

P004 Protection of pancreatic β -cells from cytokine-mediated apoptosis by inactivation of AMP-activated protein kinase
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Type 1 diabetes is characterised by the destruction of insulin-producing beta cells by apoptosis, and islet transplantation is associated with substantial loss of grafted tissue through non-immune attack mediated by inflammatory cytokines. AMPK has recently been implicated in the apoptosis of pancreatic beta-cells and in islet cell death post-transplantation. Here, we have studied the effects of cytokines on apoptosis in beta cells, focussing on the involvement of AMPK. We show that a combination of the cytokines IL1 β , TNF α and interferon- γ induce apoptosis in clonal MIN6 beta-cells and mouse pancreatic islets, as reflected by increased cleavage of caspase-3 and terminal deoxynucleotide transferase-mediated deoxyuridine trisphosphate biotin nick end-labelling (TUNEL). Apoptosis was decreased by infection of cells or islets with a recombinant adenovirus expressing a dominant-negative form of AMPK α 1 (D^{157A}; Ad(AMPK DN)). Thus, activation of AMPK appears to be involved in cytokine-mediated destruction of β -cells in type 1 diabetes, and may act through the activation of downstream stress-activated kinases, phosphorylation of p53 and cell cycle arrest, or inhibition of a PKB-mediated anti-apoptotic pathway. These data suggest that inhibition of islet AMPK activity may enhance the survival of allografts transplanted into Type 1 diabetic patients.