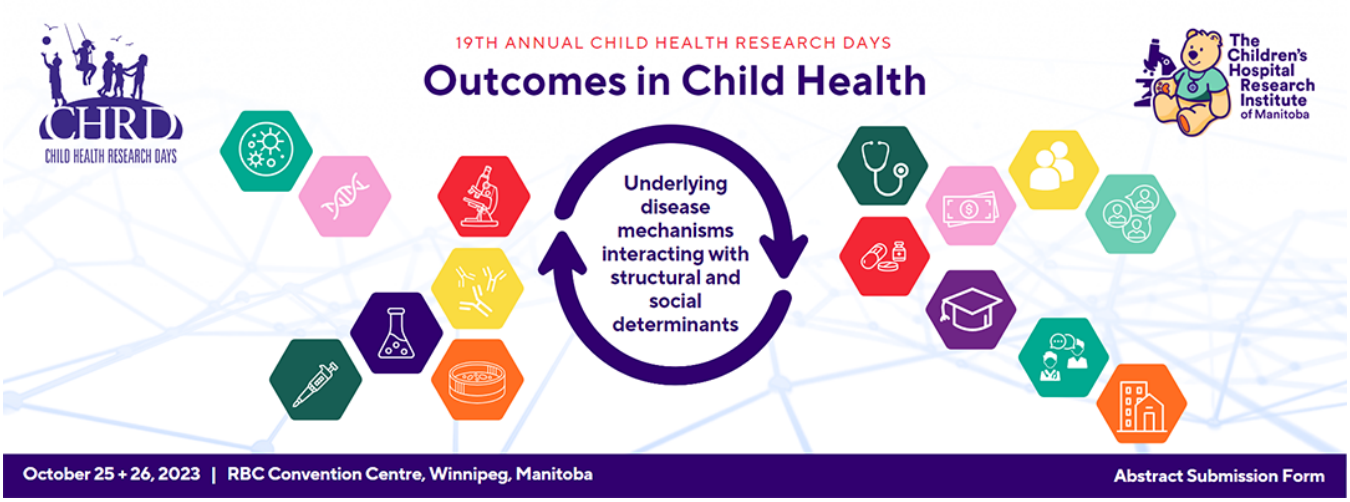

CHRD 2023: Abstract Submission Form

Submitter Name
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Presenter Status
Masters Student

Research Category
Basic Science

Role in the project
Analyze Data
Write Abstract

Title
Unraveling the Cellular Sources of Interleukin-1β Production in Amyloid-Forming Human Islets: A Potential Strategy to Enhance Human Islet Graft Survival in Type 1 Diabetes

Background
Type 1 diabetes (T1D) is characterized by immune-mediated destruction of pancreatic beta cells, leading to hyperglycemia. Islet transplantation provides a promising strategy to restore endogenous insulin and normoglycemia in T1D but is limited by insufficient pancreatic donors and islet loss post-transplantation. Islet amyloid, formed by aggregation of human islet amyloid polypeptide (hIAPP), contributes to loss of beta-cell mass/function in T2D. Amyloid also forms in human islets during pre-transplant culture and post-transplantation, thereby contributing to islet graft failure. We previously showed that amyloid formation promotes islet inflammation and interleukin (IL)-1β production, leading to β-cell upregulation of Fas cell death receptor and apoptosis.

Objective
Here, we investigated the potential cellular source(s) of IL-1β production in human islets during ex vivo amyloid formation.

Methods
Isolated human islets (n=5 cadaveric donors) were treated with or without clodronate (deplete macrophages) and cultured in elevated (11.1 mmol/l) glucose (potentiate amyloid formation) for 7 days. Quantitative immunolabeling was performed on paraffin-embedded islet sections for insulin and each IL1β, Fas, TUNEL (apoptosis), thioflavin S (amyloid), and CD68 (macrophage marker).

Results

Freshly isolated human islets had low IL-1β immunoreactivity. Islet culture resulted in amyloid formation, which was associated with increased islet IL-1β immunoreactivity (Day 0: 1.0±0.3; Day 7: 8.6±1.7, $p<0.05$), Fas-positive (Day 0: 0.8±0.2%; Day 7: 4.2±1.1%) and TUNEL-positive β-cells (Day 0: 2.2±0.5%; Day 7: 8.1±1.2%), all of which were markedly reduced by amyloid inhibition. Depletion of islet macrophages markedly reduced, but did not completely block, amyloid-induced IL-1β immunoreactivity in islet β-cells (Day 0: 0.9±0.2; Day 7: 7.6±2.3; Day 7+clodronate: 2.9±0.1).

Conclusion
These data suggest that macrophages (mainly) and β-cells are two cellular sources of amyloid-induced IL-1β production in human islets, which leads to Fas-mediated β-cell apoptosis. Blocking islet IL1β production and/or signaling may provide an effective pharmacological strategy to protect β-cells from amyloid during pre-transplant culture and post-transplantation

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