
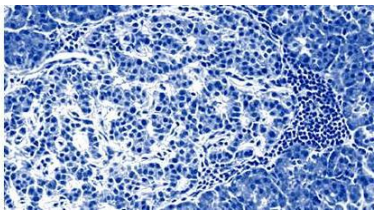

Syntaxin 4 Overexpression in Pancreatic Islet β-cells of Non-Obese Diabetic Mice Prevents Conversion to Autoimmune Diabetes

AUTHORS

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PURPOSE

Syntaxin 4 (STX4), a plasma membrane-localized SNARE protein, plays a crucial rate-limiting role in β-cell insulin secretion and significantly improves glycemic control in a minimal model of islet transplantation. The enriched STX4 expression in human islets preserves β-cell mass by blocking NF-kB signaling induced CXCL9, 10, and 11 chemokine expression from β-cells. These data are proposed that STX4 overexpression in pancreatic β-cells has a protective effect against autoimmune diabetes (T1D) by attenuating inflammatory stress

METHODS

Human Pancreas Sections and immunofluorescence: Formalin-fixed paraffin embedded (FFPE) human pancreas donor sections containing 4 non-T1D and 4 T1D were obtained from Network for Pancreatic organ donors with Diabetes (nPOD) program. Pancreatic sections were immune stained with Insulin and STX4 antibodies and analysis was performed to quantify fluorescence intensities of STX4 normalized to insulin using Keyence hybrid cell counting software, compared with non T1D or T1D.

Animals: we generated a line of non-obese diabetic (NOD) mice, the animal model of T1D, that carried two transgenes to confer inducible beta cell specific (RIP-rtTA Tg) STX4 overexpression (TRE-STX4 Tg) using speed congenics (NOD-βSTX4).

SUMMARY OF RESULTS

STX4 levels are reduced in β-cells from human new-onset T1D insulin positive cells and prediabetic NOD mouse islets. Induced STX4 expression in the NOD-βSTX4 mice significantly deters onset of hyperglycemia. In comparison to female control mice on the NOD strain background: doxycycline induced or non-induced single Tg mice, stock NOD mice, or non-induced double Tg mice, female NOD-βSTX4 were 100% diabetes free at the time at which 50% of control mice converted to diabetes (17 weeks old), reduced to 73% diabetes-free by 25 weeks of age, when 72% of control mice were fully hyperglycemic (>300 mg/dl). At 12 weeks of age, prior to diabetes conversion, the NOD-βSTX4 mice showed better whole-body glucose tolerance and β-cell glucose responsiveness in vivo compared with age-matched

control mice. RNA-seq studies revealed islets from NOD-βSTX4 mice had markedly reduced expression of IFN-γ and NOS-2, related to decreased activation of macrophages, phagocytes, or APCs related genes.

CONCLUSIONS

STX4 overexpression in the β-cells of NOD mice may indirectly provide a protective β-cell environment in the pancreas, deterring β-cell damage and preventing conversion to hyperglycemia/diabetes.

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