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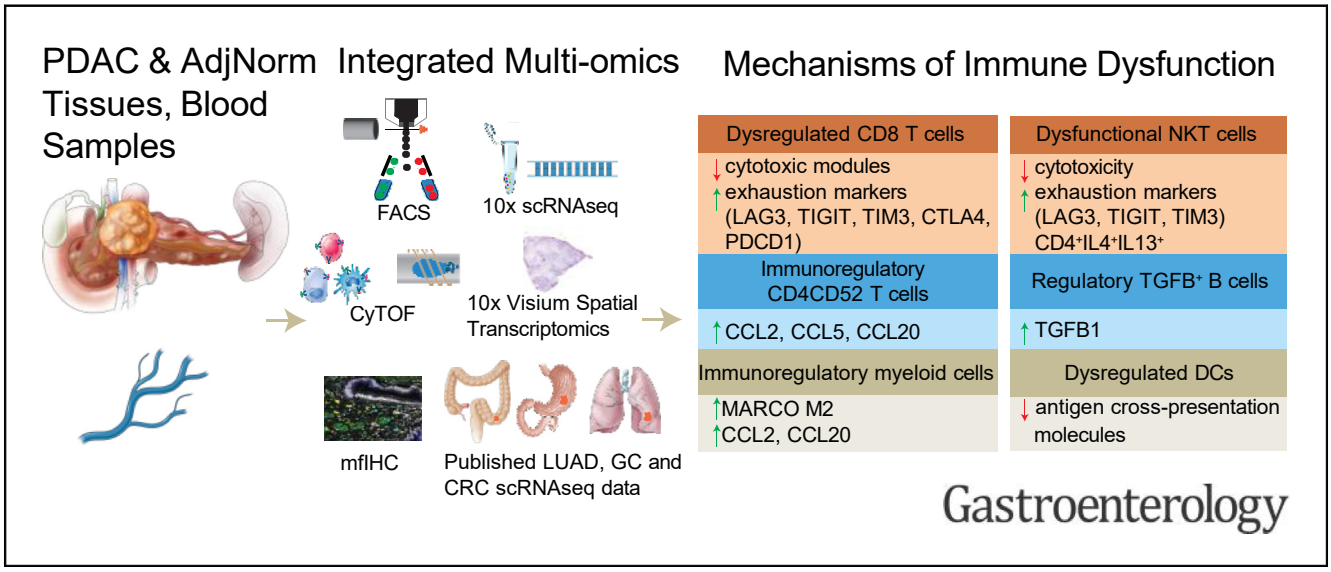
Spatially Resolved Multi-Omics Single-Cell Analyses Inform Mechanisms of Immune Dysfunction in Pancreatic Cancer

Suhail Yousuf,[1] Mengjie Qiu,[1] Lena Voith von Voithenberg,[2] Johannes Hulkkonen,[1] Igor Macinkovic,[3] Axel R. Schulz,[4] Domenic Hartmann,[1] Florian Mueller,[5] Margarete Mijatovic,[3] David Ibberson,[6] Karam T. AlHalabi,[1] Jenny Hetzer,[5] Simon Anders,[7] Bernhard Brüne,[3,8,9] Henrik E. Mei,[4] Charles D. Imbusch,[2] Benedikt Brors,[2] Mathias Heikenwälder,[5] Matthias M. Gaida,[10,11,12] Markus W. Büchler,[1] Andreas Weigert,[3,8,9] Thilo Hackert,[1] and Susanne Roth[1]

[1]Department of Surgery, Heidelberg University Hospital, Heidelberg, Germany; [2]Division of Applied Bioinformatics, German Cancer Research Center, Heidelberg, Germany; [3]Institute of Biochemistry I, Faculty of Medicine, Goethe-University Frankfurt, Frankfurt, Germany; [4]German Rheumatism Research Center, Berlin, Germany; [5]Division of Chronic Inflammation and Cancer, German Cancer Research Center, Heidelberg, Germany; [6]Deep Sequencing Core Facility, BioQuant, Heidelberg University, Heidelberg, Germany; [7]BioQuant Center, Heidelberg University, Heidelberg, Germany; [8]Frankfurt Cancer Institute, Goethe-University Frankfurt, Frankfurt, Germany; [9]German Cancer Consortium, Partner Site Frankfurt, Germany; [10]Institute of Pathology, University Medical Center Mainz, Johannes Gutenberg University, Mainz, Germany; [11]Research Center for Immunotherapy, University Medical Center Mainz, Johannes Gutenberg University, Mainz, Germany; and [12]Joint Unit Immunopathology, Institute of Pathology, University Medical Center, Johannes Gutenberg University and Translational Oncology, University Medical Center Mainz, Mainz, Germany



BACKGROUND & AIMS: As pancreatic ductal adenocarcinoma (PDAC) continues to be recalcitrant to therapeutic interventions, including poor response to immunotherapy, albeit effective in other solid malignancies, a more nuanced understanding of the immune microenvironment in PDAC is urgently needed. We aimed to unveil a detailed view of the immune micromilieu in PDAC using a spatially resolved multimodal single-cell approach. **METHODS:** We applied single-cell RNA sequencing, spatial transcriptomics, multiplex immunohistochemistry, and mass cytometry to profile the immune compartment in treatment-naïve PDAC tumors and matched adjacent normal pancreatic tissue, as well as in the systemic circulation. We determined prognostic associations of immune signatures and performed a meta-analysis of the immune microenvironment in PDAC and lung adenocarcinoma on single-cell level. **RESULTS:** We provided a spatially resolved fine map of the immune landscape in PDAC. We substantiated the exhausted phenotype of CD8 T cells and immunosuppressive features of myeloid cells, and highlighted immune subsets with potentially underappreciated roles in PDAC that diverged from immune populations within adjacent normal areas, particularly CD4 T cell subsets and natural killer T cells that are terminally exhausted and acquire a regulatory phenotype. Differential analysis of immune phenotypes in PDAC and lung adenocarcinoma revealed the presence of extraordinarily immunosuppressive subtypes in PDAC, along with a distinctive immune checkpoint composition. **CONCLUSIONS:** Our study sheds light on the multilayered immune dysfunction in PDAC and presents a holistic view of the immune landscape in PDAC and lung adenocarcinoma, providing a comprehensive resource