PO-366 CHEMOTHERAPY INDUCES PD-L1 IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Introduction Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive and lethal cancers. Chemoresistance is a major obstacle in effective treatment for ESCC patients. Programmed death ligand-1 (PD-L1) is an immunoregulatory protein that is overexpressed in various cancers. PD-L1 up-regulation contributes to chemoresistance in several cancers, but little is known with respect to changes associated with chemotherapy treatment in ESCC.

Material and methods A tissue microarray consisting of 84 ESCC tumours from Chinese patients was used to determine the PD-L1 expression and its correlation with clinicopathological parameters. Immunohistochemical (IHC) staining was performed with PD-L1 antibody and the staining intensity was scored. Two ESCC cell lines, KYSE150 and SLMT, were used. Cells were treated with either 5-Flurouracil plus cisplatin or carboplatin plus paclitaxel, which are the common regimens used for ESCC patients. The regulation of PD-L1 expression by the EGFR pathway and ERK pathway was studied using Erlotinib (EGFR inhibitor) and AZD6244 (MEK inhibitor). For the *in vivo* studies, an esophageal orthotopic mouse model was used. KYSE150 cells were injected into the mouse oesophagus. Mice were administered with 5-Flurouracil plus cisplatin or carboplatin plus paclitaxel by intraperitoneal injection. The change in PD-L1 expression was then evaluated by Western blotting and IHC staining.

Results and discussions The expression frequency of PD-L1 in Chinese ESCC patients was 21% (18/84) and the patients with positive PD-L1 staining were associated with later stage (stages III and IV) of the disease. Also, high PD-L1 expression was associated with lymph node metastasis. Both *in vitro* and *in vivo* studies demonstrate that the level of PD-L1 expression increased after the treatment with 5-Flurouracil plus cisplatin or carboplatin plus paclitaxel. *In vitro* study shows that the elevated PD-L1 level was sustained even after the drugs were removed. By using pathway inhibitors, we demonstrate the increase in PD-L1 expression in response to chemotherapy was regulated by the EGFR pathway and its downstream ERK pathway, as the PD-L1 level attenuated when Erlotinib or AZD6244 was added.

Conclusion PD-L1 expression was increased following treatment with chemotherapy in ESCC cell lines, suggesting that combining chemotherapy with PD-L1 blockade may improve treatment in ESCC patients.

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PO-367 BRAIN MICROENVIRONMENT-SECRETED CYTOKINES FACILITATE GLIOBLASTOMA PROLIFERATION AND INVASION

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Introduction Glioblastoma is the most common and lethal type of brain cancer with a median survival of under fifteen months. It is a highly angiogenic tumour exhibiting an extremely invasive nature. It is well-known that the brain microenvironment plays a crucial role in glioblastoma progression although the large multitude of interactions between the cancer cells and their microenvironment are yet to be fully unravelled. Astrocytes are the most abundant glial cells in the brain and have been shown to be involved in many types of brain pathologies as well as metastatic colonisation in the brain. Hence, we investigated the influence of astrocytes on the migratory and infiltrative abilities of glioblastoma cells.

Material and methods In order to evaluate the influence of brain microencironment on glioblastoma progression we used co-culture proliferation and migration assays as well immunohistochemistry analysis of our mouse models and patient derived samples. Using protein profiler we assessed the level of cytokines secreted following interaction of glioblastoma cells and their microenvironment.

Results and discussions Using *in vitro* and *ex vivo* assays, we found that in the presence of either astrocytes or their conditioned media, the migration rate of glioblastoma cells is significantly increased. Microglia are macrophages-like cells which possess antigen-presenting and phagocytic abilities that serve as the brain immune system. In a co-culture proliferation assay, we observed that microglia increased glioblastoma cells proliferation at a concentration-dependent manner. Furthermore, co-culture of glioblastoma cells with either astrocytes, microglia or brain endothelial cells resulted in elevated levels of several similar cytokines. Moreover, immunohistochemistry analysis of several brain tumours inoculated orthotopically in mice revealed an increased level of activated astrocytes and microglia and high microvessel density within the tumoursite

Conclusion Our findings indicate that the brain microenvironment facilitates glioblastoma proliferation and invasion by cytokines secretion paving the way for investigation of their use as targets for glioblastoma therapy.

PO-368 DIFFERENTIAL EFFECTS OF IMMUNE ACTIVITY ON MELANOMA CELL SUBTYPES

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Introduction The cytokines IFNγ and TNFα are abundantly expressed by cytotoxic T cells. These cytokines have distinct and overlapping downstream effects. In this study, we assessed the effects of IFNγ and TNFα on the expression of immune regulatory factors.

Material and methods We analysed a large panel of melanoma cell lines, including BRAF mutant (n=11), NRAS mutant (n=10), BRAF and NRAS wild type (n=10) cutaneous melanomas, and GNAQ/11-mutant uveal melanomas (n=8). These cells were treated with TNFα or IFNγ for 48 hour and the expression of PD-L1, PD-L2, HLA-ABC and HLA-DR was analysed by flow cytometry.

Results and discussions IFNγ showed consistently stronger induction of PD-L1, PD-L2, HLA-ABC and HLA-DR