ISP-12-3 Transferrin is involved in the carcinogenesis of high-grade serous ovarian cancer by facilitating the DNA double-strand breaks via transferrin receptor 1 in fallopian tube

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[Objective] Fallopian tube epithelium (FTE) is a candidate for the origin of high-grade serous ovarian cancer (HGSOC). Although accumulation of DNA double-strand breaks (DNA-DSBs) in FTE is involved in the carcinogenesis, the mechanism underlying the formation of DNA-DSBs has not been clarified. Hydroxyl radicals, the reactive oxygen species (ROS) promoting DNA-DSBs, is produced in a Fenton reaction catalyzed by iron ion. As follicular fluid contains transferrin that serves as an iron ion transporter, we investigated the involvement of transferrin in DNA-DSBs formation. [Methods] Human FTE cells and A2780 ovarian cancer cells were treated with transferrin. Phospho-histone 2AX (γH2AX) was employed as a marker for DNA-DSBs. Murine adnexes were prepared for ex vivo study. Human follicular fluid was analyzed based on the approval of the ethic board. [Results] Transferrin incorporated into the cells via transferrin receptor 1 promoted ROS formation and increased γH2AX expression. Transferrin treatment also introduced DNA-DSBs to murine FTE ex vivo. Follicular fluid contained adequate amount of transferrin, and part of the follicular fluid introduced DNA-DSBs to the cells. [Conclusion] We found the novel aspect of transferrin as a molecule facilitating DNA damage and genomic instability. It is plausible that transferrin is involved in the carcinogenesis of HGSOC.

ISP-12-4 Establishment of ovarian cancer patient-derived-xenograft

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[Objective] Patient-derived-xenograft (PDX) is created by transplanting surgically resected patient tumors into immunocompromised mice to maintain cytogenetics and tumor heterogeneity of donor tumors, thus providing resource of translational analyses. We report clinical factors that influence the establishment of PDX from ovarian cancer. [Methods] Ovarian tumor tissue fragments from patients undergoing surgery between March 2014 and March 2015 at our hospital were transplanted subcutaneously into NOD-SCID mice. After 2-6 months, tumors grown on mice were excised and serially transplanted into additional mice for propagation. We analyzed clinical information according to whether or not PDX tumors were established. Histological analysis was performed for PDX and their original tumors. [Results] PDX was successfully established with the ratio of 31.3% (10/32) ; 2 high grade serous, 4 clear cell, 2 undifferentiated and 2 non-gynecological adenocarcinomas. The ovarian cancer patients whose tumors established PDX had more advanced stage, higher grade and worse survival rate than not established ($p<0.05$, respectively). The established PDX tumors were histologically similar to the corresponding patients' tumor. [Conclusion] In ovarian cancer, PDX can be established exclusively from poor prognostic and aggressive tumors. PDX may be useful in searching effective treatments for these tumors.

ISP-12-5 Significant clinical response of glypican-3-derived peptide vaccine therapy for progressive recurrent ovarian clear cell carcinoma

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[Objective] Glypican-3 (GPC3) is carcinoembryonic antigen and it's not expressed normal cell. Vaccine immunotherapy that targeted human leukocyte antigen (HLA)/GPC3 peptide complex was reported the clinical response of advanced hepatocellular carcinoma. In previous study, we showed that 40% of ovarian clear cell carcinoma (CCC) express GPC3, so we prepared the clinical trial. We performed phase 2trial to evaluate the clinical outcome of ovarian CCC patients treated with a GPC3-derived peptide vaccine. [Method] One of the subjects this study is the recurrent CCC of chemotherapeutic agent resistance. We screened the HLA type and the patients of HLA-A2 or A24 participated in this study. [Case report] Case1. A 42y patient with advanced recurrent ovarian CCC with liver and retroperitoneal lymph node metastases, received the HLA-A24-restricted GPC3 peptide vaccine. CT at week 10 revealed a partial response (PR). Case2. A 67y female with multiple lymph node metastases. She was injected with the HLA-A2-restricted GPC3 peptide vaccine. PR was achieved at week 37. Case3. A 65y patient with peritoneal dissemination. She was treated with HLA-A24-restricted GPC3 peptide vaccine, and kept PR for 9 months. [Conclusion] This study reveals the clinical response of GPC3 peptide vaccine for the patients of CCC. In a few cases, the effectiveness of GPC3-peptide vaccine was showed, and it may improve the overall survival of CCC patient.