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Application of Urinary Exosomal Non-coding RNA as Biomarker in Prostate Caner

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Abstract: *Prostate cancer ranks among the most prevalent malignant tumors in males. Early intervention and diligent surveillance are essential for enhancing patient prognosis. In recent years, urinary exosomes have garnered significant attention as crucial mediators of intercellular communication. Non-coding RNAs (ncRNAs) found in urinary exosomes are thought to play crucial roles in tumorigenesis and development. Therefore, investigating their potential applications in prostate cancer is of significant importance. Compared to imaging examinations, biomarkers have the advantages of being less traumatic and more repeatable. Furthermore, certain urinary exosomes ncRNAs are significantly up-regulated in prostate cancer patients and have good diagnostic and prognostic value. This suggests that urinary exosomes ncRNAs can serve as potential biomarkers, providing new insights for early detection and personalized treatment of prostate cancer.*

Keywords: *prostate cancer; serum biomarkers; non-coding RNA; exosomes*

1. Introduction

According to the latest epidemiological data in 2024[1] , prostate cancer ranked sixth and seventh in incidence and mortality among male malignant tumors in China in 2022. The incidence rate is approximately 18.61/100,000, while the mortality rate is about 6.59/100,000, both showing a yearly increase. Compared to the United States, China's mortality-to-incidence ratio for prostate cancer is relatively high, indicating that diagnosed patients may face greater mortality risk despite lower overall rates. The most recent clinical guidelines indicate that prostate-specific antigen (PSA) remains the primary biomarker for early detection and diagnosis of prostate cancer. Since its inclusion in screening protocols in 1982, PSA has been widely accepted as a key indicator; however, it remains a subject of international debate. While PSA testing can moderately improve survival rates, it also raises concerns about overdiagnosis and overtreatment[2] , The poor specificity of PSA leads to unnecessary prostate biopsies, increasing both physiological and psychological burdens on patients while wasting clinical resources. In contrast to digital rectal examination (DRE) and transrectal ultrasound, prostate-specific antigen (PSA) levels are considered a more reliable prognostic indicator for prostate cancer. However, the correlation between PSA concentrations and the risk of developing prostate cancer is significantly weaker in the Chinese male population compared to Western countries[3] . Research into novel biomarkers for prostate cancer diagnosis has gained significant attention. Exosomes—extracellular vesicles found in blood, urine, saliva, semen, cerebrospinal fluid, and prostatic fluid—show great potential as biomarkers. They facilitate intercellular material exchange and signal transduction, influencing various pathophysiological processes. Exosome-mediated communication significantly impacts the progression and metastasis of prostate cancer. Their high stability protects their contents from enzymatic degradation, making them valuable sources of information about their parental cells. Additionally, their widespread presence in bodily fluids makes them ideal candidates for prostate cancer biomarkers.

2. Exosomes

Exosomes are cell-derived vesicles measuring 50 to 150 nm in diameter. They originate from multivesicular bodies formed by the invagination of intracellular lysosomal particles. These exosomes are released into the extracellular matrix after fusing with the extracellular membrane of multivesicular bodies[4] . Exosomes are released into the extracellular matrix after the fusion of multivesicular bodies' outer membrane with the cell membrane. These organelles, characterized by a single lipid bilayer, are

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abundant in proteins, lipids, nucleic acids, and glycosylated compounds[5]. All cell types can secrete exosomes[6], which naturally occur in various bodily fluids such as saliva, blood, urine, breast milk, and cerebrospinal fluid. Exosomes play a crucial role in intercellular material exchange and signal transduction, significantly impacting pathophysiological processes. The progression and metastasis of prostate cancer are influenced by exosome-mediated communication between cells[7-11]. Emerging evidence indicates that this communication is vital for both the advancement and spread of prostate cancer[10]. Their high stability, resistance to enzymatic degradation, rich content, specific conveyance of parental cell information, and widespread presence in body fluids render exosomes potential new biomarkers for prostate cancer. Urinary exosomes possess significant merits in the realm of non-invasive diagnosis and monitoring of genitourinary system tumors. Firstly, urine is easy to obtain, convenient, non-invasive, and repeatable. Secondly, the accuracy and sensitivity of using urinary exosomes for diagnosing genitourinary system tumors are high. While tumor cells shed in urine are difficult to capture, exosomes continuously released from tumor cells into urine make it easier to detect the secreted exosomes of tumor cells. Exosomes can carry cell antigens specific to the corresponding tumor source, thus offering high diagnostic specificity. Regarding stability, urinary exosomes remain for long-term at -80°C, indicating their high stability and potential use for detecting their contents[13-14].

2.1 Exosomes non-coding RNA

Non-coding RNA (ncRNA) is a unique class of RNA that does not code for proteins. This group includes well-known functional RNAs such as microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), and small nuclear RNA (snRNA), along with some whose functions are still being studied. Although ncRNAs do not translate into proteins, they play crucial roles in regulating gene expression by promoting transcript degradation or inhibiting protein synthesis. They also modify epigenetic features, regulate protein complex stability, and influence cell cycle dynamics[15]. NcRNAs can be categorized based on their length: those longer than 200 nucleotides are classified as long non-coding RNAs (lncRNAs), while small non-coding RNAs measuring ≤200 nucleotides include miRNA, piwi-interacting RNA (piRNA), and small interfering RNA (siRNA). NcRNAs show high conservation across species but also exhibit species-specific traits along with temporal and cellular variations[16-17]. In tumorigenesis, non-coding RNAs serve as key regulatory factors in cell signaling pathways. They can be detected in tumor tissues and various bodily fluids. NcRNAs may enter circulation through at least two mechanisms: binding to proteins like Ago2 or being encapsulated within extracellular vesicles (EVs). Thus, they hold significant potential as biomarkers for liquid biopsy applications[4].

2.2 The application of non-coding RNA derived from urinary exosomes in the context of prostate cancer

2.2.1 Urinary exosomes miRNA

miRNA (microRNA) is a type of short-chain non-coding RNA, typically around 22 nucleotides long, encoded by the genome. Since the discovery of lin-4 by Ambros and Ruvkun in 1993, over 38,000 distinct miRNAs have been identified across more than 50 species. These molecules are highly conserved throughout evolution and are expressed in specific tissues and developmental stages in plants, animals, and fungi. They play a crucial role in post-transcriptional gene expression regulation. miRNAs exhibit tissue specificity and temporal regulation that define the functional characteristics of various tissues and cells. Established as key regulatory factors since their discovery, miRNAs are involved in normal physiological processes as well as diverse disease mechanisms within complex biological systems. Research indicates that most miRNA genes reside at fragile genomic loci linked to tumorigenesis, closely associated with cancer onset and progression[21]. Recent evidence suggests that certain miRNAs may serve as diagnostic biomarkers for prostate cancer[22-24]. miRNAs exhibit specific expression profiles and have the ability to enter circulation, displaying relatively high chemical stability. Exosomes can be secreted from parental cells into bodily fluids; upon reaching the extracellular environment, they can bind to recipient cells and transfer their contained ncRNAs, leading to a series of phenotypic alterations[18]. This characteristic renders exosomes promising potential non-invasive tumor biomarkers for prostate cancer[19]. Furthermore, exosomes facilitate the development, invasion, and metastasis of genitourinary tumors through biologically active substances such as miRNAs. They also promote tumor angiogenesis and immune modulation responses that influence tumor progression while potentially enhancing drug resistance in tumors[20]

Haneul Lee et al. successfully separated low-protein impurities from urine extracellular vesicles (EVs) using stratum corneum and ultrafiltration techniques. They isolated EVs and identified six microRNAs

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(miR-375, miR-574-3p, miR-6756-5p, miR-16-5p, miR-21-5p, and miR-6880-5p) present in urine EVs from healthy donors and patients with castration-resistant prostate cancer (CRPC). These microRNAs are potential biomarkers for differentiating cancerous conditions from healthy individuals. Notably, CRPC patients exhibited significantly elevated levels of miR-21–5p, miR–574–3p, and miR–6880–5p, highlighting their prognostic value in CRPC[25]. Marta Rodríguez et al. extracted RNA from urine exosomes of 20 prostate cancer patients and 9 healthy males. Using next-generation sequencing (NGS) via Illumina high-throughput methods for library PCR amplification and analysis, they found that five microRNAs (miR–196a–5p, miR–34a–5p, miR–143–3p, miR–501–3p, and miR−92a−1−5p) were significantly downregulated in exosomes from prostate cancer patients. Subsequent RT-qPCR analysis on an independent cohort of 28 prostate cancer patients confirmed the downregulation of both miR−196a−5p and miR−501−3p in these samples. These findings suggest that urinalysis for exosomal content may yield valuable diagnostic biomarkers for prostate cancer through detection of specific microRNAs like mir−196a−5P and mir −501 -3P[26]. Sun Shin et al. conducted a study to analyze the differential expression of microRNAs (miRNAs) in urine exosomes from 149 prostate cancer (PCa) patients with localized and metastatic disease. They identified several miRNAs linked to metastasis, including miR-21, miR-16, miR-142-3p, miR-451, and miR-636. In multivariate analysis considering clinical factors, they found that levels of miR-21, miR-451, and miR-636 remained statistically significant alongside preoperative prostate-specific antigen (PSA) levels. Additionally, they developed the "Prostate Cancer Metastasis Risk Score (PCa-MRS)" model. The results indicated three distinct patterns associated with metastasis: upregulation of both miR-21 and miR-451 and downregulation of miR-636. These associations were validated in later phases of the study and maintained significance in multivariate analyses. This research suggests that urine exosomal miRNAs could serve as non-invasive biomarkers for predicting metastasis and prognosis in PCa patients[27]. Kyosuke Matsuzaki et al. isolated extracellular vesicles (EVs) from urine collected after digital rectal examination (DRE) in 14 men. They analyzed the microRNAs from these EVs using a microRNA array, identifying miR-30b-3p and miR-126-3p as overexpressed in prostate cancer patients' urine EVs; however, no specific microRNAs were linked to Gleason score. The sensitivity and specificity for predicting prostate cancer (PCa) were reported at 46.4% and 88.0%, respectively, while another analysis showed values of 60.7% sensitivity and 80.0% specificity, both outperforming serum PSA levels with sensitivities of only 53.5% and specificities of 64.0%[28]. RJ Bryant et al. found that the concentrations of miR-107 and miR-574-3p in urine samples from men with prostate cancer were significantly higher than those in the control group through their analysis of five different microRNAs present in urine samples[29].

2.2.2 Urinary exosomes lncRNA

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs longer than 200 nucleotides, forming a significant part of the non-coding genome. They are involved in various biological processes and play critical roles in transcriptional silencing, activation, chromatin modification, nuclear transport, and more. lncRNAs regulate gene expression at epigenetic, transcriptional, and post-transcriptional levels, participating in essential functions such as X chromosome silencing, genomic imprinting, chromatin remodeling, and other vital regulatory mechanisms. Thus, they are crucial to the onset and progression of human diseases. Additionally, lncRNAs exhibit high stability in circulation; therefore, they hold promise as reliable biomarkers for cancer detection. --- Long non-coding RNAs (lncRNAs) represent a distinct class of non-coding RNAs characterized by their length exceeding 200 nucleotides and constitute a substantial component of the non-coding genome. These molecules participate in numerous biological processes. Extensive research has shown that lncRNAs perform critical functions related to transcriptional silencing and activation as well as chromatin modification and nuclear transport among others. They can regulate gene expression through epigenetic, transcriptional, and post-transcriptional mechanisms while participating in key processes like X chromosome silencing, genomic imprinting, and chromatin remodeling. This involvement contributes to vital regulatory functions within cells. Consequently, lncRNAs are crucial for the initiation and progression of various human diseases. Additionally, their stability in circulation makes them promising candidates for reliable cancer detection biomarkers.

Yun Li et al. meticulously evaluated the expression levels of lncRNA PCA3 and MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) within a substantial cohort comprising individuals diagnosed with prostate cancer (PCa) as well as benign prostatic hyperplasia (BPH). They innovatively developed and rigorously validated a groundbreaking non-invasive methodology for detecting lncRNAs, leveraging urine exosomes to facilitate the diagnosis of prostate cancer, particularly in clinically pertinent cases during initial prostate biopsies[30]. Mustafa IŞIN et al. conducted an assessment of GAS5 and lncRNA-p21 levels in urine samples obtained from 49 patients diagnosed with BPH alongside 30 patients afflicted by prostate cancer. Their findings unveiled a significant elevation in

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exosomal lincRNA-p21 levels among PCa patients, positing that urinary exosomal lincRNA-p21 may surpass PCA3 in efficacy for the detection of PCa[31]. Anna et al. undertook a comparative analysis of the abundant expression profiles of various lncRNAs within urinary exosomes against those prominently expressed in alternative types of exosomes. Notably, PCAT6 emerged as highly expressed within uEVs and was concurrently identified in PCa cell lines along with their corresponding EVs[32]. This particular lncRNA was initially recognized as a prostate cancer-associated transcript (PCAT) within the broader transcriptome; it has recently been elucidated to play a pivotal role in modulating bladder cancer and colorectal cancer cell proliferation through miRNA sponging mechanisms[33]. To ascertain whether lncRNAs derived from urine exosomes can encode detectable and stable peptides, Anna and her colleagues executed proteomic mass spectrometry analyses on PC3, LNCaP, and HCT116 cells. The conclusive results indicated that uEVs possess the capacity to transport lncRNAs containing open reading frames (ORFs), which exhibit high translational potential—thereby yielding peptides endowed with promising predictive characteristics that could serve as novel MHC class I antigens for immunological presentation[34].

Zhao Ming et al. demonstrated that the expression of lncRNA MIR22HG was significantly elevated in macrophages induced by PC-3 exosomes, which enhanced the expression of downstream target genes associated with c-MYC and contributed to the M2 differentiation of macrophages. Furthermore, they investigated the molecular mechanism underlying lncRNA MIR22HG's role in macrophage M2 differentiation, elucidating its impact on macrophage functionality[35]. Ahadi et al. conducted a comparative analysis of four prevalent prostate cancer cell lines (LNCaP, PC3, DU145, VCaP) in conjunction with normal PNT2 cells. Their findings revealed that long non-coding RNAs (lncRNAs) can act as sponges for microRNAs (miRNAs), playing a pivotal role in both the initiation and progression of prostate cancer[36]. Wang et al. demonstrated that long non-coding RNAs (lncRNAs) upregulate c-Myc expression by competitively binding to miR-184, functioning as competing endogenous RNAs (ceRNAs). This interaction promotes the proliferation and migration of prostate cancer cells. Furthermore, MYU and c-Myc may establish a mutually regulated feedback loop; thus, MYU could serve as a significant diagnostic and therapeutic target for prostate cancer[37]. Yang et al. identified that lncRNA-PCSEAT mediates EZH2 activity in prostate cancer through competitive interactions with miR-143-3p and miR-24-2-5p. These findings suggest that lncRNA-PCSEAT may represent a promising therapeutic target for the management of prostate cancer[38].

circRNA, or circular RNA molecules, represents a distinct class of non-coding RNA. Unlike traditional linear RNA, circRNA is characterized by the absence of 5' end caps and 3' poly(A) tails, which distinguishes it as a prevalent type of non-coding RNA across various species, ranging from viruses to mammals[32]. The closed-loop structure of circRNA confers resistance to degradation by RNA exonucleases, thereby enhancing the stability of its expression. Recent studies have increasingly identified the presence of circRNA in the progression of multiple cancers, including kidney cancer, prostate cancer, bladder cancer, cervical cancer, and breast cancer. A notable mechanism through which circRNA functions is its role as competitive endogenous RNA (ceRNAs) for microRNAs (miRNAs) during tumor progression[33]. Consequently, circRNA holds significant potential as a cancer diagnostic biomarker.

Tao Wen et al. utilized third-generation microdroplet digital PCR to evaluate the expression levels of circ_0040507 in urine exosomes. The results revealed that the expression levels of circRNA-0040507 in urine exosomes from prostate cancer patients were significantly elevated compared to those observed in the benign prostatic hyperplasia (BPH) group. Moreover, it was concluded that urine exosome circ_0040507, when used in conjunction with prostate-specific antigen (PSA), exhibits substantial diagnostic value for prostate cancer. These findings suggest that urine exosome circRNA-0040507 may serve as a prostate cancer promising biomarker[36].

Anna and colleagues extracted total RNA and sequenced the PC3, LnCaP and DU145 human prostate cancer cell lines while also collecting extracellular vesicles (EVs) from the cell culture medium. Their findings revealed that circ-SMARCA5 was abundantly present in all three cell lines, leading to the hypothesis that circ-SMARCA5 may regulate cell proliferation and contribute to the tumor microenvironment as well as vesicle-mediated signaling[37].

The experiments confirmed that the modulation of the miR-1182/Tumor Protein D52 (TPD52) axis promotes resistance to docetaxel in prostate cancer (PCa). Furthermore, this axis interacts with the FUS binding protein (FUS), leading to the activation of transcription for X-linked Inhibitor of Apoptosis Protein (XIAP). This interaction subsequently enhances cellular proliferation, migration, and epithelial-mesenchymal transition (EMT). In contrast to these circRNAs that promote resistance, circFoxo3 (has_circis_0006404) inhibits FOXO3 protein expression and EMT, thereby increasing sensitivity to

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docetaxel[39]. The exosome hsa_circ_0004870 is downregulated in enzalutamide-resistant prostate cancer cells, highlighting its significant role in the development of enzalutamide resistance[40].

Zhong et al. identified that circRNAs associated with autophagy could serve as prognostic indicators for biochemical recurrence in prostate cancer. Specifically, the downregulation of hsa_circ_0001747 levels may promote disease progression, indicating that autophagy-related circRNAs could be significant predictors of biochemical recurrence among patients diagnosed with prostate cancer[41].

3. Summary and Outlook

This review explores the recent application of non-coding RNAs derived from urinary exosomes as biomarkers for prostate cancer. Exosomes, which are vesicular structures with diameters ranging from 50 to 150 nm, are rich in RNA and proteins. They exhibit high stability, abundant content, biocompatibility, permeability, low toxicity, and minimal immunogenicity while transmitting information from their parent cells. These biophysical properties position exosomes as highly promising candidates for use as diagnostic biomarkers in tumor detection[32]. Urine offers several advantages as a diagnostic specimen: it is non-invasive, easy to collect, and allows for large sample sizes. Consequently, an increasing number of studies have focused on the diagnostic potential of non-coding RNAs found in urinary exosomes. Compared to prostate-specific antigen (PSA) testing and prostate biopsy procedures, the analysis of urinary exosomes provides benefits such as enhanced sensitivity and simplicity while being entirely non-invasive. However, challenges remain in research concerning non-coding RNAs within urinary exosomes. These challenges include various methods for isolating and identifying exosomes that may result in inconsistent purity and content during extraction processes. Furthermore, these analyses often require substantial sample volumes and can be costly—factors that impede widespread clinical application. Current research is still at an early experimental stage; most studies involve small sample sizes, necessitating larger-scale multi-center investigations for prospective validation. Moreover, the mechanisms by which many non-coding RNAs influence prostate cancer remain largely unclear. Despite these obstacles, this approach represents a highly promising method for detecting prostate cancer with significant clinical implications for the early identification of aggressive forms of PCa while reducing unnecessary biopsies and minimizing waste of medical resources. We believe that in the near future, urinary exosome biopsy will find broad applications in clinical practice—bringing positive advancements to public health outcomes.

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