Abstract

Diabetes mellitus (DM) is a severe and frequent disease with increasing prevalence. It is not possible to achieve long term cure without late complications. Recent advances in cell fate modifications open a pathway to alternative cell therapies for DM cure. My doctoral thesis “Differentiation of pancreatic stem cells into insulin producing β-cells” is focused on the development of a new source of insulin secreting cells for transplantation. Combinatorial testing of numerous potential transcription factors and epigenetic modifiers resulted in a final protocol for the reprogramming pancreatic of exocrine cells into insulin secreting cells. The key transcriptional factors TF (Pdx1, Ngn3 a MafA) were applied in the form of synthetic mRNA. In four independent experiments we applied transcriptional factors in a specific sequence, thus obtaining 14.3 ± 1.9 % insulin positive cells. When challenged in vitro by the glucose levels of 2.5 and 20 mmol/l glucose, respectively, these cells exhibited glucose-sensitivity of insulin secretion (842 ± 72 and 1 157 ± 58 pg insulin/µg DNA/ml, n=5). They also demonstrated a sensitivity of insulin secretion (863 ± 78 and 1 025 ± 66 pg insulin/µg DNA/ml, n=5) to the concentration of depolarization agent KCl applied at 0 and 30 mmol/l, respectively together with 2.5 mmol/l glucose. We demonstrated that our original protocol applied to exocrine cells can generate a potential cell source for therapy of diabetes. A distinct feature of our protocol is the absence of permanent genetic modification of the cells, in the principle, avoids such serious associated risk as cancer development.