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Research Progress and Clinical Application Prospects of Exosome-Related Genes in Bladder Cancer: A Review

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Abstract: Exosomes, as critical mediators of intercellular communication, carry genetic information that plays a pivotal role in the initiation, progression, metastasis, and therapeutic resistance of bladder cancer. This review systematically summarizes the expression profiles and functional mechanisms of exosome-related genes in bladder cancer, highlighting their emerging roles as biomarkers and therapeutic targets. By integrating recent advances from high-throughput sequencing, functional validation, and clinical translational studies, we explore the potential of exosome-derived coding and non-coding RNAs in the diagnosis, prognostic evaluation, and personalized treatment of bladder cancer. The review aims to provide new theoretical insights and strategic directions for precision medicine in bladder cancer, addressing current challenges and future opportunities in the field.

1. Introduction

Bladder cancer (BCa) ranks among the most common malignancies of the urinary system worldwide, characterized by high incidence, significant morbidity, and a propensity for recurrence and progression. Despite advances in surgical and chemotherapeutic interventions, the clinical management of bladder cancer remains challenging due to its heterogeneous nature, high relapse rates, and the limited efficacy of current diagnostic and therapeutic modalities. Traditional diagnostic approaches, such as cystoscopy and histopathological examination, although considered gold standards, are invasive, costly, and sometimes insufficiently sensitive to detect early-stage or minimal residual disease. Consequently, there is an urgent need for novel, non-invasive biomarkers and therapeutic targets that can improve early detection, prognostication, and treatment outcomes in bladder cancer patients [1][2][3].

In recent years, the study of extracellular vesicles, particularly exosomes, has revolutionized our understanding of intercellular communication within the tumor microenvironment and systemic circulation. Exosomes are nanoscale lipid bilayer vesicles (40–100 nm in diameter) secreted by virtually all cell types, including tumor cells, and are enriched with diverse bioactive molecules such as proteins, lipids, and various nucleic acids—including messenger RNAs (mRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). These vesicles serve as critical mediators of cell-to-cell communication by transferring their cargo to recipient cells,

thereby modulating gene expression and cellular behavior in both local and distant microenvironments [4][1][5]. In bladder cancer, tumor-derived exosomes have been implicated in multiple facets of tumor biology, including remodeling of the tumor microenvironment, promotion of angiogenesis, facilitation of invasion and metastasis, induction of immune evasion, and mediation of chemoresistance [2][6][7].

The molecular cargo within bladder cancer-derived exosomes reflects the genetic and epigenetic landscape of the tumor cells, offering a rich source of potential biomarkers for non-invasive diagnosis and prognosis. For instance, exosomal mRNAs such as KRT6B and CDC6 have been associated with epithelial-mesenchymal transition (EMT), immune modulation, and malignant phenotypes in bladder cancer, correlating with tumor stage, grade, and patient survival [2][6]. Similarly, exosomal miRNAs, including miR-17-5p, miR-221-5p, miR-186-5p, and miR-93-5p, have been shown to regulate key signaling pathways that promote tumor growth, invasion, angiogenesis, and immune escape, highlighting their potential as therapeutic targets and diagnostic markers [8][9][10][11]. Moreover, exosomal lncRNAs such as PTENP1, SNHG16, and BCYRN1 have emerged as critical regulators of bladder cancer progression by modulating gene expression networks involved in proliferation, metastasis, and chemoresistance [12][13][14].

Beyond their role as biomarkers, exosomes have garnered attention as promising vehicles for targeted drug delivery and gene therapy in bladder cancer. Advances in exosome engineering have enabled the loading of therapeutic nucleic acids, such as artificial circular RNAs designed to inhibit oncogenic transcription factors like β-catenin and NF-κB, demonstrating enhanced tumor suppression compared to conventional gene-editing systems [1]. Additionally, mesenchymal stem cell-derived exosomes have shown potential in modulating tumor cell apoptosis and angiogenesis, further underscoring the therapeutic versatility of exosome-based approaches [15]. The unique biocompatibility, stability, and tissue-targeting capabilities of exosomes position them as ideal candidates for precision medicine strategies aimed at overcoming the limitations of current bladder cancer treatments [3][5].

The tumor microenvironment (TME) in bladder cancer is a complex and dynamic milieu where exosomes play pivotal roles in shaping immune responses and stromal interactions. Tumor-derived exosomes can induce immunosuppressive phenotypes in macrophages, promote regulatory T cell infiltration, and impair natural killer cell function, thereby facilitating immune escape and tumor progression [16][17]. Furthermore, exosomal cargo influences the epithelial-mesenchymal transition and angiogenesis, processes essential for metastasis and tumor growth [2][18]. Understanding these mechanisms is critical for developing exosome-based immunotherapies and combination treatments that can effectively modulate the TME and enhance anti-tumor immunity [3][19].

In summary, the burgeoning field of exosome research offers transformative insights into bladder cancer biology, presenting novel avenues for early diagnosis, prognostic assessment, and targeted therapy. Systematic elucidation of exosome-associated gene expression profiles and functional mechanisms holds promise for the development of innovative, non-invasive diagnostic tools and personalized therapeutic strategies. This review aims to comprehensively synthesize current knowledge on exosome-related genes in bladder cancer, focusing on their molecular characteristics, functional roles, and clinical translational potential, thereby providing a foundation for future research and clinical applications in this challenging malignancy.

2. Main Body

2.1. Characteristics and Identification of Gene Expression Profiles in Bladder Cancer Exosomes

2.1.1. Characteristics of Non-coding RNA Profiles Derived from Exosomes

Bladder cancer (BC) exosomes are enriched with specific non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), which play pivotal roles in tumor progression by modulating gene expression and signaling pathways. Among miRNAs, miR-21-5p, members of the miR-200 family, and miR-155 are notably upregulated in BC patient serum and urine exosomes. These miRNAs contribute to oncogenesis by targeting tumor suppressor genes such as PTEN and PDCD4, thereby promoting tumor cell proliferation, invasion, and epithelial-mesenchymal transition (EMT). For instance, miR-93-5p, highly expressed in urinary exosomes of BC patients, suppresses BTG2 expression, facilitating cancer cell proliferation and migration, as validated by in vitro experiments [20]. Similarly, miR-17-5p is elevated in muscle-invasive bladder cancer (MIBC) urinary exosomes and tissues, promoting tumor growth and invasion by repressing ARID4B, a tumor suppressor gene, and modulating the immune microenvironment [9]. Exosomal miR-221-5p and miR-186-5p derived from BC cells impair natural killer (NK) cell function by targeting key cytotoxicity-related genes, contributing to immune evasion [17]. These findings underscore the multifaceted roles of exosomal miRNAs in tumor progression and immune modulation.

Long non-coding RNAs (lncRNAs) such as HOTAIR, MALAT1, UCA1, and PTENP1 are aberrantly expressed in BC exosomes and serve as competitive endogenous RNAs (ceRNAs) that sponge miRNAs, thereby regulating downstream signaling pathways like Wnt/β-catenin and PI3K/Akt. For example, exosomal lncRNA PTENP1 derived from bone marrow mesenchymal stem cells suppresses BC malignancy by upregulating SCARA5 via miR-17 sponging, inhibiting proliferation and invasion both in vitro and in vivo [12]. Meta-analyses have demonstrated the diagnostic potential of exosomal lncRNAs, with pooled sensitivities and specificities around 74% and 76%, respectively, and higher diagnostic efficacy when multiple lncRNAs are combined, especially in blood samples [21]. Moreover, exosomal lncRNAs such as SNHG16 and BCYRN1 have been implicated in promoting tumor progression and lymphatic metastasis by modulating EMT and VEGF-C/VEGFR3 signaling [13][14]. These lncRNAs not only influence tumor biology but also hold promise as non-invasive biomarkers.

Circular RNAs (circRNAs), characterized by their covalently closed loop structures conferring stability, exhibit unique expression patterns in BC exosomes. CircPRMT5 and circHIPK3 have been identified as key players in BC progression. For instance, circTRPS1, an exosome-derived circRNA, promotes malignant phenotypes and CD8+ T cell exhaustion in the tumor microenvironment by sponging miR-141-3p and regulating GLS1-mediated glutamine metabolism [22]. Additionally, artificial circular RNAs (acircRNAs) engineered to mimic CRISPR-Cas systems have been successfully loaded into exosomes to inhibit oncogenic transcription factors such as β-catenin and NF-κB, resulting in suppressed proliferation and migration of BC cells, highlighting therapeutic potential [1]. CircRNAs also modulate cell cycle and metastasis by acting as miRNA sponges or interacting with RNA-binding proteins, thereby influencing key signaling cascades.

Collectively, the ncRNA cargo of BC exosomes orchestrates a complex regulatory network that promotes tumor growth, invasion, immune escape, and chemoresistance. The stability and detectability of these ncRNAs in body fluids make them attractive candidates for liquid biopsy-based diagnostics and prognostics. Furthermore, their functional roles in modulating critical pathways such as Wnt/β-catenin, PI3K/Akt, and immune checkpoints underscore their potential as therapeutic

targets. Advances in high-throughput sequencing, bioinformatics, and exosome engineering continue to unravel the intricate ncRNA landscape in BC exosomes, paving the way for precision medicine approaches in bladder cancer management.

2.1.2. mRNA and Mutated Genes Derived from Exosomes

Bladder cancer-derived exosomes carry not only non-coding RNAs but also tumor-specific messenger RNAs (mRNAs) and mutated gene sequences that reflect the molecular landscape of the tumor and contribute to intercellular communication within the tumor microenvironment. Exosomal mRNAs related to angiogenesis, such as VEGF mRNA, and cell cycle regulators like CDKs, have been detected in BC exosomes. These mRNAs can be internalized by recipient cells and translated into functional proteins, thereby influencing tumor progression and angiogenesis. For example, SLC7A7-induced angiogenesis in BC is mediated through exosomal miR-152-3p targeting FGFR3, highlighting the role of exosomal mRNAs and miRNAs in modulating angiogenic pathways [23].

Exosomal DNA (exoDNA) from BC patients contains somatic mutations in driver genes such as FGFR3, TP53, and RB1, which are critical for tumor initiation and progression. Whole-exome sequencing of urine exoDNA has revealed unique somatic variants not always detectable in tumor biopsies, likely due to intratumoral heterogeneity. This non-invasive liquid biopsy approach enables the detection of tumor-specific mutations and clonal evolution, offering a promising tool for early diagnosis, monitoring, and personalized therapy [24]. Moreover, exoDNA harbors variants in untranslated regions, including miRNA-binding sites, which may affect post-transcriptional regulation and tumor behavior.

The advent of single-cell exosome sequencing technologies has further refined our understanding of exosomal heterogeneity at the individual vesicle level. This approach allows the dissection of distinct molecular subtypes within exosome populations, facilitating the identification of more specific biomarkers and therapeutic targets. For instance, urinary exosomes predominantly express bladder tissue-specific genes and show close genetic relationships with endothelial, basal, monocyte, and dendritic cells, reflecting their cellular origins and functional roles in the tumor microenvironment [25]. Such detailed profiling enhances the specificity and sensitivity of exosome-based diagnostics.

Proteomic analyses complement nucleic acid profiling by identifying exosomal proteins involved in tumor progression. For example, exosomal KRT6B is upregulated in BC and correlates with epithelial-mesenchymal transition (EMT) and immune response pathways, serving as a potential prognostic marker [2]. Similarly, exosomal THBS1, MMP9, and CXCL12 have been identified as therapeutic targets through machine learning-based prognostic models, with experimental validation confirming their roles in BC cell migration and invasion [26]. These findings underscore the multifaceted cargo of BC exosomes and their contributions to tumor biology.

In summary, bladder cancer exosomes encapsulate a diverse array of mRNAs and mutated genes that mirror the tumor's genetic alterations and functional state. The presence of angiogenesis-related mRNAs, driver gene mutations, and tissue-specific transcripts within exosomes facilitates tumor progression, metastasis, and immune modulation. Liquid biopsy approaches leveraging exosomal nucleic acids and proteins offer non-invasive, dynamic insights into tumor heterogeneity and evolution, enabling improved diagnosis, prognosis, and therapeutic stratification. The integration of advanced sequencing technologies and bioinformatics will continue to enhance the resolution and clinical utility of exosome-based molecular profiling in bladder cancer

2.2. Functional Mechanism of Exosome-Related Genes in the Occurrence and Development of Bladder Cancer

2.2.1. Regulation of Tumor Microenvironment and Immune Escape

Exosome-associated genes play pivotal roles in modulating the tumor microenvironment (TME) and facilitating immune escape in bladder cancer (BCa). Tumor-derived exosomes carry various bioactive molecules, including microRNAs (miRNAs) such as miR-214 and long non-coding RNAs (lncRNAs) like H19, which can be internalized by tumor-associated macrophages (TAMs). This uptake induces polarization of TAMs toward the M2 phenotype, characterized by pro-tumorigenic functions. M2 macrophages secrete immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which inhibit T cell activation and cytotoxicity, thereby promoting immune evasion by tumor cells [27]. Moreover, exosomes derived from bladder cancer cells have been shown to carry programmed death-ligand 1 (PD-L1) mRNA and protein, which can directly engage the programmed death-1 (PD-1) receptor on T cells. This interaction suppresses T cell function through immune checkpoint pathways, further enabling tumor cells to escape immune surveillance [3]. The exosomal PD-L1 can also be transferred to other cells within the TME, amplifying the immunosuppressive milieu. Additionally, exosome-associated genes regulate the transformation of fibroblasts into cancer-associated fibroblasts (CAFs), which contribute to extracellular matrix (ECM) remodeling. This remodeling creates a physical and biochemical environment conducive to tumor invasion and metastasis. For instance, exosomal long non-coding RNAs and proteins can activate signaling pathways in fibroblasts, promoting their differentiation into CAFs that secrete matrix metalloproteinases and other ECM components, facilitating tumor progression [28][14]. The interplay between exosome-mediated macrophage polarization, immune checkpoint modulation, and fibroblast activation orchestrates a complex TME that supports bladder cancer growth and immune escape. These mechanisms highlight the critical role of exosome-associated genes in shaping the TME and underscore their potential as therapeutic targets to restore anti-tumor immunity and inhibit tumor progression.

2.2.2. Mediation of Therapy Resistance and Distant Metastasis

Exosome-associated genes are instrumental in mediating therapeutic resistance and facilitating distant metastasis in bladder cancer. Chemoresistant bladder cancer cells release exosomes enriched with specific miRNAs such as miR-221/222 and lncRNAs including NEAT1, which can be taken up by chemosensitive cells. These exosomal cargos downregulate pro-apoptotic proteins like PUMA and activate survival signaling pathways, thereby conferring chemoresistance to recipient cells [17][29]. This horizontal transfer of resistance traits via exosomes contributes to the heterogeneity and persistence of chemoresistant tumor cell populations. Furthermore, exosome-mediated gene transfer plays a critical role in the formation of pre-metastatic niches. For example, exosomal miR-105 disrupts the integrity of vascular endothelial barriers, increasing vascular permeability and facilitating circulating tumor cell extravasation [30]. Concurrently, exosomal lncRNA MALAT1 enhances pro-inflammatory responses in stromal cells of target organs such as the lung and liver, creating a supportive microenvironment for metastatic colonization [14]. These exosome-derived molecules orchestrate a favorable niche that promotes tumor cell survival and outgrowth at distant sites. Importantly, targeting these exosomal genes has shown promise in preclinical models. The use of antagonists or inhibitors against specific miRNAs carried by exosomes can reverse chemoresistance and suppress metastasis, highlighting the therapeutic potential of modulating exosome-mediated communication [29][30]. Collectively, exosome-associated genes contribute to the dynamic regulation of therapy resistance and metastatic dissemination in bladder cancer, offering novel

avenues for intervention to improve clinical outcomes.

2.3. Application and Challenges of Exosome-Related Genes in Clinical Diagnosis and Treatment of Bladder Cancer

2.3.1. As Novel Liquid Biopsy Biomarkers

Urinary exosomes have emerged as an ideal source for liquid biopsy in bladder cancer (BC) due to their non-invasive accessibility and rich content of urothelial cell-derived molecular information. Unlike traditional urine cytology, which suffers from limited sensitivity and specificity, especially in low-grade tumors, urinary exosomal gene signatures offer enhanced diagnostic performance. For instance, the combined detection of specific microRNAs such as miR-96, miR-183, and miR-21 in urinary exosomes has demonstrated superior sensitivity and specificity compared to conventional cytology, reflecting their potential as robust biomarkers for early BC detection [31]. High-throughput sequencing and bioinformatic analyses have identified numerous differentially expressed mRNAs and long non-coding RNAs (lncRNAs) in urinary exosomes from BC patients, implicating pathways like MAPK, PI3K-Akt, and Hippo signaling in tumorigenesis [8][1]. Notably, lncRNAs such as PCAT-1 and SNHG16 are enriched in urinary exosomes and correlate with tumor grade, stage, and recurrence risk, serving as prognostic indicators [13]. Dynamic monitoring of exosomal gene expression profiles before and after treatment enables real-time assessment of therapeutic response and early detection of minimal residual disease or acquired resistance. For example, exosomal miR-17-5p levels in urine have been linked to muscle-invasive BC progression and immune microenvironment modulation, suggesting their utility in risk stratification and prognosis [9]. Furthermore, exosomal mRNA markers such as CA9 and SDPR combined with ACBD7 have shown promising diagnostic accuracy, with area under the curve (AUC) values exceeding 0.79, highlighting the feasibility of multiplexed biomarker panels [8]. Advances in exosome isolation and enrichment technologies, including MOF-on-MOF-based microfluidic chips, have facilitated rapid and efficient urinary exosome capture, enabling high-throughput clinical applications [32]. Despite these advances, challenges remain in standardizing exosome isolation, ensuring reproducibility, and validating biomarkers in large, prospective cohorts. Nonetheless, the accumulating evidence underscores the transformative potential of urinary exosomal gene signatures as non-invasive, sensitive, and specific liquid biopsy biomarkers for bladder cancer diagnosis, prognosis, and therapeutic monitoring.

2.3.2. As Therapeutic Targets and Drug Delivery Vehicles

Exosome-related genes not only serve as biomarkers but also represent promising therapeutic targets and delivery platforms in bladder cancer management. Targeting the biogenesis and secretion pathways of tumor-derived exosomes, such as inhibiting Rab27a or neutral sphingomyelinase 2 (nSMase2), can disrupt the release of oncogenic exosomal cargo, thereby attenuating tumor progression and metastasis [2]. Moreover, antisense oligonucleotides including antagomiRs and siRNAs can be designed to neutralize pro-tumorigenic exosomal microRNAs or mRNAs, effectively silencing oncogenes within the tumor microenvironment. For example, siRNA targeting the FGFR3-TACC3 fusion gene delivered via mesenchymal stem cell-derived exosomes has demonstrated selective depletion of fusion transcripts in bladder cancer cells, reducing tumor viability without affecting wild-type gene expression [33]. Engineering exosomes derived from mesenchymal stem cells or dendritic cells to encapsulate therapeutic nucleic acids or chemotherapeutic agents leverages their innate targeting capabilities and biocompatibility, enhancing drug delivery specificity and minimizing systemic toxicity. Preclinical studies have shown that exosomes loaded with siRNA against EGFR or tumor suppressor genes like p53 can effectively inhibit bladder cancer cell

proliferation and induce apoptosis [1][15]. Additionally, exosomal delivery of microRNAs such as miR-133b and lncRNAs like PTENP1 has been reported to suppress tumor growth, invasion, and chemoresistance by modulating key signaling pathways [34][12]. The use of exosome-mimetic nanovesicles co-loaded with immune checkpoint inhibitors and CD73 inhibitors exemplifies innovative combinatorial immunotherapy strategies that enhance cytotoxic T cell infiltration and tumor suppression in vivo [19]. Despite these promising advances, challenges in scalable production, quality control, and safety evaluation of engineered exosomes remain significant hurdles for clinical translation. Nonetheless, the convergence of exosome biology and gene therapy offers a versatile and potent platform for precision treatment of bladder cancer.

2.3.3. Challenges and Future Directions

The clinical translation of exosome-related gene applications in bladder cancer faces several critical challenges. First, the lack of standardized protocols for exosome isolation, purification, and nucleic acid extraction leads to variability in biomarker detection and hampers reproducibility across studies [8]. Harmonization of methodologies is essential to ensure comparability and reliability of diagnostic assays. Second, the heterogeneity of exosomal cargo reflects the diverse cellular origins and tumor subtypes within bladder cancer, complicating the identification of universal and specific biomarker panels. For instance, exosomes secreted by different tumor cell populations or stromal cells such as cancer-associated fibroblasts and tumor-associated macrophages carry distinct lncRNAs and microRNAs that influence tumor progression and immune modulation [16][27]. This intratumoral and intertumoral heterogeneity necessitates comprehensive multi-omics profiling and integrative bioinformatics to delineate robust biomarker signatures. Third, large-scale, prospective, multicenter clinical trials are urgently needed to validate the diagnostic and prognostic efficacy of exosomal gene markers and to establish their clinical utility. Furthermore, the engineering of exosomes as therapeutic vehicles requires overcoming challenges related to scalable manufacturing, batch-to-batch consistency, targeted delivery efficiency, and immunogenicity assessment [3]. Regulatory frameworks for exosome-based therapeutics are still evolving, demanding rigorous preclinical safety and efficacy evaluations. Future directions include the development of high-throughput, sensitive, and standardized exosome isolation platforms, integration of artificial intelligence for biomarker discovery and patient stratification [35], and exploration of combinatorial therapies leveraging exosome-mediated gene delivery with immune checkpoint blockade or chemotherapy. Advances in single-cell and spatial transcriptomics will further elucidate the dynamic tumor microenvironment interactions mediated by exosomal genes, guiding personalized medicine approaches [36]. In summary, addressing these challenges through multidisciplinary collaboration will be pivotal to harness the full clinical potential of exosome-related genes in bladder cancer diagnosis and therapy.

3. Conclusions

Exosome-related genes constitute a complex and pivotal communication network within bladder cancer, intricately involved in tumor progression, immune modulation, therapeutic resistance, and metastasis through diverse molecular forms including coding and non-coding RNAs. From an expert perspective, the comprehensive identification and characterization of bladder cancer-specific exosomal gene expression profiles represent a foundational step toward unraveling the precise molecular mechanisms driving these processes. This understanding is critical not only for elucidating tumor biology but also for the development of innovative diagnostic biomarkers and therapeutic targets.

The clinical potential of urinary exosome gene detection is particularly promising, offering a non-

invasive approach for early diagnosis, prognostic evaluation, and real-time monitoring of treatment efficacy. Such liquid biopsy techniques could revolutionize patient management by enabling dynamic assessment of tumor behavior and therapeutic response without the need for invasive procedures. However, balancing the enthusiasm for these advances with the current limitations is essential. Challenges such as the standardization of exosome isolation methods, rigorous validation of biomarker specificity, and the translation of engineered exosome-based therapeutics into clinical practice remain significant hurdles.

Integrating multi-omics analyses, single-exosome technologies, and nanotechnology-driven engineering holds the key to overcoming these obstacles. These cutting-edge approaches facilitate a more granular understanding of exosomal heterogeneity and function, thereby enhancing the precision of biomarker discovery and therapeutic design. Importantly, the convergence of these technologies fosters a more holistic view of bladder cancer pathophysiology, enabling the reconciliation of diverse research findings and perspectives into a coherent framework.

Looking forward, the field must prioritize the rapid translation of foundational discoveries into clinical applications. This entails not only validating candidate biomarkers and therapeutic targets in large, well-characterized patient cohorts but also developing individualized treatment strategies informed by exosome gene signatures. Such personalized approaches have the potential to optimize therapeutic efficacy while minimizing adverse effects, ultimately improving patient outcomes.

In conclusion, exosome-related gene research in bladder cancer stands at the forefront of precision oncology, poised to transform diagnosis and treatment paradigms. By thoughtfully balancing innovative technological advances with rigorous clinical validation, the field can harness the full potential of exosomal biology. This will usher in a new era of personalized, non-invasive, and targeted interventions that address the multifaceted challenges of bladder cancer management. Continued interdisciplinary collaboration and methodological refinement will be essential to realize these goals and translate the promise of exosome research into tangible clinical benefits.

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