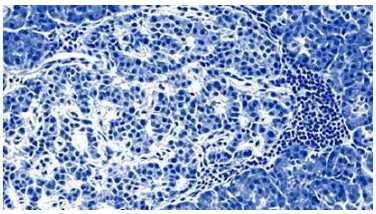
nPOD
Network for Pancreatic Organ Donors with Diabetes



Tertiary Lymphoid Organ-like Structures Associate with Insulin Containing Islets in Human Type 1 Diabetes

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PURPOSE

Tertiary lymphoid organs (TLOs) occur mainly in tissues with long-standing inflammation resulting from autoimmunity, infection or cancer (1-3). They show structural and functional similarities to lymph nodes (LNs) and modulate disease outcome. We have shown that TLO-like structures are present not only in NOD mice during development of the disease, but also in human type 1 diabetes (T1D) with insulitis where they are characterized by accumulations of inter-mixed T and B-cells and, in rare cases, B-cell follicles; the presence of a fibroblastic reticular network, and high endothelial venules. Furthermore, we detected proliferating leukocytes, plasma cells and memory T cells in pancreas samples with extensive insulitis, suggesting that TLO-like structures might contribute to perpetuation of human T1D (4). We, therefore, investigated whether is there any correlation between the frequency of TLO-like structures in the pancreas and the development of human T1D.

METHODS

Immunofluorescence stainings were performed on cryo- or paraffin-sections of pancreata with insulitis from single (n=1) and double autoantibody positive (aAb+) (n=3), T1D donors (n=17) using markers for inflammatory cells (CD45), β-cells (insulin) and basement membrane (pan-laminin, PLM). The sections were analyzed by confocal microscopy. Quantification of TLOs was performed on PLM/Insulin/CD45 stained sections.

SUMMARY OF RESULTS

The quantification data did not show a direct correlation between the presence of TLOs and the age of disease onset or disease duration, which could be due to low sample numbers for certain groups. However, the quantification of TLOs in the different samples revealed the presence of TLOs in double aAb+ but not in single aAb+ samples. The frequency of TLOs was significantly higher in young donors (age of onset < 10 years) and in T1D samples with immune cell aggregates. However, TLOs were not present in T1D donors with insulitis composed of dispersed immune cells. The TLOs were mostly associated with insulin positive

rather than with insulin negative insulitis. In only two cases, TLOs were associated with insulin negative, pseudo-atrophic islets.
Additionally, we identified TLOs associated with the pancreatic duct, where insulin positive cells were interdispersed among duct epithelial cells, which may suggest that β-cell neogenesis takes place and the immune cells sense the presence of antigen.
Furthermore, TLO-like structures occurred both in biopsies and in explants of transplanted donor samples in association with insulin positive islets, which suggests the reappearance of the disease and potentially that the formation of TLOs may contribute to disease reappearance.

CONCLUSIONS

Association of pancreatic TLOs with insulin positive and, rarely, with insulin negative islets suggests that they may contribute to exacerbation of disease and that they disappear once the autoantigen producing cells, the β-cells, are destroyed, analogous to pancreatic TLOs in NOD mice.

References

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