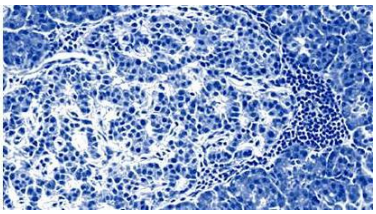
nPOD
Network for Pancreatic Organ Donors with Diabetes



Mapping Essential Elements and Toxic Metals in the Human Pancreas in Health and T1D Disease

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PURPOSE

Type 1 diabetes (T1D) is a chronic autoimmune disease that poses significant challenges to afflicted individuals, to the development of effective therapeutic interventions, and to public health initiatives at large. Initiated and perpetuated by a complex interplay of genetic and environmental risk factors, insulin-secreting pancreatic beta-cells are progressively destroyed by aberrant immune responses leading to elevated blood glucose levels as well as severe disturbances of carbohydrate, lipid and protein metabolism. At present, no cure or effective prevention is available and despite insulin treatment, serious long-term complications are frequent. Adding further urgency is an annual 2-5% worldwide increase of T1D incidence over the past few decades, a phenomenon that can only be explained by altered environmental exposures and resultant interactions with genetic variants that predispose to T1D development. However, unlike known genetic risk factors and autoimmune responses, their identities and pathogenic contributions remain poorly defined.

METHODS

To address this shortcoming, we have conducted a “proof-of-principle” study that establishes the foundation for arguably the first “exposure map” of the human pancreas in health and disease. Here, we used a combination of advanced immunohistochemistry (MICSSS: Multiplexed Immunohistochemical Consecutive Staining on Single Slides; whole-slide image acquisition at 40X) and laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) to conduct an elemental biomaging analysis of healthy as well as pre-/diabetic pancreata. Specifically, we have examined pancreatic head and tail sections of 25 nPOD cases (7 non-diabetic controls, 6 auto-antibody+ cases, 8 recent-onset T1D cases [duration ≤2 years], and 4 long-term T1D cases [8-11 years]) with a focus on hormone expression (INS, ProINS, GCG, SST, PPY, CHGA, IAPP), hematopoetic cells (CD45) and microanatomical landmarks (nuclei, CD99, Na+K+ ATPase, KRT19) that serve as geospatial referents for complementary LA-ICP-MS analyses that reveal the identity, abundance and distribution of 14 essential elements and metal toxicants.

SUMMARY OF RESULTS

Following completion of MICSSS staining and LA-ICP-MS interrogation of all 25 nPOD cases, image analyses are ongoing in a blinded fashion, preferentially employing QuPath (for MICSSS analyses) as well as custom scripts (for LA-ICP-MS). Preliminary results demonstrate definable patterns of essential element/metal toxicant distribution that co-localize with microanatomical structures and particular histological tissue properties, and therefore may provide initial evidence for the potential pathogenic involvement of selected metal toxicants or a combination thereof.

CONCLUSIONS

As based on access to rare pre-/diabetic and non-diabetic control pancreatic control tissues through the Network of Pancreatic Organ Donors with Diabetes (nPOD) as well as a suite of unique imaging technology platforms, we have developed a validated workflow for integrated multiplexed immunohistochemistry, LA-ICP-MS and advanced image analyses. Thus, we have created what we believe to be a promising conceptual and practical framework that may serve as an important foundation for future exposure analyses that seek to clarify aspects of T1D pathogenesis and to develop effective preventive treatment modalities.