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REVIEW ARTICLE

The diagnostic and therapeutic prospects of exosomes in ovarian cancer

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Abstract
Exosomes are nano-sized vesicles derived from the endosomal system and are involved in many biological and pathological processes. Emerging evidence has demonstrated that exosomes with cell-specific constituents are associated with the tumorigenesis and progression of ovarian cancer. Therefore, exosomes derived from ovarian cancers can be potential diagnostic biomarkers and therapeutic targets. In this review, we briefly present the biological characteristics of exosomes and the recent advances in isolating and detecting exosomes. Furthermore, we summarise the many functions of exosomes in ovarian cancer, hoping to provide a theoretical basis for clinical applications of exosomes in the diagnosis and treatment of ovarian cancer.

KEYWORDS
biomarker, exosomes, ovarian cancer, therapy

1 | INTRODUCTION

Ovarian cancer is one of the most common malignancies in the female reproductive system and has the highest mortality rate among gynaecological cancers.[1] Albeit the 5-year relative survival rate of patients diagnosed at the early stage (International Federation of Gynecology and Obstetrics, FIGO, stage I or II) can reach 90%, more than 70% of patients are diagnosed with advanced disease (FIGO stages III–IV).[2] Patients diagnosed at advanced stages have a poor prognosis with a 5-year survival rate of 31% for those with epithelial histological type (https://www.cancer.org). Despite novel therapies, such as targeted therapy and immunotherapy in recent years, the survival rate with current treatments for ovarian cancer remains disappointing.[3] There is an urgent need to identify biomarkers to detect and treat ovarian cancer.

Exosomes are a heterogeneous population of extracellular membranous vesicles with a diameter of 40–160 nm (approx. 100 nm on average) that are enriched in lipids, nucleic acids and protein complexes.[4,5] Exosomes play an important role in many aspects of human disease, including diabetes, neurodegeneration and cancer.[6–8] Previous reviews have summarised the functions of exosomes in regulating tumour metastasis, drug resistance and immune modulation in ovarian cancer.[9–11] In this review, we first describe the biological characteristics of exosomes and briefly introduce recent advances in isolating and detecting exosomes, in order to better understand the functional roles of exosomes in ovarian cancer. We then summarise the underlying mechanisms of exosomes regulating ovarian cancer and highlight the potential clinical application of exosomes in ovarian cancer diagnosis and therapeutics, hoping to bring new insights into precision medicine.

2 | BIOLOGICAL CHARACTERISTICS OF EXOSOMES

The biogenesis of exosomes occurs within the endosomal system.[4] It involves three main steps: the involution of cell membranes to form endosomes; the generation of intraluminal vesicles (ILVs) inside multivesicular bodies (MVBs); and the fusion of MVBs with the plasma membrane to release exosomes (Figure 1). Exosomal membranes consist of lipid bilayers, with lipid and protein profiles that are distinct from their parental cells.[12] Exosomes possess several families of proteins unique to the endosomal pathway, such as

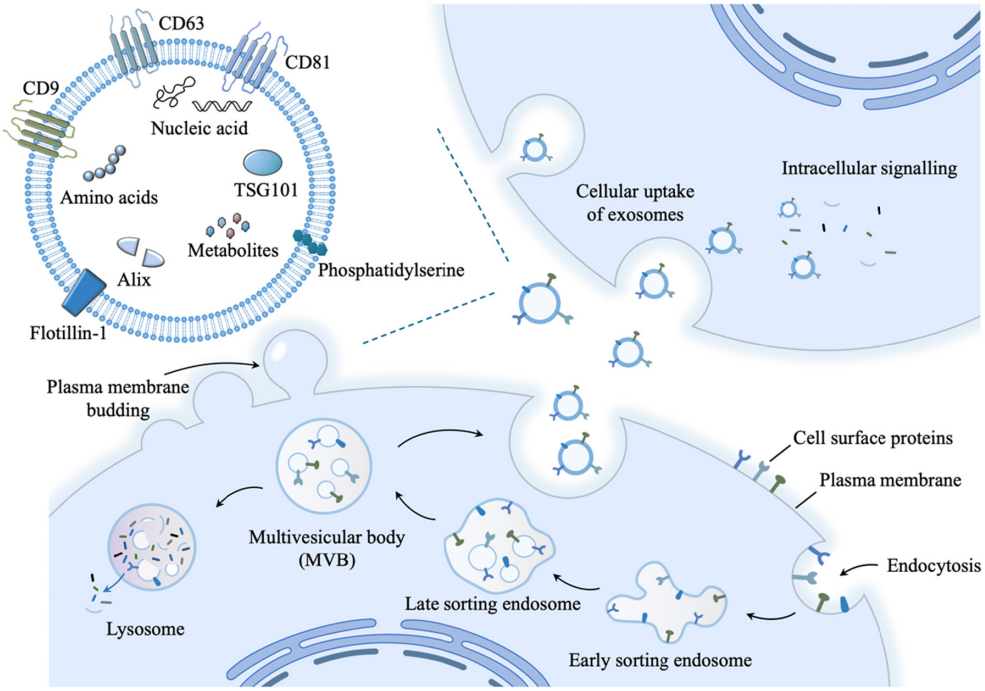

FIGURE 1 The biogenesis and characteristics of exosomes. The biogenesis of exosomes begins with an inward budding of the plasma membrane, leading to the formation of early endosomes and multivesicular bodies (MVBs). MVBs subsequently fuse with the plasma membrane and release the exosomes to the intercellular microenvironment. Exosomes contain multiple bioactive molecules, ranging from proteins, nucleic acids (e.g. RNA and DNA), lipids to metabolites

tetraspanins (CD9, CD63, CD81), tumour-sensitive gene 101 (TSG101), heat-shock proteins (Hsc70), lysosomal proteins (Lamp2b) and fusion proteins (flotillin and annexin), which are commonly used to distinguish exosomes from other vesicles.[13] Moreover, exosomes contain multiple types of bioactive molecular cargo, consisting of proteins, nucleic acids, lipids and metabolites.[4] A straightforward approach based on analysing the variety of key contents is helpful in uncovering the biological functions of exosomes associated with different tissues and cell types. The content of exosomes identified in multiple organisms are indexed by ExoCarta (http://www.exocarta.org).

3 | THE ISOLATION AND DETECTION OF EXOSOMES

The isolation and detection of exosomes in biological samples is essential for basic research and clinical translation. In recent decades, many methods have been developed to isolate exosomes from biological samples based on their size and affinity (Figure 2).[14,15] Ultracentrifugation is the most commonly used method for isolating exosomes, with density gradient ultracentrifugation using sucrose or iodixanol considered the gold standard.[16] Although ultracentrifugation is easy to operate and yields exosomes with higher purity, it is time-consuming and requires large sample volumes, limiting its large-scale clinical application. Size-based ultrafiltration is another commonly used method for isolating exosomes through membrane filters with specific size-exclusion thresholds.[17] Ultrafiltration can be coupled with ultracentrifugation, whereby ultrafiltration is used to remove cell debris and large vesicles and then ultracentrifugation provides a further purification of exosomes.[14] Many commercial kits for isolating exosomes are based on precipitation reactions, including ExoQuick (System Biosciences, Palo Alto, CA, USA) and Total Exosome Isolation Reagent (Invitrogen, Waltham, MA, USA).[18] The isolation of exosomes can also be achieved by immunoaffinity capture, microfluidics and thermophoresis techniques.[19–21]

The characterization of exosomal cargo may reveal unique components of specific exosomes and provide accurate cancer-related information. Techniques for exosomal protein detection include western blotting and enzyme-linked immunosorbent assay (ELISA). Techniques for exosomal nucleic acid detection include reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR), microarray and next-generation sequencing.[14] Newer detection platforms, such as colorimetric detection and droplet digital PCR (ddPCR), may aid in the detection of exosomes of interest.[22]

4 | ROLES OF EXOSOMES IN OVARIAN CANCER

Exosomes in biological fluids may be related to multiple pathological and physiological processes. Exosomes participate in expelling excess and/or non-functional cellular components, recycling materials between cells, intercellular

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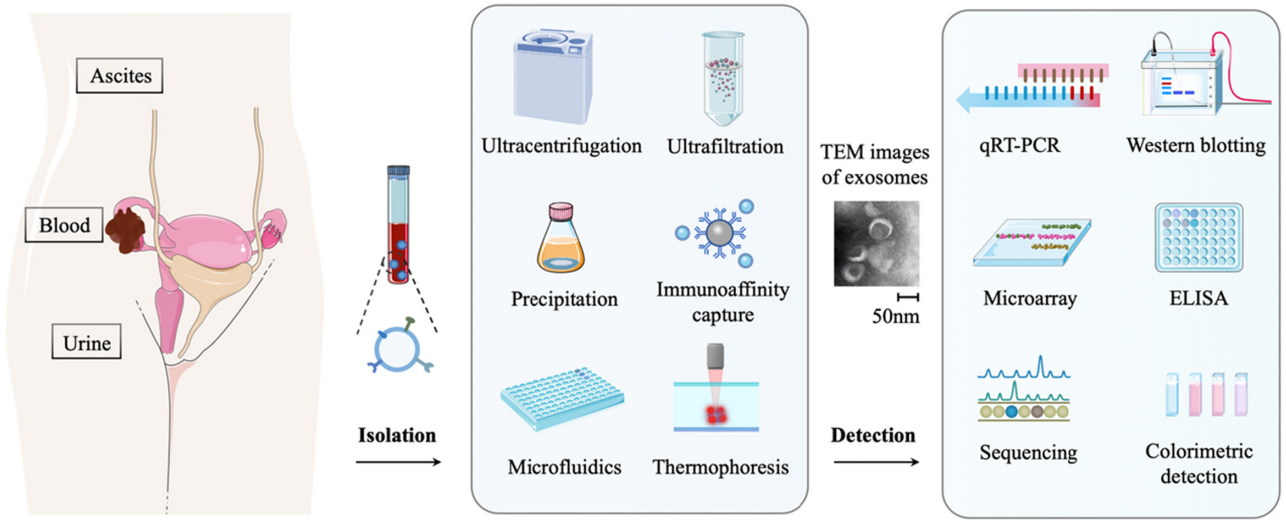

FIGURE 2 Technologies for the isolation and detection of exosomes. Traditional and advanced technologies have been used to isolate exosomes from various biological fluids and to detect specific cargoes in exosomes

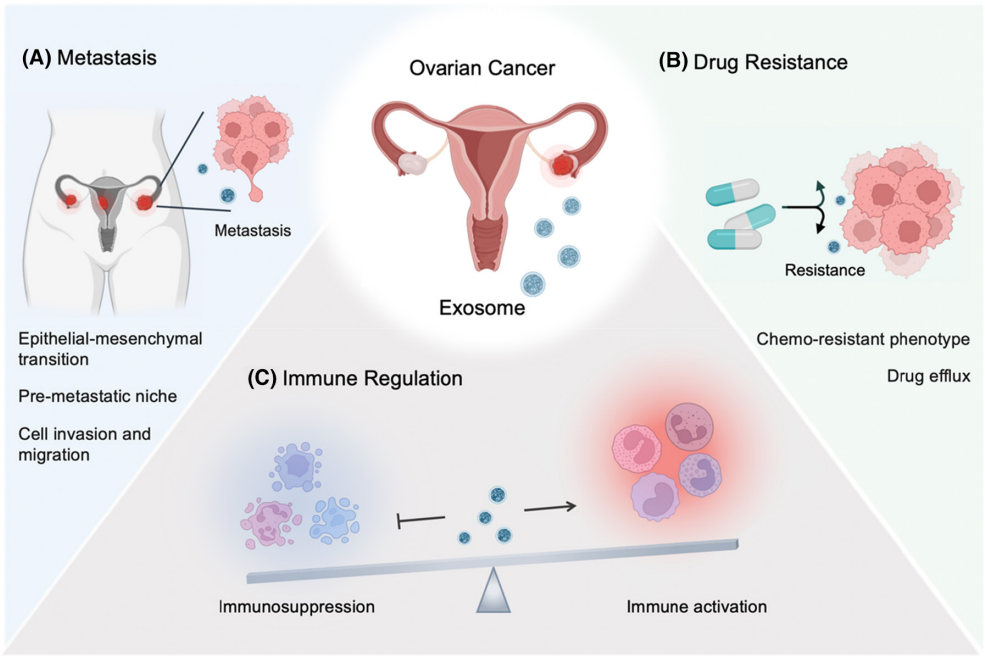

FIGURE 3 The roles of exosomes in ovarian cancer. Exosomes exert crucial regulatory influences on diverse processes of ovarian cancer development. (A) Metastasis: exosomes are essential for epithelial–mesenchymal transition and the formation of the pre-metastatic niche of ovarian cancer, coupled with promoting cell invasion and migration. (B) Drug resistance: the capability of eliciting a chemo-resistance phenotype of ovarian cancer cells and promoting cellular drug efflux enable exosomes to induce chemotherapy resistance. (C) Immune regulation: most tumour-derived exosomes perform immunosuppressive effects to boost the development of ovarian cancer, whereas some exosomes can inversely exert a positive regulation of immune response to hold back tumour progression. Figure created with https://www.biorender.com

communication and remodelling the tumour microenvironment (TME).[23] Studies have shown that tumour cells secrete more exosomes than normal cells, and that exosomes derived from tumour cells may promote tumour progression by modifying local and distant microenvironments.[8] Herein, we summarise the functions of exosomes in the metastasis, drug resistance and immune regulation of ovarian cancer (Figure 3).

4.1 | Role in metastasis

Recent studies have unravelled the contribution of TME to ovarian cancer metastasis, and the role of exosomes in shaping the TME.[24] Exosomes may facilitate metastasis by shaping pre-metastatic niches. Ovarian tumour-derived exosomes can prepare the distant TME by regulating intercellular communication between tumour cells and normal

stroma, cancer-associated fibroblasts and local immune cells.[9] Exosomes may promote epithelial-mesenchymal transition (EMT) in ovarian cancer cells and induce angiogenesis.[25–27] Proteomic analysis reveals that exosomes derived from ovarian cancer cells are associated with invasive capacity.[28,29] Taken together, exosomes modulate TME, thereby enhancing the invasion and migration of ovarian cancer cells, and reinforcing the formation of pre-metastatic niches. Decoding exosomes will provide new insights into the underlying mechanism of ovarian cancer metastasis, highlighting its potential as a novel therapeutic target for metastatic ovarian cancer.

4.2 | Role in drug resistance

Drug resistance is the major cause of treatment failure in patients with ovarian cancer.[30] Recent evidence suggests that exosomes may play a role in facilitating drug resistance. Several studies have implicated the exosomal transport of microRNA in establishing carboplatin and paclitaxel resistance in ovarian cancer.[31–34] Other endosomal cargoes have also been implicated in inducing drug resistance by trafficking proteins to ovarian cancer cells, which are implicated in cancer growth, such as signal transducers and activators of transcription 3 (STAT3) and fatty acid synthase (FAS).[35] Endosome-mediated autocrine and paracrine plasma gelsolin signalling may effect chemo-resistance in ovarian cancer cells.[36] Another mechanism by which exosomes may contribute to drug residence in ovarian cancer is through the direct efflux of drugs in a concentration-dependent manner.[37] A further understanding of the mechanisms of exosome-mediated drug resistance could help to devise novel synergistic combination therapies for overcoming drug resistance in ovarian cancer.

4.3 | Role in immune regulation

Most tumour-associated exosomes have immunosuppressive effects, which inhibit the antitumour response of tumour-specific T-cells and may induce the functional arrest of native T-cells, adoptively transferred tumour-specific T-cells or chimeric antigen receptor T-cells.[38] Consistent with this, Zhou et al. found that exosomes released from tumour-associated macrophages deliver miRNA into $CD4^+$ T-cells, which then induce a Treg/Th17 cell imbalance.[39] Additionally, exosomes carry PD-L1 on their surface, which may contribute to immunosuppression by anti-PD-1 response.[40] For immunosuppressive exosomes, targeting exosomal phosphatidylserine represents a promising strategy to enhance antitumour T-cell responses in TME.[41] However, some exosomes activate dendritic cells, natural killer cells and T cells to exert an antitumorigenic effect through stimulating both the innate and adaptive immune systems,[11] indicating the complex role of exosomes in the immune microenvironment of ovarian cancer.

5 | EXOSOMES SERVE AS BIOMARKERS OF OVARIAN CANCER

In current clinical practice, cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) are the most established biomarkers of ovarian cancer.[42,43] However, neither marker has proven to be effective for the early detection of ovarian cancer, and both markers have limitations when used for disease monitoring. Recent studies suggest that exosomes may be promising biomarkers for both applications because tumour-derived exosomes contain mobile information about the molecular make-up of parent tumours and may be detectable in blood, urine, saliva, and malignant effusions.[44] In this section, we summarise exosomal proteins and miRNAs as diagnostic and prognostic biomarkers of ovarian cancer (Figure 4). Remarkably, in addition to exosomal proteins and miRNAs, long noncoding RNAs (lncRNAs) and phosphatidylserine (PS) carried by exosomes may also be potential biomarkers.[45]

5.1 | Exosomal proteins as biomarkers

Compared with exosomes derived from normal tissue, exosomes from ovarian cancer contain some higher levels of proteins, such as CD24, Claudin-4 and small heat-shock proteins, which might serve as biomarkers of ovarian cancer.[46–48] Exosomal proteins may also have utility as prognostic biomarkers. Meshach et al. have reported that an elevated endosomal level of plasma gelsolin (pGSN) is associated with poorer overall survival and relapse-free survival in patients with ovarian cancer.[36] Other exosomal proteins that may have value in predicting the effectiveness of chemotherapy among ovarian cancer patients include annexin A3, multidrug resistance-associated protein 2 (MRP2), ATPase copper transporting alpha (ATP7A) and ATPase copper transporting beta (ATP7B).[49]

5.2 | Exosomal miRNAs as biomarkers

The miRNA profiles of circulating tumour-derived exosomes have been proposed as possible biomarkers for ovarian cancer.[50] Several groups have demonstrated that the miRNA profiles of exosomes isolated from the sera of patients with benign ovarian pathology differ from those of patients with ovarian cancer, including patients with chemo-sensitive and chemo-resistant disease.[51–53] The levels of some exosomal miRNAs have been shown to correlate with CA125 levels.[54] Although such studies suggest that exosomal miRNA profiles have potential utility as biomarkers, the clinical utility is as yet unproven.

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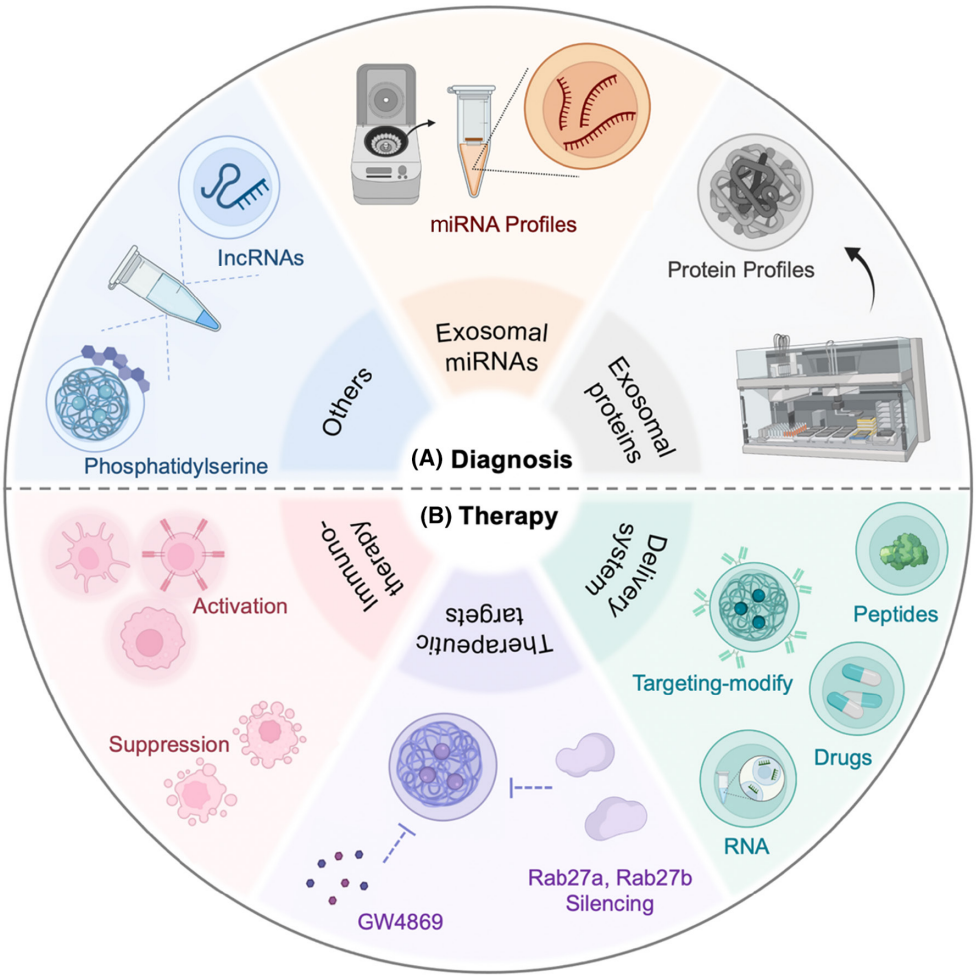

FIGURE 4 Potential clinical applications of exosomes in ovarian cancer. (A) Diagnostic potential of exosomes in ovarian cancer. These exosomal proteins and miRNAs can be detected from liquid biopsy samples, thus making them novel non-invasive diagnostic and prognostic biomarkers of ovarian cancer. The lncRNAs and phosphatidylserine carried by exosomes can also act as surrogate biomarkers for ovarian cancer. (B) Therapeutic potential of exosomes in ovarian cancer. Exosomes can be modified with diverse ligands and deliver therapeutic agents, such as RNA, peptides and chemotherapeutic drugs. Specifically removing exosomes by GW4869 and Rab27a/b silencing is the mainstay of exosome-targeting strategies. Exosomes may activate or inhibit antitumour immune responses, thereby participating in the immunotherapy of ovarian cancer. Figure created with https://www.biorender.com

6 | THERAPEUTIC POTENTIAL OF EXOSOMES

In this section, we discuss three potential therapeutic applications of exosomes in ovarian cancer: (1) exosome-mediated drug delivery systems; (2) exosome-based immunotherapy; and (3) exosomes as therapeutic targets (Figure 4).

6.1 | Exosome-mediated delivery system

Exosomes are stable in circulation and do not elicit immune rejection, making them attractive as vehicles for targeting treatment for ovarian cancer.[55,56] Recent advances in bioengineering and nanotechnology enable many classes of therapeutic agents to be encapsulated into tumour-targeted exosomes.[57] The feasibility of such strategies has been demonstrated in vitro and in xenograft models of ovarian cancer.[58,59] Doxorubicin encapsulated in exosome-like particles had superior cytotoxic and less target effects in vitro.[60] An important potential application of endosomes is in the delivery of natural products with promising anticancer activity, such as curcumin and triptolide, that have low bioavailability and non-specific selectivity.[61,62] Currently, there is an ongoing phase-I clinical trial to investigate the feasibility of plant-derived exosomes to increase the bioavailability of curcumin (NCT01294072).

6.2 | Exosome-based immunotherapy

Cancer immunotherapy is a novel type of treatment based on stimulating the host immune system to activate the antitumour immune response and/or overcome the pathway leading to tumour escape.[63] Tumour-related exosomes contribute to immunosuppression and tumour immunity

escape mechanisms in ovarian cancer.[64–66] Eliminating immunosuppressive exosomes in the TME of ovarian cancer may enhance antitumour immune responses for immunotherapy. It is possible that exosomes could also be used to induce a cytotoxic T lymphocyte-dependent antitumour response in ovarian cancer.[67,68] A separate line of study has explored the role of tumour-derived exosomes in eliciting a tumour-specific immunological response, suggesting a role for exosomes in the development of antitumour vaccines or cellular therapies.[69]

6.3 | Exosomes as therapeutic targets

As tumour-derived exosomes play an important role in the progression of ovarian cancer, removing exosomes from peripheral circulation and blocking exosome production and secretion from cancer cells are appealing therapeutic strategies. Studies in vitro have demonstrated that it is possible to remove exosomes from patient blood by using Hemopurifier® (Aethlon Medical, Inc., San Diego, CA, USA), an extracorporeal hemofiltration device containing fibres with a high affinity for exosomes.[70] Another strategy targets proteins involved in the biogenesis and secretion of exosomes.[71–73] Yet another approach focuses on blocking the production of exosomes by inhibiting sphingomyelinase and blocking the production of ceramide, a necessary component of exosomes.[74] Each strategy has the potential to generate novel target therapies for ovarian cancer.

7 | CONCLUSIONS AND PERSPECTIVES

Over the past two decades, the rapid development of biological techniques has contributed to the breakthrough in exosome research. As a part of TME, exosomes exert an important role in tumour metastasis, drug resistance and the immune regulation of ovarian cancer. Elucidating the effects of ovarian cancer-derived exosomes on the extracellular milieu will provide new insights for ovarian cancer therapy. New strategies, such as the elimination of specific exosomes to slow tumour progression and the transfection of exosomes with specific miRNAs to reverse drug resistance, are attractive, and may yield a new paradigm in ovarian cancer therapy.

Exosomes have unique advantages as drug delivery vehicles and diagnostic biomarkers. As endogenous carriers of molecular cargo, exosomes are ideal drug delivery vehicles because of their capacity to remain in circulation, augment targeting, improve biostability and reduce cytotoxicity. Preclinical trials have demonstrated that exosome-based drug delivery can improve the efficacy of conventional chemotherapy against ovarian cancer and reduce systemic side effects. Furthermore, because they resemble corresponding parent cells to a great extent and steadily circulate in various body fluids, exosomes have a unique value for non-invasive liquid biopsy. Nevertheless, the nano-size and high heterogeneity of exosomes bring technical challenges to exosomal isolation and detection. Further improvements in the isolation of exosomes from body fluids and the high-throughput analysis of exosomal contents may facilitate their development as biomarkers in ovarian cancer.

AUTHOR CONTRIBUTIONS

Conceptualization: CB and QC. Investigation: CB and QC. Writing – original draft preparation: QC and JS. Writing – review and editing: QC and DR. Visualization: JS and DR. Supervision: CB. All authors have read and agreed to the published version of the article.

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CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS APPROVAL

This study involved only literature review of previously published studies and the contained data. As such, this work was considered exempt from ethical approval.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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