学位論文の要約

Clinical and Basic Research for Ovarian Cancer

（卵巣がんに関する臨床及び基礎医学的研究）

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【Introduction】

Ovarian cancer (OvCa) is the leading causes of cancer-related death in gynecologic field. Some patients are diagnosed at an early stage of the disease, while more than half of patients are diagnosed in advanced stages due to the lack of specific symptoms and effective early detection screening system.

It is necessary to create future therapeutic strategies for OvCa at every phase of the disease from both a clinical and basic medical point of view. Prognostic relevance of limited surgery for early-stage non-serous epithelial OvCa is still unclear due to the lack of evidence and small sample size of study cohort in the literature. Regarding advanced OvCa, alternative therapeutic approachs are being explored to control progression of peritoneal metastasis, which fundamentally causes the poor prognosis.

Study Aims:

1. To investigate prognostic relevance of radical surgery compared with limited surgery, including fertility-sparing surgery, uterine preserving surgery, and partial lymphadenectomy in early-stage non-serous epithelial OvCa.
2. To uncover a novel mechanism of OvCa progression through peritoneal metastasis in advanced-stage and explore a new therapeutic target focusing on components of tumor microenvironment.

Research Plan:

We investigated the relevance of radical surgery compared with limited surgery, including fertility-sparing surgery and partial lymphadenectomy, focusing on non-serous carcinoma of the ovary. We conducted a regional multi-institutional study using data of patients under the central pathological review system. To analyze the effects of limited surgery, baseline imbalance between patients with and without limited surgery was adjusted with an inverse probability of treatment weighting using propensity scores. We also investigated how OvCa-associated mesothelial cells (OCAMs) promoted the progression of advanced OvCa. We evaluated how OCAMs affect OvCa cells through direct cell-to-cell crosstalk to identified a key molecular mechanism associated with the development of OCAM-induced platinum-resistance in OvCa cells.

【Results】

Propensity scores were estimated for each individual using a multivariate logistic regression model with predetermined variables. Based on results adjusted with an inverse probability of treatment weighting using propensity scores, patients with limited surgery were not associated with poorer prognosis regarding overall and recurrence-free survival in terms of fertility-sparing surgery, uterine preserving surgery, and partial lymphadenectomy.

Therefore, limited surgery can be a feasible therapeutic option for patients with early stage non-serous OvCa.

On the other hand, peritoneal dissemination is frequently observed in advanced OvCa patients, which 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, we reported how OvCa-associated mesothelial cells (OCAMs) induced platinum-resistance in OvCa cells through direct cell-to-cell crosstalk. We 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 showed that mesenchymal transition was induced in OCAMs primarily by transforming growth factor-β1 (TGF-β1) stimulation. Furthermore, OCAMs influenced the behavior of OvCa cells as a component of the tumor microenvironment during peritoneal metastasis. Mechanistically, OCAMs could induce decreased platinum-sensitivity in OvCa cells via induction of the fibronectin (FN1)/Akt signaling pathway via cell-to-cell interactions. Histological analysis of OvCa peritoneal metastasis also illustrated FN1 expression in stromal cells that were thought to originate from MCs. Furthermore, we also confirmed activation of Akt signaling in OvCa cells in contact with TGF-β1 stimulated peritoneum, using an *in vivo* mice model. Our 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.

【Discussion and Conclusion】

The limited surgery, including fertility-sparing surgery, uterine-preserving surgery, and reduced lymphadenectomy, evaluated in our studies demonstrated no significant association with worse prognosis than each corresponding radical surgery. Additionally, we identified a novel mechanism and therapeutic target for advanced OvCa. Based on the results of this study, we may be able to effectively control the development of peritoneal metastatic tumors even with the use of conventional platinum-based chemotherapy by inhibiting mesothelial conversion to OCAMs or the FN1/Akt signaling pathway axis.

Overall, the studies in this thesis indicate future therapeutic strategies for OvCa at every phase of the disease, which are highly diverse depending on condition of tumor and will of patients. Thus, gynecologist must respect patients' decision while considering optimal treatment for their welfare during and after cancer treatment. Both clinical and basic approaches will provide better understanding of OvCa pathophysiology and optimized

treatment for each patient. Further studies from both a clinical and basic medical point of view are needed to confirm our results and provide evidence to improve prognosis and quality of life of patients with OvCa in the future.