An Organoid-Based Model for Optimal Treatment of Pancreatic Ductal Adenocarcinoma

Chantal Woodson[1], Loryn Holokai[2], Jayati Chakrabarti[1], Jiang Wang[3], Syed Ahmad[4] Yana Zavros[1]

[1]Department of Pharmacology and Systems Physiology, University of Cincinnati [2]Department of Molecular Genetics, University of Cincinnati, [3]Department of Pathology and Lab Medicine, University of Cincinnati College of Medicine, [4]Department of Surgery, University of Cincinnati College of Medicine

Introduction: Pancreatic Ductal Adenocarcinoma (PDAC) has a survival rate of only 8.5%. Resistant tumors show increased PD-L1 expression inducing cessation of anti-tumor activity in cytotoxic T Cells (CTLs). The mechanism by which PD-L1+ PDAC tumors evade the immune response is not well understood. Myeloid cells block anti-tumor CD8+ T cell immune responses partially by activating the PD-L1 checkpoint on tumor cells, and targeting the MDSC population enables an endogenous T cell response in PDAC.

Hypothesis: 1) Organoids derived from resected PDAC tumors provide an *in vitro* model for predicting personalized therapy. **2)** Therapy-resistant PD-L1+ organoids are sensitive to combinatorial therapy involving both checkpoint inhibition and MDSC depletion.

Methods: Organoids were generated from resected PDAC patient tumors. Autologous CTLs were isolated from whole blood of PDAC patients. Monocytes and dendritic cells were differentiated from Peripheral Blood Mononuclear Cells. HLA-DR+ dendritic cells isolated by FACS were co-cultured with CTLs to activate them against autologous PDAC tumor. Activated CTLs and/or MDSCs were co-cultured with organoids derived from the same PDAC patient tumor. Organoid PD-L1 expression and CTL proliferation were measured using flow cytometry in response to standard-of-care chemotherapy alone or in combination with checkpoint inhibition and/or MDSC depletion**.**

Results: 1) Patients that exhibited chemoresistance showed increased G-MDSC infiltration within their tumor tissue. **2)** In an autologous organoid/CTL co-culture derived from a chemoresistant patient with elevated G-MDSC infiltration, approximately 50% PD-L1+ organoid cell death was observed when cultures were treated with either PD-1 inhibitor (PD-1I, Nivolumab) alone or in combination with chemotherapy. Importantly, the inclusion of G-MDSCs in the co-culture of organoids and CTLs hindered the efficacy of checkpoint inhibition by Nivolumab. Depleting the co-culture of MDSCs using Cabozantinib maximized the efficacy of checkpoint inhibition in combination with chemotherapy to induce cancer organoid death. **3)** Organoid/CTL co-cultures generated from chemo-naive patients were used to predict the efficacy of combinatorial therapy for these individuals.

Conclusions: Depletion of MDSCs within the PDAC tumor microenvironment may enable the CTL anti-tumor response. Thus, patient-derived organoid/immune cell co-cultures provide an approach to predict efficacy of combinatorial therapy and thus improve PDAC patient outcome.

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