Integrative bioinformatic and laboratory approaches shed new light on the molecular mechanisms underlying beta cell identity loss in T1D

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Background

Type 1 diabetes (T1D) is an inflammatory disease that is characterized by the destruction of beta-cells in pancreatic islets due to autoreactive actions from immune cells. The goal of this study is to characterize the inflammatory physiopathology that takes place in T1D, and explore the molecular mechanisms driving loss of beta-cell identity and function.

Methods

EndoC-βH1 cells and primary human islets were treated with various metabolic and inflammatory stressors mimicking the pathophysiological conditions in T1D. Gene expression and beta-cell function were assessed by RT-PCR and glucose-stimulated insulin secretion (GSIS), respectively. Single-cell RNA sequencing was carried out on primary human islets. Data processing, cell clustering and gene expression analysis was performed using Seurat packages from R.

Results

The combination of IL1β and IFNγ repressed gene expression of beta-cell maturity markers such as NKX6.1 (0.71-fold change) and MAFA (0.39-fold change), and reduced the expression of duct/differentiation marker HES1 (0.67-fold change) compared to untreated islets (n=3). Furthermore, treatment with IL1β/IFNγ impaired insulin secretion by 62%. Bioinformatic analysis revealed that exclusive heavy metal-related biological pathways were altered in specific endocrine pancreatic cells under cytokine treatment: IL1β/IFNγ promoted the expression of the metallothionein gene family and zinc transporter ZnT8 exclusively in beta-cells, while the expression of distinct genes involved in iron homeostasis was found to be altered in beta- (ferritin subunits) and alpha-cells (ceruloplasmin).

Discussion

IL1β/IFNγ treatment induces loss of beta-cell maturity and impairment of insulin secretion in human pancreatic islets. Further pathway analysis revealed that alpha- and beta-cells respond and adapt differently to inflammatory triggers. We hypothesize that a difference in protective molecular mechanisms between beta-cells and alpha-cells could account for the loss of beta-cells and survival of alpha-cells despite exposure to the same inflammatory stress during the onset of T1D.