Integrating single-cell and spatial genomics with computational modeling to elucidate the K17-GATA6 genetic regulatory network in pancreatic cancer

Overview

Pancreatic ductal adenocarcinoma (PDAC) is currently the third leading cause of cancer deaths nationwide and is projected to be the number two cause by 2030 (Rahib et al., 2014). PDAC patients have a five-year survival rate of 11% and is highly resistant to chemotherapy, targeted therapeutics, and immune therapies. Recent research has converged upon a new paradigm for cancer therapy resistance that involves phenotypic plasticity, including epithelial-to-mesenchymal transition (EMT) and neuroendocrine differentiation of adenocarcinomas (Quintanal-Villalonga et al., 2020). Additionally, phenotypic plasticity underlies key aspects of cancer progression including invasion and metastasis (Gupta et al., 2019).

Members of our team have recently discovered phenotypic plasticity involving the canonical PDAC subtype markers K17 and GATA6; plasticity that is associated with stromal invasion and tumor epithelial ductal formation. This discovery emerged from the evolution of a long-term project focused on Keratin 17 (K17), a tumor-cell-specific biomarker that identifies the most aggressive subtypes of cancers of diverse sites, including the pancreas (Roa-Pena et al., 2019). In the past, the two canonical subtype markers K17 and GATA6 were generally thought to be mutually exclusive -- GATA6 expression restricted to the differentiated classical PDAC subtype and K17 expression restricted to the poorly differentiated basal PDAC subtype. In addition to our own findings of subtype plasticity, another group has recently reported that some degree of subtype heterogeneity exists within most individual pancreatic tumors (Williams et al., 2022).

We propose to study K17-GATA6 phenotypic plasticity by integrating high-dimensional experimental datasets with computational modeling of the K17-GATA6 genetic regulatory network. A key missing datatype that we will generate in this study is spatial transcriptomics of histological slides, allowing us to couple transcriptomics with insights into how different local microenvironments within the same tumor are associated with K17-GATA6 switching. Other datatypes to inform our computational modeling are single-cell transcriptomic analysis of (1) primary PDAC tumors and (2) PDAC organoids. Our team includes three cancer researchers (Drs. Marchenko, Powers, Shroyer) with complimentary expertise in cancer biology, single-cell genomics, and molecular pathology; alongside Dr. MacCarthy, a computational biologist with expertise in computational modeling of gene regulatory networks. Our specific aims are:

Aim1. Obtain spatially resolved transcriptomic data of human PDAC samples displaying relevant variation in tumor cell histology. We will use the 10X Visium platform which offers 55 micron resolution to analyze eight tissue sections, carefully chosen to reflect different tumor ductal structures and areas of stromal invasion.

Aim 2. Obtain single-cell transcriptomic data of two different human PDAC organoids exposed to different conditions we hypothesize to influence K17-GATA6 switching. Organoids will be cultured with or without other tumor microenvironment cell types (pancreatic stellate cells, stromal immune cells) as well as exposure to gemcitabine, the standard chemotherapeutic used in PDAC.

Aim 3. Develop computational models of the K17-GATA6 genetic regulatory network. We will use a deep learning model that can be trained on single-cell RNA velocity data (Chen et al., 2022). We will start modeling with our scRNA-seq datasets from 27 primary PDACs and 4 PDAC organoids. We will apply model interpretability techniques to select the most important regulators for each critical gene. Once we obtain the datasets from the first two aims, we will extend the model to incorporate input from other cells in the tumor microenvironment.