Role of exosomes in the immune microenvironment of ovarian cancer (Review)

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Abstract. Exosomes are excretory vesicles that can deliver a variety of bioactive cargo molecules to the extracellular environment. Accumulating evidence demonstrates exosome participation in intercellular communication, immune response, inflammatory response and they even play an essential role in affecting the tumor immune microenvironment. The role of exosomes in the immune microenvironment of ovarian cancer is mainly divided into suppression and stimulation. On one hand exosomes can stimulate the innate and adaptive immune systems by activating dendritic cells (DCs), natural killer cells and T cells, allowing these immune cells exert an antitumorigenic effect. On the other hand, ovarian cancer-derived exosomes initiate cross-talk with immunosuppressive effector cells, which subsequently cause immune evasion; one of the hallmarks of cancer. Exosomes induce the polarization of macrophages in M2 phenotype and induce apoptosis of lymphocytes and DCs. Exosomes further activate additional immunosuppressive effector cells (myeloid-derived suppressor cells and regulatory T cells) that induce fibroblasts to differentiate into cancer-associated fibroblasts. Exosomes also induce the tumorigenicity of mesenchymal stem cells to exert additional immune suppression. Furthermore, besides mediating the intercellular communication, exosomes carry microRNAs (miRNAs), proteins and lipids to the tumor microenvironment, which collectively promotes ovarian cancer cells to proliferate, invade and tumors to metastasize. Studying proteins, lipids and miRNAs carried by exosomes could potentially be used as an early diagnostic marker of ovarian cancer for designing treatment strategies.

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1. Introduction

Ovarian cancer is one of the three primary gynecological tumors, with a 5-year survival rate of 44%. Due to its lack of specific clinical symptoms and practical measures for early diagnosis, >75% patients are diagnosed in advanced stages and quickly become prone to drug resistance during treatment (1). Ovarian cancer cells can simultaneously regulate immune activation and suppression by presenting cancer antigens to immune cells, secreting cytokines and a large number of soluble factors, as well as releasing exosomes to the tumor microenvironment affecting the proximal and distal tissues. These influencing factors together form a complex interactome called the tumor immune microenvironment (2). Innate and adaptive immune cells can stimulate an antitumor response by recognizing cancer antigens via the antigen presenting cells (APCs) (3). In addition, immune cells, such as lymphocytes, macrophages, dendritic cells (DCs), mast

cells and natural killer (NK) cells, can regulate angiogenesis, certain tumorigenic metabolic pathways and metastasis within the tumor microenvironment (4,5). Exosomes have also been shown to play an important role in affecting the tumor immune microenvironment and ensuing immune responses, such as antigen presentation, migration, metastasis and tumor invasion. Previous research indicates that exosomes carry a number of immunologically active molecules [including major histocompatibility complex (MHC I), heat shock protein (HSP) and CD81] that can stimulate an antitumor immune response (6). Conversely, some studies have shown that exosomes will weaken the antitumor immune response to effect cancer progression by potentiating immune evasion (7-9). Analyzing the immune microenvironment of ovarian cancer and understanding the role of exosomes in cancer progression could play a vital role in its early diagnosis and designing an effective immunotherapy regimen.

2. Biological characteristics of exosomes

Biological characteristics and functions. As endogenous cellular components, exosomes are vesicles (30-100 nm) derived from the endosomal compartments called multivesicular bodies (Fig. 1) that are secreted by various cells into the extracellular microenvironment. When exosomes are isolated by density gradient centrifugation or ultracentrifugation, they appear as round vesicles in solution. The ultrastructure is resolved by dehydration, where it appears cup-shaped under an electron microscope (10). Exosomes are double-membraned organelles formed by periodic endocytosis of intracellular fluid throughout the life cycle of eukaryotic cells. As early endosomes mature and develop into late endosomes, the inner membrane sprouts inward to form intraluminal vesicles (ILVs), which contain randomly engulfed parts of the cytoplasmic content, rich with mRNAs, microRNAs (miRNAs/miRs), proteins and lipids. ILVs that are released to the extracellular environment are called exosomes (11). Studies show that exosomes can be found in various extracellular fluids, such as blood, urine, ascites, semen and cerebrospinal fluid.

Exosomes can be used as delivery vehicles for a variety of bioactive molecules, for example proteins, lipids, mRNA, miRNA, long non-coding RNA (lncRNA), genomic DNA and cDNA. This unique composition is also occasionally used as an identifier for a particular exosome (12). Previous research indicates that the common proteins in exosomes include tetraspanins, co-stimulatory molecule CD86 and adhesion molecules, such as integrins, ICAM1, CD166 and CD146. Besides specialized proteins, exosomes may also carry common proteins, such as HSP-70, HSP84 and HSP90 (11). Exosomes can accelerate peptide loading onto MHC I and II, thereby mediating a rapid immune response. Exosomes also carry signal transduction proteins, for example, receptor tyrosine kinases and membrane transport and fusion proteins, such as the GTPases Rab5 and Rab7 (11). Studies have also reported that nucleic acids are carried by exosomes, comprising of a diverse mix of DNA (13,14), RNA (15), lncRNA (16) and miRNA (17,18) molecules. Exosomal miRs (miR-15, -16, 151 and -375) can promote angiogenesis and tumor progression in the TME (11). The bioactive cargo carried by exosomes can participate in the

modification of immune response of an ovarian cancer microenvironment (19).

Exosome involvement in pathological conditions. In infectious and non-infectious pathological conditions, both non-tumorous and tumorous cells tend to release exosomes more actively, whereas the number of exosomes quantified from the blood of patients with ovarian cancer is 3-4 times higher compared with in healthy individuals (11). The exosomes extracted from two human ovarian carcinoma cell lines OVCAR-3 and IGROV1 have a density ranging from 1.09-1.15 g/ml, while ~2,230 proteins are detected in the exosomal cargo, including other significant exosomal protein markers (20). Andre *et al* (6) in 2002 detected human epidermal growth factor (EGF) receptor (*Her2/neu* gene) signaling in exosomes of patients with ovarian cancer via western blotting. Activated matrix metalloproteinase (MMP)-2, MMP-9 and urokinase plasminogen activator are found in exosomes derived from the ascites of patients with ovarian cancer, which promotes protease activation to increase degradation of the extracellular matrices (ECMs) and tumor cell invasion and metastasis (21).

3. Cell signaling and exosome-mediated tumor immune microenvironment modification in ovarian cancer

The tumor microenvironment is the product of a number of cells and their accompanying extracellular matrix component (EMCs) jointly contributing towards the development of a distinct microenvironment surrounding the tumor mass. The cells comprise of stromal cells, including: Fibroblasts, macrophages, myeloid-derived suppressor cells, endothelial cells and mesenchymal stem cells. EMCs comprise of inflammatory cytokines, chemokines, MMPs, integrins and exosomes (22) (Fig.2). Tumor cells interact with stromal cells to promote angiogenesis, infiltration and metastasis that cause the tumor to grow and invade other tissues (23). TNF-α is a pro-inflammatory cytokine that is secreted primarily by macrophages along with other cells of the stroma, which promotes tumor necrosis or apoptosis. In total, ~28% of all cancer types are affected by TNF-mediated necrosis (24). 5-Lipoxygenase (*5-LOX*) is a member of the lipoxygenase family of genes that is a key enzyme in the conversion of arachidonic acid to leukotrienes. In ovarian cancer, upregulation of 5-LOX metabolites and TNF-α can promote recruitment of macrophages to the tumor site (25). In addition, the pro-inflammatory interleukin-6 (IL-6) has been shown to be an important cytokine in the ovarian cancer tumor microenvironment. IL-6 can mediate the maturation of macrophages into M2 macrophages, which enhance tumor vascular stability by VEGF and TGF-β1, thus promoting tumor progression (26-29). Upregulation of miR-217 in ovarian cancer downregulates the IL-6-dependent JAK3/STAT3 signaling pathway, thereby potentially inhibiting the maturation of macrophages from M1 to M2 stage (30). Ovarian cancer-associated mesenchymal stem cells (MSCs) highly express IL-6 and leukemia inhibitor factor that activate the JAK3/STAT3 signaling pathway to increase the tumorigenicity of ovarian cancer stem cells (31). Wang *et al* (32) have found that cancer-associated fibroblasts (CAFs) can also secrete IL-6 and promote the accumulation
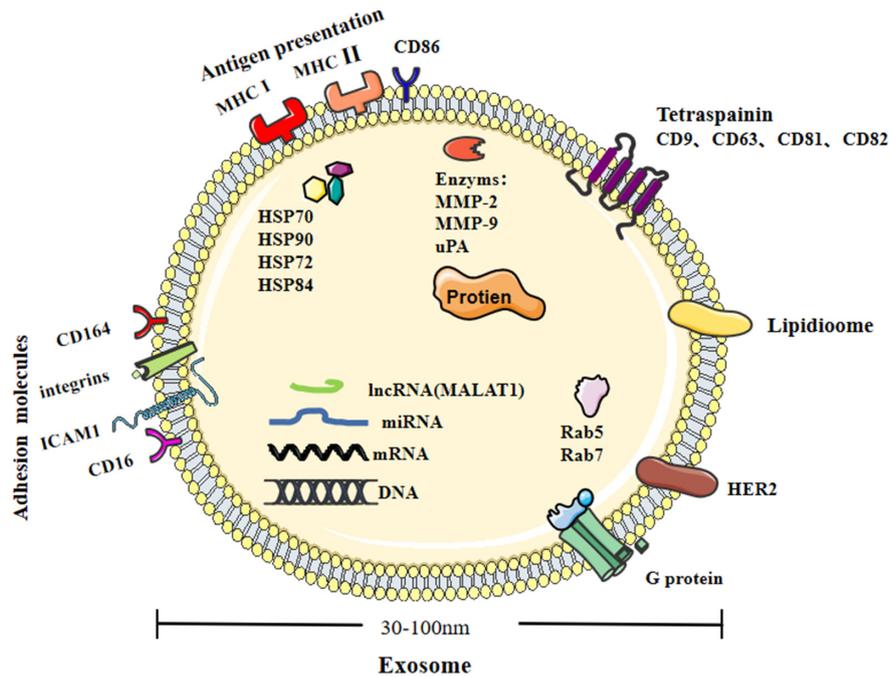
Figure 1. Biological characteristics of exosomes. Diameter of exosomes is between 30-100 nm. Exosomes carry proteins, lipids, enzymes, mRNAs, microRNAs and lncRNAs. Tetraspanin and adhesion molecules can be found on the surface of exosomes, including: Costimulatory molecules (CD86), integrins, ICAM1, CD166 and CD146. Exosomes carry proteins including heat-shock proteins HSP70, HSP84 and HSP90, which make the binding between MHC I and MHC II with peptide more rapid. Signal transduction proteins (G-proteins and protein kinases) and membrane transport and fusion proteins (Rab5 and Rab7) can be found on the surface, in addition to the Her2 signal. lncRNA, long non-coding RNA; MHC, major histocompatibility complex.

of ovarian cancer stem cells in residual tumors by activating the STAT3 signaling pathway. Exosomes derived from ascites in patients with ovarian cancer can promote the release of more IL-6 from monocytes (THP-1 cells) and activate the NF-kB and STAT3 signaling pathways, which leads to a cytokine environment conducive for immune evasion of tumor cells (33). In addition, IL-6 has been associated with chemotherapy resistance and poor prognosis in patients with ovarian cancer. Studies have shown that the level of IL-6 in the serum of patients with cancer is significantly higher compared with that of normal individuals (34,35). IL-6 can upregulate the expression of resistance-related genes *multi-drug resistance-1* and *glutathione S-transferase π;* in addition to the expression of apoptosis inhibitor protein. Moreover, IL-6 can activate the Ras/MEK/ERK and PI3K/Akt signaling pathways that jointly induce chemotherapy resistance (34,36). The value of IL-6 as a prognostic and diagnostic indicator of ovarian cancer has been confirmed (37,38).

Studies suggest that a higher ratio of M2:M1 macrophages is associated with poor prognosis in patients with ovarian cancer, whereas a higher ratio of M1:M2 macrophages is associated with good prognosis (39,40). Some investigations have shown that tumor-associated macrophages (TAMs) can activate the MMP9/HB-EGF pathway along with the production of EGF to promote ovarian cancer and breast cancer progression (41,42). TGF-β can promote the transformation of epithelial cells to mesenchymal cells, promoting angiogenesis and inducing immunosuppression, subsequently promoting tumor progression (43). TAMs release TGF-β1 and tenascin-C to promote tumor metastasis in ovarian cancer (44). CAFs can also promote invasion and metastasis of ovarian cancer in the

tumor microenvironment (45,46). Studies have shown that TGF-β1 secreted by CAFs can notably potentiate the mechanism of epithelial-mesenchymal transition (EMT), thereby promoting bladder cancer to metastasize (47). Similarly, CAFs highly express the *TGF-β* gene in ovarian cancer (48). In addition, studies have shown that CAFs in ascites can promote the production of multicellular aggregates, thereby promoting peritoneal metastasis (46,49). CAFs highly express X-linked sushi repeat-containing protein, which are peroxiredoxin enzymes that control cytokine-induced peroxide levels. Similarly, CAFs also highly express *hemicentin-1* genes in ovarian cancer tissue samples. Sequential knock-down of these two genes can weaken the ability of CAFs to promote ovarian cancer metastasis (50). Myeloid-derived suppressor cells (MDSCs) and Tregs are important components of the tumor immune evasion mechanism (51,52). A previous study confirmed that the co-culture of MDSCs and ovarian cancer cells can promote the formation of tumor spheres, cell colonies and the accumulation of cancer stem cells, thus a strong indication that MDSCs can induce tumor progression (53). VEGF-induced MDSCs inhibit the activity of CD8^{+} T cells in ovarian cancer, weakening the host's antitumor immune response and leading to a poor prognosis (54). A study showed that a higher count of Treg cells could be detected in the peripheral blood of patients with ovarian cancer and thus is associated with poor prognosis (55).

In addition to stromal cells, non-cellular components are also included in the tumor microenvironment. TGF-β is a major cytokine in the tumor microenvironment. TGF-β combines with SMADs, the main signal transducers for TGF-β receptors, to activate cells, which can promote
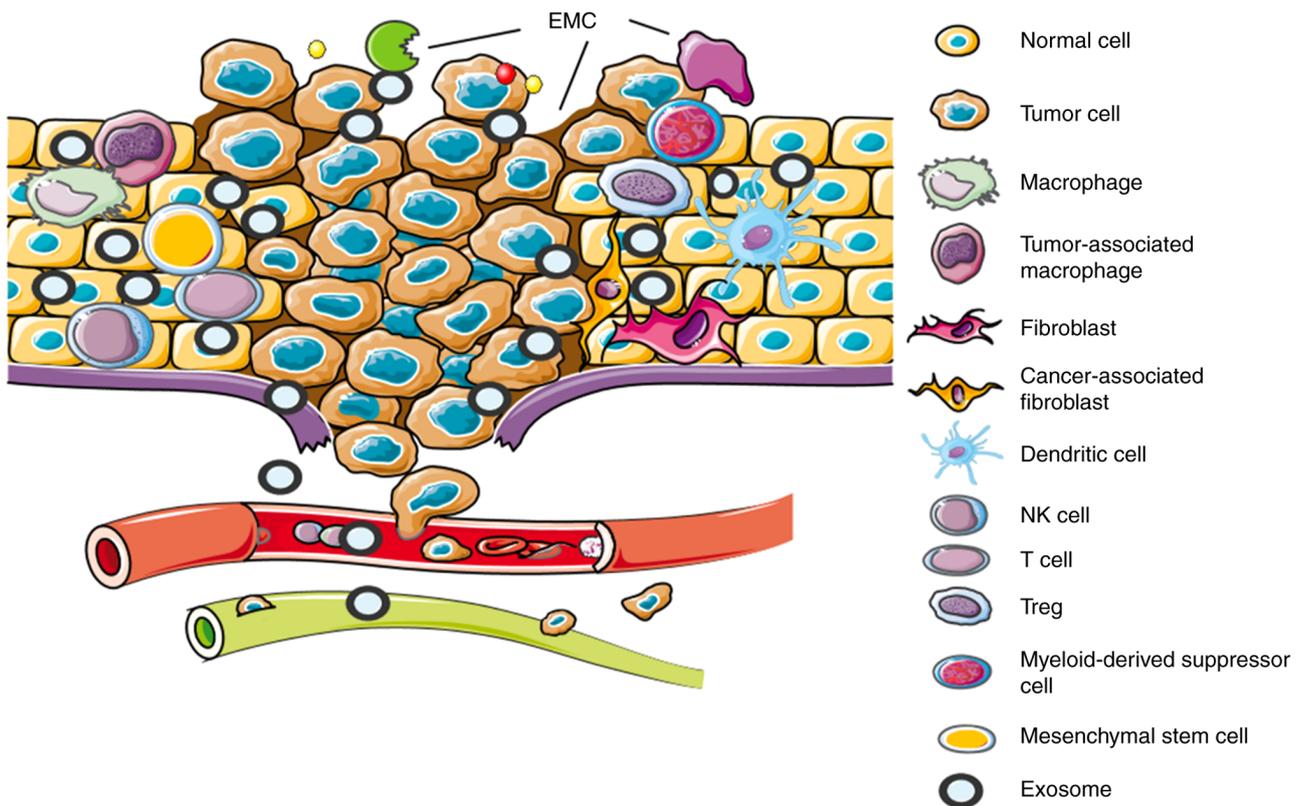
Figure 2. Ovarian cancer immune microenvironment. Tumor microenvironment consists of stromal cells (including fibroblasts, macrophages, Tregs, myeloid-derived suppressor cells, endothelial cells, mesenchymal stem cells), extracellular matrix components and exosomes. EMC, extracellular matrix component; NK, natural killer cells; Treg, regulatory T cells.

transformation of fibroblasts and regulate cell proliferation and apoptosis (56). The high expression of TGF-β3 is associated with poor prognosis of high-grade serous carcinoma, and it is a potential indicator for the evaluation of ovarian cancer prognosis (57). Recent studies have reported that in ovarian cancer stem cells, inhibition of TGF-β/SMAD pathway activation can further inhibit EMT (58-60). In 2012, Kulbe *et al* (61) first described the 'TNF' network in the ovarian cancer microenvironment. 'TNF' network means that TNF, CXCL12 and IL-6 have a paracrine effect in the tumor microenvironment, affecting angiogenesis and immune cell infiltration. In addition, cytokine-induced tumor cells can release guanylate binding-protein-1 and have an antitumor effect (62). The role of cytokines in the tumor microenvironment provides new possibilities for the treatment of ovarian cancer.

As an essential constituent of the tumor microenvironment, the role of exosomes in the tumor microenvironment can be summarized into two aspects, namely tumor-promoting and tumor-inhibiting. Exosomes modulate immune regulation to reshape the tumor microenvironment through metabolism-regulation, stimulation signal upregulation and inhibition signal evasion (63,64). Exosomes induce angiogenesis by changing the biological characteristics of endothelial cells and regulating pro-angiogenic factors (65). In addition, exosomes may induce human hepatocellular carcinoma metastasis and invasion through EMT, ECM degradation and vascular leakage (66). Ras-like in rat brain (Rab) protein is a member of the GTPase family and plays an important role in regulating the budding,

movement and fusion of microvesicles. Studies have shown that ovarian cancer cells can increase the release of exosomes by upregulating Rab27a, downregulating Rab7, lysosome-associated membrane protein-1, neuraminidase-1 mRNA and therefore promoting the secreted lysosomal phenotype (67,68). In addition, the hypoxia-induced exosomes carry oncogenic proteins STAT3 and FAS, which can significantly increase ovarian cancer cell migration, invasion and chemotherapy resistance (67). Epithelial ovarian cancer cells transfer metastasis-associated lung adenocarcinoma transcript-1 a lncRNA to human umbilical vein endothelial cells through exosomes, activating the expression of genes related to angiogenesis (69). Tang *et al* (70) demonstrated that ascites-derived exosomes highly express soluble E-cadherin, which can promote angiogenesis and ovarian cancer progression. The immune response regulated by exosomes also plays a role in suppressing tumor progression. Exosomes derived from ascites in patients with ovarian cancer can detect T cell receptors, CD20 and human leukocyte antigen-DR isotype (HLA-DR), in addition to histones H2A, B7-2 and *HER2/neu* gene, in order to participate in immune modulation (21). In addition, exosomes extracted from ascites of patients with ovarian cancer can induce apoptosis, inhibit proliferation, invasion and metastasis of tumor cells as they exert an antitumorigenic effect (21,71).

As aforementioned, the tumor immune microenvironment is a product of immune cells and immune molecules that inhibit the proliferation of tumor cells (3). There are also a variety of components that can promote the proliferation and
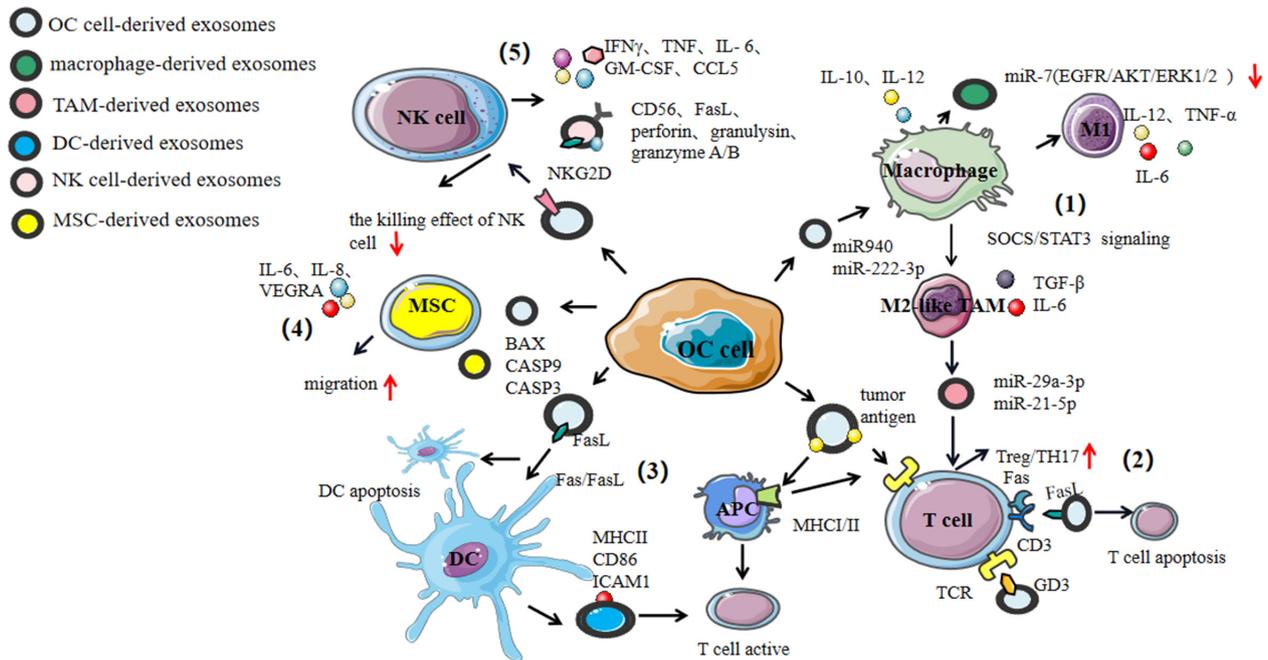
Figure 3. Exosomes cross-talk with immune cells in ovarian cancer immune microenvironment. Exosomes have a dual role in tumor immunity. (1) Exosomal miRNA induce M2-like macrophages (TAMs) to promote the progression of ovarian cancer, and macrophage-derived exosomes to exert the antitumor effect via miR-7. TAM-derived exosomes regulate the ratio of Treg/TH17. (2) Ovarian cancer cell-derived exosomes induce T cell apoptosis by Fas/FasL and FasL/CD3, and active T cell by presenting tumor antigens. (3) Ovarian cancer cell-derived exosomes induce DC apoptosis by Fas/FasL, DC-derived exosomes express MHCII, CD86 and ICAM1 to active T cell. (4) Ovarian cancer cell-derived exosomes enhance the migration of MSC, and exosomes derived from MSC upregulate pro-apoptotic signaling molecules (BAX, CASP9 and CASP3) to inhibit the progression of ovarian cancer. (5) Ovarian cancer cell-derived exosomes downregulate the killing effect of NK cell, NK cell-derived exosomes express NKG2D/DNAM-1 to kill the tumor cell and antitumor protein (CD56), FasL, perforin, granulysin, granzyme A and B. miR, microRNA; TAM, tumor-associated macrophages; DC, dendritic cells; MHC, major histocompatibility complex; NKG2D/DNAM-1, natural killer group 2, member D/DNAX accessory molecule-1; MSC, mesenchymal stem cells; CASP, caspase; OC, ovarian cancer.

invasion of tumor cells, including immunosuppressive cells such as Tregs, TAMs, CAFs, MDSCs and some immunosuppressive signaling factors (72).

4. Immune cells

In the tumor immune microenvironment, the host gives an innate immune response against the tumor mass while an adaptive immune response is given against the tumor antigens, thus preventing tumor progression. Innate immune cells include NK cells, macrophages and DCs. Adaptive immune effectors include CD8^{+}, cytotoxic T lymphocyte (CTL) and CD4^{+} Th cells (72). Exosomes play a role in mediating cross-talk with immune cells to exert an antitumorigenic and/or a pro-tumorigenic effect (Fig. 3).

Macrophages. Macrophages are the first line of defense against foreign pathogens and key effectors of innate immunity, they are the key cells to bridge innate and adaptive immunities (73). According to their activation pathways, macrophages can be divided into two types: Classically-activated macrophages (named M1) and alternatively-activated macrophages (named M2) (74). Macrophages are usually polarized into M1 phenotype after being induced by IFN-γ, TNF-α, IL-6 and lipopolysaccharides. Their surface highly expresses MHC II and co-stimulatory proteins, such as CD80 and CD86 (75). M1 macrophages are generally considered pro-inflammatory and release IL-6, IL-12, TNF-α and reactive oxygen species

(ROS), which are considered intermediates that are associated with cytotoxicity and anti-tumorigenic properties (76,77). M2 macrophages are polarized by IL-4, IL-13, IL-10 and IL-33 (56). The markers on the surface of M2 macrophages include found in inflammatory zone 1, mannose receptor 1 and MHC II (74). M2 macrophages have the capacity to secrete TGF-β, IL-6 and arginase-1 to facilitate neovascularization, inhibit the adaptive immune response, ensure tumor cell survival and remodel the ECM, which are all generally considered as tumor-promoting functions (78,79). In addition, TAMs are the main cells in the tumor immune microenvironment that have two phenotypes: M1-Like TAMs and M2-like TAMs (80). In the immune microenvironment of ovarian cancer TAMs usually manifest as the M2-like phenotype. The variety of biomarkers on the surface are scavenging receptor B (CD163), mannose receptor (CD204), IL-10 and chemotactic factor ligands CCL18 and CCL22 (81,82). IL-10 secreted by TAMs can activate Treg cells and promote tumor progression (83). miR-29a-3p and -21-5p, which are abundant in TAM-derived exosomes, can be transferred to CD4^{+}T cells; thereby inhibiting STAT3 from regulating the ratio of Treg:Th17 and creating an immunosuppressive microenvironment that is necessary for the ovarian tumor to evade an active immune response, thus helping in tumor progression (84).

Tumor-derived exosomes can induce macrophages to differentiate into the M2 phenotype and TAMs, which have been confirmed in extracts from various organs, including: Ovaries, colorectal regions, endometrium, pancreas, melanoma,

liver, breast and lung cancer cells (85-91). In a hypoxic microenvironment, high expression of miR-940 in exosomes has been derived from epithelial ovarian cancer cells, which induces macrophages to differentiate into the M2 phenotype, thus promoting proliferation and metastasis of epithelial ovarian cancer (92). Similar research shows that under hypoxic conditions, exosomes derived from epithelial ovarian cancer activate hypoxia-inducible factors that induce macrophages to highly express miR-21-3p, -125b-5p and -181d-5p and promotes their polarization to the M2 phenotype through the cytokine signal transduction 4/5/STAT3 signaling pathway, which was also verified in vivo. The JAK-STAT pathway mediates inflammatory immune response by converting cytokine signals, and SOCS is the key regulator of the pathway (76). Through microarray analyses, some researchers found that the expression of miR-221-3p was upregulated in exosomes that were derived from M2 macrophages. Additionally, miR-221-3p can target the inhibition of cyclin-dependent kinase inhibitor 1B, thus promoting the proliferation of ovarian cancer cells via transition from G_1 to S (93). In addition, epithelial ovarian cancer-derived exosomes overexpress miR-222-3p and transfer it to macrophages to induce them into M2-like polarization by the SOCS3/STAT3 pathway. miR-222-3p targets downregulation of SOCS3 gene expression and activates STAT3 expression (94). This transfer of miR-222-3p can facilitate the progression of ovarian cancer (94). Wu et al (95) have shown that TAM-derived exosomes inhibit endothelial cell migration by targeting the miR-146b-5p/TRAF6/NF-kB/MMP2 pathway, whereas ovarian cancer-derived exosomes can reverse the role of TAMs in endothelial cells by transferring lncRNAs.

In order for macrophages to differentiate into TAMs, macrophage-derived exosomes are important components involved in the antitumor immune response (84,93,96). The TNF-related weak inducer of apoptosis (TNSFS12 or TWEAK)-stimulated macrophage-derived exosomes can be internalized by the tumor cells, which can inhibit ovarian cancer metastasis. A study revealed that TWEAK-stimulation increased the expression of miR-7 (a tumor suppressor) in exosomes released by macrophages, which downregulates the activity of the EGFR/AKT/ERK1/2 signaling pathway and inhibits ovarian cancer metastasis (96). This was performed in mouse models where TWEAK-stimulated macrophage-derived exosomes blocked the metastasis of epithelial ovarian cancer (96). In addition, Baj-Krzyworzeka et al (97) have shown that tumor-derived exosomes can activate monocytes by increasing HLA-DR expression, upregulating reactive oxygen intermediates and TNF and by accumulating and secreting IL-10 and IL-12 mRNA. Exosomes activate monocytes and induce them to differentiate into macrophages (97-99). At present, there are few studies on macrophage-derived exosomes in ovarian cancer, which is an area that needs to be explored further. Exosomes derived from breast cancer cells have upregulated levels of miR-130 and miR-33, which can alter the polarization of macrophages from M2 to M1 phenotype and inhibit tumor progression (100). The exosomes derived from TAMs of progranulin (PGRN)-negative tumor tissues have upregulated expression of miR-5100, which inhibits the invasion, migration and EMT of breast cancer cells by targeting the CXCL12/CXCR4 axis (101). Although a similar study in ovarian cancer has not been performed, studies have shown that expression of PGRN protein relates to poor ovarian cancer prognosis (102,103). Moreover, high expression of PGRN can induce EMT in ovarian cancer cells (104). This suggests that exosomes are a potential therapeutic target for ovarian cancer.

NK cells. In a tumor environment, NK cells are the first line of defense within the immune system. NK cells mainly kill target cells in four ways: i) Antibody-dependent cell-mediated cytotoxicity via the Fas/FasL pathway (105), ii) the perforin-granzyme pathway (106), iii) binding to target cells through adhesion molecules (107) and iv) releasing cytokines to attack target cells (108,109). NK cells are important effectors in the cancer immune surveillance (110,111). Upon activation, they secrete pro-inflammatory factors and chemokines, for example IFN-γ, TNF, IL-6, GM-CSF and chemotactic cytokine ligand 5 to mediate antitumor immune responses, affect antitumor activity and promote formation of the tumor microenvironment (112). IL-15 enhances the antitumor activity of NK cell-derived exosomes and has been validated in mouse models (113). Exosomes derived from NK cells express the killer protein (CD56), FasL, perforin, granulysin, and granzyme A and B, which show antitumor activity and play a role in immune surveillance (114). Killer proteins expressed by NK cell-derived exosomes can participate in NK cell-mediated cytotoxic killing effects (115), and the expressed DNAX accessory molecule 1 (DNAM-1/CD226) receptor can bind to DNAM-1 ligands on the cell membrane of tumor cells to exert a cytotoxic tumor cell killing effect (116). This is an important role of NK cells in cancer immune surveillance. NK cell-derived exosomes express FasL and perforin and exert cytotoxic effects in melanoma (117). NK cell-derived exosomes carry miR-186, which can inhibit neuroblastoma growth (118). The antitumor effect of NK cell-derived exosomes on invasive melanoma and neuroblastoma has been confirmed, exosomes derived from NK cells can potentially be used in cancer treatment (117,118).

Although NK cells are a part of the innate immune system and are capable of killing tumor cells, tumor microenvironment also affects the cytotoxicity of NK cells (119). Exosomes released by ovarian cancer cells highly express KLRK1/ natural killer group 2 (NKG2D) ligands in the manner of MHC I chain-related protein A and B and UL16-binding protein. This downregulates the expression of NKG2D receptors on peripheral blood mononuclear cells, affecting the activation of NK cells and suppressing their natural killing effect (120).

Lymphocytes. Adaptive immune effector cells include CD8^{+}, CTL and CD4^{+}Th. In acute infection, CTL is the main effector cell and has a specific killing effect on tumors through the perforin-granzyme, Fas/FasL and TNF pathways (121). CD4^{+}Th cells play an auxiliary role in activating CTL (122). In contrast, during chronic infections and cancer, T cell dysfunction occurs due to continuous stimulation of antigens (123). In addition, the cytokines produced by CD4^{+}Th cells can indirectly participate in antitumor immune effects. In theory, dendritic cell-derived exosomes can stimulate T cells through three different mechanisms: i) Direct presentation of exosomal MHC I and II to T cells, ii) indirect stimulation

via exosomal MHC presentation to APCs and iii) degradation and recycling of the exosomal MHC/peptide complex in the microenvironment (124).

Research shows that T cell-derived exosomes can regulate gene expression and extracellular signal transduction of DCs by carrying miRNA and T cell receptor protein (TCR)-rich vesicles (125). MHC I, MHC II and T cell co-stimulatory molecules on the surface of B lymphocyte-derived exosomes can stimulate the proliferation of T lymphocytes and thus prevent tumor progression (126). T follicular helper cell-derived exosomes facilitate the proliferation of B lymphocytes (127). CD4+T cell-derived exosomes regulate the gene expression of B lymphocytes by transporting their miRNA cargo to B lymphocytes, which therefore decreases the level of antibodies produced by B cells (128).

However, a previous study confirmed that tumor cell-derived exosomes recruit lymphocytes to suppress the antitumor immune response, promoting tumor progression by increasing tumor invasion, angiogenesis and upregulating proinflammatory cytokines, such as IL-6 and VEGFA (129). Exosomes can induce T cell apoptosis and weaken the immune response to achieve immune escape. FasL is a transmembrane protein in the TNF family of proteins that is increased in malignant tumors. FasL is overexpressed in tumor-derived exosomes (11,130). FasL recognizes the Fas receptor on the surface of target cells and triggers intrinsic apoptosis of target cells via the FADD-procaspase-8 pathway, to induce T cell apoptosis and suppress the immune response (11). In addition, Fas can also mediate the apoptosis of lymphocytes through antibody-dependent direct cytotoxicity. A previous study has showed 41 kDa FasL and HLA class I antigens are upregulated in ovarian cancer-derived exosomes and inhibit T cell anti-tumor immune function through FasL/CD3-ζ ligand-receptor binding (131). This inhibitory function has also been observed in other tumors, such as exosomes derived from human prostate cancer cells that induce CD8+T cell apoptosis by FasL/Fas (132). FasL is also found in exosomes from melanoma and colorectal cancer, which is considered a new immune escape pathway (133). The expression of circ-0001068 (a novel biomarker for ovarian cancer and inducer of PD1 expression in T cells) in exosomes derived from ovarian cancer cells is upregulated and can be delivered to T cells as well. Once in T cells, circ-0001068 downregulates the expression level of miR-28-5p and thus induces the expression of PD1 (134). Exosomes released by ovarian cancer cells can carry plasma gelsolin and induce CD8+ T cell apoptosis, which weakens immune surveillance (135).

Exosomes from the ascites of patients with ovarian cancer can inhibit T cell signaling molecules, inhibit the expression of CD3-ζ and JAK 3, and induce T cell apoptosis (136). In the ascites of patients with ovarian cancer, the ganglioside GD3 expressed on the surface of exosomes binds with the TCR and actively arrest T cell function, which greatly reduces the anti-tumorigenic effect of T cells (137,138). Moreover, a previous study showed that this inhibitory effect mediated by GD3 and TCR is related to the sialic acid group in exosomes (137). When the sialic acid group is hydrolyzed, this inhibitory effect disappears, which indicates that GD3 can be a new target for ovarian cancer immunotherapy (137). In addition, the ascites-derived exosomes of patients with ovarian cancer can effectively block

T cells in a reversible manner due to the early translocation of NF-kB and later functional activation of IFN-γ. Researchers have demonstrated that this can be reversed within 24-48 h by the removal of exosomes. Therefore, targeted removal of exosomes will increase the antitumorigenic effect of the host T cells (139).

Tumor-derived exosomes can also inhibit T cell activation to cause immunosuppression. Functional CD39 and CD73 expressed by exosomes can dephosphorylate exogenous ATP and cAMP to form adenosine, and inhibit T cell activation through the adenosine A2A receptor. Therefore, exosomes increase the production of extracellular adenosine to regulate the antitumor immune effect of the T cells (140). In addition, phosphatidylserine (PS)-positive exosomes derived from the ascites of patients with ovarian cancer block the NF-kB and NFAT pathway signaling cascade in T cells, and reversibly inhibit T cell activation (141). Thus, depletion of anti-PS antibodies or blocking PS can notably eliminate the inhibition of T cells, which could be another new treatment method for patients with ovarian cancer (142).

DCs. DCs are unique, in that they can activate T cells. They can also activate immune responses or induce immune tolerance (143). Mast cell-derived exosomes contain HSP60 and HSP70, which can promote DC maturation and exert antitumorigenic immune effects in a mouse model (144). The ovarian cancer microenvironment is rich in cytokines and angiogenic factors, which can change the phenotype and function of DCs. Most studies corroborate that the ability of exosomes to stimulate T cells can be enhanced through the interaction of exosomes with DCs (145-147). Exosomes derived from the ascites of patients with ovarian cancer present tumor antigens and can induce differentiation of dendritic cells and tumor-specific cytotoxic T lymphocytes (6). Exosomes isolated from the ascites of patients with ovarian cancer express MHC I molecules, HSP70 and HSP90. DCs treated with these exosomes can promote T cell activation and produce cytotox-icity (148). DC-derived exosomes present antigens to DCs, and then these DCs can activate T cells. These results suggest that the exosome is a potential safe and feasible immunotherapy for advanced tumors (149). At present, the antitumor immuno-therapy of exosomes derived from DCs is in phase II clinical trials of advanced malignant tumors.

Although DCs have antitumorigenic activity, their function may be inhibited in tumor immune microenvironment. The ovarian cancer microenvironment is rich in factors that inhibit monocyte differentiation into DCs. Ascites-derived exosomes from patients with ovarian cancer induce apoptosis in DCs by activation of the Fas/FasL pathway and mediating TRAIL apoptosis-inducing signal molecules in mature DC precursors. In one investigation, ovarian cancer-derived exosomes were cultured with dendritic precursor cells for 48 h. Exosome co-cultured DCs had an apoptotic rate of 12.6% while the control group had an apoptotic rate of 8.6% (21). Overall, exosomes may induce apoptosis of DCs and stimulate precur-sors of mature DCs.

Mesenchymal stem cells. MSCs are an important member of the stem cell family, which play an important role in cancer progression. They are present, albeit in small numbers, in
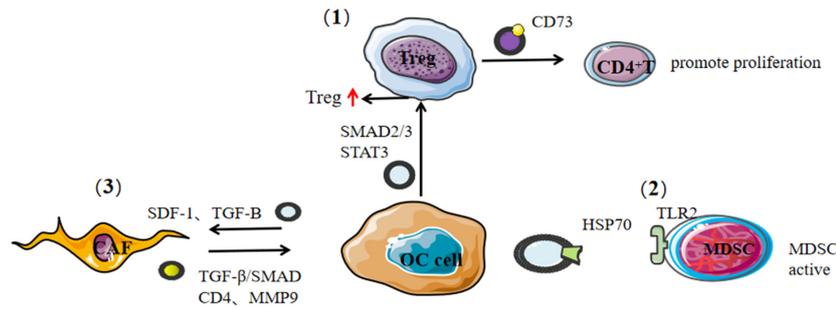
Figure 4. Exosomes mediate immune modulation. (1) Ovarian cancer cell-derived exosomes increase the amount of Treg cells and upregulate their immunosuppressive function. Treg-derived exosomes express CD73 to promote the proliferation of CD4+T cell. (2) Ovarian cancer cell-derived exosomal HSP-70 binds with TLR2 to activate MDSCs and promote cancer progression. (3) Ovarian cancer cell-derived exosomes induce stem cells to differentiate into cancer-associated fibroblasts and upregulate tumorigenic factors (stromal cell-derived factor 1, TGF-β), and CAF-derived exosomes promote tumor cell proliferation. Treg, regulatory T cells; HSP, heat shock proteins; TLR2, toll-like receptor 2; MDSCs, myeloid-derived suppressor cells; CAF, cancer-associated fibroblasts; MMP, matrix metalloproteinase.

a variety of tissues (bone marrow, umbilical cord blood, umbilical cord, placenta and adipose) and are reported to have multidirectional differentiation and regeneration properties (150). In addition, MSCs also have the capability of immune modulation, which in a number of cases can cause immunosuppressive effects. De Miguel *et al* (151) demonstrated *in vitro* that MSCs can inhibit the proliferation of immune cells (lymphocytes, NK cells and DCs) and inhibit secretion of cytokines, thereby inhibiting the cytotoxic effect of T and NK cells via indoleamine 2,3-dioxygenase, while also activating and inducing the maturation of DCs. A co-culture of ovarian cancer cell lines (SKOV-3 and OVCAR-3) and MSCs demonstrates that adhesion, migration, invasion, proliferation and chemical resistance of ovarian cancer cells is enhanced, leading to accelerated tumorigenicity (152). In the tumor microenvironment, exosomes derived from MSCs also play an immunoregulatory role. Bone marrow MSC-derived exosomes have anti-inflammatory, anti-apoptotic, pro-angiogenic and immune-regulating effects (153). Bone marrow MSC-derived exosomes inhibit the proliferation of T and B cells and affect mRNA function; downregulating the expression of CXCL8 and marginal zone B and B1 cell-specific protein the level of IgM to affect the anti-tumorigenic function of B cells (154). MSC-derived exosomes upregulate MMP-2 and activate ecto-5'-nucleases, causing tumor cells to become more malignant and thus altering the tumor microenvironment, as well as enhancing tumor heterogeneity (155). In addition, cancer cell-derived exosomes affect the tumorigenicity of MSCs. *In vitro* analysis demonstrates that SKOV-3 and OVCAR-3 cell line-derived exosomes can enhance the migration capacity of MSCs (156). In the microenvironment of ovarian cancer, cancer stem cells are associated with creating drug resistance and making the tumor mass refractory to a specific drug (147,157). Vera *et al* (158) have revealed that upon treatment with cisplatin, exosomes released by ovarian cancer that are rich in cancer stem cells can upregulate IL-6, IL-8 and VEGFA, increasing the migration capacity of cancer cells. In addition, factors secreted by MSCs can induce endothelial cell angiogenesis and accelerate the migration of low-invasive ovarian cancer cells. Exosomes have also been shown to enhance the oncogenicity of MSCs, leading to drug resistance and tumor

progression (158). The expression of miR-146a in MSC-derived exosomes is upregulated, which targets laminin γ-2 to regulate the phosphoinositide 3-kinase (PI3K/Akt) signaling pathway. This subsequently inhibits the proliferation of ovarian cancer cells and induces chemotherapy resistance (159).

Previous studies have confirmed the antitumor effect of MSC-derived exosomes. Human adipose MSC-derived exosomes can induce apoptotic signals by upregulating pro-apoptotic signaling via BAX, CASP9, CASP3 and downregulating the anti-apoptotic protein BCL2 to inhibit A2780 and SKOV-3 cell proliferation, wound-repair and colony-forming ability (160). In mouse models of ovarian cancer, paclitaxel-loaded MSC-derived exosomes have strong antitumor effects, which suggests that they can be used as drug carriers to target ovarian cancer (161).

5. Immunosuppressive effector cells

The host immune system recognizes the tumor during progression, allowing immune cells to enter the tumor microenvironment under the action of chemokines. Subsequently, immune cells such as CD4+T, CD8+T, B lymphocytes, NK cells, macrophages and DCs are recruited to suppress the tumor *in vivo*. However, during the course of tumor development, immune monitoring through cancer immune editing is less selective for cancer cells that are less immunogenic, allowing them to escape the immune attack and thus achieve immune escape (Fig. 4). The clinical manifestations of tumor immune editing trigger the establishment of an immunosuppressive tumor microenvironment (112).

Tregs. Tregs negatively regulate the antitumor response in both a direct and indirect manner while also playing a key role in immune escape (162). The increase of Tregs in the tumor microenvironment of patients is related to poor prognosis and shortened overall survival (OS) time (55). Treg-derived exosomes can exert immunosuppressive effects by expressing CD73 and inhibiting the proliferation of CD4+T cells (107). Curiel *et al* (163) in 2004 analyzed 104 specimens of epithelial ovarian cancer and found that CD4+CD25+FOXP3+ Tregs inhibited T cells *in vivo* and promoted tumor development.

After tumor-derived exosomes activate Tregs, the expression levels of STAT3/SMAD2/3/IL-10/TGF-B increase and the expression of granzyme B, perforin and FasL are upregulated, thereby reducing the antitumor immune response. In addition, exosomes act on the SMAD2/3 and STAT3 signaling pathways to convert CD4+CD25T cells into CD4+CD25+FOXP3+ Tregs, which upregulates their immunosuppressive function and anti-apoptotic potential (164).

MDSCs. MDSC is an immunosuppressive cell of marrow-derived cells, which are induced to differentiate into DCs, macrophages and granulocytes. These MDSCs can depress the activity of T and NK cells, which can significantly suppress immune cell response (165). IL-6 is produced by autocrine activation in a Toll-like receptor 2 (TLR2)/myeloid differentiation primary response 88-dependent manner, triggering STAT3 activation and promoting the immunosuppressive function of MDSCs (166). A similar study found that HSP70 is highly expressed on the surface of ovarian cancer-derived exosomes, which fuses with and activates MDSCs by binding TLR2 to promote cancer progression (166,167). Notably, the study found that the A8 peptide blocked this HSP70/TLR2 binding to weaken the ability of tumor-derived exosomes to activate MDSCs in a mouse model. Drugs, such as cisplatin and 5-fluorouracil, cause tumor cells to release more exosomes with HSP70 surface expression to activate MDSCs. When cisplatin or 5-fluorouracil is used in combination with A8 peptide, it can effectively antagonize the activation of MDSCs caused by cisplatin or 5-fluorouracil, which greatly enhances the antitumor effect of these drugs. Overall, this study has notable implications for novel ovarian cancer therapies (168).

CAFs. As an important element of the tumor microenvironment, CAFs secrete a variety of growth factors and pro-inflammatory cytokines (TGF-β, VEGF, IL-6 and CXCL12) which promotes angiogenesis and recruits immunosuppressive cells into the tumor microenvironment to assist in immune evasion (169). Exosomes derived from epithelial ovarian cancer induce adipose tissue-derived mesenchymal stem cells to differentiate into tumor-associated myofibroblasts and upregulate tumorigenic factors such as stromal cell-derived factor 1 and TGF-β (170). TGF-β receptor and SMAD signaling can regulate the expression of multifunctional proteoglycan VERISCAN protein, encoded by the *VCAN* gene. Upregulating *VCAN* activates the NF-kB signal pathway, which upregulates the expression of CD44, MMP-9 and hyaluronic acid-mediated motor receptors that collectively promote the migration and invasion of ovarian cancer cells (171). Further the CAF-derived exosomes can be internalized by SKOV-3 and CAOV-3 cell lines leading to a more aggressive tumorous phenotype, promoting the EMT of ovarian tumors. This evidence suggests that CAF-derived exosomes have the potential to provide a breakthrough in the treatment of ovarian cancer (172).

6. Exosomal miRNAs, proteins and lipids in the tumor microenvironment

Exosomes can carry a variety of biologically active molecules. miRNA is a type of non-coding RNA molecule (range, 9-25 nucleotides in length) encoded by an endogenous gene, that specifically binds to the 3'-untranslated region of target mRNA to effectively repress gene expression after it has been transcribed (173,174). Cancer-associated adipocytes and CAFs transfer miR-21 to cancer cells via exosomes, thereby inhibiting ovarian cancer cell apoptosis (175). Releasing exosomal miRNA into the tumor microenvironment is a mechanism for reprogrammed gene expression at the epigenetic level. Ovarian cancer cells excrete unnecessary genetic material by releasing exosomes to maintain their aggressiveness and tumor immunogenicity (176-178). As a tumor-inhibiting factor, miR-6126 inhibits tumor progression by decreasing integrin β1 mRNA level to promote metastatic behavior (177). miR-940 can inhibit ovarian cancer cell proliferation, colony formation, invasion and migration, and is highly expressed in exosomes derived from SKOV3-IP1, HeyA8 and HeyA8-MDR cell lines. Ovarian cancer cells enhance the tumorigenicity of cells through miRNA excretion mechanisms (178). A recent study provided supporting evidence that exosomes derived from epithelial ovarian cancer cells carry miR-141-3p, which activates the JAK/STAT3 and NF-kB signaling pathways in endothelial cells. This increases the level of VEGFR-2 in endothelial cells and enhances migration and angiogenesis (179). Exosomal miR-99a-5p derived from epithelial ovarian cancer cells affects human peritoneal mesothelial cells (HPMCs) by upregulating fibronectin and vitronectin to promote ovarian cancer progression (180). miRNAs carried by exosomes play a pro-tumorigenic role in the immune microenvironment of ovarian cancer (Table I).

In different ovarian cancer cell lines, the miRNA profile of exosomes varies. The miR-200 family inhibits EMT, which is only detected in the exosomes of poorly-invasive cell line OVCAR-3 (181). In a study of 109 patients with ovarian cancer and eight with ovarian cystadenoma, exosomal miRNA analysis revealed that miR-200b and miR-320 have a positive correlation with cellular proliferation and apoptosis. Additionally, the levels of exosomal miR-200b is related to cancer antigen 125 (CA125) and the OS rate of patients. Exosomal miR-200b has the potential to become a new prognostic indicator. The expression of miR-23a and miR-92a in ovarian cystadenoma-derived exosomes is lower compared with that of ovarian cancer-derived exosomes and exosomes derived from healthy individuals (182). Therefore, exosomal miRNAs can be used as biomarkers of ovarian cancer. In 2018 Kobayashi *et al* (183) found that miR-1290 is a potential biomarker for high-grade serous ovarian cancer and can be used to distinguish patients with other histologically malignant tumor types. This means that studying miRNAs carried by exosomes can provide new directions for the early diagnosis of ovarian cancer and in the search for novel and improved tumor markers for targeted therapy.

Proteomic analysis of ovarian cancer-derived exosomes revealed that these exosomes are rich in proteins related to antigen processing, and that they can effectively initiate antitumor immune responses (20). Exosomes from different types of malignant tumors show varying protein and lipid mass spectra. By comparing the proteome and lipid profiles of exosomes derived from SKOV-3 cell line and ovarian surface epithelial cells, it becomes clear that collagen α-2(V) (also known as COL5A2) and lipoprotein lipase are highly expressed in SKOV-3 derived exosomes (184). Plus, CD44

Table I. Role of exosomal miRNAs in the tumor microenvironment.

Exosomal miRs	Source	Mechanism	Function	Recipient cells	(Refs.)
miR-6126	Ovarian cancer	Release tumor suppressor	Promote invasion and migration	Ovarian cancer cell	(177)
miR-141-3p	Ovarian cancer	Upregulate JAK/STAT3 and NF-κb, VEGFR-2	Promote endothelial cell angiogenesis	Endothelial cell	(179)
miR-99a-5p	Ovarian cancer	Affect HPMCs via fibronectin and vitronectin upregulation	Promote invasion	Human peritoneal mesothelial cell	(180)
miR-200b	Ovarian cancer plasma	NA (Not discussed in original research)	Proliferation and apoptosis	OVCAR3 and SKOV3 cell	(182)
miR-1290	Ovarian cancer	NA (Not discussed in original research)	Biomarker		(183)
miR-222-3p	Ovarian cancer	Induce M2 phenotype via SOCS3/STAT3	Induce TAM and tumor progression	Macrophage	(94)
miR-1246	Ovarian cancer	Cav1/p-GP/M2 macrophage axis	Resistant to paclitaxel	Macrophage	(194)
miR-940	Ovarian cancer	Induce macrophage M2 polarization	Promote proliferation and metastasis	Macrophage	(92)
miR-21-3p, -125b-5p and -181d-5p	Ovarian cancer	Induce macrophage M2 polarization	Promote proliferation and metastasis	Macrophage	(76)
miR-223	Macrophage	PTEN-PI3K/AKT pathway	Promote drug resistance	Ovarian cancer cell	(193)
miR-7	Macrophage	Inhibit EGFR/AKT/ ERK1/2	Inhibit metastasis	Ovarian cancer cell	(96)
miR-221-3p	M2 Macrophage	Inhibit CDKN1B	Promote proliferation	Ovarian cancer cell	(93)
miR-21	CAF and CAA	NA (Not discussed in original research)	Inhibit apoptosis	Ovarian cancer cell	(175)
miR-98-5p	CAF	Downregulate CDKN1A	Resistant to cisplatin	Ovarian cancer cell	(195)
miR-146a	MSC	LAMC2-P13K/Akt signaling pathway.	Inhibit proliferation and chemotherapy resistance	Ovarian cancer cell	(159)

AKT, protein kinase B; Cav1/p-gp, caveolin-1/ multidrug resistance protein 1; CDKN, cyclin-dependent kinase inhibitor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; HPMC, human peritoneal mesothelial cell; JAK/STAT, the Janus kinase/signal transducer and activator of transcription; LAMC2, laminin γ2; PI3K, Phosphatidylinositol 3-kinase; PTEN, gene of phosphate and tension homology deleted on chromosome ten; SOCS/ STAT, suppressors of cytokine signaling/signal transducer and activator of transcription; VEGFR, vascular endothelial growth factor receptor.

is commonly found in the ovarian cancer-derived exosomes that become internalized by HPMCs. Increased expression of CD44 in HPMCs induces HPMCs to secrete MMP9 and allows HPMCs to clear the mesothelial barrier thus promoting cancer cell invasion and peritoneal metastasis (185). The ovarian cancer-derived exosomes promote tumor progression, and the proteins they carry have a role in malignancy of the tumor. These proteins include membrane proteins such as programmed cell death 6-interacting protein, tumor suscepti-bility gene 101, tetraspanins, HSPs and a variety of enzymes such as phosphate isomerase, peroxidase, aldehyde reductase and fatty acid synthase (186). Ovarian cancer cell-derived exosomes that overexpress LIN28 (an RNA-binding protein that promotes pluripotency) can enhance cell invasion and migration (187). HSP27 can also enhance the invasiveness and

drug resistance of ovarian cancer and is a potential biological marker of ovarian cancer. Stope *et al* (188) demonstrated that exosomes can carry HSP27 secreted by OVCAR-3 and SKOV-3 cell lines to the tumor microenvironment, thereby promoting tumor progression.

7. Significance of exosomes in ovarian cancer immunotherapy

Cancer immunotherapy is a relatively new treatment option. By understanding the exosome profile and signal transduc-tion mechanism, it can be better applied to cancer treatment. The advantages of exosomes are summarized as follows: i) Tumor-derived exosomes have the heterogeneity profile of tumor cells, ii) exosomes derived from homologous or

allogeneic cells can reduce unnecessary immune responses, iii) exosomes have good stability, iv) the bio-distribution of exosomes can be adjusted by modifying the surface of exosomes to target a specific tumor location, v) exosomes have a long half-life and can improve the efficacy of drugs loaded into them as cargo and vi) exosomes have multiple types of internalization methods and can avoid the degradation of lysosomes, so as to efficiently transport drugs to the recipient cells.

At present, numerous achievements have been made in applying exosomes to cancer treatment. Small interfering RNAs and miRNAs carried by exosomes target and inhibit tumor cell proliferation and drug resistance (175). The reorganization of the exosomal membrane can improve the efficiency of drug loading and the sustained release of drugs (189). Exosomes can overcome the weak immunogenicity of tumor antigens that are likely to be used in a cancer vaccine (190). DC-derived exosomes can stimulate T cells by transporting MHC molecular complexes to the surface and facilitating T cells binding to tumor cells. At present, the antitumor immunotherapy of DC-derived exosomes has undergone II clinical trials in advanced non-smooth cell lung carcinoma, showing the feasibility and safety of antitumor exosome immunotherapy. It also has a new importance in ovarian cancer therapy (131). Exosomes derived from NK cells have a natural killing effect on melanomas, which is a potential cancer immunotherapy strategy (117) and exosomes have potential for ovarian cancer treatment.

In addition, exosomes can be used as carriers of antitumor drugs. In mouse models, a combination of mesenchymal stem cell-derived exosomes and paclitaxel increases the antitumor effect of paclitaxel (191). Previous studies have clarified the mechanism of miRNA generated resistance when carried by exosomes in ovarian cancer (192-194). Exosomes released by macrophages carry miR-223, which downregulates the PTEN-PI3K/AKT signaling pathway that can make ovarian cancer drug resistant (193). In addition, Kanlikilicer *et al* (194) demonstrated that miR-1246 expressed by ovarian cancer-derived exosomes can make ovarian cancer resistant to paclitaxel via the Cav1/multidrug resistance protein 1 (p-gp)/M2 phenotype macrophage axis, miR-1246 targets the *Cav1* gene and acts though platelet-derived growth factor receptor target recipient cells, induces polarization of M2 macrophages. Exosomes derived from CAFs carry miR-98-5p to promote the resistance of cisplatin in ovarian cancer (195). Using specific exosome inhibitors can effectively prevent this mechanism of drug resistance. Ovarian cancer-derived exosomes are enriched with DNA methyltransferase 1 that makes cancer cells resistant to cisplatin, but the exosomal inhibitor gw4869 can reverse this resistance and restore their drug sensitivity (196). This information will provide new avenues of exploration for targeted therapies against ovarian cancer. Cancer-derived exosomes can carry CRISPR/Cas9 to other ovarian cancer cells, inhibit PARP-1 expression, cause ovarian cancer cell apoptosis and enhance the sensitivity to cisplatin (197). Until now, there have been no reports on the application of exosomes to ovarian cancer immunotherapy, but it is an area should continue to be explored in the future.

8. Conclusions

As outlined in this article, the role of exosomes in the immune microenvironment of ovarian cancer can be described as a double-edged sword. Exosomes derived from immune cells can target tumor cells to exert antitumor immune effects. NK cell-derived exosomes mediate NK cell cytotoxicity through their surface receptors NKG2D and DNAX accessory molecule-1 (115,116); NK cell-derived exosomes can carry killer protein (CD56), FasL, perforin, granulysin, granzymes A and B to the tumor microenvironment of distant tumors (114). DC-derived exosomes can activate T cells to exert antitumor effects (145). Exosomes can also mediate cellular communication between immune cells. Mast cell-derived exosomes can promote the maturation of DCs (144). T cell-derived exosomes can regulate miRNA and TCR-rich vesicles to regulate gene expression and extracellular signal transduction of DCs (125). Treg-derived exosomes can inhibit CD4$^+$T cell proliferation by expressing CD73 (140).

However, tumor cell-derived exosomes exert immunosuppression and immune escape through a variety of pathways in the tumor microenvironment. Exosomes derived from epithelial ovarian cancer can induce macrophages to differentiate into TAMs, downregulate the killing effect of NK cells on tumors, induce T cell apoptosis through Fas/FasL interactions and induce DC apoptosis. Ovarian cancer-derived exosomes also upregulate the functions of Tregs and MDSCs, induce the differentiation of CAFs and induce the tumorigenic activity of mesenchymal stem cells; forming a microenvironment that is beneficial to tumor proliferation, invasion, metastasis and tumor progression.

A study has shown that the tumor microenvironment contains functionally heterogeneous B lymphocytes and regulates tumor immunity by producing immunoglobulins and presenting costimulatory molecules (198). However, in ovarian cancer, research on the interaction between exosomes and B lymphocytes is rare, and is thus an area that requires further exploration. The regulation of the immune system by exosomes highlights the great potential of exosomes in cancer immunotherapy. The release of exosomes in patients with ovarian cancer is 3-4 times higher compared with in individuals without ovarian cancer. If the production of tumor-derived exosomes can be reduced, this could theoretically weaken the impact on immune suppression and thus would make immune escape more difficult. At present, preventing the excessive production of cancer cell-derived exosome has shown significant antitumor and anti-metastatic effects in breast cancer (199). If this technology can be applied to ovarian cancer, it will become a new strategy for ovarian cancer treatment.

Chemoresistance is common during the treatment of ovarian cancer and is usually associated with poor prognosis. Current biological techniques can effectively load chemotherapeutic drugs into exosomes through co-culture, electroporation or ultrasound (200). Studies have verified that exosomes loaded with paclitaxel and cisplatin can induce apoptosis of ovarian cancer cells (175,192,194). If the exosomes loaded with paclitaxel and cisplatin can be used in clinical treatment, it will be a novel strategy for the treatment of drug-resistant ovarian cancer. Of course, this requires a large number of clinical trials for the verification of the treatment efficacy, and would require the joint efforts of various research centers and hospitals. At present, Clinicaltrials. gov (https://clinicaltrials.gov/) has reported 198 studies on

exosomes, including three studies on exosomes as biomarkers of ovarian cancer, and one study on polycystic ovary syndrome and exosomes. There are no clinical trials using exosomes in the treatment of ovarian cancer, to the best of our knowledge. Before clinical trials, large-scale separation and purification of exosomes is still a huge challenge. Fortunately, research on the production of exosome mimics has made preliminary progress. Pisano *et al* (201) used monocytes as raw materials to produce exosome mimics through filters of different porosity and size exclusion chromatography columns. The development of immune-derived exosome mimics is expected to solve the problems of yield and reproducibility, which greatly improves the feasibility of applying exosomes to clinical trials (201).

The RNA, protein and lipid profiles of exosomes derived from different ovarian tumors are different, and the circular RNAs carried by ovarian tumor cell-derived exosomes are also different from healthy volunteers (134). In addition, serum exosomal piwi-interacting RNAs are considered to be a promising biomarker for patients with gastric cancer (202). Researchers have found that the detection level of CA125 in exosomes is higher compared with that in serum, which significantly improves the sensitivity of ovarian cancer diagnosis (203). This suggests that exosomes have the potential to become biomarkers for clinical analysis of ovarian cancer. With the development of biochips, microfluidic Raman biochips have been successfully used to monitor exosomes in prostate clinical serum samples (204). These devices can be similarly applied for ovarian cancer investigations based on exosomes.

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Authors' contributions

GYL designed the review. XL drafted the manuscript and prepared the figures. YL, TYZ, SSZ, JZZ, JW, and YS helped to modify the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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