Neutralizing Interleukin-1 beta Protects Islet β-cells From Intracellular Amyloid

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INTRODUCTION
Type 2 Diabetes (T2D; adult-onset diabetes) is characterized by the progressive loss of pancreatic β-cell mass and function.
Aggregation of the toxic protein, amyloid, contributes to the loss of β-cell mass. Amyloid formation is also observed during pre-transplant islet culture and islet graft failures in patients with type 1 diabetes (T1D).
Amyloid formation contributes to islet inflammation by stimulating the production of the pro-inflammatory cytokine interleukin-1 beta (IL-1β) in islets.

AIMS
We examined if:
1. Blocking IL-1β signalling can reduce the intracellular amyloid-induced β-cell death.
2. Blocking IL-1β signalling can enhance β-cell survival in the presence of intracellular amyloid.

METHODS
INS-1 β-cells (n=3 independent studies) were cultured in RPMI-1640 medium after transduction with prohAPP-adenovirus to induce intracellular amyloid formation.
INS-1 β-cells were treated with nAb (1 μg/mL)
Quantitative immunohistochemistry was performed on INS-1 β-cells for insulin and A11 (small intracellular aggregates), TUNEL (apoptosis), or PCNA (proliferation).

RESULTS

Fig 3. INS-1 β-cells were immunolabelled for insulin and A11, TUNEL, or PCNA

RESULTS, continued

Fig 5. The proportion of TUNEL-positive (apoptotic) β-cells after 7-day treatment with nAb. Day 0 (C) and Day 7 (nAb) for comparison. Data are expressed as mean±SEM of three independent studies, *p<0.05.

Treating with nAb significantly reduced TUNEL-positive and amyloid-positive β-cells. PCNA-positive β-cells were also increased post treatment.

CONCLUSION
Treatment with nAb significantly reduced intra-cellular amyloid formation, decreased amyloid-induced β-cell death, and enhanced β-cell survival (proliferation).
Reducing amyloid formation by blocking IL-1β signalling may provide an effective approach to decrease loss of β-cell mass in patients with T2D.
Reducing amyloid-induced IL-1β signalling may also prove to be of benefit in increasing the longevity of islet grafts patients with T1D.

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Fig 7. The proportion of amyloid-positive transduced INS-1 β-cells with and without treatment with nAb. Day 0 (C) and Day 7 (nontreated, NT) are shown for comparison. Data are expressed as mean±SEM of three independent studies, *p<0.05.

RESULTS, continued

Fig 6. The proportion of PCNA-positive (proliferative) β-cells after 7-day treatment with nAb. Day 0 (C) and Day 7 (nontreated, NT) are shown for comparison. Data are expressed as mean±SEM of three independent studies, *p<0.05.

Fig 4. INS-1 β-cells from control, non-treated and treated (with neutralizing IL-1β antibody (nAb)) were immunolabelled for insulin and PCNA (top row) or TUNEL (bottom row). Micrographs represent three independent studies.