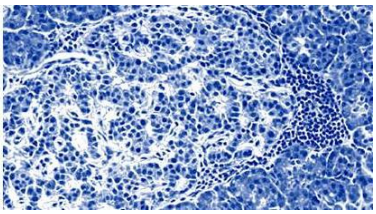
nPOD
Network for Pancreatic Organ Donors with Diabetes



Elevated levels of surface and intracellular expression of MHC class I on beta and alpha cells precedes immune infiltration in antibody positive organ donors

AUTHORS

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PURPOSE

Our aim is to define the intracellular localization of MHC-I, quantify its expression in the surroundings of CD8 T infiltrating cells and define its distribution between alpha and beta cells.

METHODS

Pancreatic tissue sections from a non-diabetic (ND) donors, autoantibody positive (AAb+) donors, and donors with T1D provided by the Network for Pancreatic Organ Donors with Diabetes (nPOD) were imaged using high-resolution laser scanning confocal microscopy (LSCM).

SUMMARY OF RESULTS

Our analysis show that MHC-I is internalized and accumulated primarily in the Golgi apparatus in AAB+ and T1D donors. MHC-I is upregulated in T1D donors as well as AAB+ donors and is not driven by the immune infiltration. In T1D and AAB+ donors, MHC-I is primarly expressed on Alpha cells compared to ND donors as shown by quantitative colocalization assay.

CONCLUSIONS

Increased MHC-I is a hallmark of T1D pathology and already occurs prior to clinical diagnosis in islets of antibody positive organ donors, a time when immune infiltration is rare and sparse. Our detailed proximity analysis of upregulated MHC-I in relation to CD8 cells in ecoxrine pancreas and islets further supports the conclusion that the immune inflitration (or potential humoral mediators) are not the primary cause for the elevated MHC-I. Rather, the fact that MHC-I is not only increased on the surface but also intracellularly (mostly Golgi) in affected cells is indicative of a functional defect of beta cells (and maybe islets) preceding immune infiltration. Interestingly, despite the fact that alpha cells also show elevated MHC-I, they do not seem to become immune targets as easily as beta cells (maybe a question of epitope display?).