A proteomic study of the regulatory role for STAT-1 in cytokine-induced beta-cell death - DTU Orbit (11/02/2019)

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**PURPOSE:** Signal transducer and activator of transcription 1 (STAT-1) plays a crucial role in cytokine-induced beta-cell destruction. However, its precise downstream pathways have not been completely clarified. We performed a proteome analysis of cytokine-exposed C57Bl/6 and STAT-1-/- mouse islets and prioritized proteins for their potential in relation to type 1 diabetes (T1D).

**EXPERIMENTAL DESIGN:** Differential proteins were identified using a combination of 2D-DIGE and MALDI-TOF/TOF analysis and were subjected to Ingenuity Pathway Analysis (IPA). Protein-protein interaction networks were created and a phenome-interactome ranking of the differential proteins based on their assignment to T1D was performed.

**RESULTS:** Numerous STAT-1-regulated proteins were identified and divided in different groups according to their biological function. The largest group of proteins was the one involved in protein synthesis and processing. Network analysis revealed a complex interaction between proteins from different functional groups and IPA analysis confirmed the protective effect of STAT-1 deletion on cytokine-induced beta-cell death. Finally, a central role in this STAT-1-regulated mechanism was assigned to small ubiquitin-related modifier 4 (SUMO4).

**CONCLUSIONS AND CLINICAL RELEVANCE:** These findings confirm a central role for STAT-1 in pancreatic islet inflammation induced destruction and most importantly elucidate the underlying proteomic pathways involved.