

P049 β -cell maturation enhances cytokine sensitivity via iron metabolism

**Morten Tonnesen¹, Lars Groth Grunnet¹,
Josefine Friberg¹, Nils Billestrup¹, Flemming Pociot¹
and Thomas Mandrup-Poulsen^{1,2}**

¹Steno Diabetes Center, Gentofte, Denmark, ²Dept. of Translational Diabetology, University of Copenhagen, Denmark

Background: Interleukin-1 (IL-1) is implicated in pancreatic β -cell destruction in Type 1 diabetes mellitus (T1DM) and in islet transplantation. β -cell acquisition of sensitivity to IL-1 is associated with pancreatic duodenal homeobox factor-1 (Pdx-1) expression. **Aims:** (1) Compare IL-1-induced apoptosis/signalling in INS-1 $\alpha\beta$ cells +/- Pdx-1 overexpression. (2) Based on gene expression profiling and functional studies reveal mechanisms behind differentiation-acquired β -cell-sensitivity to IL-1.

Results: Pdx-1 over-expressing INS-1 $\alpha\beta$ cells were more sensitive to the toxic effect of IL-1 β (310% increase in apoptosis compared to wildtype, $p < 0,05$). IL-1 β -induced NF κ B transcriptional activity was increased ($>200\%$, $p < 0,05$) in Pdx-1 overexpressing cells. Bioinformatic analysis/textmining of microarray data suggested altered iron homeostasis as an important factor in IL-1-sensitivity. We observed increased expression (400%, $p < 0,01$) of the NF κ B-regulated iron transporter divalent metal transporter 1 (DMT1) in cytokine-treated rat and human islets, correlating with increased IL-1-induced iron uptake and Reactive Oxygen Species (ROS) production ($>100\%$ increase in Pdx-1 overexpressing cells, $p < 0,05$). SiRNA-mediated DMT1 knockdown completely protected against IL-1-induced caspase-3 cleavage and reduced apoptosis measured by cytosolic Histone-DNA complexes $>50\%$ ($p < 0,05$). **Conclusion:** Final β -cell maturation-enhanced IL-1-sensitivity depends upon the expression of the NF κ B-regulated iron transporter DMT1 leading to increased iron uptake and ROS production.