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Dual Roles of Exosomes in Precision Cancer Diagnosis and Therapy

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Abstract. As core subsets of extracellular vesicles, exosomes mediate intercellular signal communication and carry diverse biomolecules that faithfully reflect the phenotypic characteristics of parent cells. In oncology research, exosomes exert two opposing biological effects on tumor progression and clinical intervention. This paper systematically sorts the dual regulatory functions of exosomes and summarizes their translational prospects for tumor liquid biopsy and targeted drug delivery. Tumor-derived exosomes remodel local and distant tumor microenvironments, suppress anti-tumor immune responses, facilitate angiogenesis and epithelial-mesenchymal transition, and transmit drug-resistant traits to sensitive tumor cells. Meanwhile, exosomes with intact lipid bilayer structures can protect internal nucleic acids and proteins from enzymatic degradation, serving as stable non-invasive biomarkers for early tumor screening and efficacy monitoring. Genetically modified engineered exosomes can load chemotherapeutics, small interfering RNAs and immune regulators to achieve tumor-specific targeted delivery. This paper systematically elaborates the molecular mechanisms, clinical diagnostic value, therapeutic potential and translational bottlenecks of exosomes in precision oncology. Current evidence proves exosome-based liquid biopsy supports early tumor detection, primary lesion tracing and dynamic efficacy evaluation. However, standardized separation protocols, unified quality control standards and long-term safety evaluation systems have not been fully established, restricting large-scale clinical transformation. Follow-up interdisciplinary research needs to form unified technical specifications to promote the clinical application of exosome-based diagnosis and treatment integrated strategies.

Keywords: Exosomes, liquid biopsy, drug delivery, precision medicine, tumor microenvironment

1. Introduction

Malignant neoplasms continue to be a major global cause of mortality and place substantial economic and medical strains on public healthcare systems. Early detection, accurate molecular classification, continuous tracking of treatment results, and timely identification of recurrence are essential for improving patient survival. Conventional tissue biopsy remains the gold standard for pathological assessment and molecular analysis. However, tissue biopsy is an invasive procedure and typically only reveals a single lesion at a specific moment. Because malignant neoplasms are

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characterized by spatiotemporal variability, one-time sampling often fails to capture the dynamic development of cancer under therapeutic pressure.

Liquid biopsy technology emerges to overcome the limitations of tissue biopsy by detecting tumor-derived substances in peripheral blood, urine and ascites. Common targets for liquid biopsy involve circulating tumor cells, circulating tumor DNA, circulating cell-free RNA, tumor-related proteins, and extracellular vesicles [1]. Among these, circulating tumor DNA has become extensively applied for detecting mutations, monitoring minimal residual disease, and identifying resistance mutations. For instance, in non-small cell lung carcinoma, liquid biopsy is applicable to track EGFR T790M mutations subsequent to epidermal growth factor receptor tyrosine kinase inhibitor treatment. Nevertheless, circulating tumor DNA could be restricted by low quantity, swift degradation, and reliance on tumor load or anatomical position.

Exosomes have gradually become a high-potential auxiliary liquid biopsy carrier compared with other detection markers. Extracellular vesicles are mainly composed of exosomes, microparticles, and apoptotic vesicles. Exosomes are minuscule membrane-surrounded vesicles, usually ranging from 30 to 150 nm in dimension. They are generated through the endosomal pathway and released upon the fusion of multivesicular bodies with the cell membrane. Micro-scale vesicles typically possess a greater size and directly form buds from the plasma membrane. In comparison, apoptotic bodies are released during the course of apoptosis and may contain nuclear fragments or organelles. Since exosomes are surrounded by a stable lipid-bilayer membrane, the substances within them are protected from enzymatic degradation. Exosomes can transport DNA, mRNA, microRNA, long non-coding RNA, circular RNA, proteins, lipids, and metabolites, thereby reflecting the molecular characteristics of the cells they originate from [2, 3].

Present research verifies that exosomes bring about two-way impacts in tumor growth and clinical treatment. Exosomes originating from tumors may potentially promote the progression of cancer by mediating the communication between tumor cells and the nearby stromal or immune cells. They engage in immune evasion, blood vessel formation, invasion, metastasis, and drug resistance. Simultaneously, exosomes might also act as valuable diagnostic indicators and treatment instruments. Particular exosomal molecular markers can aid in cancer screening, prediction of tissue of origin, treatment categorization, and prognosis assessment. Furthermore, engineered exosomes can be crafted to convey therapeutic molecules to neoplastic cells or immune cells.

Published reviews mostly conduct independent discussions on exosome biogenesis, single diagnostic applications or simple drug loading functions, lacking systematic sorting of their dual pro-tumor and anti-tumor properties. Consequently, this paper sums up the molecular mechanisms through which exosomes modulate the tumor microenvironment, assesses their clinical and translational proof as liquid biopsy biomarkers and therapeutic carriers, and deliberates on the main challenges that need to be tackled before exosome-based technologies can be extensively used in precision oncology.

2. Molecular mechanisms of bidirectional exosomal functions in tumor

2.1. Pro-tumor biological effects of tumor-derived exosomes

The tumor microenvironment consists of tumor cells, immune infiltrates, vascular endothelial cells, cancer-associated fibroblasts and extracellular matrix components, among which exosomes act as core soluble signaling messengers to transmit bioactive cargo between donor and recipient cells. In most malignant tumor models, tumor-originated exosomes remodel local and distant microenvironments to accelerate malignant progression.

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The first core pro-tumor pathway is immunosuppressive regulation. Tumor exosomes carry abundant TGF-β, PD-L1 and miR-155; after being internalized by immune cells, these molecules activate STAT3 and NF-κB signaling cascades to induce M2-type macrophage polarization. M2 macrophages produce anti-inflammatory effects, encourage vascular growth and suppress the activation of cytotoxic T cells. Together, they create an immune-suppressive microenvironment that is favorable for tumor survival and multiplication.

Secondly, exosomes stimulate pathological angiogenesis during hypoxic stress. Tumor cells facing nutrient shortage or chemotherapeutic stress release exosomes abundant in angiogenic microRNAs and lipid mediators. These vesicles are taken up by endothelial cells to trigger VEGF and hypoxia-associated signaling, promoting endothelial cell proliferation and the formation of tubular structures. Irregularly shaped tumor blood vessels offer nutrients for the spread of lesions and create circulatory pathways for distant metastasis.

Thirdly, exosomes initiate epithelial-mesenchymal transformation to improve invasive ability. Exosomal cargo modulates cytoskeleton re-organization and matrix metalloproteinase release, reducing epithelial markers and increasing mesenchymal proteins to enhance tumor migration. Exosomes can also prompt normal fibroblasts to change into cancer-associated fibroblasts. These fibroblasts then secrete inflammatory factors to enhance invasive signals in the surrounding tissues.

Fourth, exosomes construct pre-metastatic niches in distant organs. Primary tumor exosomes enter systemic circulation and selectively accumulate in specific organs relying on surface integrin and glycoprotein profiles. After uptake by parenchymal cells of distant tissues, exosomes increase vascular permeability, recruit bone marrow-derived suppressor cells and reconstruct the extracellular matrix, forming a permissive microenvironment for circulating tumor cell colonization.

Fifth, exosomes mediate horizontal transmission of drug resistance. Drug-resistant tumor cells release exosomes carrying efflux transporters, anti-apoptotic proteins and repair-related non-coding RNAs. After sensitive cells internalize these vesicles, they acquire persistent drug-resistant phenotypes, reducing the efficacy of chemotherapy, targeted therapy and immunotherapy simultaneously.

2.2. Context-dependent anti-tumor functions of exosomes

Although exosomes derived from tumors are frequently linked to cancer advancement, the function of exosomes is highly context-dependent. In certain biological or therapeutic situations, exosomes may exert anti-tumor effects. Their function depends on the kind of the parent cell, the molecular cargo, the target cell, the phase of the tumor, and the immune state of the microenvironment.

Exosomes produced by immune cells can enhance anti-tumor immune response. Exosomes originating from dendritic cells can carry major histocompatibility complex molecules, co-stimulatory molecules, and tumor-associated antigens. These extracellular vesicles could improve antigen presentation and initiate tumor-specific T-cell responses. Exosomes originating from natural killer cells could carry cytotoxic proteins and induce the demise of tumor cells. Consequently, exosomes obtained from immune cells are able to serve as natural agents for immune surveillance.

Some therapy-induced exosomes might also improve treatment sensitivity. For example, radiation therapy or chemical therapy can alter exosomal contents and promote the discharge of molecules that enhance immunogenic cell demise or activate innate immune routes. In hepatocellular liver cancer, it was reported that radiation-induced cancer-derived exosomal circTMEM56 enhanced the efficacy of radiotherapy through the miR-136-5p/STING axis [4]. This finding suggests that not all tumor-originated exosomes uniformly boost tumors; their effects may differ according to the treatment context and molecular composition.

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Engineered exosomes further enhance the anti-tumor ability of this vesicular system. By furnishing exosomes with tumor-inhibiting RNAs, small interfering RNAs, circular RNAs, proteins, or anti-cancer medications, researchers can turn exosomes into therapeutic vehicles. For instance, exosomes transporting circPRKD3 were shown to hinder STAT3 signaling, remodel the glioblastoma microenvironment, and restrain tumor growth [5]. Similarly, genetically engineered exosomes that transport focal adhesion kinase siRNA overcame resistance to cetuximab in colon cancer by blocking FAK-related pathways [6].

In general, the judgment of whether exosomes promote or suppress cancer relies on three principal factors. The primary element is the cell where it comes from. Exosomes coming from tumor cells, immune cells, mesenchymal stem cells, or dendritic cells may have various biological impacts. The second component is the molecular payload. Exosomes that convey oncogenic microRNAs, immunosuppressive proteins, or drug-resistance molecules usually facilitate cancer advancement. In contrast, those that carry tumor-suppressive RNAs or immune-activating molecules can exert therapeutic effects. The third factor is the state of recipient cells and the tumor micro-milieu. A milieu with immune suppression may augment pro-tumor effects, while a milieu with immune activation can foster anti-tumor responses. This duality associated with the context explains why exosomes must be comprehensively evaluated before their clinical application [7].

3. Exosomes as non-invasive biomarkers for tumor liquid biopsy

Liquid biopsy has become a vital component in precision oncology, allowing non-invasive and repeated tracking of tumor advancement. Unlike tissue biopsy, liquid biopsy is more suitable for dynamic assessment in the course of treatment. Currently, liquid biopsy analytes include circulating cancerous cells, circulating tumor DNA, cell-free ribonucleic acid, proteins, metabolites, and extracellular vesicles. Every analyte comes with benefits and drawbacks. Circulating cancer cells offer complete cellular details yet are scarce in peripheral blood. Circulating cancer-derived DNA is valuable for mutation analysis, yet it might be influenced by low quantity and quick elimination. Exosomes, in comparison, are fairly plentiful, structurally steady, and replete with molecular details.

Exosomal multi-molecular composite signatures better reflect tumor heterogeneity than single biomarkers. Exosomal microRNAs, long non-coding RNAs, circular RNAs, mRNAs, and proteins stay stable in body fluids as they are safeguarded by the exosomal membrane. These molecules are able to act as biomarkers regarding the initiation, progression, metastasis, treatment response, and prognosis of cancer. In comparison with individual biomarkers, multi-molecule exosomal profiles are able to more efficiently capture the heterogeneity of tumors and improve diagnostic efficacy.

Recent multi-site research has provided more substantial evidence for exosome-based liquid biopsy. A multi-step, multi-site study analyzed plasma exosomal RNA from patients suffering from eight types of cancer, including breast cancer, colorectal cancer, and pancreatic cancer. Researchers utilized machine learning to identify a 12-marker exosomal tumor RNA pattern. This diagnostic model distinguished cancer patients from healthy individuals with an area under the receiver-operating characteristic curve of 0. 915. It also predicted the tissue source with a macro-AUC of 0. 983 [8]. These discoveries suggest that the features of exosomal RNA may be advantageous for the early detection of multiple cancers and the localization of tumors.

Exosomal microRNAs are also able to predict therapeutic response. The EXONERATE study investigated the value of cell-free plasma microRNAs and exosomal microRNAs in patients with RAS wild-type metastatic colorectal cancer receiving first-line chemotherapy. The study identified a molecular profile composed of eight free microRNAs and nine exosomal microRNAs. This signature predicted progression-free survival, overall survival, and objective response rate after

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cetuximab or panitumumab treatment [9]. In contrast to choosing treatments based only on the location of the primary tumor, this exosome-related signature can improve the precision of anti-EGFR therapy selection and reduce unnecessary treatment.

Even if there are such promising findings, exosome-focused liquid biopsy still faces a number of hurdles. Pre-analytical factors, such as sample type, blood collection tubes, storage temp, processing time, and freeze-thaw cycles, can influence exosome concentration and cargo composition. Methods for separation vary significantly too. Ultra-high-speed centrifugation, size-exclusion chromatographic methods, polymer precipitation approaches, immunoaffinity capture strategies, and microfluidic technologies differ in terms of output, purity level, cost, and reproducibility. In complex biological fluids, lipoproteins, protein aggregates, and other extracellular particles may potentially pollute exosome isolations. Furthermore, various detection platforms for RNA, proteins, or lipids could produce inconsistent results. Consequently, standardized protocols for specimen gathering, exosome isolation, molecular recognition, and data interpretation are essential for clinical utilization.

4. Engineered exosomes as therapeutic delivery vehicles

Exosomes have several traits making them attractive as carriers for drug delivery. They are nanoscale vesicles that have natural lipid bilayer membranes, display low immunogenicity, possess good biocompatibility, and demonstrate potential tissue-targeting abilities. Compared with synthetic nanoparticles, exosomes may have better biological compatibility and can cross certain biological barriers more efficiently. By employing engineering methods, exosomes can be modified to improve cargo loading, targeting accuracy, and therapeutic efficacy.

Approaches for therapeutic exosomes can be divided into two primary categories. The first method makes use of the built-in biological activity of exosomes derived from certain cell types. The second method utilizes exosomes as carriers for chemotherapeutic drugs, nucleic acids, proteins, or immunomodulating agents. Exosomes derived from mesenchymal stem cells are among the most extensively investigated platforms since they are relatively simple to obtain and may possess tumor-targeting properties. A starting clinical method utilized mesenchymal stem cell-derived exosomes to carry siRNA targeting the KRAS G12D mutation for the therapy of pancreatic cancer. This approach aims to suppress a key oncogenic activator and present a new option for a form of cancer with restricted treatment choices.

Exosomes can also be filled with chemotherapeutic drugs. Prior to-clinical investigation has shown that doxorubicin, paclitaxel, and other anti-cancer medications can be incorporated into exosomes through electroporation, sonication, incubation, or chemical transfection. The exosome membrane can protect drugs, improve biodistribution, increase tumor accumulation, and reduce toxicity to normal tissues. Surface alteration, such as ligand display, antibody conjugation, or membrane protein change, can further enhance tumor targeting.

Transport of nucleic acids represents another notable approach in exosome-based therapy. Exosomes can deliver microRNAs, anti-microRNAs, siRNAs, mRNAs, and circular RNAs to regulate tumor-related gene expression. For example, exosome-mediated delivery of miR-146b inhibited the growth of glioma. The delivery of anti-miR-9 increased chemotherapy resistance in glioblastoma, and siRNA targeting Polo-like kinase 1 hindered bladder cancer development [10]. Engineered exosomes delivering FAK siRNA overcame cetuximab resistance in colon cancer by inhibiting FAK signaling and initiating paraptosis-like cell death [6]. These studies indicate that exosomes may help overcome therapeutic resistance by targeting specific oncogenic pathways.

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Circular RNA-related exosome therapy has also attracted attention. In hepatocellular-type liver cancer, radiation-induced exosomal circTMEM56 promoted anti-tumor immune response through the miR-136-5p/STING axis and improved the effectiveness of radiotherapy [4]. Based on this principle, investigators carried out a further exploration of the delivery of synthetic circTMEM56 through the utilization of brain-targeted lipid nanoparticles in conjunction with anti-PD-1 therapy. Animal experiments showed prolonged survival in tumor-bearing mice [4]. In glioblastoma, exosomes transporting circPRKD3 hindered STAT3 signaling, reduced immune suppression, and restricted tumor growth [5]. These findings indicate that exosome-based nucleic acid delivery is capable of modulating both tumor-specific signaling and the immune microenvironment.

Exosomes are also capable of serving as cancer vaccines or immunotherapy platforms. Dendritic cell-derived exosomes can carry tumor-associated antigens and cytokines, thereby initiating antigen-specific anti-tumor immune responses. Early clinical studies in renal cell carcinoma and colorectal cancer showed that exosome-based vaccines obtained from dendritic cells have immune-activating properties, even when the sample sizes were restricted. In an alternative approach, exosomes obtained from breast cancer cells were engineered to carry immunogenic cell death inducers and Toll-like receptor 3 agonists, during which the breast cancer-associated antigen alpha-lactalbumin was presented. Trials in animal model systems and patient-derived tumor organoids demonstrated that these engineered exosomes reformed the tumor microenvironment and promoted dendritic cell- and CD8-positive T-cell-mediated anti-tumor immune responses.

However, the utilization of therapeutic exosomes continues to present technical difficulties. High-volume manufacturing and quality control present notable challenges. The makeup of exosomes is affected by the kind of parental cells, cell cultivation conditions, collection moment, and the purification process. Conditions of good manufacturing practice demand strict control of sterility, endotoxin levels, particle size distribution, purity, potency, and stability. Ways of drug loading also need improvement. Electroporation may result in RNA aggregation or membrane damage. Sonication has the potential to alter membrane-associated proteins, and chemical transfection may introduce toxic residues. As a result, gentler and more flexible loading methods are required.

The distribution within the body and long-term safety remain unclear. After systemic administration, exosomes may be rapidly cleared by the liver, spleen, and reticuloendothelial system, or they could accumulate in non-target organs. Different exosome sources may have diverse immunogenicity and biological effects. Before clinical application, therapeutic exosomes require a thorough evaluation of pharmacokinetics, biodistribution, toxicity, immunogenicity, and long-term outcomes.

In the future, technological progress could integrate exosomes with lipid-based nanocarriers, microfluidic manufacturing methods, and state-of-the-art protein-loading approaches. Methods based on exosomes may eventually support an integrated precision oncology model that connects early diagnosis, treatment classification, targeted drug delivery, and real-time treatment surveillance.

5. Conclusion

Exosomes have two-way regulatory impacts that span tumor progression and accurate clinical intervention during the entire course of malignant disease evolution. Exosomes secreted by tumors reshape suppressive microenvironments to facilitate angiogenesis, metastasis, and the transmission of intercellular drug resistance. Meanwhile, steady exosomal biomolecules can be utilized as liquid biopsy markers for early screening and efficacy surveillance, and artificially modified exosomes function as biocompatible targeted therapeutic vehicles loaded with various anti-cancer substances. Multi-vesicular exosomal markers achieve tumor classification and prognosis assessment, whereas

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engineered particles overcome delivery obstacles of nucleic acids and chemotherapeutic agents. However, numerous technical and standardization obstacles impede large-scale clinical conversion. There is a lack of consistent exosome isolation, purification, and molecular detection methods in different laboratories. Therapeutic exosomes encounter challenges in standardized large-scale production, controllable payload loading, and long-term biosafety evaluation. Subsequent interdisciplinary combination of fundamental medicine, clinical oncology, bioengineering, and large-scale data analysis is necessary to set up comprehensive technical guidelines, verified diagnostic marker sets, and secure exosome modification frameworks. Through continuous technological refinement, exosome-integrated platforms that combine non-invasive early detection and targeted treatment will offer comprehensive diagnosis and treatment plans for diverse solid tumors.

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