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

Subjects: Biochemistry & Molecular Biology | Oncology | Obstetrics & Gynaecology

Contributor: Pilar Sandoval

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.

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**).

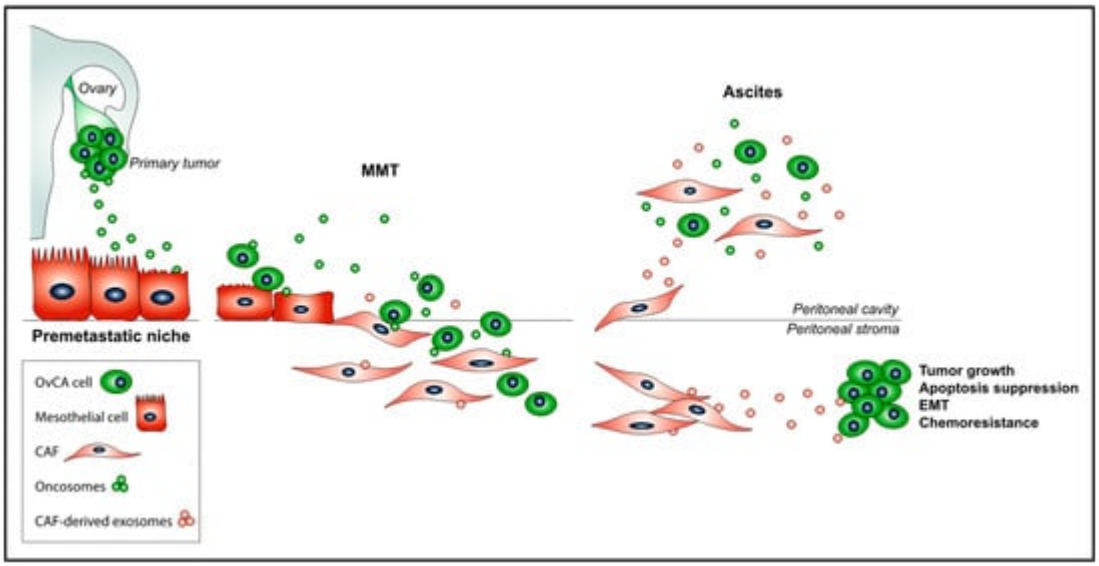

Figure 1. The promoting role of exosomes impinges on crucial steps of the OvCA peritoneal metastasis process: (i) Primary tumor-derived oncosomes educate a pre-metastatic peritoneal niche; (ii) during MMT, exosomes participate in the processes of adherence of OvCA cells to the mesothelium and co-invasion 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.

References

1. Hyuna Sung; Jacques Ferlay; Rebecca L. Siegel; Mathieu Laversanne; Isabelle Soerjomataram; Ahmedin Jemal; Freddie Bray; Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians* **2021**, *71*, 209-249, 10.3322/caac.21660.
2. A.P.M. Heintz; F. Odicino; P. Maisonneuve; U. Beller; J.L. Benedet; W.T. Creasman; H.Y.S. Ngan; S. Pecorelli; Carcinoma of the ovary. *International Journal of Gynecology & Obstetrics* **2003**, *83*, 135-166, 10.1016/s0020-7292(03)90118-4.
3. Martin Köbel; Steve E. Kalloger; David G. Huntsman; Jennifer L. Santos; Kenneth D. Swenerton; Jeffrey D. Seidman; C. Blake Gilks; Differences in Tumor Type in Low-stage Versus High-stage Ovarian Carcinomas. *International Journal of Gynecological Pathology* **2010**, *29*, 203-211, 10.1097/pgp.0b013e3181c042b6.
4. Rebecca L. Siegel; Kimberly D. Miller Mph; Ahmedin Jemal; Cancer statistics, 2019. *CA: A Cancer Journal for Clinicians* **2018**, *69*, 7-34, 10.3322/caac.21551.
5. Eric L. Eisenhauer; Nadeem R. Abu-Rustum; Yukio Sonoda; Carol Aghajanian; Richard R. Barakat; Dennis S. Chi; The effect of maximal surgical cytoreduction on sensitivity to platinum-taxane chemotherapy and subsequent survival in patients with advanced ovarian cancer. *Gynecologic Oncology* **2008**, *108*, 276-281, 10.1016/j.ygyno.2007.10.022.
6. J. McGee; M. Bookman; P. Harter; C. Marth; Iain McNeish; K. N. Moore; A. Poveda; F. Hilpert; K. Hasegawa; M. Bacon; et al.C. GatsonisA. BrandF. KridelkaJ. BerekN. OttevangerT. LevyS. SilverbergB.-G. KimH. HirteA. OkamotoG. StuartK. Ochiai Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors. *Annals of Oncology* **2017**, *28*, 702-710, 10.1093/annonc/mdx010.
7. Desai, J.P.; Moustarah, F.. Peritoneal Metastasis; StatPearls: Treasure Island: FL, USA, 2021; pp. Jan–.

8. David Sp Tan; Roshan Agarwal; Stanley B Kaye; Mechanisms of transcoelomic metastasis in ovarian cancer. *The Lancet Oncology* **2006**, *7*, 925-934, 10.1016/s1470-2045(06)70939-1.
9. N Di Paolo; G Sacchi; Atlas of peritoneal histology.. *Peritoneal Dialysis International: Journal of the International Society for Peritoneal Dialysis* **2000**, *20*, Suppl 3:S5-96.
10. Pilar Sandoval; Jose Antonio Jiménez-Heffernan; Angela Rynne-Vidal; Maria-Luisa Pérez Lozano; Álvaro Gilsanz; Vicente Ruiz-Carpio; Raquel Reyes; Julio García-Bordas; Konstantinos Stamatakis; Javier Dotor; et al.Pedro L MajanoManuel FresnoCarlos CabañasManuel López-Cabrera Carcinoma-associated fibroblasts derive from mesothelial cells via mesothelial-to-mesenchymal transition in peritoneal metastasis. *The Journal of Pathology* **2013**, *231*, 517-531, 10.1002/path.4281.
11. Angela Rynne-Vidal; José Antonio Jiménez-Heffernan; Concepción Fernández-Chacón; Manuel López-Cabrera; Pilar Sandoval; The Mesothelial Origin of Carcinoma Associated-Fibroblasts in Peritoneal Metastasis. *Cancers* **2015**, *7*, 1994-2011, 10.3390/cancers7040872.
12. Angela Rynne-Vidal; Chi Lam Au-Yeung; José A Jiménez-Heffernan; Maria-Luisa Pérez Lozano; Lucía Cremades-Jimeno; Carmen Bárcena; Ignacio Cristobal; Concepción Fernández-Chacón; Tsz Lun Yeung; Samuel C Mok; et al.Pilar SandovalManuel López-Cabrera Mesothelial-to-mesenchymal transition as a possible therapeutic target in peritoneal metastasis of ovarian cancer. *The Journal of Pathology* **2017**, *242*, 140-151, 10.1002/path.4889.
13. María Yáñez-Mó; Enrique Lara-Pezzi; Rafael Selgas; Marta Ramírez-Huesca; Carmen Domínguez-Jiménez; José A. Jiménez-Heffernan; Abelardo Aguilera; José A. Sánchez-Tomero; M. Auxiliadora Bajo; Vincente Álvarez; et al.M. Angeles CastroGloria Del PesoAntonio CirujedaCarlos GamalloFrancisco Sánchez-MadridManuel López-Cabrera Peritoneal Dialysis and Epithelial-to-Mesenchymal Transition of Mesothelial Cells. *New England Journal of Medicine* **2003**, *348*, 403-413, 10.1056/nejmoa020809.
14. Vicente Ruiz-Carpio; Pilar Sandoval; Abelardo Aguilera; Patricia Albar-Vizcaíno; Maria-Luisa Pérez Lozano; Guadalupe Tirma González-Mateo; Adrián Acuña-Ruiz; Jesus Garcia-Cantalejo; Pedro Botías; María Auxiliadora Bajo; et al.Rafael SelgasJosé Antonio Sánchez-TomeroJutta Passlick-DeetjenDorothea PiechaJanine BüchelSonja SteppanManuel López-Cabrera Genomic reprograming analysis of the Mesothelial to Mesenchymal Transition identifies biomarkers in peritoneal dialysis patients. *Scientific Reports* **2017**, *7*, srep44941, 10.1038/srep44941.
15. Emma Kipps; David Tan; Stan B. Kaye; Meeting the challenge of ascites in ovarian cancer: new avenues for therapy and research. *Nature Reviews Cancer* **2013**, *13*, 273-282, 10.1038/nrc3432.
16. Vanessa M. Peterson; Cesar M. Castro; Jaehoon Chung; Nathan C. Miller; Adeeti V. Ullal; Maria D. Castano; Richard T. Penson; Hakho Lee; Michael J. Birrer; Ralph Weissleder; et al. Ascites analysis by a microfluidic chip allows tumor-cell profiling. *Proceedings of the National Academy of Sciences* **2013**, *110*, E4978-E4986, 10.1073/pnas.1315370110.

17. Qinglei Gao; Zongyuan Yang; Sen Xu; Xiaoting Li; Xin Yang; Ping Jin; Yi Liu; Xiaoshui Zhou; Taoran Zhang; Cheng Gong; et al.Xiao WeiDan LiuChaoyang SunGang ChenJunbo HuLi MengJianfeng ZhouKenjiro SawadaRobert FruscioThomas W. GruntJörg WischhusenVíctor Manuel Vargas-HernándezBhavana PothuriRobert L. Coleman Correction: Heterotypic CAF-tumor spheroids promote early peritoneal metastatis of ovarian cancer. *Journal of Experimental Medicine* **2019**, *216*, 2448-2448, 10.1084/jem.2018076508222019c.

18. Qing Han; Bangxing Huang; Zaiju Huang; Jing Cai; Lanqing Gong; Yifan Zhang; Jiahong Jiang; Weihong Dong; Zehua Wang; Tumor cell-fibroblast heterotypic aggregates in malignant ascites of patients with ovarian cancer. *International Journal of Molecular Medicine* **2019**, *44*, 2245-2255, 10.3892/ijmm.2019.4361.

19. Tongtong Kan; Wei Wang; Philip P. Ip; Shengtao Zhou; Alice S. Wong; Xin Wang; Mengsu Yang; Single-cell EMT-related transcriptional analysis revealed intra-cluster heterogeneity of tumor cell clusters in epithelial ovarian cancer ascites. *Oncogene* **2020**, *39*, 4227-4240, 10.1038/s41388-020-1288-2.

20. Hyungsoon Im; Huilin Shao; Yong Il Park; Vanessa M. Peterson; Cesar M. Castro; Ralph Weissleder; Hakho Lee; Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. *Nature Biotechnology* **2014**, *32*, 490-495, 10.1038/nbt.2886.

21. Wenlong Feng; Dylan C. Dean; Francis J. Hornicek; Huirong Shi; Zhenfeng Duan; Exosomes promote pre-metastatic niche formation in ovarian cancer. *Molecular Cancer* **2019**, *18*, 1-11, 10.1186/s12943-019-1049-4.

22. María Yáñez-Mó; Pia R.-M. Siljander; Zoraida Andreu; Apolonija Bedina Zavec; Francesc E. Borras; Edit I. Buzas; Krisztina Buzas; Enriqueta Casal; Francesco Cappello; Joana Carvalho; et al.Eva ColasAnabela Cordeiro-Da-SilvaStefano FaisJuan M. Falcon-PerezIrene M. GhobrialBernd GiebelMario GimonaMichael GranerIhsan GurselMayda GurselNiels H. H. HeegaardAn HendrixPeter KierulfKatsutoshi KokubunMaja KosanovićVeronika Kralj-IglicEva-Maria Krämer-AlbersSaara LaitinenCecilia LässerThomas LenerErzsébet LigetiAija LinēGeorg LippsAlicia LlorenteJan LötvallMateja Manček-KeberAntonio MarcillaMaría MittelbrunnIrina NazarenkoEsther N.M. Nolte-‘T HoenTuula NymanLorraine O'DriscollMireia OlivanCarla OliveiraÉva PállingerHernando A. Del PortilloJaume ReventósMarina RigauEva RohdeMarei SammarFrancisco Sánchez-MadridNuno SantaremKatharina SchallmoserMarie Stampe OstenfeldWillem StoorvogelRoman StukeljSusanne G. Van Der GreinM. Helena VasconcelosMarca WaubenOlivier De Wever Biological properties of extracellular vesicles and their physiological functions. *Journal of Extracellular Vesicles* **2015**, *4*, 27066, 10.3402/jev.v4.27066.

23. Simona Serratì; Letizia Porcelli; Francesco Fragassi; Marianna Garofoli; Roberta Di Fonte; Livia Fucci; Rosa Iacobazzi; Antonio Palazzo; Francesca Margheri; Grazia Cristiani; et al.Anna AlbanoRaffaele De LucaDonato AltomareMichele SimoneAmalia Azzariti The Interaction between

Reactive Peritoneal Mesothelial Cells and Tumor Cells via Extracellular Vesicles Facilitates Colorectal Cancer Dissemination. *Cancers* **2021**, *13*, 2505, 10.3390/cancers13102505.

24. Jing Gao; Song Li; Qian Xu; Xue Zhang; Miao Huang; Xin Dai; Lian Liu; Exosomes Promote Pre-Metastatic Niche Formation in Gastric Cancer. *Frontiers in Oncology* **2021**, *11*, 652378, 10.3389/fonc.2021.652378.
25. Emanuela Carollo; Bianca Paris; Priya Samuel; Paschalia Pantazi; Thais Fernanda Bartelli; Emmanuel Dias-Neto; Susan Ann Brooks; Ryan Charles Pink; David Raul Francisco Carter; Detecting ovarian cancer using extracellular vesicles: progress and possibilities. *Biochemical Society Transactions* **2019**, *47*, 295-304, 10.1042/bst20180286.
26. Xiaoduan Li; Xipeng Wang; The emerging roles and therapeutic potential of exosomes in epithelial ovarian cancer. *Molecular Cancer* **2017**, *16*, 1-10, 10.1186/s12943-017-0659-y.
27. Jiayu Shen; Xiaoqing Zhu; Jing Fei; Pengyao Shi; Shuqian Yu; Jianwei Zhou; Advances of exosome in the development of ovarian cancer and its diagnostic and therapeutic prospect. *OncoTargets and Therapy* **2018**, *ume 11*, 2831-2841, 10.2147/ott.s159829.
28. Ernst Lengyel; Ovarian Cancer Development and Metastasis. *The American Journal of Pathology* **2010**, *177*, 1053-1064, 10.2353/ajpath.2010.100105.
29. Hilary A. Kenny; Kristin Nieman; Anirban K. Mitra; Ernst Lengyel; The First Line of Intra-abdominal Metastatic Attack: Breaching the Mesothelial Cell Layer: Figure 1.. *Cancer Discovery* **2011**, *1*, 100-102, 10.1158/2159-8290.cd-11-0117.
30. Mingtian Wei; Tinghan Yang; Xiangzheng Chen; Yangping Wu; Xiangbing Deng; Wanbin He; Jinliang Yang; Ziqiang Wang; Malignant ascites-derived exosomes promote proliferation and induce carcinoma-associated fibroblasts transition in peritoneal mesothelial cells. *Oncotarget* **2017**, *8*, 42262-42271, 10.18632/oncotarget.15040.
31. Koji Nakamura; Kenjiro Sawada; Yasuto Kinose; Akihiko Yoshimura; Aska Toda; Erika Nakatsuka; Kae Hashimoto; Seiji Mabuchi; Ken-Ichirou Morishige; Hirohisa Kurachi; et al.Ernst LengyelTadashi Kimura Exosomes Promote Ovarian Cancer Cell Invasion through Transfer of CD44 to Peritoneal Mesothelial Cells. *Molecular Cancer Research* **2016**, *15*, 78-92, 10.1158/1541-7786.mcr-16-0191.
32. Khashayar Lessan; Dean J. Aguiar; Theodore Oegema; Lisa Siebenson; Amy P.N. Skubitz; CD44 and β1 Integrin Mediate Ovarian Carcinoma Cell Adhesion to Peritoneal Mesothelial Cells. *The American Journal of Pathology* **1999**, *154*, 1525-1537, 10.1016/s0002-9440(10)65406-5.
33. T Strobel; L Swanson; S A Cannistra; In vivo inhibition of CD44 limits intra-abdominal spread of a human ovarian cancer xenograft in nude mice: a novel role for CD44 in the process of peritoneal implantation.. *Cancer Research* **1997**, *57*, 1228–1232.

34. Youngmi Kim; Yun-Sil Lee; Jongseon Choe; Hansoo Lee; Young-Myeong Kim; Dooil Jeoung; CD44-Epidermal Growth Factor Receptor Interaction Mediates Hyaluronic Acid-promoted Cell Motility by Activating Protein Kinase C Signaling Involving Akt, Rac1, Phox, Reactive Oxygen Species, Focal Adhesion Kinase, and MMP-2. *Journal of Biological Chemistry* **2008**, *283*, 22513-22528, 10.1074/jbc.m708319200.

35. M. J. Gardner; J. B. Catterall; L. M. H. Jones; G. A. Turner; Human ovarian tumour cells can bind hyaluronic acid via membrane CD44: a possible step in peritoneal metastasis. *Clinical & Experimental Metastasis* **1996**, *14*, 325-334, 10.1007/bf00123391.

36. Lilly Y. W. Bourguignon; Hongbo Zhu; Bo Zhou; Falko Diedrich; Patrick A. Singleton; Mien-Chie Hung; Hyaluronan Promotes CD44v3-Vav2 Interaction with Grb2-p185HER2 and Induces Rac1 and Ras Signaling during Ovarian Tumor Cell Migration and Growth. *Journal of Biological Chemistry* **2001**, *276*, 48679-48692, 10.1074/jbc.m106759200.

37. Douglas D. Taylor; Cicek Gercel-Taylor; MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecologic Oncology* **2008**, *110*, 13-21, 10.1016/j.ygyno.2008.04.033.

38. Marilena Iorio; Rosa Visone; Gianpiero Di Leva; Valentina Donati; Fabio Petrocca; Patrizia Casalini; Cristian Taccioli; Stefano Volinia; Chang-Gong Liu; Hansjuerg Alder; et al.George CalinSylvie MénardCarlo M. Croce MicroRNA Signatures in Human Ovarian Cancer. *Cancer Research* **2007**, *67*, 8699-8707, 10.1158/0008-5472.can-07-1936.

39. Weiwei Wang; Li-Rong Wu; Chunyu Li; Xin Zhou; Ping Liu; Xuemei Jia; Yan Chen; Wei Zhu; Five serum microRNAs for detection and predicting of ovarian cancer. *European Journal of Obstetrics & Gynecology and Reproductive Biology: X* **2019**, *3*, 100017, 10.1016/j.eurox.2019.100017.

40. Akihiko Yoshimura; Kenjiro Sawada; Koji Nakamura; Yasuto Kinose; Erika Nakatsuka; Masaki Kobayashi; Mayuko Miyamoto; Kyoso Ishida; Yuri Matsumoto; Michiko Kodama; et al.Kae HashimotoSeiji MabuchiTadashi Kimura Exosomal miR-99a-5p is elevated in sera of ovarian cancer patients and promotes cancer cell invasion by increasing fibronectin and vitronectin expression in neighboring peritoneal mesothelial cells. *BMC Cancer* **2018**, *18*, 1-13, 10.1186/s12885-018-4974-5.

41. Hilary A. Kenny; Chun-Yi Chiang; Erin A. White; Elizabeth M. Schryver; Mohammed Habis; Iris Romero; Andras Ladanyi; Carla V. Penicka; Joshy George; Karl Matlin; et al.Anthony MontagKristen WroblewskiS. Diane YamadaAndrew P. MazarDavid BowtellErnst Lengyel Mesothelial cells promote early ovarian cancer metastasis through fibronectin secretion. *Journal of Clinical Investigation* **2014**, *124*, 4614-4628, 10.1172/jci74778.

42. Loraine Heyman; Sabrina Kellouche; Julien Fernandes; Soizic Dutoit; Laurent Poulain; Franck Carreiras; Vitronectin and Its Receptors Partly Mediate Adhesion of Ovarian Cancer Cells to Peritoneal Mesothelium in vitro. *Tumor Biology* **2008**, *29*, 231-244, 10.1159/000152941.

43. Conghui Wang; Jiaying Wang; Xiameng Shen; Mingyue Li; Yongfang Yue; Xiaodong Cheng; Weiguo Lu; Xinyu Wang; Xing Xie; LncRNA SPOCD1-AS from ovarian cancer extracellular vesicles remodels mesothelial cells to promote peritoneal metastasis via interacting with G3BP1. *Journal of Experimental & Clinical Cancer Research* **2021**, *40*, 1-18, 10.1186/s13046-021-01899-6.

44. Xue Guan; Zhi-Hong Zong; Yao Liu; Shuo Chen; Li-Li Wang; Yang Zhao; circPUM1 Promotes Tumorigenesis and Progression of Ovarian Cancer by Sponging miR-615-5p and miR-6753-5p. *Molecular Therapy - Nucleic Acids* **2019**, *18*, 882-892, 10.1016/j.omtn.2019.09.032.

45. Zhi-Hong Zong; Yu-Ping Du; Xue Guan; Shuo Chen; Yang Zhao; CircWHSC1 promotes ovarian cancer progression by regulating MUC1 and hTERT through sponging miR-145 and miR-1182. *Journal of Experimental & Clinical Cancer Research* **2019**, *38*, 1-10, 10.1186/s13046-019-1437-z.

46. Leilei Tao; Guichun Huang; Haizhu Song; Yitian Chen; Longbang Chen; Cancer associated fibroblasts: An essential role in the tumor microenvironment. *Oncology Letters* **2017**, *14*, 2611-2620, 10.3892/ol.2017.6497.

47. Tong Su; Panpan Zhang; Fujun Zhao; Shu Zhang; Exosomal MicroRNAs Mediating Crosstalk Between Cancer Cells With Cancer-Associated Fibroblasts and Tumor-Associated Macrophages in the Tumor Microenvironment. *Frontiers in Oncology* **2021**, *11*, 631703, 10.3389/fonc.2021.631703.

48. Hua Guo; Chunfang Ha; Hui Dong; Zhijuan Yang; Yuan Ma; Yonghui Ding; Cancer-associated fibroblast-derived exosomal microRNA-98-5p promotes cisplatin resistance in ovarian cancer by targeting CDKN1A. *Cancer Cell International* **2019**, *19*, 1-15, 10.1186/s12935-019-1051-3.

49. Wenqian Li; Xiaoxue Zhang; Ji Wang; Mengchen Li; Canhui Cao; Jiahong Tan; Ding Ma; Qinglei Gao; TGFβ1 in fibroblasts-derived exosomes promotes epithelial-mesenchymal transition of ovarian cancer cells. *Oncotarget* **2017**, *8*, 96035-96047, 10.18632/oncotarget.21635.

50. Chi Lam Au Yeung; Ngai-Na Co; Tetsushi Tsuruga; Tsz-Lun Yeung; Suet Ying Kwan; Cecilia S. Leung; Yong Li; Edward S. Lu; Kenny Kwan; Kwong-Kwok Wong; et al.Rosemarie SchmandtKaren H. LuSamuel C. Mok Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1. *Nature Communications* **2016**, *7*, 11150-11150, 10.1038/ncomms11150.

51. Melisa Lopez-Anton; Mark Lambie; Manuel Lopez-Cabrera; Claus P. Schmitt; Vicente Ruiz-Carpio; Maria Bartosova; Betti Schaefer; Simon Davies; Timothy Stone; Robert Jenkins; et al.Philip TaylorNicholas TopleyTimothy BowenDonald Fraser miR-21 Promotes Fibrogenesis in Peritoneal Dialysis. *The American Journal of Pathology* **2017**, *187*, 1537-1550, 10.1016/j.ajpath.2017.03.007.

52. Mohammed Akhtar; AbdulRazzaq Haider; Sameera Rashid; Ajayeb Dakhilalla M.H. Al-Nabet; Paget’s “Seed and Soil” Theory of Cancer Metastasis: An Idea Whose Time has Come. *Advances*

in Anatomic Pathology **2019**, *26*, 69-74, 10.1097/pap.0000000000000219.

53. Marta Szajnik Magdalena Derbis; Exosomes in Plasma of Patients with Ovarian Carcinoma: Potential Biomarkers of Tumor Progression and Response to Therapy. *Gynecology & Obstetrics* **2012**, *s4*, 003, 10.4172/2161-0932.s4-003.
54. Tsz-Lun Yeung; Cecilia S. Leung; Kwong-Kwok Wong; Goli Samimi; Melissa S. Thompson; Jinsong Liu; Tarrik M. Zaid; Sue Ghosh; Michael J. Birrer; Samuel C. Mok; et al. TGF-β Modulates Ovarian Cancer Invasion by Upregulating CAF-Derived Versican in the Tumor Microenvironment. *Cancer Research* **2013**, *73*, 5016-5028, 10.1158/0008-5472.can-13-0023.
55. Jianghong Li; Cheryl A Sherman-Baust; Miyun Tsai-Turton; Robert E Bristow; Richard B Roden; Patrice J Morin; Claudin-containing exosomes in the peripheral circulation of women with ovarian cancer. *BMC Cancer* **2009**, *9*, 244-244, 10.1186/1471-2407-9-244.
56. Olga Vaksman; Claes Tropé; Ben Davidson; Reuven Reich; Exosome-derived miRNAs and ovarian carcinoma progression. *Carcinogenesis* **2014**, *35*, 2113-2120, 10.1093/carcin/bgu130.
57. Vu Hong Loan Nguyen; Chenyang Yue; Kevin Y. Du; Mohamed Salem; Jacob O'Brien; Chun Peng; The Role of microRNAs in Epithelial Ovarian Cancer Metastasis. *International Journal of Molecular Sciences* **2020**, *21*, 7093, 10.3390/ijms21197093.
58. Soudeh Ghafouri-Fard; Hamed Shoorei; Mohammad Taheri; miRNA profile in ovarian cancer. *Experimental and Molecular Pathology* **2020**, *113*, 104381, 10.1016/j.yexmp.2020.104381.
59. Sascha Keller; Anne-Kathleen König; Frederik Marmé; Steffen Runz; Silke Wolterink; Dominique Koensgen; Alexander Mustea; Jalid Sehouli; Peter Altevogt; Systemic presence and tumor-growth promoting effect of ovarian carcinoma released exosomes. *Cancer Letters* **2009**, *278*, 73-81, 10.1016/j.canlet.2008.12.028.
60. Mona Alharbi; Felipe A. Zuniga; Omar Elfeky; Dominic Guanzon; Andrew Lai; Gregory E Rice; Lewis Perrin; John Hooper; Carlos Salomon; The potential role of miRNAs and exosomes in chemotherapy in ovarian cancer. *Endocrine-Related Cancer* **2018**, *25*, R663-R685, 10.1530/erc-18-0019.
61. Teresa Bernadette Steinbichler; Jozsef Dudas; Sergej Skvortsov; Ute Ganswindt; Herbert Riechelmann; Ira-Ida Skvortsova; Therapy resistance mediated by exosomes. *Molecular Cancer* **2019**, *18*, 1-11, 10.1186/s12943-019-0970-x.
62. Jie Yin; Xuedong Yan; Xin Yao; Yongli Zhang; Ying Shan; Ning Mao; Yili Yang; Lingya Pan; Secretion of annexin A3 from ovarian cancer cells and its association with platinum resistance in ovarian cancer patients. *Journal of Cellular and Molecular Medicine* **2011**, *16*, 337-348, 10.1111/j.1582-4934.2011.01316.x.
63. Roohangiz Safaei; Barrett J. Larson; Timothy C. Cheng; Michael A. Gibson; Shinji Otani; Wiltrud Naerdemann; Stephen B. Howell; Abnormal lysosomal trafficking and enhanced exosomal export

of cisplatin in drug-resistant human ovarian carcinoma cells. *Molecular Cancer Therapeutics* **2005**, *4*, 1595-1604, 10.1158/1535-7163.mct-05-0102.

64. Ya-Lei Cao; Ting Zhuang; Bao-Heng Xing; Na Li; Qin Li; Exosomal DNMT1 mediates cisplatin resistance in ovarian cancer. *Cell Biochemistry and Function* **2017**, *35*, 296-303, 10.1002/cbf.3276.
65. Steffen Runz; Sascha Keller; Christian Rupp; Alexander Stoeck; Yasmin Issa; Dominique Koensgen; Alexander Mustea; Jalid Sehouli; Glen Kristiansen; Peter Altevogt; et al. Malignant ascites-derived exosomes of ovarian carcinoma patients contain CD24 and EpCAM. *Gynecologic Oncology* **2007**, *107*, 563-571, 10.1016/j.ygyno.2007.08.064.
66. Shingo Tayama; Takeshi Motohara; Dashdemberel Narantuya; Chenyan Li; Koichi Fujimoto; Isao Sakaguchi; Hironori Tashiro; Hideyuki Saya; Osamu Nagano; Hidetaka Katabuchi; et al. The impact of EpCAM expression on response to chemotherapy and clinical outcomes in patients with epithelial ovarian cancer. *Oncotarget* **2017**, *8*, 44312-44325, 10.18632/oncotarget.17871.
67. Jennifer Crow; Safinur Atay; Samagya Banskota; Brittany Artale; Sarah Schmitt; Andrew K. Godwin; Exosomes as mediators of platinum resistance in ovarian cancer. *Oncotarget* **2017**, *8*, 11917-11936, 10.18632/oncotarget.14440.
68. Ryan Pink; Priya Samuel; Davide Massa; Daniel Paul Caley; Susan Ann Brooks; David Raul Francisco Carter; The passenger strand, miR-21-3p, plays a role in mediating cisplatin resistance in ovarian cancer cells. *Gynecologic Oncology* **2015**, *137*, 143-151, 10.1016/j.ygyno.2014.12.042.
69. Karolina Weiner-Gorzel; Eugene Dempsey; Malgorzata Milewska; Aloysius McGoldrick; Valerie Toh; Aoibheann Walsh; Sinead Lindsay; Luke Gubbins; Aoife Cannon; Daniel Sharpe; et al.Jacintha O'SullivanMadeline MurphyStephen F. MaddenMalcolm KellAmanda McCannFiona Furlong Overexpression of the microRNA miR-433 promotes resistance to paclitaxel through the induction of cellular senescence in ovarian cancer cells. *Cancer Medicine* **2015**, *4*, 745-758, 10.1002/cam4.409.
70. Xiaolan Zhu; Huiling Shen; Xinming Yin; Meiling Yang; Hong Wei; Qi Chen; Fan Feng; Yueqin Liu; Wenlin Xu; Yuefeng Li; et al. Macrophages derived exosomes deliver miR-223 to epithelial ovarian cancer cells to elicit a chemoresistant phenotype. *Journal of Experimental & Clinical Cancer Research* **2019**, *38*, 1-14, 10.1186/s13046-019-1095-1.
71. Arash Rafii; Pejman Mirshahi; Mary Poupot; Anne-Marie Faussat; Anne Simon; Elodie Ducros; Eliane Mery; Bettina Couderc; Raphael Lis; Jerome Capdet; et al.Julie BergaletDenis QuerleuFrancoise DagonnetJean-Jacques FourniéJean-Pierre MarieEric Pujade-LauraineGilles FavreJeanine SoriaMassoud Mirshahi Oncologic Trogocytosis of an Original Stromal Cells Induces Chemoresistance of Ovarian Tumours. *PLOS ONE* **2008**, *3*, e3894, 10.1371/journal.pone.0003894.

72. Rocco Cappellesso; Andrea Tinazzi; Thomas Giurici; Francesca Simonato Bd; Vincenza Guzzardo; Laura Ventura; Marika Crescenzi Bd; Silvia Chiarelli; Ambrogio Fassina; Programmed cell death 4 and microRNA 21 inverse expression is maintained in cells and exosomes from ovarian serous carcinoma effusions. *Cancer Cytopathology* **2014**, *122*, 685-693, 10.1002/cncy.21442.

73. Kalpana Deepa Priya Dorayappan; John J. Wallbillich; David Cohn; Karuppaiyah Selvendiran; The biological significance and clinical applications of exosomes in ovarian cancer. *Gynecologic Oncology* **2016**, *142*, 199-205, 10.1016/j.ygyno.2016.03.036.

74. Benoît Thibault; Magali Castells; Jean-Pierre Delord; Bettina Couderc; Ovarian cancer microenvironment: implications for cancer dissemination and chemoresistance acquisition. *Cancer and Metastasis Reviews* **2013**, *33*, 17-39, 10.1007/s10555-013-9456-2.

75. Priya Samuel; Laura Mulcahy; Fiona Furlong; Helen McCarthy; Susan Ann Brooks; Muller Fabbri; Ryan Charles Pink; David Raul Francisco Carter; Cisplatin induces the release of extracellular vesicles from ovarian cancer cells that can induce invasiveness and drug resistance in bystander cells. *Philosophical Transactions of the Royal Society B: Biological Sciences* **2017**, *373*, 20170065, 10.1098/rstb.2017.0065.

76. Findlay Bewicke-Copley; Laura Ann Mulcahy; Laura Ann Jacobs; Priya Samuel; Naveed Akbar; Ryan Pink; David Raul Francisco Carter; Extracellular vesicles released following heat stress induce bystander effect in unstressed populations. *Journal of Extracellular Vesicles* **2017**, *6*, 1340746-1340746, 10.1080/20013078.2017.1340746.

77. Alexandre de la Fuente; Lorena Alonso-Alconada; Clotilde Costa; Juan Cueva; Tomas Garcia-Caballero; Rafael Lopez-Lopez; Miguel Abal; M-Trap: Exosome-Based Capture of Tumor Cells as a New Technology in Peritoneal Metastasis. *JNCI: Journal of the National Cancer Institute* **2015**, *107*, 107, 10.1093/jnci/djv184.

78. Kalpana Deepa Priya Dorayappan; Miranda L. Gardner; Colin L. Hisey; Roman A. Zingarelli; Brentley Q. Smith; Michelle D.S. Lightfoot; Rajan Gogna; Meghan M. Flannery; John Hays; Derek J. Hansford; et al.Michael A. FreitasLianbo YuDavid E. CohnKaruppaiyah Selvendiran A Microfluidic Chip Enables Isolation of Exosomes and Establishment of Their Protein Profiles and Associated Signaling Pathways in Ovarian Cancer. *Cancer Research* **2019**, *79*, 3503-3513, 10.1158/0008-5472.can-18-3538.

79. Michihiko Nakamura; Yoshihiro J. Ono; Masanori Kanemura; Tomohito Tanaka; Masami Hayashi; Yoshito Terai; Masahide Ohmichi; Hepatocyte growth factor secreted by ovarian cancer cells stimulates peritoneal implantation via the mesothelial–mesenchymal transition of the peritoneum. *Gynecologic Oncology* **2015**, *139*, 345-354, 10.1016/j.ygyno.2015.08.010.

80. Isabelle Matte; Denis Lane; Claude Laplante; Perrine Garde-Granger; Claudine Rancourt; Alain Piché; Ovarian cancer ascites enhance the migration of patient-derived peritoneal mesothelial

cellsviacMet pathway through HGF-dependent and -independent mechanisms. *International Journal of Cancer* **2014**, *137*, 289-298, 10.1002/ijc.29385.

81. Haiyang Zhang; Yi Wang; Ming Bai; Junyi Wang; Kegan Zhu; Rui Liu; Shaohua Ge; Jialu Li; Tao Ning; Ting Deng; et al.Qian FanHongli LiWu SunGuoguang YingYi Ba Exosomes serve as nanoparticles to suppress tumor growth and angiogenesis in gastric cancer by delivering hepatocyte growth factor siRNA. *Cancer Science* **2017**, *109*, 629-641, 10.1111/cas.13488.
82. Jennifer Crow; Safinur Atay; Samagya Banskota; Brittany Artale; Sarah Schmitt; Andrew K. Godwin; Exosomes as mediators of platinum resistance in ovarian cancer. *Oncotarget* **2017**, *8*, 11917-11936, 10.18632/oncotarget.14440.
83. Ryan Pink; Priya Samuel; Davide Massa; Daniel Paul Caley; Susan Ann Brooks; David Raul Francisco Carter; The passenger strand, miR-21-3p, plays a role in mediating cisplatin resistance in ovarian cancer cells. *Gynecologic Oncology* **2015**, *137*, 143-151, 10.1016/j.ygyno.2014.12.042.
84. Karolina Weiner-Gorzel; Eugene Dempsey; Malgorzata Milewska; Aloysius McGoldrick; Valerie Toh; Aoibheann Walsh; Sinead Lindsay; Luke Gubbins; Aoife Cannon; Daniel Sharpe; et al.Jacintha O'SullivanMadeline MurphyStephen F. MaddenMalcolm KellAmanda McCannFiona Furlong Overexpression of the microRNA miR-433 promotes resistance to paclitaxel through the induction of cellular senescence in ovarian cancer cells. *Cancer Medicine* **2015**, *4*, 745-758, 10.1002/cam4.409.
85. Xiaolan Zhu; Huiling Shen; Xinming Yin; Meiling Yang; Hong Wei; Qi Chen; Fan Feng; Yueqin Liu; Wenlin Xu; Yuefeng Li; et al. Macrophages derived exosomes deliver miR-223 to epithelial ovarian cancer cells to elicit a chemoresistant phenotype. *Journal of Experimental & Clinical Cancer Research* **2019**, *38*, 1-14, 10.1186/s13046-019-1095-1.
86. Arash Rafii; Pejman Mirshahi; Mary Poupot; Anne-Marie Faussat; Anne Simon; Elodie Ducros; Eliane Mery; Bettina Couderc; Raphael Lis; Jerome Capdet; et al.Julie BergaletDenis QuerleuFrancoise DagonnetJean-Jacques FourniéJean-Pierre MarieEric Pujade-LauraineGilles FavreJeanine SoriaMassoud Mirshahi Oncologic Trogocytosis of an Original Stromal Cells Induces Chemoresistance of Ovarian Tumours. *PLOS ONE* **2008**, *3*, e3894, 10.1371/journal.pone.0003894.
87. Rocco Cappellesso; Andrea Tinazzi; Thomas Giurici; Francesca Simonato Bd; Vincenza Guzzardo; Laura Ventura; Marika Crescenzi Bd; Silvia Chiarelli; Ambrogio Fassina; Programmed cell death 4 and microRNA 21 inverse expression is maintained in cells and exosomes from ovarian serous carcinoma effusions. *Cancer Cytopathology* **2014**, *122*, 685-693, 10.1002/cncy.21442.
88. Kalpana Deepa Priya Dorayappan; John J. Wallbillich; David Cohn; Karuppaiyah Selvendiran; The biological significance and clinical applications of exosomes in ovarian cancer. *Gynecologic Oncology* **2016**, *142*, 199-205, 10.1016/j.ygyno.2016.03.036.

89. Benoît Thibault; Magali Castells; Jean-Pierre Delord; Bettina Couderc; Ovarian cancer microenvironment: implications for cancer dissemination and chemoresistance acquisition. *Cancer and Metastasis Reviews* **2013**, *33*, 17-39, 10.1007/s10555-013-9456-2.

90. Priya Samuel; Laura Mulcahy; Fiona Furlong; Helen McCarthy; Susan Ann Brooks; Muller Fabbri; Ryan Charles Pink; David Raul Francisco Carter; Cisplatin induces the release of extracellular vesicles from ovarian cancer cells that can induce invasiveness and drug resistance in bystander cells. *Philosophical Transactions of the Royal Society B: Biological Sciences* **2017**, *373*, 20170065, 10.1098/rstb.2017.0065.

91. Findlay Bewicke-Copley; Laura Ann Mulcahy; Laura Ann Jacobs; Priya Samuel; Naveed Akbar; Ryan Pink; David Raul Francisco Carter; Extracellular vesicles released following heat stress induce bystander effect in unstressed populations. *Journal of Extracellular Vesicles* **2017**, *6*, 1340746-1340746, 10.1080/20013078.2017.1340746.

92. Alexandre de la Fuente; Lorena Alonso-Alconada; Clotilde Costa; Juan Cueva; Tomas Garcia-Caballero; Rafael Lopez-Lopez; Miguel Abal; M-Trap: Exosome-Based Capture of Tumor Cells as a New Technology in Peritoneal Metastasis. *JNCI: Journal of the National Cancer Institute* **2015**, *107*, 107, 10.1093/jnci/djv184.

93. Kalpana Deepa Priya Dorayappan; Miranda L. Gardner; Colin L. Hisey; Roman A. Zingarelli; Brentley Q. Smith; Michelle D.S. Lightfoot; Rajan Gogna; Meghan M. Flannery; John Hays; Derek J. Hansford; et al.Michael A. FreitasLianbo YuDavid E. CohnKaruppaiyah Selvendiran A Microfluidic Chip Enables Isolation of Exosomes and Establishment of Their Protein Profiles and Associated Signaling Pathways in Ovarian Cancer. *Cancer Research* **2019**, *79*, 3503-3513, 10.1158/0008-5472.can-18-3538.

94. Michihiko Nakamura; Yoshihiro J. Ono; Masanori Kanemura; Tomohito Tanaka; Masami Hayashi; Yoshito Terai; Masahide Ohmichi; Hepatocyte growth factor secreted by ovarian cancer cells stimulates peritoneal implantation via the mesothelial–mesenchymal transition of the peritoneum. *Gynecologic Oncology* **2015**, *139*, 345-354, 10.1016/j.ygyno.2015.08.010.

95. Isabelle Matte; Denis Lane; Claude Laplante; Perrine Garde-Granger; Claudine Rancourt; Alain Piché; Ovarian cancer ascites enhance the migration of patient-derived peritoneal mesothelial cellsviacMet pathway through HGF-dependent and -independent mechanisms. *International Journal of Cancer* **2014**, *137*, 289-298, 10.1002/ijc.29385.

96. Haiyang Zhang; Yi Wang; Ming Bai; Junyi Wang; Kegan Zhu; Rui Liu; Shaohua Ge; Jialu Li; Tao Ning; Ting Deng; et al.Qian FanHongli LiWu SunGuoguang YingYi Ba Exosomes serve as nanoparticles to suppress tumor growth and angiogenesis in gastric cancer by delivering hepatocyte growth factor siRNA. *Cancer Science* **2017**, *109*, 629-641, 10.1111/cas.13488.