Abstract

Diabetes mellitus affects nearly 300 million people in the world. The development of diabetes is caused by dysfunction or by reduction of insulin-producing β-cells that are part of the endocrine pancreas. Therefore, the most critical step for understanding the pathophysiology of diabetes and for restoring lost β cells is the identification of molecular cues that specify the cellular phenotype in the pancreas. This work is based on the hypothesis that the transcription factor NEUROD1 is a key factor for the development of the pancreas and for the maintenance of endocrine tissue function. *Neurod1* conditional KO mutants (*Neurod1CKO*) were generated using the Cre-loxP system by crossing floxed *Neurod1* mice with *Isl1-Cre* line. Immunohistochemical analyses of the pancreas at embryonic day 17.5 and postnatal day 0 showed that the deletion of *Neurod1* negatively affected the development, organization of endocrine tissue, and total mass of pancreatic endocrine cells. To better understand molecular changes, quantitative PCR was used to analyse mRNA expression in the developing pancreas at the age of embryonic day 14.5 and postnatal day 1. Genes important for the development and function of the pancreas have been selected for the study of expression changes. These analyses showed changes in expression of genes serving as endocrine pancreatic markers (*Pdx1*, *Neurog3*, *Pax6*), genes for producing endocrine hormones (*Insulin 1*, *Insulin 2*, *Glucagon*), genes important for endocrine cell differentiation (*MafA*, *MafB*), and gene for development of exocrine pancreas (*Ptf1a*) in *Neurod1CKO* compared to controls. These results confirm the initial hypothesis that NEUROD1 is important for the development and function of the pancreas. Newly, these results show that NEUROD1 already affects pancreatic development during the secondary transformation, and that the loss of endocrine cells is not due to apoptosis during the endocrine maturation stage but due to abnormal development and production of endocrine precursors.