News Release

Title

Ovarian cancer-associated mesothelial cells induce acquired platinum-resistance in peritoneal metastasis via the FN1/Akt signaling pathway

Key Points

- The clinical characteristics of refractory advanced ovarian cancer suggest that the peritoneum acts as an anchoring point for metastatic tumors, which promotes the survival of ovarian cancer cells.
- Ovarian cancer cells acquired platinum-resistance via activation of the Akt signaling pathway, which is induced by FN1 on ovarian cancer-associated mesothelial cells.
- Findings in this study highlight the potential for targeting OCAMs as a novel therapeutic strategy for preventing peritoneal dissemination of ovarian cancer.

Summary

The research group led by Graduate Student Masato Yoshihara, Associate Professor Hiroaki Kajiyama, Professor Fumitaka Kikkawa (Obstetrics and Gynecology), Professor Akihiro Nawa (Bell Research Center, Obstetrics and Gynecology) of Graduate School of Medicine, Nagoya University (Dean: Professor Kenji Kadomatsu), Senior Staff Scientist Yusuke Yamamoto (National Cancer Research Institute), Dr. Carmela Ricciardelli (The University of Adelaide) reported a novel mechanism of acquired platinum-resistance in ovarian cancer peritoneal metastasis via the FN1/Akt signaling pathway, caused by ovarian cancer-associated mesothelial cells.

Peritoneal dissemination of ovarian cancer (OvCa) arises from the surface of the peritoneum, covered by monolayer of mesothelial cells (MCs). Given that both OvCa cells and MCs are present in the same peritoneal metastatic microenvironment, they may establish cell-to-cell crosstalk or phenotypic alterations including the acquisition of platinum-resistance in OvCa cells. Herein, they report how OvCa-associated mesothelial cells (OCAMs) induce platinum-resistance in OvCa cells through direct cell-to-cell crosstalk. They evaluated mutual associations between OvCa cells and human primary MCs with *in vitro* co-culturing experimental models and *in silico* omics data analysis. The role of OCAMs was also investigated using clinical samples and *in vivo* mice models. Results of in vitro experiments show that mesenchymal transition is induced in OCAMs primarily by TGF-β1 stimulation. Furthermore, OCAMs influence the behavior of OvCa cells as a component of the tumor microenvironment of peritoneal metastasis. Mechanistically, OCAMs can induce decreased platinum-sensitivity in OvCa cells via induction of the FN1/Akt signaling pathway via cell-to-cell interactions. Histological analysis of OvCa peritoneal metastasis also illustrated FN1 expression in stromal cells that is supposed to originate from MCs. Further, they also confirmed activation of Akt

signaling in OvCa cells in contact with TGF-ß1 stimulated peritoneum, using an *in vivo* mice model. Their results suggest that the tumor microenvironment, enhanced by direct cell-to-cell crosstalk between OvCa cells and OCAMs, induces acquisition of platinum-resistance in OvCa cells, which may serve as a novel therapeutic target for prevention of OvCa peritoneal dissemination.

Research Background

Ovarian cancer (OvCa) is one of the leading causes of death among gynecological malignancies. More than half of the patients with OvCa are diagnosed at an advanced stage due to lack of specific symptoms and effective early detection screening methods. Peritoneal dissemination, which is one of the most common causes of metastasis in the abdominal cavity, is frequently observed in patients with advanced OvCa Even when metastatic tumors are optimally resected, persistent cancerous cells often emerge to form new tumors despite the use of conventional platinum-based chemotherapy. This is the fundamental reason for the observed poor prognoses in patients with therapy-resistant OvCa, an issue that has not improved significantly over the past few decades.

Peritoneal dissemination of OvCa is presumed to arise from the spread of cancer cells via the ascites. Furthermore, the surface of the peritoneum is histologically covered by a single layer of mesothelial cells (MCs), which may have a key function in development of the tumor microenvironment that supports peritoneal metastasis of OvCa. Moreover, recent studies have shown that activated MCs play an important role in the development of peritoneal metastasis; these studies further demonstrated that MCs increase the adhesive and proliferative properties of OvCa cells. In fact, mesenchymal transition of MCs was reported to be induced by a variety of soluble factors in malignant ascites, and modification of extracellular matrix (ECM) on the mesothelial cells also promoted peritoneal metastasis of OvCa. These findings suggest that MCs no longer function as simply passive bystanders, but rather act as coordinators for the progression of OvCa. Additionally, cancer-associated fibroblasts (CAFs) are recognized as a key component in the tumor microenvironment, and are reported to originate from various types of cells, including MCs, which have been described as a potential source of CAFs in peritoneal metastasis of OvCa, specifically. Given that both OvCa cells and MCs are present in the same peritoneal metastatic microenvironment, it may, therefore, be possible to establish cell-to-cell crosstalk or phenotypic alterations including the acquisition of platinum-resistance in OvCa cells. However, to-date few studies have examined the direct interactions between these two cell types.

Research Results

Results of in vitro experiments showed that mesenchymal transition was induced in OCAMs primarily by TGF-ß1 stimulation (Figure 1). Furthermore, OCAMs influenced the behavior of OvCa cells as a component of the tumor microenvironment of peritoneal metastasis. OCAMs also induced decreased platinum-sensitivity in OvCa cells via induction of the FN1/Akt

signaling pathway via cell-to-cell interactions (Figure 2). Histological analysis of OvCa peritoneal metastasis also illustrated FN1 expression in stromal cells that was supposed to originate from MCs. Further, they also confirmed activation of Akt signaling in OvCa cells in contact with TGF-β1 stimulated peritoneum, using an in vivo mice model. Their results suggested that the tumor microenvironment, enhanced by direct cell-to-cell crosstalk between OvCa cells and OCAMs, induces acquisition of platinum-resistance in OvCa cells, which may serve as a novel therapeutic target for prevention of OvCa peritoneal dissemination (Figure 3).

Figure 1. Mesenchymal transition was induced in OCAMs primarily by TGF-β1 stimulation

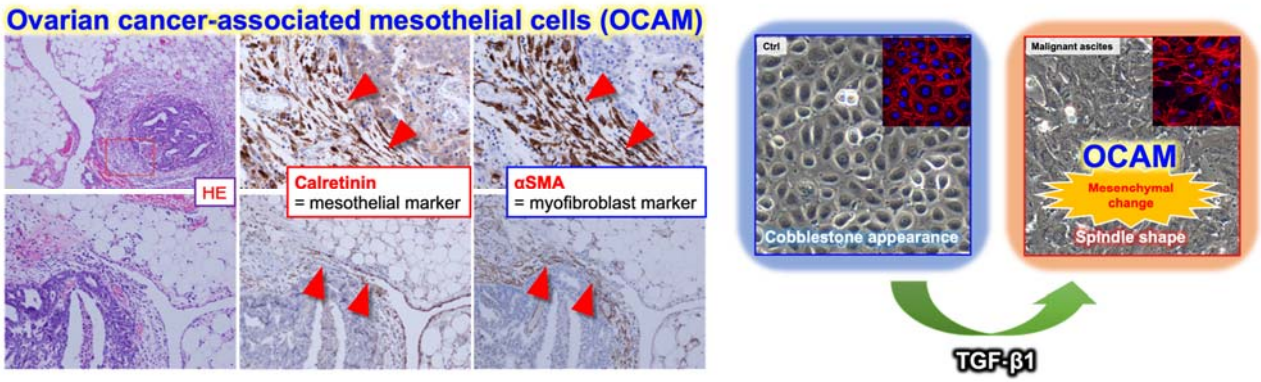


Figure 2. OCAMs also induced decreased platinum-sensitivity in OvCa cells

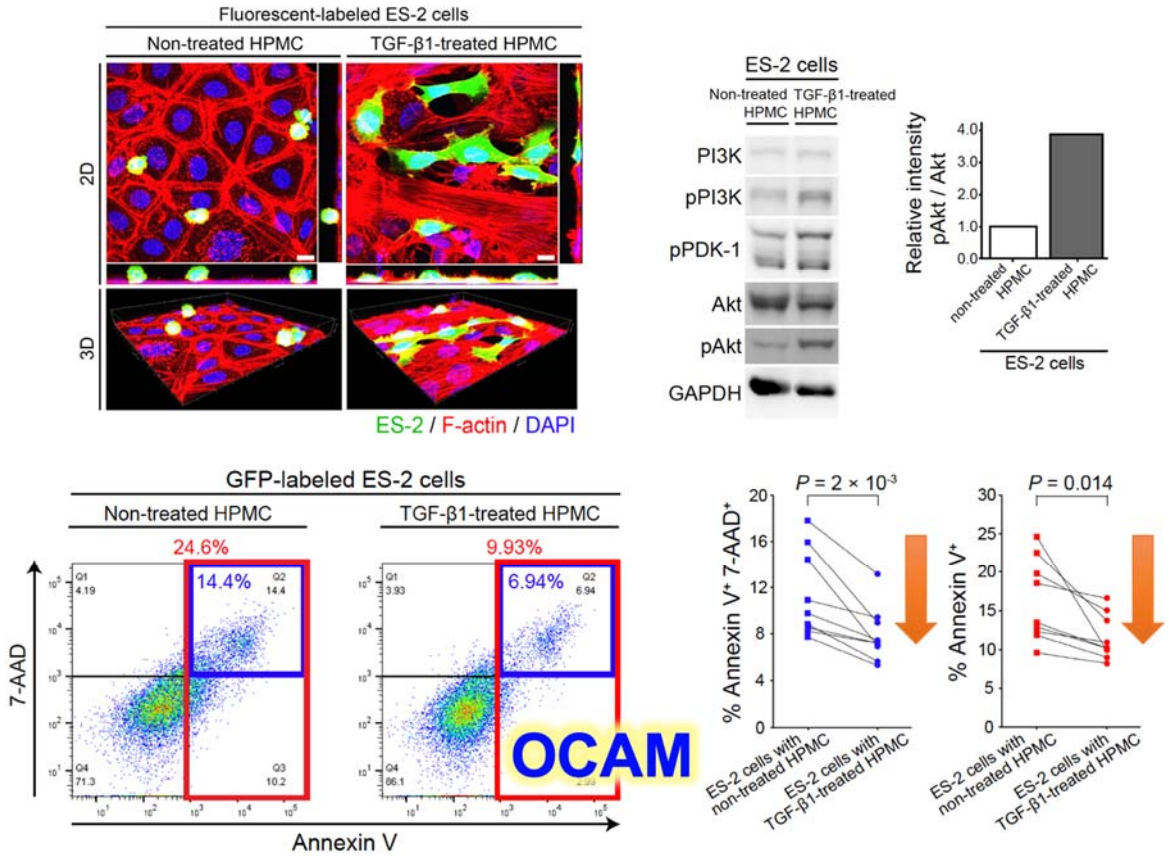
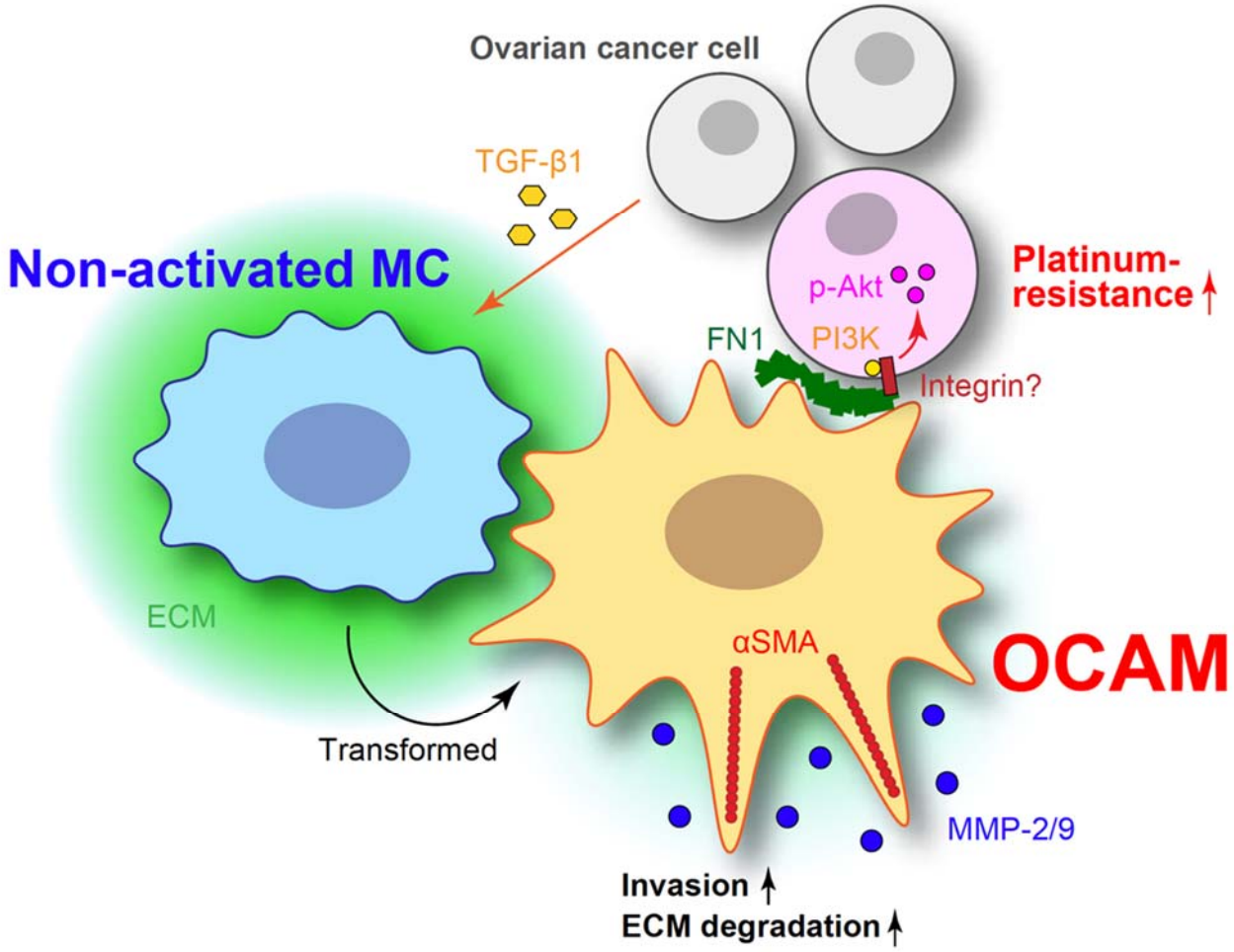


Figure 3. A hypothetical model describing the cell-to-cell crosstalk between OvCa cells and

OCAMs in the tumor microenvironment during peritoneal dissemination



Research Summary and Future Perspective

Tumor microenvironment enhanced by mutual association with OvCa cells and OCAMs promotes progression of peritoneal dissemination and acquired platinum-resistance in OvCa. Targeting OCAMs in peritoneal metastatic niche can be a novel therapeutic strategy in advanced OvCa.

Publication

Masato Yoshihara, Hiroaki Kajiyama, Akira Yokoi, Mai Sugiyama, Yoshihiro Koya, Yoshihiko Yamakita, Wenting Liu, Kae Nakamura, Yoshinori Moriyama, Hiroaki Yasui, Shiro Suzuki, Yusuke Yamamoto, Carmela Ricciardelli, Akihiro Nawa, Kiyosumi Shibata, and Fumitaka Kikkawa. Ovarian cancer-associated mesothelial cells induce acquired platinum-resistance in peritoneal metastasis via the FN1/Akt signaling pathway. *International Journal of Cancer*, published online on 24-Jan-2020.
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