CANCER RESEARCH

Clinical Trials

Abstract 5381: Elevated PD-L1 and HER2 expression on aneuploid carcinoma cells in malignant ascites accelerate stumor cell immune evasion in gastrointestinal cancer patients

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Abstract

Background Peritoneal dissemination (PD) is a type of metastasis frequently found in gastrointestinal (GI) cancer patients, resulting in the production of massive malignant ascites which associate with poor prognosis. However, the question of how the expression of tumor biomarkers on cancer cells in malignant ascites correlates with PD is yet to be answered. This study aims to investigate the clinical significance of PD-L1 and HER2 expression on malignant ascites disseminated tumor cells (maDTCs) in GI carcinoma patients.

Patients and Methods Paired blood and malignant ascites specimens were respectively collected from 24 of metastatic GI subjects, including 15 gastric, 2 pancreatic, 1 esophageal, and 6 colorectal cancer patients. Non-hematologic CTCs and maDTCs were enriched by subtraction enrichment (SE), followed by immunostaining-FISH (iFISH) to co-examine PD-L1 and HER2 expression on aneuploid maDTCs and CTCs. In addition, $CD4^+$, $CD8^+$, Treg and naive T cells in the same cohort of samples were quantified by flow cytometry.

Results *In situ* karyotypic and phenotypic characterization performed by iFISH showed that the average number of maDTCs in the 24 patients was 32755/ml ascites, which was significantly higher than the average number of CTCs detected (3.5/ml blood) (P<0.0001). The number of maDTCs and CTCs exhibited no correlation between each other (Pearson's product-moment correlation coefficient, R=-0.03, P=0.89). Further examination indicated that PD-L1 was expressed on 50% of maDTCs compared to only 11% for CTCs (P=0.0002). No correlation of PD-L1 expression between maDTCs and CTCs was observed (Pearson's product-moment correlation coefficient, R=0.25, P=0.24). Co-expression of PD-L1 and HER2 on CTCs and maDTCs was respectively examined in the recruited 15 gastric cancer (GA) patients. All 15 patients were histopathological $HER2^-$ negative ($hHER2^-$). One subject (1/15=6.7%) showed 1 double $HER2^+$/$PD\text{-}L1^+$ CTC (1/63 CTCs in 15 GA patients=1.6%). In comparison, 6 patients (6/15=40%) had a total of 290377 $HER2^+$/$PD\text{-}L1^+$ maDTCs detected (290377/1306783 overall maDTCs=22%). In addition, flow cytometry analyses revealed that 5% of lymphocytes in malignant ascites were immunosuppression relevant regulatory T cells (Tregs), compared to only 2% of Tregs identified in the paired peripheral blood sample of the same patient.

Conclusions Our study suggested that a higher proportion of Tregs in malignant ascites may contribute towards fostering an immunosuppressive microenvironment.$PD\text{-}L1^+$/$HER2^+$ maDTCs, in such an immunosuppressive microenvironment, might be able to evade immune system attack. Moreover, PD-L1 and HER2 identified on maDTCs could serve as therapy targets with respect to inhibition of peritoneal metastasis, potentially leading to an additional treatment strategy for GI cancer patients with malignant ascites.

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