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Title of Presentation: The IL-1 Receptor Antagonist Anakinra Reduces Amyloid Formation and Enhances Beta-Cell Survival and Function in Cultured Human Islets: Implications in Clinical Islet Transplantation

Abstract

Introduction: Human islet transplantation provides a feasible approach for treatment of type 1 diabetes (T1D) but is currently limited by shortage of donors and islet loss during pre-transplant culture and post-transplantation that eventually leads to graft failure in most patients. Islet amyloid, formed by aggregation of human islet amyloid polypeptide (hIAPP), is a pathologic characteristic of pancreas in type 2 diabetes (T2D) that also forms in cultured and transplanted islets. Importantly, hIAPP aggregates are toxic to beta cells and contribute to beta-cell death in all conditions associated with islet amyloid formation such as in T2D, islet culture, and transplantation. The mechanism(s) by which hIAPP aggregates mediate beta-cell death are still unclear. We recently showed that endogenously formed hIAPP aggregates induce upregulation of cell death receptor Fas in beta cells which is likely mediated by IL-1beta.

Objectives: In this study, we examined if treatment with Anakinra (Kineret), a clinically approved IL-1 receptor antagonist, can reduce amyloid toxicity thereby enhance survival and function of isolated human islets during pre-transplant culture as a potential approach to improve quality and/or quantity of islets for transplantation.

Methods: Freshly isolated human islets (n=7 donors) were cultured in CMRL with normal (5.5 mmol/l) or elevated glucose (11.1 mmol/l; to potentiate amyloid formation) in the presence or absence of Anakinra (10 μg/ml) for up to 7 days. Islet IL-1beta level, amyloid formation, beta-cell Fas expression, apoptosis, and function were assessed.

Results: hIAPP aggregates were present in cultured (but not freshly isolated) human islets which was associated with increased islet IL-1beta immunoreactivity, Fas upregulation, and progressive beta-cell apoptosis. IL-1beta release from human islets during culture correlated with amyloid formation. Interestingly, Anakinra-treated islets had lower beta-cell apoptosis, greater insulin response to elevated glucose and insulin content than non-treated cultured islets, which was associated with lower amyloid formation and beta-cell Fas expression.

Conclusion: These data suggest that amyloid-induced beta-cell Fas upregulation is associated with IL-1beta release from human islets during culture resulting in beta-cell death. Treatment with IL-1 receptor antagonists may provide a new approach to prevent amyloid beta-cell toxicity thereby enhance islet survival and function during pre-transplant culture.