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EDITORIAL

Malignant peritoneal effusion acting as a tumor environment in ovarian cancer progression: Impact and significance

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Abstract

Until recently, ovarian cancer research has mainly focused on the tumor cells themselves ignoring for the most part the surrounding tumor environment which includes malignant peritoneal effusions. However, one of the major conceptual advances in oncology over the last few years has been the appreciation that cancer progression cannot be explained by aberrations in cancer cells themselves and is strongly influenced by the surrounding tumor environment. The mechanisms of ovarian cancer progression differ from that of other solid tumors because ovarian cancer cells primarily disseminate within the peritoneal cavity. Malignant peritoneal effusion accumulates in the peritoneal cavity during ovarian cancer progression. These exudative fluids act as a unique tumor environment providing a framework that orchestrates cellular and molecular changes contributing to aggressiveness and disease progression. The composition of ascites, which includes cellular and acellular components, constantly adapts during the course of the disease in response to various cellular cues originating from both tumor and stromal cells. The tumor environment that represents peritoneal effusions closely constitute an ecosystem, with specific cell types and signaling molecules increasing and decreasing during the course of the disease progression creating a single complex network. Although recent advances aiming to understand the ovarian tumor environment have focused one at a time on components, the net impact of the whole environment cannot be understood simply from its parts or outside is environmental context.

Key words: Ovarian cancer; Tumor environment; Peritoneal effusions; Ascites; Dissemination; Multicellular spheroids

Core tip: The malignant peritoneal effusion that accumulates during ovarian cancer dissemination and progression constitutes a unique tumor environment. Bidirectional

communications between tumor cells and their surrounding environment influence ovarian cancer dissemination, progression and patient prognosis. To solve the complexity of this tumor environment and understand how it affects cancer progression, a paradigm shift is necessary. Peritoneal effusions should be studied as integrated systems with innovative modeling approaches.

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MAIN TEXT

Malignant peritoneal effusions (ascites) commonly occur during the progression of certain types of cancers such as ovarian and pancreatic adenocarcinomas[1]. These exudative fluids contain a large number of tumor cells and are by definition metastatic. For example, patients with ovarian cancer will often present at diagnostic with multiple omental and peritoneal tumor implants. These patients will usually have accumulation of large amount of peritoneal fluids (often several liters). The presence of malignant effusion is associated with a poor prognosis. Because of their nature, malignant effusions, in which tumor cells proliferate and metastasize, constitute a distinct and unique tumor environment compared to solid cancers that develop in a tissue microenvironment. The cell-free fraction of malignant effusions is rich in cytokines, chemokines, growth factors and extracellular matrix components[2-4]. In addition to tumor cells, effusions contain of a large number of non-malignant cells such as fibroblasts and mesothelial cells, and various immune cells including macrophages and lymphocytes[5]. Although the importance of the bidirectional communication between tumor cells and their adjacent tissue microenvironment for supporting cancer progression is well recognized now, much less is known regarding the role peritoneal effusions in cancer progression. Nonetheless, it has been shown that extracellular cues provided by soluble factors contain in effusions can drive certain aspects of cancer progression such as cell proliferation, migration, and invasion. For example, effusion-associated hepatocyte growth factor[6-8], lysophosphatidic acid[9] and CCL18[10] have been shown to promote ovarian cancer cell growth and survival. Furthermore, cell-free ascites can promote drug resistance in ovarian cancer cells[11,12]. In support of the critical role of cell-free ascites, a number of factors contained in effusions are predictor of clinical prognosis[13,14]. The overall effect of cell-free ascites results from the complex integration of various extracellular cues, which leading to receptor-induced signaling in both tumor cells and stromal cells. For example, in contact with ascites, mesothelial cells undergo a pro-tumoral shift[15] whereas ovarian cancer cells display a more invasive phenotype with a shift along an epithelial-to-mesenchymal transition (EMT)[16]. As a result of this extensive cellular crosstalk, peritoneal effusions are constantly adapting during the course of the disease in response to the different cues[1]. The functional role of these changes in effusion composition during cancer dissemination and progression is mostly unknown.

Beyond the potential contribution of specific soluble factors to cancer progression, non-malignant cells present in peritoneal effusions probably play an essential supporting role, particularly in the early stages of dissemination, by preventing anoikis and stimulating proliferation of tumor cells. Paracrine signaling through mesenchymal stem cells can confer resistance to chemotherapy in ovarian cancer cells via IL-6/IL-6 R pathway and CXCL12[17,18]. Similarly, paracrine secretion of anti-apoptotic from ascites-primed mesothelial cells promote ovarian cancer cell drug resistance[15]. Cancer-associated fibroblasts isolated from omentum can be activated by tumor cells to promote ovarian cancer growth, adhesion and invasiveness through TGFβ1 pathway[19]. Expression of HOXA9 by ovarian cancer cells induce TGFβ2 secretion, which in turn, promote by secretion of IL-6 and CXCL12 by fibroblasts leading to tumor growth[20]. The presence of tumor-infiltrating $CD8^+$ T cells in primary tumors is associated with prolonged progression-free and overall survival in ovarian cancer patients[21,22]. These data suggest that several cell types within peritoneal effusions may have a robust influence on ovarian cancer cells. Bidirectional communications between tumor cells and their surrounding environment are at play, however identifying these crosstalks and validating their functional roles in a

systemic approach remains challenging because of complex interactions among multiple cell types in effusions.

Getting a better understanding of the complex ecosystem that constitute malignant peritoneal effusions also have the potential to enhance our insight to limit the accumulation of these effusions and to overcome platinum resistance in ovarian cancer, which represents a yet unmet need. Both soluble factors and cancer-associated stromal and immune cells constitute potential targets for novel therapies. Examples of soluble factors in the tumor environment of ovarian cancer targeted by novel therapies (mostly humanized monoclonal antibodies) include VEGF, VEGFR, PDFR, PDGFR, c-kit, PD-1 and PD-L1[23]. However, drug-associated toxicity and resistance often limit the clinical benefits associated with these novel therapies. These studies highlight the fact that targeting a single component of the tumor environment is likely to have limited clinical benefits and the secretome of malignant peritoneal effusions should be considered as a whole that cannot be understood simply from its parts. Given the progression-enhancing role of cancer-associated stromal cells in malignant peritoneal effusions, cell therapy may represent of novel approach to limit ovarian cancer dissemination. For example, it has been shown that genetically-engineered human mesothelial cells with the Herpes Simplex virus thymidime kinase (HSV-tk) efficiently deliver anticancer modalities to ovarian cancer cells within the peritoneal cavity when mice were treated with ganciclovir[24]. Conversion of ganciclovir pro-drug in a toxic apoptosis-inducing drug by HSV-TK results in the transfer of apoptotic bodies to adjacent tumor cells. Alternatively, the cells could be used to locally deliver in the peritoneal cavity other anti-cancer molecules potentially circumventing the toxicity associated with systemic delivery.

Tumor such as ovarian cancer does not usually use the classic patterns of metastasis via the hematogenous route[25]. The current view is that ovarian cancer spreads mainly via the peritoneal circulation with a high affinity for the omentum. Cells detach from the primary tumor to form free-floating multicellular spheroids, which then travel through the peritoneal fluid at distant sites onto the mesothelial lining where metastatic outgrowth occurs[26]. It is believed that the formation of multicellular spheroids is an essential step in the initiation of peritoneal implantation metastasis for ovarian cancer. In this context, spheroids can be considered the primary vehicles of ovarian cancer dissemination. However, the mechanisms of spheroid formation are for the most part unknown. Before tumor cells detach, they will usually undergo an EMT characterized by decreased expression of E-cadherin acquiring therefore a proliferative and invasive phenotype. However, it is not clear if tumor cells detached as single cell entity and then aggregate together to form homotypic multicellular spheroids or if clumps of the primary tumor exfoliate and stay together to form heterotypic spheroids. Alternatively, exfoliated single tumor cells could aggregate with floating mesothelial cells forming heterotypic unvascularized multicellular spheroids. Recent studies aiming to characterize ascites-derived spheroids suggested that spheroids are heterotypic containing mesothelial-derived myofibroblatic cells[27] and macrophages[28]. The binding of ovarian cancer cells to mesothelial cells to form spheroids could be mediated by integrins, CD44 and MUC16[27,29,30]. Further work however is needed to gain a comprehensive understanding of the cellular composition of the multicellular spheroids found in ascites and how this influences cancer progression. Another interesting hypothesis is that multicellular spheroids potentially constitute a chemoresistant niche that continuously repopulates the peritoneal cavity despite chemotherapy treatments as they are potentially endowed with a high tumor-initiating potential and increased drug resistance linked to the expression of stemness-associated genes[31]. However, the presence of mesenchymal stem cells in ovarian cancer spheroids remains to be demonstrated. The generation of unvascularized 3D spheroids would generate a structure with a metabolite density gradient that can inhibit the access of chemotherapy agents to internal cells[32]. Ovarian cancer cell grown as spheroids display enhanced resistance to common chemotherapeutic drugs such as taxol and cisplatin compared monolayers[31,33]. Because of their role in ovarian cancer dissemination and their potential role in disease recurrence after chemotherapy, a much better understanding of multicellular spheroid biology is necessary.

PERSPECTIVE

As highlighted here, most research on the ovarian cancer environment has focused one at a time on components, such as particular signaling cascades, specific ascites factors or specific cell types, *etc*. This knowledge is essential, but obviously not sufficient. The tumor environment that represents peritoneal effusions closely

resembles an ecosystem, with specific cell types and signaling molecules increasing and decreasing during the course of the disease progression creating a single complex network. This environment is an archetypical complex system in which the functioning of the whole cannot be understood simply from its parts or outside is environmental context. Perhaps to understand the role of peritoneal effusions on cancer progression, a paradigm shift is necessary and effusions should be studied as integrated systems using bioinformatic modeling to quantify system-level biodiversity changes[34].

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