



Regulation of Pancreatic β Cell Gene Expression and Function

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Diabetes mellitus primarily occurs when pancreatic β cells fail to secrete sufficient levels of insulin necessary to maintain normal blood glucose concentrations. In the case of Type I diabetes, inadequate insulin release results after autoimmune destruction of β cells. For Type II diabetes, molecular defects limit insulin release, insulin biosynthesis, and β cell growth required to overcome insulin resistance typically associated with obesity. Mechanisms that account for failure of β cells in Type II diabetes are uncertain but might result from prolonged exposure of β cells to elevated glucose and/or fatty acids. Over the past 8 years, our laboratory has focused on molecular mechanisms whereby exposure of β cells to elevated glucose concentrations reduces insulin gene transcription. Our studies have indicated that chronic hyperglycemia suppresses insulin gene transcription by causing a reduction in binding of two crucial transcription factors Pdx-1 and MafA. Pdx-1 has been shown to be involved in regulation of both pancreas development and β cell gene expression. The importance of Pdx-1 is exemplified by the observation that mutation of two alleles for Pdx-1 in humans results in complete loss of pancreas development, whereas mutation of a single allele is associated with maturity-onset diabetes in the young. MafA also appears to play a role in β cell development and glucose-induced activation of insulin promoter activity. Loss of insulin gene transcription after chronic exposure of β cells to elevated glucose has also been shown to be associated with activation of the JNK-signaling pathway. Current studies are focused on therapeutic interventions designed to prevent damage of β cells exposed to elevated glucose and/or fatty acids.

Insulin injections have been used for decades to treat Type 1 diabetes, however, this therapy is not been sufficient to prevent diabetic complications including retinopathy, neuropathy, nephropathy or cardiac dysfunction. This is likely due to the inability of insulin injections to faithfully mimic regulated insulin release from β cells. Recent successes in pancreatic islet transplantation has indicated that replacement of β cells may serve as a means for achieving regulated insulin release. Nevertheless, this approach is hampered because of limited availability of human islets. One potential renewable source of human pancreatic β cells could be derived from adult pluripotent precursor cells associated with the pancreatic duct epithelium and islets of Langerhans. Recently we have developed a method for isolation of pancreatic precursor cells from adult human islets (Figure 1). Under culture conditions conducive for cell growth the cells express the embryonic stem cell marker, Oct4 (Figure 2 and 3). These cells also express genes associate with liver and pancreatic exocrine cells. When cultured in a differentiation media Oct4 gene expression is suppressed and the cells express small amounts of pancreatic endocrine hormones including insulin (Figure 3). Ongoing studies are designed to increase insulin production from these cells and determine whether they can correct diabetes when transplanted into diabetic mice.

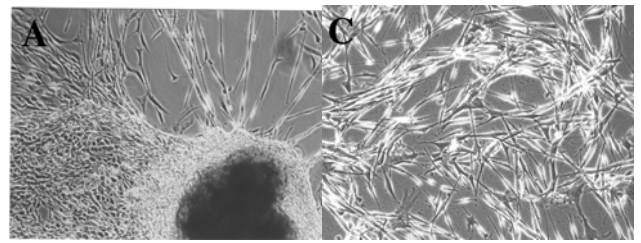


Fig 1 – Expansion of putative human pancreatic progenitor/stem cells under proliferative culture conditions. Left panel, human islet cultured for one week. Right panel, human pancreatic progenitor/cells, one week after replating.

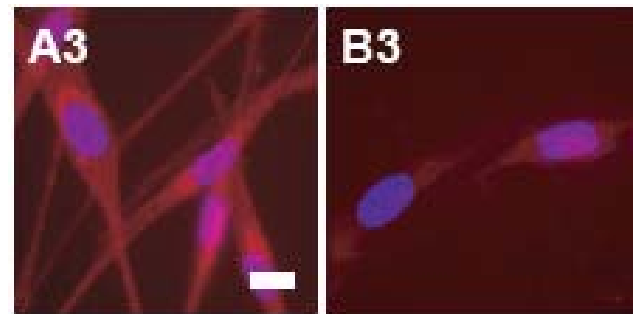


Fig 2 – Oct4 staining of putative human pancreatic progenitor/stem cells. Left panel, cells cultured under proliferative conditions. Note punctuate nuclear staining. Right panel, cells cultured under conditions that induce differentiation.

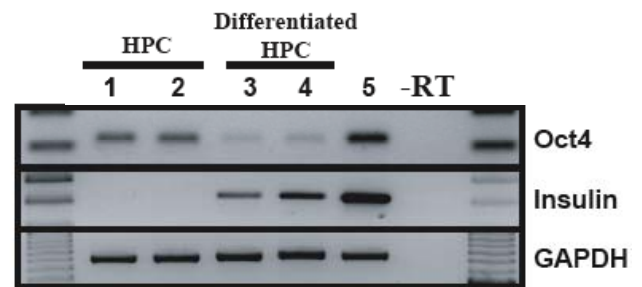


Fig 3 – Insulin and Oct4 gene expression in human pancreatic progenitor/stem cells. Lanes 1 and 2, Oct4, but not insulin, mRNA is expressed under proliferative conditions. Lanes 3 and 4, differentiation of pancreatic progenitor/stem cells causes increased expression of insulin along with a subsequent reduction in Oct4 mRNA.