World Journal of Surgical Oncology

https://doi.org/10.1186/s12957-025-04135-z

Article in Press

Advances in the use of exosomes for the diagnosis and treatment of ovarian cancer

Received: 24 September 2025

Accepted: 24 November 2025

Published online: 05 December 2025

Cite this article as: Chen J. & Tan Q. Advances in the use of exosomes for the diagnosis and treatment of ovarian cancer. *World J Surg Onc* (2025). https://doi.org/10.1186/s12957-025-04135-z

Jiyu Chen & Qingqing Tan

Title page

Article title:

Advances in the use of Exosomes for the Diagnosis and Treatment of Ovarian Cancer

Short title for running head:

REVIEW OF EXOSOMES AND OVARIAN CANCER

Author:

Jiyu Chen

(Department of Gynecology and Obstetrics, Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University, Changzhou, China)

Corresponding Author:

Qingqing Tan

Mail: Department of Gynecology and Obstetrics, Changzhou Maternal and Child Health Care Hospital, 16 Dingxiang Road, Changzhou 213000, Jiangsu, China.

Telephone: +86-135884505335

Email: cztanqq@163.com

Abstract:

Ovarian cancer (OC) is the most lethal gynecologic malignancy, with insidious early symptoms and a lack of effective screening often leading to late-stage diagnosis and poor prognosis. Exosomes, extracellular vesicles carrying diverse bioactive molecules, play key roles in OC pathogenesis and progression. This review systematically outlines recent advances in exosome research, highlighting their dual potential as liquid biopsy biomarkers for early diagnosis and prognosis, and as natural drug delivery systems for targeted therapy. We also critically analyze the major challenges in clinical translation. Despite existing hurdles, exosome-based strategies hold significant promise for advancing precision medicine in OC.

Keywords: ovarian cancer; exosomes; biomarkers; diagnosis; targeted therapy

1. Introduction

Ovarian cancer (OC), one of the most common malignant tumors in the female reproductive system, ranks as the 7th most prevalent cancer among women globally and the 10th most common cancer among Chinese women(1). It has the highest mortality rate among gynecologic malignancies(2). Due to atypical early clinical manifestations and the lack of specific and sensitive diagnostic biomarkers, 70–90% of patients are diagnosed at advanced stages, missing the optimal treatment window. Consequently, OC is characterized by high recurrence rates, poor prognosis, and a 5-year survival rate of only 20–30%(3, 4). The World Health Organization (WHO) classifies OC into epithelial, germ cell, sex cord-stromal, and mesenchymal types.

Epithelial ovarian cancer (EOC) is the most common, accounting for approximately 90% of all cases and originating from the epithelial cells(5). OC is not a single disease but a group of histologically and molecularly distinct entities. Based on histotype-specific immunological features and molecular markers, EOC is further subdivided into high-grade serous carcinoma (HGSC), low-grade serous ovarian carcinoma (LGSOC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC). High-grade serous ovarian cancer (HGSOC) is the most prevalent and aggressive form of OC, responsible for approximately 70-80% of all EOC-related deaths(6). These histotypes differ in their cell of origin, molecular pathways, risk factors, clinical behavior, and response to therapy. Therefore, identifying diagnostic markers with high sensitivity and specificity to improve early detection rates, exploring the mechanisms underlying OC initiation, progression, and metastasis, and implementing standardized surgical interventions with adjuvant therapies are critical for increasing survival rates and quality of life in OC patients.

Traditional tumor diagnosis often relies on imaging and pathological examination of tissues; however, these screening strategies are invasive and carry an increased risk of organ injury. As an alternative to conventional biopsy, liquid biopsy is a representative diagnostic technology in precision medicine that enables noninvasive sampling to obtain disease-related information, thereby assisting in disease management. Exosomes, extracellular vesicles secreted by living cells that carry various genetic materials, such as nucleic acids and proteins, are widely distributed in diverse human bodily fluids and play a significant role in the field of liquid biopsy.

Exosomes are extracellular vesicles with diameters ranging between 30 and 150 nm that are ubiquitously distributed in various biofluids, such as cerebrospinal fluid, blood, saliva, urine, and ascites. They function as molecular cargo carriers, transporting diverse components, including microRNAs (miRNAs), circular RNA (circRNA), long noncoding RNAs (lncRNAs), DNAs, proteins, and enzymes(7). By shuttling biomolecules from donor to recipient cells, exosomes play an important role in cellular signaling(8). Notably, cancer cells secrete exosomes at significantly higher rates than normal cells (9), and tumor-derived exosomes have been extensively implicated in the initiation, progression, and biological behavior of OC.

This review outlines the roles of exosomes in OC, focusing on their dual value as reservoirs of diverse biomarkers (proteins, miRNAs, lncRNAs, circRNAs) and drug delivery systems. Unlike previous studies focused on single molecules, it integrates their mechanisms in carcinogenesis and progression, evaluates clinical translation in liquid biopsy and targeted therapy, and analyzes challenges from bench to bedside. It bridges gaps in multi-omics integration and translational pathways, proposing a framework for exosome-based precision medicine.

2. Overview of Exosomes

Exosomes are a subset of extracellular vesicles (EVs) first identified in cultured sheep reticulocytes(10) and were later termed "exosomes" by Johnstone to describe these small, double-membrane-enclosed vesicles(11). EVs are endosome-derived, lipid bilayer nanoscale vesicles secreted by various cell types, primarily including exosomes,

microvesicles, and apoptotic bodies. Owing to the lack of specific markers, exosomes are difficult to distinguish from other particles; hence, the term "exosomes" is often used to encompass all particles ranging from 30–150 nm in diameter(12).

Exosomes are present in almost all bodily fluids, including blood, sweat, tears, saliva, urine, breast milk, ascites, and cerebrospinal fluid, among others(7). Earlier researchers regarded exosomes as garbage bins for eliminating cellular waste(10). However, further investigations revealed that exosomes play significant roles in tumor growth, metastasis, angiogenesis, and immune regulation. Additionally, in the field of liquid biopsy, exosomes can serve as biomarkers for early tumor diagnosis, assessment of treatment response, prognosis evaluation, and monitoring of chemotherapy resistance(13).

2.1 Composition of Exosomes

Exosomes are composed primarily of various soluble proteins, nucleic acids, and lipids. They carry diverse proteins, including tetraspanins (CD82, CD81, CD63, and CD9), heat shock proteins (HSP70, HSP90), and proteins involved in membrane transport and fusion (such as the multivesicular body (MVB)-associated proteins Alix and TSG101, annexins, Rab GTPases, and flotillin)(14, 15). These proteins are not only associated with the biogenesis of exosomes but also serve as markers for their authentication.

Exosomes contain various nucleic acids (DNA and RNA). In addition to the most extensively studied mRNAs and miRNAs, other RNA types, such as lncRNAs, transfer

RNAs(tRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs(snoRNAs), and circRNAs, are also enriched within exosomes(16). Lipids such as cholesterol, phospholipids, sphingolipids, and ceramides form the bilayer membrane structure of exosomes(17).

2.2 Biogenesis of Exosomes

The classical process of exosome generation involves dual invagination of the plasma membrane and the formation of intracellular MVBs containing intraluminal vesicles (ILVs)(18). It originates from endocytosis of the plasma membrane, which then invaginates inward to form early endosomes that mature into late MVBs. These MVBs contain ILVs enriched with various proteins, lipids, nucleic acids, amino acids, and metabolites(19). Subsequently, the fate of MVBs can diverge. One subset of MVBs may fuse with lysosomes or autophagosomes, leading to the degradation of their ILVs content. The resulting degradation products can then be recycled by the cell. The precise mechanisms governing this pathway remain incompletely understood, and theories involving specific protein sorting have been proposed. Alternatively, another subset of MVBs is transported via the cytoskeleton and microtubule network to the plasma membrane. Upon fusion with the plasma membrane, these MVBs release their ILVs into the extracellular space through exocytosis. These released vesicles are defined as exosomes (18). Numerous proteins, such as Rab GTPases, endosomal sorting complexes required for transport (ESCRT) proteins, tetraspanins, and other proteins

that can serve as exosomal biomarkers, are involved in the origin and biogenesis of exosomes. Additionally, lipids, including phospholipids, ceramides, and sphingomyelinases, also participate in this process. Overall, the process of exosome biogenesis is highly complex. Although the mechanisms underlying exosome formation and secretion are not fully understood, aspects of their origin, composition, functions, and modes of action have been partially elucidated. (Figure 1)

Exosome formation occurs via two pathways: the ESCRT-dependent pathway and the ESCRT-independent pathway. The widely recognized mechanism of exosome formation is driven by the ESCRT machinery(20). The primary function of ESCRT is to sort specific components into ILVs, which are precursors of exosomes. Initially discovered in yeast, the ESCRT complex consists of approximately 20 proteins assembled into five functional subcomplexes (ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III, and the Vps4-VTA1 complex)(21). All subcomplexes interact closely, play distinct roles in exosome biogenesis, and are involved in local membrane remodeling processes such as viral budding, cytokinesis, and autophagy(22). The ESCRT-0 complex recognizes and sequesters ubiquitinated proteins on the endosomal membrane. The ESCRT-I and ESCRT-II complexes participate in the membrane invagination of MVBs and the formation of vesicles containing clustered ubiquitinated proteins. The ESCRT-III complex subsequently drives membrane scission and vesicle release from MVBs, whereas the Vps4 complex ensures final membrane abscission and/or recycling of ESCRT components(23, 24).

The ESCRT-independent pathway relies on lipid components, particularly

ceramide. Ceramide, produced by neutral sphingomyelinase, induces the budding of ILVs into MVBs(25). Additionally, tetraspanins such as CD63, CD9, and CD81 are involved in this process and promote exosome secretion(26). During this process, cholesterol also plays a regulatory role in MVB maturation. Studies have demonstrated that MVBs with high cholesterol content are preferentially routed to fuse with the plasma membrane of the parent cell, leading to the release of their intraluminal vesicles (exosomes) into the extracellular space. Conversely, MVBs with low cholesterol content are more likely to be directed toward fusion with lysosomes, resulting in their degradation(27). Experimental evidence indicates that both the ESCRT-dependent and ESCRT-independent pathways can coexist and operate concurrently within cells.(28)

2.3 Physiological Functions of Exosomes

Exosomes are ubiquitously present in bodily fluids and can be generated under both pathological and physiological conditions. They may serve as a cellular clearance mechanism to eliminate surplus and/or unnecessary components, thereby maintaining intracellular homeostasis(29). With respect to physiological functions, the central role of exosomes lies in mediating intercellular communication through the transfer of biomolecules and signals. Various cells achieve mutual communication by secreting exosomes laden with distinct molecular cargoes. These exosomes are internalized by recipient cells, facilitating information exchange and signal transduction via cargo transfer or the release of their contents(26). For instance, exosomes secreted by immune cells carry cytokines capable of modulating the immune activity of surrounding cells,

while stem cell-derived exosomes harbor specific proteins that promote the repair of damaged tissues. This mode of communication is highly targeted, as proteins on the exosomal membrane can specifically recognize receptors on the surface of target cells, ensuring the precision of information delivery(30).

In the field of disease research, the roles of exosomes are becoming increasingly elucidated. Tumor cells secrete exosomes at a significantly higher rate than normal cells, and these tumor-derived exosomes possess a remarkable capacity to drive tumor progression by remodeling both local and distant microenvironments(16). This underscores the pivotal role of exosomes in regulating intercellular communication, positioning them as key mediators of information exchange. Furthermore, by carrying cancer-specific biomarkers, exosomes hold immense potential for disease diagnosis and therapeutic applications.

2.4 Isolation and Detection of Exosomes

The isolation and detection of exosomes from biological samples are crucial for subsequent basic research and clinical translation. Common isolation methods include ultracentrifugation, ultrafiltration, size-exclusion chromatography (SEC), polymer-based precipitation, immunoaffinity capture, and microfluidic technology.

Ultracentrifugation separates particulate components on the basis of density, size, and shape through sequential processing, which can be categorized into density gradient centrifugation and differential centrifugation. Owing to its high processing capacity, it is currently considered the "gold standard" for exosome isolation. Ultrafiltration is a

size-based separation technique with simple operation and is often used in combination with ultracentrifugation. SEC is another size-based method in which substances are eluted according to their particle size. This technique preserves the natural biological activity of isolated exosomes(31). Polymer-based precipitation, which is frequently used in commercial kits, offers convenience in operation. Subsequent centrifugation and filtration of samples can increase the purity of exosome preparations(32). Immunoaffinity capture provides high specificity and yields exosomes of high purity but is suitable for only cell-free samples. Microfluidic technology refers to the use of devices that employ microfluidics to rapidly and efficiently isolate exosomes on the basis of various properties. In addition to common approaches such as size, density, and immunoaffinity, this technology enables innovative sorting mechanisms such as acoustic, electrophoretic, and electromagnetic manipulation(33, 34). Recent studies have proposed a high-throughput, rapid, ultrasensitive, and low-detection-level method for the quantitative analysis of exosomes, utilizing spatially patterned antibody barcodes based on carbon dots (CDs), self-assembled substrates, and microfluidic technology in combination with fluorescence-labeled specific antibodies. This approach not only enables the identification of exosomes but also confirms the expression of targeted membrane markers on exosomes. On the basis of the results of serum exosome detection, this method achieved a 100% accuracy in distinguishing OC patients from healthy donors(35). Although existing exosome isolation techniques have seen many improvements over time, they also present a series of new challenges for researchers in the field. The principles, advantages, and disadvantages of various

exosome isolation techniques are detailed in Table 1.

Characterization of exosomal cargo can reveal the unique composition of specific exosomes and provide accurate cancer-related information. Techniques commonly used for characterization include flow cytometry (FC), resistive pulse sensing (RPS), dynamic light scattering (DLS), electron microscopy (EM) techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and cryogenic electron microscopy (Cryo-EM),atomic force microscopy (AFM), and nanoparticle tracking analysis (NTA)(36). Protein detection technologies for exosomes include Western blotting and enzyme-linked immunosorbent assay (ELISA). Nucleic acid detection techniques include quantitative real-time reverse transcription PCR (qRT–PCR), microarrays, and sequencing(37). In summary, as an essential foundation for studying the biological characteristics and medical applications of exosomes, isolation techniques and subsequent identification methods still require further refinement.

3. Role of Exosomes in OC Pathogenesis

3.1 Formation of the Tumor Microenvironment (TME)

The tumor microenvironment (TME) refers to the dynamic niche formed by interactions between tumor cells and host stromal components, including cancer cells, endothelial cells, the microvasculature, immune cells, cancer-associated fibroblasts(CAFs), the extracellular matrix, and infiltrating biomolecules(38).

Crosstalk between tumor cells and stromal cells promotes angiogenesis, invasion, and metastasis, leading to tumor growth and invasion of other tissues. As a dominant stromal component, CAFs primarily mediate stromal activation and tumor desmoplasia, which are closely associated with increased metastatic potential and poor prognosis in patients with OC(39).

In addition to stromal cells, the tumor microenvironment also includes noncellular elements. Exosomes, critical components of the TME, are released by nearly all cell types and modulate tumor and host cell functions through different pathways. By orchestrating metabolic reprogramming, signal upregulation, and immune evasion, exosomes remodel the TME(40). OC-derived exosomes reconfigure the TME via intercellular transfer between cancer cells and normal stromal cells, immune cells, or CAFs, thereby stimulating metastatic invasion(41). As illustrated in Figure 2, this review will detail the multiple key roles exosomes play in shaping the TME, driving angiogenesis, promoting invasion and metastasis, and inducing immune evasion, among other pathogenic processes.

Tumor-associated macrophages (TAMs), the most abundant immune infiltrates in the TME, play pivotal roles in tumor cell proliferation and migration. Many studies have demonstrated that tumor-derived exosomal miRNAs regulate TAM polarization. M2 macrophages, which are characterized by the secretion of anti-inflammatory cytokines (e.g., CCL17, CCL22, and IL-10), promote cancer progression(42). Exosomal *miR-222-3p* and *miR-940* from EOC cells induce M2 macrophage polarization(43, 44). Under hypoxic conditions, exosomal *miR-125b-5p*, *miR-21-3p*,

miR-940, and *miR-181d-5p* from EOC cells drive TAM differentiation toward the M2 phenotype, accelerating cancer progression(44).

Collectively, these studies demonstrate that OC-derived exosomes are master regulators of the TME, primarily by reprogramming immune cells like TAMs towards a pro-tumorigenic M2 phenotype, which is pivotal for tumor progression.

3.2 Exosome-mediated Tumor Angiogenesis

Angiogenesis, the formation of new capillaries from preexisting vasculature, is a physiological process critical to embryogenesis, tissue repair, and organ regeneration. Tumor angiogenesis is driven by proangiogenic factors secreted by cancer cells that activate host endothelial cells to induce neovascularization(45). Unlike normal vessels, tumor vessels exhibit aberrant structural dynamics and hyperpermeability, ultimately losing polarity and tight junction integrity. This results in impaired vascular function, increased permeability, augmented cellular motility, and heightened metastatic potential(46). Angiogenesis plays a fundamental role in both normal ovarian physiology and the pathogenesis of OC. The tumor-derived vasculature supplies oxygen and nutrients to OC, facilitates tumor growth through ascites formation and metastatic dissemination, and is indispensable for peritoneal cavity colonization and metastasis(47).

Tumor-derived exosomes carry angiogenesis-associated proteins that induce phenotypic and functional alterations in endothelial cells and tumor microenvironment cells, increasing epithelial cell proliferation and migration to support vascular

formation. Studies have demonstrated that circulating exosomal *miR-205* is significantly upregulated in OC-derived exosomes, promoting angiogenesis in vitro and in vivo via the PTEN-AKT pathway(48). Hypoxia-induced exosomal *miR-130a* from OC cells enhance vascular endothelial cell proliferation and angiogenesis(49). Ye and colleagues revealed that the OC-derived exosomal circRNA nuclear factor IX (*circNFIX*) positively regulates tripartite motif-containing protein 44 (TRIM44) expression by targeting *miR-518a-3p* and that exosomal *circNFIX* promotes OC angiogenesis by regulating the JAK/STAT1 pathway through the *miR-518a-3p/TRIM44* axis(50). Additionally, Zhang and colleagues reported that prokineticin receptor 1 (PKR1)-positive exosomes exert proangiogenic effects by enhancing endothelial cell migration and tube formation. These findings suggest that PKR1 can be transferred to surrounding cells via exosomal uptake, inducing angiogenesis through intercellular communication and intracellular signaling(51). Studies have demonstrated that *lncRNA ATB (lncRNA ATB, activated by TGF-β)* can directly promote the development of OC. Exosomal *lncRNA ATB* derived from OC cells promotes tumorigenesis by facilitating angiogenesis within the tumor microenvironment via regulating the *miR-204-3p/TGFβR2* axis(52).In addition to tumor-derived exosomes, exosomes secreted by TAMs and CAFs have also been found to be involved in promoting angiogenesis and metastasis(53).

These findings underscore the close relationship between tumor angiogenesis and exosomes. Further research will improve our understanding of OC angiogenesis mechanisms, identify novel therapeutic targets, and ultimately reduce tumor recurrence

and metastasis.

3.3 Exosome Involvement in OC Invasion and Metastasis

Unlike most cancers that metastasize primarily via hematogenous or lymphatic routes, implantation metastasis is the predominant metastatic pathway in OC. The transcoelomic(metastasis via the peritoneal cavity) mechanism of OC involves the detachment of cancer cells from the primary lesion, resistance to anoikis (a form of programmed cell death triggered by detachment from the extracellular matrix), dissemination through ascitic fluid into the peritoneal cavity, adhesion of disseminated cells to the peritoneal surface via enhanced tissue affinity, invasion into mesothelial cells, subsequent colonization, and eventual growth at secondary sites(54). Accumulating evidence highlights epithelial–mesenchymal transition (EMT) as a critical event in OC metastasis, enabling tumor cells to achieve systemic spread via intraperitoneal implantation and hematogenous routes. EMT, characterized by the loss of epithelial polarity and the acquisition of mesenchymal traits, confers invasive and metastatic potential to cancer cells during tumor progression.

OC-derived exosomes transfer CD44 to peritoneal mesothelial cells, reprogramming them into an EMT phenotype to promote OC cell invasion and migration(55). Ascites-derived exosomes deliver *miR-6780b-5p* to OC cells, which has been demonstrated to induce EMT and accelerate metastasis(56). Furthermore, omentum-derived exosomes confer chemoprotection to EOC cells and drive EMT and invasion by downregulating E-cadherin and upregulating N-cadherin (57). Adipose

tissue-derived exosomal *miR-421* serves as a novel regulator of chromobox 7 (CBX7) expression; downregulation of CBX7 promotes OC cell migration and enhances metastatic potential(58). Recent studies revealed that collagen type VI alpha 3 chain (COL6A3), which is secreted via exosomes from OC cells and the tumor stroma, is upregulated and may potentiate OC cell invasion and metastasis(59).

Furthermore, other non-coding RNAs such as circRNAs and lncRNAs are also recognized as major regulators of tumor metastasis, including in OC (60).For example, exosomal *circWHSC1(circWHSC1, derived from the Wolf-Hirschhorn syndrome candidate 1 gene)* promotes MUC1 expression, peritoneal dissemination, and adhesion, thereby facilitating OC metastasis(61). Mesothelial–mesenchymal transition(MMT) of mesothelial cells has also been shown to be involved in cancer cell adhesion and peritoneal colonization(62) . Wang and colleagues identified an uncharacterized lncRNA, *SPOCD1-AS(SPOC D1 Antisense RNA)*, in OC cell-derived EVs, which regulate the MMT phenotype in mesothelial cells, thereby promoting cancer cell adhesion to mesothelial cells in vitro and facilitating peritoneal metastasis in vivo(63).

In summary, exosomes play a central role in driving OC invasion and peritoneal metastasis by precisely orchestrating key biological processes, including EMT and MMT, through the delivery of critical functional molecules such as CD44 and various non-coding RNAs.

3.4 Exosomes Drive the Proliferation of OC Cells

Exosomes directly stimulate OC cell proliferation, which is crucial for primary

tumor growth and metastasis. They carry specific molecules that activate proliferative pathways. For instance, downregulated exosomal *miR-543* from OC cells targets insulin-like growth factor 2 (IGF2), inhibiting proliferation via the proteoglycan pathway, revealing its tumor-suppressive role(64). Conversely, tumor-derived exosomes often carry oncogenic molecules. Exosomal *circRNA051239* promotes proliferation and migration by acting as a ceRNA for *miR-509-5p* to regulate serine protease 3 (PRSS3) expression(65). Similarly, M2 macrophage-derived exosomes deliver *circTMCO3(Transmembrane and coiled-coil domains 3)*, enhancing proliferation and metastasis by targeting the *miR-515-5p/ITGA8* axis(66). Lai and colleagues found that exosomal *lncRNA SOX2-OT (SOX2 overlapping transcript)* is upregulated in OC patient plasma and promotes malignant phenotypes through the *miR-181b-5p/SCD1* axis (67). Additionally, exosome-associated proteins like cellular retinoic acid binding protein 2(CRABP2) are upregulated in OC and enhance recipient cell proliferation by inducing fatty acid oxidation-related genes (68).

In summary, exosomes drive OC proliferation by delivering diverse bioactive molecules (non-coding RNAs and proteins), providing direct molecular impetus for tumor expansion while synergizing with their pro-invasion and pro-metastasis functions to collectively drive disease progression.

3.5 Exosome-mediated Immune Evasion in OC

Immune evasion is a pivotal mechanism enabling sustained tumor growth and

metastasis. Tumor cells evade immune surveillance and attack through various strategies, including inducing the polarization of immunosuppressive cells, carrying and transferring immunosuppressive molecules, and orchestrating the immune microenvironment via non-coding RNAs(69).

Multiple studies have demonstrated that tumor-derived exosomes are key contributors to the formation of an immunosuppressive TME, thereby promoting immune evasion in OC. OC-derived exosomes can induce macrophage polarization toward the M2 phenotype, fostering an immunosuppressive milieu. For instance, exosomes from OC cells carry *miR-205* and deliver it to macrophages. Exosomal *miR-205* downregulates PTEN expression, activating the PI3K/AKT/mTOR signaling pathway and subsequently inducing M2-like macrophage polarization. In mouse models, these exosome-induced M2 macrophages significantly accelerated OC progression(70). Similarly, tumor-derived exosomal Chemokine-like factor (CKLF)-like MARVEL transmembrane domain-containing 4 (CMTM4) can be internalized by macrophages, promoting M2 polarization via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway activation, upregulating intercellular adhesion molecule-1(ICAM1) expression, enhancing the secretion of immunosuppressive cytokines, and ultimately suppressing T-cell function to facilitate tumor progression(71). Furthermore, extracellular vesicles secreted by TAMs foster an immunosuppressive microenvironment conducive to OC progression. Studies have demonstrated that downregulation of tumor-associated macrophage-derived exosomal *miR-29a-3p* modulates the FOXO3-AKT/GSK3β axis to increase PD-L1 expression,

ultimately suppressing OC cell proliferation and immune evasion(72). Exosomes derived from M2-type TAM are enriched with the *lncRNA NEAT1(Nuclear enriched abundant transcript 1)*. These exosomes deliver *NEAT1* to OC cells, where it acts as a molecular "sponge" for *miR-101-3p*, leading to upregulated expression of downstream zinc finger E-box binding homeobox 1 (ZEB1) and PD-L1 proteins, ultimately promoting OC cell proliferation and inducing CD8+ T-cell apoptosis(73).

Exosomes can directly inhibit T-cell function by carrying immune checkpoint molecules. Checkpoint proteins such as PD-L1 and CD47 are pivotal mediators of immune evasion. CD47 overexpression is associated with a poor prognosis in OC patients, underscoring the importance of immune evasion. Inhibition of exosome secretion and uptake can enhance the phagocytic capacity of M1 macrophages against cancer cells, thereby suppressing peritoneal dissemination(74). *HOXA transcript at the distal tip (HOTTIP)*, a homeobox-containing lncRNA, plays a critical role in the progression of OC. Studies have shown that *HOTTIP* overexpression upregulates the expression and secretion of IL-6 in OC cells. IL-6 binds to the IL-6 receptor on the surface of neutrophils surrounding cancer cells, activating the STAT3 signaling pathway. This leads to increased PD-L1 expression on neutrophils, which further suppresses T-cell activity, promotes immune evasion in OC, and ultimately facilitates cancer cell growth and metastasis(75, 76).

As important carriers of non-coding RNAs, exosomes deliver these regulatory molecules into target cells, where they post-transcriptionally modulate gene expression and participate in the complex network of immune evasion. Zheng and colleagues

reported that cancer-associated adipocyte-derived exosomes upregulate *long intergenic non-coding RNA 1119* (*LINC01119)* expression, which increases suppressor of cytokine signaling 5(SOCS5) levels in OC. *LINC01119*-loaded cancer-associated adipocyte-derived exosomes induce M2 macrophage polarization, suppress CD3+ T-cell proliferation, increase PD-L1 expression, and attenuate T-cell cytotoxicity in OC cells, thereby promoting immune evasion(77). A recent study identified that exosomes secreted by highly invasive OC cells are enriched with *hsa-miR-328-3p*. These exosomes transfer the miRNA to less invasive cells, where it interferes with Raf1, disrupts the mTOR pathway, and promotes autophagy, thereby enhancing their invasive capacity(78). Although this study primarily focused on invasiveness, the mechanism of exosomal miRNA transfer elucidates a potential pathway relevant to immune evasion. Another study found that TAM-derived extracellular vesicles can deliver the transcription factor (GATA3) to OC cells. Upon entry, GATA3 upregulates the CD24/Siglec-10 axis, promoting tumor cell immune evasion and conferring cisplatin chemoresistance(79). Collectively, these studies indicate that exosomes, via their specific molecular "cargo," can precisely regulate downstream signaling pathways to ultimately establish an immunosuppressive TME.

While some studies suggest the immunostimulatory potential of exosomes, the majority of evidence confirms their role in promoting immune evasion. The key determinants underlying this functional dichotomy, and strategies to exploit or engineer exosomes for enhancing anti-tumor immune responses, remain incompletely understood and warrant further investigation.

3.6 Exosome-Mediated Metabolic Reprogramming in OC

Metabolic reprogramming is a hallmark of cancer and an adaptive mechanism through which rapidly growing cancer cells meet their increasing energy demands, thereby facilitating rapid tumor growth and proliferation(80). In the TME of OC, exosomes coordinate this process. Recognized as key mediators of cancer progression, exosomes deliver bioactive cargo to modulate the metabolic state of recipient cells. By reprogramming the metabolism of both cancer cells and surrounding stromal cells, they promote cancer progression, angiogenesis, metastasis, drug resistance, and immunosuppression.

A key mechanism involves the regulation of glucose metabolism. Dysregulation of enzymes involved in glycogen metabolism is associated with the proliferation, migration, and invasion of tumor cells, ultimately leading to malignancy(81). Proteoglycan dysregulation contributes to cancer development, with epigenetic alterations, including changes in miRNA-mediated processes and RNA methylation, implicated in the proliferation of various invasive cancers. A study revealed that exosomes downregulate *miR-543* via methylation, thereby rescuing the inhibition of IGF2. By engaging the proteoglycan signaling pathway, this mechanism ultimately promotes OC proliferation(64).

Additionally, exosomes contribute to lipid metabolic reprogramming. They can transport lipids and enzymes involved in lipid synthesis to recipient cells, supporting

membrane biogenesis and energy storage. CRABP2 affects the mitochondrial oxidation phosphorylation. It is possible that CRABP2 as an exosome protein could affect the neighboring cell and microenvironment, which resulted in escaping from immunosurveillance and drug resistance by reprogramming cell metabolism(68).

In summary, exosomes drive metabolic reprogramming in OC by modulating glucose, lipid, and amino acid metabolism, thereby underpinning malignant processes such as tumor growth, metastasis, and drug resistance.

3.7 The Role of Exosomes in Mediating Drug Resistance in OC

Chemoresistance, particularly to platinum-based agents, is a major challenge in OC management. Exosomes have been shown to transmit the resistant phenotype from resistant to sensitive cells, thereby facilitating the establishment and spread of chemoresistance, making them a crucial research area for overcoming this issue(82).

Acting as intercellular messengers, exosomes directly confer resistance by transferring functional molecules, with ncRNAs playing a pivotal role (83). For instance, *miR-223* is abundant in exosomes derived from TAMs under hypoxic conditions and can enhance chemoresistance in EOC cells via the PTEN-PI3K/AKT signaling pathway(84). The *lncRNA UCA1(urothelial cancer associated 1)* is upregulated in serum exosomes from cisplatin-resistant patients and mediates cisplatin resistance by modulating the *miR-143/FOSL2* axis in OC(85). Conversely, ascites-

derived exosomal *lncRNA PLADE(Platinum sensitivity-associated lncRNA in ascites-derived exosomes)* promotes cisplatin sensitivity by inhibiting cell proliferation, migration, and invasion, while enhancing apoptosis both in vitro and in vivo(86). Similarly, exosomal circRNAs have been shown to mediate chemoresistance by influencing processes such as the cell cycle, apoptosis, and autophagy(87). For example, *hsa_circ_0010467* promotes platinum resistance via the *AUF1/miR-637/LIF/STAT3* axis, revealing a potential therapeutic target(88).

Furthermore, exosomes indirectly foster resistance by modulating key processes in recipient cells, including DNA damage repair, apoptosis, EMT, and remodeling the tumor immune microenvironment. For example, exosomes highly enriched with DNA methyltransferase 1 (DNMT1) promote tumor resistance(89).

In summary, exosomes play a pivotal role in driving chemoresistance in OC. Targeting their biogenesis or functional pathways may offer novel therapeutic strategies for reversing drug resistance.

4. Role of Exosomes in OC Diagnosis and Therapy

4.1 Early Screening and Diagnosis

Owing to nonspecific clinical symptoms and the lack of effective early screening methods, approximately 80% of OC patients are diagnosed at advanced stages, and the

5-year survival rate is only 20–30%(4). Thus, identifying biomarkers and screening modalities with high sensitivity and specificity for early diagnosis is critically important and may greatly improve the prognosis of many OC patients. Exosomes can be stably present in biofluids such as serum and ascites and are promising noninvasive biomarkers for early diagnosis owing to their low acquisition cost and noninvasiveness.

Studies have indicated that exosomal miRNAs represent promising diagnostic biomarkers for OC. Compared with those under normal or benign conditions, the serum levels of miRNAs (such as *miR-141*, *miR-200a*, *miR-200b*, and *miR-200c*) are increased in OC patients. The concentrations of serum exosomal *miR-200a, miR-200b, and miR-200c* can distinguish patients with EOC from healthy women, as well as differentiate malignant from benign ovarian tumors. Their expression levels may also correlate with OC staging, with more advanced tumors exhibiting lower *miRNA-200c* and higher *miRNA-141* levels(90, 91). Furthermore, the expression of exosomal *miR-93, miR-145, and miR-200c* is significantly elevated in the serum of OC patients. The areas under the receiver operating characteristic (ROC) curve for *miR-145, miR-200c,* and *miR-93* were 0.910, 0.802, and 0.755, respectively. *MiR-145* demonstrated excellent sensitivity (91.6%), suggesting that serum exosomal *miR-145* may be the most promising biomarker for the preoperative diagnosis of OC(92). Another study reported that, compared to the benign ovarian tumor group, *miR-1290* was significantly overexpressed in both serum exosomes and tissues of the EOC group. The area under the curve (AUC), sensitivity, and specificity for serum exosomal *miR-1290* were 0.794, 69.2%, and 87.3%, respectively. Despite a small sample size and lack of pathological

analysis, serum exosomal *miR-1290* could still be considered a potential biomarker for the differential diagnosis of benign ovarian tumors and EOC(93). Liu and colleagues found that plasma-derived exosomal *miR-4732-5p* demonstrated 85.7% sensitivity, 82.4% specificity, and an AUC of 0.889 in distinguishing OC patients from healthy controls, indicating its promise as a non-invasive diagnostic biomarker(94).

Exosomal proteins are highly enriched in carcinogenesis-related signaling pathways. Currently, HE4 and CA125 remain the primary serum biomarkers for OC diagnosis, offering good sensitivity but poor specificity. Chen and colleagues found that the combination of serum exosomal CA125 and serum HE4 improved the diagnostic efficiency for OC(95). Furthermore, many proteins are overexpressed in both tissues and exosomes, such as tubulin beta 3 class III (TUBB3), epithelial cell adhesion molecule (EpCAM), claudin 3 (CLDN3), proliferating cell nuclear antigen (PCNA), EGFR, apolipoprotein E (APOE) and fatty acid synthase (FASN), may serve as diagnostic markers or therapeutic targets for OC(96). In a study of the role of exosomes in the noninvasive diagnosis of OC, Zhang and colleagues validated the overexpression of APOE and EpCAM in serum exosomes from EOC patients and reported that their ELISA expression profiles align with those of proteomic analyses. These findings confirm the presence of OC tissue-associated proteins in serum exosomes, laying the groundwork for further biomarker exploration(97). The exosomal protein CRABP2 is particularly highly expressed in OC and is more closely associated with patient survival. It can even distinguish OC from low malignant potential (LMP) tumors and LGSOC, suggesting that exosomal CRABP2 may be a promising diagnostic and prognostic

biomarker for OC(68, 98).

CircRNAs are enriched and stable within exosomes in the circulatory system and can serve as molecular biomarkers for tumor diagnosis， such as *circ-0001068*, *circ-Foxo3(Forkhead box O3)* and *circFoxp1*, have led to increasing evidence indicating the diagnostic value of circRNAs in OC(99-101). Additionally, lncRNAs, including *ATB*(52) and *SOX2-OT*(67), have demonstrated potential as biomarkers for the early diagnosis of OC.

To systematically summarize the most promising exosomal biomarkers reported in recent studies for OC diagnosis, prognosis, and treatment, we have compiled the following four tables (Tables 2-5). These tables detail the biomarker type, specific molecule, source of exosomes, expression change, functional effects on OC, and potential clinical utility, providing a concise and valuable reference for readers.

These findings collectively underscore the considerable promise of exosomes as biomarkers for cancer diagnosis; however, extensive further research is necessary to translate this potential into clinical applications.

4.2 Prognostic Evaluation

Accurate prognostic evaluation can guide treatment decisions, improve outcomes, and reduce recurrence rates in OC patients. Yang and colleagues assessed the prognostic value of plasma exosomal caveolin 1(CAV1) in OC and reported significant downregulation of exosomal CAV1 levels in patient plasma. Low exosomal CAV1

levels are significantly correlated with FIGO stage, tumor grade, lymph node metastasis and prognosis, suggesting that plasma exosomal CAV1 is a potential prognostic biomarker for OC(102). EOC is the most aggressive and lethal OC. Zhang and colleagues reported that both fibrinogen gamma chain (FGG) and lipopolysaccharide binding protein (LBP) could be used to predict the prognosis of EOC patients via proteomic analysis of EOC plasma exosomes. Elevated mRNA expression of FGG or LBP was associated with shorter progression-free survival and overall survival, indicative of poorer prognosis in EOC patients(103).

Li and colleagues reported that high levels of *miR-149-3p* and *miR-222-5p* in peritoneal exosomes derived from EOC were associated with reduced 5-year survival and overall survival in EOC patients. A high level of miR-1246 was also linked to lower survival rates in EOC patients, although this association was not statistically significant. Therefore, peritoneal exosomal *miR-149-3p, miR-222-5p*, and *miR-1246* may represent novel biomarkers for the diagnosis and prognostic assessment of OC patients(104).

Research has found that *hsa_circ_0010467* is highly expressed in both tissues and plasma exosomes of platinum-resistant patients, and its high expression is correlated with poor survival, suggesting that *hsa_circ_0010467* could be a promising biomarker for predicting prognosis in OC patients receiving platinum-based chemotherapy(88). Yin and colleagues demonstrated that increased expression of *circ_C20orf11* in serum exosomes was associated with advanced FIGO stage, high histological grade, and significant lymph node metastasis in EOC patients. Furthermore, exosomal *circ_C20orf11* expression was significantly upregulated in the serum of cisplatin

(DDP)-resistant patients compared to the DDP-sensitive cohort, and patients with excessively high exosomal *circ_C20orf11* had significantly lower survival rates. These findings provide valuable clues supporting the application of exosome-derived circRNA cargo as clinical markers in EOC(105). Additionally, an independent predictor of OS rate in OC patients is elevated exosomal *lncRNA MALAT1*, which was found to be substantially associated with the progression and metastatic phenotype of OC. Overexpression of serum exosomal *MALAT1* indicates a poorer prognosis in EOC patients and can serve as a promising predictive indicator for EOC prognosis(106).

Beyond the prognostic value of single exosomal molecules, recent advances in bioinformatics and machine learning have enabled the construction of comprehensive exosome-related gene signatures, offering a more robust and multifaceted approach for predicting outcomes in OC patients.

A typical example is the exosome-related gene risk model (ERGRM) developed by Zhu and colleagues, which effectively stratified patients into low-risk and high-risk groups with significantly different overall survival. The high-risk group, characterized by a more immunosuppressive tumor microenvironment, exhibited a poorer prognosis, indicating that the ERGRM is closely related to immune infiltration. It can effectively predict the prognosis of OV patients and guide the selection of immunotherapy strategies(107). Building on this, the integration of lncRNAs further optimizes prognostic prediction. Another study employed machine learning algorithms to construct an Exosome-related LncRNA Signature (ERLS) model. This signature not only served as an independent prognostic factor but was also closely associated with

the tumor immune landscape. Importantly, patients in the low-risk group exhibited higher tumor mutational burden, greater immune cell infiltration, and increased expression of immune checkpoint molecules such as PD-1 and cytotoxic T-lymphocyte-associated protein 4（CTLA-4）. Specifically, patients with low PDL1 or high CTLA4 expression combined with a low ERLS had the best prognosis. This suggests that the combination of PDL1 or CTLA4 with the ERLS can distinguish prognosis and optimize the clinical management of OC(108). Zhu and colleagues established a prognostic model for OC patients based on Immune-related OC-derived Exosomes (IOCEs) and found that the IOCE-low subgroup had a favorable prognosis, while the IOCE-high subgroup exhibited higher levels of immune cell infiltration and immune response. These findings may contribute to the development of immunotherapy-based interventions for OC patients(109).

In summary, these novel studies signify a paradigm shift from single-marker analysis towards multi-dimensional, exosome-based prognostic models. They not only achieve superior predictive accuracy but also provide valuable insights into the underlying biological mechanisms and patient immune status, paving the way for more personalized and effective management strategies for OC.

The exosomal molecules discussed in this section, along with numerous other promising candidates with prognostic value, are systematically summarized in Tables 2-5, providing a comprehensive overview of this rapidly advancing field.

4.3 Therapeutic Applications

4.3.1 Exosomes as Drug Delivery Vehicles

Surgery and chemotherapy remain the primary treatments for OC. However, patients usually relapse due to chemotherapy resistance. Exosomes are considered ideal drug delivery vehicles for targeted cancer therapy owing to their superior stability and inherent targeting capability. These properties enable them to overcome existing pharmacokinetic complications, evade the immune system, and facilitate the delivery of a broad range of therapeutic agents, including small molecules, siRNAs, and gene-editing tools such as CRISPR–Cas9.

For example, Kim and colleagues demonstrated that encapsulating paclitaxel in exosomes from $MDCK_{MDR1}$ (Madin-Darby canine kidney cells overexpressing the multidrug resistance protein 1)cells enhanced drug solubility and cytotoxicity by over 50-fold, overcoming P-glycoprotein-mediated drug efflux(110). Li and colleagues engineered hybrid nanoparticles by fusing liposomes with exosomes to co-deliver *miR-497* and tiptolide (TP). These nanoparticles selectively inhibited the PI3K/AKT/mTOR pathway in OC cells, promoted M1 macrophage polarization, and effectively overcame chemoresistance in both in vitro and in vivo models(111). Exosomes can be engineered to overexpress specific miRNAs or carry specific siRNAs, which are incorporated into the exosomal cargo and delivered in vivo to specifically target diseases. Studies have demonstrated that patient-derived exosomes can be utilized as therapeutic siRNA delivery vehicles for the treatment of OC. Exosomes collected from patient-derived

fibroblasts were employed as carriers of tumor-suppressive siRNA, enabling targeted delivery of encapsulated siRNA to intraperitoneal tumors in mouse models of OC. The siRNA was shown to inhibit the peritoneal dissemination of OC cells and prolong survival in mice(112). Thus, siRNA-based replacement therapy has promising potential in treating peritoneal dissemination of OC and may contribute to personalized medicine for OC patients.

While exosomes as drug carriers can enhance therapeutic efficacy and overcome drug resistance, their clinical translation is constrained by several challenges. A major technological bottleneck lies in the large-scale, standardized production and isolation of high-purity exosomes. The absence of unified technical standards results in high product heterogeneity, compromising the reproducibility of treatment outcomes(113). Another critical technical hurdle is the efficient loading of therapeutic agents into exosomes while preserving drug activity. Current loading methods generally suffer from low efficiency, which limits their therapeutic potential(114). Nevertheless, as natural nanocarriers, exosomes demonstrate significant advantages in delivering chemotherapeutic agents and nucleic acid drugs, showing promise for overcoming the limitations of conventional therapies.

4.3.2 Exosome-Targeted Therapy

Exosomes possess an inherent homing capacity to target tissues, and the clearance of tumor-derived exosomes by targeting their biogenesis and secretion has significant clinical implications for prospective cancer therapeutics. The molecules summarized in

Tables 2-5 represent a rich repository of potential therapeutic targets. Li and colleagues identified exosomal *miR-429* as a key regulator of chemoresistance and malignant phenotypes in EOC by activating the NF-κB pathway via calcium sensing receptor (CASR) targeting, suggesting its potential as a therapeutic target(115). Additionally, elevated solute carrier family 11 member 2 (SLC11A2) mRNA and protein expression in the serum exosomes of OC patients is correlated with poor prognosis. Knockdown of SLC11A2 reduces OC cell migration and enhances cisplatin-induced apoptosis, positioning SLC11A2 as a dual therapeutic target and diagnostic biomarker(116). Zhou and colleagues reported that the expression of *AFAP1-AS1* (Actin Filament Associated Protein 1 Antisense RNA 1) was significantly increased in serum exosomes and ascites from OC patients, which was correlated with adverse pathological features such as advanced FIGO stage and increased tumor diameter. Exosomes isolated from ascites and treated with siRNAs targeting *AFAP1-AS1* were shown to inhibit cell migration and invasion(117). Zhang and colleagues demonstrated that exosomes secreted by SKOV3 cells could suppress the PTEN/AKT signaling pathway by transferring the lncRNA *FAL1(Focally Amplified lncRNA on chromosome 1)*, thereby inhibiting OC cell metastasis both in vitro and in vivo(118). These findings provide new insights into the mechanisms of OC and highlight potential novel targets for molecularly targeted therapies.

Furthermore, modern multi-omics and bioinformatics approaches are being employed to systematically identify and validate targets that render exosomes suitable for targeted therapy. For instance, Trefoil Factor 3 (TFF3), a secreted protein implicated

in remodeling the TME to promote cancer progression, was analyzed using multi-omics. This approach identified poliovirus receptor-related 2 (PVRL2) as a promising immunosuppressive target showing a significant association with TFF3, suggesting that a co-targeting strategy against both TFF3 and PVRL2 could be an effective immunosuppressive strategy in cancer(119). Similarly, through integrated bioinformatics analysis, the gene low density lipoprotein receptor-related protein 1 (LRP1) has been identified and validated as a potential prognostic biomarker for OC, highlighting its promise not only as a prognostic indicator but also as a therapeutic target and a key regulator of the TME(120).

Although the intrinsic targeting potential of exosomes makes them amenable to engineering for enhanced targeted therapy, ensuring the safety and efficacy of engineered exosomes in vivo remains a key issue to be addressed in future research.

4.3.3 Immunotherapy

The inherent immunogenicity of OC positions immunotherapy as a promising strategy. Within this paradigm, exosomes play a dual role: they can suppress anti-tumor immunity to facilitate immune evasion, yet they also hold significant potential as immunotherapeutic agents (121). Cancer immunotherapy itself functions by activating the host's anti-tumor immune responses and counteracting tumor escape mechanisms.

Exosomes from specific sources can reactivate suppressed immune cells. Removing immunosuppressive exosomes from the TME may enhance the anti-tumor immune response of immunotherapy. For instance, NK cell-derived exosomes exhibit

cytotoxic effects, augmenting cisplatin-mediated OC cell killing in vitro and reversing NK cell immunosuppression(122). Exosomes might also be harnessed to induce cytotoxic T lymphocyte-dependent anti-tumor responses in OC. It is well-documented that exosomal PD-L1 inhibits T-cell activation by binding to PD-1 on T cells, effectively inducing T-cell exhaustion and apoptosis(72). Consequently, targeting the biogenesis, secretion, or function of exosomal PD-L1 represents a novel strategy to overcome resistance to anti-PD-1/PD-L1 therapies.

The cargo within exosomes, such as immune checkpoint molecules or specific genes, can serve as biomarkers for predicting immunotherapy response. For example, the level of exosomal CMTM4 is associated with poor prognosis and reduced sensitivity to anti-PD-1 therapy in OC patients, suggesting its potential as an indicator for predicting immunotherapeutic efficacy(71). Furthermore, as mentioned earlier, the construction of comprehensive exosome-related gene signature models, are all associated with immune cell infiltration. These findings may contribute to the development of immunotherapy-based interventions for OC patients.

Additionally, exosomes can be employed as cell-free tumor vaccines. Exosomes carry tumor-associated antigens and major histocompatibility complex (MHC) molecules from their parent cells on the surface. They can be captured and processed by antigen-presenting cells (e.g., dendritic cells), thereby effectively activating specific $CD8^+$ T cells and $CD4^+$ T cells to induce potent anti-tumor immune responses(123). Owing to their autologous origin, low immunogenicity, and non-toxic nature, they are considered an ideal platform for developing safe and effective personalized cancer

vaccines(124).

In summary, exosomes play a dual-edged sword role in tumor immunology, capable of both suppressing and activating immunity. The relationship between exosomes and OC immunotherapy is multifaceted. While naturally occurring tumor-derived exosomes pose a significant obstacle to current immunotherapies, they also offer novel therapeutic targets. Moreover, engineered exosomes provide a versatile and promising platform for developing next-generation immunotherapy strategies. A deeper understanding of these roles is crucial for unlocking the full potential of immunotherapy in OC.

Overall, the multifunctional nature of exosomes provides broad scope for synergistic applications in combination therapies. They can be co-loaded with chemotherapeutic agents and immunomodulators to achieve coordinated delivery of chemotherapy and immunotherapy. Furthermore, exosomes can serve as vehicles for the targeted delivery of gene-editing tools (e.g., CRISPR/Cas9) or therapeutic nucleic acids (e.g., siRNA, miRNA) to OC cells, enabling the silencing of key oncogenes or correction of dysregulated signaling pathways. When combined with targeted drugs, this approach facilitates a multi-pronged therapeutic attack (125). Although clinical translation of exosome-based therapies faces several challenges, systematically addressing these key bottlenecks is essential to advancing them from basic research to widespread clinical application.

4.4 Progress in Exosome-related Clinical Trials for OC

Currently, the clinical translation of exosomes in the field of OC is rapidly advancing. Multiple prospective clinical trials are exploring the application value of exosomes in OC diagnosis, prognosis prediction, and treatment. For instance, a multicenter observational study registered on ClinicalTrials.gov (NCT06558019) aims to validate the clinical utility of an exosome-based Ovarian Cancer Score (OCS) product for predicting and monitoring OC recurrence(126). Simultaneously, a cross-sectional study registered in the Chinese Clinical Trial Registry (ChiCTR2400095082) is dedicated to screening exosomal biomarkers for early OC diagnosis from serum, ascites, and cyst fluids using transcriptomic technologies(127).

Beyond these registered clinical trials, research on engineered exosomes as drug delivery systems has also made significant progress, with numerous preclinical studies confirming their potential in overcoming chemotherapy resistance and achieving targeted therapy(128, 129).

These advancements collectively indicate the broad application prospects of exosomes in precision medicine for OC, laying a solid foundation for the transition from basic research to clinical translation.

5. Artificial Intelligence (AI) and Exosomes

Artificial intelligence (AI), particularly machine learning (ML) and deep learning

(DL), is profoundly transforming medical research and clinical practice, driven by its exceptional capacity to process vast and complex datasets(130). AI enables the extraction of high-throughput information from medical images, histopathological slides, and multi-omics data—including genomics and transcriptomics—to identify intricate patterns, thereby refining paradigms for cancer screening, diagnosis, and treatment(131). The convergence of AI technologies with exosome analysis offers unprecedented opportunities to address critical clinical challenges in OC, such as difficulties in early detection and limited treatment options, and holds strong potential for advancing precision oncology.

5.1 AI-Powered Exosomal Omics Analysis for Biomarker Discovery

The integration of AI with exosomal omics data represents a core strategy for enhancing diagnostic and prognostic capabilities in OC. Molecules carried by exosomes—such as proteins, nucleic acids (particularly miRNAs), and lipids—constitute high-dimensional datasets that reflect the tumor state. AI algorithms, especially ML, can efficiently process these complex data to identify specific biomarker patterns associated with OC(132).

Multiple review studies have highlighted the potential of this integrated approach. Analyzing molecular expression changes, including miRNAs and mRNAs, within exosomes can facilitate the development of biomarkers for diagnosis, prognosis, and treatment of OC(133). A recently published review indicated that biomarker-driven ML

models demonstrate exceptional performance in diagnosing OC, achieving an AUC exceeding 0.90 and effectively distinguishing malignant from benign tumors. Both ensemble learning methods (e.g., Random Forest) and deep learning approaches (e.g., Recurrent Neural Networks) have shown outstanding results in classification accuracy (up to 99.82%) and survival prediction (AUC up to 0.866)(134). Furthermore, AI models can improve tumor detection, subtype classification, and therapy response monitoring by analyzing exosomal RNA biomarkers, such as circRNAs, miRNAs, and lncRNAs(135).

Despite the promising outlook, this field faces challenges. Many studies are limited by small sample sizes, a lack of independent external validation, and homogeneous data types, which impede clinical translation. To advance practical application, future research should prioritize large-scale, multi-center prospective clinical trials and integrate multi-omics data to build more robust predictive models.

5.2 AI-Driven Exosome Engineering and Therapeutic Applications

Beyond diagnostics, AI demonstrates significant potential in advancing the development of exosomes as therapeutic vectors. Through bioengineering, exosomes can be designed for the targeted delivery of chemotherapeutic agents, gene therapies or other therapeutic molecules, enabling precise treatment of OC.

AI contributes to this process in several key ways. Firstly, AI models can analyze multi-omics data to help identify key molecular targets involved in therapy resistance

or immune evasion in OC, thereby guiding the design of engineered exosomes for more precise targeting of tumor cells or the tumor microenvironment(136). Secondly, AI can optimize exosome drug loading efficiency and targeting capability. For instance, machine learning algorithms can predict the interactions between different drugs and the exosomal membrane, enabling the selective and efficient loading of specific chemotherapeutic agents into exosomes(133). Additionally, AI-powered analytical techniques aid in evaluating the therapeutic efficacy and safety profiles of engineered exosomes.

Currently, although significant progress has been made in research on exosomes as drug delivery vehicles, challenges remain, including exosome population heterogeneity, the lack of standardized isolation protocols, and difficulties in scalable production. The application of AI technology is expected to accelerate solutions to these problems, thereby promoting the translation of exosome-based therapies from laboratory research to clinical application.

6.Challenges and Future Perspectives

A growing body of evidence underscores the critical role of exosomes in the pathogenesis and progression of OC. However, their translation from basic research to clinical application faces multifaceted challenges.

Firstly, challenges exist in production standardization and quality control. The large-scale, standardized production of exosomes remains a primary hurdle. Current

isolation techniques—such as ultracentrifugation, ultrafiltration, size-exclusion chromatography, and immunoaffinity capture—have significant limitations. Ultracentrifugation is inefficient and difficult to scale, ultrafiltration can induce exosome aggregation or damage, and the high cost of size-exclusion chromatography and immunoaffinity methods restricts their widespread use. Emerging microfluidic technologies offer potential for high-throughput and automation but are not yet mature for processing clinical samples. Furthermore, the lack of standardized protocols for preparation and characterization, alongside an absence of robust quality control systems, leads to poor comparability between studies and batch-to-batch variability(137). Establishing production and quality control systems compliant with good manufacturing practice (GMP) is a fundamental prerequisite. International collaborative initiatives are actively working to develop standardized protocols to address this challenge(138).

Secondly, there are significant hurdles in targeted delivery and drug loading. As drug carriers, exosomes face dual challenges in achieving efficient drug loading and specific targeting. Current drug loading methods are often inefficient and lack standardization. The inherent targeting capability of natural exosomes is frequently limited, necessitating surface engineering modifications to enhance specificity; however, such modifications can potentially alter their native biological functions(139). Additionally, exosomes typically exhibit a short circulatory half-life *in vivo* and are rapidly cleared by the mononuclear phagocyte system, limiting their accumulation at the target site(140). Real-time monitoring of their biodistribution, pharmacokinetics,

and targeting efficacy remains technically difficult(141).

Thirdly, bottlenecks persist in safety, regulation, and industrialization. The clinical application of exosomes must also overcome obstacles related to safety, regulatory approval, and economic viability. While generally exhibiting low immunogenicity, their source, purity, and *in vivo* metabolic pathways could potentially trigger immune responses or toxic effects, requiring further validation of long-term safety(142). From a regulatory perspective, the global classification, evaluation criteria, and clinical pathways for exosome-based products are still evolving. Regulatory bodies have issued preliminary guidance, but a comprehensive framework is yet to be fully established(143). Moreover, the complex production processes and high costs severely hinder industrial scalability(144). Ethical considerations, particularly concerning certain biological sources, also require careful attention(145).

To address these challenges, future efforts should focus on several key directions. First, it is crucial to establish standardized technical systems by developing scalable, automated production platforms that ensure batch-to-batch consistency(146). Second, targeted delivery strategies must be optimized by engineering "smart" exosome systems with improved drug loading and controlled release, while preserving their natural functions. Third, a deeper understanding of their *in vivo* behavior is needed through integrated imaging and tracking studies to inform dosing regimens(141). Fourth, promoting international harmonization of standards will enhance the comparability of global research data(147). Fifth, clinical evaluation pathways should be refined through rigorous preclinical safety studies and

well-designed multicenter clinical trials. Finally, deepening interdisciplinary collaboration among scientists, clinicians, and regulators is essential to build synergistic innovation mechanisms and establish clear regulatory frameworks.

In conclusion, by integrating knowledge from oncology, immunology, and bioengineering, and through sustained innovation, exosomes hold the potential to reshape the landscape of early cancer detection and therapy, offering a promising avenue for advancing precision medicine.

7. Conclusion

Ovarian cancer (OC) remains one of the most lethal gynecologic malignancies due to its high mortality rate. Exosomes, serving as pivotal mediators of intercellular communication, have opened new avenues for understanding its pathogenesis and demonstrate significant potential in diagnostics and therapeutics. This review has systematically elaborated on the multifaceted roles of exosomes in core biological processes of OC, including remodeling of the tumor microenvironment, angiogenesis, metastasis, immune evasion, and chemoresistance, facilitated by the delivery of bioactive molecules such as proteins and nucleic acids. Furthermore, we have highlighted their clinical translational value as novel diagnostic biomarkers and natural drug delivery vehicles.

Nevertheless, translating this considerable promise into tangible clinical benefits is confronted with a series of challenges, spanning from production standardization and

targeting efficiency to safety and regulatory oversight. Looking forward, by fostering interdisciplinary collaborations—for instance, integration with artificial intelligence—and by systematically addressing these translational bottlenecks, exosome research is poised to herald a new era in OC management, steering it towards a future that is more predictive, preventive, and personalized within the framework of precision medicine.

Ethics declaration

Not applicable.

Consent to Participate declaration

Not applicable.

Data availability statement

Not applicable.

Declaration of competing interests

None declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

Jiyu Chen: Wrote the main manuscript text and prepared the figure and table;

Qingqing Tan: Conceived the study and revised the manuscript.

Acknowledgments

Not applicable.

Abbreviations

AFM: Atomic force microscopy

AFAP1-AS1: Actin filament associated protein 1 antisense RNA 1

ATB: Activated TGF-β-induced lncRNA

AI: Artificial intelligence

APOE: Apolipoprotein E

AUC: Area under the curve

CAFs: Cancer-associated fibroblasts

CASR: Calcium sensing receptor

CAV1: Caveolin 1

CBX7: Chromobox 7

CCC: Clear cell carcinoma

circNFIX: CircRNA nuclear factor IX

circRNA: Circular RNA

CLDN3: Claudin 3

COL6A3: Collagen type VI alpha 3 chain

Cryo-EM: Cryogenic electron microscopy

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4

DL: Deep learning

DLS: Dynamic light scattering

DNMT1: DNA methyltransferase 1

EC: Endometrioid carcinoma

ELISA: Enzyme-linked immunosorbent assay

EM: Electron microscopy

EMT: Epithelial–mesenchymal transition

EOC: Epithelial ovarian cancer

EpCAM: Epithelial cell adhesion molecule

ERGRM: Exosome-related gene risk model

ERLS: Exosome-related LncRNA Signature

ESCRT: Endosomal sorting complexes required for transport

EVs: Extracellular vesicles

FAL1: Focally amplified long non-coding RNA on chromosome 1

FASN: Fatty acid synthase

FC: Flow cytometry

FGG: Fibrinogen gamma chain

FOXO3: Forkhead box O3

GATA3: GATA binding protein 3

GMP: Good manufacturing practice

HGSC: High-grade serous carcinoma

HGSOC: High-grade serous ovarian cancer

HOTTIP: HOXA transcript at the distal tip

ICAM1: Intercellular adhesion molecule 1

ILV: Intraluminal vesicles

IGF2: Insulin-like growth factor 2

IOCEs: Immune-related OC-derived Exosomes

LBP: Lipopolysaccharide binding protein

LGSOC: Low-grade serous ovarian carcinoma

LMP: Low malignant potential

lncRNA: Long non-coding RNA

LRP1: Low density lipoprotein receptor-related protein 1

MC: Mucinous carcinoma

MDR1: Multidrug resistance protein 1

MHC: Major histocompatibility complex

miRNA: MicroRNA

ML: Machine learning

MMT: Mesothelial-to-mesenchymal transition

MUC1: Mucin 1, cell surface associated

MVB: Multivesicular body

NEAT1: Nuclear enriched abundant transcript 1

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

NTA: Nanoparticle tracking analysis

OC: Ovarian cancer

OCS: Ovarian cancer score

PCNA: Proliferating cell nuclear antigen

PKR1: Prokineticin receptor 1

PLADE: Platinum sensitivity-associated lncRNA in ascites-derived exosomes

PRSS3: Serine protease 3

PVRL2: Poliovirus receptor-related 2

qRT–PCR: Quantitative real-time reverse transcription PCR

ROC: receiver operating characteristic

RPS: Resistive pulse sensing

SEC: Size-exclusion chromatography

SEM: Scanning electron microscopy

siRNA: Small interfering RNA

SLC11A2: Solute carrier family 11 member 2

snRNA: Small nuclear RNA

snoRNA: Small nucleolar RNA

SOCS5: Suppressor of cytokine signaling 5

SOX2-OT: SOX2 overlapping transcript

SPOCD1-AS: SPOC domain containing 1 antisense RNA

TEM: Transmission electron microscopy

TFF3: Trefoil Factor 3

TME: Tumor microenvironment

TMCO3: Transmembrane and coiled-coil domains 3

TP: Tiptolide

TRIM44: Tripartite motif-containing protein 44

tRNA: Transfer RNA

UCA1: Urothelial cancer associated 1

TAMs: Tumor-associated macrophages

TUBB3: Tubulin beta 3 class III

WHO: World Health Organization

WHSC1: Wolf-Hirschhorn syndrome candidate 1

ZEB1: Zinc finger E-box binding homeobox 1

References

1. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer biology & medicine. 2017;14(1):9-32.

2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA: a cancer journal for clinicians. 2024;74(1):12-49.

3. Tropé CG, Elstrand MB, Sandstad B, Davidson B, Oksefjell H. Neoadjuvant chemotherapy, interval debulking surgery or primary surgery in ovarian carcinoma FIGO stage IV? European journal of cancer (Oxford, England : 1990). 2012;48(14):2146-54.

4. Caruso G, Weroha SJ, Cliby W. Ovarian Cancer: A Review. Jama. 2025;334(14):1278-91.

5. Lu Z, Chen J. [Introduction of WHO classification of tumours of female reproductive organs, fourth edition]. Zhonghua bing li xue za zhi = Chinese journal of pathology. 2014;43(10):649-50.

6. Kurman RJ, Shih Ie M. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. The American journal of pathology. 2016;186(4):733-47.

7. Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature. 2015;523(7559):177-82.

8. de Jong OG, Kooijmans SAA, Murphy DE, Jiang L, Evers MJW, Sluijter JPG, et al. Drug Delivery with Extracellular Vesicles: From Imagination to Innovation. Accounts of chemical research. 2019;52(7):1761-70.

9. Tian W, Lei N, Zhou J, Chen M, Guo R, Qin B, et al. Extracellular vesicles in ovarian cancer chemoresistance, metastasis, and immune evasion. Cell death & disease. 2022;13(1):64.

10. Trams EG, Lauter CJ, Salem N, Jr., Heine U. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. Biochimica et biophysica acta. 1981;645(1):63-70.

11. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte

maturation. Association of plasma membrane activities with released vesicles (exosomes). The Journal of biological chemistry. 1987;262(19):9412-20.

12. Théry C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. Journal of extracellular vesicles. 2018;7(1):1535750.

13. Chang L, Ni J, Zhu Y, Pang B, Graham P, Zhang H, et al. Liquid biopsy in ovarian cancer: recent advances in circulating extracellular vesicle detection for early diagnosis and monitoring progression. Theranostics. 2019;9(14):4130-40.

14. Simons M, Raposo G. Exosomes--vesicular carriers for intercellular communication. Current opinion in cell biology. 2009;21(4):575-81.

15. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annual review of cell and developmental biology. 2014;30:255-89.

16. Malgundkar SH, Tamimi Y. Exosomes as crucial emerging tools for intercellular communication with therapeutic potential in ovarian cancer. Future science OA. 2023;9(1):Fso833.

17. Subra C, Grand D, Laulagnier K, Stella A, Lambeau G, Paillasse M, et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. Journal of lipid research. 2010;51(8):2105-20.

18. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science (New York, NY). 2020;367(6478).

19. Beach A, Zhang HG, Ratajczak MZ, Kakar SS. Exosomes: an overview of biogenesis, composition and role in ovarian cancer. Journal of ovarian research. 2014;7:14.

20. Hanson PI, Cashikar A. Multivesicular body morphogenesis. Annual review of cell and developmental biology. 2012;28:337-62.

21. Babst M. MVB vesicle formation: ESCRT-dependent, ESCRT-independent and everything in between. Current opinion in cell biology. 2011;23(4):452-7.

22. Henne WM, Buchkovich NJ, Emr SD. The ESCRT pathway. Developmental cell. 2011;21(1):77-91.

23. Colombo M, Moita C, van Niel G, Kowal J, Vigneron J, Benaroch P, et al. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. Journal of cell science. 2013;126(Pt 24):5553-65.

24. Juan T, Fürthauer M. Biogenesis and function of ESCRT-dependent extracellular vesicles. Seminars in cell & developmental biology. 2018;74:66-77.

25. Elsherbini A, Bieberich E. Ceramide and Exosomes: A Novel Target in Cancer Biology and Therapy. Advances in cancer research. 2018;140:121-54.

26. Dzhugashvili E, Tamkovich S. Exosomal Cargo in Ovarian Cancer Dissemination. Current issues in molecular biology. 2023;45(12):9851-67.

27. Doyle LM, Wang MZ. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. Cells. 2019;8(7).

28. Xie S, Zhang Q, Jiang L. Current Knowledge on Exosome Biogenesis, Cargo-Sorting Mechanism and Therapeutic Implications. Membranes. 2022;12(5).

29. Shimizu A, Sawada K, Kimura T. Pathophysiological Role and Potential Therapeutic Exploitation of Exosomes in Ovarian Cancer. Cells. 2020;9(4).

30. Qin T, Chen F, Zhu J, Ding Y, Zhang Q. Advances in Exosomal microRNAs and Proteins in Ovarian Cancer Diagnosis, Prognosis, and Treatment. Current molecular medicine. 2023;23(6):509-20.

31. Gámez-Valero A, Monguió-Tortajada M, Carreras-Planella L, Franquesa M, Beyer K, Borràs FE. Size-Exclusion Chromatography-based isolation minimally alters Extracellular Vesicles' characteristics compared to precipitating agents. Scientific reports. 2016;6:33641.

32. Lai JJ, Chau ZL, Chen SY, Hill JJ, Korpany KV, Liang NW, et al. Exosome Processing and Characterization Approaches for Research and Technology Development. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2022;9(15):e2103222.

33. Li P, Kaslan M, Lee SH, Yao J, Gao Z. Progress in Exosome Isolation Techniques. Theranostics. 2017;7(3):789-804.

34. Yang D, Zhang W, Zhang H, Zhang F, Chen L, Ma L, et al. Progress, opportunity, and perspective on exosome isolation - efforts for efficient exosome-based theranostics. Theranostics. 2020;10(8):3684-707.

35. Qiu J, Wu Y, Wang Y, Wang C, Cho S-Y, Huang H, et al. High-throughput exosomes analysis for ovarian cancer screening based on a double-positive surface marker detection biochip.n/a(n/a):e70015.

36. Dilsiz N. A comprehensive review on recent advances in exosome isolation and characterization: Toward clinical applications. Translational oncology. 2024;50:102121.

37. Chen Q, Shi J, Ruan D, Bian C. The diagnostic and therapeutic prospects of exosomes in ovarian cancer. BJOG : an international journal of obstetrics and gynaecology. 2023;130(9):999-1006.

38. Luo Z, Wang Q, Lau WB, Lau B, Xu L, Zhao L, et al. Tumor microenvironment: The culprit for ovarian cancer metastasis? Cancer letters. 2016;377(2):174-82.

39. Yue H, Li W, Chen R, Wang J, Lu X, Li J. Stromal POSTN induced by TGF-β1 facilitates the migration and invasion of ovarian cancer. Gynecologic oncology. 2021;160(2):530-8.

40. Garlisi B, Lauks S, Aitken C, Ogilvie LM, Lockington C, Petrik D, et al. The Complex Tumor Microenvironment in Ovarian Cancer: Therapeutic Challenges and Opportunities. Current oncology (Toronto, Ont). 2024;31(7):3826-44.

41. Feng W, Dean DC, Hornicek FJ, Shi H, Duan Z. Exosomes promote pre-metastatic niche formation in ovarian cancer. Molecular cancer. 2019;18(1):124.

42. Baig MS, Roy A, Rajpoot S, Liu D, Savai R, Banerjee S, et al. Tumor-derived exosomes in the regulation of macrophage polarization. Inflammation research : official journal of the European Histamine Research Society [et al]. 2020;69(5):435-51.

43. Chen X, Ying X, Wang X, Wu X, Zhu Q, Wang X. Exosomes derived from hypoxic epithelial ovarian cancer deliver microRNA-940 to induce macrophage M2 polarization. Oncology reports. 2017;38(1):522-8.

44. Ying X, Wu Q, Wu X, Zhu Q, Wang X, Jiang L, et al. Epithelial ovarian cancer-secreted exosomal miR-222-3p induces polarization of tumor-associated macrophages. Oncotarget. 2016;7(28):43076-87.

45. Lim D, Do Y, Kwon BS, Chang W, Lee MS, Kim J, et al. Angiogenesis and vasculogenic mimicry as therapeutic targets in ovarian cancer. BMB reports. 2020;53(6):291-8.

46. Asante DB, Tierno D, Woode M, Scaggiante B. Angiogenesis and Ovarian Cancer: What Potential Do Different Subtypes of Circulating Endothelial Cells Have for Clinical Application? International journal of molecular sciences. 2024;25(11).

47. Jayson GC, Kerbel R, Ellis LM, Harris AL. Antiangiogenic therapy in oncology: current status and future directions. Lancet (London, England). 2016;388(10043):518-29.

48. He L, Zhu W, Chen Q, Yuan Y, Wang Y, Wang J, et al. Ovarian cancer cell-secreted exosomal miR-205 promotes metastasis by inducing angiogenesis. Theranostics. 2019;9(26):8206-20.

49. Chen X, Zhou J, Li X, Wang X, Lin Y, Wang X. Exosomes derived from hypoxic epithelial ovarian

cancer cells deliver microRNAs to macrophages and elicit a tumor-promoted phenotype. Cancer letters. 2018;435:80-91.

50. Ye H, Wang RY, Yu XZ, Wu YK, Yang BW, Ao MY, et al. Exosomal circNFIX promotes angiogenesis in ovarian cancer via miR-518a-3p/TRIM44 axis. The Kaohsiung journal of medical sciences. 2023;39(1):26-39.

51. Zhang X, Sheng Y, Li B, Wang Q, Liu X, Han J. Ovarian cancer derived PKR1 positive exosomes promote angiogenesis by promoting migration and tube formation in vitro. Cell biochemistry and function. 2021;39(2):308-16.

52. Yuan D, Guo T, Zhu D, Ge H, Zhao Y, Huang A, et al. Exosomal lncRNA ATB Derived from Ovarian Cancer Cells Promotes Angiogenesis via Regulating miR-204-3p/TGFβR2 Axis. Cancer management and research. 2022;14:327-37.

53. Zhu Y, Wang C, Ma Z, Li F, Xu C, Pan W, et al. Role of Exosomes in the Invasion and Metastasis of Ovarian Cancer and Application Potential of Clinical Diagnosis and Treatment. Journal of Cancer. 2023;14(7):1141-50.

54. Yousefi M, Dehghani S, Nosrati R, Ghanei M, Salmaninejad A, Rajaie S, et al. Current insights into the metastasis of epithelial ovarian cancer - hopes and hurdles. Cellular oncology (Dordrecht, Netherlands). 2020;43(4):515-38.

55. Nakamura K, Sawada K, Kinose Y, Yoshimura A, Toda A, Nakatsuka E, et al. Exosomes Promote Ovarian Cancer Cell Invasion through Transfer of CD44 to Peritoneal Mesothelial Cells. Molecular cancer research : MCR. 2017;15(1):78-92.

56. Cai J, Gong L, Li G, Guo J, Yi X, Wang Z. Exosomes in ovarian cancer ascites promote epithelial-mesenchymal transition of ovarian cancer cells by delivery of miR-6780b-5p. Cell death & disease. 2021;12(2):210.

57. Williams ME, Howard D, Donnelly C, Izadi F, Parra JG, Pugh M, et al. Adipocyte derived exosomes promote cell invasion and challenge paclitaxel efficacy in ovarian cancer. Cell communication and signaling : CCS. 2024;22(1):443.

58. Zhang Y, Tedja R, Millman M, Wong T, Fox A, Chehade H, et al. Adipose-derived exosomal miR-421 targets CBX7 and promotes metastatic potential in ovarian cancer cells. Journal of ovarian research. 2023;16(1):233.

59. Ho CM, Yen TL, Chang TH, Huang SH. COL6A3 Exosomes Promote Tumor Dissemination and Metastasis in Epithelial Ovarian Cancer. International journal of molecular sciences. 2024;25(15).

60. Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic non-coding RNA. Nature reviews Molecular cell biology. 2018;19(3):143-57.

61. Zong ZH, Du YP, Guan X, Chen S, Zhao Y. CircWHSC1 promotes ovarian cancer progression by regulating MUC1 and hTERT through sponging miR-145 and miR-1182. Journal of experimental & clinical cancer research : CR. 2019;38(1):437.

62. Gordillo CH, Sandoval P, Muñoz-Hernández P, Pascual-Antón L, López-Cabrera M, Jiménez-Heffernan JA. Mesothelial-to-Mesenchymal Transition Contributes to the Generation of Carcinoma-Associated Fibroblasts in Locally Advanced Primary Colorectal Carcinomas. Cancers. 2020;12(2).

63. Wang C, Wang J, Shen X, Li M, Yue Y, Cheng X, et al. LncRNA SPOCD1-AS from ovarian cancer extracellular vesicles remodels mesothelial cells to promote peritoneal metastasis via interacting with G3BP1. Journal of experimental & clinical cancer research : CR. 2021;40(1):101.

64. Zhang S, Pan D, Zhang S, Wu Q, Zhen L, Liu S, et al. Exosomal miR-543 Inhibits the Proliferation of Ovarian Cancer by Targeting IGF2. Journal of immunology research. 2022;2022:2003739.

65. Ma R, Ye X, Cheng H, Cui H, Chang X. Tumor-derived exosomal circRNA051239 promotes proliferation and migration of epithelial ovarian cancer. American journal of translational research. 2021;13(3):1125-39.

66. Ran XM, Yang J, Wang ZY, Xiao LZ, Deng YP, Zhang KQ. M2 macrophage-derived exosomal circTMCO3 acts through miR-515-5p and ITGA8 to enhance malignancy in ovarian cancer. Communications biology. 2024;7(1):583.

67. Lai Y, Dong L, Jin H, Li H, Sun M, Li J. Exosome long non-coding RNA SOX2-OT contributes to ovarian cancer malignant progression by miR-181b-5p/SCD1 signaling. Aging. 2021;13(20):23726-38.

68. Li N, Lin G, Zhang Y, Zhang Q, Zhang H. Exosome-related protein CRABP2 is upregulated in ovarian carcinoma and enhances cell proliferation. Discover oncology. 2022;13(1):33.

69. Lu Y, Zheng J, Lin P, Lin Y, Zheng Y, Mai Z, et al. Tumor Microenvironment-Derived Exosomes: A Double-Edged Sword for Advanced T Cell-Based Immunotherapy. ACS nano. 2024;18(40):27230-60.

70. He L, Chen Q, Wu X. Tumour-derived exosomal miR-205 promotes ovarian cancer cell progression through M2 macrophage polarization via the PI3K/Akt/mTOR pathway. Journal of ovarian research. 2025;18(1):28.

71. Yin B, Ding J, Liu J, Hu H, Zhu Y, Yang M, et al. Exosomal CMTM4 Induces Immunosuppressive Macrophages to Promote Ovarian Cancer Progression and Attenuate Anti-PD-1 Immunotherapy. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2025;12(30):e04436.

72. Lu L, Ling W, Ruan Z. TAM-derived extracellular vesicles containing microRNA-29a-3p explain the deterioration of ovarian cancer. Molecular therapy Nucleic acids. 2021;25:468-82.

73. Yin L, Wang Y. Extracellular vesicles derived from M2-polarized tumor-associated macrophages promote immune escape in ovarian cancer through NEAT1/miR-101-3p/ZEB1/PD-L1 axis. Cancer immunology, immunotherapy : CII. 2023;72(3):743-58.

74. Shimizu A, Sawada K, Kobayashi M, Yamamoto M, Yagi T, Kinose Y, et al. Exosomal CD47 Plays an Essential Role in Immune Evasion in Ovarian Cancer. Molecular cancer research : MCR. 2021;19(9):1583-95.

75. Shang A, Wang W, Gu C, Chen C, Zeng B, Yang Y, et al. Long non-coding RNA HOTTIP enhances IL-6 expression to potentiate immune escape of ovarian cancer cells by upregulating the expression of PD-L1 in neutrophils. Journal of experimental & clinical cancer research : CR. 2019;38(1):411.

76. Wang M, Fu L, Xu Y, Ma S, Zhang X, Zheng L. A comprehensive overview of exosome lncRNAs: Emerging biomarkers and potential therapeutics in gynecological cancers. Frontiers in oncology. 2023;13:1138142.

77. Zheng Q, Zhang J, Liu Y, Dong W, Dai X, Du X, et al. LINC01119 encapsulated by cancer-associated adipocytes-derived exosomes promotes M2 polarization of macrophages to induce immune escape in ovarian cancer in a 3D co-culture cell-based model. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2023;25(11):3174-87.

78. Sun H, Huo X, Bi X, Cao D, Yang J, Shen K, et al. Exosome transmit the ability of migration and invasion in heterogeneous ovarian cancer cells by regulating autophagy via targeting hsa-miR-328. Gynecologic oncology. 2025;194:60-70.

79. Chen C, Zhang L, Ruan Z. GATA3 Encapsulated by Tumor-Associated Macrophage-Derived Extracellular Vesicles Promotes Immune Escape and Chemotherapy Resistance of Ovarian Cancer Cells by Upregulating the CD24/Siglec-10 Axis. Molecular pharmaceutics. 2023;20(2):971-86.

80. Yang E, Wang X, Gong Z, Yu M, Wu H, Zhang D. Exosome-mediated metabolic reprogramming: the

emerging role in tumor microenvironment remodeling and its influence on cancer progression. Signal transduction and targeted therapy. 2020;5(1):242.

81. Khan T, Sullivan MA, Gunter JH, Kryza T, Lyons N, He Y, et al. Revisiting Glycogen in Cancer: A Conspicuous and Targetable Enabler of Malignant Transformation. Frontiers in oncology. 2020;10:592455.

82. Tuscharoenporn T, Apaijai N, Charoenkwan K, Chattipakorn N, Chattipakorn SC. Emerging roles of exosomes in diagnosis, prognosis, and therapeutic potential in ovarian cancer: a comprehensive review. Cancer gene therapy. 2025;32(2):149-64.

83. Guo QR, Wang H, Yan YD, Liu Y, Su CY, Chen HB, et al. The Role of Exosomal microRNA in Cancer Drug Resistance. Frontiers in oncology. 2020;10:472.

84. Zhu X, Shen H, Yin X, Yang M, Wei H, Chen Q, et al. Macrophages derived exosomes deliver miR-223 to epithelial ovarian cancer cells to elicit a chemoresistant phenotype. Journal of experimental & clinical cancer research : CR. 2019;38(1):81.

85. Li Z, Niu H, Qin Q, Yang S, Wang Q, Yu C, et al. lncRNA UCA1 Mediates Resistance to Cisplatin by Regulating the miR-143/FOSL2-Signaling Pathway in Ovarian Cancer. Molecular therapy Nucleic acids. 2019;17:92-101.

86. Liu H, Deng S, Yao X, Liu Y, Qian L, Wang Y, et al. Ascites exosomal lncRNA PLADE enhances platinum sensitivity by inducing R-loops in ovarian cancer. Oncogene. 2024;43(10):714-28.

87. Li Q, Zhang Y, Jin P, Chen Y, Zhang C, Geng X, et al. New insights into the potential of exosomal circular RNAs in mediating cancer chemotherapy resistance and their clinical applications. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2024;177:117027.

88. Wu Y, Xu M, Feng Z, Wu H, Wu J, Ha X, et al. AUF1-induced circular RNA hsa_circ_0010467 promotes platinum resistance of ovarian cancer through miR-637/LIF/STAT3 axis. Cellular and molecular life sciences : CMLS. 2023;80(9):256.

89. Cao YL, Zhuang T, Xing BH, Li N, Li Q. Exosomal DNMT1 mediates cisplatin resistance in ovarian cancer. Cell biochemistry and function. 2017;35(6):296-303.

90. Gao YC, Wu J. MicroRNA-200c and microRNA-141 as potential diagnostic and prognostic biomarkers for ovarian cancer. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2015;36(6):4843-50.

91. Meng X, Müller V, Milde-Langosch K, Trillsch F, Pantel K, Schwarzenbach H. Diagnostic and prognostic relevance of circulating exosomal miR-373, miR-200a, miR-200b and miR-200c in patients with epithelial ovarian cancer. Oncotarget. 2016;7(13):16923-35.

92. Kim S, Choi MC, Jeong JY, Hwang S, Jung SG, Joo WD, et al. Serum exosomal miRNA-145 and miRNA-200c as promising biomarkers for preoperative diagnosis of ovarian carcinomas. Journal of Cancer. 2019;10(9):1958-67.

93. Jeon H, Seo SM, Kim TW, Ryu J, Kong H, Jang SH, et al. Circulating Exosomal miR-1290 for Diagnosis of Epithelial Ovarian Cancer. Current issues in molecular biology. 2022;44(1):288-300.

94. Liu J, Yoo J, Ho JY, Jung Y, Lee S, Hur SY, et al. Plasma-derived exosomal miR-4732-5p is a promising noninvasive diagnostic biomarker for epithelial ovarian cancer. Journal of ovarian research. 2021;14(1):59.

95. Chen Z, Liang Q, Zeng H, Zhao Q, Guo Z, Zhong R, et al. Exosomal CA125 as A Promising Biomarker for Ovarian Cancer Diagnosis. Journal of Cancer. 2020;11(21):6445-53.

96. Liang B, Peng P, Chen S, Li L, Zhang M, Cao D, et al. Characterization and proteomic analysis of ovarian cancer-derived exosomes. Journal of proteomics. 2013;80:171-82.

97. Zhang W, Peng P, Ou X, Shen K, Wu X. Ovarian cancer circulating extracelluar vesicles promote coagulation and have a potential in diagnosis: an iTRAQ based proteomic analysis. BMC cancer. 2019;19(1):1095.

98. Zhang P, Zhou X, Zeng Y. Multiplexed immunophenotyping of circulating exosomes on nano-engineered ExoProfile chip towards early diagnosis of cancer. Chemical science. 2019;10(21):5495-504.

99. Wang X, Yao Y, Jin M. Circ-0001068 is a novel biomarker for ovarian cancer and inducer of PD1 expression in T cells. Aging. 2020;12(19):19095-106.

100. Wang L, Chen J, Lu C. Circular RNA Foxo3 enhances progression of ovarian carcinoma cells. Aging. 2021;13(18):22432-43.

101. Luo Y, Gui R. Circulating exosomal circFoxp1 confers cisplatin resistance in epithelial ovarian cancer cells. Journal of gynecologic oncology. 2020;31(5):e75.

102. Yang L, Wu H, Zhu Y, Chen X, Chen Y. Plasma exosomal caveolin-1 predicts Poor Prognosis in Ovarian Cancer. Journal of Cancer. 2021;12(16):5005-12.

103. Zhang W, Ou X, Wu X. Proteomics profiling of plasma exosomes in epithelial ovarian cancer: A potential role in the coagulation cascade, diagnosis and prognosis. International journal of oncology. 2019;54(5):1719-33.

104. Li Y, Liu C, Liao Y, Wang W, Hu B, Lu X, et al. Characterizing the landscape of peritoneal exosomal microRNAs in patients with ovarian cancer by high-throughput sequencing. Oncology letters. 2019;17(1):539-47.

105. Yin J, Huang HY, Long Y, Ma Y, Kamalibaike M, Dawuti R, et al. circ_C20orf11 enhances DDP resistance by inhibiting miR-527/YWHAZ through the promotion of extracellular vesicle-mediated macrophage M2 polarization in ovarian cancer. Cancer biology & therapy. 2021;22(7-9):440-54.

106. Qiu JJ, Lin XJ, Tang XY, Zheng TT, Lin YY, Hua KQ. Exosomal Metastasis-Associated Lung Adenocarcinoma Transcript 1 Promotes Angiogenesis and Predicts Poor Prognosis in Epithelial Ovarian Cancer. International journal of biological sciences. 2018;14(14):1960-73.

107. Zhu Z, Geng R, Zhang Y, Liu J, Bai J. Exosome-Associated Gene Signature for Predicting the Prognosis of Ovarian Cancer Patients. Journal of immunology research. 2023;2023:8727884.

108. Cui Y, Zhang W, Lu W, Feng Y, Wu X, Zhuo Z, et al. An exosome-derived lncRNA signature identified by machine learning associated with prognosis and biomarkers for immunotherapy in ovarian cancer. Frontiers in immunology. 2024;15:1228235.

109. Zhu K, Ma J, Tian Y, Liu Q, Zhang J. An immune-related exosome signature predicts the prognosis and immunotherapy response in ovarian cancer. BMC women's health. 2024;24(1):49.

110. Kim MS, Haney MJ, Zhao Y, Mahajan V, Deygen I, Klyachko NL, et al. Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells. Nanomedicine : nanotechnology, biology, and medicine. 2016;12(3):655-64.

111. Li L, He D, Guo Q, Zhang Z, Ru D, Wang L, et al. Exosome-liposome hybrid nanoparticle codelivery of TP and miR497 conspicuously overcomes chemoresistant ovarian cancer. Journal of nanobiotechnology. 2022;20(1):50.

112. Shimizu A, Sawada K, Kobayashi M, Oi Y, Oride T, Kinose Y, et al. Patient-Derived Exosomes as siRNA Carriers in Ovarian Cancer Treatment. Cancers. 2024;16(8).

113. Liu C, Xia C, Xia C. Biology and function of exosomes in tumor immunotherapy. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2023;169:115853.

114. Chen L, Wang L, Zhu L, Xu Z, Liu Y, Li Z, et al. Exosomes as Drug Carriers in Anti-Cancer Therapy. Frontiers in cell and developmental biology. 2022;10:728616.

115. Li T, Lin L, Liu Q, Gao W, Chen L, Sha C, et al. Exosomal transfer of miR-429 confers chemoresistance in epithelial ovarian cancer. American journal of cancer research. 2021;11(5):2124-41.
116. Tian L, Li X, Lai H, Sun T, Li X, Wu L, et al. SLC11A2: a promising biomarker and therapeutic target in ovarian cancer. Scientific reports. 2023;13(1):1132.
117. Zhou F, Xu X, Wei W, Chen X, Sun L. Regulations of Exosomal-Transmitted AFAP1-AS1 LncRNA on Ovarian Cancer Cell Migration and Invasion. Discovery medicine. 2023;35(178):877-86.
118. Zhang Q, Len TY, Zhang SX, Zhao QH, Yang LH. Exosomes transferring long non-coding RNA FAL1 to regulate ovarian cancer metastasis through the PTEN/AKT signaling pathway. European review for medical and pharmacological sciences. 2020;24(21):10921.
119. Huang P, Wolde T, Bhardwaj V, Zhang X, Pandey V. TFF3 and PVRL2 co-targeting identified by multi-omics approach as an effective cancer immunosuppression strategy. Life sciences. 2024;357:123113.
120. Wolde T, Bhardwaj V, Reyad-Ul-Ferdous M, Qin P, Pandey V. The Integrated Bioinformatic Approach Reveals the Prognostic Significance of LRP1 Expression in Ovarian Cancer. International journal of molecular sciences. 2024;25(14).
121. Gong X, Chi H, Strohmer DF, Teichmann AT, Xia Z, Wang Q. Exosomes: A potential tool for immunotherapy of ovarian cancer. Frontiers in immunology. 2022;13:1089410.
122. Luo H, Zhou Y, Zhang J, Zhang Y, Long S, Lin X, et al. NK cell-derived exosomes enhance the anti-tumor effects against ovarian cancer by delivering cisplatin and reactivating NK cell functions. Frontiers in immunology. 2022;13:1087689.
123. Lyu C, Sun H, Sun Z, Liu Y, Wang Q. Roles of exosomes in immunotherapy for solid cancers. Cell death & disease. 2024;15(2):106.
124. Zhao G, Wang Y, Xing S, Jiang Y, Ding J, Cai Y, et al. Exosome-based anticancer vaccines: From Bench to bedside. Cancer letters. 2024;595:216989.
125. Ubanako P, Mirza S, Ruff P, Penny C. Exosome-mediated delivery of siRNA molecules in cancer therapy: triumphs and challenges. Frontiers in molecular biosciences. 2024;11:1447953.
126. A Study to Validate the Exosome Ovarian Cancer Score (OCS) for Recurrence Prediction and Monitoring in Ovarian Cancer. ClinicalTrialsgov2024.
127. Development of early diagnostic markers for ovarian cancer based on exosomes from different body fluids. Chictrorgcn2024.
128. Liu Y, Liu H, Zhu C, Yang Y, Shen Z, Shan G, et al. Tumor Small Extracellular Vesicle-Transmitted LncRNA CATED Promotes Platinum-Resistance in High-Grade Serous Ovarian Cancer. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2025;12(31):e05963.
129. Si C, Wang Y, Li Y, Chen Y, Fan Y, Wang Y, et al. Engineered NK92 Cell-derived Exosomes Inhibit Ovarian Cancer Progression by Degrading GPRC5A.16:1613178.
130. Wolde T, Bhardwaj V, Pandey V. Current Bioinformatics Tools in Precision Oncology. MedComm. 2025;6(7):e70243.
131. Wang Y, Lin W, Zhuang X, Wang X, He Y, Li L, et al. Advances in artificial intelligence for the diagnosis and treatment of ovarian cancer (Review). Oncology reports. 2024;51(3).
132. Kumar RMR. Exosome-Machine Learning Integration in Biomedicine: Advancing Diagnosis and Biomarker Discovery. Current medicinal chemistry. 2025;32(27):5760-71.
133. Keyvani V, Ghale-Noie ZN, Mollazadeh S, Mahmoudian RA, Ghorbani E, Naderi H, et al. Recent Progress in the Application of Exosome Analysis in Ovarian Cancer Management. Current cancer drug targets. 2024;24(9):920-9.
134. Hormaty S, Seiwan AN, Rasheed BH, Parvaz H, Gharahzadeh A, Ghaznavi H. A Review on Biomarker-

Enhanced Machine Learning for Early Diagnosis and Outcome Prediction in Ovarian Cancer Management. Cancer medicine. 2025;14(17):e71224.

135. Hussen BM, Abdullah SR, Hidayat HJ, Samsami M, Taheri M. Integrating AI and RNA biomarkers in cancer: advances in diagnostics and targeted therapies. Cell communication and signaling : CCS. 2025;23(1):430.

136. Youssef E, Palmer D, Fletcher B, Vaughn R. Exosomes in Precision Oncology and Beyond: From Bench to Bedside in Diagnostics and Therapeutics. Cancers. 2025;17(6).

137. Ma CY, Zhai Y, Li CT, Liu J, Xu X, Chen H, et al. Translating mesenchymal stem cell and their exosome research into GMP compliant advanced therapy products: Promises, problems and prospects. Medicinal research reviews. 2024;44(3):919-38.

138. Ansarian MA, Fatahichegeni M, Wang Y, Ren J, Zhang T, Wang X. Exosomal biomarkers in leukemia: translational potential and regulatory challenges for precision medicine applications. Frontiers in immunology. 2025;16:1677088.

139. Tian J, Han Z, Song D, Peng Y, Xiong M, Chen Z, et al. Engineered Exosome for Drug Delivery: Recent Development and Clinical Applications. International journal of nanomedicine. 2023;18:7923-40.

140. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-Based Drug Delivery: Translation from Bench to Clinic. Pharmaceutics. 2023;15(8).

141. Ranjan P, Colin K, Dutta RK, Verma SK. Challenges and future scope of exosomes in the treatment of cardiovascular diseases. The Journal of physiology. 2023;601(22):4873-93.

142. Rezabakhsh A, Sokullu E, Rahbarghazi R. Applications, challenges and prospects of mesenchymal stem cell exosomes in regenerative medicine. Stem cell research & therapy. 2021;12(1):521.

143. Sharma A, Yadav A, Nandy A, Ghatak S. Insight into the Functional Dynamics and Challenges of Exosomes in Pharmaceutical Innovation and Precision Medicine. Pharmaceutics. 2024;16(6).

144. Liu X, Teng X, Wang J, Zhang G, Guo W, Zhang W, et al. Exosome-based mucosal therapeutic and diagnostic system: towards clinical translation. Journal of controlled release : official journal of the Controlled Release Society. 2025;385:113966.

145. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal transduction and targeted therapy. 2024;9(1):17.

146. Amondarain M, Gallego I, Puras G, Saenz-Del-Burgo L, Luzzani C, Pedraz JL. The role of microfluidics and 3D-bioprinting in the future of exosome therapy. Trends in biotechnology. 2023;41(11):1343-59.

147. Nelson BC, Maragh S, Ghiran IC, Jones JC, DeRose PC, Elsheikh E, et al. Measurement and standardization challenges for extracellular vesicle therapeutic delivery vectors. Nanomedicine (London, England). 2020;15(22):2149-70.

Table 1. Principles, Advantages, and Disadvantages of Exosome Isolation Techniques

Separation Method	Principle	Advantages	Disadvantages	References
Ultracentrifugation	Sequential separation of particle components based on density, size, and shape	➢ Gold standard ➢ Large sample capacity	● High equipment cost and long processing time ● Labor-intensive ● High-speed centrifugation may damage exosome morphology and affect downstream analysis ● Low purity and recovery yield ● Not suitable for small sample volumes	[32, 33]
Ultrafiltration	Separation using ultrafine nanoporous membranes with specific molecular weight cut-offs	➢ Low equipment cost ➢ High portability	● Low yield and low purity ● High pressure during filtration may cause deformation or rupture of large vesicles, clog membrane pores, and affect downstream analysis	[33, 34]
Size-exclusion chromatography (SEC)	Utilizes a porous stationary phase to separate molecules by size; larger molecules elute first as they cannot enter the pores	➢ High purity ➢ Preserves exosome integrity and bioactivity ➢ Applicable to all sample types	● High equipment cost and long processing time ● Labor-intensive ● Requires additional exosome enrichment methods	[31, 34]
Polymer-based precipitation	Alters exosome solubility via water-excluding polymers, leading to precipitation from biological fluids	➢ Easy to use, no specialized equipment required ➢ High efficiency ➢ Suitable for both small and large sample volumes	● Variable quality of commercial kits ● Co-precipitation of non-exosomal materials (e.g., protein aggregates and polymer contaminants) may interfere with downstream analysis	[31, 134]
Immunoaffinity capture	Relies on specific binding between exosome surface markers and antibody-conjugated ligands	➢ High purity and specificity ➢ No special equipment required ➢ Suitable for small sample volumes	● High reagent cost ● Targets only specific exosome subpopulations; surface proteins and functionality may be damaged during elution ● Low yield ● Only applicable to cell-free samples	[33, 34]

Microfluidic technology	Employs microfluidic devices to separate exosomes based on various properties (e.g., size, affinity) quickly and efficiently	➢ Rapid separation, easy automation and integration ➢ High purity and recovery rate ➢ Applicable to very small sample volumes	● Low sample capacity ● Complex device design and high development cost ● Lack of standardization and large-scale validation for clinical samples	[33, 37, 141]

Table 2. Summary of potential exosomal miRNAs for OC diagnosis, prognosis, and treatment.

Source of exosomes	Potential exosomal miRNAs	Expression Change vs. Control	Functional effects on OC	Potential clinic utility for OC	References
Serum	miR-200a, miR-200b, miR-200c, miR-141	↑	-	Diagnosis, Staging	[90, 91]
Serum	miR-145, miR-93, miR-1290	↑	-	Diagnosis	[92, 93]
Plasma	miR-4732-5p	↑	-	Diagnosis	[94]
Cells	miR-222-3p, miR-940, miR-21-3p, miR-125b-5p, miR-181d-5p (Hypoxia)	↑	Induces M2 macrophage polarization / Drives TAM differentiation towards M2 phenotype (Hypoxia)	Therapeutic Target	[43, 45]
Cells	miR-205	↑	Promotes angiogenesis via the PTEN-AKT pathway	Therapeutic Target	[48]
Tissue	miR-205	↑	Downregulates PTEN, activates PI3K/AKT/mTOR pathway, induces M2-like polarization / Promotes cancer cell invasion and metastasis	Therapeutic Target	[70]
Cells (Hypoxia)	miR-130a	↑	Enhances vascular endothelial cell proliferation and angiogenesis	Therapeutic Target	[49]
Ascites	miR-6780b-5p	↑	Induces EMT and accelerates metastasis	Therapeutic Target	[56]
Adipose Tissue	miR-421	↑	Downregulates CBX7 to promote migration	Therapeutic Target	[58]
TAMs (Hypoxia)	miR-223	↑	Enhances chemoresistance via the PTEN-PI3K/AKT pathway	Therapeutic Target	[84]
Peritoneum	miR-149-3p, miR-222-5p, miR-1246	↑	Associated with decreased survival	Diagnosis, Prognosis	[103]
Cells	miR-543	↓	Targets IGF2 to inhibit proliferation (Tumor suppressive role)	Diagnosis, Therapeutic Target	[64]
Cells	hsa-miR-328-3p	↑	Interferes with Raf1, disrupts mTOR pathway, promotes autophagy	Therapeutic Target	[78]
TAMs	miR-29a-3p	↓	Increases PD-L1 expression via FOXO3-AKT/GSK3 β axis, promotes OC cell proliferation and immune escape	Therapeutic Target	[72]
Serum	miR-429	↑	Enhances OC cell proliferation and drug resistance by targeting the CASR/STAT3 pathway	Therapeutic Target	[114]

Table 3. Summary of potential exosomal circRNAs for OC diagnosis, prognosis, and treatment.

Source of exosomes	Potential exosomal circRNAs	Expression Change vs. Control	Functional effects on OC	Potential clinic utility for OC	References
Tissue, Plasma, Cells	circRNA051239	↑	Promotes proliferation and migration via ceRNA mechanism	Therapeutic Target	[65]
M2-TAMs	circTMCO3	↑	Enhances proliferation, migration, invasion, and metastasis via the miR-515-5p/ITGA8 axis	Therapeutic Target	[66]
Tissue, Serum	hsa_circ_0010467	↑	Promotes platinum resistance via the AUF1/miR-637/LIF/STAT3 axis	Prognosis, Therapeutic Target	[88]
Cells	circFoxo3	↑	Promotes proliferation, migration, and invasion via the miR-422a/PUM2 axis	Diagnosis	[99]
Serum	circFoxp1	↑	Promotes cell proliferation, confers DDP resistance; an independent predictor of survival and recurrence	Prognosis, Therapeutic Target	[100]
Tissue, Serum	circ_C20orf11	↑	Associated with advanced FIGO stage, high grade, lymph node metastasis; promotes DDP resistance via miR-527/YWHAZ axis and EV-mediated M2 macrophage polarization	Prognosis, Therapeutic Target	[104]
Serum	circ-0001068	↑	Acts as a ceRNA for miR-28-5p to induce PD1 expression in T cells	Diagnosis, Immunotherapy Target	[99]
Tissue, Cells	circWHSC1	↑	Promotes peritoneal dissemination, adhesion, and metastasis	Diagnosis, Therapeutic Target	[61]
Cells	circNFIX	↑	Promotes angiogenesis via the miR-518a-3p/TRIM44 axis	Therapeutic Target	[50]

Table 4. Summary of potential exosomal lncRNAs for OC diagnosis, prognosis, and treatment.

Source of exosomes	Potential exosomal lncRNAs	Expression Change vs. Control	Functional effects on OC	Potential clinic utility for OC	References
Plasma	SOX2-OT	↑	Enhances migration, invasion, proliferation, and malignant phenotype via the miR-181b-5p/SCD1 axis	Diagnosis, Therapeutic Target	[67]
Serum	UCA1	↑	Mediates cisplatin resistance via the miR-143/FOSL2 axis	Therapeutic Target	[85]
Ascites	PLADE	↑	Enhances platinum sensitivity by inducing R-loops	Therapeutic Target	[86]
Serum	MALAT1	↑	Associated with OC progression and metastatic phenotype	Prognosis	[105]
Cells	ATB	↑	Promotes angiogenesis and tumor microcirculation via the miR-204-3p/TGF β R2 axis	Diagnosis, Therapeutic Target	[52]
Cells	SPOCD1-AS	↑	Remodels mesothelial cells via G3BP1 interaction to promote peritoneal metastasis	Therapeutic Target	[63]
M2-TAMs	NEAT1	↑	Promotes proliferation and immune escape via the miR-101-3p/ZEB1/PD-L1 axis	Therapeutic Target	[73]
Serum, Ascites	AFAP1-AS1	↑	Associated with advanced FIGO stage and larger tumor diameter; promotes migration and invasion	Therapeutic Target	[116]
Cells	FAL1	↑	Suppresses metastasis via the PTEN/AKT signaling pathway	Therapeutic Target	[117]

Table 5. Summary of potential exosomal proteins for OC diagnosis, prognosis, and treatment.

Source of exosomes	Potential exosomal proteins	Expression Change vs. Control	Functional effects on OC	Potential clinic utility for OC	References
Serum	CA125	↑	Improves diagnostic efficiency when combined with serum HE4	Diagnosis	[95]
Tissue	TUBB3, EpCAM, CLDN3, PCNA, EGFR, APOE, FASN	↑	-	Diagnosis, Therapeutic Target	[96]
Serum	APOE, EpCAM	↑	-	Diagnosis	[97]
Serum	CRABP2	↑	Enhances cell proliferation; reprograms metabolism	Diagnosis, Prognosis, Distinguishes LMP and LGSOC	[68]
Plasma	CAV1	↓	Low expression associated with advanced stage and poor prognosis	Prognosis	[101]
Plasma	FGG, LBP	↑	High expression associated with shorter survival	Prognosis	[102]
Cells	PKR1	↑	Enhances endothelial cell migration and tube formation; promotes angiogenesis	Therapeutic Target	[51]
Cells	CD44	↑	Reprograms peritoneal mesothelial cells to an EMT phenotype; promotes invasion and migration	Therapeutic Target	[55]
Tissue	CMTM4	↑	Promotes M2 macrophage polarization; suppresses T-cell function	Prognosis, Therapeutic Target	[71]
Cells	CD47	↑	High expression associated with poor PFS; inhibits macrophage phagocytosis; promotes immune escape	Prognosis, Therapeutic Target	[74]
Cells	DNMT1	↑	Promotes tumor drug resistance	Therapeutic Target	[89]
Serum	SLC11A2	↑	Promotes cell migration; inhibits cisplatin-induced apoptosis	Diagnosis, Therapeutic Target	[115]

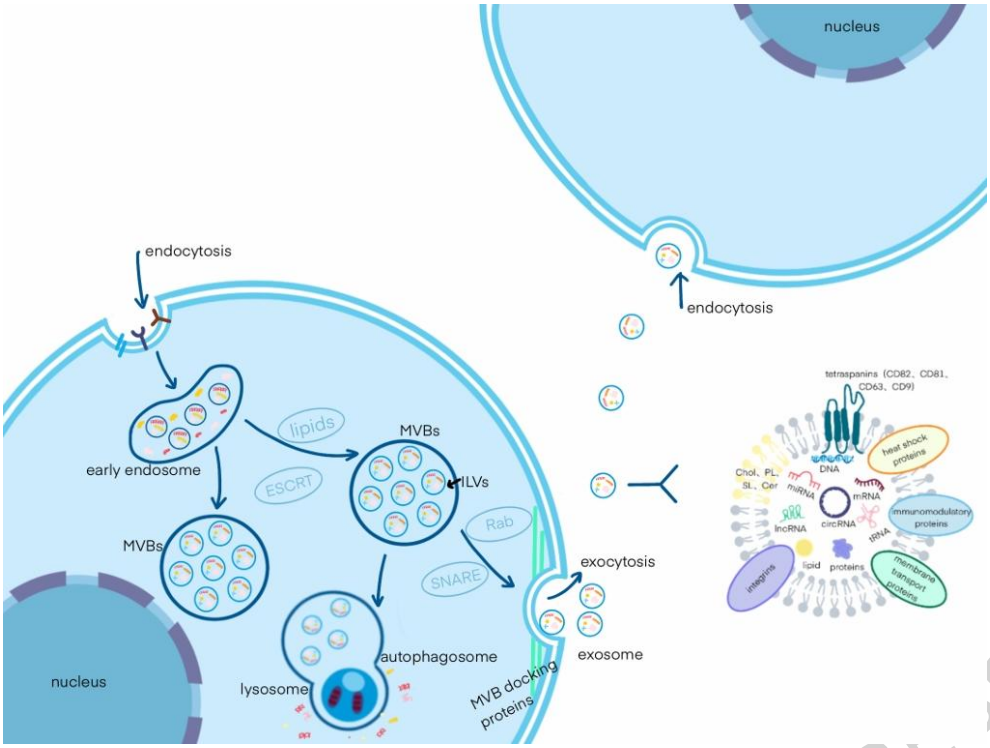
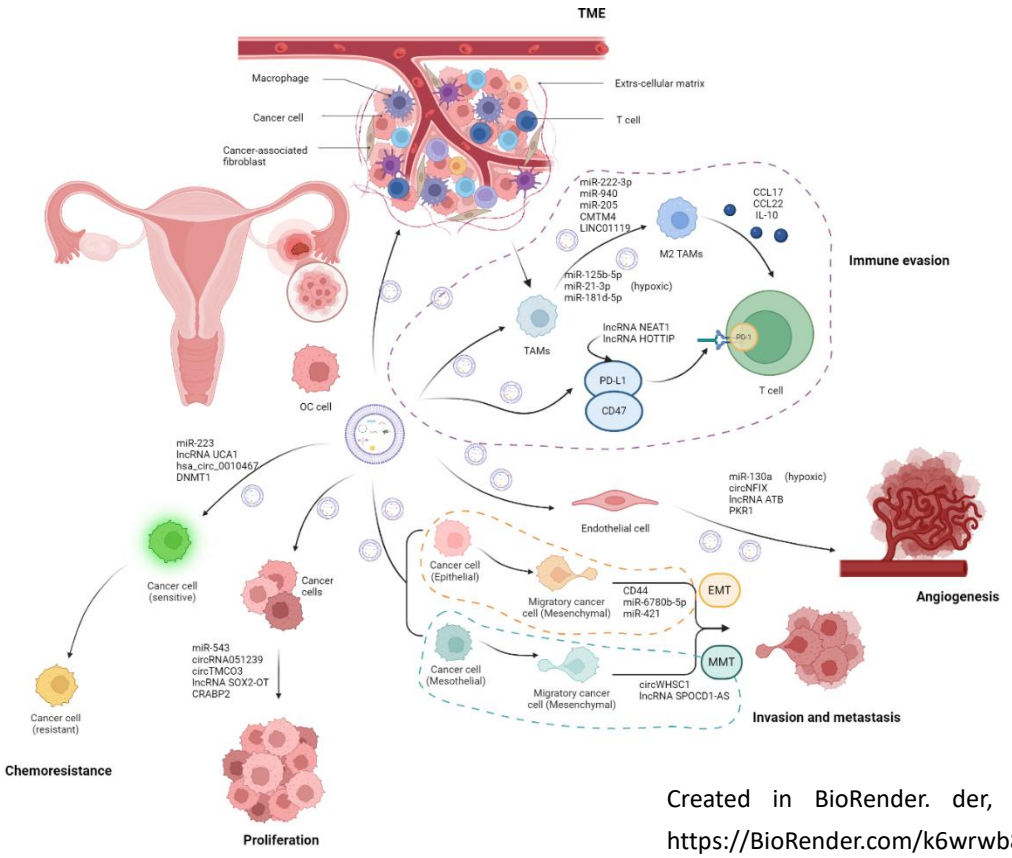


Figure1. Schematic Diagram of Exosome Biogenesis, Release, and Structure

Exosomes are formed through the budding of early endosomes and the generation of multivesicular bodies (MVBs), which contain intraluminal vesicles (ILVs). A subset of MVBs may fuse with autophagosomes for degradation in lysosomes or directly fuse with lysosomes for degradation; the resulting degradation products can be recycled by the cell. Another subset of MVBs is transported to the plasma membrane, where they dock on the luminal side with the assistance of MVB-docking proteins and subsequently release exosomes via exocytosis. The biogenesis of MVBs involves ESCRT complexes, lipids, and tetraspanins. RAB and SNARE proteins are involved in the trafficking of MVBs to the plasma membrane and the secretion of exosomes. Exosome surface proteins include tetraspanins, integrins, immunomodulatory proteins, among others. The main components of exosomes consist of proteins, nucleic acids, and lipids.



Created in BioRender. der, b. (2025) https://BioRender.com/k6wrwb8

Figure 2. Schematic diagram of the multiple roles of exosomes in the pathogenesis of OC

Exosomes facilitate intercellular communication by transferring bioactive molecules (such as miRNAs, circRNAs, lncRNAs, and proteins) between tumor cells and the tumor microenvironment. This illustration demonstrates how ovarian cancer-derived exosomes coordinate multiple pro-tumor processes, including: (1) TME remodeling and immune evasion; (2) angiogenesis; (3) invasion and metastasis; (4) proliferation; and (5) drug resistance. Key molecules involved (e.g., miR-222-3p, CD47, circNFIX, CD44, etc.) are annotated in the figure. Created with BioRender.