P046 Improving survival and function of pancreatic islets using an adenoviral-driven super-repressor of NF-κB.

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Transplanted islets in patients with T1D are exposed to an immune attack, with a central role for NF-κB. The aim of this study was to deliver proof-of-concept that blocking NF-κB can protect β-cells against inflammation-induced cell death. Mutant, non-phosphorable IκBα, was introduced into mouse islets with an adenoviral construct (Ad-pCMV-HA-IκBα). To determine transduction efficacy and effect of transduction on β-cell viability, islets were transduced with Ad-pCMV-EGFP. Fluorescence in Ad-pCMV-EGFP-transduced islets was already intense day 1 post-transduction and increased over time without affecting cell viability. Confocal microscopy analysis within Ad-pCMV-HA-IκBα-transduced islets showed that the mutant IκBα co-localized with both insulin- and glucagon-positive cells in islets. Ad-pCMV-HA-IκBα-transduced islets exposed to IL-1β+IFN-γ showed less cell death and NO production compared to IL-1β+IFN-γ-treated non-transduced islets. Even more, the inability to secrete insulin after an acute rise in glucose in non-transduced islets exposed to inflammatory cytokines was prevented with Ad-pCMV-HA-IκBα-transduced islets. These data suggest that NF-κB is a “master switch” of cytokine-induced β-cell death and dysfunction and is a potential target for drug development in prevention of β-cell destruction following islet transplantation.