Large-scale electron microscopy database for human type 1 diabetes

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The underlying mechanism(s) initiating beta cell destruction resulting in type 1 diabetes (T1D) are still poorly understood. T1D etiology demands full knowledge of cellular composition and microenvironment of the islets of Langerhans. Electron microscopy (EM) allows to study ultrastructure, but typically only reveals high resolution of limited subcellular areas.

We routinely perform large-scale EM for unbiased analysis of complete islet cross-sections at nanometer-resolution, which we call 'nanotomy' for nano-anatomy and thereby transform biobanked material from the Network for Pancreatic Organ donors with Diabetes (nPOD) into an open access EM database[1]. The repository currently contains over 50 datasets from 45 donors (asymptomatic autoantibody-positive (n=13), T1D (n=16), and control (n=16)). Analysis of these gigabytes grey-scaled data was aided by label-free elemental fingerprinting of secretory granule content.

Our analysis of the database revealed significant increased presence of specific mast cell subtypes in both autoantibody-positive (p = 0.02) and T1D (p = 0.005) compared to control donors. Moreover, we found that endocrine cells co-appearing with exocrine granules were present in a greater extent among autoantibody-positive (23%) and T1D donors (38%) compared to control donors (13%). Furthermore, these 'intermediate' cells in both autoantibody-positive and T1D donors display a stressed morphology.

The first datamining showed innate immune cell alterations as well as aberrant exocrine and endocrine interactions that fit with the growing notion that T1D is a pancreas-wide disease. We are currently addressing a possible cause-consequence relationship between exocrine alterations and T1D pathology in a model for dynamic *in vivo* imaging experiments. In conclusion, we present the largest repository for human EM data. The information-dense character of these zoomable EM maps is excellent for data reuse and can now be accessed by researchers worldwide to address their own questions on T1D pathology at the nanometer scale.

1. de Boer, P. *et al*. Large-scale electron microscopy database for human type 1 diabetes. *Nat. Commun.* **11**, 2475-020-16287-5 (2020)