S015  Cytokine signalling in the beta-cell: dual role for IFN-gamma
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IFN-γ, together with other cytokines such as IL-1β and TNF-α or dsRNA, has the potential to alter expression of several genes/proteins and mediate β-cell destruction in insulin-producing cells. This suggests that IFN-γ synergizes with IL-1β, TNF-α or dsRNA in triggering β-cell apoptosis via regulation of gene/protein expression. IFN-γ acts mostly via JAK activation with the transcription factor STAT-1 playing a central role in the downstream pathway. The ability of STAT-1 to activate gene expression may also be modulated by its interaction with transcription factor IRF-1. We demonstrated that inhibition of IRF-1 does not prevent cytokine-induced β-cell apoptosis, while absence of STAT-1 in β-cells prevents IFN-γ plus IL-1β- and IFN-γ plus dsRNA-mediated β-cell death in vitro. Surprisingly, lack of the IRF-1 gene in pancreatic islets promotes low-dose streptozotocin-induced diabetes in vivo, whereas lack of STAT-1 confers resistance against β-cell death following low-dose streptozotocin-induced diabetes. Additionally, IRF-1−/− islets are more sensitive to primary non-function (PNF) after transplantation in spontaneously diabetic NOD mice, while STAT-1−/− islets are fully protected against PNF in this model. We conclude that STAT-1 plays a central role in inflammation-induced β-cell death. Disrupting IFN-γ signaling at this level, but not at the level of IRF-1, confers β-cell protection.