IS-AC-1-1 Casein kinase I epsilon is a novel molecular target for c-Myc driven ovarian cancers

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[Objective] The MYC oncosgene is a central driver in many human cancers. Not only overexpression but gene amplification of c-Myc have been observed in epithelial ovarian cancers. We have explored a target molecule whose inhibition can selectively halt c-Myc driven cancers. [Methods] We carried out a high throughput siRNA screening and identified casein kinase I epsilon (CKIε) as a MYC synthetic lethal gene. We studied CKIε expressions in patients' samples and the prognosis based on the c-Myc states. We also investigated the effects of IC-261, a small molecule CKIε inhibitor, in in vitro and in vivo. All experiments were conducted on the approval of the ethic board at Tohoku University School of Medicine. [Results] CKIε expressions were significantly correlated with c-Myc expressions in ovarian cancer samples. High CKIε group showed significantly poor prognosis in only c-Myc high ovarian cancer patients. Both siRNA for CKIε and IC-261 treatment selectively inhibited c-Myc driven ovarian cancers, but IC-261 administration showed a curative effect in mouse carcinomatous peritonitis model. [Conclusion] Through this functional genomics approach, we have identified CKIε as a new therapeutic target for c-MYc driven ovarian cancers. These results indicate rational combination treatments and biomarkers to aid therapeutic choices for molecularly defined patient populations.

IS-AC-1-2 EMT-related gene Snail inhibits anti-tumor immunity in ovarian cancer through recruitment of MDSC

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[Objective] Epithelial–mesenchymal transition (EMT) is a key process in tumor invasion and metastasis, and recent studies on tumor microenvironment suggest that MDSC (myeloid-derived suppressor cells) suppress anti-tumor immunity via expression of CXCR2 ligands. The aim of this study is to explore the functional relationship between EMT and local immunity in ovarian cancer progression. [Methods] The expression of EMT-related gene Snail was analyzed using TCGA microarray dataset. From mouse ovarian cancer cell line HM-1, a Snail-silenced cell line, HM1-sh-Snail was established. Using these cell lines, EMT, peritoneal dissemination, survival, and local immunity were analyzed. [Results] High Snail expression was correlated with short overall survival in TCGA (p<0.05). In the immunocompetent mouse model, HM1-sh-Snail demonstrated longer survival and smaller tumor volume than control (p<0.05), but in immunosuppressive mouse model, there was no difference between the two groups. Flow cytometric analysis of mouse tumors showed that CD4+ and CD8+ T cells increased and MDSC decreased in number in HM1-sh-Snail group (p<0.05). In HM1-sh-Snail, expression of CXCR2 ligands, CXCL2/3/5, were decreased (p<0.05). [Conclusion] EMT-related gene Snail plays an important role in ovarian cancer progression possibly via expression of CXCR2 ligands and recruitment of MDSCs.

IS-AC-1-3 Investigation for the antineoplastic effect of lovastatin on ovarian cancer using metabolomic analysis

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[Objective] Omics analysis recently has shown that metabolic abnormalities are involved in onset of many malignant tumors. We have previously shown an antitumor effect of statins, which are antidyslipidemic drugs, on ovarian cancer in vitro and in vivo. In this study, we performed a metabolomic analysis to investigate the mechanism of action of lovastatin from a metabolic perspective. [Methods] Metabolites were analyzed with or without lovastatin in SKOV3 ovarian cancer cells by capillary electrophoresis coupled with mass spectrometry. The frequency of autophagy and apoptosis, which were found to have relationships with metabolites, and changes in resistance to antineoplastic agents were examined by quantitative RT-PCR, western blotting and cell count analysis. [Results] Production of ATP and GTP significantly decreased, and reduced and oxidized glutathione, an antioxidant, also decreased in lovastatin-treated cells compared to controls. Lovastatin treatment significantly increased expression of autophagy marker LC3A/B and apoptosis markers caspase-3 and PARP. Furthermore, lovastatin had inhibitory effects on cell growth in both paclitaxel- and carboplatin-resistant strains. [Conclusion] Lovastatin has an inhibitory effect on tumor cell growth probably due to regulation of glutathione, and it may be involved with autophagy, apoptosis and changes in resistance to antineoplastic agents.