Effect of Acute IFN-α Exposure on β-cell Survival and Function in the Absence of Functional Autophagy

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Background and Hypothesis: It has been demonstrated that the protective degradative process of autophagy is defective in the context of human T1D. Additionally, a type I interferon-inducible transcriptional signature has been detected in blood cells of children genetically at risk for T1D prior to the appearance of autoantibodies**.** Preliminary data demonstrate that autophagy can be stimulated by IFN-α in β-cells of non-diabetic mice, but this response is defective in β-cells of nonobese diabetic (NOD) mice, a mouse model for autoimmune diabetes. We hypothesize that impaired autophagy and exposure to IFN-α will lead to reduced β-cell survival and impaired function.

Methods:
Bafilomycin A, a lysosomal inhibitor, was used to inhibit autophagy in INS-1 832/13 cells and pancreatic human islets. We then utilized western blot analysis, Caspase-Glo® 3/7 Assay, and Insulin HTRF Assay to assess β-cell survival and function in response to IFN-α exposure.

Results: Western blot analysis was used to monitor inhibition of autophagy and stimulation of IFN-α pathway in INS-1 832/13 cells (n=4) and pancreatic human islets (n=1). An increase in LC3II/LC3I ratio was observed after treatment with Baf A, indicating accumulation of autophagosomes. Phosphorylation of STAT2 was observed in IFN-α treated cells, indicating stimulation of the IFN-α pathway. Impaired autophagy and IFN-α exposure did not induce apoptosis in INS-1 832/13 cells (n=2). Following Baf A and IFN-α treatment, glucose stimulated insulin secretion was measured. Glucose stimulated insulin secretion is decreased in INS-1 832/13 cells following Baf A and IFN-α treatment (n=2).

Conclusions: These data suggest that inhibition of autophagy followed by an acute treatment with IFN-α does not induce significant cell death, but modestly impairs β-cell function. Future studies will determine the effects of prolonged IFN-α exposure on β-cell survival and function as well as investigate other potential mechanisms of cell death.