PROGNOSTIC IMPACT OF CD73 EXPRESSION IN EPITHELIAL OVARIAN CANCER

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Introduction CD73 (ecto-5′-nucleotidase) is a membrane-bound enzyme crucial in adenosine generation. The adenosine pathway plays a critical role in immunosuppressive tumor-microenvironment (TME). The purpose of the study was to evaluate CD73 expression in TME, and its association with clinicopathological features to better understand the role of CD73-adenosine pathway in epithelial ovarian cancer (EOC).

Methods A total of 48 patients (treatment-naïve, n=35; recurrent, n=13) with epithelial ovarian cancer were enrolled in the current study. For each patient, a retrospective review of medical records was conducted. Immunohistochemical staining for CD73 was performed using paraffin embedded tissue block. CD73 expression level were graded on a scale of 0 to 3.

Results Median age was 59 years (range 38–84 years), and the majority of the patients presented with high-grade serous carcinoma (HGSC, 85.4%) and stage III-IV disease (89.6%) at diagnosis. Among the treatment-naive patients, 17.1% of patients (n=6) showed low CD73 expression (grade 1), whereas 60.0% of patients (n=21) showed high CD73 expression (grade 2/3). All of the BRCA1/2-mutated tumors were high CD73 (n=7), whereas 20% of BRCA1/2-non-mutated tumors (n=5) were low CD73 expression. The CD73 high group showed better PFS compared to the CD73 low group (median PFS 20.1 versus 11.9 months, P=0.043). Among the recurrent patients, 84.6% of patients (n=11) showed high CD73 expression (All HGSC [n=10] were high; all clear cell carcinoma [n=2] were low).

Conclusion/Implications Our study suggests that higher CD73 expression is associated with favorable survival outcomes in EOC. Further studies are needed to explore the role of CD73 in EOC.

ORGANOIDS AS PRE-CLINICAL MODELS TO ASSESS THE EFFICACY OF HEATED INTRAPERITONEAL CHEMOTHERAPY IN MUCINOUS OVARIAN CANCER

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Introduction Mucinous ovarian cancer (MOC) is a rare subtype of epithelial ovarian cancer (EOC) comprising <5% of cases. Despite its rarity MOC contributes significantly to the poor outcomes seen with EOC due to its inherent resistance to platinum-based chemotherapy regimens. Heated intraperitoneal chemotherapy (HIPEC), where a single dose of heated chemotherapy is given at surgery, has gained traction in recent years following benefits seen in high grade serous ovarian carcinoma and colorectal carcinoma. Data on the use of HIPEC in MOC remains limited.

Methods Following the development of successful MOC organoid models, we undertook drug screening with eight chemotherapy agents often used in HIPEC. To simulate HIPEC conditions, we incubated our organoid models at 43°C for 120 minutes following addition of the chemotherapy agent. Drug
In the HIPEC model, platinum-based chemotherapy appears to have a cytostatic effect on MOC organoids in comparison to normothermic conditions. Variable responses were seen to gemcitabine, mitomycin C and 5FU with the addition of heat having no therapeutic effect. Strongest response was seen to irinotecan with the addition of heat again having no additional effect.

Conclusion/Implications

Utilising organoids to assess HIPEC chemotherapy regimens in MOC provides a unique opportunity to assess drug response. HIPEC appears to improve response to platinum-based chemotherapy in MOC organoids whilst having little additional benefit with other agents. Going forward we aim to assess further combination chemotherapy regimens and to correlate results with genetic and gene expression characteristics to further understand treatment response.

Introduction

Whether adaptive immune cells are required for the formation of pre-metastatic niches critical for tumor metastasis remains unknown. Prior research indicates that Signal transducer and activator of transcription 3 (STAT3) contributes to the accumulation and function of innate immune cells in these niches. This study investigates whether CD4+ T cells can directly condition future metastatic sites and if STAT3 is necessary for CD4+ T cell-mediated niche formation.

Methods

We evaluated CD4+ T cell infiltration in non-metastatic lung regions of mice and examined the role of STAT3 signaling using CD4Cre-Stat3Flox transgenic mice lacking functional Stat3 in T cells. Clinical correlations in ovarian cancer patients’ disease-free lung and liver tissue sites from rapid autopsy tissue collection were also analyzed.

Results

Our findings reveal that CD4+ T cells accumulate in distant tumor-free sites, forming pre-metastatic niches and subsequently promoting tumor metastasis in mice. Moreover, STAT3 activation is necessary for CD4+ T cell-mediated pre-metastatic niche formation. Depleting CD4+ T cells and STAT3 activation prior to primary tumor establishment significantly reduced tumor growth and almost completely blocked spontaneous lung metastasis, as evidenced in CD4-Stat3–/– mice. Importantly, analysis of presumed disease-free lung and liver tissue sites of ovarian cancer patients showed CD4+ T cell accumulation with activated STAT3 in non-tumor regions and surrounding micro-metastases.

Conclusion/Implications

Blocking the pre-metastatic niche has the potential to prevent tumor cell seeding at distant sites, and our studies now show that targeting STAT3 in CD4+ T cells may be an effective strategy to prevent tumor metastasis.