SUMMARY

Type 2 diabetes (T2D) is a common metabolic disease that affects a large number of people worldwide and decreases the quality of life of patients. T2D is caused by varying degrees of abnormalities of pancreatic islet β-cells (PBCs), together with irreversible and progressive insulin resistance and hyperglycemia. Defects in glucose-induced signal transduction can lead to a decrease in the insulin release from PBCs and subsequently T2D. A number of proteins, including binding receptors, kinases, phosphatases, and transcription factors, play a role in the glucose-mediated signaling cascade by altered posttranslational modifications (PTMs). The aim of this PhD project is to molecularly characterize the signaling mechanisms underlying glucose-stimulated insulin secretion (GSIS) through quantifying PTMs and proteins expression within the pancreatic islet β-cells environment treated with or without low/high glucose concentrations in diabetic obese model mice or normal condition.

Brief glucose stimulation of PBCs results in the secretion of insulin together with a number of other intracellular molecular events through complex mechanisms controlled by PTMs of proteins, primarily reversible phosphorylation, but most probably also through glycosylation such as sialylation. In manuscript 1, we characterized PTMs-dependent signal transduction pathways in PBC induced by brief glucose stimulation, by a time-resolved quantitative phosphoproteomics/sialiomics/proteomics strategy, recently developed in our group. In manuscript 2, we characterized the signaling mechanisms of the nuclear environment in response to short-term high glucose stimulation in PBCs.

Decreased insulin secretion from PBCs in mice with induced obesity and T2D are caused by changes in the protein expression and phosphorylation of proteins that are essential for the overall insulin processing and secretion mechanism. In manuscript 3, we characterized the quantitative global changes using phosphoproteomics and proteomics, as well as general changes in the protein composition in freshly isolated islets from normal and *db/db* mice (mouse model of obesity-linked T2D) after basal glucose stimulation.