SUMMARY (Clinical) 5/14/25 ciT1zen science

Cathepsin S is elevated in pancreatic islets and plasma in new-onset type 1 diabetes and positively associates with systemic inflammatory cytokines

ciT1zen science summary

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Key Focus: Investigation of cathepsin protease expression in pancreatic islets during Type 1 Diabetes (T1D) development and progression, with a specific focus on the biomarker potential of Cathepsin S (CTSS) in new-onset T1D.

Main Themes and Important Ideas/Facts:

1. **Cathepsin Proteases and T1D:** The study is based on the premise that cathepsin proteases play a role in the development and progression of T1D. Previous research by the authors indicated that CTSS is induced and secreted from beta-cells during T1D and is elevated in children with new-onset T1D and autoantibody-positive siblings.
2. **Differential Expression of Cathepsins in Pancreatic Islets during T1D:** Analysis of microarray data from laser-dissected pancreatic islets revealed that several cathepsins are differentially expressed in individuals with T1D compared to healthy controls.

- "Seven cathepsins were differentially expressed in islets from individuals with T1D as compared to healthy controls: *CTSD*, *CTSH*, *CTSL*, and *CTSS* in new-onset T1D, and *CTSA*, *CTSB*, and *CTSZ* after longer T1D duration (FDR-adjusted $P < 0.05$)."

1. **Specific Induction of Cathepsin S (CTSS) in New-Onset T1D:** Of the cathepsins found to be differentially expressed, *CTSS* was the *only* one specifically induced in the pancreatic islets during the new-onset phase of T1D.

- "Only *CTSS* was induced in new-onset T1D."

1. **Elevated CTSS in Plasma of New-Onset T1D Patients:** Measurements of CTSS plasma levels in children with new-onset T1D showed that these levels were elevated at the time of onset.

- The results section indicates that CTSS plasma levels were measured at onset, 6 months, and 12 months after onset in a cohort of children with new-onset T1D. While the text explicitly states that levels were *decreased* at 12 months compared to earlier time points, the background section and the conclusion strongly imply an elevation at the new-onset stage. The key finding here is the change in levels over time, indicating higher levels closer to onset.

1. **Decrease in CTSS Plasma Levels Over Time After Onset:** CTSS plasma levels decreased significantly over the 12 months following the onset of T1D.

- "The CTSS plasma levels were decreased 12 months after onset compared to at onset ($P < 0.05$) and 6 months after onset ($P < 0.01$), after adjusting for age and sex."

1. **Positive Association Between CTSS and Systemic Inflammatory Cytokines:** CTSS plasma levels were found to be positively associated with several key systemic inflammatory cytokines at different time points after T1D onset.

- "CTSS was positively associated with IFNγ (6 months, $P < 0.001$), IL-10 (baseline, $P < 0.05$; 12 months, $P < 0.05$), and TNFα (baseline, $P < 0.05$), after adjusting for age." This finding suggests a link between CTSS levels and the inflammatory processes involved in T1D.

1. **Potential of CTSS as an Early Biomarker:** Based on the findings of elevated CTSS in both islets and plasma at new-onset and its association with inflammatory markers, the study concludes that CTSS has potential as an early biomarker for T1D.

- "CTSS is elevated in both the islets and plasma in new-onset T1D and shows potential as an early biomarker of islet inflammation and T1D progression."

Methodology Highlights:

- Used microarray data from laser-dissected pancreatic islets from various groups (new-onset T1D, AAb+, T1D, T2D, healthy controls) to compare cathepsin gene expression.
- Measured CTSS plasma levels in a cohort of children with new-onset T1D at multiple time points using ELISA.
- Analyzed associations between CTSS plasma levels and systemic inflammatory cytokines (IFNγ, IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNFα) using MSD V-PLEX assays.
- Employed statistical methods (ANOVA, Fisher's LSD, linear mixed effect model, linear regression) with appropriate corrections for multiple comparisons and confounding factors (age, sex).

Overall Significance:

This study reinforces the involvement of cathepsin proteases in T1D pathogenesis and specifically highlights CTSS as a promising early indicator. The elevation of CTSS in both the pancreas and plasma at the time of diagnosis, coupled with its association with inflammatory markers, suggests its potential utility as a non-invasive biomarker for detecting or monitoring the progression of T1D, particularly in its early stages. The decrease in CTSS levels over time after onset could also provide insights into disease activity or remission. Further research would be needed to validate its clinical utility.