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REVIEW

# Small Extracellular Vesicles: Unraveling Their Roles in Ovarian Cancer Progression and Tapping Into Clinical Application Potential

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**Abstract:** Among gynecologic malignancies, ovarian cancer (OC) stands out as a highly aggressive disease with the highest mortality rate and the poorest prognosis. At the beginning stage, it demonstrates high sensitivity to platinum-based chemotherapy. Nevertheless, most patients will encounter recurrence following the initial surgery and chemotherapy. Small extracellular vesicles (sEVs), characterized by a "cup-shaped" morphology and with a diameter of 40 to 160 nm, encompass diverse biologically active substances including nucleic acids (such as DNA, mRNA, microRNA (miRNA), and other non-coding RNAs (ncRNAs)), as well as oncogenic proteins, lipids, and metabolites, which play a crucial role as mediators of intercellular communication. Increasing evidence shows that sEVs promote various cancers' progression (including OC) via transporting molecular cargoes to target cells or organs. It is worth mentioning that existing literature often focuses on sEVs from a single cell type and lacks a comprehensive review of multiple cell sources. In this review, we summarize the biological functions of sEVs derived from different cell types in OC, including regulating cell proliferation, promoting metastasis, mediating drug resistance, inducing angiogenesis, facilitating immune escape, and maintaining stemness. Meanwhile, we focus on exploring the clinical value of sEVs as biomarkers for the diagnosis and prognosis of OC, as well as their application potential in translational medicine fields related to cancer vaccine development, targeted drug delivery, and precision tumor-targeted therapy. Additionally, we analyze the major challenges currently faced in sEV-based OC treatment research and propose potential strategies to overcome these limitations.

**Keywords:** small extracellular vesicles, ovarian cancer, biological functions, biomarker, therapeutic research

## Introduction

Ovarian cancer (OC) ranks third in terms of commonality and is the most lethal malignant tumor within the female reproductive system. Globally, 313,959 cases of OC occur annually, while more than 150,000 deaths from OC occur annually.[1–4] Numerous challenges exist in the early diagnosis of OC. Owing to the absence of specific early symptoms and effective screening approaches, 70% of patients are diagnosed at advanced stages (FIGO stage III or IV) when distant metastases have already occurred.[5] The typical treatment protocol for OC (integrating tumor cytoreduction and platinum-based chemotherapy) proves effective merely in a limited number of patients. The majority of patients experience relapse after undergoing initial surgery and chemotherapy, and the overall 5-year survival rate is 49.7%.[6] Notably, the application of anti-programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) has exerted a transformative impact on the treatment paradigm of OC to a certain extent.[7] Regrettably, however, regardless of whether they are utilized as a monotherapy or in a combination regimen, their efficacy in the treatment of OC has never managed to meet the expected level.[8] Relevant clinical trials have shown that OC patients undergoing ICI-based therapy have only a 10–15% therapeutic response rate and are limited to some extent by multiple

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inflammatory toxicities.[9,10] Given the existing dilemmas in the early diagnosis and treatment of OC, there is an urgent need to further explore more precise and efficient detection methods and develop more effective treatment strategies.

Small extracellular vesicles (sEVs) are nanoscale vesicles that possess a single membrane and can be secreted by multiple cell types (including tumor cells, stromal cells, and immune cells). They have diameters of 40–160 nm and display a characteristic "cup-shaped" morphology under transmission electron microscopy (TEM), as shown in Figure 1.[11,12] They have been widely reported to carry diverse molecular cargos like nucleic acids (including DNA, mRNA, microRNA (miRNA), and other non-coding RNAs (ncRNAs)), oncogenic proteins, lipids, and metabolites, and are crucial for the intricate communication among different cells and tissues.[13] Notably, sEVs are stably present in nearly all bodily fluids, including ascites, plasma, serum, urine, breast milk, and tear fluid, and are endowed with key characteristics such as high biocompatibility, low immunogenicity, a long circulatory half-life, and low cytotoxicity.[14] As a critical parameter influencing the biological activity and clinical application value of sEVs, their circulating half-life typically ranges from several minutes to a few hours and is regulated by multiple factors, such as the cellular source of sEVs, surface modification status, mononuclear phagocyte system, and administration route.[15,16] For instance, the surface molecule CD47, polyethylene glycolation modification, and cyclic peptide modification can all effectively prolong their circulatory half-life.[17–19] Based on the aforementioned characteristics, sEVs can offer minimally invasive access to disease-specific biomarkers, enabling earlier and more accurate diagnosis and prognosis by reflecting the molecular profile of their parent cells and disease progression.[20] In addition, sEVs play a key role in cancer translational therapy by being utilized for tumor vaccine development to activate antitumor immunity, serving as carriers for targeted drug delivery, and blocking tumor progression via targeted strategies and assisting in the optimization of therapeutic regimens.

Emerging evidence has confirmed that sEVs, as a critical component of the tumor microenvironment (TME), promote the initiation and progression of various cancers, including OC, through multiple mechanisms. These mechanisms include upregulating the expression of stem cell-specific markers, enhancing cell proliferation, facilitating metastatic capacity, increasing chemoresistance, inducing angiogenesis, regulating TME homeostasis, and modulating immune escape-related factors.[21,22] Notably, the TME in OC drives tumor growth, metastasis, and drug resistance through complex crosstalk between cancer cells, stromal cells, and extracellular matrix (ECM) components, and these diverse cellular constituents of the TME all secrete sEVs that collectively mediate the aforementioned regulatory effects. These intercellular interactions within the TME further modulate signaling pathways and immune responses, ultimately shaping disease progression and therapeutic outcomes.[23,24] However, most of the existing review literature focuses on the action mechanisms of sEVs derived from a single type of cell on OC. Although a small number of review studies have involved the exploration of sEVs from multiple cell sources, these studies are often not comprehensive enough and only select certain cells for analysis and discussion rather than systematically covering the full spectrum of TME-derived sEVs.

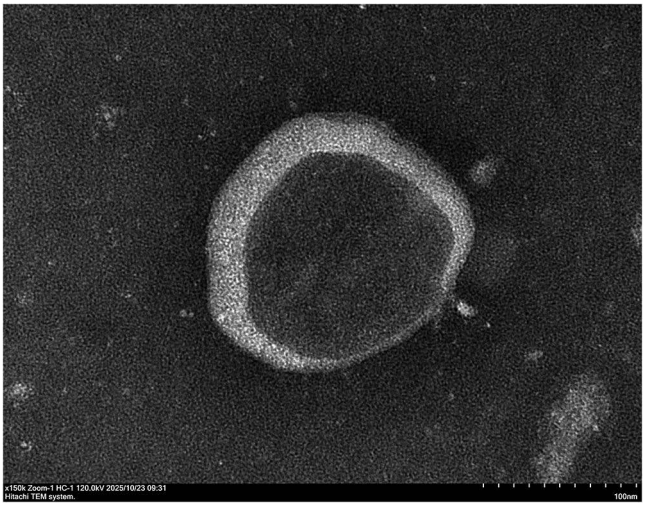


**Figure 1** TEM image of sEVs.

Accordingly, this review summarizes the potential molecular mechanisms by which sEVs derived from different cell types regulate the oncogenesis and progression of OC, elucidates their clinical value as biomarkers for the diagnosis and prognosis of OC, and outlines their application potential in OC vaccine development, targeted drug delivery, and precision tumor-targeted therapy. Meanwhile, we explore the current challenges faced by sEV-based OC treatment research and seek innovative approaches to break through these barriers.

# Methods

## Search Strategy

To ensure the transparency of literature retrieval and selection, this review refers to the PRISMA guidelines for reporting standardization (note: this is a narrative review, not a systematic review/meta-analysis).[25] PubMed, Embase, and Web of Science were comprehensively searched for three categories of research studies: (1) those investigating sEVs derived from different cell types that promote the development and progression of OC; (2) those reporting sEVs isolated from various bodily fluids as biomarkers for OC; and (3) those analyzing the translational applications of sEVs in OC vaccine development, targeted drug delivery, and tumor-targeted therapy. The search timeframe spanned from January 1, 2016, to July 31, 2025. The search strategy included the following terms: ("extracellular vesicles" OR "small extracellular vesicles" OR "exosomes" OR "ectosomes" OR "sEVs" OR "EVs" OR "microvesicles") AND ("ovarian" OR "ovary") AND ("cancer" OR "carcinoma" OR "neoplasia" OR "adenocarcinoma" OR "serous carcinoma" OR "mucinous carcinoma" OR "endometrioid carcinoma" OR "clear cell carcinoma").

## Inclusion and Exclusion Criteria

We included original in vivo, in vitro, and clinical studies that either: (1) investigate sEVs that promote OC progression, (2) explore sEVs from body fluids as OC biomarkers, or (3) analyze the application of sEVs in OC vaccine development, drug delivery, or tumor-targeted therapy.

We excluded case reports, case series, editorials, comments, letters to the editor, narrative reviews, meta-analyses, systematic reviews, and non-English full-text articles.

## Data Extraction

For each included study, the extracted data included: the cell type and biofluid type from which sEVs were derived, the molecular cargo carried by sEVs, the role and underlying mechanisms of sEVs in OC development and progression, biomarker types, details, and performance metrics (eg, area under the receiver operating characteristic curve (AUC), 95% confidence interval (95% CI), sensitivity, specificity, and hazard ratio (HR)), sample size and sample type, as well as the drugs loaded by sEVs as a targeted drug delivery system.

# Results

Figure 2 is a flowchart illustrating the process of searching, screening, and selecting references from the literature. According to our research strategy, a total of 3,552 studies were initially retrieved from the databases. After removing 1,099 duplicates, 2,453 articles were subjected to title and abstract screening, with 2,338 excluded primarily due to irrelevance to the core themes. Of the remaining 115 studies undergoing full-text evaluation, 28 were excluded for failing to meet the inclusion criteria (eg, non-original research, non-English full texts, or insufficient data). Finally, 87 studies were included in this review.

# Review

# The Promoting Effects of the Cargo of Tumor-Derived sEVs on OC

In recent years, with the continuous deepening of medical research, numerous studies have centered on the field of tumor-derived sEVs. These sEVs can be regarded as "messengers" dispatched by tumor cells, which directly and crucially promote multiple malignant behaviors of OC cells, such as proliferation, metastasis, chemoresistance, angiogenesis, and stem cell characteristics, through a variety of complex mechanisms.[26] The specific action mechanisms are detailed in

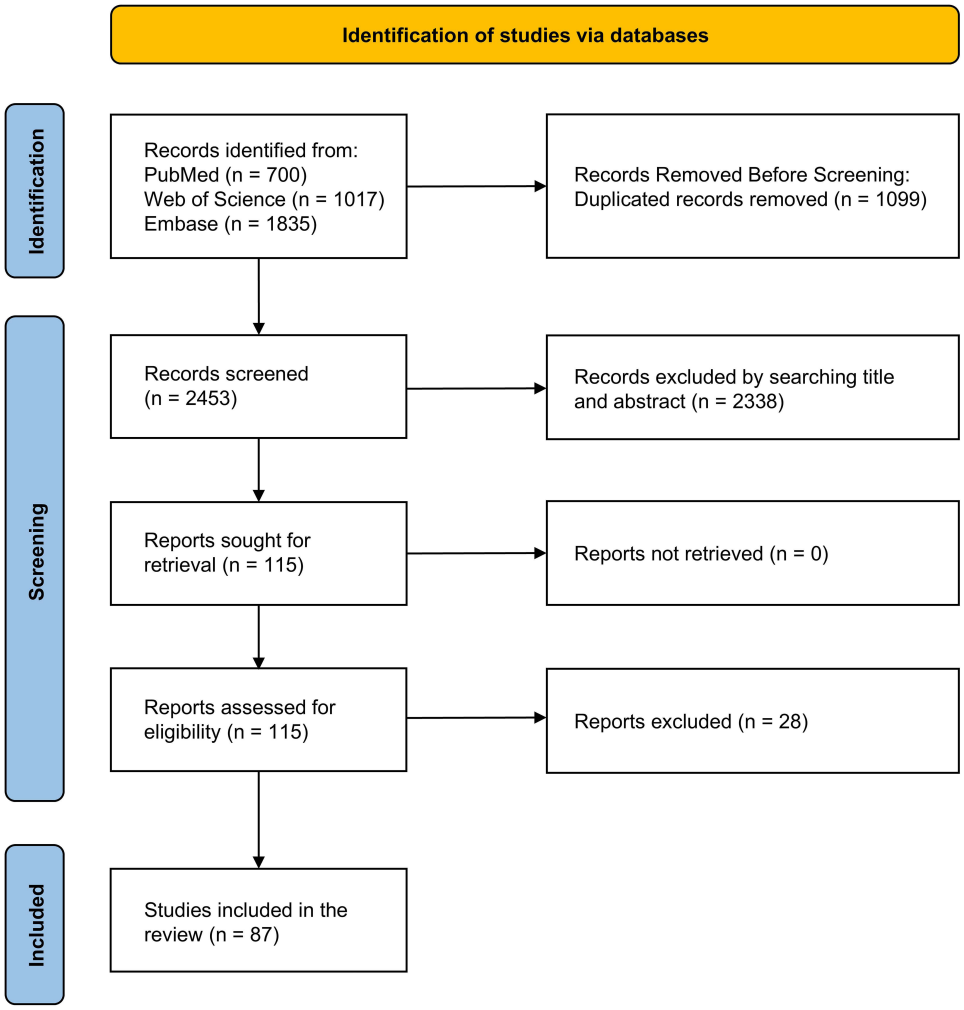


**Figure 2** Literature search flowchart.

Table 1 and Figure 3. Identifying the specific targets or molecular pathways through which tumor-derived sEVs act can pave the way for effective treatment of OC.

## The Cargo of sEVs Under Hypoxic Conditions Promotes OC Cell Proliferation

Hypoxia represents a common feature of numerous solid tumors and serves as a key driver in tumor progression. In recent years, it has been demonstrated that hypoxia can not only directly drive macrophage polarization towards an

**Table 1** Intrinsic Mechanisms by Which Cargoes of Tumor-Derived sEVs Promote OC

| sEVs Origin | sEVs Cargo | Functions | Signaling Pathways/Mechanism | Refs |
|---|---|---|---|---|
| Hypoxic SKOV3, HO-8910, A2780 | miR-181d-5p, miR-125b-5p, and miR-21-3p | Proliferation | M2 macrophage polarization | [27] |
| Hypoxic SKOV3 | miR-181c-5p | Proliferation | KAT2B/HOXA10 axis | [28] |
| ES-2, ES-2-HM, A2780, SKOV3 | miR-320a | Metastasis | ITGA7 ↓ | [29] |

(*Continued*)

**Table 1** (Continued).

| sEVs Origin | sEVs Cargo | Functions | Signaling Pathways/Mechanism | Refs |
|---|---|---|---|---|
| ES-2, SKOV3, CAOV3, OVCA433, OVKATE, COV413, A2780cp, OVMANA | miR-141 | Metastasis | YAP1 | [30] |
| SKOV3, ES-2, CAOV3 | miR-106a-5p | Metastasis | KLF6↓ | [31] |
| SKOV3, A2780 | lncRNA SPOCD1-AS | Metastasis | G3BP1 | [32] |
| SKOV3, A2780 | circATP2B4 | Metastasis | miR-532-3p/SREBF1 axis | [33] |
| A2780, CAOV3 | circPUM1 | Metastasis | NF-κB↑, MMP2↑ | [34] |
| ES-2-HM, ES-2, A2780, SKOV3 | piR-25783 | Metastasis | TGF-$\beta$/SMAD2/SMAD3 pathway | [35] |
| HO-8910, A2780 | laminin | Metastasis | integrin $\alpha v\beta 5$/AKT/SP1 signaling pathway | [36] |
| ES-2, OVCAR3, ES-2-HM | ANXA2 | Metastasis | LCN2↑ | [37] |
| A2780-cisplatin, HO-8910PM, A2780 | lncRNA PANDAR | Drug resistance (cisplatin) | SRSF9-SIRT4/SIRT6 axis | [38] |
| SKOV3, COV504 | lncRNA CATED | Drug resistance (cisplatin) | DHX36-RAP1A-MAPK pathway | [39] |
| CAOV3, SKOV3, OVCAR3, A2780 | miR-6836 | Drug resistance (cisplatin) | DLG2-YAP1 signaling pathway | [40] |
| SKOV3/cisplatin | miR-21-5p | Drug resistance (cisplatin) | PDHA1↓ | [41] |
| OCSCs from SKOV3 | miR-4516 | Drug resistance (cisplatin) | GAS7 ↓ | [42] |
| SKOV3 | miR-429 | Drug resistance (cisplatin) | CASR/STAT3 pathway | [43] |
| HeyA8-MDR, SKOV3-TR, A2780-CP20, HeyA8, SKOV3-ip1, A2780 | miR-1246 | Drug resistance (paclitaxel) | CAV1↓ | [44] |
| SKOV3 | miR-141-3p | Angiogenesis | JAK/STAT3 and NF-κB signaling pathways | [45] |
| HO-8910PM, SKOV3-ip1, HO-8910, SKOV3 | miR-205 | Angiogenesis | PTEN-AKT pathway | [46] |
| SKOV3.ip1, HO8910.PM, SKOV3, HO8910 | MALAT1 | Angiogenesis | VEGF-A, VEGF-D, ENA-78, PlGF, IL-8, angiogenin, bFGF and leptin | [47] |
| A2780, HO-8910 | PKR1 | Angiogenesis | STAT3 | [48] |

**Notes**: The upward arrow indicates upregulated molecular expression level; the downward arrow indicates downregulated molecular expression level.

angiogenic phenotype and an immunosuppressive phenotype but also exert an indirect influence by altering the communication of sEVs between tumor cells and macrophages.[49]

Chen et al have reported that miR-181d-5p, miR-125b-5p, and miR-21-3p are expressed at high levels within sEVs under hypoxia-inducible factor (HIF)-mediated hypoxic conditions. These miRNAs facilitate the proliferation and migration of epithelial ovarian cancer (EOC) cells via promoting the polarization of M2-type macrophages.[27] Another study has demonstrated that miR-181c-5p is highly expressed in sEVs induced by hypoxia and promotes the growth and metastasis of EOC by targeting lysine acetyltransferase 2B (KAT2B) to upregulate homeobox A10 (HOXA10) and by

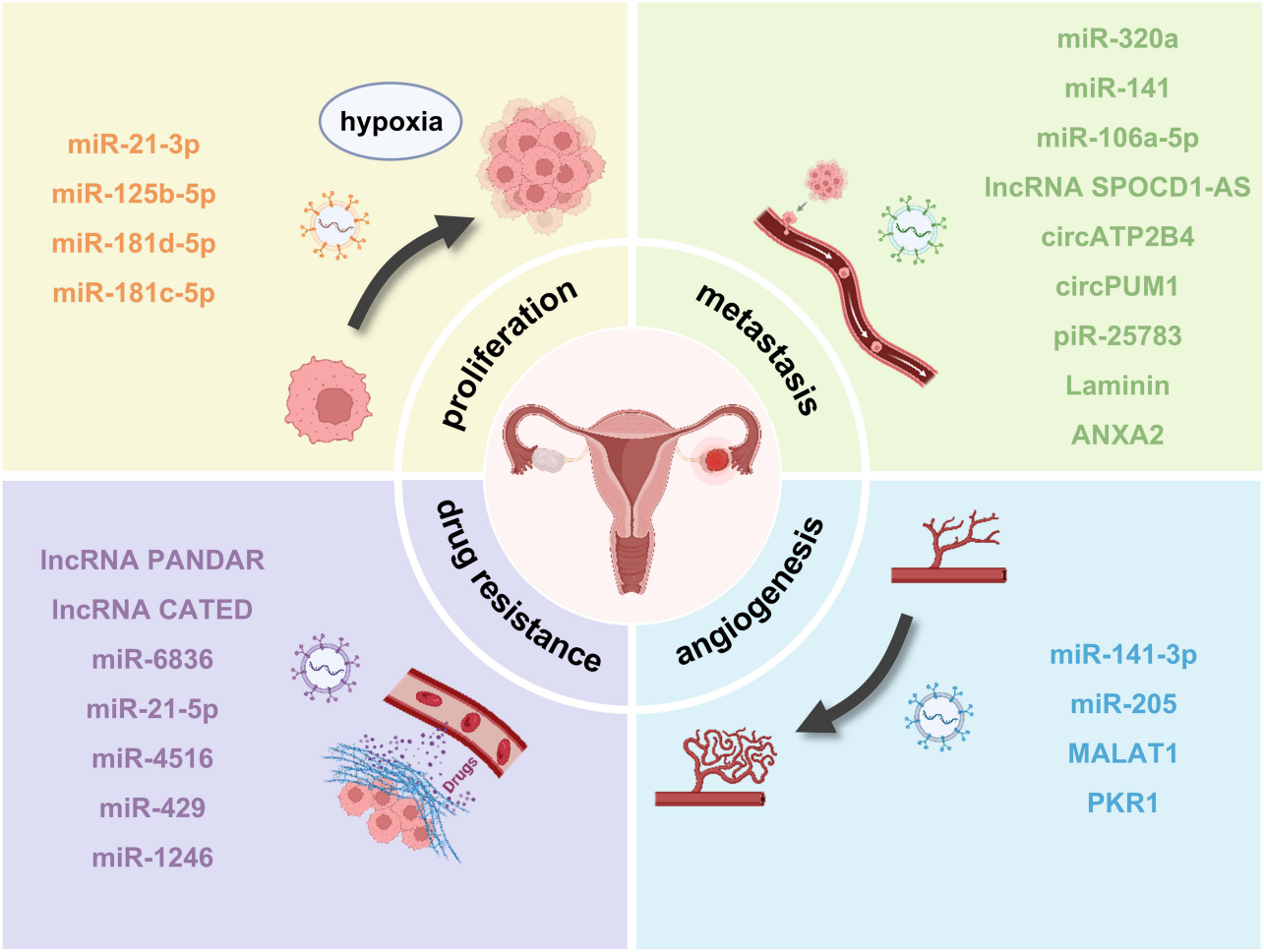


**Figure 3** Promoting effects of tumor-derived sEVs' cargo in OC. By BioRender.

activating the janus kinase 1 (JAK1)/signal transducer and activator of transcription 3 (STAT3) signaling pathway to induce the polarization of M2-type macrophages.[28]

In conclusion, when the human body is in a hypoxic state, sEVs are closely associated with OC cells and may promote malignant behaviors such as the proliferation of OC cells by influencing relevant signaling pathways. This finding offers original insights into the clinical diagnosis and treatment of OC and holds significant potential application value.

## The Cargo of sEVs Promotes OC Cell Metastasis

Metastasis constitutes a vital phase in the course of cancer development, which entails the dissemination of cancer cells from the original tumor location to remote areas. The biological process of tumor metastasis is referred to as the invasion and metastasis cascade response, encompassing local invasion, invasion and survival in the circulation, extravasation, distant colonization and reactivation.[50,51] Apart from the well-known hematogenous and lymphatic metastasis routes, cancer cells can spread through the peritoneal cavity route, presenting a challenge to treatment and prognosis in the advanced stages of OC.[52]

Given the capacity of sEVs to transport biologically active molecules such as miRNAs, lncRNAs, circRNAs, piRNAs, and functional proteins, a mounting number of studies have demonstrated a robust correlation between sEVs and tumor metastasis. Among these, the miRNA cargoes carried by sEVs have been widely investigated. For instance, miR-320a, which is derived from sEVs of highly metastatic OC cells, targets integrin subunit alpha 7 (ITGA7) and activates the transforming growth factor beta (TGF-$\beta$) signaling pathway, facilitating OC omental metastasis.[29]

Analogous to miR-320a, sEV miR-141 and miR-106a-5p have enhanced expression in OC and promote OC cell proliferation, migration, invasion, and metastasis. Mechanistically, sEV miR-141 directly targets yes-associated protein 1 (YAP1), which acts as a critical downstream effector of the Hippo signaling pathway. Additionally, sEV miR-106a-5p directly targets krueppel-like factor 6 (KLF6), decreases KLF6 binding to the pituitary tumor transforming gene 1 (PTTG1) promoter, and upregulates PTTG1 transcription, thereby mediating OC metastasis.[30,31]

Recent investigations have revealed that the lncRNA SPOCD1-AS encapsulated within sEVs associates with the RAS GTPase-activating protein-binding protein 1 (G3BP1) to induce the mesothelial-mesenchymal transition (MMT) process. This process facilitates the adherence of cancer cells to mesothelial cells, thereby promoting peritoneal metastasis.[32] Another experiment demonstrated that sEVs deliver circATP2B4 to infiltrating macrophages, specifically bind miR-532-3p to inhibit the downstream target gene sterol regulatory element-binding factor 1 (SREBF1), modulate the miR-532-3p/SREBF1/Phosphatidylinositol 3-kinase alpha (PI3K$\alpha$)/protein kinase B (AKT) axis, and subsequently promote macrophage M2 polarization, ultimately leading to immunosuppression and OC metastasis.[33] Similarly, sEVs transport circPUM1 to peritoneal mesothelial cells, thereby promoting tumor metastasis. The underlying mechanism is that circPUM1 upregulates the expressions of nuclear factor kappa B (NF-κB) and matrix metallopeptidase 2 (MMP2) by adsorbing miR-615-5p and miR-6753-5p.[34] In addition, sEVs containing high expression levels of piR-25783 facilitate the formation of the premetastatic microenvironment (PMM). Intrinsically, it activates the TGF-$\beta$/SMAD2/SMAD3 pathway to induce fibroblast-to-myofibroblast transition (FMT).[35]

Laminin is highly expressed in cancer cells at the site of peritoneal metastasis, facilitating the self-renewal and invasion of cancer cells.[53,54] Li H et al found that OC cells overexpressing erythroblast transformation specific 1 (ETS1) secreted higher levels of sEV laminin. Subsequently, this laminin drove macrophage M2-type polarization by targeting integrin alpha v beta 5 ($\alpha v\beta 5$)/AKT/specificity protein 1 (SP1) signaling and significantly elevated the expression levels of C-X-C motif chemokine ligand 5 (CXCL5) and C-C motif chemokine ligand 2 (CCL2) in macrophages, ultimately leading to the omental metastasis of OC.[36] Annexin A2 (ANXA2), which is a multifunctional protein, contributes significantly to cancer and inflammation due to its dysregulated expression.[55] ANXA2 secreted by tumor cells binds to Toll-like receptor 2 (TLR2), which activates human peritoneal mesothelial cells (HPMCs). This activation prompts the phenotype of HPMCs to transform towards mesenchymal cells, enhancing their migratory and invasive abilities. Subsequently, it triggers the upregulation of lipocalin 2 (LCN2) expression in HPMCs, and ultimately promotes the peritoneal metastasis of OC.[37]

Taken together, the above findings emphasize the intricate part of sEVs in the metastasis of OC cells and propose potential therapeutic targets for combating OC metastasis, which has significant implications for OC-related research and clinical practice that cannot be overlooked.

## The Cargo of sEVs Promotes OC Cell Chemotherapy Resistance

Currently, chemotherapy remains an effective treatment for OC, especially for advanced OC. However, both intrinsic and acquired resistance not only significantly hamper its effectiveness in treating OC but also closely correlate with the dismal prognosis of OC patients.[56] The mechanisms underlying chemotherapy resistance in OC are intricate and include the upregulation of drug efflux pumps, the capacity for scavenging reactive oxygen species (ROS), and DNA damage repair.[57]

Recent investigations have revealed that sEVs can indirectly augment the resistance of OC cells to chemotherapeutic agents by delivering drug-resistance-related components to OC cells and activating related pathways. In OC, sEV lncRNA has been shown to augment chemoresistance. PANDAR is a lncRNA with oncogenic properties that is widely overexpressed in numerous cancers. It has been reported to negatively regulate cisplatin sensitivity in OC via an intranuclear PANDAR-serine/arginine-rich splicing factor 2 (SFRS2)-p53 feedback regulatory mechanism.[58] Under cisplatin-induced stress, the lncRNA PANDAR packed in sEVs promotes a more malignant and chemotherapy-resistant phenotype in OC through a mechanism involving triggering SRSF9 activity and altering the sirtuin4/6 (SIRT4/6) mRNA ratio.[38] In addition, in the research on the drug resistance mechanism of OC, lncRNA CATED has also been found to have a significant impact. It promotes the platinum drug resistance of high-grade serous ovarian cancer (HGSOC) by regulating the DHX36-RAP1A-mitogen-activated protein kinase (MAPK) pathway.[39] Specifically,

lncRNA CATED binds and upregulates DHX36 via protein inhibitor of activated STAT1 (PIAS1)-mediated SUMOylation at the K105 site. Consequently, the elevated DHX36 level boosts RAP1A mRNA translation and activates the MAPK pathway.

The impact of miRNAs within sEVs derived from tumor cells on the drug resistance of OC has been widely studied. For instance, sEVs derived from drug-resistant tumor cells and carrying miR-6836 target discs large MAGUK scaffold protein 2 (DLG2) and facilitate Yap1 nuclear translocation to mediate cisplatin resistance in OC.[40] sEV-derived miR-21-5p facilitates cell viability and glycolysis and enhances cisplatin tolerance in OC cells by inhibiting PDHA1.[41] sEVs derived from ovarian cancer stem cells (OCSCs) transfer miR-4516, which inhibits the downstream target growth arrest specific 7 (GAS7), thereby reducing the chemosensitivity of OC cells to cisplatin.[42] Similarly, miR-429 in sEVs promotes NF-κB to suppress the expression level of calcium sensing receptor (CASR), consequently leading to cisplatin resistance in EOC.[43] When OC cells were cultured simultaneously with macrophages, they could deliver their oncogenic sEVs containing miR-1246 to M2-type macrophages, suggesting that sEVs derived from OC promote tumorigenesis by modulating the adjacent infiltrating immune cells. On the other hand, overexpressed sEVs containing miR-1246 straightforwardly target the caveolin-1 (CAV1), and by reducing the expression levels of the multidrug resistance 1 (MDR1), they significantly augment the resistance of OC cells to paclitaxel.[44]

These discoveries highlight the impact of tumor cell-derived sEVs on the development of OC chemoresistance, underscoring their significant value for the exploration and application of novel alternative therapeutic agents capable of reversing chemoresistance. However, current research on sEVs has primarily focused on conventional chemotherapeutic agents such as platinum-based drugs and taxanes. It remains unclear whether the cargo of tumor-derived sEVs is involved in the action transmission of poly(ADP-ribose) polymerase (PARP) inhibitors and anti-angiogenic agents, nor has it been elucidated whether sEVs regulate the formation and transmission of drug-resistant phenotypes to these agents. Future studies should further expand into the field of the aforementioned targeted therapies, systematically investigating the function of sEV cargo in their mechanisms of action and chemoresistance regulation, with the aim of filling the research gap in this area.

## The Cargo of sEVs Promotes OC Cell Angiogenesis

Angiogenesis is an intricate process, specifically referring to the formation of new microvessels from pre-existing blood vessels.[59] Excessive angiogenesis represents a key tumorigenic phenomenon and is closely associated with tumor initiation, malignant progression, and poor prognosis.[60] sEVs derived from OC can be internalized by endothelial cells (ECs), and this process not only enhances the proliferation, migration, and sprouting capabilities of ECs but also effectively promotes angiogenesis in the peri-OC region.[61]

The release of sEVs by OC cells represents among the principal mechanisms for inducing angiogenesis. A previous study has demonstrated that miR-141-3p delivered via sEVs can markedly boost the expression of vascular endothelial growth factor receptor-2 (VEGFR-2) in ECs, thereby facilitating EC migration and angiogenesis.[45] Similar to miR-141-3p, miR-205 is secreted extracellularly and translocated into neighboring ECs in an sEV-dependent manner, where it targets the phosphatase and tensin homolog (PTEN)-AKT pathway and exerts pro-angiogenic effects.[46] In addition, metastasis associated lung adenocarcinoma transcript 1 (MALAT1) encapsulated in sEVs can be transferred to recipient human umbilical vein endothelial cells (HUVECs), thereby stimulating the expression of angiogenesis-related genes, including basic fibroblast growth factor (bFGF), placental growth factor (PlGF), interleukin-8 (IL-8), vascular endothelial growth factor-A (VEGF-A), VEGF-D, epithelial neutrophil-activating peptide 78 (ENA-78), leptin, and angiogenin, and inducing angiogenesis in OC cells.[47] Proteins that contribute to the regulation of angiogenesis are also present in sEVs. sEVs positive for prokineticin receptor 1 (PKR1) activate the phosphorylation of STAT3, thereby facilitating the migration and lumen formation of HUVECs and regulating angiogenesis in OC cells.[48]

Collectively, these findings underscore the involvement of sEVs amid tumor angiogenesis via diverse mechanistic pathways, and each step playing a distinct role. Specifically, during the initiation phase, they transmit signals to activate ECs; when it comes to basement membrane degradation, they assist in the release of enzymes to disrupt the basement membrane; in the stages of migration and proliferation, they transmit regulatory signals; during lumen formation, they

facilitate the formation of EC lumens; and in the process of vascular maturation, they contribute to strengthening the structure. All these actions synergistically promote tumor angiogenesis.

### sEVs Enhance the Expression Levels of OCSC Markers

Cancer stem cell (CSC) markers, which are molecules specifically expressed on the surface of CSCs, display tissue-specific expression modes that reflect the heterogeneity and complex biology of tumors. Substantial evidence indicates that sEVs derived from OC can upregulate stemness markers, including key molecules like EpCAM, CD24, CD44, CD163, CD206, OCT4, NANOG, SPINT2, and SOX2. Tumor cells expressing CSC markers have the ability to initiate tumors and promote tumor metastasis, which reflects the enhanced stemness characteristics of cancer.

Researchers constructed a straightforward and dependable microfluidic continuous-flowing platform (sEVs search chip) to quantitatively isolate sEVs by targeting EpCAM and CD24. It was observed that the protein levels of EpCAM and CD24 were significantly upregulated in sEVs from OC patients relative to those of healthy controls.[62] Moreover, when comparing the sEVs in peritoneal fluid with the tumor-derived sEVs in ascites, it was observed that the latter exhibited an increased expression of two mRNAs, NANOG and SPINT2, and furthermore, the activity of both played a regulatory role in OC progression and metastasis.[63] In addition, the sEV miR-6836 extracted from drug-resistant tumor cells has been demonstrated to upregulate stemness markers including NANOG, CD44, SOX2, and OCT4, thus promoting the stemness of OC cells.[40] CD44 functions as an adhesion molecule in cell migration. Meanwhile, CD163 and CD206 serve as markers for M2 tumor-associated macrophage (TAM) polarization. OC cell-derived sEVs significantly upregulated the CD44 protein level in HO8910 cells and the CD163 and CD206 protein levels in THP-1 cells, and consequently promoted tumor migration, invasion, metastasis, proliferation and immune escape.[64,65] Overall, the collective evidence underscores the functional contribution of sEVs in promoting the expression of CSC markers and enhancing the stemness characteristics of OC.

## The Promoting Effects of Non-Tumor-Derived sEVs on OC

In the context of OC, the origin of sEVs plays a crucial role in determining their distinct impacts on the progression of OC. Specifically, upon release, the sEVs originating from cancer cells are taken up by both the cancer cells that release them and the surrounding cancer cells, thereby exerting an influence on the progression of OC. In contrast, a subset of sEVs is derived from non-cancer cells, such as stromal cells and immune cells. These sEVs possess a broader range of influence. They can affect the state of tumor cells and simultaneously reshape TME by altering the biological behaviors of the surrounding cells. Consequently, this promotes the malignant behaviors of cancer, as shown in Table 2 and Figure 4.

**Table 2** Intrinsic Mechanisms by Which Cargoes of Non-Tumor-Derived sEVs Promote OC

| sEVs Origin | sEVs Cargo | Functions | Signaling Pathways/ Mechanism | Refs |
|---|---|---|---|---|
| CAFs | miR-296-3p | Proliferation, migration, invasion, and drug resistance | PTEN/AKT and SOCS6/STAT3 pathways | [66] |
| CAFs | miR-98-5p | Drug resistance (cisplatin) | CDKN1A | [67] |
| CAFs | Low miR-29c-3p | Metastasis | MMP2 | [68] |
| CAFs | SLPI | Growth, invasion, and adhesion | PI3K/AKT pathway | [69] |
| MSCs | COL6A3 | Invasion, metastasis | - | [70] |
| Adipocytes | LINC01119 | Immune escape | SOCS5 | [71] |

(*Continued*)

**Table 2** (Continued).

| sEVs Origin | sEVs Cargo | Functions | Signaling Pathways/ Mechanism | Refs |
|---|---|---|---|---|
| Adipocytes | SIRT1 | Immune escape | CD24/Siglec-10 axis | [72] |
| Adipocytes | miR-421 | Metastasis | CBX7↓ | [73] |
| Adipocytes | let-7b, miR-92a, miR-16 and miR-21 | Proliferation, drug resistance (paclitaxel) | - | [74] |
| ECs | - | Angiogenesis | Wnt/$\beta$-catenin signaling pathway | [75] |
| TAMs | circTMCO3 | Proliferation, migration, and invasion | miR-515-5p/ITGA8 axis | [76] |
| TAMs | miR-221-3p | Proliferation, adhesion, migration, and drug resistance (cisplatin) | CDKN1B, ADAMTS6↓ | [77,78] |
| TAMs | miR-21-5p, miR-29a-3p | Metastasis | STAT3 | [79] |
| TAMs | miR-223 | Drug resistance (cisplatin) | PTEN-PI3K/AKT signaling pathway | [80] |
| TAMs | miR-29a-3p | Proliferation, immune escape | FOXO3-AKT/GSK3β pathway | [81] |
| TAMs | NEAT1 | Immune escape | miR-101-3p/ZEB1/PD-L1 axis | [82] |
| TAMs | GATA3 | Drug resistance (cisplatin), immune escape | CD24/Siglec-10 axis | [83] |
| lymphocytes | miR-330-3p | Metastasis | JAM2 | [84] |

**Notes**: The downward arrow indicates downregulated molecular expression level.

## sEVs Derived from Stromal Cells

The stromal cells are composed of multiple cell types, such as cancer-associated fibroblasts (CAFs), mesenchymal stem cells (MSCs), adipocytes, and ECs. These stromal cells do not exist in isolation. Instead, they interact with tumor cells to construct a complex and dynamically changing TME.[85] In this microenvironment, stromal cells can conduct paracrine signaling through their derived sEVs to support tumor progression, which includes tumor proliferation, migration, invasion, metastasis, angiogenesis, the development of drug resistance, and immune escape.[86] This provides a unique entry point for the diagnosis and treatment of cancer.

### sEVs Derived from Cancer-Associated Fibroblasts

The significance of CAFs in cancer development is underscored by their involvement in a multitude of cancer characteristics, such as ECM remodeling, tumor cell proliferation, invasion, metastasis, angiogenesis, and immunosuppression, along with the stimulation of tumor stem cell properties within the tumor.[87] CAFs are functionally diverse and heterogeneous on account of the differences in their precursor cells of origin and the stimulatory factors present in the TME.[88] While it remains controversial whether they play a promotional or inhibitory part concerning the growth of different tumors, in the case of OC, it has been established that the sEVs originated from them can facilitate the progression of tumor malignant behaviors.

A study conducted by Sun et al demonstrated that miR-296-3p was specifically overexpressed within the sEVs originating from activated CAFs and could be transferred to tumor cells to modulate the malignant phenotype of OC cells.[66] In terms of mechanism, the miR-296-3p with overexpression significantly augments the proliferation, migration, invasion, and drug resistance of OC cells when it is in vitro. In addition, it spurs tumor growth in vivo by governing the PTEN/AKT and suppressor of cytokine signaling 6 (SOCS6)/STAT3 pathways. miR-98-5p has been shown to promote malignant behaviors in multiple cancers. Specifically, sEVs derived from OC cells and containing miR-98-5p were found to promote OC cell proliferation and facilitate cell cycle entry, suppress OC cell apoptosis, and downregulate cyclin-

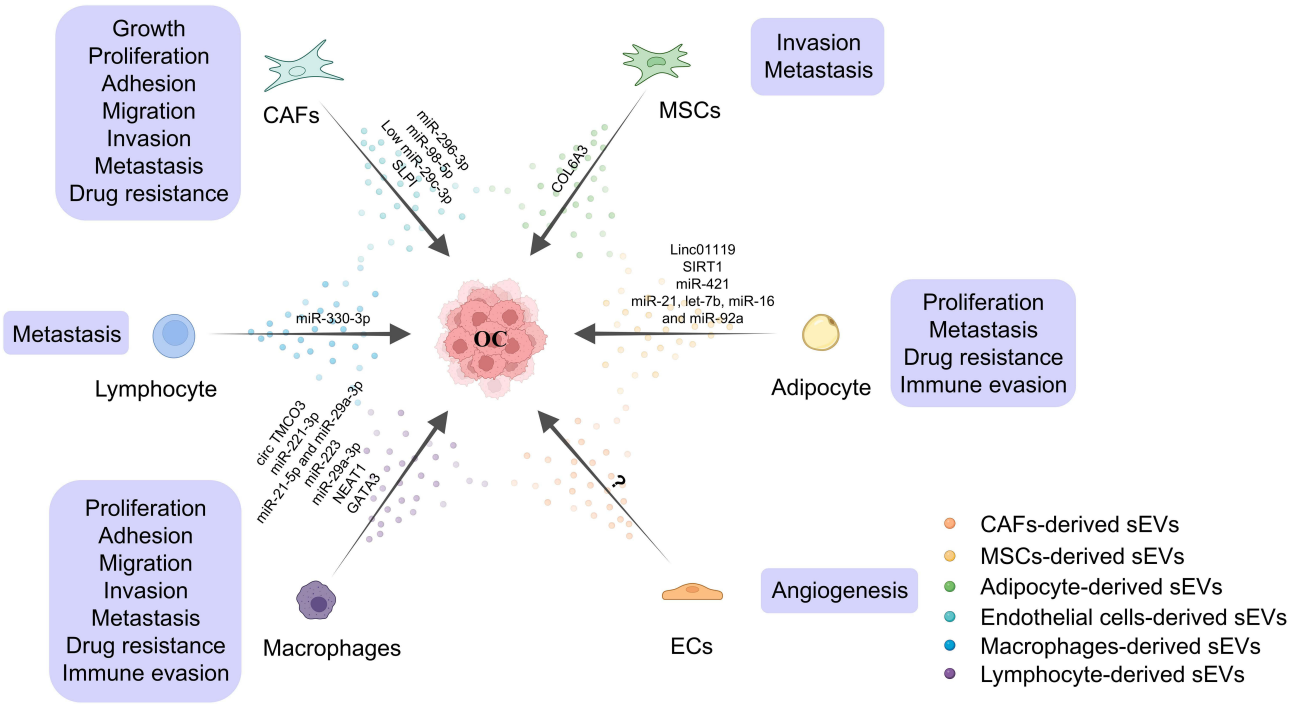


**Figure 4** Promoting effects of non-tumor-derived sEVs' cargo in OC. By BioRender.

dependent kinase inhibitor 1A (CDKN1A), thereby promoting OC cisplatin resistance.[67] In addition, the low expression of miR-29c-3p in sEVs derived from large omental CAFs promotes the peritoneal metastasis of OC by deregulating the inhibition of MMP2 expression in cancer cells.[68] Secretory leukocyte protease inhibitor (SLPI), a multifunctional protein that plays a part in regulating immune responses and suppressing protease activity, has its role as a protease inhibitor associated with multiple malignancies.[89] SLPI proteins contained within sEVs originating from CAFs can be transported to OC cells. Subsequently, these proteins can promote the growth, motility, invasion, and adhesion of OC cells by triggering the PI3K/AKT and downstream signaling pathways.[69]

## sEVs Derived from Mesenchymal Stem Cells

MSCs are a kind of stem cells with multidirectional differentiation capacity, allowing them to differentiate into various types of cells or tissues.[90] MSCs have the potential to be recruited into TME via tumor homing, and thereby acquire the ability to exert a dynamic effect on cancer progression. Notably, existing studies have different views on the function of MSC-derived sEVs in OC: on the one hand, there is evidence of their inhibitory effect on OC; on the other hand, there are also studies that suggest their promotional effect on OC.

Existing studies have confirmed that sEVs derived from MSCs can inhibit OC progression in multiple ways by carrying specific miRNAs and targeting key molecules and signaling pathways. For instance, miR-424 encapsulated in MSC-sEVs can target and bind to the oncogene MYB to downregulate its expression, thereby inhibiting the proliferation, migration, and tube formation of HUVECs and ultimately achieving dual suppression of OC tumorigenesis and angiogenesis.[91] Furthermore, miR-124 carried by bone marrow MSC-derived sEVs specifically targets monocarboxylate transporter 1 (MCT1) on the surface of regulatory T cells (Treg), thereby reversing the immunosuppressive state in the TME and enhancing the efficacy of PD-1 blockade therapy.[92] MSC-sEVs can also deliver various functional miRNAs to reverse chemoresistance. miR-18a-5p inhibits the proliferation, migration, invasion, and cisplatin resistance of OC cells by blocking the nucleus accumbens-associated protein 1 (NACC1)-mediated AKT/mammalian target of rapamycin (mTOR) pathway, while miR-146a reduces the resistance of OC cells to docetaxel and paclitaxel through targeted regulation of the LAMC2-mediated PI3K/AKT axis.[93,94]


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Notably, not all MSC-derived sEVs exert an inhibitory effect on OC. Instead, their biological functions may be regulated by specific bioactive molecules encapsulated within them, among which collagen VI alpha 3 (COL6A3) is a key regulatory factor. Characterized by cancer-specific expression, COL6A3 is rarely expressed in normal human tissues but shows aberrant overexpression in multiple cancer cell types, and previous studies have confirmed that its expression level is tightly associated with cancer patient prognosis.[95] Recently, a related study reported that high levels of COL6A3 expression in SKOV3 cells overexpressing COL6A3, mesenchymal stem cell-ovarian cancer stromal progenitor cells (MSC-OCSPCs), and their sEVs were linked to poorer overall survival among EOC patients.[70] Further exploration by in vitro experiments revealed that COL6A3 mediates invasion and metastasis of EOC cells through EOC tissues and sEVs transported by MSC-OCSPCs.

### sEVs Derived from Adipocytes

Adipocytes, being a component of the metastatic TME, are capable of interacting with cancer cells in nearly all organs. Additionally, they can release various factors such as sEVs, cytokines, chemokines, and proteases.[96] Previous reports have indicated that these factors exert significant influences on cancer progression, which encompasses the implantation, survival, and expansion of cancer cells at metastatic sites.

Notably, sEVs derived from adipocytes have been demonstrated to enhance the proliferation, metastasis, immune escape, and chemoresistance of OC. In a 3D co-culture cell model, researchers observed that LINC01119 contained within sEVs derived from cancer-associated adipocytes (CAA-sEVs) repressed the proliferation of $CD3^+$ T cells and elevated the PD-L1 level.[71] This, in turn, attenuated the cytotoxicity of T cells towards SKOV3 cells. Mechanistically, LINC01119 carried by sEVs induces macrophage M2 polarization by significantly upregulating the expression level of SOCS5 in OC cells. This ultimately promotes the immune escape of OC cells. This conclusion was supported by another study which demonstrated that sirtuin 1 (SIRT1) delivered by sEVs derived from CAA-sEVs promoted the immune escape of OC cells.[72] Further studies revealed that SIRT1 carried by sEVs derived from CAA-sEVs triggered the apoptosis of $CD8^+$ T cells by initiating the CD24/sialic acid binding lg like lectin 10 (Siglec-10) axis. As a regulator of multiple signaling pathways within the TME, miR-421 exerts an extremely complex role in cancer. In OC, miR-421 contained in adipose-derived sEVs mediates the down-regulation of CBX7, induces epigenetic changes in OC cells, and promotes the metastatic potential of OC.[73] Furthermore, let-7b, miR-92a, miR-16, and miR-21 were considerably increased in expression in sEVs derived from large omental adipocytes in tumor patients. These miRNAs were able to induce the proliferation of OC cells, drive epithelial-mesenchymal transition (EMT), and reduce the response to paclitaxel treatment.[74]

### sEVs Derived from Endothelial Cells

As the lining of the tumor vascular system, ECs can both align the existing blood vessels and initiate the construction of new blood and lymphatic channels during vascular development, playing a crucial role in cancer development.[97] It has been shown that ECs treated with IL-3 can release sEVs by transferring active molecules, which serves as a paracrine mechanism for neighboring ECs. Further exploration of the underlying mechanism reveals that the wingless-related integration site/beta-catenin (Wnt/$\beta$-catenin) signaling pathway is a crucial regulator for the pro-angiogenic influences of sEVs derived from tumor endothelial cells (TECs).[75] However, to date, research on the functions of sEVs derived from ECs in OC remains extremely scarce.

## sEVs Derived from Immune Cells

The complex immune cell system encompasses a variety of components, including macrophages, lymphocytes, and so on. Under normal conditions, these components can play anti-tumor roles, such as recognizing, monitoring, and killing tumor cells. This process constitutes a key link in the body's anti-tumor immune defense mechanism.[98] However, as the tumor progresses to a certain stage, significant changes will occur in the TME. Tumor cells will "domesticate" and "transform" immune cells via a variety of mechanisms. Hence, the original anti-tumor functions of immune cells will be gradually inhibited or even undergo functional transformation, and then these immune cells will play a tumor-promoting role. Specifically, on the one hand, tumor cells may secrete cytokines like IL-10 and TGF-$\beta$ that possess

immunosuppressive properties. These cytokines act on immune cells to either induce their differentiation into cells with an immunosuppressive phenotype or directly impede the activation and effector functions of immune cells. On the other hand, tumor cells can elevate the expression of immune checkpoint molecules including PD-1 and PD-L1. These molecules couple with the specific receptors on the surface of immune cells and transmit inhibitory signals, thereby causing immune cells to fall into a state of functional exhaustion. As a result, immune cells are unable to effectively exert their anti-tumor effects and instead facilitate the proliferation, invasion, and metastasis of tumor cells. Ultimately, this leads to the transformation of immune cells from their original anti-tumor role to a pro-tumor role.[99] In this section, we present an overview of the mechanisms through which immune cell-derived sEVs promote the occurrence and development of OC.

### sEVs Derived from Macrophages

Macrophages differentiate into different types of TAMs, mainly consisting of classically activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages).[100] Among them, M1 macrophages play a part in promoting inflammation and exerting anti-tumor action, while M2 macrophages play a part in suppressing inflammation and contributing to tumorigenesis. As key carriers of intercellular communication, sEVs exhibit functional characteristics highly consistent with their parental cells. M1 macrophage-derived sEVs can reshape the TME into an anti-tumor niche by activating cytotoxic $CD8^+$ T cells and enhancing macrophage phagocytic activity, thereby facilitating tumor cell clearance.[101] In contrast, M2 macrophage-derived sEVs induce immunosuppression by inhibiting anti-tumor immune responses, including $CD8^+$ T cell exhaustion and disruption of the Treg/T helper 17 (Th17) cell balance, ultimately driving pro-tumor processes.[102,103]

In OC tissues, numerous TAMs are converted into M2-type macrophages, which release sEVs and enable the immune escape of OC, thereby facilitating the proliferation, metastasis, and chemoresistance of OC. It was found that sEVs derived from M2-type macrophages contribute to malignancy by targeting the miR-515-5p/integrin alpha 8 (ITGA8) axis via the delivery of circTMCO3.[76] Furthermore, reduced expression of cyclin-dependent kinase inhibitor 1B (CDKN1B) and a disintegrin and metalloproteinase with thrombospondin motifs 6 (ADAMTS6) correlates with poor prognosis in EOC. Research has established that sEVs derived from TAMs deliver miR-221-3p to EOC cells, where this microRNA directly targets and downregulates CDKN1B and ADAMTS6, thereby facilitating EOC cell proliferation, adhesion, migration, and cisplatin resistance.[77,78] Microarray analysis of sEVs from TAMs identified miR-21-5p and miR-29a-3p as being abundant in these vesicles. Both miRNAs directly suppressed STAT3 in $CD4^+$ T cells and induced an imbalance of Treg/Th17 cells, thus giving rise to an immunosuppressive microenvironment conducive to the progression and metastasis of OC.[79] In parallel, research has further shown that miR-223, delivered from macrophages to OC cells via sEVs, activates the PTEN-PI3K/AKT signaling pathway and promotes cisplatin chemoresistance.[80]

PD-L1 can be found on the surface of tumor cells. It decreases T-cell activity and inhibits T-cell responses by interacting with PD-1 on T cells. Various cancers express high levels of PD-L1 and utilize the PD-L1/PD-1 axis to achieve immune evasion.[104] For instance, miR-29a-3p and nuclear enriched abundant transcript 1 (NEAT1) are enriched in TAM-EVs. They target the forkhead box O3 (FOXO3)-AKT/glycogen synthase kinase 3 beta (GSK3β)/PD-L1 axis and miR-101-3p/zinc finger e-box-binding homeobox 1 (ZEB1)/PD-L1 axis respectively, significantly elevating the PD-L1 expression level and facilitating the proliferation and immune evasion of OC cells.[81,82] Similarly, GATA-binding protein-3 (GATA3) is aberrantly expressed in sEVs derived from TAMs. When transferred to OC cells, GATA3 enhances chemoresistance and immune evasion of OC cells through modulation of the CD24/Siglec-10 axis.[83]

### sEVs Derived from Lymphocytes

Plasma cells, a sub-population of antibody-producing B cells, are enriched in the mesenchymal subtype of high-grade plasmacytoid OC.[84] A study on miR-330-3p revealed that sEVs which originated from plasma cells transferred miR-330-3p into non-mesenchymal OC cells and bound to the promoter region of junctional adhesion molecule 2 (JAM2). This interaction triggers the core EMT program in OC, promoting the metastatic ability of OC.[84] Up to now, research on lymphocyte-derived sEVs in OC is lacking.

## Diagnostic and Prognostic Potential of sEVs in OC

Early diagnosis and prognosis prediction are crucial for the precision treatment of OC. Currently, the drawbacks of tissue biopsy have increasingly been perceived in the area of precision medicine. In comparison, liquid biopsy is non-invasive, accessible, reusable, and enables dynamic analysis.[105] sEVs possess a typical phospholipid bilayer structure, allowing them to be widely and stably distributed in various body fluids. Meanwhile, they can carry diverse information reflecting the state of tumor progression. Recent studies have indicated the growing significance of sEVs in liquid biopsies for early diagnosis, prognosis prediction, and treatment monitoring in OC.[106] Herein, we sum up the capability of sEVs as diagnostic and prognostic biomarkers in OC, as shown in Table 3.

### Ascites

This section aims to present recent reports on sEV markers in OC ascites. sEVs containing specific proteins are frequently utilized as biomarkers in OC. For instance, CUB structural domain protein 1 (CDCP1), a type I transmembrane glycoprotein, is often considered a key hub for oncogenic signaling in the cancer field. The proportion of the CDCP1-positive sEVs subpopulation and the level of CDCP1 have been observed to be notably increased in the ascites of OC patients, suggesting that CDCP1-positive sEVs serve as a molecular biomarker for the early monitoring and diagnosis of OC.[107] In patients with advanced high-grade plasmacytoid ovarian cancer (HGSC), EpCAM-positive sEVs in their ascites possess potential as prognostic biomarkers for predicting early recurrence. In a study of paired ascites and plasma samples from 37 patients with advanced HGSC who were receiving different first-line therapies, the concentrations of total sEVs and EpCAM-positive sEVs were examined by flow cytometry. The outcomes showed that the higher the concentration of EpCAM-positive sEVs in ascites was, the shorter the progression-free survival (PFS) of the patients was, demonstrating their important value in prognostic judgment.[108] In another study, sEVs were isolated from samples of OC patients and studied in depth using quantitative real-time polymerase chain reaction (qRT-PCR) technology. Five mRNAs (CA11, MEDAG, LAMA4, SPINT2, NANOG) and six miRNAs (let-7b, miR-30d, miR-23b, miR-29a, miR-720, miR-205) exhibited notable disparate expression while they were being compared cancerous ascites with cancerous peritoneal fluid. Meanwhile, the RNA expression profile of OC ascites sEVs differed from that of benign peritoneal fluid. The upregulated mRNA markers SPINT2 and NANOG not only reflected disease staging but also had the promise to be used as diagnostic biomarkers.[63]

### Plasma

In the field of OC-related research, there have been numerous new developments in the exploration of plasma sEVs markers. In terms of diagnosis and staging evaluation, Zhu et al detected by qRT-PCR that the expression level of miR-205 in plasma sEVs of OC patients was significantly higher than that in the benign disease group and the healthy control group. Furthermore, it increased more significantly when the cancer progressed to stage III–IV or lymph node metastasis occurred, suggesting that it can not only serve as a potential marker for the early detection of OC but also assist in clinical tumor staging judgment.[109] Apart from upregulated miRNAs, miR-6763-5p, miR-4479 and miR-320d in plasma sEVs were significantly downregulated in OC patients. Besides, the expression levels of all three were associated with lymph node metastasis. Among them, miR-4479 and miR-320d were also closely related to tumor staging, further enriching the options for markers in OC diagnosis and disease assessment.[110] Moreover, miR-4732-5p, MUC1 in plasma sEVs and the surface proteins of sEVs including CD9, CD81, CD151 have also been confirmed to serve as novel non-invasive diagnostic markers for OC, further improving the diagnostic system.[111–113]

Multiple studies on OC prognosis have found that there are significant associations between the expression levels of CAV1 and FATS and FIGO staging, tumor grading, lymph node metastasis as well as patient prognosis.[114,115] Relevant studies have shown that the levels of CAV1 and FATS in plasma sEVs of OC patients are significantly downregulated compared with those of healthy people, suggesting that the lower levels of CAV1 and FATS in plasma sEVs can serve as prognostic indicators for OC, opening up a new direction for the assessment of OC prognosis. It is worth noting that some markers of plasma-derived sEVs have the dual application value for both OC diagnosis and prognosis assessment. Previous studies have confirmed that miR-200b, SCNN1A and EFNA1 are significantly upregulated in OC

**Table 3** Summary of sEVs as Biomarkers for OC

| Biofluid | sEVs Cargo | Level | Biomarker | AUC | 95% CI (AUC) | Sensitivity (%) | Specificity (%) | HR | 95% CI (HR) | Cohort Type | Sample Size | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ascites | CDCP1 | Up | Diagnostic and prognostic biomarkers | 0.9375 | – | – | – | – | – | Case-control study | 26 | [107] |
| Ascites | EpCAM | Up | Prognostic biomarkers | - | - | - | - | 1.071 (PFS) | 1.007–1.138 (PFS) | Prospective cohort study | 37 | [108] |
| Ascites | SPINT2, NANOG | Up | Diagnostic biomarkers | - | - | - | - | - | - | Case-control study | 18 | [63] |
| Plasma | miR-205 | Up | Diagnostic biomarkers | 0.715 | 0.590–0.841 | 66.7 | 78.1 | - | - | Case-control study | 99 | [109] |
| Plasma | miR-6763-5p, miR-4479 and miR-320d | Down | Diagnostic biomarkers | 0.6834 (miR-6763-5p) 0.7781 (miR-4479) 0.6549 (miR-320d) 0.7799 (combined) | 0.627–0.740 (miR-6763-5p) 0.728–0.828 (miR-4479) 0.596–0.714 (miR-320d) | 75.2 (miR-6763-5p) 75.8 (miR-4479) 35.4 (miR-320d) 73.3 (combined) | 53.6 (miR-6763-5p) 71.4 (miR-4479) 91.7 (miR-320d) 72.0 (combined) | - | - | Case-control study | 363 | [110] |
| Plasma | miR-4732-5p | Up | Diagnostic biomarkers | 0.889 | - | 85.7 | 82.4 | - | - | Case-control study | 55 | [111] |
| Plasma | MUC1 | Up | Diagnostic biomarkers | 0.73 (ELISA) 0.75 (PRM) | - | 83.3 (ELISA) | 55.6 (ELISA) | - | - | Case-control study | 114 | [112] |
| Plasma | CD9, CD81, and CD151 | Up | Diagnostic biomarkers | - | - | - | - | - | - | Case-control study | 48 | [113] |
| Plasma | CAV1 | Down | Prognostic biomarkers | 0.76 (DFS) 0.78 (OS) | 0.68–0.82 (DFS) 0.70–0.84 (OS) | 52.9 (DFS) 65.1 (OS) | 88.7 (DFS) 81.2 (OS) | - | - | Cohort study | 205 | [114] |
| Plasma | FATS | Down | Prognostic biomarkers | 0.85 (5-DFS) 0.91 (5-OS) | 0.76–0.91 (5-DFS) 0.83–0.96 (5-OS) | 73.9 (5-DFS) 81.1 (5-OS) | 81.0 (5-DFS) 91.9 (5-OS) | - | - | Retrospective cohort study | 195 | [115] |
| Plasma | miR-200b | Up | Diagnostic and prognostic biomarkers | 0.868 | - | 64 | 86 | - | - | Case-control study | 143 | [116] |

(*Continued*)

**Table 3** (Continued).

| Biofluid | sEVs Cargo | Level | Biomarker | AUC | 95% CI (AUC) | Sensitivity (%) | Specificity (%) | HR | 95% CI (HR) | Cohort Type | Sample Size | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Plasma | SCNN1A, EFNA1 | Up | Diagnostic and prognostic biomarkers | 0.955 (combined) | - | - | - | - | - | Case-control study | 194 | [117] |
| Plasma | miR-181a, miR-1908, miR-21, miR-486 and miR-223 | Up | Platinum resistance-predictive biomarkers | - | - | - | - | - | - | Case-control study | 30 | [118] |
| Plasma | EpCAM, CD45 | Up | Platinum resistance-predictive biomarkers | 0.82 (EpCAM) 0.76 (CD45) 0.79 (combined) | 0.64–0.99 (EpCAM) 0.59–0.94 (CD45) 0.61–0.98 (combined) | 76.5 (EpCAM) 53.0 (CD45) 59.0 (combined) | 81.8 (EpCAM) 91.0 (CD45) 91.0 (combined) | - | - | Case-control study | 28 | [119] |
| Serum | CA125, HE4 and C5a | Up | Diagnostic biomarkers | 0.912 (EOC) 0.888 (early-stage EOC) | 0.879–0.946 (EOC) | 80.0 (EOC) 88.0 (early-stage EOC) | 89.0 (EOC) 74.0 (early-stage EOC) | - | - | Multi-center case-control study | 299 | [120] |
| Serum | CA125 | Up | Diagnostic biomarkers | 0.9755 | - | 94.55 | 92.73 | - | - | Case-control study | 143 | [121] |
| Serum | miR-145, miR-200c | Up | Diagnostic biomarkers | 0.910 (miR-145) 0.802 (miR-200c) | 0.840–0.980 (miR-145) 0.698–0.906 (miR-200c) | 91.7 (miR-145) 72.9 (miR-200c) | 75.0 (miR-145) 90.0 (miR-200c) | - | - | Case-control study | 68 | [122] |
| Serum | miR-1307, miR-375 | Up | Diagnostic biomarkers | 0.671 (miR-1307) 0.788 (miR-375) 0.837 (combined) | 0.550–0.791 (miR-1307) 0.665–0.890 (miR-375) 0.725–0.917 (combined) | 33.33 (miR-1307) 61.76 (miR-375) | 94.29 (miR-1307) 87.88 (miR-375) | - | - | Case-control study | 150 | [123] |
| Serum | miR-34a | Down | Diagnostic biomarkers | - | - | - | - | - | - | Case-control study | 58 | [124] |
| Serum | miR-1290 | Up | Diagnostic biomarkers | 0.71 (HGSOC vs healthy controls) 0.76 (HGSOC vs non-HGSOC) | - | 63.0 (HGSOC vs healthy controls) 47.0 (HGSOC vs non-HGSOC) | 85.0 (HGSOC vs healthy controls) 85.0 (HGSOC vs non-HGSOC) | - | - | Case-control study | 83 | [125] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum | ZNF587B | Down | Diagnostic biomarkers | - | - | 79.0 | 84.7 | 1.71 | - | Case-control study | 128 | [126] |
| Serum | SLC11A2 | Up | Diagnostic biomarkers | 0.80 | - | - | - | - | - | Case-control study | 81 | [127] |
| Serum | EFEMP1, SERPINC1 | Up | Diagnostic biomarkers | 0.8071 (EFEMP1, EOC vs healthy donors) 0.7898 (EFEMP1, EOC vs benign ovarian tumors) 0.7963 (EFEMP1, early-stage EOC vs healthy donors) 0.7755–0.8667 (SERPINC1, EOC vs healthy donors) 0.7087–0.8398 (SERPINC1, EOC vs benign ovarian tumors) 0.7762–0.9395 (SERPINC1, early-stage EOC vs healthy donors) 0.7896–0.8792 (combined, EOC vs healthy donors) 0.7405–0.8687 (combined, EOC vs benign ovarian tumors) 0.7803–0.9451 (combined, early-stage EOC vs healthy donors) | - | - | - | - | - | Case-control study | 376 | [128] |
| Serum | MALAT1 | Up | Prognostic biomarkers | - | - | - | - | 2.437 | 1.122–5.293 | Case-control study | 60 | [47] |

(*Continued*)


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**Table 3** (Continued).

| Biofluid | sEVs Cargo | Level | Biomarker | AUC | 95% CI (AUC) | Sensitivity (%) | Specificity (%) | HR | 95% CI (HR) | Cohort Type | Sample Size | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum | CFH, TMEM205 | Up | Platinum resistance-predictive biomarkers | 0.95 (CFH) 0.84 (TMEM205) 0.973 (combined) | - | 96.8 (CFH) 93.7 (TMEM205) 93.8 (combined) | 90.7 (CFH) 65.7 (TMEM205) 93.8 (combined) | - | - | Case-control study | 112 | [129] |

**Abbreviations**: DFS, disease-free survival; 5-DFS, 5-year disease-free survival; OS, overall survival; 5-OS, 5-year overall survival; ELISA, enzyme-linked immunosorbent assay; PRM, parallel reaction monitoring.

patients.[116,117] They can not only effectively distinguish OC patients from healthy people, but also their expression levels are directly related to patient prognosis. Furthermore, in vitro cell experiments have further verified the functional roles of these markers in the progression of OC. Specifically, miR-200b can inhibit the proliferation of OC cells and promote their apoptosis, while SCNN1A and EFNA1 contribute to the establishment of the PMM and participate in the tumor immune escape process. In conclusion, these biomolecules are not only reliable biomarkers but also may influence the progression of OC by regulating the biological behaviors of tumor cells.

In the field of efficacy prediction, the integrated analysis process based on next-generation sequencing (NGS) has found that there are significant differences in the expression of mature miRNAs such as miR-486, miR-21, miR-181a, miR-223 and miR-1908 in the plasma sEVs of platinum-sensitive and platinum-resistant OC patients. The expression patterns of these miRNAs can serve as potential indicators for predicting patients' sensitivity to platinum-based drugs, providing a reference for the clinical formulation of individualized chemotherapy regimens.[118] Similarly, in the field of predicting the sensitivity of OC to platinum-based drugs, the detection and analysis based on nano-flow cytometry has found that the expression levels of Ep $CAM^+$ and $CD45^+$ sEVs in the plasma of patients with HGSOC are closely related to the patients' platinum sensitivity. Their expression patterns can serve as potential indicators for predicting the platinum-based drug sensitivity of HGSOC patients.[119]

## Serum

This part centers on the latest reports regarding plasma sEV markers in OC. Currently, CA125, as the most widely utilized serum tumor marker in gynecology, has certain limitations in the diagnosis of OC. Specifically, only 50% of early-stage OC patients exhibit elevated serum CA125 levels, while in 20% of advanced OC patients, the level of this marker remains within the normal range.[130] Additionally, its specificity is influenced by benign gynecologic diseases (eg, pelvic inflammatory disease, endometriosis) as well as pregnancy status.[131] Numerous studies have shown that the levels of CA125 and HE4 in serum sEVs can be utilized for OC identification, and that CA125 can be detected at higher levels in serum-derived sEVs than in serum, which significantly enhances the diagnostic sensitivity of OC.[120,121] A study on serum sEV miRNAs revealed that miR-145 was the optimal single marker for predicting OC, with a sensitivity of 91.7%, and miR-200c had the highest specificity of 90.0%.[122] When tested in combination, the sensitivity of the three (CA125, miR-145, and miR-200c) could reach 100%. Hence, serum sEVs miR-145 and miR-200c are anticipated to serve as biomarkers for distinguishing OC from benign lesions to overcome the limitations of CA125. Likewise, miR-1307 was associated with the OC stage, while miR-375 was associated with the lymph node metastasis of OC. Both were markedly upregulated in serum sEVs of OC and possessed the ability to independently diagnose when detected in combination with CA125 and HE4, which could improve the diagnostic accuracy of traditional biomarkers.[123] Moreover, miR-34a in serum sEVs can also be utilized as a potential biomarker for EOC.[124] sEV miR-1290 is another biomarker for OC. Serum sEV miR-1290 is overexpressed in patients with HGSOC, and can serve as a biomarker to differentiate patients with HGSOC from those with other histological types of malignancies. Notably, the relative expression of this miRNA is higher in advanced HGSOC than in the early stage, and its expression is significantly reduced after surgery, which can reflect the tumor burden.[125]

Studies on potential biomarkers for HGSC have shown that the expression level of zinc finger protein 587B (ZNF587B) in serum-derived sEVs from HGSC patients is downregulated, and this downregulation is significantly associated with tumor stage.[126] It highlights its valuable potential as a biomarker for early liquid biopsy screening of OC. Additionally, the expression levels of solute carrier family 11 member 2 (SLC11A2), containing fibulin extracellular matrix protein 1 (EFEMP1), and serpin family C member 1 (SERPINC1) in sEVs are significantly upregulated, supporting their potential as diagnostic biomarkers.[127,128]

Combining it with traditional biomarkers like HE4 and CA125 can provide a more precise diagnosis of HGSOC. Notwithstanding the limited amount of studies that have been carried out as of yet, it has been shown that sEV lncRNA can be detected in serum and may serve as a biomarker for OC. For instance, Qiu et al demonstrated that raised levels of serum sEV MALAT1 were tightly correlated with advanced and metastatic characteristics of EOC.[47] Thus, circulating sEV MALAT1 is anticipated to be a serum-based, non-invasive, and predictive biomarker for EOC prognosis. In the field of predicting platinum resistance in OC, studies have shown that the expression of complement factor H (CFH) and

transmembrane protein 205 (TMEM205) in serum-derived sEVs is significantly upregulated in patients with platinum-resistant high-grade serous ovarian cancer (PR-HGSOC) compared to those with platinum-sensitive high-grade serous ovarian cancer (PS-HGSOC).[129] Furthermore, CFH expression levels increase in the early stage of treatment among PR-HGSOC patients, suggesting that it can serve as a potential indicator for the early prediction of platinum resistance and provide a reference for the timely adjustment of clinical chemotherapy regimens and the reduction of drug toxicity.

## Dual-Functional sEVs: Oncogenic Drivers with Diagnostic and Prognostic Value

Some molecular cargo carried by sEVs exerts dual functions: on one hand, it promotes OC progression by regulating the biological behaviors of tumor cells; on the other hand, it serves as a potential marker for clinical diagnosis and prognostic evaluation due to its specific expression characteristics in body fluids.[132,133] This section will focus on this core direction, systematically elaborating on the latest research progress regarding the functional regulatory mechanisms of sEV-associated molecular cargo in OC and their application potential as clinical markers, as shown in Table 4.

From the perspective of the functional classification of molecular cargo, nucleic acid molecules exert multidimensional roles in OC progression, diagnosis, and treatment. sEV-derived miR-200b enhances the proliferative and invasive capacities of OC cells by downregulating the expression of the tumor suppressor gene KLF6.[134] Its high expression level in plasma sEVs is directly associated with disease occurrence and poor prognosis, endowing it with both diagnostic and prognostic efficacy.[116] Both miR-205 and lncRNA MALAT1 carried by sEVs contribute to OC progression by targeting angiogenesis as the core. Specifically, miR-205 promotes angiogenesis via the PTEN-AKT pathway, and its expression level in plasma sEVs can effectively assist in the early diagnosis and staging of OC.[46,109] In contrast, lncRNA MALAT1 facilitates the formation of tumor vascular networks by regulating the expression of various angiogenic factors such as VEGF-A, VEGF-D, IL-8, and bFGF. Moreover, its specific high expression in serum sEVs serves as a crucial molecular indicator for predicting poor prognosis in patients.[47] Addressing the urgent challenge of chemotherapy resistance in OC, sEVs carrying miR-223, miR-21, and miR-181a mediate tumor treatment resistance through their respective specific mechanisms.[74,80,135] miR-223 induces cisplatin resistance via the PTEN-PI3K/AKT pathway while miR-21 enhances tumor cell proliferation and concurrently reduces their sensitivity to paclitaxel. miR-181a causes PARP inhibitor

**Table 4** Summary of sEV Molecular Cargo in OC with Dual Roles in Tumor Progression Promotion and Clinical Biomarkers

| Biofluid | sEVs Cargo | Functions | Signaling Pathways/ Mechanism | Biomarker | Refs |
|---|---|---|---|---|---|
| Plasma | miR-200b | Proliferation, invasion | KLF6↓ | Diagnostic and prognostic biomarkers | [116,134] |
| Plasma | miR-205 | Angiogenesis | PTEN-AKT pathway | Diagnostic biomarkers | [46,109] |
| Serum | MALAT1 | Angiogenesis | VEGF-A, VEGF-D, ENA-78, PlGF, IL-8, angiogenin, bFGF and leptin | Prognostic biomarkers | [47] |
| Plasma | miR-223 | Drug resistance (cisplatin) | PTEN-PI3K/AKT signaling pathway | Platinum resistance-predictive biomarkers | [79,118] |
| Plasma | miR-21 | Proliferation, drug resistance (paclitaxel) | - | Platinum resistance-predictive biomarkers | [74,118] |
| Plasma | miR-181a | Drug resistance (PARPi) | STING | Platinum resistance-predictive biomarkers | [118,135] |
| Plasma | SCNN1A, EFNA1 | Metastasis, TME | MDK-SDC2/NCL | Diagnostic and prognostic biomarkers | [117] |

**Notes**: The downward arrow indicates downregulated molecular expression level.

resistance by targeting the STING gene. The expression patterns of all three in body fluid-derived sEVs provide key references for predicting the efficacy of platinum-based drugs in OC.[118]

Protein molecular cargo also exhibits unique dual functions. SCNN1A and EFNA1 in sEVs remodel the TME and promote metastatic dissemination via the MDK-SDC2/NCL signaling pathway. Meanwhile, these two proteins are specifically expressed in plasma sEVs, rendering them potential non-invasive biomarkers for the diagnosis and prognostic stratification of OC.[117]

In summary, various molecular cargoes loaded by sEVs promote OC progression through well-defined mechanisms. Meanwhile, their detectable nature in body fluids enables them to serve as diagnostic and therapeutic biomarkers. The dual properties of these cargoes, namely functional regulation and biomarker potential, provide core research ideas and theoretical support for the development of integrated diagnosis and treatment strategies for OC.

## sEVs in the Translational Therapy of OC: Vaccine Development, Drug Delivery, and Precision Targeting Strategies

sEVs, as natural intercellular communication carriers, have emerged as prominent tools in the translational research of OC therapy owing to their inherent advantages, including a unique lipid bilayer structure, excellent biocompatibility, low immunogenicity, and tropism for specific targets.[136] In recent years, the exploration of sEV-based applications in cancer therapy has advanced considerably, with their core value in vaccine development, drug delivery, and precision targeted therapy being extensively explored. This has thus provided a novel direction for addressing clinical challenges in OC, such as recurrence, metastasis, and chemoresistance. This section systematically reviews the immunomodulatory mechanisms of sEVs in OC vaccines, focusing on their synergistic effects in drug delivery, and technological advances in engineered sEV-mediated precision targeting, providing crucial reference for subsequent clinical translation studies.

### sEV-Driven OC Vaccine Development

In the field of tumor vaccine development, engineered sEVs represent a core research direction, with research primarily focusing on two types of vesicles: dendritic cell (DC)-derived sEVs and tumor cell-derived sEVs. DCs, as key initiators of the immune response, play a central role in antigen recognition and T cell presentation.[137] Their derived DC-sEVs can efficiently mimic this antigen-presenting function, providing a crucial theoretical foundation for designing sEV-based tumor vaccines. Research teams have developed a personalized nanovaccine platform using DC-sEVs loaded with patient-specific neoantigens. This platform not only offers efficient cargo loading and stable lymph node-targeted delivery but also effectively activates broad-spectrum antigen-specific T/B cell immune responses, demonstrating excellent biosafety and tissue compatibility. In tumor models such as B16F10 melanoma, this vaccine significantly suppressed tumor proliferation, prolonged survival of tumor-bearing animals, delayed tumor progression, and effectively eliminated lung metastases, fully validating its therapeutic potential.[138]

Tumor cell-derived sEVs exhibit strong immunogenicity due to their cargo of multiple tumor antigens. They can present tumor antigens from malignant cells to DCs, promote DC maturation, and thereby effectively elicit tumor-specific cytotoxic T lymphocyte (CTL) immune responses.[132] In studies aiming to enhance the immunogenicity of tumor cell-derived sEVs via engineering, a research team successfully developed an engineered tumor-derived sEV vaccine loaded with the immunogenic cell death (ICD) inducers human neutrophil elastase (ELANE) and Hiltonol (a TLR3 agonist), as well as α-lactalbumin (α-LA).[139] This vaccine induces the activation of in situ type one conventional DCs (cDC1s) in triple-negative breast cancer models and patient-derived organoids, potently stimulates $CD8^+$ T cell responses, and ultimately markedly inhibits tumor growth.

The bionic principle of nanomedicines leverages the biomembranes of cellular and subcellular structures to endow nanomaterials with excellent biocompatibility, low immunogenicity, and active targeting capability. As a subcellular structural coating material, sEV membranes have garnered attention.[140] Based on this principle, bionic sEV membrane-coated nanovaccines can be designed by exploiting the inherent advantages of sEV membranes. Previous studies have constructed a photothermal nanovaccine (hEX@BP) through encapsulating black phosphorus quantum dots (BPQDs) with immunogenic sEVs derived from the serum of tumor-bearing mice post-photothermal therapy. Endowed with the

natural targeting ability and long-circulating property of sEV membranes, this vaccine achieves efficient photothermal ablation of tumor sites under near-infrared laser irradiation.[141] Despite significant advancements in the development of sEV-based tumor vaccines, current research primarily focuses on common tumor types such as malignant melanoma, lung cancer, and breast cancer. The development of sEV-based vaccines targeting OC remains relatively scarce and urgently requires further exploration and breakthroughs.

## sEV-Mediated OC Drug Delivery Systems

The lipid bilayer membrane of sEVs is highly homologous to that of host cell membranes. This structural advantage enables sEVs to efficiently penetrate biological barriers such as the blood-brain barrier and tumor vascular barrier, while reducing the recognition and clearance efficiency by the reticuloendothelial system. Consequently, the in vivo circulation half-life of encapsulated drugs is significantly prolonged, laying a crucial biological foundation for the precise delivery and optimization of therapeutic efficacy of OC treatment drugs.[142]

In the delivery of chemotherapeutic drugs, cisplatin can be delivered by sEVs through clathrin-independent endocytosis, evade endosomal trapping, and diffuse uniformly in the cytoplasm, thereby enhancing therapeutic efficacy and overcoming chemoresistance.[143,144] Cisplatin-loading strategies using sEVs derived from different cell types have all demonstrated significant advantages. Specifically, cisplatin-loaded sEVs derived from expanded natural killer (eNK) cells can significantly sensitize chemoresistant OC cells to the antiproliferative effects of cisplatin.[145] Macrophage-derived sEVs also exhibit potent synergistic effects: cisplatin-loaded M1-type macrophage sEVs from umbilical cord blood increased the cytotoxicity against chemoresistant A2780/DDP cells by 3.3-fold and drug-sensitive A2780 cells by 1.4-fold compared with single-agent chemotherapy, while cisplatin-loaded M2-type macrophage sEVs enhanced the cytotoxicity against A2780/DDP cells by nearly 1.7-fold and A2780 cells by 1.4-fold.[146] Paclitaxel encapsulated in sEVs can significantly enhance the targeted enrichment and retention of the drug in OC tissues, thereby achieving efficient inhibition of paclitaxel-highly resistant OC cells.[147,148] Quantitative analysis via liquid chromatography-tandem mass spectrometry (LC-MS/MS) showed that the concentration of paclitaxel encapsulated in MSC-derived sEVs was 7.6-fold lower than that of free paclitaxel required to achieve equivalent in vitro cytotoxicity. This finding indicates that the sEV-based delivery system exhibits specific and highly efficient tumor-targeting capabilities, which significantly enhance therapeutic efficacy.[149] Additionally, the sEV-mediated doxorubicin delivery system exerts excellent antiproliferative activity against doxorubicin-resistant OC and can effectively reverse tumor multidrug resistance.[150] More importantly, the inherent carrier properties of sEVs minimize drug-induced damage to normal tissues. For instance, sEV-mediated doxorubicin delivery significantly mitigates cardiotoxicity by restricting drug penetration into cardiac ECs, confirming that this delivery system holds greater clinical applicability compared to free doxorubicin.[151]

For natural compounds including curcumin, tetramethylpyrazine, triptolide, berry anthocyanins, and β-lapachone, sEV-mediated delivery significantly enhances their anti-OC efficacy.[152–156] On one hand, sEVs effectively address the inherent drawbacks of these natural compounds such as poor water solubility and low oral bioavailability, thereby substantially improving drug accumulation at the tumor site. On the other hand, sEVs promote the synergistic action of multiple mechanisms including enhanced inhibition of cancer cell proliferation, exacerbated tumor cell oxidative stress, remodeling of the TME, and reversed chemoresistance, leading to a marked increase in the anti-OC activity of natural compounds compared with their free drug forms.

## sEV-Enabled Precision Targeted Therapy for OC

In the field of tumor-targeted therapy, the core advantage of sEVs lies in their inherent high tissue tropism. This property is mainly achieved through specific binding between sEV surface-specific molecules (such as integrins, adhesion molecules, and receptors) and ligands on the surface of tumor cells or relevant cells in the TME. It provides a natural biological basis for targeted drug delivery.[157] However, natural sEVs have inherent limitations, including limited targeting efficiency and insufficient loading capacity, which hinder their ability to meet the clinical needs of precision therapy.[158] Thus, targeted engineering of sEVs can significantly enhance the specificity, efficiency, and stability of their drug delivery, rendering them an ideal tool for precise modulation of the TME and realization of tumor-targeted therapy.[159]

In the engineering modification of surface-modified targeting ligands, researchers have developed various highly efficient targeting strategies based on the specific molecular characteristics of OC cells and the TME. Fusion of the specific ligand ephrin-B2 with the membrane protein lysosome-associated membrane glycoprotein 2b (LAMP2b) enables engineered sEVs to specifically bind to ephrin-B4 receptors on the surface of OC cells, significantly enhancing cellular internalization efficiency and in vivo targeting.[160] Similarly, construction of the arginylglycylaspartic acid (RGD)-LAMP2b vector for displaying RGD peptides on the sEV surface not only enhances sEV accumulation in tumor tissues, tumor cells, and ECs but also enables targeted inhibition of VEGF-A expression via loading miR-484, inducing vascular normalization and improving chemosensitivity.[161] Additionally, a mesothelin (MSLN)-targeted platform constructed using the biotin-streptavidin binding strategy can achieve specific targeting through MSLN highly expressed in OC, efficiently delivering TP53 protein to restore tumor suppressor function, and thereby effectively inhibiting OC cell proliferation both in vitro and in vivo.[162]

Through specialized functional modification and structural design, the tumor-targeting effect can be further optimized. Leveraging the acidic characteristic of the TME, researchers have designed pH-responsive two-dimensional niobium carbide nanosheets loaded with circPUM1 siRNA. Polyethyleneimine (PEI) grafting enables efficient siRNA loading, while subsequent surface polyethylene glycol (PEG) modification significantly reduces off-target effects and systemic toxicity, thereby effectively inhibiting OC angiogenesis and peritoneal metastasis.[163] Using magnetic guidance as a physical regulation approach, biomimetic nanovesicles encapsulating iron oxide nanoparticles and β-lapachone can precisely target OC tissues under the guidance of an external magnetic field, enhancing the tumor-suppressive effect through the Fenton reaction and amplified oxidative stress.[156] By means of the interdisciplinary integration of genetic engineering and biomimetic materials, artificial sEVs derived from Siglec-10-positive M1 macrophages, combined with hydrogel-encapsulated efferocytosis inhibitor MRX-2843, form a targeting system.[164] This system regulates peritoneal macrophage function to synergistically enhance tumor phagocytosis and antigen presentation, and ultimately achieves efficient targeted therapy for OC.

## Conclusions, Limitations, and Future Perspectives

During the recent period, sEVs have risen to prominence as a trendy research focus in the realm of OC. Mounting evidence indicates that sEVs, regardless of whether they are derived from non-tumor cells or tumor cells, can promote the malignant behaviors of OC cells through intercellular communication. Specifically, they can accelerate cell proliferation, facilitate tumor metastasis, enhance chemoresistance, induce angiogenesis, trigger immune escape, and upregulate the expression of stem cell characteristic markers. Consequently, targeting sEVs offers promising approaches for OC treatment. Furthermore, sEVs exhibit substantial potential in clinical settings, including the early diagnosis and prognostic prediction of OC, while also holding broad application prospects in the field of translational medicine such as OC vaccine development, targeted drug delivery, and precise tumor-targeted therapy. These versatile capabilities provide a multi-dimensional breakthrough for the advancement of OC diagnosis and treatment systems.

A growing body of research has unraveled the mechanisms underlying the role of sEVs in the initiation and progression of OC, highlighting the considerable potential of sEV-targeted therapeutic strategies. Nevertheless, current studies in this field still exhibit limitations, which can be specifically summarized in the following three aspects:

First, the understanding of molecular mechanisms remains incomplete. Existing research primarily focuses on the functions of ncRNAs within sEVs, while exploration of other molecular "cargoes" carried by sEVs—such as proteins, lipids, and metabolites—remains relatively scarce. This has resulted in only a partial understanding of how sEVs regulate OC among researchers, making it difficult to fully elucidate the core role of sEVs in disease development.

Second, there is insufficient in vivo experimental data to provide robust support. Most current studies are confined to the in vitro cell experiment level, lacking adequate in vivo animal experimental data for verification. Consequently, it is challenging to accurately reflect the pharmacokinetic profiles, pharmacodynamic effects, and toxicological responses of sEVs in the human body. On this basis, the clinical efficacy of sEV-based strategies has not yet been fully validated and still requires further confirmation through more high-quality clinical trials.

Third, standardized systems for the production, isolation, and purification of sEVs have not yet been established. Due to the overlap in components between sEVs and other types of EVs, coupled with the limited capacity of cells to secrete

sEVs, existing methods for large-scale isolation and purification of sEVs from tissues lack unified standardized protocols.[165] Additionally, these methods face the issue of high costs, which severely hinders the subsequent research and clinical translation of sEVs.

In conclusion, sEVs demonstrate broad application prospects in the diagnosis, treatment, and other relevant fields of OC. Future research should advance around two core directions: on one hand, by conducting more basic research and clinical trials to deeply validate the mechanisms of action and clinical applicability of sEVs, thereby providing solid evidential support for their clinical translation; on the other hand, focusing on exploring more efficient and stable sEV isolation technologies, while developing personalized therapeutic strategies based on the disease characteristics and individual differences of OC patients. These efforts will effectively overcome the key barriers restricting the translation of sEV research from the laboratory to clinical practice, ultimately promoting the widespread application of sEVs in the clinical management of OC.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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