ImmunoTools *special* Award 2025

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The role of oral bacteria-monocyte interaction in shaping the PDAC microenvironment& chemoresistance

Background

Pancreatic ductal adenocarcinoma (PDAC) is a highly fatal malignancy (predicted to become the second leading cause of cancer-related deaths by 2030), with a limited number of known risk-factors and diagnostics tools, nor effective systemic treatments. The remarkable chemoresistance of PDAC has been attributed to several key features including genetic instability, metabolic aberrations, and a complex tumor microenvironment (TME) dominated by stromal and immune-suppressive cells.

Although the oral cavity is distant from the pancreas, the microbiota in these two locations are similar. Mounting evidence suggests that pancreatic and oral microbiota play a role in the multifactorial chemoresistance of PDAC, involving immunosuppressive properties of monocytes/macrophages.

Thus, our working hypothesis is that “oral bacteria-educated” monocytes and/or macrophages could be altered into myeloid cells which underpin the suppressive PDAC-TME, and contribute to chemoresistance.

Methods

(1) Determine the effects of oral microbes on monocyte activation and macrophage skewing. Using our recently-developed protocol, monocytes from patients will be exposed to candidate oral bacteria (3 bacteria, selected from studies on PDAC microbiome and chemoresistance), and their “bacteria-educated” phenotypes will be evaluated by analyses of cytokines and immunological profiling . We will determine whether monocytes exposed to oral bacteria become activated, or whether they assemble immune suppressive features. Monocytes will be cultured with or without oral microbes, and their cytokine-secretion

profiles will be studied. Multi-parameter flow cytometry will also be used to study whether the presence of oral microbes skews these macrophages towards a more inflammatory M1-type macrophage or immune suppressive M2-type macrophage. The ImmunoTools special Award will significantly aid this initial phase of the project.

(2) Study macrophage-phenotype in PDAC tissue and in PDAC-TME models incorporating bacteria-educated monocytes/macrophages. By multi-parameter flow cytometry, we will assess the phenotype of PDAC-associated macrophages using single cell suspensions obtained from 10 PDAC biopsies. These profiles will be compared to the oral bacteria-educated macrophages in the Workpackage 1 and to PDAC-TME models. The PDAC-TME models including cancer cells, pancreatic stellate cells, and bacteria-educated monocytes or macrophages will be generated. Monocytes/macrophages without bacteria will be integrated to the co-cultures with primary PDAC and stellate cells as controls.

(3) Determine the contribution of oral microbes to PDAC chemoresistance. We already successfully demonstrated the ability of some bacteria to induce chemoresistance in PDAC cells, but the models created in WP-2 will be essential to determine the influence of PDAC-TME and bacteria-educated monocytes/macrophages. In particular, the established bacteria-host co-culture models will be tested with selected drugs currently used in the clinical setting (gemcitabine, 5-fluorouracil, oxaliplatin, irinotecan, and nab-paclitaxel), at various concentrations, for 24 - 72 hours. Growth inhibition and apoptosis induction will be evaluated by SRB/MTT, resazurin, and fluorescence assays.

In conclusion, our ultimate goal is to identify key microbiome and immune-cell features that could guide more effective therapeutic treatments. Therefore, we would like to take advantage of the excellent initiative from ImmunoTools achieve this goal.

ImmunoTools *special* AWARD for **Chen Sun** includes 10 reagents

FITC - conjugated anti-human CD14 (MEM-18)

PE - conjugated anti-human CD14 (MEM-18)

PerCP - conjugated anti-human CD45 (HI30), HLA-DR (HI43), Mouse IgG1 control (MOPC-21)

recombinant human cytokines: rh IL-6, IL-8, IL-10, IL-12, TNF-α

DETAILS more AWARDS