Ovarian Cancer Peritoneal Metastasis: Exosomes and Mesothelial-to-Mesenchymal Transition

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Most patients with ovarian cancer (OvCA) present peritoneal disseminated disease at the time of diagnosis. During peritoneal metastasis, cancer cells detach from the primary tumor and disseminate through the intraperitoneal fluid. The peritoneal mesothelial cell (PMC) monolayer that lines the abdominal cavity is the first barrier encountered by OvCA cells. Subsequent progression of tumors through the peritoneum leads to the accumulation into the peritoneal stroma of a sizeable population of carcinoma-associated fibroblasts (CAFs), which is mainly originated from a mesothelial-to-mesenchymal transition (MMT) process. A common characteristic of OvCA patients is the intraperitoneal accumulation of ascitic fluid, which is composed of cytokines, chemokines, growth factors, miRNAs, and proteins contained in exosomes, as well as tumor and mesothelial suspended cells, among other components that vary in proportion between patients. Exosomes are small extracellular vesicles that have been shown to mediate peritoneal metastasis by educating a pre-metastatic niche, promoting the accumulation of CAFs via MMT, and inducing tumor growth and chemoresistance. This review summarizes and discusses the pivotal role of exosomes and MMT as mediators of OvCA peritoneal colonization and as emerging diagnostic and therapeutic targets.

Keywords: ovarian cancer ; peritoneal metastasis ; mesothelial-to-mesenchymal transition ; exosomes

1. Introduction

Worldwide, 314,000 new cases of ovarian cancer (OvCA) were diagnosed in 2020, with over 207,000 disease-related deaths. OvCA is the fifth leading cause of cancer-related deaths among women, and the second one amongst gynecologic cancers (following cervical cancer) [1]. Epithelial OvCA (EOC), also known as ovarian carcinoma, is the most common type, accounting for over 90% of the ovarian malignancies [2]. High-grade serous ovarian carcinoma (HGSOC) is the most common subtype, accounting for 70–75% of EOCs. Most HGSOC patients experience non-specific symptoms, and, usually at diagnosis, the tumor presents peritoneal extension [3]. The 5-year survival rate is only 29% for these patients with clinically advanced disease [4]. Cytoreductive surgery and platinum-based chemotherapy are the keystone therapy for advanced stage OvCA [5]. However, multidrug-resistant disease is still a major problem for the overall survival of these patients, critically needing new and extending windows of therapeutic opportunities [6].

In contrast to other cancers, which metastasize via hematogenous or lymphatic routes, OvCA mostly disseminates intraperitoneally due to the anatomic location of the primary tumor [7]. OvCA cells detach from the primary tumor and are transported by the peritoneal fluid, where they spread by colonizing the pelvic and abdominal peritoneum [8]. The membrane that lines the abdominal cavity and all peritoneal organs is formed by a monolayer of peritoneal mesothelial cells (PMCs) with epithelial characteristics that rests on an underlying stroma composed of extracellular matrix (ECM) and connective tissue with few capillaries and resident fibroblasts [9]. The accumulation of a sizeable population of carcinoma-associated fibroblasts (CAFs), which can derive from the PMCs through a mesothelial-to-mesenchymal transition (MMT) process, is an important effect of tumor nesting in the peritoneal membrane [10][11][12]. During MMT, PMCs first dissociate from each other in the monolayer, then lose their apical-basolateral polarity, and reorganize their actin cytoskeleton to progressively acquire migratory and invasive properties [13][14]. The mesothelial cell conversion into CAFs is the result of a complex cellular reprogramming, where diverse pathways can be triggered by multiple promoting stimuli. As a result of MMT, CAFs derived from PMCs synthesize ECM and secrete a variety of cytokines and growth factors that collectively promote tumor implantation, invasion, vascularization, and growth in the peritoneal stroma [10][11][12] (**Figure 1**).

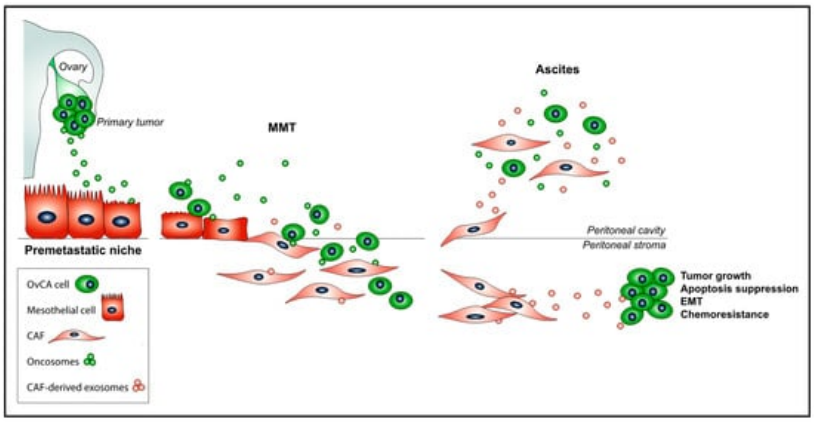

Figure 1. The promoting role of exosomes impinges on crucial steps of the OvCA peritoneal metastasis process: (i) Primary tumor-derived oncosomes educate a pre-metastatic peritoneal niche; (ii) during MMT, exosomes participate in the processes of adherence of OvCA cells to the mesothelium and co-invasion of OvCA cells and PMC-derived CAFs into the peritoneal stroma; and (iii) exosomes derived from CAFs induce EMT in tumor cells and suppress cancer cell apoptosis, as well as confer tumor growth and chemoresistance. Finally, OvCA cells, PMC-derived CAFs, and their, respectively, secreted exosomes are accumulated in the intraperitoneal ascitic fluid.

OvCA is often accompanied by intraperitoneal accumulation of ascitic fluid, which is associated with poor prognosis [8]. Within this intraperitoneal fluidic microenvironment, tumor cells, mesothelial-derived CAFs, and infiltrating leukocytes produce a multitude of factors, including but not limited to cytokines, chemokines, and growth factors [12][15][16][17][18][19]. These autocrine and paracrine soluble molecules form complex signaling networks that govern, in part, tumor-peritoneum interactions [11]. However, large quantities of both, tumorproduced exosomes (termed “oncosomes”) and CAF-secreted exosomes, have been found in malignant ascites from OvCA patients [20]. In fact, more and more studies point to exosomes as principal mediators of tumor-stroma crosstalk and suggest that these small extracellular vesicles play an important role in favoring peritoneal metastasis, through facilitating cell adhesion, invasion, angiogenesis, proliferation, immune evasion, and chemoresistance in OvCA (reviewed in Reference [21]).

Exosomes are a subtype of 30–150-nm-sized extracellular vesicles with endocytic origin that are released to the extracellular space upon fusion of intracellular multivesicular bodies with the plasma membrane [22]. Although the content of exosomes shows specificity to the cell of origin and depends, as well, on the functional state and regulated sorting mechanisms of the cell, common components including proteins, lipids, mRNAs, non-coding RNAs and DNA molecules, have been described for exosomes released by different cells (reviewed in Reference [23]). Exosomes are important vehicles of intercellular communication through the transfer of their cargo of proteins, nucleic acids, and lipids between donor and recipient cells [24][25]. The interaction with exosomes can induce direct stimulation of target cells, the transfer of membrane receptors, or the intracellular reception and integration of molecular information carried by exosomes in recipient cells.

2. The Role of Exosomes in Ovarian Cancer Peritoneal Metastasis

Tumors originating in the abdominal cavity, such as ovarian, endometrial, pancreatic, gastric, and colorectal cancers, frequently colonize the peritoneum [7]. Interestingly, exosome-related peritoneal metastasis mechanisms have been described for these types of cancer [21][23][24]. Exosomes can be found in almost all biological fluids, including serum, saliva, urine, amniotic fluid, breast milk, and seminal fluid [28][29][30][31][32]. In recent years, the detection of exosomes in serum samples of oncological patients has raised great interest, since they have been found to play crucial roles in tumorigenesis, progression, and metastasis in different cancers that mainly disseminate through the hematogenous or lymphatic routes [33][34][35][36]. However, in the context of peritoneal metastasis, the abundance of exosomes in intra-abdominal ascitic fluid acquires a special relevance. On this note, exosomes show up to 3–4-fold increased concentrations in the malignant ascites of ovarian carcinoma patients as compared to the peritoneal fluid of non-oncological individuals [25][26]. In OvCA, exosomes exert important roles, acting directly on cancer cells, facilitating their shedding from the primary tumor, promoting their survival in the peritoneal fluid, and favoring their attachment to the PMC monolayer and subsequent invasion into the underlying peritoneal stroma [39]. Additionally, exosomes participate in the process of peritoneal metastasis by mediating complex networks of intercellular communication between OvCA cells and resident cells of the peritoneal microenvironment. In this regard, exosomes participate in the formation of a peritoneal pre-metastatic niche susceptible of being subsequently metastasized through different mechanisms, including the conversion of PMCs into CAFs via MMT, inducing immunosuppression, and promoting tumor vascularization [21] (**Figure 1**). On the

other hand, an increasing number of studies point to exosomes as promising tools to improve OvCA outcome by reducing rates of peritoneal metastatic lesions, by facilitating early diagnosis and by interfering with tumor chemoresistance mechanisms (reviewed in References [40][27]).

3. Oncosomes and Their Recipient Target Cells in the Peritoneum: Peritoneal Mesothelial Cells

At the initial steps of peritoneal metastasis, OvCA cells directly encounter the monolayer formed by PMCs. Until recent years, it was believed that PMCs only acted as a passive mechanical barrier, avoiding tumor cell adhesion and invasion in the peritoneum and, as a consequence, preventing the formation of secondary tumor nodules into the submesothelial peritoneal stroma [28]. However, more recently, it has been reported that PMCs exert an active role in establishing a pre-metastatic niche required for the subsequent colonization of the peritoneum [29]. As in any distant metastatic process, peritoneal colonization requires the previous education of a pre-metastatic niche, a peritoneal microenvironment that favors the subsequent OvCA cell invasion through the submesothelium.

PMCs are considered the principal recipient target cells for a wide range of molecules packed in oncosomes, which are initially released to the peritoneal cavity from the primary tumor site. On this note, Yokoi et al. proposed a mechanism of apoptotic PMC death via OvCA-produced extracellular vesicles carrying MMP1 mRNA [25]. Undoubtedly, the destruction of the peritoneal mesothelium barrier facilitates the establishment of metastatic implants into the peritoneal stroma. Nevertheless, in the context of peritoneal metastasis, PMCs can be converted into CAFs through an MMT process [10][11][12]. In this regard, an increasing number of reports point to oncosomes as key mediators of peritoneal metastasis through the mesenchymal reprograming of PMCs [30][31]. In fact,Wei et al. revealed the expression of specific fibroblast markers, including fibroblast activation protein (FAP) and alpha-smooth muscle actin (α-SMA), in PMCs upon in vitro and in vivo treatments with malignant ascites-derived exosomes [30].

The MMT is a consequence of a sequential process [11], and oncosome-containing proteins have been noticed to play an important role in many MMT-related steps. On this note, TGF-β1 has been found to be overexpressed in malignant ascites-derived exosomes, therefore being proposed as the principal inducer of mesenchymal conversion in the peritoneum [30]. On the other hand, the molecule CD44, a cell surface glycoprotein, has been found to be enriched in EOC-derived exosomes [31]. Interestingly, CD44 has an important role in many cellular functions, such as cell-cell interaction, adhesion, migration, and metastasis [32][33][34][35][36]. CD44 mediates tumor cell adhesion to the mesothelial monolayer through its interaction with hyaluronic acid, and, indeed, this interaction partly mediates the adhesion of OvCA cells to the peritoneal membrane [35]. In OvCA peritoneal metastasis, CD44 is transferred in oncosomes to PMCs. As a consequence, PMCs are induced to secrete MMP9, promoting ECM remodeling, clearing the mesothelial barrier, and participating in OvCA cell invasion through the peritoneal membrane [31].

In addition to proteins, ascites-isolated exosomes contain a unique miRNA signature specific to OvCA cells [37][38][39]. In this regard, it has been described that miR-99a-5p is up-regulated in oncosomes and transferred to PMCs, where, in turn, it up-regulates the expression of ECM components, such as fibronectin and vitronectin [40]. Interestingly, these two matrix proteins have been involved in OvCA cell adhesion to, and invasion through, the mesothelial monolayer that lines the peritoneal cavity [41][42]. lncRNAs have also been found to take part in OvCA progression. For example, the lncRNA SPOCD1-AS, embedded in OvCA-secreted extracellular vesicles, is transported to recipient PMCs, inducing MMT-related changes via interacting with G3BP1 protein and enhancing peritoneal colonization [43]. Besides miRNAs and lncRNAs, the exosomal circular RNA (circRNA) circPUM1 has been recently reported to participate in the peritoneal progression of OvCA. CircPUM1 can exert its tumorigenic effects by acting directly on cancer cells, but it can also be released in oncosomes and transferred to PMCs, where it up-regulates both MMP2 and NF-B expression [44]. Zong et al. described how the circRNA circWHSC1 induces EOC metastasis by acting on the peritoneal mesothelium. CircWHSC1 is secreted by OvCA cells contained in exosomes and is taken up by PMCs, inducing up-regulation of MUC1 expression and MMT, which favors peritoneal tumor implantation [45] (**Figure 1**).

4. CAFs Generated via MMT Produce Exosomes That Impact on Recipient Target Ovarian Cancer Cells

While most studies are focused on oncosomes, little is known about exosomes released by cells of the surrounding tumor microenvironment and their effects in tumor progression at secondary metastatic sites.

Solid tumors are complex and unstructured organs that, in addition to cancer cells, also contain stromal cell types. It is known that CAFs represent an important population in the tumor microenvironment and participate in providing a suitable ECM and blood vessel formation to support tumor cell survival at secondary metastatic sites [46]. Furthermore, in the last

few years, a number of studies have provided critical evidence regarding the significance of exosome-mediated intercellular crosstalk between CAFs and cancer cells for tumor progression [47]. For instance, in OvCA, it has been reported that CAF-derived exosomal miR-98-5p increases tumor cell proliferation and cell cycle entry, as well as confer cisplatin resistance, by targeting CDKN1A [48].

The origin of peritoneal CAFs associated with OvCA metastasis has been the subject of intense debate. However, our group demonstrated, for the first time, that an important proportion of CAFs, in peritoneal OvCA tumor implants, derives from PMCs as a consequence of an MMT process [10][11][12]. Regardless their origin, peritoneal CAFs can produce and secrete exosomes containing molecules that can be transferred, in turn, to tumor cells. On this note, it has been observed that omental CAF-derived exosomes are enriched in TGF-β1, which can be transferred to OvCA cells, triggering the acquisition of a more aggressive tumoral phenotype through undergoing EMT-related changes [49]. Interestingly, TGF-β1 has been found to be significantly up-regulated in MMT-derived CAFs isolated from the ascitic fluid of OvCA patients as compared to normal PMCs, suggesting that targeting exosomes secreted by PMCs undergoing MMT could be a potential mechanism to be interfered in the treatment of peritoneal metastasis [12]. On the other hand, Au Yeung et al. showed that miR21, a very recently identified cargo biomolecule in CAF-derived exosomes [47], is transferred from neighboring stromal cells in the omental tumor microenvironment (including CAFs and cancer-associated adipocytes) to cancer cells, where it suppresses OvCA apoptosis and confers chemoresistance by binding to its direct target APAF1 [50]. Accordingly, miR-21 has been identified as one of the most abundant miRNAs in PMCs, exhibiting mesenchymal changes upon TGF-β1 stimulation, thus providing a novel approach in the context of peritoneal carcinomatosis [51] (**Figure 1**).

5. Exosomes in the Diagnosis, Prognosis, and Therapy of Ovarian Cancer Peritoneal Metastasis

The majority of women with EOC present peritoneal metastasis at the time of diagnosis. The metastatic process, however, starts long before secondary cancer implants are detected. Exosomes derived from the primary tumor prepare a cancer-favorable microenvironment in the pre-metastatic niche before the target organ is already colonized [52]. On this note, OvCA-secreted exosomes from the primary site could represent a unique opportunity to assist patients in the early detection of peritoneal dissemination. As an example, oncosomes isolated from OvCA patients carried TGF-β1, which distinguished OvCA patients from those with benign lesions [53]. Interestingly, despite their elevated TGF-β1 production, this factor has limited effects in OvCA cells, being that its contribution to peritoneal metastasis is mainly mediated through activation of Smad3-dependent TGF-β1-signaling in surrounding PMC-derived CAFs [12][54]. Moreover, high levels of oncosomal CA125 and claudin-4 have been detected in OvCA patients, significantly contributing to improved diagnosis [55]. Im et al. developed a nano-plasmonic sensor to identify oncosomes expressing CD24 and EpCAM in malignant ascites samples from OvCA patients, highlighting their potential for diagnostics [20]. Alternatively, a large battery of miRNAs has been described to be highly dysregulated in exosomes of patients with EOC [37][38][56][57][58]. Therefore, the oncosomal miRNA profiling could also be highly informative for the early diagnosis of OvCA peritoneal metastasis.

On the other hand, OvCA malignant ascites-derived exosomes display a cargo of tumor progression related proteins, such as L1CAM, CD24, ADAM10, and EMMPRIN, which have been found to correlate with worse prognosis [59]. After completion of first-line treatment, chemoresistance frequently develops, and recurrent peritoneal malignant disease is subsequently observed; this development of chemoresistance by tumor cells is a major hurdle in the treatment of OvCA. In this regard, oncosomal cargoes could also have the potential to serve as prognostic biomarkers of chemoresistance in patients with peritoneal carcinomatosis as exosomes have been proposed to play a pivotal role in the acquisition of chemotherapy resistance by OvCA cells. They have been found to mediate the acquisition of the chemoresistant phenotype in OvCA cells through multiple mechanisms, including inhibition of apoptosis, enhanced DNA repair, increased drug effluxion through the transfer of multidrug resistance (MDR) transporters, and by reducing the cellular concentration of chemotherapeutic drugs in tumoral donor cells through their expulsion in these vesicles (reviewed in References [27][60][61]. Several proteins have been found to be overexpressed in exosomes produced by chemoresistant OvCA cells, including Annexin A3 [62][62], cisplatin export transporters (MRP2 and ATP7A/B) [63], DNA methyltransferase 1 (DNMT1) [64], EpCAM [65][66], and MAGE3/6 [53]. In addition, acquired SMAD4 mutations enhance the chemoresistance profile of epithelial OvCA cells, representing a mechanism in which exchange of tumor-derived exosomes perpetuates an EMT phenotype, leading to the development of subpopulations of platinum-refractory tumor cells [67]. In addition, some miRNAs have also been found to be overexpressed in OvCA tumor chemoresistance, including miR-21-3p [68], miR21[50], miR-433 [69], miR-1246, and miR-223 [70], which could bear potential diagnostic and prognostic value for patients [68].

The singular condition of the peritoneal cavity microenvironment not only affects the chemoresistant oncosome profile but also the amount of CAF-secreted exosomes, and their cargo could be particularly relevant from a prognostic standpoint [20]. Little is known about the value of exosomes produced by MMT-derived CAFs to predict peritoneal tumor progression

or therapeutic response to chemotherapy in patients with advanced OvCA. Intriguingly, Rafii et al. isolated from ascites of OvCA patients a particular type of cells with common characteristics to MCs, referred to as “Hospicells”. These cells represent a differentiated stromal subset of mesenchymal stem cells with expression of multi-drug resistance proteins. Hospicells preferentially interact with EOC cells, inducing their chemoresistance to platin and taxanes through the capture of stromal cell membrane patches by a process termed onco-trogocytosis [71]. This work led us to speculate that PMC-derived CAFs could transfer information to OvCA cells by an exosome-dependent mechanism in order to confer them a chemo-resistant phenotype. Accordingly, miR-21 is transferred in exosomes from peritoneal CAFs to cancer cells, where it suppresses OvCA apoptosis and confers chemoresistance, as it is mentioned before [50]. On this note, miR-21, known for its pro-oncogenic and pro-fibrotic activities, is highly present in OvCA-associated acites [72]. Effusion fluid-derived exosomes containing miR-21 have been associated to TGF-β-related pathways, extracellular matrix-receptor interaction, mesothelial clearance and worse prognosis value in metastatic OvCA [56]. Therefore, the detection of exosomes containing miR-21 could improve prognosis in OvCA peritoneal metastasis.

Exosomes are continuously being investigated for their applications in the therapeutic field, and, increasingly, novel options for exploiting exosomes in the treatment of OvCA peritoneal metastases are emerging [73][74]. For example, interfering with exosomal secretion or uptake mechanisms could represent an important target for therapeutical intervention. On this note, drug-resistant OvCA cells abnormally sort some lysosomal proteins showing enhanced exosomal export of cisplatin, thus this being a characteristic to be explored as a target in advanced OvCA patients [63]. Samuel et al. described that cisplatin treatment of OvCA cells led to the release of extracellular vesicles that could induce invasion and increased resistance via p38 and JNK signaling when taken up by neighboring unstressed tumor cell populations. In addition, extracellular vesicle uptake inhibitors prevented this extracellular vesicle-mediated crosstalk and, thus, sensitized cancer cells to the effects of chemotherapy [75][76]. Alternatively, removal of exosomes from malignant ascites could also contribute to improve OvCA clinical outcome. De la Fuente et al. employed exosomes purified from the ascitic fluid of OvCA patients in a murine model of peritoneal metastasis as traps to interfere with tumor cell peritoneal attachment [77]. On the other hand, interfering with the exosome-mediated MMT process could be highly advantageous in the context of peritoneal metastasis. On this note, hepatocyte growth factor (HGF) has been validated as an exosome-contained protein of interest in HGSOC patients [78]. In addition, OvCA-produced HGF is known to transform the peritoneum via MMT into a more suitable niche for subsequent tumor invasion [11][79][80]. Interestingly, siRNA against HGF packed in exosomes has been described to be transported into tumor cells metastasizing peritoneum, suppressing proliferation and migration [81]. These data lead us to speculate that exosomes delivering MMT-blocking drugs could have potential therapeutic value in OvCA peritoneal metastasis.

6. Conclusions

Development of peritoneal carcinomatosis is a frequent outcome in OvCA patients, which still today represents mostly a deadly incurable stage of this disease, despite the improved surgical and chemotherapeutic approaches resulting in increased progression-free disease intervals achieved in these patients over the past 30 years. A better understanding of the precise roles played by peritoneal exosomes released by tumor and stromal cells and of the mechanisms by which these extracellular vesicles deliver their biomolecular cargoes and alter the properties of recipient target cells is urgently needed. Furthermore, exosomes in OvCA are increasingly becoming recognized as key players in the conversion of PMCs into tumor-promoting CAFs through an MMT reprogramming process, which has important implications in the pathogenesis of the disease. This new knowledge on exosomes in OvCA will undoubtedly lead to the development of novel disease biomarkers, leading to earlier diagnostic procedures, and will open novel and more effective therapeutic avenues, which will collectively improve the clinical management of these women and the survival rates of this disease.

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