Dysfunction of pancreatic isles in type 2 diabetes – role of fatty acids and epigenetic mechanisms in maintenance of pancreatic α- and β-cells identity

Type 2 diabetes (T2D) is a metabolic disorder characterized by high blood glucose level. The maintenance of blood glucose homeostasis is regulated by hormones - insulin (secreted by pancreatic β-cells) and glucagon (secreted by pancreatic α-cells). Obesity is one of the major risk factors for T2D development. In the light of recent studies, epigenetic regulation of gene expression in pancreatic islets of obese individuals may be crucial for better understanding the mechanisms responsible for the development of endocrine pancreas dysfunction in T2D. Over the past decade, genetic and epigenetic studies have indicated that the stable pattern of transcription factors expression is essential for the pancreatic endocrine cells identity and function maintenance. In effect, changes in the identity transcription factors expression can lead to the loss of adult α- and β-cells dedifferentiated state and disturb their secretory functions.

The stearoyl-CoA 1 desaturase (SCD1) is a lipogenic enzyme which plays significant role in fatty acids metabolism and the development of obesity-related disorders. Our preliminary results suggest that SCD1 activity in pancreatic islets may also play the key role in endocrine cells functional identity maintenance. Therefore, in the proposed project, we are going to define the role of SCD1 in maintenance of insulin-secreting and glucagon-secreting cells identity in pancreatic islets. Our research hypothesis assumes that SCD1 influences the expression of transcription factors involved in pancreatic α- and β-cells identity maintenance through epigenetic mechanisms (DNA methylation).

To verify the research hypothesis described above, our research will be carried out using α and β pancreatic cell lines as well as the unique mouse model with the *Scd1* gene knockout. Additionally, the animals will be fed with diet enriched in fat to induce the lipotoxicity which is characteristic for obesity and T2D development. Our experiments will be performed using a wide range of molecular biology and biochemical techniques. During project realization we will determine the effect of SCD1 activity on: (1) pancreatic islets secretory functions (including quantity and quality of secretory granules assessment), (2) the mass of insulin- and glucagon-secreting cells in pancreatic islets and (3) DNA methylation-dependent expression of transcription factors involved in α- and β-cells identity maintenance. The proposed experiments will also allow to identify the potential signs of α- and β-cell dedifferentiation or transdifferentiation.

The knowledge obtained during the project realization will significantly contribute to the better understanding of the molecular mechanisms responsible for the development of T2D associated with obesity. Also, if our research hypothesis comes true, this work will provide the new insights into the role of SCD1 in pancreatic islets.