Cellular mechanisms of intra-organ crosstalk in diabetes

The pancreas is a biglandular organ that exerts digestive as well as endocrine functions. Its exocrine component, making up the vast majority of the organ's mass, is crucial for manufacturing, storing and secreting digestive enzymes for food processing. The endocrine part of the organ is comprised by ca. 1 million islets of Langerhans, which are scattered throughout the entire organ. These clusters of endocrine cells are crucial for systemic blood glucose homeostasis.

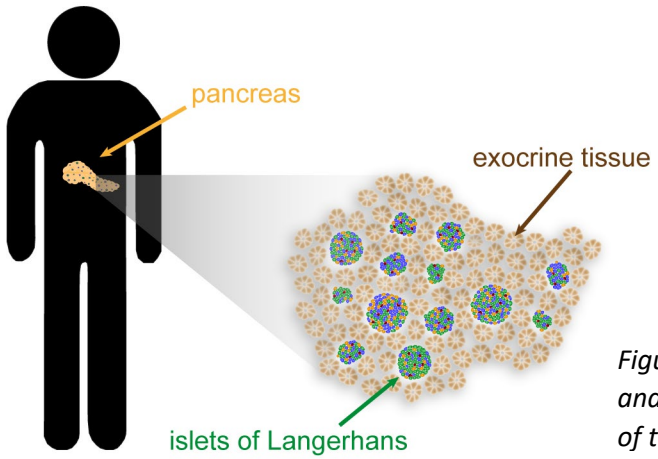

Figure: Schematic representation of the exocrine and endocrine (islets of Langerhans) compartments of the pancreas.

While their roles within the body are very different, the close anatomical and functional relationship of the exocrine and endocrine components of the pancreas has been suggested to enable interactions effecting each other's function and maintenance (Overton & Mastracci, 2022). Most noticeable, dysfunction in one part is inevitably affecting the other. For instance, exocrine diseases like acute or chronic pancreatitis, fibrosis or cancer increase the risk for endocrine dysfunction such as diabetes mellitus (Czako et al, 2009). Conversely, endocrine dysfunctions like diabetes and also its treatment with some antidiabetic drugs can functionally and morphologically impair the exocrine pancreas, especially in close proximity to the islets (Egozi et al, 2020). However, it is currently not understood which cellular interactions and mechanisms lead to these observations.

We therefor aim to investigate the interactions between the endocrine cells of the islets of Langerhans and their surrounding exocrine cells under physiological as well as under disease related conditions like diet-induced obesity and type 2 diabetic conditions as well as during the development of type 1 diabetes. This will be primarily performed by the study of cell physiology in viable pancreas tissue slices that preserves the native environment of the organ. We will investigate islet and acinar tissue function, e.g. by 4D live cell imaging of distinct functional cell markers like $[Ca^{2+}]_i$ or mitochondrial activity, and by biochemical approaches to measure hormone and enzyme secretion. Functional assessment will be complemented by molecular (e.g. spatial transcriptomics) and morphological analyses that will enable us to link cellular phenotypes and function to the organ microenvironment for a better understanding of local and systemic effects on the pancreas throughout diabetes pathogenesis.

Next to performing detailed studies on tissue from animal models, our aim is to translate our findings to the human situation. Therefore, we will make use of our unique access to viable donor tissue and organs through local and international networks. Thus, with this study we hope to be able to shed light on disease correlations and to uncover treatment targets for the development of future therapeutic approaches.