Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Single-cell RNA Sequencing Analysis of The Tumor Microenvironment During Breast Cancer Progression

By

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The tumor microenvironment (TME) plays an important role in breast cancer progression, but the development and functional heterogeneity of its sub-compartments is only partially understood. To gain further insight, we have applied scRNA-seq analysis to examine over 30,000 cells from different stages of progression using transgenic MMTV-PyMT and C3(1)/SV40 T-antigen mouse breast cancer models. We performed an integrative analysis comparing the diverse scRNA-seq datasets and observed pronounced accumulation of several non-tumor cell types during cancer progression, including cancer-associated fibroblasts (CAFs), distinct sub-types of macrophages, lymphocytes, and endothelial cells. In the MMTV-PyMT model we found three types of CAFs: reticular matrix associated, myofibroblasts, and a 'papillary' type. All three appear to evolve from normal resident fibroblasts/pericytes by a program involving the c-MAF transcription factor and resulting in a massive alteration of extracellular matrix expression. Furthermore, we found in the C3(1)/SV40 T-antigen model that during progression subsets of tumor epithelial cells undergo either partial epithelial-mesenchymal transition (EMT), meaning cells expressing both epithelial and mesenchymal markers, or full EMT. As part of our comprehensive study, we also performed spatial transcriptomic analyses using nucleic acid in situ hybridization (ISH), and we discovered distinct spatial locations for the CAF subtypes found in the MMTV-PyMT murine model. Fluorescent ISH shows one CAF subtype to be found surrounding epithelial tumor nests with myofibroblasts intermingled between these nests, while the other subtype is more distally located in the collagen-rich stroma compartment. Meanwhile, the chromogenic ISH results of the C3(1) Tag mouse model indicate that the EMT process is initiated by sporadic conversion of single tumor epithelial cells within the nest, and that as the tumor progresses, the full EMT cells are located at different areas within the tumor than cells that have retained epithelial cell type identity. Lastly, we used NicheNet to study ligand-receptor interactions between the different compartments of the TME. We found that certain alterations in the paracrine signaling between subpopulations of CAFs and immune cells contribute to tumor development.

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(*If an outside member of the community would like to attend the defense, please contact the Graduate Program Director at martha.furie@stonybrook.edu.)