Background

- 1.6 million Americans are living with Type 1 Diabetes (T1D)
- Incidence and prevalence of T1D are rising with a current annual cost of $15 billion
- T1D is commonly managed by use of exogenous insulin, but risks of chronic complications persist
- Incidence and prevalence of T1D are rising with a current annual cost of $15 billion
- Transplantation of native islets offers superior glucose control, but therapeutic benefits are hindered by lack of donors as well as poor islet survival1, 2
- Stem cell derived islets offer an alternate method of generating β-cells
  - By providing scaffolding to the cells and creating aggregate clusters, we investigate the functionality of stem cell derived islet organoids

Methods

- Human pluripotent stem cells were used to derive β-cells through a 6-stage differentiation protocol
  - Single cell dispersals were seeded onto microporous PLG scaffolds at either SSD1 or S6D1, cells were reaggregated into clusters at S6D7 and seeded onto scaffolds at S6D10
- Transplantation occurred on day of seeding into the epididymal fat pads of diabetic NSG mice
- Analysis occurred through glucose stimulated insulin secretion (GSIS)
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Results

- Reaggregated clusters were able to reverse hyperglycemia though levels were not fully normalized
- Significantly higher count of monocytes at scaffold with cells, indicating dendritic cell response to foreign antigen
- Innate immune response levels off after 7 days

Discussion

- Cells in later stages can reaggregate to form islet organoids and be seeded onto the scaffold for transplantation
- Reaggregated cells had greater insulin secretion in comparison to cultures from SSD1
- Reaggregated cells showed a significant difference in insulin secretion during GSIS assays at S6D10 in comparison to SSD1 seeded scaffolds
- Reaggregated clusters were able to reverse hyperglycemia though levels were not fully normalized
- Significantly higher count of monocytes at scaffold with cells, indicating dendritic cell response to foreign antigen
- Innate immune response levels off after 7 days

Conclusions

- 3D stem cell derived islet organoids supports cell maturation and enhances function
- Organoids produce insulin and reduce hyperglycemia
- S6D1 seeded scaffolds and reaggregated clusters secreted more insulin than SSD1 seeded scaffolds
- Day 4 time point for immune cell study needs further investigation in order to understand how the innate immune system acts over time
- Cell seeded scaffold transplantation causes an inflammatory immune response 24 hours after transplantation. Future therapeutics are needed to protect stem cell derived islet organoids from inflammation-related cell death

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References