CHRD 2021: Abstract & Poster Submission Form

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Research Category:

- ◉ Basic Science
- ○ Clinical
- ○ Community Health / Policy

What was your role in the project?

- ☐ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Presenter Status:

- ○ Undergraduate Students
- ◉ Masters Student
- ○ PhD Student
- ○ Post-Doctoral Fellows
- ○ Residents
- ○ Non-Trainee

Title

Blocking Interleukin-1 beta Signaling Protects Pancreatic Islet Beta Cells From Intracellular and Extracellular Amyloid – Implications in Childhood Type 2 Diabetes

Background

Type-2 diabetes (T2D) is characterized by peripheral insulin resistance, beta-cell loss and dysfunction, leading to hyperglycemia. Despite being prevalent in adults, incidence of T2D in progressively increasing in children and adolescents. A key factor contributing to beta-cell death in T2D is intracellular and extracellular aggregation of a toxic protein called amyloid in pancreatic islets. Amyloid formation plays a key role in islet inflammation by stimulating interleukin-1beta (IL-1beta) production in islets.

Objective

In this study, we used two pharmacological strategies, IL-1 receptor antagonist (anakinra) and IL-1beta neutralizing monoclonal antibody (nAb), to examine if blocking IL-1beta signaling can reduce amyloid-induced beta-cell toxicity and enhance beta-cell survival.

Methods

Human islets (n=4 donors) were cultured free-floating in CMRL medium (11.1 mmol/l glucose; 7 days) to form amyloid. INS-1 beta-cells (n=3 independent studies) were cultured in RPMI medium after adenoviral transduction to induce intracellular amyloid formation. Human islets and INS-1 beta-cells were treated with anakinra (10 µg/ml) or nAb (1 µg/ml), respectively. Quantitative immunohistochemistry was performed on INS-1 beta-cells and paraffin-embedded human islet sections for insulin and Thioflavin S (large aggregates), A11 (small aggregates), TUNEL (apoptosis), or PCNA (proliferation).

Results

Cultured human islets formed amyloid which was mainly extracellular. Treatment with anakinra reduced amyloid-positive human islets (anakinra(-): 12±4%, anakinra(+): 4±0.8%, $p<0.05$) and decreased TUNEL-positive beta-cells (anakinra(-): 7.4±0.9%, anakinra(+): 3.9±0.7%, $p<0.05$). Transduced INS-1 beta-cells formed intracellular amyloid and treatment with nAb reduced the proportion of amyloid-positive (nAb(-): 70±5%, nAb(+): 48%±6%, $p<0.05$) and TUNEL-positive (nAb(-): 3.1±1.0%, nAb(+): 1.5±0.2%, $p<0.05$) INS-1 beta-cells. PCNA-positive beta-cells were increased in treated human islets and INS-1 beta-cells (anakinra(-): 0.6±0.3%, anakinra(+): 1.0±0.3%, nAb(-): 0.5±0.1%, nAb(+): 1.0±0.2%, $p<0.05$).

Conclusion

Treatment with anakinra or nAb reduced intracellular and extracellular amyloid formation, decreased amyloid-induced beta-cell death, and enhanced beta-cell proliferation. Blocking IL-1beta may provide an effective strategy to protect beta-cells in T2D in children and adults.

Authors

- For each author, please click "**[+] Add Item**" and provide the author's information

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