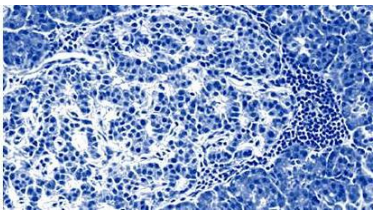
nPOD
Network for Pancreatic Organ Donors with Diabetes



Differential Expression of Genes Associated with Host Viral Responses in Insulitic Islets

AUTHORS

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PURPOSE

Type 1 diabetes (T1D) is an autoimmune condition hypothesized to be enhanced or triggered by viral infections. Islet pathology in T1D is characterized by destruction and loss of insulin producing pancreatic beta cells. In this study we evaluated specific physiological pathways associated with the disorder's pathogenesis by examining differential expression of host genes within islets, with special emphasis on identifying evidence suggestive of responses to a viral infection.

METHODS

Pancreatic tissue samples were obtained from non-diabetic donors, autoantibody positive, non-diabetic donors, and donors with T1D through the Network for Pancreatic Organ donors with Diabetes (nPOD) program. Laser capture microdissection was used to isolate individual islets based on immunohistochemical documentation of presence or absence of insulin (INS+) and T-lymphocytes (CD3+). Islets were classified into four groups, designated as Islet Status:INS+CD3- (Normal), INS+CD3+ (Insulitic), INS-CD3+, INS-CD3-. RNA was isolated and microarray used to assess transcriptomes. Genes identified in the literature as important for host viral response were analyzed for expression levels in each islet type.

SUMMARY OF RESULTS

Increased expression in insulitic islets (INS+CD3+) compared to normal islets (INS+CD3-) was seen in 18 genes involved in viral response pathways.

Table 1: Increased Expression in insultic compared to normal islets.

Gene	*P-Value	Gene	*P-Value	Gene	*P-Value
RIGI (DDX58)	6.4E-10	OAS3	1.04E-8	IRF3	4.69E-6
TLR3	7.35E-10	IFNG	5.9E-8	TLR6	2.45E-5
TLR4	1.4E-9	STAT1	1.64E-7	NFKB1	4.89E-5
MDA5 (IFIH1)	2.75E-9	TLR2	3.79E-7	PKR	5.17E-3
Casp1	4.7E-9	TLR1	2.72E-6	TGFB2	5.5E-3
TLR8	5.5E-9	IRAK4	6.41E-6	MyD88	5.92E-3

**P-Value for comparison of expression in Insulitic vs Normal Islets.*

In-depth analysis of RIGI (DDX58) and MDA5 (IFIH1) demonstrated that 87.5% (14/16) of TID donors had expression of either gene in at least one islet. In 75% (12/16) of the T1D donors at least 20% of their islets were positive. In 43% (7/16) of the T1D donors at least 50% of their islets were positive. Of the all the islets from T1D donors 49% (54/110) were positive for expression of either gene. In AB+ donors 18% (2/11) had expression of either gene in at least one islet. Of all islets from AB+ donors 10% (8/77) were positive. In Control Donors only 12.5% (2/16) had expression of either gene in at least one islet. Of all islets from Control Donors only 3% (2/73) were positive for either gene. When looking at islet status, regardless of donors, 6% (9/147) of Normal islets were positive, while 48.7% (38/78) of insulitic islets were positive.

CONCLUSIONS

These studies noted an increased expression of multiple host genes associated with anti-viral responses. RIGI and MDA5 are both known to respond specifically to dsRNA (a common part of viruses and viral replication). Our data demonstrate increased expression of a large number of genes involved in host responses to infection in insulitic islets. It is not clear whether the presence of CD3 T cells are in response to viral presence. Alternatively, the stress of insulitic activity could allow reactivation of latent viruses.