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Cancer stem cell marker EpCAM is involved in resistance to chemotherapy and poor prognosis in ovarian cancer patients

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The cancer stem cell hypothesis considers cancer stem cells as the main culprits of driving tumor initiation, metastasis, and resistance to conventional chemotherapy. Several previous studies have supported the premise that EpCAM proves to be a useful marker for the isolation of subsets enriched for cancer stem cells in many solid cancers, including ovarian cancer. We investigated the role of EpCAM in the resistance to platinum-based chemotherapy and the potential relevance of EpCAM to the clinical outcomes of patients with epithelial ovarian cancer. Here, we have showed that ovarian cancers containing high levels of EpCAM have a significantly much lower probability of achieving overall responsive rates after first-line platinum-based chemotherapy. Furthermore, multivariate analysis demonstrated that EpCAM expression in primary tumors is an independent risk factor for tumor resistance to chemotherapy, indicating that EpCAM expression is a predictive biomarker of chemotherapeutic response. Consistent with these clinical observations, in *in vitro* assays, we also found that treatment with chemotherapeutic agents enhances the cell surface expression of EpCAM in ovarian cancer cells. In association with anti-apoptotic mechanisms, the subpopulation of EpCAM-positive cancer cells showed a significantly higher viability than EpCAM-negative cells in response to chemotherapy. In an *in vivo* mouse model, platinum agents preferentially eliminated EpCAM-negative cells in comparison with EpCAM-positive cells, indicating that the remaining subpopulation of EpCAM-positive cells contributes to tumor recurrence after chemotherapy. Finally, we revealed that an increased expression of EpCAM in primary tumors was involved in a shortened overall- and progression-free survival in ovarian cancer patients. Our findings highlight the clinical significance of EpCAM in the resistance to chemotherapy and provide a rationale for EpCAM-targeted therapy to improve chemoresistance in ovarian cancer patients. Targeting EpCAM should be a promising approach to effectively eradicate the cancer stem cells as the putative root of ovarian cancer.

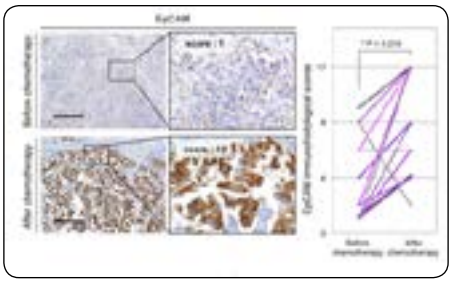

Figure 1: Immunohistochemical analysis with anti-EpCAM antibody of ovarian cancer tissues from patients treated without preoperative chemotherapy. Statistical analysis of the immunohistochemical scores of EpCAM in paired samples. The scores of EpCAM expression are significantly higher in ovarian cancer tissues from patients treated with chemotherapy than in those from matched patients treated without chemotherapy.

Recent Publications:

1. Tayama S, Motohara T, Fujimoto K, Narantuya D, Li C, et al. (2017) The impact of EpCAM expression on response to chemotherapy and clinical outcomes in patients with epithelial ovarian cancer. Oncotarget 8:44312–44325.
2. Motohara T, Fujimoto K, Tayama S, Narantuya D, Sakaguchi I, et al. (2016) CD44 variant 6 as a predictive biomarker for distant metastasis in patients with epithelial ovarian cancer. Obstet Gynecol. 127:1003–1011.
3. Tjhay F, Motohara T, Tayama S, Narantuya D, Fujimoto K, et al. (2015) CD44 variant 6 is correlated with peritoneal dissemination and poor prognosis in patients with advanced epithelial ovarian cancer. Cancer Sci. 106:1421–1428.
4. Motohara T, Masuko S, Ishimoto T, Yae T, Onishi N, et al. (2011) Transient depletion of p53 followed by transduction of c-Myc and K-Ras converts ovarian stem-like cells into tumor-initiating cells. Carcinogenesis. 32:1597–1606.

Biography

Takeshi Motohara is Assistant Professor in Department of Obstetrics and Gynecology, Kumamoto University, Japan. He is now engaged in research on molecular biology of ovarian cancer in Ovarian Cancer Cell Laboratory, Weatherall Institute of Molecular Medicine, Nuffield Department of Obstetrics and Gynaecology, University of Oxford as a Visiting Postdoctoral Research Scientist. He is distinguished gynecologic oncologist in Japan. His research is focused on understanding the molecular mechanisms of evolution of ovarian cancer, especially cancer stem cell, and on the development of novel therapeutic strategies for ovarian cancer.

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