IS-MW-1-1 Oncogenes (K-ras and c-Myc) modulate tumor immune system and enhance peritoneal carcinomatosis in the ovarian cancer

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[Objective] Little is known whether oncogenes involve the modulation of tumor microenvironment (TME) favorable for cancer development. We here addressed the contribution of K-ras and c-Myc oncogenes in the TME of peritoneal carcinomatosis accompanied by disseminated ovarian cancer. [Methods] K-ras and c-Myc were stably introduced into murine ovarian cancer cell line, ID8, named ID8-Kras and ID8-cMyc. Each cell line was intra-peritoneal injected into mice. Concentrations of VEGF and inflammatory cytokines (IL6, TNFa) in ascites were assessed by specific ELISA. 3T3-L1, adipocyte cell line, was cultured with medium of each cell and expression of IL-6 in 3T3-L1 was assessed by RT-PCR. [Results] ID8-Kras and ID8-cMyc cells accelerated production of ascites compared with ID8 cell. VEGF concentration was higher in ID8-cMyc-induced ascites while IL-6 was higher in ID8-Kras-induced ascites when compared with the others. Medium from ID8-Kras promoted IL-6 expression in the 3T3-L1 adipocytes. [Conclusion] K-ras and c-Myc altered cancer-induced peritonitis (TME) in a different way. c-Myc induced VEGF secretion into ascites followed by angiogenesis. K-ras induced IL-6 secretion probably from adipocytes leading to severe inflammation. These oncogenes were involved in the characteristics of disseminated ovarian cancers through modulation of the TME.

IS-MW-1-2 Combination of MDM2 inhibitor and PI3K/mTOR inhibitor showed synergistic anti-tumor effect in ovarian clear cell carcinomas

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[Objective] In ovarian clear cell carcinoma (OCCC), PI3K/mTOR signaling pathway is frequently activated, while p53 mutation is only detected in 10%. MDM2 inhibitor activates p53 by inhibiting the binding of MDM2 and p53. We aimed to elucidate whether dual inhibition of MDM2 and PI3K/mTOR suppresses cell growth in OCCC cells with wild-type p53. [Methods] We treated 7 OCCA cell lines with a MDM2 inhibitor, RG7112, and/or a PI3K/mTOR inhibitor, DS7423. Cell proliferation and apoptotic cell population were evaluated by MTT assay and Annexin-V assay. In vivo anti-tumor effect was analyzed by using a mouse xenograft model. [Results] Sensitivity to DS7423 was not distinct between p53 wild-type and p53 mutant OCCC cells. However, dose-dependent suppression of cell proliferation by RG7112 was only observed in cells with wild-type p53. The IC50 values of DS7423 were drastically decreased when combined with RG7112. Combination of RG7112 at 2.5μ M and DS7423 at 156nM increased the ratio of apoptotic cells up to 23% in OVTOKO cells. In mouse xenograft models, oral administration of combination DS7423 (3mg daily) and RG7112 (50mg daily) significantly suppressed the tumor growth, compared with each single agent alone ($p<0.05$). [Conclusion] Targeting both PI3K/mTOR pathway and MDM2 might be a promising therapeutic strategy in OCCC with wild-type p53, by synergistically causing the cytotoxic effect.

IS-MW-1-3 A novel biomarker that distinguishes early stage ovarian clear cell adenocarcinomas from benign endometriomas

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[Objective] While certain fraction of endometriomas can develop ovarian clear cell carcinoma (OCCC), there is currently no useful biomarker available for early detection of OCCC from endometriomas. The aim of this study was to describe the diagnostic utility of a novel biomarker for OCCC to distinguish from endometrioma. [Methods] After receiving institutional review board approval, more than 100,000 glycan structures of serum glycoproteins obtained from 134 pretreatment all stage epithelial ovarian cancer (EOC) patients (including 45 OCCCs) and 159 non-cancer control women (including 36 endometriomas) were explored for a mass spectrum approach. Diagnostic accuracy of identified biomarker was compared to the one of CA-125 by comparing area under curve (AUC) and positive/negative predictive values (PPV and NPV). [Results] A2160, a fully-sialylated alpha-chain of complement 4-binding protein, was identified as the candidate target marker. A2160 was significantly elevated in all stage OCCC compared to endometrioma. Diagnostic accuracy of A2160 (cutoff 1.6 U/mL) to distinguish early stage OCCC from endometrioma is significantly higher than that of CA-125 (cutoff 35 IU/L) : AUC for A2160 versus CA-125, 0.92 versus 0.67 ; PPV 95% versus 64% ; and NPV 85% versus 58%. [Conclusion] Our study suggested that A2160 may be a useful biomarker to distinguish early-stage OCCC from endometrioma.