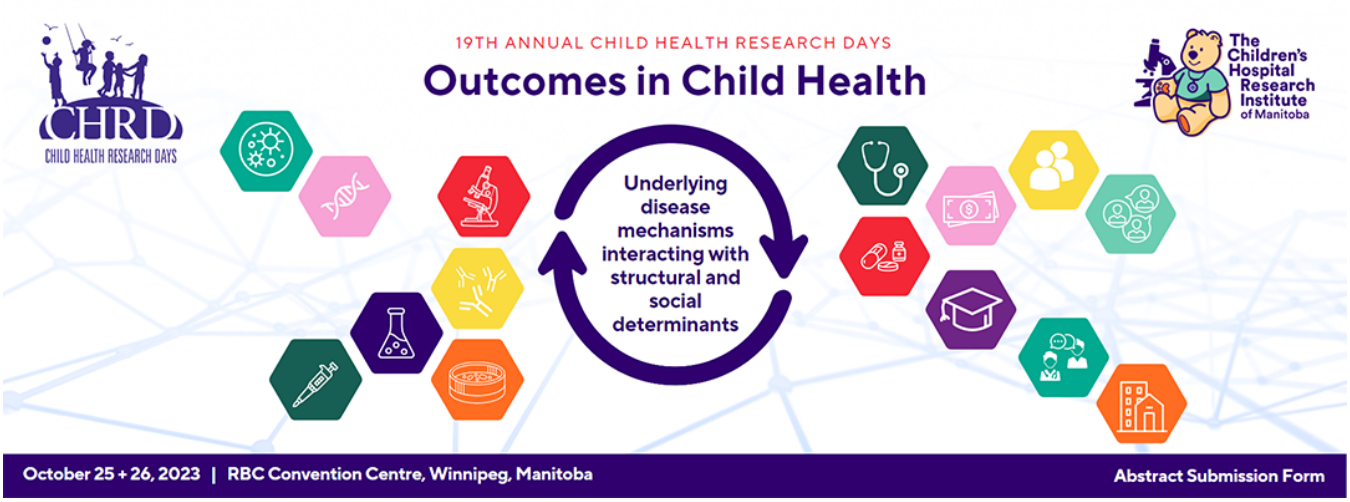

CHRD 2023: Abstract Submission Form

Submitter Name
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Presenter Status
Masters Student

Research Category
Basic Science

Role in the project
Analyze Data
Write Abstract

Title
A potential cellular mechanism for amyloid-induced beta-cell death in human islets – Implications in pre-transplant human islet culture

Background
In type 1 diabetes (T1D), immune-mediated beta-cell destruction leads to reduced islet beta-cell mass, elevated blood glucose, and life-time insulin therapy. Islet transplantation as a means of beta-cell replacement is a promising treatment approach but is currently limited by loss of islets during pre-transplant culture period and post-transplantation. Formation of toxic protein aggregates named amyloid in human islets due to fibrillogenesis of the beta-cell hormone, human islet amyloid polypeptide (hIAPP), contributes to islet loss during pre-transplant culture and post-transplantation, potentially leading to islet graft failure. The cellular mechanisms by which amyloid destroys beta cells are unclear.

Objective
We examined the potential role of islet-derived extracellular vesicles (EVs) in amyloid-induced beta-cell death.

Methods
Isolated human islets (n=4 cadaveric donors) were cultured in normal (5.5 mM, no amyloid) or elevated (11.1 mM; form amyloid) glucose for 7 days. EVs were isolated from islet culture medium and their purity was assessed by EV specific markers. Freshly isolated human islets were then cultured for 3 or 7 days without or with EVs purified from control or amyloid-forming human islets (conditioned medium). Amyloid formation and beta-cell death were assessed by quantitative immunolabelling for insulin and thioflavin S (amyloid) or insulin and TUNEL (apoptosis), respectively.

Results
Human islets cultured with the conditioned medium containing EVs isolated from amyloid-forming islets (elevated glucose) had higher amyloid formation than islets cultured with isolated EVs from non-amyloid forming islets (normal glucose) or non-treated islets. Increased amyloid formation in human islets cultured with conditioned medium containing EVs from amyloid-forming islets closely correlated with the increased number of TUNEL-positive beta-cells in those islets.

Conclusion
These data suggest that EVs released from non-healthy amyloid-forming human islets can promote amyloid formation and beta-cell death in healthy islets. Thus, modulating islet-derived EVs may provide a potential strategy to improve beta-cell survival during pre-transplant culture.

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