine examination, urine cytology, urine tumor markers, abdominal and pelvic ultrasound, and other examinations. Based on the above examination results, it is decided whether to undergo cystoscopy, intravenous urography, pelvic CT or pelvic MRI to confirm the diagnosis. Among them, cystoscopy is the most important method to diagnose bladder cancer. However, due to its high cost and many contraindications, cystoscopy has limitations in its applicability to certain populations, and is an invasive examination. Postoperative complications such as urinary tract infections, fever, and lower back pain may occur.

The expression pattern of miRNA may play an important role in the diagnosis of bladder cancer. The expression levels of some miRNAs are closely related to the occurrence, malignancy and prognosis of bladder cancer, so they can be used as potential diagnostic markers and prognostic indicators. ANDREU et al. [2] used human miRNA probe technology to identify 23 kinds of down-regulated miRNAs and 3 kinds of up-regulated miRNAs in the urine of patients with high-level bladder cancer. Further PCR analysis also showed that the urine exocrine miR-375 can identify high-level bladder cancer patients, and the urine exocrine miR-146a can identify low-grade bladder cancer patients. Because of the limitations of urine exfoliation cytology and cystoscopy in bladder cancer screening, EL SHAL et al. [3] studied the expression of miR-96-5p and miR-183-5p in the urine of patients with bladder cancer, patients with benign bladder lesions, and healthy people. They found that the expression of miR-96-5p and miR-183-5p in the urine of patients with bladder cancer was significantly increased, and was closely related to the pathological stage and surgical condition of bladder cancer patients, It shows good sensitivity and specificity, which proves that the exocrine miR-96-5p and exocrine miR-183-5p in urine may be used as non-invasive biomarkers for good and accurate diagnosis of bladder cancer. In order to screen the biomarkers that are useful for the diagnosis of bladder cancer, G ü ll ü Amuran G ö k ç e et al. [4] also detected the expression of miR-19b1-5p, miR-21-5p, miR-136-3p, miR-139-5p, miR-210-3p in the urine samples of 59 patients with bladder cancer, 34 healthy controls and 12 patients without recurrence. The results showed that miR-19b1-5p, miR-136-3p MiR-139-5p showed good sensitivity and specificity in the early detection of bladder cancer. ARMSTRONG and his team [5] have examined the miRNA molecular profiles of three different biological samples: tumor tissue, white blood cells and urine, and found that a large number of up-regulated miRNAs can be identified in the urine exocrine body and WBC of bladder cancer patients, which indicates that miRNAs in the urine exocrine body may distinguish bladder cancer from other malignant tumors. ZHANG et al. [6] proposed a fluorescent biosensor based on inorganic Nanoflare and DNAzyme Walker. The biosensor not only shows high sensitivity and specificity in detecting miRNA, but also can realize the simultaneous analysis of miR-133b and miR-135b in clinical serum samples related to bladder cancer, which has taken a big step for the practical application of miRNAs in the clinical diagnosis of bladder cancer. All the above studies have proved that exocrine miRNA,

especially in urine, can be used as a simple and non-invasive diagnostic tool for patients with bladder cancer, and has great potential as a biomarker for early diagnosis of bladder cancer. CHEN et al. [7] summarized 1019 cases of bladder cancer and 690 cases of control group in 30 articles, and found that in the diagnosis of bladder cancer, the sensitivity and specificity of multiple miRNAs were significantly higher than that of single miRNA. MIAH et al. [8] divided volunteers into 68 patients with bladder cancer and 53 healthy controls, and analyzed 15 kinds of miRNAs. They found that the sensitivity of miR-1224-3p in diagnosing bladder cancer was 77%, and the specificity was 83%, while the sensitivity of miR-1224-3p combined with miRs 15b and miRs 1224-3p reached 94%. The above research shows that the combined detection of multiple miRNAs has a stronger application prospect in the early diagnosis of bladder cancer than that of single miRNA. A few studies have also explored the impact of combined detection of miRNA in the exocrine body on the diagnosis of bladder cancer. G Ⅴ LL Ⅴ AMURAN et al. [4] detected the difference in the expression of miR-19b1-5p, miR-21-5p, miR-136-3p, miR-139-5p, miR-210-3p in the urinary exosomes, and used the logical regression model of the detected effective miRNA groups (miR-19b1-5p, miR-136-3p, miR-139-5p) to construct bladder cancer patients and non cancer samples for ROC analysis, The results confirmed that the combined detection of secreted miRNA has a high sensitivity for the early diagnosis of bladder cancer.

MiRNA also showed certain application value in assisting bladder cancer grading. ANDREU et al. [2] isolated extracellular vesicles from the urine of 9 healthy people, 16 low-grade and 18 high-grade bladder cancer patients and evaluated their miRNA composition. The results showed that miR-375 was significantly up-regulated in the urine of high-grade bladder cancer patients (P=0. 03), while miR-146a was significantly up-regulated in low-grade bladder cancer patients. The extracellular vesicles in urine were significantly up-regulated (P=0. 03), so miR-375 may be a biomarker of high-grade bladder cancer, and miR-146a may be used to identify low-grade bladder cancer patients. BAUMGART et al. [9] found that the expression of miR-155-5p, miR-138-5p, miR-144-5p and miR-200a-3p in tissue samples and urine external vesicles was higher in myometrial invasive bladder cancer (MIBC) than in non myometrial invasive bladder cancer (NMIBC), which could distinguish MIBC and NMIBC. Another gene chip technology of BAUMGART et al. [9] also showed that different invasive bladder cancer cells have different expression characteristics of exocrine miRNA. BAUMGART's two studies show that exocrine miRNA is a promising biomarker for identifying MIBC and NMIBC, which can select patients who need early cystectomy, and provide help for treatment decisions of bladder cancer patients. Similarly, studies by LIN [10] have also shown that the expression of exosomal miR-93-5p in MIBC is significantly increased compared to NMIBC, which can distinguish between MIBC and NMIBC.

3. Expression of miRNA in the treatment of bladder cancer

3.1. Current status and shortcomings of bladder cancer treatment

Bladder urothelial carcinoma can be divided into non muscular infiltrating urothelial carcinoma and muscular infiltrating urothelial carcinoma. Non muscular infiltrating urothelial carcinoma patients often undergo transurethral resection of bladder tumors, followed by postoperative bladder infusion therapy to prevent recurrence. Patients with myometrial infiltrating urothelial carcinoma, bladder squamous cell carcinoma, and adenocarcinoma are often treated with total cystectomy, while some patients can be treated with partial cystectomy. BCG infusion therapy is commonly used for moderate to high-risk NMIBC and bladder cancer in situ. Compared with simple TURBt, the combination of TURBt and BCG bladder infusion can prevent postoperative recurrence of NMIBC and significantly reduce the risk of moderate to high-risk tumor progression. Patients with myometrial infiltrating urothelial carcinoma can also undergo neoadjuvant chemotherapy and surgical treatment

first. Metastatic bladder cancer is mainly chemotherapy. The commonly used chemotherapy schemes are M-VAP (methotrexate+vinblastine+adriamycin+cisplatin), GC (gemcitabine+cisplatin) and MVP (methotrexate+vinblastine+cisplatin). The effective rate of chemotherapy is 40%~65%. The main problem of drug therapy for bladder cancer is drug resistance, especially for recurrent tumors. Because of acquired drug resistance, the therapeutic effect is not ideal.

3.2. Extracellular vesicle mediated microenvironmental signal transduction and molecular metastasis in bladder tumors

Many studies have shown that the communication between exosomes and tumor cells or surrounding normal tissue cells can affect the occurrence and development of tumors, which is of great significance for developing new strategies for the treatment of bladder cancer. For example, HUANG et al. [11] found that LINC00960 and LINC02470 derived from exosomes of advanced bladder cancer cells were up-regulated β-Catenin signaling pathway, Notch signaling pathway and Smad2/3 signaling pathway promote the malignant behavior of bladder cancer cells downstream of the receptor and induce epithelial mesenchymal transformation. LIN et al [12] found that microRNA-21 (miR-21), an exosome derived from bladder cancer cells, inhibits the activation of PI3K/Akt signaling pathway by phosphatase and tensin homologues in macrophages, enhances the expression of STAT3, promotes M2 phenotype polarization, and accelerates tumor progression. JIA et al. [13] found that the exosome miR-139-5p derived from mesenchymal stem cells can inhibit the proliferation, migration and invasion of bladder cancer cells by targeting the polycomb repressive complex 1 (PRC1). In addition, CAI et al. [14] also found that miR-133b in exosomes may inhibit the proliferation of bladder cancer by up regulating dual specific protein phosphatase 1 (DUSP1).

3.3. miRNA and chemoresistance in bladder cancer

Although some progress has been made in the treatment of bladder cancer against drug resistance, the drug resistance of bladder tumor cells is still a difficulty in the treatment of bladder cancer. The migration and invasion of tumor cells are important factors leading to poor clinical treatment outcomes and treatment failures. Exploring the mechanisms of tumor cell migration and invasion is particularly important. In recent years, the discovery of extracellular vesicle derived miRNAs has provided new insights into the mechanism of drug resistance in bladder tumor cells. SHAN and his team [15] found that the expression of miR-148b-3p derived from cancer associated fibroblasts (CAF) in the exosomes was increased in bladder cancer tissues and body fluids of bladder cancer patients. Therefore, in vitro and in vivo experiments such as Transwell, MTT, flow cytometry, colony formation assay, xenotransplantation mouse models, etc. found that reducing the expression of miR-148b-3p in the exosomes could reduce Wnt/ β-Catenin pathway protein expression and up regulation of PTEN protein expression inhibit EMT, proliferation, metastasis and drug resistance of bladder cancer cells. WU et al. [16] found that extracellular vesicle miR-21 and mT OR from M2 tumor associated macrophages (M2 TAMs)/ β-The catenin/CDK6 pathway can be inhibited by Ovatodiolide (OV) isolated from Anisomeles indica and play a role in inhibiting the occurrence of bladder cancer and overcoming cisplatin (CDDP) resistance. In other words, the exosome miR-21 can promote the occurrence of bladder cancer and enhance drug resistance. This study proves that the exosome miR-21 can be used in the treatment of drug-resistant bladder cancer and the development of adjuvant drugs.

3.4. miRNA and targeted therapy of bladder cancer

YOSHIDA et al. [17] found that the CT10 regulator of kinase (CRK) junction increased the

expression of ErB B2/3 in the exocrine body of bladder cancer cells. These tyrosine kinases or junction units migrated from the host bladder cancer cells to the transfer receptor cells through the exocrine body, causing vascular leakage and cancer cell proliferation, and promoting distant metastasis. It is suggested that blocking ErB B2/3 by reducing CRK may be an effective treatment strategy for reducing distant metastasis and invasion in patients with advanced and metastatic bladder cancer. YAN et al. [18] found through research that the exosomes released by cancer related fibroblasts can promote the proliferation and invasion of bladder cancer cells. The mechanism of this effect is at least partially related to the increase of LINC00355. This suggests that regulating the expression of LINC00355 in the secretion released by cancer related fibroblasts may be a therapeutic strategy for the pathogenesis of bladder cancer. CAI et al. [19] identified the exosomes secreted by bone marrow mesenchymal stem cells (BMSCs) through co culture with bladder cancer cells. The results showed that the expression of miR-9-3p in bladder cancer tissue was reduced, and the expression of endothelial cell specific molecule 1 (ESM1) was increased, indicating that BMSCs inhibited the survival, migration and invasion of bladder cancer cells, and induced apoptosis, while the addition of exocrine secretion inhibitor GW4869 played an opposite role. In addition, up regulation of miR-9-3p or silencing ESM1 can inhibit the viability, migration and invasion of bladder cancer cells, induce apoptosis, and inhibit the growth and metastasis of tumors in vivo. The results showed that the exocrine miR-9-3p from BMSCs inhibited the progress of bladder cancer by down regulating ESM1, which provided a potential therapeutic target for bladder cancer. YIN et al. [20] isolated exosomes from the plasma of bladder cancer patients and healthy people, and found that the level of miR-663b in the plasma of bladder cancer patients was higher than that of the healthy control group. Studies have found that miR-663b can promote the proliferation and epithelial mesenchymal transformation of bladder cancer cells. In addition, the exosome miR-663b can be used as a tumor promoter in bladder cancer cells. These results indicate that miR-663b is a potential biomarker and a potential target for clinical detection and treatment of bladder cancer. YANG et al. [21] found that circT RPS1 derived from exosomes of bladder cancer cells can regulate intracellular reactive oxygen species balance and CD8+T cell depletion through circT RPS1/miR141-3p/GLS1 axis, which may provide potential biomarkers and therapeutic targets for bladder cancer. YAN et al. [22] studied and analyzed the miRNA profile of ex somes from blood plasma of bladder cancer patients (BCA ExO). Compared with normal control subjects (NC ExO), BCA ExO had 8 miRNAs differentially expressed, of which hsa-miR-4644 was the only miRNA up-regulated (multiple>2. 0, P<0. 05), which confirmed that its expression was up-regulated in bladder cancer patients' plasma and bladder cancer cell lines. Further in vitro studies found that miR-4644 negatively regulates the expression of UBIAD1 by directly binding to the 3 '- UTR domain of UbiA isoprene transfer domain protein 1 (UBIAD1), and UBIAD1 overexpression can effectively eliminate the promotion of miR-4644 on the proliferation, migration and invasion of bladder cancer. In addition, intratumoral administration of miR-4644 antagonists can downregulate the expression of miR-4644 in tumors and inhibit the occurrence of xenograft tumors in mice. These results indicate that miR-4644 promotes the proliferation and invasion of bladder cancer cells, while miR-4644 antagonist inhibits the proliferation and invasion of bladder cancer cells. This study is the first to confirm that miR-4644 is up-regulated in the plasma of bladder cancer patients and promotes the progress of bladder cancer by targeting UBIAD1.

4. Expression of miRNA in prognostic evaluation of bladder cancer

Strømme Olaf et al. [23] compared the expression level of miRNA in the urine samples of bladder cancer patients before surgery, after surgery and non cancer patients (cystoscopy results are benign). Compared with the samples after surgery, miR-451a and miR-486-5p in the urine extracellular vesicles were significantly up-regulated in the preoperative samples of T1 patients, and no

differentially expressed miRNA was found in the urine extracellular vesicles of Ta patients before and after surgery. Therefore, miR-451a and miR-486-5p may be potential biomarkers for recurrence free survival in patients with stage T1 bladder cancer, suggesting that urinary exocrine miRNAs may be used as recurrence prediction markers. It has also been reported that the high expression of miR-149-5p and miR-193a-5p in urine is significantly related to the poor overall survival rate of bladder cancer patients, which may be used as a prognostic biomarker of bladder cancer [24]. The expression level of miR-663b in plasma exosomes of bladder cancer patients increased [20]. Alexandru A. Sabo et al. [25] detected the expression level of sncRNAs in plasma extracellular vesicles of 47 male patients with bladder cancer and 46 healthy controls. The results showed that miR-4508 was down regulated in plasma extracellular vesicles of patients with myometrial invasive bladder cancer, and miR-4508 showed a downward trend from the control group to the high-risk bladder cancer group, and miR-126-3p was up regulated in plasma and urine extracellular vesicles of patients with grade 3 bladder cancer compared with the control group. In terms of predicting prognosis, this study found that bladder cancer patients with low expression of miR-185-5p and miR-106a-5p in plasma extracellular vesicles had a higher risk of death, whereas bladder cancer patients with high expression of miR-10b-5p had a shorter survival period. This study suggests that specific miRNAs in urine exosomes may serve as a simpler and faster non-invasive method for predicting the prognosis and recurrence of bladder tumors, but there is still limited research on this topic.

5. Summary and Outlook

MiRNA has broad application prospects in the diagnosis, treatment and prognosis of bladder cancer. Future research will further explore the mechanism of miRNA in bladder cancer and provide new ideas for early diagnosis, treatment and prognosis of bladder cancer. Numerous studies have shown that miRNA can serve as a molecular marker for disease diagnosis and prognosis assessment. The source of extracellular vesicle derived miRNAs is convenient and can be obtained from urine, serum, plasma, saliva, and semen samples. The readily available sample sources make it possible to use them for cancer screening in a large sample population. The use of extracellular vesicle derived miRNAs for assisted diagnosis is also a solution. Based on existing research evidence, extracellular vesicle derived miRNA can not only serve as a supplement to existing diagnostic staging methods, but also be used to predict tumor recurrence and metastasis, as well as to evaluate treatment efficacy to help patients choose suitable treatment methods. Moreover, compared to a single exosome derived miRNA, the diagnostic value and stability of multiple miRNAs in combination with other indicators are better. Therefore, the joint diagnostic model may be the main form for translating exosomal miRNA research into clinical applications. At present, chemotherapy is an important treatment for bladder cancer. However, due to the emergence of drug resistance and drug resistance, the therapeutic effect of chemotherapy on bladder cancer is limited. More and more studies show that miRNA is involved in the regulation of chemosensitivity and drug resistance of bladder cancer cells, so miRNA may become a potential therapeutic target of bladder cancer chemotherapy. By regulating the expression level of miRNA, it can interfere with the biological behaviors of tumor cells such as growth, proliferation, and invasion, thereby achieving therapeutic effects.

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