P044 Expression of a mutant, dominant negative form of TAK1 in insulin-secreting INS-1 cells reduces cytokine-induced apoptosis

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Type 1 diabetes is characterized by complete destruction of the insulin-producing pancreatic β-cells in an immune-mediated process. In this process, the pro-inflammatory cytokines interleukin (IL)-1β and interferon (IFN)-γ are thought to play an important role. Mitogen-activated protein kinases (MAPKs) and nuclear factor (NF) κB have been established as crucial mediators of cytokine-induced β-cell inducible nitric oxide synthase (iNOS) expression and apoptosis *in vitro*. However, the exact upstream kinases responsible for MAPK and NFκB activation are unclear. One candidate kinase leading to activation of both the MAPK and NFκB signalling pathways is TGFβ-activated kinase (TAK)-1. To investigate if TAK1 plays a role in mediating cytokine signal transduction in β-cells, we examined the impact of transfecting insulin-secreting INS-1 cells with a mutant, dominant negative (DN) form of TAK1. By reporter gene assay, we found that co-transfection with DN-TAK1 blocked IL-1β-induced iNOS promoter activity by 55%. IL-1β-induced NFκB-driven reporter gene activity was reduced by 23% by DN-TAK1. These effects of DN-TAK1 correlated with suppression of IL-1β+IFNγ-induced apoptotic cell death by 60% as compared to mock-transfected control cells. In conclusion, our results suggest that cytokine-induced NFκB activation, iNOS expression and apoptosis are partially dependent on TAK1.