論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Name	伊東　優
論文題名 Title	Ex vivo chemosensitivity assay using primary ovarian cancer organoids for predicting clinical response and screening effective drugs （CTOS法による卵巣がんの化学療法感受性予測と新規治療法の探索）

論文内容の要旨

〔目　的(Purpose)〕

More than half of the cases with ovarian cancer are diagnosed at an advanced stage with distant metastasis. Ovarian cancer has poor prognosis because not all the patients respond well to the chemotherapy. Paclitaxel/carboplatin (TC) has been widely accepted as the standard of care for treating primary ovarian cancer. However, as ovarian cancer is a heterogeneous disease, a single standard treatment is unlikely to benefit all patients.

The aim of this study is to evaluate the clinical relevance of a newly developed chemosensitivity assay in ovarian cancer. In addition, we performed drug screening using carboplatin-resistant organoid lines to identify alternative combinations of drugs with carboplatin.

〔方法ならびに成績(Methods/Results)〕

We previously developed cancer tissue-originated spheroid (CTOS) method, a primary organoid culture system to prepare cancer cells from patient tumors. We prepared CTOS organoids from 61 ovarian cancer. The overall success rate of organoid formation was 100% (61/61 cases). Characteristics of the original tumors were well retained in the organoids. Among these 61 cases, 50 patients underwent TC chemotherapy. In this study, we conducted sensitivity assay for paclitaxel and carboplatin using the organoids from ovarian cancer. The success rate of sensitivity assay was 84.0% (42/50 cases). There were substantial differences in sensitivity among the organoids from different patients. Next, we compared the results of the organoid sensitivity assay with the clinical responses of 18 cases in which RECIST information was available. The organoids from all four clinically resistant patients (4/4, 100%) were resistant to both drugs in the assay. Five cases (5/18, 28%) were double-resistant, and the response rate of which was compatible with the clinical remission rate after extensive cytoreductive surgery and platinum- and taxane-based antineoplastic therapy.

We further explored alternative drug combinations other than paclitaxel with carboplatin. To obtain organoids in sufficient quantities for high-throughput screening, we established xenograft tumors. The success rate of establishing xenograft tumor lines more than two passages was low, 18% (11/61). We selected two lines of organoids, screened Food and Drug Administration (FDA) approved 1135 drugs, and found several drugs with better combinatory effects with carboplatin than with paclitaxel. Some drugs, including afatinib, have shown an additive effect with carboplatin.

Finally, we tracked the clinical outcomes of the patients for > 4 years. The organoid sensitivity assay did not predict the clinical outcomes, both progression free and overall survival.

〔総　括(Conclusion)〕

Ex vivo chemosensitivity assay using the primary ovarian cancer organoids reflected the RECIST of the patients. We performed high-throughput screening using established organoid lines and detected candidate drugs. Sensitivity assays using ovarian CTOS might be useful in precision medicine as well as development of novel therapeutic strategy.

論文審査の結果の要旨及び担当者

（申請者氏名）　伊東　優

論文審査担当者	（職）	氏名
主　査	大阪大学教授	木村　正
副　査	大阪大学教授	土岐祐一郎
副　査	大阪大学教授	森井英一

論文審査の結果の要旨

卵巣がんに対する初回化学療法としてパクリタキセルとカルボプラチンの併用療法（TC療法）が代表的であるが、患者により感受性が異なる。本研究ではがん患者検体から純化したがん細胞を効率よく初代培養を行う技術であるcancer tissue-originated spheroid （CTOS）法を用いて卵巣がんの初代培養を行い、化学療法感受性試験と臨床経過との関連を評価し、有効な薬剤を探索した。

61検体から卵巣がんオルガノイドを調製し、調製成功率は100%と高率であった。TC療法を受けた50例に関して卵巣がんオルガノイドを用いた感受性試験を行ったところ、84.0%と高確率で実行可能であり、その結果は臨床的な抗腫瘍効果を反映していた。新規治療候補薬を探索するためCTOS法を用いたHigh-throughput screeningを行った結果、現在臨床試験が行われているAfatinibなどが検出された。

本研究の成果はPrecision medicineに応用できる可能性があり、学位に値すると考える。