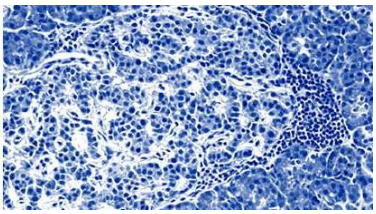
nPOD
Network for Pancreatic Organ Donors with Diabetes



Protecting stem cell-derived beta like cells (sBCs) from an immune attack

AUTHORS

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PURPOSE

Show for the first time how stem cell-derived beta like cells (sBCs) respond to a T1D mimicking environment and determine if PD-L1 expression on sBCs can avoid activation of immune cells.

METHODS

sBCs and human islets were exposed to pro-inflammatory cytokines (IFN-γ, IL1β, TNFα) *in vitro* in a chronic manner. Immunofluorescence and qPCR analysis of immune related genes were performed to determine the sBCs respond to an inflammation environment. Human islets were used as control. Further, to provide sBCs with local PD-L1 mediated immune modulation, we employed genome engineering to stably and site specifically integrate an inducible PD-L1 expression system in human pluripotent stem cells (hPSCs). Further, direct differentiation of hPSCs into sBCs was used to generate sBCs that can express PD-L1 in a controlled manner. Immune cell activation assays are performed by co-culturing sBCs with avatar CD8+ T cells using IL2 secretion as an activation readout.

SUMMARY OF RESULTS

Exposure of sBCs to T1D modeling conditions results in upregulation of HLA-C but not HLA-A, -B or PD-L1 at the mRNA and protein levels while similarly treated healthy human islets upregulated immune receptors HLA-A, B, C as well as the immune checkpoint inhibitor PD-L1. We further show that sBCs treated with cytokines can present antigens and activate avatar CD8+ T cells as measured by IL-2 secretion. Experiments are being focused right now on using the inducible PD-L1 sBCs to determine if PD-L1 expression can rescue the activation of immune cells.

CONCLUSIONS

We show here for the first time how sBCs respond to a T1D mimicking environment. This study also confirmed known molecules important for the response of cadaveric human islets to T1D modeling conditions. Based on these results we provided novel strategies for the design of encapsulation-free cell therapy modalities that may efficiently evade an autoimmune attack.