SUMMARY (Cutting Edge) 5/30/25 ciT1zen science

Spatial transcriptomics from pancreas and local draining lymph node tissue reveals a lymphotoxin-β signature in T1D ciT1zen science summary

Source: Medina-Serpas, M. A., Brusko, M., Golden, G. J., Campbell-Thompson, M., Rogers, T., Posgai, A. L., Luning Prak, E. T., Kaestner, K. H., Betts, M. R., McIntyre, L. M., Atkinson, M. A., & Brusko, T. M. (2025). Spatial transcriptomics from pancreas and local draining lymph node tissue reveals a lymphotoxin-β signature in human type 1 diabetes. *bioRxiv*, 2025.05.19.654940. https://doi.org/10.1101/2025.05.19.654940
Date: May 24, 2025
Subject: Novel inflammatory signatures in the pancreas and pancreatic lymph nodes (pLNs) in Type 1 Diabetes (T1D) progression.
Key Findings:
This study utilizes spatial transcriptomics (ST) to investigate the inflammatory landscape of both the pancreas and its local draining lymph node (pLN) across the spectrum of T1D development, from non-diabetic individuals to autoantibody-positive individuals highly susceptible to T1D, and those with established T1D. The research integrates ST data with publicly available single-cell RNA sequencing (scRNA-seq) data to provide a detailed view of transcriptional changes at both the tissue and cellular levels.
The central findings highlight distinct inflammatory signatures in the pancreas and the pLN:

- **Pancreas:** In the T1D pancreas, the study observed a widespread increase in the expression of several inflammation-associated genes. These include members of the **regenerating islet-derived (*REG*) family genes, complement factor 3 (*C3*), *SOD2*, and *OLFM4***. The study also identifies potential cellular contributors to these observed gene expression patterns.
- **Pancreatic Lymph Node (pLN):** A spatially restricted upregulation of **lymphotoxin-β (*LTB*)** was a significant finding within the T1D pLN. This *LTB* signature was observed alongside the upregulation of transcripts associated with **follicular dendritic cells (FDCs)**, specifically including ***FDCSP*, *CLU*, and *FCER2***.

Most Important Ideas/Facts:

1. **Spatial Transcriptomics Provides Valuable Insights:** The use of ST is crucial as it allows researchers to not only identify which genes are upregulated but also their spatial location within the tissues. This provides a more comprehensive understanding of the inflammatory processes in T1D compared to methods that examine gene expression across the entire tissue.
2. **Distinct Inflammatory Profiles in Pancreas and pLN:** The study demonstrates that the inflammatory responses in the pancreas and the regional pLN during T1D are not uniform. There are specific sets of genes upregulated in each tissue, suggesting different roles for these organs in the disease progression.
3. **Upregulation of *LTB* and FDC-associated Genes in the pLN is a Key Finding:** The spatially restricted upregulation of *LTB* and FDC-associated transcripts in the T1D pLN

is a novel and potentially significant observation. Lymphotoxin-β is a cytokine known to be involved in the development and maintenance of secondary lymphoid organs, including the formation of follicular structures and the function of FDCs. FDCs play a critical role in immune responses by presenting antigens to B cells and supporting germinal center formation. The co-occurrence of *LTB* and FDC-associated gene upregulation suggests potential alterations in the lymphoid architecture or function within the pLN during T1D.

4. **Identification of Cellular Candidates:** The integration with scRNA-seq data allows for the identification of specific cell types that are likely contributing to the observed transcriptional signatures in both the pancreas and pLN. This provides valuable targets for further investigation and potential therapeutic intervention.
5. **Implications for Therapeutic Development:** The identification of these distinct inflammation signatures offers potential new avenues for developing targeted therapeutic interventions for T1D. By understanding the specific molecular pathways involved in the inflammatory process in different tissues, therapies could be designed to precisely target these pathways and potentially halt or reverse disease progression.

Key Quotes:

- "This study explores the inflammatory response observed in pancreata and pancreatic lymph node (pLN) samples obtained throughout the natural history of type 1 diabetes (T1D) including non-diabetic individuals and non-diabetic autoantibody positive individuals with high susceptibility using spatial transcriptomics (ST)."
- "In the T1D pancreas, we observed global upregulation of multiple inflammation-associated transcripts, including regenerating islet-derived (*REG*) family genes, complement factor 3 (*C3*), *SOD2*, and *OLFM4*, and highlighted cellular candidates potentially contributing to these signatures."
- "Within the T1D pLN, we observed spatially restricted upregulation of lymphotoxin-β (*LTB*) alongside follicular dendritic cell (FDC)-associated transcripts including *FDCSP*, *CLU*, and *FCER2*."
- "Collectively, these findings highlight a distinct inflammation signatures in the pancreas and regional pLN which can help inform the development of future therapeutic interventions."

Further Considerations:
While this study provides compelling evidence for distinct inflammatory signatures, further research is needed to fully elucidate the functional consequences of these transcriptional changes. Specifically, the role of the *LTB*-FDC axis in the T1D pLN warrants further investigation to understand its contribution to the autoimmune attack on pancreatic beta cells. This research lays the groundwork for more targeted investigations into the specific cellular interactions and molecular pathways involved in T1D pathogenesis.