Molecular Mechanisms Involved in Cytoprotection and Malignant Transformation of Human Beta-Cells

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Transplantation of pancreatic islets constitutes an alternative for type 1 diabetes; however, it is limited by the shortage of organ donors. We investigated the role of recombinant human prolactin (rhPRL), shown to have beneficial effects on beta-cells, in islet survival. Human pancreatic islets were isolated using an automated method, pre-treated in the presence or absence of rhPRL and subjected to serum starvation or cytokine treatment. Apoptotic beta-cells, evaluated using flow cytometry, quantitative RT-PCR, Western blot and fluorimetric assays were decreased in the presence of rhPRL. Cytoprotection involved increased BCL2/BAX ratio and inhibition of caspase-8, -9 and -3. Our study provides new direct evidence for a protective effect of lactogens on human beta-cell apoptosis. These findings are relevant for improvement of the islet isolation procedure and for clinical islet transplantation. In view of the increasing demand for human beta-cells studies, we generated cell lines derived from human insulinomas which secrete hormones and express the same markers pattern as their original tissue. Moreover, we set out to further characterize these lineages by comparing them to primary beta-cells using two-dimensional gel electrophoresis. Differentially expressed proteins were mapped by mass spectrometry and validated by Western blotting. An average of 1,800 spots was detected with less than 1% exhibiting differential expression. Proteins upregulated in islets, as Caldesmon, are involved in cytoskeletal organization, thus influencing hormone secretion. In contrast, almost all proteins upregulated in insulinoma cells, as MAGE-A2, were first described here and could be related to cell survival and resistance to chemotherapy. Our results provide, for the first time, a molecular snapshot of the changes in proteins expression which are correlated with the altered phenotype of insulinomas, collectively prompting research towards the establishment of bioengineered human beta-cells, and the development of new therapeutic strategies for insulinomas.

Keywords: Type 1 diabetes and apoptosis, Human beta-cells protein profiles, Human insulinoma cell lines