CHRD 2024: Abstract Submission Form

Presenter Name
Danish Malhotra

Presenter Status
Masters Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Amyloid-Associated Shift in the Phenotype of Resident Macrophages in Human Islets – A Potential Mechanism for Islet Inflammation in Type 2 Diabetes

Background
The incidence and prevalence of type 2 diabetes (T2D) are increasing in Manitoba, Canada, and worldwide, not only in adults but also in children. In patients with T2D, formation of toxic protein aggregates named amyloid in pancreatic islets contributes to islet inflammation, beta-cell dysfunction, and death, by promoting IL-1beta production and activation of the Fas-mediated apoptotic pathway. Islet macrophages are the main source of amyloid-induced IL-1beta production in human islets and are classified into pro-inflammatory (M1) and anti-inflammatory (M2) macrophages.

Objective
We examined the potential effects of amyloid formation on the M1 and M2 macrophage population in human islets.

Methods
Human islets (n=4 cadaveric donors) were cultured in normal glucose as control (5.5 mM; no or minimal amyloid formation) or elevated glucose (11.1 mM; islets form amyloid) for 7 days. Quantitative immunolabelling was performed on paraffin-embedded human islet sections for insulin and each CD68 (general macrophage marker), iNOS (M1 marker), CD163 (M2 marker), IL-1beta, Fas, thioflavins S (amyloid), TUNEL (apoptosis). Also, IL-1beta release from human islets was assessed.

Results
Human islets progressively formed amyloid during 7-day culture in elevated glucose (but not in normal glucose), leading to increased number of apoptotic beta-cells. Amyloid formation was associated with elevated islet IL-1beta levels, upregulation of the Fas cell death receptor in beta cells, and a shift in the phenotype of islet resident macrophages, manifested as elevated iNOS-positive (M1) and reduced CD163-positive (M2) macrophages. The mean of total macrophages per islet was comparable in pre-culture and 7-day cultured islets at both glucose levels.

Conclusion
Amyloid formation in human islets led to a shift in macrophage phenotype towards pro-inflammatory (M1), thereby promoting IL-1beta production and IL-1bteta/Fas-mediated beta-cell apoptosis. Thus, modulation of islet macrophage phenotype may provide a therapeutic strategy to improve beta-cell survival in children and adults with T2D by reducing amyloid-induced beta-cell death.

Do you have a table/figure to upload?
Yes

Authors

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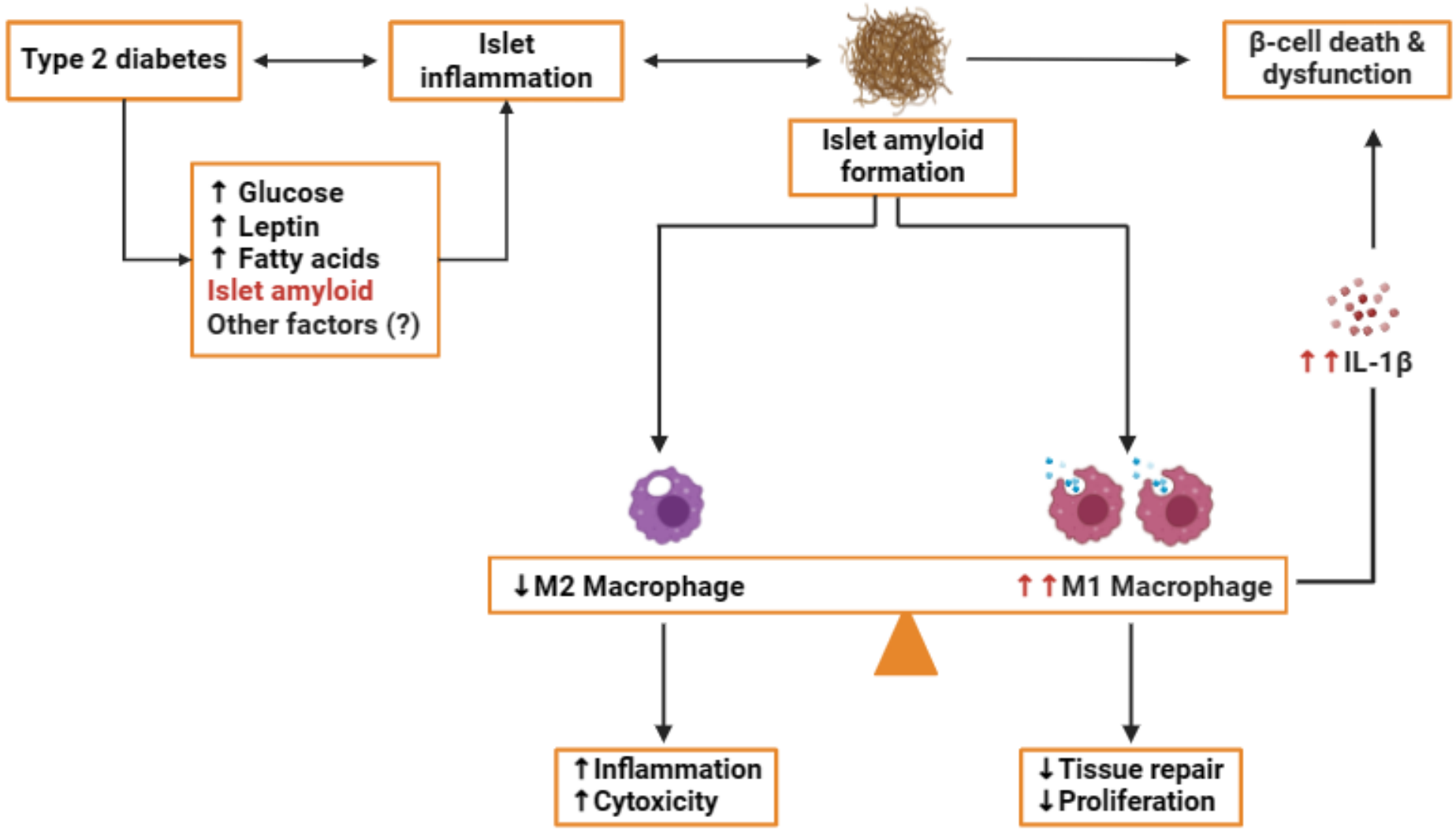
Type 2 diabetes
Islet inflammation
β-cell death & dysfunction
↑ Glucose
↑ Leptin
↑ Fatty acids
Islet amyloid
Other factors (?)
Islet amyloid formation
↑↑IL-1β
↓M2 Macrophage
↑↑M1 Macrophage
↑Inflammation
↑Cytoxicity
↓Tissue repair
↓Proliferation