Research progress of extracellular vesicles in the treatment of ovarian diseases (Review)

YIXIN ZHANG[1,2*], JINGYU ZHAO[1,2*], LINQI HAN[1,2], ZIHAN ZHANG[1,2], CAIQIN WANG[1,2], WEI LONG[1,2], KAI MENG[1,3] and XIAOMEI WANG[4]

[1]Collaborative Innovation Center for Birth Defect Research and Transformation of Shandong Province; [2]College of Second Clinical Medicine; [3]Lin He's Academician Workstation of New Medicine and Clinical Translation; [4]College of Basic Medicine, Jining Medical University, Jining, Shandong 272067, P.R. China

Received April 26, 2023; Accepted November 2, 2023

DOI: 10.3892/etm.2023.12303

Abstract. The ovary is an essential reproductive organ in the female organism and its development seriously affects the physical and mental health of female patients. Ovarian diseases include ovarian cancer, premature ovarian insufficiency (POI) and polycystic ovary syndrome (PCOS). Women should pay attention to the most effective treatments for this condition because it is one of the most prevalent gynecological illnesses at present. Extracellular vesicles (EVs), which are smaller vesicles that mediate the exchange of cellular information, include the three categories of exosomes, microvesicles and apoptotic bodies. They are able to transport proteins, RNA and other substances to adjacent or distal cells, thus allowing cellular and tissue homeostasis to be maintained. Numerous previous studies have revealed that EVs are crucial for the treatment of ovarian diseases. They are known to transport its contents to ovarian cancer cells as well as other ovarian cells such as granulosa cells, affecting the development of ovarian disease processes. Therefore, this extracellular vesicle may be involved as a target in the therapeutic process of ovarian disease and may have great potential in the treatment of ovarian disease. In the present review, the role of EVs in the development of three ovarian diseases, including ovarian cancer, POI and PCOS, was mainly summarizes. It is expected that this will provide some theoretical support for the treatment of ovarian disease.

Correspondence to: Dr Kai Meng, Collaborative Innovation Center for Birth Defect Research and Transformation of Shandong Province, Jining Medical University, 133 Hehua Road, Jining, Shandong 272067, P.R. China
E-mail: mengkai521888@126.com

Dr Xiaomei Wang, College of Basic Medicine, Jining Medical University, 133 Hehua Road, Jining, Shandong 272067, P.R. China
E-mail: xichebingqing@163.com

*Contributed equally

Abbreviations: BMSCs, bone marrow mesenchymal cells; CTX, cyclophosphamide; EOC, epithelial ovarian cancer; EVs, extracellular vesicles; ECM, extracellular matrix; GCs, granulosa cells; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; HUCMSCs, human umbilical cord mesenchymal stem cells; MSC, mesenchymal stem cell; MVBs, multivesicular bodies; PCOS, polycystic ovary syndrome; POI, premature ovarian insufficiency; AMSCs, adipose mesenchymal stem cells; DOX, doxorubicin; TP, triptolide; OS, osteosarcoma; 5-FU, 5-fluorouracil

Key words: extracellular vesicles, treatment, ovarian cancer, premature ovarian insufficiency, polycystic ovary syndrome

Contents

1. Introduction

Extracellular vesicles (EVs) are lipid bilayer membrane vesicles released by varying types of activated and apoptotic cells through different mechanisms. They are mainly divided into three categories: Exosomes, microvesicles and apoptotic bodies according to different sizes, sources and markers. Among them, exosomes and smaller microvesicles can be considered as small EVs (sEVs) (1). EVs can be used as intercellular communication media to carry proteins, RNA, free fatty acids, metabolites, and other substances to the distal or adjacent cells, which play a biological function of maintaining cell and tissue homeostasis (2,3). EVs are extracellular matrix (ECM)-specific regulators that carry proteases and signaling molecules that can alter the composition of the ECM by modulating target cells and are thus an integral part of the extracellular environment (4). In previous years, EVs have received extensive attention, having been recognized

as potential biomarkers and drug delivery systems that play important role in the diagnosis and treatment of diseases (5).

Ovarian disease is a common gynecological and obstetric disease, which can be divided into malignant ovarian cancer, premature ovarian insufficiency (POI), polycystic ovary syndrome (PCOS), and other non-malignant diseases. Ovarian cancer is a gynecological disease entity that is mostly diagnosed at late stage and has a high recurrence rate. More than 95% of ovarian cancer occurs in middle-aged women over 45 years-old and most of them are epithelial ovarian cancer (EOC) of various histological types. EOC can be stratified into two categories: slow-growing type I ovarian cancer and inert tumors and type II ovarian cancer with clinically invasive tumors (6-8). EOC can be classified into four histological subtypes: serous carcinomas, endometrioid carcinomas, mucinous carcinomas and clear cell carcinomas (9). Among the aforementioned subdivisions, serous carcinomas are the most common, accounting for ~45%. High-grade serous ovarian cancer (HGSOC) is derived from serous tubal intraepithelial carcinoma and is often characterized by mutations in TP53, distinct from specific mutations in genes such as KRAS, BRAF, or ERBB2 that are common in low-grade serous ovarian cancer (LGSOC). These two types of HGSOC and LGSOC are considered to develop through two independent pathways (10,11). For HGSOCs, prevention through resection of ovarian cancer or use of oral contraceptive pills to prevent oviposition may reduce its mortality (12). Endometrioid ovarian cancer accounts for ~13% of EOC, and its incidence varies by region. According to statistics, the incidence of endometrioid ovarian cancer in Asia is higher than that in other regions of the world (9). Mucinous ovarian cancer is a rare but important subtype of ovarian cancer, accounting for ~13% of EOC (9). This subtype of ovarian cancer is usually associated with mutations in genes such as KRAS and HER2, and its development is mainly confined to the pelvic cavity (13). The incidence of clear cell carcinoma accounts for ~3% of EOC. And the pathogenesis of this tumor is associated with frequent mutations in AT-rich interaction domain 1A (ARID1A) and PIK3CA (9,13). Compared with other ovarian cancers, there are significant geographical and ethnic differences in its incidence (14).

Ovarian cancer metastasizes in two ways: Passive dissemination and hematogenous metastasis. Passive dissemination of ovarian cancer cells is the most common, where the cancer cells dislodge from the primary tumor and spread to the greater omentum of the peritoneum and adjacent organs with peritoneal fluid, whereas hematogenous metastasis of ovarian cancer cells spreads through two links of introgression and extravasation to surrounding tissues (15). Currently, effective early screening methods for ovarian cancer are lacking, and the survival rate of patients after a late diagnosis is low. The disease is mainly treated with traditional treatment modalities, including chemotherapy and surgery, whereas new treatment methods, such as targeted therapy and immunomodulation therapy, are constantly improving and are gradually being applied in the clinic. However, effective treatment of ovarian cancer remains a difficult problem, and seeking effective treatment is the key to curing ovarian cancer (16,17).

POI is an ovarian disease characterized by insufficient estrogen secretion, increased gonadotropin secretion, and premature menopause in women under the age of 40 years (18). As a common gynecological disease with an incidence rate of ~1% in women before the age of 40 years, POI has various causes, including genetic factors such as chromosomal abnormalities (X-chromosome terminal deletion and reduced number) and gene mutations [mutations in forkhead box L2 (FOXL2), basonuclin zinc finger protein 1 (BNC1)], spontaneous factors such as autoimmune diseases (primary adrenal insufficiency, hypothyroidism), and iatrogenic factors such as radiotherapy and chemotherapy (19-22). POI is mainly caused by genetic mechanisms leading to the reduction of gene dosage and the destruction of meiosis, but also includes autoimmune attacks on the ovary and some rare causes, such as galactosemia (23-25). Patients with POI present with a pathological state of estrogen insufficiency; therefore, hormone replacement therapy can be used to relieve various adverse symptoms. However, this therapy does not fundamentally solve the problems of impaired ovarian function and low fertility, and exosomal therapy may be an effective treatment option (25,26).

PCOS is a disease characterized by increased androgen secretion (acne, hirsutism, alopecia, and other symptoms), polycystic ovary, and menstrual disorders (>35 days), which greatly affect a woman's quality of life (27,28). As a common heritable endocrine disease with a prevalence of 3-10% at a certain geographical location and race, its genetic, environmental, behavioral, and endocrine factors greatly affect a woman's life. PCOS will transform from a reproductive disease to a metabolic disorder with age, which will also predispose women to cardiovascular disease and type II diabetes in later life (29,30). Treatment of PCOS includes both medical and surgical treatments. Among these, inositol and insulin have been confirmed as therapeutic agents for PCOS (31,32). In severe cases, laparotomy can be performed and laparoscopic ovarian drilling is an effective method (33).

EVs have been shown to be extensively involved in ovarian cancer drug resistance and promote cancer cell metastasis *in vivo* through molecules such as mixed cargoes carrying biological effectors and microRNAs (miRNAs or miRs) (34). They can also regulate the function of immune cells and promote cellular immune evasion by inducing macrophage polarization, inhibiting dendritic cell (DC) activation, suppressing natural killer (NK) cell cytotoxicity, and regulating T cell function, among other key processes in ovarian carcinogenesis (35). Simultaneously, EVs in the ovarian follicular fluid of female patients with PCOS contain a variety of differentially expressed miRNAs and proteins, which are widely involved in the transfer of genetic information between somatic cells and oocytes, as well as in the hormone metabolism pathway of oocytes (36). Moreover, exosomes derived from mesenchymal stem cell (MSC) species regulate androgen production *in vitro* by virtue of their cargo carrier function as the main molecule for reversing PCOS, thereby restoring fertility in PCOS mice (37). In the development of POI, EVs derived from a variety of stem cells such as embryonic stem cells and human umbilical cord MSCs (HUCMSCs) play an important role in intercellular communication by transporting several molecules such as miRNAs from donors to recipients through their own transport function leading to the occurrence of increased follicular growth, decreased follicular atresia

and restoration of hormone levels, thus playing an important role (38,39). EVs are closely associated with the development of ovarian cancer, POI and PCOS. Therefore, in the present review, the role of the biological characteristics of EVs in ovarian cancer, POI and PCOS was mainly highlighted.

2. EVs

As a small vesicle that can be separated from cells and biological fluids, EVs can be divided into exosomes, microvesicles and apoptotic bodies according to different sizes and sources (2). An exosome is a small vesicle with a diameter of ~20-100 nm. As a carrier that shuttles microRNA, drug molecules, and other substances, exosome proteins can mediate the exchange of information between cells (40). Exosomes are initially multivesicular bodies (MVBs) produced by the inward budding of cells. After fusing with the plasma membrane, the contents are secreted into the extracellular environment. Regulated by proteins, ceramides and other substances, its biosynthesis and secretion are complex. For example, ISGy modification, which belongs to ubiquitination modification, can induce the aggregation and degradation of MVB protein TSG101, reduce the number of MVB, and thus inhibit the secretion of exosomes (41-43). Various bioactive molecules including DNA, proteins, mRNA, and non-coding RNA are released by exosomes, and its lipid bilayer structure can effectively protect its contents from the decomposition of extracellular nuclease and proteinase; hence, it can stably exist in body fluids. The biological characteristics of exosomes include stability and low toxicity. Furthermore, they play an important role in targeted drug therapy of ovarian diseases through binding with targeted ligand/homing peptide and exosome transmembrane structure (44,45). Among the contents of exosomes, proteins such as tetraspanins (CD9, CD63, CD81 and CD151), Rab protein, connexin, and exosomal nucleic acid molecules, such as miR-214 and miR-10b can be used as biomarkers for cancer treatment. Moreover, compared with normal cells, tumor cells release more exosomes; thus, their biomarker characteristics for diagnosis and treatment have become a major focus; however, exosome separation and purification are time-consuming and costly. Therefore, at present, medical researchers are exploring electrochemical sensing and other technologies to manufacture various devices to address this problem so that this exosome feature can be applied to the clinical treatment of cancer (46,47). Microvesicles, as vesicles with a diameter of ~200-1,000 nm formed through an outward extrusion of the plasma membrane, can affect disease occurrence by regulating cell processes including promoting cell growth and invasion, angiogenesis, and cell type changes, among others, and play an important role in the research and treatment of ovarian diseases (48). Apoptotic bodies are small vesicles formed by the decomposition of cells after apoptosis, which can carry substances that can be used in apoptotic cells to normal cells. Concurrently, studies have shown that apoptotic bodies can transfer chemotherapeutic drugs with proximity effect to tumor cells to play a therapeutic role. Hence, drugs can penetrate into the tumor and maximize its destructive effect (49,50). The biological characteristics of the three types of EVs allow us to discuss their role in ovarian diseases.

3. Exosomes and the treatment of ovarian cancer

Contents of exosomes and ovarian cancer metastasis. Exosomal content miRNAs are a group of endogenous, 22 nt-long non-coding regulatory genes that function as gene regulatory molecules in the control of life activities in multicellular plants and animals (51). Chen *et al* (52) discovered that the conserved gene sequence can preserve the genome structure by comparing the human-mouse genome and examining the gene order stability of nearby miRNA regions. In order to cleave or suppress translational activity, miRNAs may interact with their target mRNAs (51). In a study by John *et al* (53) employed three validation techniques-retrospective, statistical and indirect experimental-to demonstrate that the majority of miRNAs are selective in the mRNAs they interact with and cleave. They are both multiplexed (one miRNA may target several genes) and synergistic (several miRNAs can regulate one gene) (53). MiRNAs are now considered to have a role in the development of ovarian cancer. In consequence, because of their affinity for the raft-like outer part of the MVB membrane, miRNAs can be specifically mediated into exosomes (54). Exosomes are vesicle carriers that facilitate cellular information transfer and may carry different miRNAs that affect ovarian cancer cells. Rashed *et al* (55) identified that miR-940 targets the proto-oncogene tyrosine protein kinase and inhibits the expression of its downstream protein, preventing the invasive metastasis of ovarian cancer cells. MiR-940 is enriched in exosomes derived from ovarian cancer SKOV3-IP1, HeyA8 and HeyA8-MDR cells. MiR-124, another exosomal component produced from ovarian cancer cells, similarly prevents cell metastasis. By inhibiting the production of the protein sphingosine kinase 1, which has a pro-carcinogenic impact, this miRNA achieves its oncogenic mechanism (56). Moreover, ovarian cancer-derived exosomal miR-205 and ascites-derived exosomal miR-6780b-5p enhance ovarian cancer cell metastasis by promoting angiogenesis and epithelial-mesenchymal transition (EMT) of cells, respectively (57,58). In addition, exosomal miR-323-3p derived from adipose MSCs (AMSCs) can reduce the apoptosis of cumulus cells and promote their proliferation by acting on PDCD4 in patients with PCOS. Additionally, miR-199a-5p, an ovarian cancer cell-derived exosome, has the ability to control hypoxia-inducible factor-2, which enhances tight junctions in vascular endothelial cells and prevents the spread of cancer cells (59). It is clear that the overexpression of these tumor suppressor exosomal miRNAs can prevent cancer cell metastasis, obstruct ovarian carcinogenesis, and potentially function as biomarkers and therapeutic targets in the treatment of ovarian cancer. Exosomal miRNAs can also encourage the spread of ovarian cancer cells. In a recent study, Cao *et al* (60) revealed that miR-21-5P, which is highly expressed in the exosomes of patients with ovarian cancer, promotes the expression of cyclin synthesis-dependent kinase 6 and anti-apoptotic proteins in cancer cells while inhibiting the expression of pro-apoptotic proteins to facilitate the migration of ovarian cancer cells. Exosomes from ovarian cancer and ascites, respectively, can promote angiogenesis and EMT, which can both increase ovarian cancer cell metastasis (57,58). In addition, EOC exosomes have the ability to carry miR-125b-5p, miR-181d-5p and miR-21-3p to M2 macrophages, where they can increase their polarization

and aid in the metastasis of EOC cells (61). These exosomal miRNAs that encourage tumor cell metastasis may serve as targets in the therapy of ovarian cancer. In conclusion, both strategies-blocking the release of exosomes that restrict cancer cell metastasis from ovarian cancer tissues and focusing on exosomes that promote it-can decrease tumor cell metastasis and may prove to be useful modalities for the treatment of ovarian cancer.

In addition to exocytotic miRNAs, non-miRNA substances such as plasmids and proteins can also be used as information carriers to influence the metastasis of ovarian cancer. Transforming growth factor 1 (TGF-1) may be carried by cancer-associated fibroblast-derived exosomes, according to a research by Li *et al* (62). This TGF-1-carrying exosome, when ingested by ovarian cancer, initiates the disease's EMT process and encourages the spread of ovarian cancer cells. Meanwhile, studies have shown that exosomes derived from DC carrying Killer Cell Lectin Like Receptor K1 (NKG2D) ligands can bind to the NKG2D receptor on the surface of NK cells and activate NK cells, thus promoting the immune rejection of tumors and inhibiting tumor growth. In addition, Viaud *et al* (63) have injected dexamethasone vaccine into 15 patients with melanoma in Phase I clinical trials and found an increase in the number of NK cells in some patients. In two of these patients, the tumor decreased. It has also been demonstrated that exosomes released by ovarian cancer cells allow subpopulations of cells with high invasive metastatic properties to transmit those qualities to cells with lower metastatic capacities. By way of their endoplasmic CD44 transfer, for instance, exosomes released by highly metastatic H08910PM cells might encourage the metastasis of low metastatic HO8910 cells (64). Pro-metastatic action of exosomes, in turn, is associated with the ability of the cells from whence they come to invade. Exosomes produced from highly metastatic ovarian cancer cell lines include specific, highly expressed pro-metastatic proteins that can control the Wnt/β-catenin signaling pathway and encourage the spread of tumor cells. Additionally, these exosomes are more likely to promote metastasis than exosomes from ovarian cancer cells with little metastatic potential (65). Other RNA molecules in the exosome also influence the spread of ovarian cancer. Exosomes containing the cyclic RNAs CircPUM1 and CircWHSC1, for instance, operate on peritoneal mesothelial cells and promote peritoneal metastasis of ovarian cancer by taking up and releasing miRNAs in the form of sponges to maintain high expression levels (66,67). Therefore, by blocking metastasis as therapeutic targets, such exosomes carrying non-miRNA components may potentially be used in the treatment of ovarian cancer. The part exosomes play in the spread of ovarian cancer was reviewed by the authors and the remarkable therapeutic potential of exosomes was identified.

Targeted therapy of ovarian cancer with exosome. At present, no optimal treatment for ovarian cancer, as a gynecological disease with high incidence, has been found, however studies have revealed that targeted treatment of ovarian cancer may address this issue. Therapeutic exosome targeting to treat ovarian cancer may include passive targeting of exosomes utilizing the tropism of natural exosomal cells and active targeting of exosomes utilizing tissue exosome surface engineering (68). Exosomes are tiny, extensively dispersed in bodily fluids, and readily pass through blood vessel walls. At the same time, compared with *in vitro* manufactured carriers, human-derived exosomes are less immunogenic and more biocompatible (69). The structure can easily escape pursuit by the immune system and can carry nano-molecules for targeted transport to specific tissues (70). Additionally, it has been demonstrated that hybrid exosomes, which combine the benefits of exosome and liposome delivery methods, have great stability and high drug release rates, and may differently target medications to normal and tumor cells, making the targeting of tumor therapy easier (71). Because of the characteristics summarized in the previous section, exosomes may be useful as delivery vehicles for drugs used to treat ovarian cancer. For example, bone marrow-derived MSC exosomes have specific targeting functions and can activate signaling pathways of ovarian cancer cell proliferation and metastasis, thus promoting tumor formation (72). It is possible to treat ovarian cancer using a strategy that specifically inhibits MSC exosomes. Meanwhile, Hadla *et al* (73) found that exosomes increase the therapeutic index of doxorubicin (DOX) in a mouse model of ovarian cancer. In that study a human HGSOC mouse model of ovarian cancer was constructed, when $5x10^6$ spontaneously transformed mouse ovarian surface epithelial cells mixed with 30% stromal gel was subcutaneously implanted into the lateral abdomen of FVB/N mice. A total of 3 mg/kg of DOX and 3 or 6 mg/kg of exoDOX were injected intraperitoneally bi-weekly after tumors had reached a size of >50 mm^3. It was found that at high concentrations, exoDOX was more effective than free DOX alone, while having lower toxicity, thereby increasing the potential of DOX in the treatment of ovarian cancer. Triptolide (TP) is an herbal ingredient with anti-tumor effects. In 2019, Liu *et al* (74) found that the transportation of TP through exosomes, a carrier, significantly inhibited the proliferation of ovarian cancer cells and attenuated or delayed drug toxicity. A total of $2x10^6$ SKOV3 cells were injected subcutaneously into Balb/c nude mice to perform mouse ovarian cancer modeling. When the tumor volume reached ~100 mm^3, TP content of 0.2 mg/kg was injected intraperitoneally into mice twice a week for 4 weeks. This may be a promising strategy for TP treatment of ovarian cancer. In conclusion, exosomes play an important role in the treatment of ovarian cancer and can be used as the main safety delivery vehicle for future ovarian cancer drugs. In addition, Huang *et al* (75) prepared engineered exosomes (cRGD-Exo-MEG3) modified with c(RGDyK) and carrying the long non-coding RNA maternally expressed gene 3 (lncRNA MEG3) by engineering technology. Both *in vivo* and *in vitro*, this exosome can target the lncRNA MEG3, which exerts anti-osteosarcoma (OS) effects, to tumors more efficiently, enhancing the anti-OS effects of MEG3 and thus inhibiting tumor growth. Moreover, Liang *et al* (76) combined 10 μg 5-fluorouracil (5-FU) and 400 nm miR-21 inhibitor oligonucleotide (miR-21i) with exosomes at a protein concentration of 10 μg. They obtained engineered exosomes loaded with 5-FU and miR-21i and injected them into a human colon cancer cell line (HCT-1165FR) using electroporation. The results revealed that the combination of 5-FU and miR-21i significantly inhibited cancer cell proliferation. Moreover, injection of 5-FU and miR-21i exosomes into nude mice inhibited tumor growth. This further demonstrated that

miR-21i and 5-FU exosomes can target cancer cell delivery and improve the efficacy of CRC treatment. Exosomes play an important role in the targeted treatment of cancer, so that the targeted treatment of exosomes may have potential therapeutic value in ovarian cancer.

Immunotherapy of ovarian cancer with exosome. Spontaneous immune responses and immune evasion mechanisms are present in ascites, peripheral blood, and tumors of patients with multiple ovarian cancers, and unlike conventional surgical and platinum-based treatments, immunotherapy for ovarian cancer is emerging (77). At present, the main direction of ovarian cancer immunotherapy is the development of biomarkers and targeted therapy. Some treatment pathways based on immunotherapy have proven pre-clinical success and entered clinical trials, such as immune checkpoint blockade and cancer vaccines (78,79). For example, the intravenous anti-programmed cell death protein 1 (PD-1) antibody nivolumab to block PD-1 signaling in 20 patients with platinum-resistant, recurrent, or advanced ovarian cancer has been tested in a phase II clinical trial. The results demonstrated a disease control rate of 45% (78). Nivolumab is currently approved by the Food and Drug Administration for the treatment of ovarian cancer (80). At the same time, another study has injected oxidized whole-tumor lysate DC vaccine into the nodules of patients with recurrent ovarian cancer and found that the injection of the vaccine was associated with prolonged survival (79). As the vaccine in the present study was only in the pilot clinical stage, and due to certain limitations, such as production difficulties and lack of immunogenicity of lysates, it is not currently approved for human treatment. In addition, several studies have shown that lymphocyte infiltration is the manifestation of tumor immune response. Tumor-infiltrating T cells are closely associated with improved clinical outcomes and prolonged survival in advanced ovarian cancer and are considered to have clinical significance as an independent prognostic marker for ovarian cancer (81,82). Zhang *et al* (81) analyzed the distribution of tumor-infiltrating T cells in 186 frozen specimens of stage III or IV ovarian cancer and found that the 5-year overall survival rate of patients with tumors containing T-cell infiltration (38%) was higher than that of patients without T-cell infiltration (4.5%). Meanwhile, Han *et al* (82) conducted T cell infiltration analysis on tumor samples of 150 EOC patients and also found that T cell tumor infiltration was significantly associated with improved survival rate of patients. Despite numerous advances in ovarian cancer immunotherapy strategies, new strategies for immunotherapy still need to be explored to improve the survival of ovarian cancer patients. Exosomes, which can act as carriers to mediate cell communication and evade immune rejection by the human body, have the potential for immune modulation. It has been identified that ascites and plasma of patients with ovarian cancer contain tiny EVs with internal Arginase 1 that may infiltrate antigen-presenting cells, lowering T-cell activity and assisting the tumor in evading immune system surveillance. However, the arginase inhibitor (OAT-1) can block the immune escape process of cancer cells and reverse the tumor growth-promoting effects of EV (83). Labani-Motlagh *et al* (84) also demonstrated that exosome-derived NKG2D from patient ovarian cancer cells or ascites promoted cytotoxicity of NK cells, leading to immunological escape. CD47, a protein expressed on the surface of most tumours, interacts with signal-regulated protein alpha (SIRPα) on the surface of phagocytes, thereby inhibiting the phagocytic ability of phagocytes to engulf tumour cells (85). Overexpression of CD47 in tumor cell-derived exosomes facilitates an immune evasion response in ovarian cancer cells. Exosomes can be used as a novel immune checkpoint, its biogenesis/release inhibitor GW4869 can inhibit the spread of ovarian cancer cells by indirectly reducing the expression of CD47 through the inhibition of exosome secretion for the treatment of ovarian cancer (86). Meanwhile, it was found that exosomes carrying SIRPα variants could block the normal interaction between CD47 and SIRPα, enhancing phagocytosis in the T-cell response and facilitating tumor clearance (85). Furthermore, PD-1, secreted by exosomes derived from activated T cells, can interact with programmed death-ligand 1 to impede the inhibitory effect of PD-1 on the activity of toxic T cells, with implications for tumour clearance (87). It is clear that exosomes may have some effect on tumours by altering the immune response of the organism. For the treatment of ovarian cancer, this immunotherapy of ovarian cancer by exosomes may become an effective modality (Fig. 1).

Implications of exosomes for the treatment of ovarian cancer. Numerous studies have shown that the interaction between the tumor and its microenvironment is the key for tumor therapy, and exosomes, as the mediators between tumor cells and the tumor microenvironment, are of great significance for the treatment of ovarian cancer (88). In targeting and in immunotherapy of ovarian cancer, exosomes undoubtedly play an irreplaceable role. the possible role of exosomal targeted therapies and immunotherapy in ovarian cancer as well as in numerous other cancers has been already summarized in the aforementioned paragraphs, showing the potential of exosomes in cancer therapy. In ovarian cancer treatment, exosomes have shown therapeutic potential in addressing the issue of drug resistance in ovarian cancer cells. For example, the downregulation of circular RNA, cerebellar degeneration related 1 as in the exosomes of cisplatin in patient cells can sensitize ovarian cancer to cisplatin and reduce ovarian cancer cell resistance by promoting miR-1270 expression, which regulates the suppressor of cancer cell invasion and favors cisplatin treatment of ovarian cancer (89). Meanwhile, exosomes widely exist in body fluids such as peripheral blood and are widely distributed and highly stable. Studies have proved that exosomal microRNAs in patients with ovarian cancer exhibit characteristics different from those in healthy women and can be used as a biomarker to aid in the treatment of ovarian cancer (90,91). At present, the screening and diagnostic methods of ovarian cancer are not advanced. Coupled with the asymptomatic growth of ovarian cancer, most ovarian cancers are diagnosed late, resulting in poor survival. Moreover, the current traditional treatment technologies such as combined platinum compounds and taxane chemotherapy failed to achieve favorable treatment results, and a high recurrence rate remains present. Currently, different targeted therapies and biological drug therapies that are expected to transform ovarian cancer into a chronic disease have not shown to be efficacious in terms of cure (92,93). The exosome

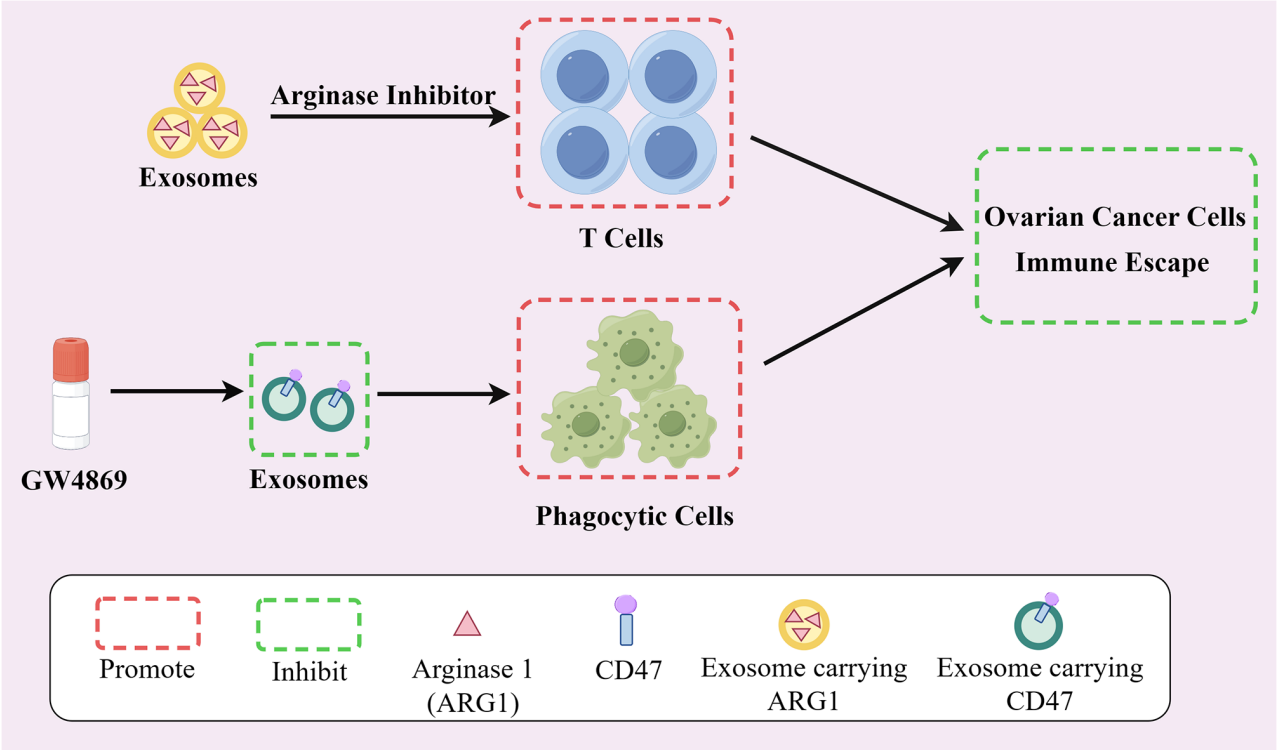

Figure 1. Role of exosomes in ovarian cancer immunotherapy. Exosomes carrying ARG1 in the plasma and ascites of patients with ovarian cancer can promote T cell proliferation under the action of arginase inhibitors, thus inhibiting the immune escape of ovarian cancer cells. In addition, GW4869 can inhibit the process of ovarian cancer cells by secreting CD47 exosomes, reducing the number of exosomes expressing CD47 and promoting the ability of phagocytic cells to phagocytose ovarian cancer cells, inhibit the immune escape of ovarian cancer cells, and ultimately hinder the occurrence and development of ovarian cancer. Therefore, exosomes can be used as a new type of immune checkpoint and a new method for the treatment of ovarian cancer. ARG1, arginase 1.

is an important participant in ovarian cancer therapies such as targeted therapy and immunotherapy, and its presence is undoubtedly of great value in the treatment of ovarian cancer.

4. Exosomes and non-ovarian cancer disease

Exosomes and the treatment of POI. As transferable vesicles, the miRNA in exosomes affects POI treatment. Chemotherapeutic agents have been widely used in the construction of POI animal models. A previous study has reported that for the construction of POI mouse models, cyclophosphamide (CTX) (120 mg/kg)/busulfan (12 mg/kg) treatment for at least 2 weeks or cisplatin (2 mg/kg) treatment for more than 10 days was found to be the most effective way to construct POI mice (94). For the induction of POI rats, a loading dose of 200 mg/kg CTX and a maintenance dose of 8 mg/kg CTX for 14 days is the most effective method (95). A study has shown that exosomes derived from bone marrow mesenchymal cells (BMSCs) can carry miR-144-5p that can mediate the activation of pI3K/AKT pathway and target ovarian granulosa cells (GCs) damaged by CTX, so as to inhibit GC apoptosis in rats with POI caused by CTX and improve ovarian function (96). Concurrently, the exocrine miR-644-5p from this cell can regulate the expression of p53 ovarian GCs in POI mice model induced by cisplatin and then inhibit apoptosis (97). This shows that miR-144-5p and miR-644-5p in BMSCs play an important role in the treatment of POI caused by CTX and cisplatin, respectively. Other studies have revealed that miRNA-1246 and miRNA-21-5p carried by human amniotic epithelial cell-derived exosomes can be transferred to ovarian GCs, reducing chemotherapy-induced GC apoptosis in POI mice model by inhibiting the expression of cleaved caspase 3 protein (98); exosome miR-10a derived from amniotic fluid stem cells can also inhibit the apoptosis of ovarian GCs in POI mice model induced by chemotherapy and is conducive to ovarian growth and development. They can all be used as therapeutic targets for chemotherapy-induced POI (99). In addition to treating chemotherapy-induced POI mouse models, some studies have found that exosomes derived from HUCMSCs can carry miR-146a-5p or miR-21-5p to regulate the activation of primitive follicles and improve fertility in natural aging mice model with low ovarian reserve (100). This exocrine, highly expressed miR-21 from human MSCs can reduce the expression of phosphorylated lysine oxidase like 2 and Yes-associated protein by reducing the expression of its target large tumor suppressor 1, thereby increasing the secretion of estrogen from ovarian GCs (KGN and SVOG) and repairing ovarian function, which affects the treatment of POI (101). These studies indicated that various cell-derived exocrine miRNAs play an important role in the treatment of POI by CTX, cisplatin, chemotherapy and other injuries.

Exosomes and the treatment of PCOS. In the current treatment of PCOS, the use of exosomes may be considered effective. A study has demonstrated that S100 calcium-binding protein A9 (S100-A9) contained within the follicular fluid-derived exosomes of the ovary of PCOS patients can activate nuclear factor kappa B of steroid human granulosa tumor cell

Table I. Role of exosomal miRNA in the occurrence and development of ovarian diseases.

miRNA	Source of exosomes	Model	*In vitro* or *in vivo* study	Function	(Refs.)
Ovarian cancer					
miR-940	Ovarian cancer cells	HeyA8, SKOV3IP1, A2780-PAR, A2780-CP20, HIO-180	*In vitro*	Target the proto-oncogene SRC and inhibits the expression of its downstream protein, preventing the invasive metastasis of ovarian cancer cells	(55)
miR-124	Ovarian cancer cells	SKOV3, HO8910pm cell lines	*In vitro*	Inhibit the production of the protein SphK1, which has a pro-carcinogenic impact, to achieve its oncogenic mechanism	(56)
miR-199a-5p	Ovarian cancer cells	A2780, UWB, and Hey, Anglne cell line	*In vitro*	Control hypoxia-inducible factor-2 to enhance tight junctions in vascular endothelial cells and prevent the spread of cancer cells	(59)
miR-21-5P	Ovarian cancer cells	A2780, SKOV3, BALB/C nude mice	*In vitro* and *in vivo*	Promote the expression of CDK6 and anti-apoptotic proteins in cancer cells while inhibiting the expression of pro-apoptotic proteins to facilitate the migration of ovarian cancer cells	(60)
miR-205	Ovarian cancer cells	HUVECs, BALB/c nude mice	*In vitro* and *in vivo*	Enhance ovarian cancer cell metastasis by promoting angiogenesis and EMT of cells	(57)
miR-6780b-5p	Hydroperitoneum	A2780, SKOV3, CAOV3, ES2, orthotopic xenograft mouse model of ovarian cancer	*In vitro* and *in vivo*	Enhance ovarian cancer cell metastasis by promoting angiogenesis and EMT of cells	(58)
miR-125b-5p, miR-181d-5p, miR-21-3p	EOC	SKOV3, HO-8910, the monocyte cell line U937	*In vitro*	Delivered to M2 macrophages and induce their polarization and aid in the metastasis of EOC cells	(61)
POI					
miR-144-5p	BMSCs	CTX-damaged GCs, CTX-induced rats	*In vitro* and *in vivo*	Mediate the activation of pI3K/AKT pathway and target ovarian GCs damaged by CTX, so as to inhibit GC apoptosis in rats with POI caused by CTX and improve ovarian function	(96)
miR-644-5p	BMSCs	Cisplatin-induced primary GCs, Cisplatin-induced POI mouse	*In vitro* and *in vivo*	Regulate the expression of p53 ovarian GCs in POI mice model induced by cisplatin and then inhibit apoptosis	(97)
miR-21-5P, miRNA-1246	hAEC	Chemotherapy-induced GC, chemotherapy-induced POI mice	*In vitro* and *in vivo*	Delivered to ovarian GCs and reduce chemotherapy-induced GC apoptosis in POI mice model by inhibiting the expression of cleaved caspase 3 protein	(98)
miR-10a	AFSC	CTx-damaged GCs, CTx-induced POI mice	*In vitro* and *in vivo*	Inhibit the apoptosis of ovarian GCs in POI mice model induced by chemotherapy and is conducive to ovarian growth and development	(99)
miR-21	hMSCs	KGN, SVOG	*In vitro*	Reduce the expression of LOXL2 and YAP by reducing the expression of its target LATS1, thereby increasing the secretion of estrogen from ovarian GCs (KGN and SVOG) and repairing ovarian function	(101)

Table I. Continued.

miRNA	Source of exosomes	Model	*In vitro* or *in vivo* study	Function	(Refs.)
miR-146a-5p, miR-21-5p	HucMSC	Primordial oocytes, aged female mice	*In vitro* and *in vivo*	Regulate the activation of primitive follicles and improve fertility in female mice with low ovarian reserve	(100)
PCOS					
miR-323-3p	AMSCs	GCs, letrozole-induced PCOS mouse	*In vitro* and *in vivo*	Reduce the apoptosis of cumulus cells and promote their proliferation by acting on PDCD4 in mice with PCOS	(106)
miR-143-3p	Follicular fluid	KGN	*In vitro*	Act on the target BMPR1A, inhibit the activity of KGN Smad1/5/8 signaling pathway, and promote the increase of apoptotic factors in GCs (Primary GCs and KGN)	(103)

miR, microRNA; SRC, tyrosine-protein kinase; SphK1, sphingosine kinase 1; EMT, epithelial-mesenchymal transition; EOC, epithelial ovarian cancer; GCs, granulosa cells; CTX, cyclophosphamide; POI, premature ovarian insufficiency; LOXL2, Lysyl Oxidase Like 2; LATS1, large tumor suppressor 1; PCOS, polycystic ovary syndrome; BMPR1A, protein receptor type 1A.

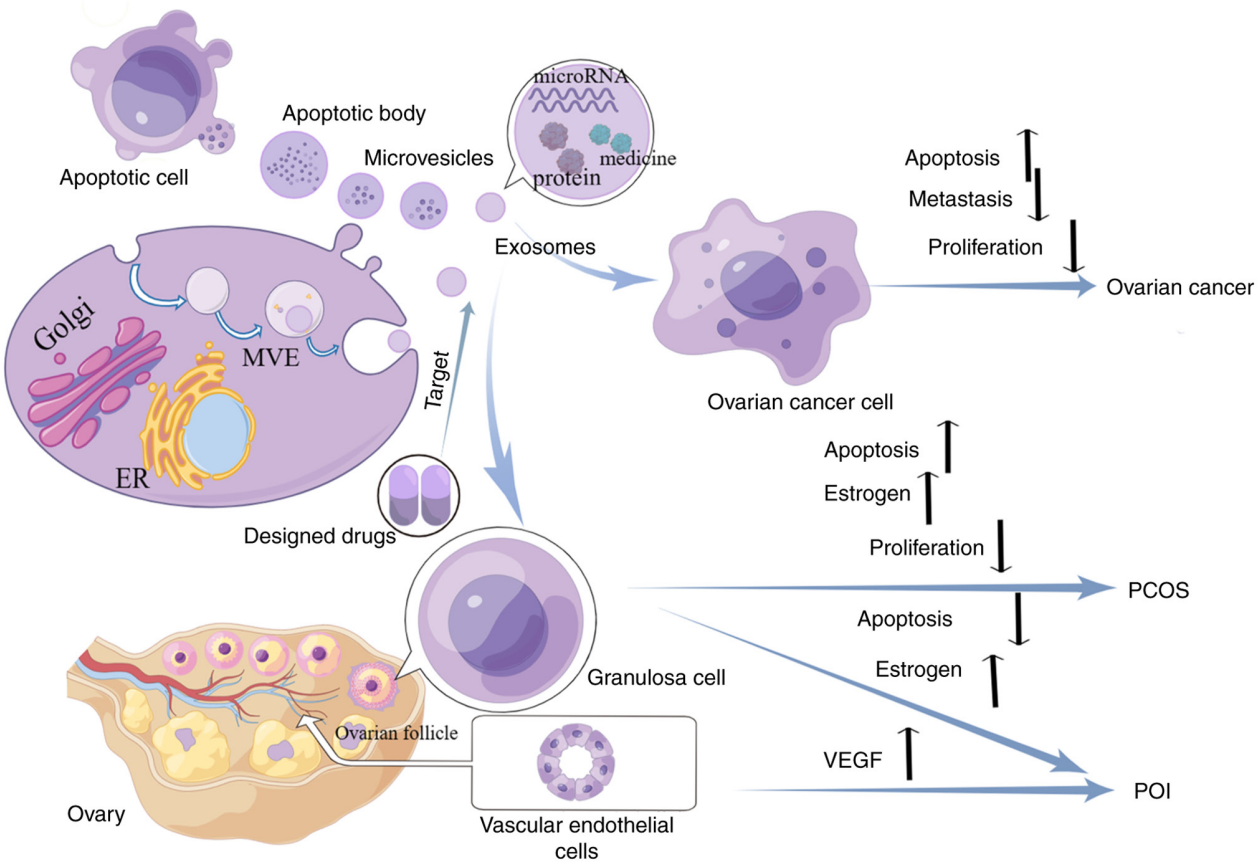

Figure 2. EVs in the treatment of ovarian diseases. EVs carry microRNAs, drugs and other substances that can act on ovarian cancer cells, ovarian granulosa cells and vascular endothelial cells. EVs that inhibit the development of ovarian disease can treat the disease by downregulating the factors that promote the development of ovarian disease and upregulating the inhibitory factors. On the other hand, drugs target EVs that promote the occurrence of ovarian diseases and inhibit their promoting function. Together with the first pathway, it is involved in the treatment of three ovarian diseases. EVs, extracellular vesicles.

signaling pathways, which in turn promote the occurrence of inflammatory reactions and reduce steroid production (102). Simultaneously, miR-143-3p exosomes from the same source can act on the target bone morphogenetic protein receptor

Table II. Role of non-miRNA in EVs in the occurrence and development of ovarian diseases.

Non-microRNA	Types of EVs	Source of EVs	Model	*In vitro* or *in vivo* study	Function	(Refs.)
Ovarian cancer						
TGF-1	Exosome	Cancer-associated fibroblast	SKOV-3 and CAOV-3 cell lines	*In vitro*	Initiates the epithelial-mesenchymal transition process of the disease and encourages the spread of ovarian cancer cells	(62)
CD44	Exosome	H08910PM cells	HO8910 cells	*In vitro*	Metastasis of low metastatic HO8910 cells may be encouraged	(64)
CircPUM1, CircWHSC1	Exosome	Ovarian cancer cells	A2780, CAOV3, OVCAR3, BALB/c nude mice	*In vitro* and *in vivo*	Operates on peritoneal mesothelial cells and promotes peritoneal metastasis of ovarian cancer	(66,67)
ARG1	Exosome	Ascites, plasma	Murine ovarian cancer cell line ID8, C57BL/6 mice	*In vitro* and *in vivo*	Enters antigen-presenting cells to reduce T-cell activity and help tumors escape surveillance by the immune system	(83)
NKG2D	Exosome	Ovarian cancer cells, ascites	OVCAR-3, K562 cells	*In vitro*	Promotes the cytotoxicity of NK cells and causes immune escape	(84)
CD47	Exosome	Ovarian cancer cells	BALB/c nude mice	*In vivo*	Facilitates an immune evasion response in ovarian cancer cells	(86)
PD-1	Exosome	T cells	PY8119, C57BL/6 mice	*In vitro* and *in vivo*	Interacts with programmed death-ligand 1 to impede the inhibitory effect of programmed death-1 on the activity of toxic T cells	(87)
Cdr1as	Exosome	Ovarian cancer cells	A2780, SKOV-3, BALB/c athymic mice	*In vitro* and *in vivo*	Downregulation of cdr1as can promote the expression of miR-1270, which regulates cancer cell invasion inhibitor, sensitizing ovarian cancer to cisplatin and reducing the drug resistance of ovarian cancer cells	(89)
Proapoptotic and growth inhibitory factors	Microvesicle	Human immortalized mscs	ES-2, OAW-42	*In vitro*	It can inhibit the proliferation of ovarian cancer by acting on ovarian cancer target cells through different pathways	(107)
Dox	Microvesicle	M1 macrophages	SKOV3, CHO BALB/c nude mice	*In vitro* and *in vivo*	Specifically recognizes tumor cells and transports Dox to the nucleus, which can induce apoptosis and significantly inhibit metastasis of advanced ovarian cancer cells	(108)
PCOS						
S100-A9	Exosome	Follicle fluid of the ovary of PCOS patients	KGN	*In vitro*	Activates nuclear factor kappa B of steroid human granulosa tumor cell	(102)

Table II. Continued.

Non-microRNA	Types of EVs	Source of EVs	Model	*In vitro* or *in vivo* study	Function	(Refs.)
					signaling pathways, which in turn promote the occurrence of inflammatory reactions and reduce steroid production	
CircLDLR	Exosome	Follicle fluid	KGN	*In vitro*	Inhibits miR-1294 expression that can directly bind to CYP19A1 gene in KGN cells and promotes the expression of CYP19A1 gene	(104)
Gas6 ligand, PS	Apoptotic body	Cancer cells	MDA-MB-231, HCC827, SK-MES-1	*In vitro*	Promotes the spread of tumor cells through the PS-Gas6-AXL signaling pathway	(114)

EVs, extracellular vesicles; ARG1, arginase; NKG2D, killer cell lectin-like receptor K1; PCOS, polycystic ovary syndrome; S100-A9, S100 calcium binding protein A9; DOX, doxorubicin; CYP19A1, cytochrome P450 family 19 subfamily A member 1; Gas6, growth arrest-specific 6; AXL, receptor tyrosine kinase.

type 1A, inhibit the activity of KGN Smad 1/5/8 signaling pathway, and promote the increase of apoptotic factors in GCs (Primary GCs and KGN) (103). Additionally, circLDLR in exosomes can inhibit miR-1294 expression that can directly bind to Cytochrome P450 Family 19 Subfamily A Member 1 (CYP19A1) gene in KGN cells and promote the expression of CYP19A1 gene. Patients with PCOS with a decreased CYP19A1 gene expression in GCs can be treated by increasing the secretion of estrogen E2, which can be used as a treatment tool by regulating the function of PCOS GCs (104). There are also numerous miRNAs in exosomes that have therapeutic targets for PCOS. For example, exosome miR-424-5p in PCOS follicular fluid can target GC cell division cycle associated 4 gene, block the Rb/E_2F_1 pathway mediated by this gene, and promote apoptosis and aging of GCs in patients with PCOS (105). In addition, exosomal miR-323-3p derived from AMSCs can reduce the apoptosis of cumulus cells and promote their proliferation by acting on PDCD4 in mice with PCOS (106). In conclusion, exosomes and their contents have great potential and may help in the treatment of PCOS.

5. Microvesicles and ovarian disease

Microvesicles and the treatment of ovarian cancer. As a therapeutic carrier, microvesicles have great potential in the treatment of ovarian cancer. It was demonstrated that microvesicles derived from adipose tissue-derived human immortalized MSCs could carry proapoptotic and growth inhibitory factors to inhibit the proliferation of ovarian cancer by acting on ovarian cancer target cells through different pathways (107). Microvesicles derived from M1 macrophages simultaneously carrying DOX can specifically recognize tumor cells and transport DOX to the nucleus, which can induce apoptosis and significantly inhibit metastasis of advanced ovarian cancer cells (108). Microvesicles can not only act as a substance inhibiting ovarian cancer metastasis but also serve as a promotive substance for ovarian cancer development, thus inhibiting the release of microvesicles from tumor cells can be a therapeutic modality. A study has shown that simvastatin can effectively inhibit the production of HGSOC cell-derived microvesicles, hinder the secretion of microvesicles, and inhibit cell spreading and metastasis by regulating the content and action of microvesicles in ovarian cancer cells (109). Additionally, O^2-3-aminopropyldiazeniumdiolate (3f) can prevent the generation of triple-negative breast cancer-derived microvesicles by epigenetic modification, thereby attenuating the microvesicle pro-metastatic function and inhibiting the metastasis of cancer cells, which suggests that 3f plays a role in hindering microvesicle secretion from cancer cells. This therapeutic potential requires further research (110). Moreover, it has been investigated that combined microbubble and ultrasound irradiation may be effective as an ovarian cancer gene therapy to increase the metastatic efficiency of siRNA-TPX2 plasmids that can inhibit the phosphorylation of p38 and Mitogen-Activated Protein Kinase 8, preventing the metastasis and invasion of ovarian cancer cells (111). In summary, microvesicles play an important role in the treatment of ovarian cancer.

Microvesicles and the treatment of POI and PCOS. POI and PCOS are ovarian disorders that are considered distressing for women. Microvesicles have shown therapeutic potential in addition to the common treatments such as hormone therapy and pharmacotherapy. In the treatment of POI, studies have shown that transplantation of HUCMSC-derived microvesicles can favorably activate the phosphatidylinositol-3-kinase-serine/threonine kinase signaling pathway and promote the production of proangiogenic factors, restoring the angiogenic function in the ovaries of mice with PCOS (112). In the treatment of PCOS, MSCs-MVs have been reported to be able to rescue ovarian function by regulating hormone

levels, inhibiting follicular atresia and promoting follicle development (113). The current understanding of the role that microvesicles play in the treatment of POI and PCOS remains unclear, and its research remains in its infancy. However, existing studies have demonstrated that microvesicles may be promising in the treatment of POI and PCOS, and exploring the therapeutic relationship between microvesicles and both disease entities is warranted.

6. Apoptotic bodies and the treatment of ovarian disease

Recently, studies of apoptotic bodies in the treatment of ovarian diseases mainly focus on the relationship between apoptotic bodies and tumor treatment; however, there are very few studies on its role in the treatment of POI and PCOS. Therefore, the potential role of apoptotic bodies in the treatment of ovarian cancer was mainly summarized in the present review. First, apoptotic bodies can carry the remaining proapoptotic drugs deep into the tumor interior through a proximity effect, improving the efficiency of drug-induced apoptosis, treating tumors, and inhibiting tumor growth (50). Second, studies have shown that tumor cell-derived apoptotic bodies contribute to tumorigenesis. For example, cancer cell-produced apoptotic bodies with growth arrest specific 6 (Gas6) ligand of receptor tyrosine kinase (AxL) as well as phosphatidylserine (PS) are able to promote the spread of tumor cells through the PS-Gas6-AxL signaling pathway (114). Meanwhile, fibroblasts that can take up cellular chromosomal DNA tumor cell-derived apoptotic bodies favor the horizontal transfer of oncogenes between cells and promote tumorigenesis (115). The highly potent procoagulant effect exerted by the apoptotic bodies produced by tumor cells induced by the chemotherapeutic treatment of additional tumors invite the formation of tumor thrombi (116). These studies suggested that apoptotic bodies may serve as therapeutic targets in cancer. As there are few related literatures regarding the relationship between current apoptotic bodies and ovarian cancer treatment, the potential of apoptotic bodies in the treatment of ovarian cancer through the role it plays in tumor therapy should be further investigated.

7. Conclusion and outlook

In the present review, the role and therapeutic potential of EVs in the management of three ovarian diseases, namely, ovarian cancer, POI and PCOS were mainly summarized (Fig. 2). These three types of EVs are able to participate in ovarian disease development by transporting miRNAs (Table I) or non-miRNAs (Table II). Currently, ovarian disease is considered a common disease of women. However, until present, no suitable treatment has been identified. The application of EV therapy may have higher therapeutic benefits relative to conventional therapies. There are currently three reasons why exosomes for the treatment of human ovarian disease are not approved by the Food and Drug Administration or other regulatory agencies. First, the absolute isolation and definition of the size or biogenesis of various EVs (including exosomes) has not yet been determined. Secondly, the mechanism of action of exosome therapy is also lacking in-depth and detailed exploration. Finally, exosomes change their properties after manipulation *in vitro*, which can have adverse effects on patients. Therefore, investment in these novel therapeutic therapies should be applied to realize the potential of EVs in the treatment of ovarian diseases. Hopefully, in the near future, the most suitable therapy for ovarian disease will be discovered to successfully solve this medical dilemma.

Acknowledgements

All the figures in this article are made using Figdraw (www.figdraw.com).

Funding

The present study was supported by the Research Fund for Lin He's Academician Workstation of New Medicine and Clinical Translation in Jining Medical University (grant nos. JYHL2021MS13 and JYHL2021MS10) and College Students' Innovation Training Program of Jining Medical University (grant nos. S202310443062 and cx2023062z).

Availability of data and materials

Not applicable.

Authors' contributions

KM and XW contributed to the study conception and design. YZ and JZ performed the research and were major contributors in writing the manuscript. LH, ZZ, CW and WL contributed to the acquisition, analysis and systematization of data. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Walbrecq G, Margue C, Behrmann I and Kreis S: Distinct cargos of small extracellular vesicles derived from hypoxic cells and their effect on cancer cells. Int J Mol Sci 21: 5071, 2020.
2. Zarà M, Guidetti GF, Camera M, Canobbio I, Amadio P, Torti M, Tremoli E and Barbieri SS: Biology and role of extracellular vesicles (EVs) in the pathogenesis of thrombosis. Int J Mol Sci 20: 2840, 2019.
3. Skotland T, Sagini K, Sandvig K and Llorente A: An emerging focus on lipids in extracellular vesicles. Adv Drug Deliv Rev 159: 308-321, 2020.
4. Wang W, Jo H, Park S, Kim H, Kim SI, Han Y, Lee J, Seol A, Kim J, Lee M, *et al*: Integrated analysis of ascites and plasma extracellular vesicles identifies a miRNA-based diagnostic signature in ovarian cancer. Cancer Lett 542: 215735, 2022.

5. Kuhlmann JD, Chebouti I, Kimmig R, Buderath P, Reuter M, Puppel SH, Wimberger P and Kasimir-Bauer S: Extracellular vesicle-associated miRNAs in ovarian cancer-design of an integrated NGS-based workflow for the identification of blood-based biomarkers for platinum-resistance. Clin Chem Lab Med 57: 1053-1062, 2019.
6. Koshiyama M, Matsumura N and Konishi I: Subtypes of ovarian cancer and ovarian cancer screening. Diagnostics (Basel) 7: 12, 2017.
7. US Preventive Services Task Force; Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, Doubeni CA, Epling JW Jr, Kemper AR, Krist AH, *et al*: Screening for ovarian cancer: US preventive services task force recommendation statement. JAMA 319: 588-594, 2018.
8. Stewart C, Ralyea C and Lockwood S: Ovarian cancer: An integrated review. Semin Oncol Nurs 35: 151-156, 2019.
9. Coburn SB, Bray F, Sherman ME and Trabert B: International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer 140: 2451-2460, 2017.
10. Kurman RJ: Origin and molecular pathogenesis of ovarian high-grade serous carcinoma. Ann Oncol 24 (Suppl 10): x16-x21, 2013.
11. Singer G, Oldt R III, Cohen Y, Wang BG, Sidransky D, Kurman RJ and Shih IeM: Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. J Natl Cancer Inst 95: 484-486, 2003.
12. Karnezis AN, Cho KR, Gilks CB, Pearce CL and Huntsman DG: The disparate origins of ovarian cancers: Pathogenesis and prevention strategies. Nat Rev Cancer 17: 65-74, 2017.
13. Prat J: New insights into ovarian cancer pathology. Ann Oncol 23 (Suppl 10): x111-x117, 2012.
14. Chan JK, Teoh D, Hu JM, Shin JY, Osann K and Kapp DS: Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol 109: 370-376, 2008.
15. Yeung TL, Leung CS, Yip KP, Au Yeung CL, Wong ST and Mok SC: Cellular and molecular processes in ovarian cancer metastasis. A review in the theme: Cell and molecular processes in cancer metastasis. Am J Physiol Cell Physiol 309: C444-C456, 2015.
16. Chandra A, Pius C, Nabeel M, Nair M, Vishwanatha JK, Ahmad S and Basha R: Ovarian cancer: Current status and strategies for improving therapeutic outcomes. Cancer Med 8: 7018-7031, 2019.
17. Kurnit KC, Fleming GF and Lengyel E: Updates and new options in advanced epithelial ovarian cancer treatment. Obstet Gynecol 137: 108-121, 2021.
18. Woad KJ, Watkins WJ, Prendergast D and Shelling AN: The genetic basis of premature ovarian failure. Aust N Z J Obstet Gynaecol 46: 242-244, 2006.
19. Howell S and Shalet S: Gonadal damage from chemotherapy and radiotherapy. Endocrinol Metab Clin North Am 27: 927-943, 1998.
20. Ishizuka B: Current understanding of the etiology, symptomatology, and treatment options in premature ovarian insufficiency (POI). Front Endocrinol (Lausanne) 12: 626924, 2021.
21. Wang F, Liu Y, Ni F, Jin J, Wu Y, Huang Y, Ye X, Shen X, Ying Y, Chen J, *et al*: BNC1 deficiency-triggered ferroptosis through the NF2-YAP pathway induces primary ovarian insufficiency. Nat Commun 13: 5871, 2022.
22. Domniz N and Meirow D: Premature ovarian insufficiency and autoimmune diseases. Best Pract Res Clin Obstet Gynaecol 60: 42-55, 2019.
23. Goswami D and Conway GS: Premature ovarian failure. Hum Reprod Update 11: 391-410, 2005.
24. Szeliga A, Calik-Ksepka A, Maciejewska-Jeske M, Grymowicz M, Smolarczyk K, Kostrzak A, Smolarczyk R, Rudnicka E and Meczekalski B: Autoimmune diseases in patients with premature ovarian insufficiency-our current state of knowledge. Int J Mol Sci 22: 2594, 2021.
25. Sullivan SD, Sarrel PM and Nelson LM: Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril 106: 1588-1599, 2016.
26. Zhang S, Zhu D, Mei X, Li Z, Li J, Xie M, Xie HJW, Wang S and Cheng K: Advances in biomaterials and regenerative medicine for primary ovarian insufficiency therapy. Bioact Mater 6: 1957-1972, 2021.
27. Sirmans SM and Pate KA: Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 6: 1-13, 2013.
28. Meier RK: Polycystic ovary syndrome. Nurs Clin North Am 53: 407-420, 2018.
29. Wolf WM, Wattick RA, Kinkade ON and Olfert MD: Geographical prevalence of polycystic ovary syndrome as determined by region and race/ethnicity. Int J Environ Res Public Health 15: 2589, 2018.
30. Louwers YV and Laven JSE: Characteristics of polycystic ovary syndrome throughout life. Ther Adv Reprod Health 14: 2633494120911038, 2020.
31. Patel S: Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy. J Steroid Biochem Mol Biol 182: 27-36, 2018.
32. Pauli JM, Raja-Khan N, Wu X and Legro RS: Current perspectives of insulin resistance and polycystic ovary syndrome. Diabet Med 28: 1445-1454, 2011.
33. Mitra S, Nayak PK and Agrawal S: Laparoscopic ovarian drilling: An alternative but not the ultimate in the management of polycystic ovary syndrome. J Nat Sci Biol Med 6: 40-48, 2015.
34. Tian W, Lei N, Zhou J, Chen M, Guo R, Qin B, Li Y and Chang L: Extracellular vesicles in ovarian cancer chemoresistance, metastasis, and immune evasion. Cell Death Dis 13: 64, 2022.
35. Ingenito F, Roscigno G, Affinito A, Nuzzo S, Scognamiglio I, Quintavalle C and Condorelli G: The Role of Exo-miRNAs in cancer: A focus on therapeutic and diagnostic applications. Int J Mol Sci 20: 4687, 2019.
36. Yang Y, Lang P, Zhang X, Wu X, Cao S, Zhao C, Shen R, Ling X, Yang Y and Zhang J: Molecular characterization of extracellular vesicles derived from follicular fluid of women with and without PCOS: Integrating analysis of differential miRNAs and proteins reveals vital molecules involving in PCOS. J Assist Reprod Genet 40: 537-552, 2023.
37. Park HS, Cetin E, Siblini H, Seok J, Alkelani H, Alkhrait S, Liakath Ali F, Mousaei Ghasroldasht M, Beckman A and Al-Hendy A: Therapeutic potential of mesenchymal stem cell-derived extracellular vesicles to treat PCOS. Int J Mol Sci 24: 11151, 2023.
38. Geng Z, Guo H, Li Y, Liu Y and Zhao Y: Stem cell-derived extracellular vesicles: A novel and potential remedy for primary ovarian insufficiency. Front Cell Dev Biol 11: 1090997, 2023.
39. Fu YX, Ji J, Shan F, Li J and Hu R: Human mesenchymal stem cell treatment of premature ovarian failure: New challenges and opportunities. Stem Cell Res Ther 12: 161, 2021.
40. Dorayappan KDP, Wallbillich JJ, Cohn DE and Selvendiran K: The biological significance and clinical applications of exosomes in ovarian cancer. Gynecol Oncol 142: 199-205, 2016.
41. Li SP, Lin ZX, Jiang XY and Yu XY: Exosomal cargo-loading and synthetic exosome-mimics as potential therapeutic tools. Acta Pharmacol Sin 39: 542-551, 2018.
42. Savina A, Furlán M, Vidal M and Colombo MI: Exosome release is regulated by a calcium-dependent mechanism in K562 cells. J Biol Chem 278: 20083-20090, 2003.
43. Villarroya-Beltri C, Baixauli F, Mittelbrunn M, Fernández-Delgado I, Torralba D, Moreno-Gonzalo O, Baldanta S, Enrich C, Guerra S and Sánchez-Madrid F: ISGylation controls exosome secretion by promoting lysosomal degradation of MVB proteins. Nat Commun 7: 13588, 2016.
44. Yang H, Fu H, Xu W and Zhang X: Exosomal non-coding RNAs: A promising cancer biomarker. Clin Chem Lab Med 54: 1871-1879, 2016.
45. Lin Y, Lu Y and Li X: Biological characteristics of exosomes and genetically engineered exosomes for the targeted delivery of therapeutic agents. J Drug Target 28: 129-141, 2020.
46. Jalalian SH, Ramezani M, Jalalian SA, Abnous K and Taghdisi SM: Exosomes, new biomarkers in early cancer detection. Anal Biochem 571: 1-13, 2019.
47. Makler A and Asghar W: Exosomal biomarkers for cancer diagnosis and patient monitoring. Expert Rev Mol Diagn 20: 387-400, 2020.
48. Sedgwick AE and D'Souza-Schorey C: The biology of extracellular microvesicles. Traffic 19: 319-327, 2018.
49. Xu X, Lai Y and Hua ZC: Apoptosis and apoptotic body: Disease message and therapeutic target potentials. Bioscience reports 39: BSR20180992, 2019.
50. Zhao D, Tao W, Li S, Chen Y, Sun Y, He Z, Sun B and Sun J: Apoptotic body-mediated intercellular delivery for enhanced drug penetration and whole tumor destruction. Sci Adv 7: eabg0880, 2021.
51. Bartel DP: MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 116: 281-297, 2004.
52. Chen J, Chen W and Li Y: Conservation of gene order in human microRNA-neighboring regions. Genome 55: 701-704, 2012.
53. John B, Enright AJ, Aravin A, Tuschl T, Sander C and Marks DS: Human microRNA targets. PLoS Biol 2: e363, 2004.

54. Janas T, Janas MM, Sapoń K and Janas T: Mechanisms of RNA loading into exosomes. FEBS Lett 589: 1391-1398, 2015.
55. Rashed MH, Kanlikilicer P, Rodriguez-Aguayo C, Pichler M, Bayraktar R, Bayraktar E, Ivan C, Filant J, Silva A, Aslan B, *et al*: Exosomal miR-940 maintains SRC-mediated oncogenic activity in cancer cells: A possible role for exosomal disposal of tumor suppressor miRNAs. Oncotarget 8: 20145-20164, 2017.
56. Zhang H, Wang Q, Zhao Q and Di W: MiR-124 inhibits the migration and invasion of ovarian cancer cells by targeting SphK1. J Ovarian Res 6: 84, 2013.
57. He L, Zhu W, Chen Q, Yuan Y, Wang Y, Wang J and Wu X: Ovarian cancer cell-secreted exosomal miR-205 promotes metastasis by inducing angiogenesis. Theranostics 9: 8206-8220, 2019.
58. Cai J, Gong L, Li G, Guo J, Yi X and Wang Z: Exosomes in ovarian cancer ascites promote epithelial-mesenchymal transition of ovarian cancer cells by delivery of miR-6780b-5p. Cell Death Dis 12: 210, 2021.
59. Lian XY, Zhang H, Liu Q, Lu X, Zhou P, He SQ, Tang RX and Cui J: Ovarian cancer-excreted exosomal miR-199a-5p suppresses tumor metastasis by targeting hypoxia-inducible factor-2α in hypoxia microenvironment. Cancer Commun (Lond) 40: 380-385, 2020.
60. Cao J, Zhang Y, Mu J, Yang D, Gu X and Zhang J: Exosomal miR-21-5p contributes to ovarian cancer progression by regulating CDK6. Human Cell 34: 1185-1196, 2021.
61. Chen X, Zhou J, Li X, Wang X, Lin Y and Wang X: Exosomes derived from hypoxic epithelial ovarian cancer cells deliver microRNAs to macrophages and elicit a tumor-promoted phenotype. Cancer Lett 435: 80-91, 2018.
62. Li W, Zhang X, Wang J, Li M, Cao C, Tan J, Ma D and Gao Q: TGFβ1 in fibroblasts-derived exosomes promotes epithelial-mesenchymal transition of ovarian cancer cells. Oncotarget 8: 96035-96047, 2017.
63. Viaud S, Terme M, Flament C, Taieb J, André F, Novault S, Escudier B, Robert C, Caillat-Zucman S, Tursz T, *et al*: Dendritic cell-derived exosomes promote natural killer cell activation and proliferation: A role for NKG2D ligands and IL-15Ralpha. PLoS One 4: e4942, 2009.
64. Shen X, Wang C, Zhu H, Wang Y, Wang X, Cheng X, Ge W and Lu W: Exosome-mediated transfer of CD44 from high-metastatic ovarian cancer cells promotes migration and invasion of low-metastatic ovarian cancer cells. J Ovarian Res 14: 38, 2021.
65. Alharbi M, Lai A, Guanzon D, Palma C, Zuñiga F, Perrin L, He Y, Hooper JD and Salomon C: Ovarian cancer-derived exosomes promote tumour metastasis in vivo: An effect modulated by the invasiveness capacity of their originating cells. Clin Sci (Lond) 133: 1401-1419, 2019.
66. Guan X, Zong ZH, Liu Y, Chen S, Wang LL and Zhao Y: circPUM1 promotes tumorigenesis and progression of ovarian cancer by sponging miR-615-5p and miR-6753-5p. Mol Ther Nucleic Acids 18: 882-892, 2019.
67. Zong ZH, Du YP, Guan X, Chen S and Zhao Y: CircWHSC1 promotes ovarian cancer progression by regulating MUC1 and hTERT through sponging miR-145 and miR-1182. J Exp Clin Cancer Res 38: 437, 2019.
68. Choi H, Choi Y, Yim HY, Mirzaaghasi A, Yoo JK and Choi C: Biodistribution of exosomes and engineering strategies for targeted delivery of therapeutic exosomes. Tissue Eng Regen Med 18: 499-511, 2021.
69. Zhang Y, Bi J, Huang J, Tang Y, Du S and Li P: Exosome: A review of its classification, isolation techniques, storage, diagnostic and targeted therapy applications. Int J Nanomedicine 15: 6917-6934, 2020.
70. Sharma S, Zuñiga F, Rice GE, Perrin LC, Hooper JD and Salomon C: Tumor-derived exosomes in ovarian cancer-liquid biopsies for early detection and real-time monitoring of cancer progression. Oncotarget 8: 104687-104703, 2017.
71. Rayamajhi S, Nguyen TDT, Marasini R and Aryal S: Macrophage-derived exosome-mimetic hybrid vesicles for tumor targeted drug delivery. Acta Biomater 94: 482-494, 2019.
72. Xie X, Wu H, Li M, Chen X, Xu X, Ni W, Lu C, Ni R, Bao B and Xiao M: Progress in the application of exosomes as therapeutic vectors in tumor-targeted therapy. Cytotherapy 21: 509-524, 2019.
73. Hadla M, Palazzolo S, Corona G, Caligiuri I, Canzonieri V, Toffoli G and Rizzolio F: Exosomes increase the therapeutic index of doxorubicin in breast and ovarian cancer mouse models. Nanomedicine (Lond) 11: 2431-2441, 2016.
74. Liu H, Shen M, Zhao D, Ru D, Duan Y, Ding C and Li H: The effect of triptolide-loaded exosomes on the proliferation and apoptosis of human ovarian cancer SKOV3 cells. Biomed Res Int 2019: 2595801, 2019.
75. Huang X, Wu W, Jing D, Yang L, Guo H, Wang L, Zhang W, Pu F and Shao Z: Engineered exosome as targeted lncRNA MEG3 delivery vehicles for osteosarcoma therapy. J Control Release 343: 107-117, 2022.
76. Liang G, Zhu Y, Ali DJ, Tian T, Xu H, Si K, Sun B, Chen B and Xiao Z: Engineered exosomes for targeted co-delivery of miR-21 inhibitor and chemotherapeutics to reverse drug resistance in colon cancer. J Nanobiotechnology 18: 10, 2020.
77. Coukos G, Tanyi J and Kandalaft LE: Opportunities in immunotherapy of ovarian cancer. Ann Oncol 27 (Suppl 1): i11-i15, 2016.
78. Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, Kanai M, Mori Y, Matsumoto S, Chikuma S, *et al*: Safety and antitumor activity of Anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol 33: 4015-4022, 2015.
79. Tanyi JL, Bobisse S, Ophir E, Tuyaerts S, Roberti A, Genolet R, Baumgartner P, Stevenson BJ, Iseli C, Dangaj D, *et al*: Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. Sci Transl Med 10: eaao593, 2018.
80. Sangwan K, Sharma V and Goyal PK: Pharmacological profile of novel anti-cancer drugs approved by USFDA in 2022: A review. Curr Mol Med: Jun 22, 2023 (Epub ahead of print).
81. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, Makrigiannakis A, Gray H, Schlienger K, Liebman MN, *et al*: Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 348: 203-213, 2003.
82. Han LY, Fletcher MS, Urbauer DL, Mueller P, Landen CN, Kamat AA, Lin YG, Merritt WM, Spannuth WA, Deavers MT, *et al*: HLA class I antigen processing machinery component expression and intratumoral T-Cell infiltrate as independent prognostic markers in ovarian carcinoma. Clin Cancer Res 14: 3372-3379, 2008.
83. Czystowska-Kuzmicz M, Sosnowska A, Nowis D, Ramji K, Szajnik M, Chlebowska-Tuz J, Wolinska E, Gaj P, Grazul M, Pilch Z, *et al*: Small extracellular vesicles containing arginase-1 suppress T-cell responses and promote tumor growth in ovarian carcinoma. Nat Commun 10: 3000, 2019.
84. Labani-Motlagh A, Israelsson P, Ottander U, Lundin E, Nagaev I, Nagaeva O, Dehlin E, Baranov V and Mincheva-Nilsson L: Differential expression of ligands for NKG2D and DNAM-1 receptors by epithelial ovarian cancer-derived exosomes and its influence on NK cell cytotoxicity. Tumour Biol 37: 5455-5466, 2016.
85. Koh E, Lee EJ, Nam GH, Hong Y, Cho E, Yang Y and Kim IS: Exosome-SIRPα, a CD47 blockade increases cancer cell phagocytosis. Biomaterials 121: 121-129, 2017.
86. Shimizu A, Sawada K, Kobayashi M, Yamamoto M, Yagi T, Kinose Y, Kodama M, Hashimoto K and Kimura T: Exosomal CD47 plays an essential role in immune evasion in ovarian cancerexosomal CD47 regulates immune evasion in ovarian cancer. Mol Cancer Res 19: 1583-1595, 2021.
87. Qiu Y, Yang Y, Yang R, Liu C, Hsu JM, Jiang Z, Sun L, Wei Y, Li CW, Yu D, *et al*: Activated T cell-derived exosomal PD-1 attenuates PD-L1-induced immune dysfunction in triple-negative breast cancer. Oncogene 40: 4992-5001, 2021.
88. Tang MK and Wong AS: Exosomes: Emerging biomarkers and targets for ovarian cancer. Cancer Lett 367: 26-33, 2015.
89. Zhao Z, Ji M, Wang Q, He N and Li Y: Circular RNA Cdr1as upregulates SCAI to suppress cisplatin resistance in ovarian cancer via miR-1270 suppression. Mol Ther Nucleic Acids 18: 24-33, 2019.
90. Taylor DD and Gercel-Taylor C: MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. Gynecol Oncol 110: 13-21, 2008.
91. Cheng L, Wu S, Zhang K, Qing Y and Xu T: A comprehensive overview of exosomes in ovarian cancer: Emerging biomarkers and therapeutic strategies. J Ovarian Res 10: 73, 2017.
92. Ryu J and Thomas SN: Quantitative mass spectrometry-based proteomics for biomarker development in ovarian cancer. Molecules 26: 2674, 2021.
93. Cortez AJ, Tudrej P, Kujawa KA and Lisowska KM: Advances in ovarian cancer therapy. Cancer Chemother Pharmacol 81: 17-38, 2018.

94. Lee EH, Han SE, Park MJ, Kim HJ, Kim HG, Kim CW, Joo BS and Lee KS: Establishment of effective mouse model of premature ovarian failure considering treatment duration of anticancer drugs and natural recovery time. J Menopausal Med 24: 196-203, 2018.
95. Qi Y, Zhu YM and Li B: Comparison of Animal Models for Premature Ovarian Insufficiency Induced by Different Doses of Cyclophosphamide: A Network Meta-analysis. 2022.
96. Yang M, Lin L, Sha C, Li T, Zhao D, Wei H, Chen Q, Liu Y, Chen X, Xu W, *et al*: Bone marrow mesenchymal stem cell-derived exosomal miR-144-5p improves rat ovarian function after chemotherapy-induced ovarian failure by targeting PTEN. Lab Invest 100: 342-352, 2020.
97. Sun B, Ma Y, Wang F, Hu L and Sun Y: miR-644-5p carried by bone mesenchymal stem cell-derived exosomes targets regulation of p53 to inhibit ovarian granulosa cell apoptosis. Stem Cell Res Ther 10: 360, 2019.
98. Zhang Q, Sun J, Huang Y, Bu S, Guo Y, Gu T, Li B, Wang C and Lai D: Human amniotic epithelial cell-derived exosomes restore ovarian function by transferring microRNAs against apoptosis. Mol Ther Nucleic Acids 16: 407-418, 2019.
99. Xiao GY, Cheng CC, Chiang YS, Cheng WT, Liu IH and Wu SC: Exosomal miR-10a derived from amniotic fluid stem cells preserves ovarian follicles after chemotherapy. Sci Rep 6: 23120, 2016.
100. Yang W, Zhang J, Xu B, He Y, Liu W, Li J, Zhang S, Lin X, Su D, Wu T and Li J: HucMSC-Derived exosomes mitigate the age-related retardation of fertility in female mice. Mol Ther 28: 1200-1213, 2020.
101. Cai JH, Sun YT and Bao S: HucMSCs-exosomes containing miR-21 promoted estrogen production in ovarian granulosa cells via LATS1-mediated phosphorylation of LOXL2 and YAP. Gen Comp Endocrinol 321: 114015, 2022.
102. Li H, Huang X, Chang X, Yao J, He Q, Shen Z, Ji Y and Wang K: S100-A9 protein in exosomes derived from follicular fluid promotes inflammation via activation of NF-κB pathway in polycystic ovary syndrome. J Cell Mol Med 24: 114-125, 2020.
103. Zhao Y, Pan S, Li Y and Wu X: Exosomal miR-143-3p derived from follicular fluid promotes granulosa cell apoptosis by targeting BMPR1A in polycystic ovary syndrome. Sci Rep 12: 4359, 2022.
104. Huang X, Wu B, Chen M, Hong L, Kong P, Wei Z and Teng X: Depletion of exosomal circLDLR in follicle fluid derepresses miR-1294 function and inhibits estradiol production via CYP19A1 in polycystic ovary syndrome. Aging (Albany NY) 12: 15414-15435, 2020.
105. Yuan D, Luo J, Sun Y, Hao L, Zheng J and Yang Z: PCOS follicular fluid derived exosomal miR-424-5p induces granulosa cells senescence by targeting CDCA4 expression. Cell Signal 85: 110030, 2021.
106. Zhao Y, Tao M, Wei M, Du S, Wang H and Wang X: Mesenchymal stem cells derived exosomal miR-323-3p promotes proliferation and inhibits apoptosis of cumulus cells in polycystic ovary syndrome (PCOS). Artif Cells Nanomed Biotechnol 47: 3804-3813, 2019.
107. Szyposzynska A, Bielawska-Pohl A, Krawczenko A, Doszyn O, Paprocka M and Klimczak A: Suppression of ovarian cancer cell growth by AT-MSC microvesicles. Int J Mol Sci 21: 9143, 2020.
108. Guo L, Zhang Y, Wei R, Zhang X, Wang C and Feng M: Proinflammatory macrophage-derived microvesicles exhibit tumor tropism dependent on CCL2/CCR2 signaling axis and promote drug delivery via SNARE-mediated membrane fusion. Theranostics 10: 6581-6598, 2020.
109. Mancilla P, Liberona M, Kato S, Barra J, Gonzalez A and Cuello M: Simvastatin modifies the internalization, endocytic trafficking, and the content of ovarian cancer cellderived extracellular microvesicles which are responsible of inducing migration and invasion in vitro. Int J Gynecol Cancer 30 (Suppl 3): A192-A193, 2020.
110. Kang F, Zhu J, Wu J, Lv T, Xiang H, Tian J, Zhang Y and Huang Z: O^2-3-Aminopropyl diazeniumdiolates suppress the progression of highly metastatic triple-negative breast cancer by inhibition of microvesicle formation via nitric oxide-based epigenetic regulation. Chem Sci 9: 6893-6898, 2018.
111. Huang D, Chen J, Yang C and Wang M: TPX2 silencing mediated by joint action of microvesicles and ultrasonic radiation inhibits the migration and invasion of SKOV3 cells. Mol Med Rep 17: 7627-7635, 2018.
112. Yang Z, Du X, Wang C, Zhang J, Liu C, Li Y and Jiang H: Therapeutic effects of human umbilical cord mesenchymal stem cell-derived microvesicles on premature ovarian insufficiency in mice. Stem Cell Res Ther 10: 250, 2019.
113. Faruk EM: El desoky RE, El-Shazly AM and Taha NM: Does exosomes derived bone marrow mesenchymal stem cells restore ovarian function by promoting stem cell survival on experimentally induced polycystic ovary in adult female albino rats?(Histological and Immunohistochemical Study). J Stem Cell Res Ther 8: 1000442, 2018.
114. Zweemer AJM, French CB, Mesfin J, Gordonov S, Meyer AS and Lauffenburger DA: Apoptotic bodies Elicit Gas6-mediated migration of AXL-Expressing tumor cell. Mol Cancer Res 15: 1656-1666, 2017.
115. Bergsmedh A, Szeles A, Henriksson M, Bratt A, Folkman MJ, Spetz AL and Holmgren L: Horizontal transfer of oncogenes by uptake of apoptotic bodies. Proc Natl Acad Sci USA 98: 6407-6411, 2001.
116. Muhsin-Sharafaldine MR, Kennedy BR, Saunderson SC, Buchanan CR, Dunn AC, Faed JM and McLellan AD: Mechanistic insight into the procoagulant activity of tumor-derived apoptotic vesicles. Biochim Biophys Acta Gen Subj 1861: 286-295, 2017.