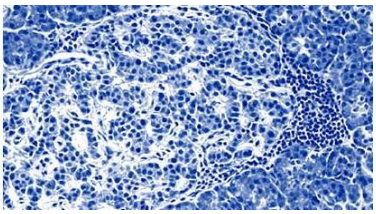
nPOD
Network for Pancreatic Organ Donors with Diabetes



Markers Associated with Viral Infections Correlates with Genes from the Insulin Secretion Pathway

AUTHORS

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PURPOSE

Type 1 diabetes (T1D) is an autoimmune condition, thought by some, to be enhanced or triggered by certain viral infections. While a variety of studies suggest an association of viruses with the development of T1D, it is difficult to prove this. One way to approach this question is to further elucidate the mechanism by which viral infections may affect islets and beta cells. In this study we isolated the islets that expressed known signs of viral infections and subsequently investigated pathways that may be secondarily affected through analysis of gene expression profiles.

METHODS

nPOD OCT slides were obtained from non-diabetic donors (Control), autoantibody positive non-diabetic donors (AB+) and donors with T1D (T1D). Islets were categorized based on the presence of markers associated with viral infection (VIMs), HLA, Mx1, dsRNA, and PKR, identified via immunohistochemical staining. Laser capture was used to manually isolate islets. From each donor islet were pooled based on the number of VIMs (0 VIMs, 1 VIMs or ≥2VIMs). After pooled islets were obtained, RNA was extracted, and microarray used to assess transcriptomes. We used GeneSpring software (version 13.0, Silicon Genetics, Redwood, CA) to generate a list of genes that showed differential expression between donors/VIMs. Using webgestalt we were then able to identify pathways enriched by the list of differentially expressed genes.

SUMMARY OF RESULTS

A total of 85 genes with a fold change of ≥1.1 and p-value=0.001 were differentially expressed between islets with 0 VIMs and islets with ≥1 VIMs. Pathway analysis showed strongest enrichment for the insulin secretion pathway (enrichment ratio of 6.9 and a P-value of 5.7E-7). Closer analysis of this gene list indicated decreased expression of genes involved in insulin secretion in islets with 1 or more VIMs. Two genes of particular interest, KCNJ11 and ABCC8, both had significantly lower expression in the islets with ≥1VIMs

compared to islets with 0 VIMs (p=0.01). This general pattern was maintained within all clinical groups.

CONCLUSIONS

Islets selected for high expression for genes associated with viral infection had decreased expression of genes important for insulin secretion, including KCNJ11 and ABCC8(SUR1) the genes responsible for the K-ATP channel necessary for insulin release in response to glucose. This may suggest a pattern of dedifferentiation and/or functional impairment of beta cells in the setting of viral infection.