Abnormalities of PTPN2 Increases BETA-cell Apoptosis in PP2-Beta Cells Derived from hESCs

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The genetic contribution to the development of type 1 diabetes (T1D) remains unclear; however, certain gene variants contribute to the risk of developing this metabolic disorder. Elucidating the genetic impact on Beta-cell functionality is crucial to understanding T1D pathology. Protein tyrosine phosphatase non-receptor type 2 (PTPN2) has been linked to T1D through gene-wide association studies (GWAS), yet its influence on Beta-cell metabolism and function remains unknown. Thus, this study used the model of human embryonic stem cells (hESCs) to investigate whether the loss of PTPN2 (PTPN2-/-) impairs the metabolism and function of pancreatic Beta-cells. CRISPR was employed to construct the PTPN2-/- hESCs cell lines and the results were verified by DNA sequencing and immunoblotting. Flow cytometry and immunofluorescent followed with confocal microscopy were performed to determine if the knockout of PTPN2 affects the pancreatic progenitor Beta-cells differentiation and apoptosis of pancreatic progenitor 2 (PP2)-Beta cells. We found that in the PTPN2-/- cell lines there was an increase in apoptosis markers: Annexin V and Caspase 3 ($p<0.05$, $p<0.01$). However, there was no significant difference in the embryonic differentiation markers expressed in the hESCs cell lines. We discovered that PTPN2-/- elevated the apoptosis of PP2 Beta-cells, without impacting the differentiation process. These findings help identify the role of PTPN2 on the apoptosis of Beta-cells and T1D development. Furthermore, we demonstrate a novel human stem cell differentiation system that can serve as a platform to investigate other gene-disease relationships.

Awards Won:
Third Award of $1,000