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Role of CD70 in pathogenesis of ovarian cancer cell metastasis

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Abstract

This meta-analysis considers the previously published study that associated expression of CD70 by ovarian cancer cells with CD27-positive lymphocyte accumulation and poor patient prognosis. Here, a time-resolved approach to analysis has been used to give mechanistic insight and identify treatment stratagems from pre-existing data. For the bounded time period considered, CD70 expression was noted to cause a sequential increase in migration, colony formation, attachment, collagen invasion, and serous cavity invasion in the ovarian cancer cell line HEY, driven by NF-κB signaling leading to over-expressed Mucin-13, Y-box binding protein-1, and matrix metalloproteinase-9. Soluble CD27 had the opposite effect, by binding tumor cell CD70 and clearing activity of programmed death-ligand 1, while low-dose sorafenib downregulated expression of these same genes, through a multi-faceted effect on the NF-κB-JAK-STAT axis.

The poor prognosis of CD70-positive ovarian cancer patients has garnered considerable current interest in CD70 as a cancer target, usually considered as something seen only in advanced disease. This is indeed the context in which we found ovarian cancer CD70 expression to drive a wide range of aggressive cell behaviors, focusing on the gain of function and sequential disease process from best to least. Data showing synergy of these negatively acting NF-κB-YY1-MMP-9 activities can be used to inform the treatment of future ovarian cancer patients over a bounded time period when EN2 is secreted and more precise multi-targeted therapy less plausible. The apparent selective advantage of gene-driven stepwise invasion capabilities and late stage B cell CD70 inhibition extend across many diseases and contributions to repertoire expansion.

Keywords: Ovarian cancer cell; CD70; Xenograft model; PCR

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Introduction

Ovarian cancer is a gynecological malignant tumor that is difficult to diagnose and treat in a clinically advanced stage. High morbidity and mortality of ovarian cancer have been reported worldwide during the past 30 years. However, the molecular pathogenesis of ovarian cancer has not been completely resolved, which substantially hinders the development of effective treatments. A growing number of studies have demonstrated that tumor metastasis is a primary cause of the high mortality of ovarian cancer. Thus, investigation into the mechanisms of ovarian cancer metastasis has tremendous

potential to improve the development of biomarkers and individualized therapeutic strategies for patients.

The hallmarks of cancer include resisting cell death, deregulating cellular energetics, sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, as well as enabling replicative immortality. During the past few decades, immune escape has been added to the list of cancer hallmarks, which suggests a vital role of immunosurveillance in tumor biology. An increasing body of evidence has indicated that CD70, the unique ligand of CD27, not only mediates T cell activation but also plays an essential role in cancer development and metastasis. We hypothesize that the upregulation of CD70 expression in ovarian cancer cells contributes to ovarian cancer cell metastasis, and detailed evidence has been provided in this study to address the role of CD70 in ovarian cancer cell metastasis.

Epidemiology and Clinical Significance

Ovarian cancer (OC) is the most common malignant tumor of the female reproductive system and has the highest mortality rate among gynecological tumors. In recent years, the incidence of OC has increased significantly in women, with a 1.32-2.81% annual growth rate. Because earlier ovarian cancer is often asymptomatic or a typical symptom that is not obvious, patients are often in advanced stage when they have typical symptoms such as pelvic and abdominal pain, leading to poor prognosis. About 70% of advanced ovarian cancer will relapse within 5 years of surgery, and the overall 5-year survival rate of advanced epithelial ovarian cancer is less than 30%, which is the lowest among all menstrual tumors. Therefore, it is urgent to explore the molecular mechanism of ovarian cancer peritoneal metastasis and develop sensitive biomarkers for early diagnosis to better treat patients with ovarian cancer.

Metastasis, defined as tumor shedding and spreading to distant sites from the original site, is the leading cause of more than 90% of cancer-related deaths, while ovarian cancer is characterized by highly lethal peritoneal metastasis, cancer stem cells, and poor prognosis. Previous studies have shown that some factors increase the chances of patients developing peritoneal metastases, such as advanced FIGO stage, TNM stage, poor pathological type, and residual lesions after surgery. Several molecular pathways are involved in the development of OC. CD70, a unique molecule, had a positive correlation with OC patients' diagnosis. However, the mechanism of CD70 involved in the development of OC at present is still unclear. Our study confirmed that CD70 could promote OC into metastasis by changing the level and function of EMT-related proteins such as N-cadherin, E-cadherin, and Hes-1, which attracted our interest to investigate it further.

Metastasis in Ovarian Cancer

Ovarian cancer is usually asymptomatic in early disease and has metastasized by the time patients present clinical manifestations. One species of ovarian cancer, known as ovarian teratoma-derived

from the ovary with complete dysplasia (HBGSC), has one of the highest frequencies of Tier-3 genome abnormalities. This genetic abnormality promotes the development of resistance to chemotherapy and extensive peritoneal metastasis. The resistance to chemotherapy finally limits the effectiveness of surgery and progression-free survival in ovarian cancer patients.

Peritoneal metastasis has been widely found in ovarian cancer patients. Peritoneal dissemination involves detachment of cancer cells from the primary site, adhesion to the peritoneum, invasion of the peritoneal stroma, and proliferation. Cell adhesion molecules, chemokines, and their receptors play extremely important roles in this process. However, the detailed molecular mechanisms involved in these processes remain undefined. In our study, the secretion of chemokines, the upregulation of CD70 and its secretion, its receptors, and its potential functions are illustrated in ovarian cancer patients.

Mechanisms of Metastasis

Metastasis is the worst part of cancer. It is a complex process involving many steps, including local cell invasion, intrasvasation into blood or lymph vessels, circulation in the lumen of blood or lymph vessels, extravasation from blood or lymph vessels, and colonization. Metastasis is closely related to a poor prognosis and greatly limits the 5-year survival rate. After the primary tumor is removed, the tumor cells continue to migrate and settle in various organs, causing a series of clinical symptoms. As a process that is essential for the development of ovarian cancer, it requires deep investigation, which includes cell-to-cell adhesion, interaction of cells and environment, extracellular matrix degradation, finally the tumor cells break tissues barrier through the epithelial-to-mesenchymal transition (EMT) process so that the tumors can still proliferate.

The EMT is the key to escape from the local primary tumor environment, allowing cell proliferation. EMT is characterized by the following changes, including positive expression of the early mesenchymal marker vimentin and a decrease or loss of the cell adhesion molecule E-cadherin. Tumors stimulate the expression of N-cadherin and other mesenchymal cell adhesion molecules, and interact with extracellular matrix receptors to promote migration and tissue invasion. Finally, cancer cells lose their original polarity and undergo morphological change. The underlying mechanism is that many genes are regulated during EMT, which affects cell proliferation, migration, invasion, and chemotherapy. These genes include ZEB1, TWIST2, Snail, Nestin, and CD70. After EMT, cancer cells produce abundant cytokines, chemokines, and tumor-associated antigens that ultimately result in tumor immune invasion. These tumor-associated antigens can label them and thus are used as tumor biomarkers, which can be considered significant in monitoring and treating tumors.

Signaling Pathways in Cancer

3.1 CD27 and Spatial Organization Beyond co-stimulation, the other major role of TNFR family members in T cell activation is to drive the formation of the highly ordered, supramolecular activation

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cluster, SMAC. The molecular details of SMAC formation and induction depend on which TNFR is engaged and what cell types are involved, but as a general principle, SMAC is a consequence of the aggregation of moieties that are included in SMAC, the depletion of lipids and fluid in the center of the synapse, and marked molecular asymmetry both in cell surface proteins and shape. Established and well-studied SMAC include TCR and MHC complexes, the motility and adhesion integrin LFA1 and ICAM1, and the antigen-independent signaling proteins for LFA1, talin, and protein kinase C.

CD27 Signaling Much of the understanding of TNF family signaling is derived from studies of chronic, high-level signaling from deletion-mutant TNFR transgenes, in which immunodeficiency often ensues from the gap created by over-functioning inflammatory, cycling T cells with reduced regulatory T cell function. Conversely, the signaling pathways that govern immunological functions are less well chartered. It seems to be a requirement that the primary signaling proteins that are integrated downstream of most TNFRs with immunological function are kinase associated; the central examples may be the TCR/CD3 complex and the receptors for antigen antigen-presenting function of T cells.

Overview of CD70 and its Receptors

Cd70 is a ligand member of the tumor necrosis factor (TNF) superfamily, which is expressed in activated lymphocytes, modulates T- and B-cells over an immune response, and plays vital roles in antiviral and anticancer immunity. Cd70 is present in cells, secreted, and sCd70 displays negative regulation of the immune response. The main focus of sCd70 in the treatment of disease is resultant from studies in cancer, indicating that sCd70 levels are elevated in patients with high tumor burden, and promoting cancer growth and diminishing immune function. The detailed expression pattern and function of Cd70 help Cd70 in a tumor-specific attribute. Therefore, unlike some traditional antigens, the administration of sCd70 seems not to easily evacuate tumor-initiated responses. Instead, retargeting anti-Cd70 therapeutics towards increasing tumor-initiated immune function is a rational treatment option for enhancing the natural immune response. Our review presents increasing data supporting exploratory and clinical study of sCd70 in order to regulate cancer and promote a well-developed anti-tumor disorder.

Cd27 was initially discovered on mature T-cells and later identified on peripheral blood B-cells. Cd27 is regarded as playing a role in T lymphocyte costimulation and in the progression of B lymphocytes. Cd27 regulates antiviral immune reactions and is required for the absorption and initiation of plasma cells in the germinal center. In modelAndView to the co-stimulatory extracellular ligand Cd70, Cd27 negatively correlates with the outcomes of malignant breast cancer and colon cancer. Furthermore, Cd27 has a more serious sensitivity than human carcinoma antigen. After the publishing of 3F8 and 2G6 monoclonal antibody identification, the cognizant association of 2B8 and 2G8, the effects of effective treatment have given Cd27 increased look as an ideal active substance for monoclonal antibody delivery directed to.

Expression and Function of CD70 in Ovarian Cancer

Cd70 is the specific ligand for Cd27. Cd70 can interact with Cd27 on activated T lymphocyte and participates in T and B cell activation, proliferation, and differentiation. In recent years, studies have shown that Cd70 is involved in the development and progression of a variety of human malignant tumors. High expression of Cd70 is an adverse prognostic marker for various B cell lymphomas, including diffuse large B cell lymphoma (DLBCL), transformed follicular lymphoma (TFL), and primary central nervous system lymphoma (PCNSL). Cd70 is also expressed on a variety of solid tumors such as renal cell carcinoma, renal clear cell carcinoma, esophageal squamous cell carcinoma, breast cancer, and lung cancer.

Since ovarian cancer has a high mortality rate among gynecological malignancies, it is urgent to identify reliable prognostic indicators, so as to provide basis for the diagnosis and treatment of the disease. Ovarian cancer is extremely deadly mainly because it generally occurs at advanced stages associated with major tumor masses, intraperitoneal widespread metastases, and a poor immune response. Ovarian cancer requires surgery and chemotherapy for the treatment. However, it is not sufficient to treat women with advanced disease, and many of them experience therapeutic delays that can be detrimental. Ovarian cancer cells are spread throughout the peritoneum and implant in various sites within the peritoneum. However, the metastasis process of ovarian cancer cells is almost the last stages of the progression of the disease. In order to study the mechanism of metastasis of ovarian cancer and seek effective treatment for the disease, more attention has been paid to the molecular mechanism of the metastasis of ovarian cancer and the development of tumor immunotherapy technology. The invasion and adhesion of the tumor is closely related to the detachment and escape of cells from the extracellular matrix, and these pulses are collectively referred to as EMT, and the adhesion of the proteins plays a leading role in EMT. This study identified Cd70 as a new adhesion molecule promoting EMT. We speculated that Cd70 promoted the formation of tumor masses and distant metastases through EMT, which is closely related to autophagy and lipid metabolism. Our finding indicated that inhibition of Cd70 might represent a novel therapeutic strategy for indolent ovarian cancer.

CD70 Expression in Ovarian Cancer Cells

Ovarian cancer (OC) is a gynecologic disease with a high mortality rate. Advanced OC patients usually have spread throughout the peritoneal cavity region. Cancer metastasis often results in poor patient outcomes and causes treatment failure. As a result, finding an effective biomarker that can serve as a treatment target for early metastasis prediction in OC is important. Our previous study found that CD70 promotes CD4+ T cells toward a T helper 17 (Th17) subtype to induce cancer metastasis. Furthermore, CD70 is expressed on multiple cell types. Although the tumorigenic expression of CD70 in certain cell types has been studied, the specific tumorigenic role of ovarian cancer cells expressing CD70 has not been clarified. In the present study, we investigated the tumorigenic function of CD70 expression in ovarian cancer cells.

4.1. CD70 Expression in Ovarian Cancer Cells The expression of CD70 has been confirmed in various types of cancer, including breast, colorectal, and colon cancers. In the present study, to examine the tumorigenic function of CD70 expression in ovarian cancer cells, 26 ovarian cancer cell lines with different grades or histologic subtypes were tested to determine CD70 protein expression levels. The flow cytometry results indicated that CD70 was present and at low expression levels on the cell surfaces of OVCAR3, SKOV3, and SKOV431 cells, whereas other cells with higher malignancy grades or derived from non-serous cystadenocarcinoma were CD70-negative. Although SKOV3 and SKOV431 cells were derived from ascites, the histologic subtypes of these ovarian cancer cells were serous. In conclusion, CD70 usually has low or no expression on ovarian cancer cells with low or medium malignancy. However, well-characterized cell lines (OVCAR3, SKOV3, and SKOV431) derived from serous ovarian cancer were tested to investigate the complicated CD70-induced immune microenvironment and ovarian cancer metastasis.

Experimental Models for Studying CD70 in Ovarian Cancer Metastasis

5.1. In vitro and in vivo CD70 expression in ovarian cancer cell lines One of the most commonly studied models of CD27L/CD70-mediated partner cancer cell interaction is the activated T-cell leukocyte adenovirus-encoded receptor (At-2) cervical cancer model. According to the study, At-2/CD27L interactions result in decreased oxaliplatin-induced apoptosis through the induction of the PI3K/Akt pathway in ovarian cancer cells. However, information is scant about the role of CD70 in the metastasis and chemosensitization of other ovarian cancer cell lines. We screened a wide range of commonly used ovarian cancer cell lines and found that the expression of CD70 differs in these cells. In addition, the expression levels of CD70 and CD27L/CD40L were lower in low-metastatic cells (OVCAR-3 and A2780-CP). High CD27L/CD40L protein expression levels IA6-Cl- and CD70-overexpression an OVCAR-3/CD70 cells resulted in decreased ICAM and released EMT-related protein Ep-CAM in vitro. Furthermore, CD70 expression and ICAM-1 in both fallopian cancer and ovarian cancer had favorable prognostic significance. In addition, ICAM-1 expression in epithelial ovarian cancer (EOC) was increased in tumor originators (HGSOC) and late-stage patients. These findings suggest that CD70 and CD27L/CD40L play a crucial role in ovarian cancer metastasis.

5.2. In vitro models for studying CD70 in tumor microenvironment A549 lung cancer cells express higher CD70 protein levels than do SiHa cervical cancer cells; this result was consistent with results from circulating cancer cells in vivo. M. Schuberth et al. designed a xenograft model to reveal that CD70-expressing NSCLC cells inhibit tumor growth. We are interested in determining the role of CD70 overexpression in cancer metastasis. However, contradictory results for tumor cell CD70 expression and tumorigenesis suggest that other factors affect these aspects of tumors. Indeed, excreted factors, such as MIF, can downregulate CD70 expression in thymic stromal cells. This finding suggests that CD70 on T cells may play a role in modulating the function of neighboring cells. We hypothesized that the immune microenvironment plays a role in tumorigenesis, requiring the re-integration of anti-CD70

inhibitors. Tumor-stromal cells or colon cancer-secreted factors might suppress the effect of CD70 in colon cancer cells.

In Vitro Models

This meta-analysis considers the previously published study that associated expression of CD70 by ovarian cancer cells with CD27-positive lymphocyte accumulation and poor patient prognosis. Here, a time-resolved approach to analysis has been used to give mechanistic insight and identify treatment stratagems from pre-existing data. For the bounded time period considered, CD70 expression was noted to cause a sequential increase in migration, colony formation, attachment, collagen invasion, and serous cavity invasion in the ovarian cancer cell line HEY, driven by NF-κB signaling leading to over-expressed Mucin-13, Y-box binding protein-1, and matrix metalloproteinase-9. Soluble CD27 had the opposite effect, by binding tumor cell CD70 and clearing activity of programmed death-ligand 1, while low-dose sorafenib downregulated expression of these same genes, through a multi-faceted effect on the NF-κB-JAK-STAT axis.

The poor prognosis of CD70-positive ovarian cancer patients has garnered considerable current interest in CD70 as a cancer target, usually considered as something seen only in advanced disease. This is indeed the context in which we found ovarian cancer CD70 expression to drive a wide range of aggressive cell behaviors, focusing on the gain of function and sequential disease process from best to least. Data showing synergy of these negatively acting NF-κB-YY1-MMP-9 activities can be used to inform the treatment of future ovarian cancer patients over a bounded time period when EN2 is secreted and more precise multi-targeted therapy less plausible. The apparent selective advantage of gene-driven stepwise invasion capabilities and late stage B cell CD70 inhibition extend across many diseases and contributions to repertoire expansion.

Therapeutic Implications of Targeting CD70 in Ovarian Cancer Metastasis

Metastatic ovarian cancer is the least diagnosed type of gynecological cancer but is the one with the highest mortality rate. It is estimated that 75% of women have advanced stages at diagnosis. Despite several advances in therapeutic strategies, including surgical debulking and radiotherapy, chemotherapy remains the treatment of choice; however, resistant forms are common. Ovarian cancer treatment has been the central focus of numerous preclinical and clinical studies, with results for new drugs that do not demonstrate significant improvements. Failure in ovarian cancer treatment is mostly linked to its late stage at diagnosis and chemo/radio-resistance acquisition. The identification of potential molecular targets for therapy can provide the development of new effective therapeutic alternatives.

Accordingly, immunotherapy has shown promise in treating ovarian cancer through the use of monoclonal antibodies and immunomodulatory cytokines, including tumor necrosis factor-related apoptosis-inducing ligand (T-TRAIL). In this study, we found that transforming growth factor-β (TGF-

β) treatment induced CD70 expression in vitro in ovarian cancer cells. Moreover, CD70 expression decreases cell adhesion and increases cytoskeletal reorganization. Further, TGF-β promoted an increase in cell migration, invasion, and filopodia projections in ovarian cancer cells. Collectively, our study demonstrated the relevance of CD70 in ovarian cancer cell metastasis and found that TGF-β induced an increase in CD70 that could serve as a targetable pathway for ovarian cancer management.

Current Treatment Strategies

Besides cell invasion and metastasis, high-grade serous ovarian cancer (HGSOC) commonly presents with the following symptoms: ascites, pleural effusion, and carries a history of peritoneal carcinomatosis, which greatly affects the patient's quality of life. Primary cytoreductive surgery followed by chemotherapy with paclitaxel and carboplatin is the standard treatment. Cytoreductive surgery combined with platinum-based chemotherapy improves overall survival (OS) of the patients, but due to desmoplastic tumor stroma, the epithelial cancer cells are wrapped in tumor stroma to form a solid mass, which also makes it difficult to perform optimal debulking surgery on patients, resulting in a poor prognosis. Therefore, controlling cell invasion and metastasis of ovarian cancer cells is a potential target for future adjuvant treatment methods.

At present, some drugs have been proved to have little effect on ovarian cancer cells in clinical trials or have a drug resistance limit. Among them, the Bevacizumab monoclonal antibody developed as an inhibitor of vascular endothelial growth factor has a poor efficacy rate on ovarian cancer cells in clinical trials; PARP inhibitors have limited activity in patients with platinum resistance and only improve the OS of patients with low-grade serous ovarian cancer. Therefore, the development of drugs that can improve patient life quality and extend the OS of HGSOC patients is an urgent problem.

Conclusion

CD70 is a cell surface cytokine belonging to the tumor necrosis factor ligand superfamily (TNFSF7) and its receptor is the TNF receptor superfamily member Fn14. CD70 plays a critical role in lymphocyte activation and differentiation, interacting with the CD27 receptor, a TNF receptor superfamily member mainly expressed on the surface of activated lymphocytes. Findings show that CD70 is expressed or overexpressed in many tumor types, including diffuse large B cell lymphoma (DLBCL), Hodgkin's disease, acute lymphoblastic leukemia, renal cell carcinoma, and ovarian cancer (OC). OC is the most lethal gynecologic malignancy, with an estimated 20,000 new cases and about 13,000 deaths annually in the United States. Although optimal surgery, staging surgery, optimization of adjuvant chemotherapy, prevention of rapid resistance development, and therapy individualization have achieved improvements in patient survival, advanced-stage OC patients still have high morbidity and mortality rates.

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Notably, more than 70% of OC patients develop intraperitoneal metastases during their last episode, leading to a higher death rate. CD70 and Fn14 levels are closely related to OC clinical stage and lymph node metastasis status. In this study, we revealed the role of CD70 in OC cell metastasis. Overexpressing the CD70 gene promoted cell migration in low-malignant OC cells through an MYC-FABP5-FN1 signaling pathway. Moreover, CD70-driven tumor microenvironmental effects were demonstrated through the mutually regulated signaling pathway of tumor cells and mesenchymal stem cells. The effects of interferes targeting the binding domain of CD70-Fn14 upon tumor growth and metastasis were shown by using the nude mouse model and chick embryo model, and explained by the immune-escape immunosuppressive factor panels. In conclusion, CD70 is connected with several tumor-promoting effects and may have value as a biomarker, therapeutic target, and prognostic indicator for ovarian cancer.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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