World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:14, No:07, 2020

Computational Approaches to Study Lineage Plasticity in Human Pancreatic Ductal Adenocarcinoma

Authors : Almudena Espin Perez, Tyler Risom, Carl Pelz, Isabel English, Robert M. Angelo, Rosalie Sears, Andrew J. Gentles

Abstract : Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadly malignancies. The role of the tumor microenvironment (TME) is gaining significant attention in cancer research. Despite ongoing efforts, the nature of the interactions between tumors, immune cells, and stromal cells remains poorly understood. The cell-intrinsic properties that govern cell lineage plasticity in PDAC and extrinsic influences of immune populations require technically challenging approaches due to the inherently heterogeneous nature of PDAC. Understanding the cell lineage plasticity of PDAC will improve the development of novel strategies that could be translated to the clinic. Members of the team have demonstrated that the acquisition of ductal to neuroendocrine lineage plasticity in PDAC confers therapeutic resistance and is a biomarker of poor outcomes in patients. Our approach combines computational methods for deconvolving bulk transcriptomic cancer data using CIBERSORTx and high-throughput single-cell imaging using Multiplexed Ion Beam Imaging (MIBI) to study lineage plasticity in PDAC and its relationship to the infiltrating immune system. The CIBERSORTx algorithm uses signature matrices from immune cells and stroma from sorted and single-cell data in order to 1) infer the fractions of different immune cell types and stromal cells in bulked gene expression data and 2) impute a representative transcriptome profile for each cell type. We studied a unique set of 300 genomically well-characterized primary PDAC samples with rich clinical annotation. We deconvolved the PDAC transcriptome profiles using CIBERSORTx, leveraging publicly available single-cell RNA-seq data from normal pancreatic tissue and PDAC to estimate cell type proportions in PDAC, and digitally reconstruct cell-specific transcriptional profiles from our study dataset. We built signature matrices and optimized by simulations and comparison to ground truth data. We identified cell-type-specific transcriptional programs that contribute to cancer cell lineage plasticity, especially in the ductal compartment. We also studied cell differentiation hierarchies using CytoTRACE and predict cell lineage trajectories for acinar and ductal cells that we believe are pinpointing relevant information on PDAC progression. Collaborators (Angelo lab, Stanford University) has led the development of the Multiplexed Ion Beam Imaging (MIBI) platform for spatial proteomics. We will use in the very near future MIBI from tissue microarray of 40 PDAC samples to understand the spatial relationship between cancer cell lineage plasticity and stromal cells focused on infiltrating immune cells, using the relevant markers of PDAC plasticity identified from the RNA-seq analysis.

Keywords : deconvolution, imaging, microenvironment, PDAC
Conference Title : ICCCRI 2020 : International Conference on Clinical Cancer Research and Immunology
Conference Location : Helsinki, Finland
Conference Dates : July 17-18, 2020