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

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INTRODUCTION

- Type 2 Diabetes (T2D; adult-onset diabetes) is characterized by the progressive loss of pancreatic ß-cell mass and function.
- Aggregation of the toxic protein, amyloid, contributes to the loss of ß-cell mass. Amyloid formation is also observed during pre-transplant islet culture and islet grafts 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-1ß) in islets.

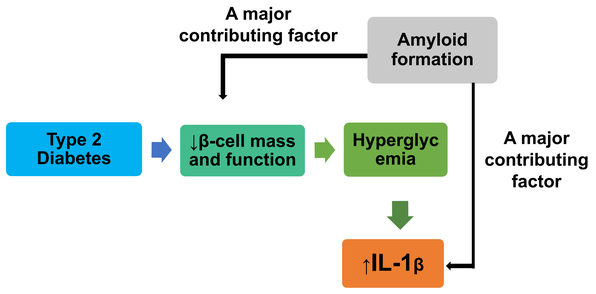


Fig 1. Pathogenesis of T2D.

- IL-1ß neutralizing monoclonal antibodies (nAb) are able to effectively block IL-1ß action by targeting IL-1ß.

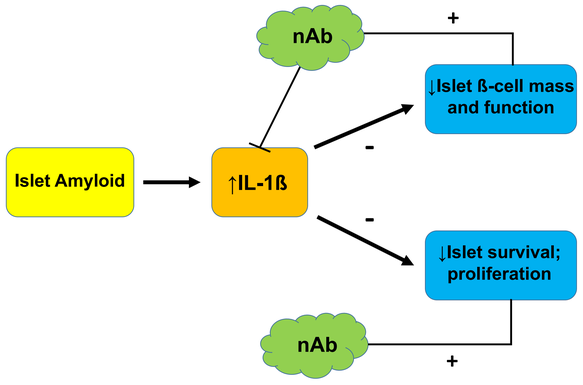


Fig 2. The mechanism of amyloid-induced ß-cell toxicity and proposed protecting mechanism of neutralizing antibody (nAb).

AIMS

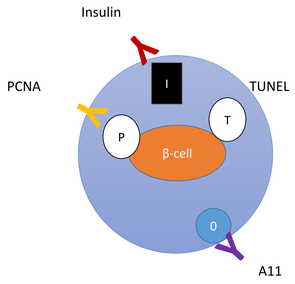
We examined if:

1. Blocking IL-1ß signalling can reduce the intracellular amyloid-induced ß-cell death.
2. Blocking IL-1ß signalling can enhance ß-cell survival in the presence of intracellular amyloid.

METHODS

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

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



RESULTS

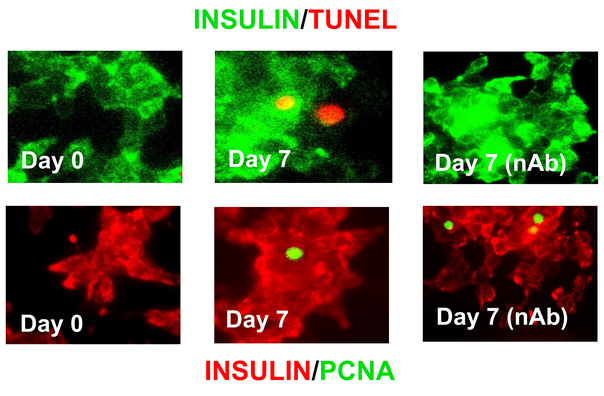


Fig 4. INS-1 ß-cells from control, non-treated and treated (with neutralizing IL-1ß antibody (nAb)) were immunolabelled for insulin and PCNA (top row) or TUNEL (bottom row). Micrographs represent three independent studies.

RESULTS, continued

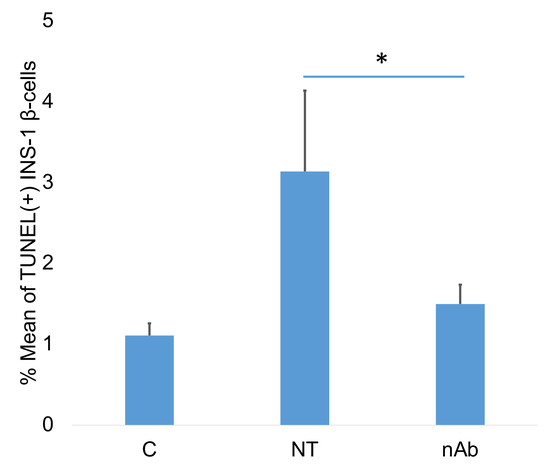


Fig 5. The proportion of TUNEL-positive (apoptotic) ß-cells after 7-day treatment with nAb. Day 0 (C) and Day 7 (nontreated, NT) are shown for comparison. Data are expressed as mean±SEM of three independent studies, *=p<0.05.

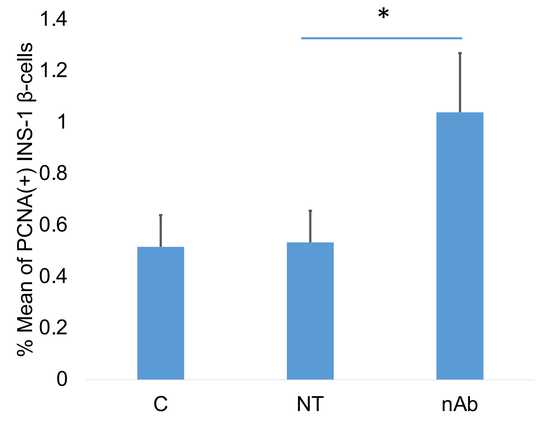


Fig 6. The proportion of PCNA-positive (proliferative) β-cells after 7-day treatment with nAb. Day 0 (C) and Day 7 (nontreated, NT) are shown for comparison. Data are expressed as mean±SEM of three independent studies, *=p<0.05.

RESULTS, continued

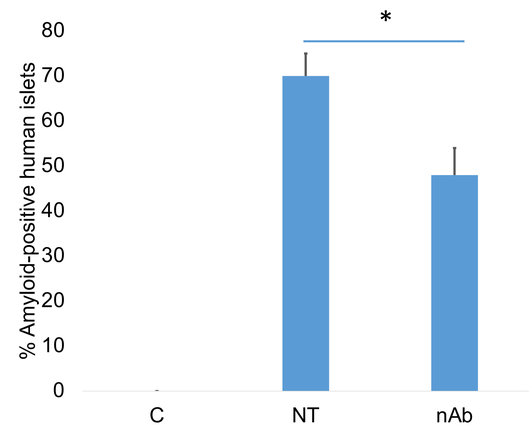


Fig 7. The proportion of amyloid-positive transduced INS-1 ß-cells with and without treatment with nAb. Day 0 (C) and Day 7 (nontreated, NT) are shown for comparison. Data are expressed as mean±SEM of three independent studies, *=p<0.05.

- Treatment of INS-1 ß-cells with nAb significantly reduced TUNEL-positive and amyloid-positive ß-cells. PCNA-positive ß-cells were also increased post treatment.

CONCLUSION

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

ACKNOWLEDGEMENTS

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