Immune-associated Cancer-associated Fibroblasts Define a Distinct Spatial Stromal State in Pancreatic Ductal Adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a highly complex stromal microenvironment, in which cancer-associated fibroblasts (CAFs) constitute a major but heterogeneous component. However, the spatial organization, biological features, and potential clinical relevance of distinct CAF states remain incompletely understood. We performed an integrative analysis of PDAC centered on spatial transcriptomics, together with single-cell transcriptomic data, complementary molecular datasets, and clinical information. CAF populations were characterized according to their transcriptional features, spatial distribution, and microenvironmental context. Cross-platform integration was further used to evaluate immune-associated CAF states and prioritize candidate markers and related biological programs. We identified multiple CAF subtypes with distinct spatial and molecular characteristics in PDAC. These CAF states exhibited non-random spatial organization and were associated with different local microenvironmental contexts. Among them, an immune-associated CAF state was enriched in immune-related spatial regions. In a small exploratory cohort, this CAF state showed a trend toward favorable prognosis. Integrative analyses across spatial transcriptomics, single-cell data, molecular profiles, and clinical datasets further supported the robustness of this immune-associated CAF phenotype and identified candidate markers and pathways potentially related to this CAF state. Our findings support the existence of a spatially and biologically distinct immune-associated CAF state in PDAC. This CAF population may have prognostic relevance and warrants further mechanistic and clinical validation.

Keywords

Pancreatic Ductal Adenocarcinoma, Cancer-associated Fibroblasts, Spatial Transcriptomics, Tumor Microenvironment, Immune-associated CAFs