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BACKGROUND: Pancreatic Ductal Adenocarcinoma (PDAC) is the most common and aggressive form of pancreatic cancer, originating from the cells lining the pancreatic ducts. The tumor growth can obstruct adjacent structures, damage the pancreas, and metastasize to other organs. PDAC's deep anatomical location contributes to late diagnosis, resulting in less than 13% of patients surviving beyond 5 years.[1] Understanding the tumor microenvironment (TME) is crucial for characterizing PDAC's complex biology. Matrix-Assisted Laser Desorption and Ionization Mass Spectrometry Imaging (MALDI-MSI) enables spatial visualization of biomolecules such as lipids, N-glycans, and peptides within tissue samples without the need for chemical labeling. Spatial Omics techniques facilitate the identification of molecular distributions within the tissue, allowing researchers to correlate specific biomolecules to their exact locations. This study aims to use MALDI-MSI to spatially map lipids, N-glycans, and peptides in PDAC tissues to identify molecular patterns and potential biomarkers associated with tumor regions, providing insights into the TME.

METHODS: Fresh frozen PDAC tissue from the KPC mouse model was cryosectioned and prepared for sequential MALDI-MSI analysis. A time-of-flight (TOF) mass spectrometer was used to sequentially profile lipids, N-glycans, and peptides on the same tissue section. Appropriate matrix application, enzyme digestion, and matrix removal steps were performed between analyses to preserve sample integrity. Data were acquired at a spatial resolution of 100 µm. Molecular ion images were generated, allowing the mapping of distinct biomolecules to specific tissue regions and enabling comparison of molecular profiles across different tumor areas, all performed on a single slide to maintain spatial context.

RESULTS & DISCUSSION: After mapping lipids, N-glycans, and peptides within the PDAC tumor microenvironment on the same tissue section to preserve spatial information, using the combination of previously studied multi-omic features, tissue slices were segmented into three distinct regions using the k-means algorithm. One of these regions is representative of the interface between the PDAC tumor and healthy tissue, and the other two regions are representative of the heterogeneous PDAC TME. For instance, the intensity of a glycerophospholipids(PC 30:4) is significantly higher in the interface TME region. Conversely, the intensity of PC 34:0 shows up more strongly in the two internal heterogeneous TME regions. More examples of these signature biomolecules used to define the TME regions will be explored in the poster. This exploratory study highlights the feasibility of profiling multiple biomolecular classes from the same tissue slice to gain a better understanding of PDAC while minimizing spatial mismatches between different modules. Future research aims to enhance spatial resolution to 20µm for more detailed molecular analysis, enabling us to investigate the profiles of TME regions by segmenting them into smaller, more precise areas.

(1) Siegel, R. L.; Kratzer, T. B.; Wagle, N. S.; Sung, H.; Jemal, A. Cancer Statistics, 2026. *CA A Cancer J Clinicians* **2026**, *76* (1), e70043. https://doi.org/10.3322/caac.70043.