Medical & healthcare, Drug discovery

Completion of a detailed “single cell map” of pancreatic cancer tissue and its application in drug discovery

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Abstract

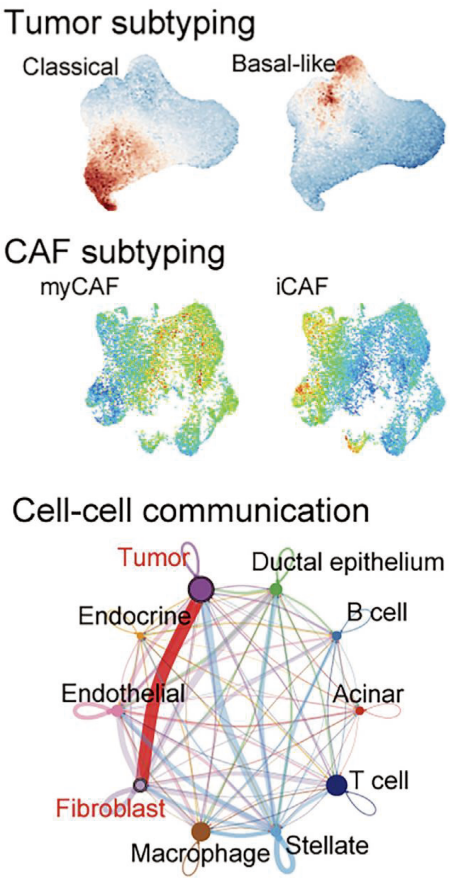
Pancreatic cancer is notorious for its extremely poor prognosis, and overcoming it requires the development of groundbreaking technologies capable of accurately diagnosing early stages and detecting disease progression, as well as establishing a drug discovery platform based on these insights. Our team has successfully completed the most detailed “single-cell map” of pancreatic cancer to date by integrating single-cell RNA sequencing (scRNAseq) data from patients treated at Osaka University Hospital with data from existing scRNAseq studies both domestically and internationally. This comprehensive dataset includes over 70 samples and more than 130,000 cells, forming a single-cell atlas of pancreatic ductal adenocarcinoma (PDAC). In addition to the integrative analysis of traditional transcriptomic data, we conducted a detailed investigation of intercellular communication. Our analysis has unraveled the cellular diversity that constitutes pancreatic cancer, providing foundational information for the development of breakthrough therapeutics. The findings reveal that pancreatic cancer cells adopt survival strategies based on fibroblast subtypes within the tumor microenvironment niche, offering potential new therapeutic targets.

Background & Results

Pancreatic ductal adenocarcinoma (PDAC) arises from the ductal epithelial cells of the pancreas and is characterized by extremely limited treatment options and a notably low survival rate. The five-year survival rate is a mere 9%, with poor prognosis largely attributed to the challenges in early detection and the frequent occurrence of metastasis, making complete surgical resection difficult. During the progression of PDAC, critical genetic mutations accumulate, including those in KRAS, TP53, SMAD4, and CDKN2A; however, effective targeted therapies for these mutations remain elusive. The tumor microenvironment (TME) comprises a diverse array of cell types, including blood vessels, immune cells, and fibroblasts, which significantly influence the tumor’s heterogeneity and malignancy. Recent advances in single-cell RNA sequencing (scRNA-seq) have deepened our understanding of the TME, yielding crucial insights into cellular states and interactions. This has led to the identification of new tumor subtypes and enhanced precision in the study of PDAC biology. Utilizing scRNA-seq datasets containing over 130,000 cells, we conducted a cell-level analysis of PDAC and reanalyzed RNA-seq data from The Cancer Genome Atlas (TCGA) to elucidate the communication between tumors and cancer-associated fibroblasts (CAFs). Although publicly available reference single-cell transcriptome datasets have been reported by various research groups, inconsistencies arise due to differences in clinical settings, sampling methods, and scRNA-seq platforms. To address this, we integrated five publicly available datasets (PRJCA001063, GSE111672, GSE154778, GSE155698, GSM4293555) with our own data (OUGS) and performed batch correction to establish a reference tool. This integration allowed us to identify ten distinct cell types, including both normal and malignant epithelial cells, using differential gene expression. Despite differences in cellular ratios among patients, consistent trends were observed across the datasets, indicating successful integration. As a part of the analysis, we visualized the integrated data using UMAP, revealing key cell-derived genes responsible for gene expression changes in TCGA-PAAD. Fibroblasts, B cells, and macrophages contribute to stromal tissue formation and immune infiltration, while a marked loss of acinar cell function reflects the pathology of pancreatic cancer.

Significance of the research and Future perspective

he completion of the detailed “single-cell map” in this study has revealed the precise location of cancer stem cells, uncovered the composition of the cancer microenvironment niche, and decoded the content of intercellular communication. This breakthrough marks a significant step forward in the implementation of precision medicine in society.



Patent

Treatise
Chijimatsu, Ryota; Kobayashi, Shogo; Takeda, Yu et al. Establishment of a reference single-cell RNA sequencing dataset for human pancreatic adenocarcinoma. iScience. 2022, 25(8), 104659. doi: 10.1016/j.isci.2022.104659
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