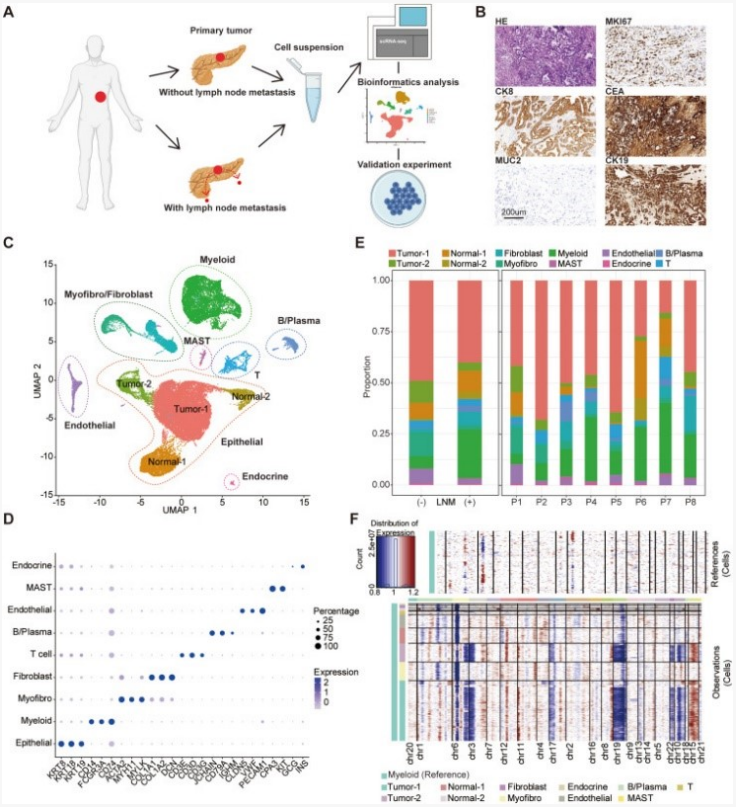
Transcriptional Landscape of PDAC Shows Distinct Cell Populations

Single-cell RNA sequencing (scRNA-seq) on a PDAC cohort identified distinct cell populations associated with tumor initiation and progression



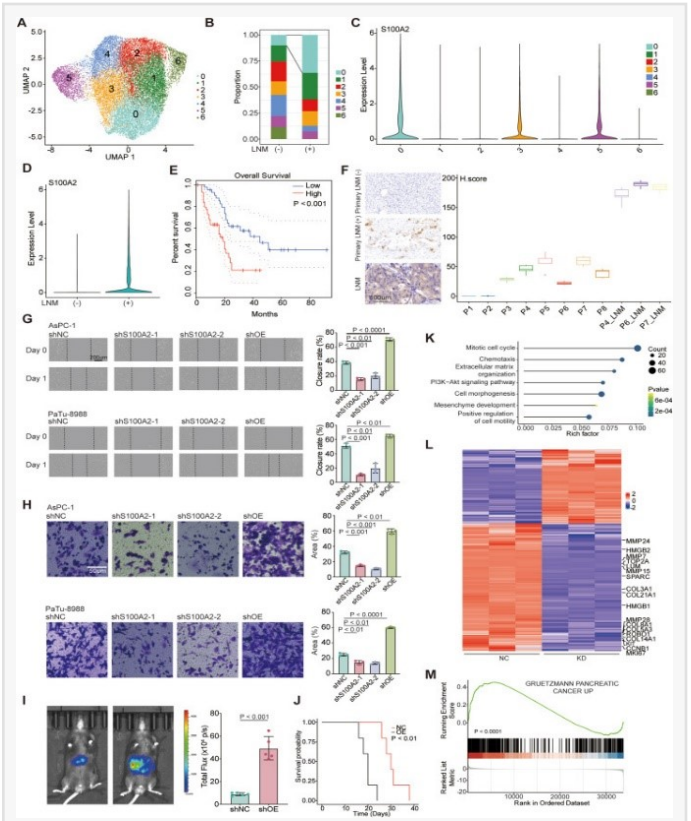
(A) Schematic workflow of sample collection for further single-cell RNA sequencing. (B) The hematoxylin and eosin staining and immunohistochemistry staining of tumor sample from P6. (C) UMAP plots of all cells from 8 PDAC samples colored by cell types. (D

CHINA, March 17, 2025 /EINPresswire.com/ -- Pancreatic cancer is one of the leading causes of cancer-related mortality, with pancreatic ductal adenocarcinoma (PDAC) accounting for 90% of all cases. As most PDAC cases are diagnosed at advanced stages, surgical interventions are ineffective, and consequently, lymph node metastasis manifests in 70% of PDAC patients. Moreover, since the number of genetic mutations giving rise to PDAC are low, there are fewer available targeted therapeutic modalities. Analysis of gene expression at the single-cell level may help understand the tumor dynamics of PDAC.

In a recent study published in the Genes & Diseases journal, researchers at Fudan University Shanghai Cancer Center and Shanghai Jiao Tong University School of Medicine performed single-cell RNA sequencing (scRNA-seq) on eight PDAC patients with varying lymph node metastasis (LNM) statuses to understand the transcriptional landscape regulating PDAC development and identify novel therapeutic targets.

scRNA-seq of LNM and non-LNM primary PDAC showed a heterogeneous cellular composition and identified four distinct cell populations: the MMP1+ & S100A2+ tumor cells, CCL2+ macrophages, and OMD+ fibroblasts. An integrated analysis comparing PDAC and normal pancreatic epithelial tissues revealed a pancreatic intraepithelial neoplasia (PanIN) subset with

increased ONECUT2 (one cut domain family member 2) expression. This subset had a high MMP1 expression and is an intermediary between normal acinar cells and PDAC cells. Further results showed that MMP1 predicts unfavorable prognosis in PDAC patients and plays an important role in sustaining ductal identity in PDAC.



(A) Pancreatic ductal adenocarcinoma cells were integrated with public datasets and re-clustered with unsupervised clustering. (B) Bar plot of the proportion of subclusters in LNM and non-LNM groups. (C) S100A2 was specifically expressed in cluster 0. (D)

The S100A2+subset cells had increased expression of genes associated with tumor progression and poor prognosis. In vitro studies showed that S100A2 enhances the migratory capability of cancer cells while its knockdown led to decreased expression of EMT genes and cell-adhesion mediated drug resistance. Analysis of the immune cell subsets in the PDAC microenvironment showed a higher presence of pro-metastatic sub-populations within the immune cell milieu in PDAC tumors with LNM than in PDAC without LNM. This population was rich in CCL2+ macrophages, which play a role in EMT, immunosuppression, and indirect activation of cytotoxic CD8+ cells and are associated with poor disease-specific survival. Analysis of the stromal compartment revealed a subset of OMD+ fibroblasts that regulate tumorigenesis and metastasis by recruiting CCL2+ macrophages to create a pro-tumor environment.

In conclusion, this study identified OMD+ fibroblasts, CCL2+ macrophages, S100A2+, and MMP1+ tumor cells as key cell subsets that collectively contribute to a pro-tumor microenvironment conducive to LNM in PDAC and may serve as potential therapeutic targets.

Reference

Title of the original paper - The scRNA-sequencing landscape of pancreatic ductal adenocarcinoma revealed distinct cell populations associated with tumor initiation and progression

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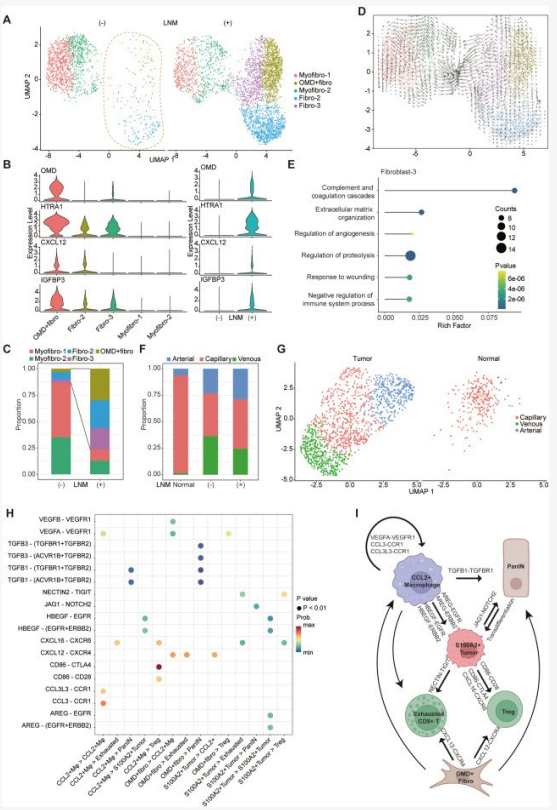

(A) UMAP plots comparing fibroblast subsets between non-lymph node metastasis (non-LNM) and LNM PDAC. (B) OMD+ fibroblasts specifically expressed OMD, HTRA1, CXCL12, and IGFBP3. (C) Bar plot of the proportion of fibroblast subsets in LNM and non-LNM group

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