The pancreas develops from Pdx1 expressing progenitors that emerge from the foregut endoderm to form ventral and dorsal buds. Pdx-1 is necessary for pancreatic development and beta cell maturation. The formation of the pancreas and its subsequent differentiation to the exocrine and endocrine cell types results from the ordered activation of a large number of genes (1). Ngn3 is an important regulator of pancreatic endocrine cell formation. Notch signaling regulates ngn3 gene expression negatively (2). Nicotinamide (NA) is a precursor of nicotinamide adenine dinucleotide that protects beta cells from several toxic agents. It is known to increase the mitotic index of beta cells after pancreatectomy, and is a potent inducer of endocrine differentiation of human fetal pancreatic cells in vitro (3,4). We investigated the relationship in between expression of notch1, jagged1, ngn3 and pdx1 with pancreatic beta cell regeneration and/or differentiation of NA treated neonatal diabetic rats.

Three groups were performed. The first group was the control group. The second group was STZ diabetic (100 mg/kg i.p on the second day after birth; n2-STZ). The third group received, 500mg/kg/day NA for 5 days (n2-STZ+NA) by starting from third day. The pancreatic tissue sections were immunostained with insulin, pdx-1, notch1, jagged1 and ngn3 antibodies and also double immunostained with insulin and PCNA antibodies. Body weight and blood glucose levels of the animals in all groups were measured. All values were analyzed with statistical methods.

The increase of the blood glucose levels in n2-STZ+NA group were significantly decreased by NA treatment (p<0.01). The number of insulin/PCNA double-positive cells significantly increased in the n2-STZ+NA group compared with the other groups (p<0.001). n2-STZ group had lower number of insulin and pdx-1 positive cells compared to NA treated diabetic group in islet. We found that immunopositive insulin, pdx1 and ngn3 cells were located in small cell clusters or scattered in exocrine tissue and close to ducts in n2-STZ+NA. We did not observe the expression of ngn3 in any islet. There was significant difference between the numbers of notch1 and jagged1 immunopositive cells in islets when the n2-STZ+NA group was compared with the other groups.

In conclusion, we showed that NA treatment stimulates duct epithelium or acinar cell differentiation into the beta cell via up regulation of ngn3 and pdx1, and down regulation of notch1 in exocrine pancreas.

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Fig. 1: Immunolocalisation of jagged1 in the pancreas of all groups. A, Control; B, n2-STZ; C, n2-STZ+NA groups.