

SUMMARY FOR THE GENERAL PUBLIC

Mitochondria lie at the very basis of the functionality and viability of every cell. They not only contain electron transport chain (ETC) and ATP synthases responsible for energy production but also regulate the redox balance and orchestrate cell differentiation. As a result, mitochondrial damage is particularly dangerous: it leads to cell death, predominantly apoptosis or autophagy and is a hallmark of many pathological conditions, ranging from neurodegenerative diseases and cardiac injury to fibrosis. To prevent this fatal scenario, damaged mitochondria can be removed from the cell via one of mitochondrial quality control mechanisms - mitophagy (mitochondrial autophagy). A growing body of evidence suggests that defects in mitochondrial functionality, as well as mitophagy dysregulation, may play a crucial role in the development of fibrotic disorders, such as liver and pulmonary fibrosis.

For years, fibrosis has been standing out as a critical medical challenge worldwide. This excessive deposition of collagen fibres within the tissue often leads to irreversible changes in organ architecture and loss of tissue functionality. Pancreatic fibrosis is a particularly relevant example of fibrotic disease. The global incidence rate of pancreatic disorders associated with fibrosis exceeded 5,000,000 patients in 2016 and continues to increase by several percent annually. To make matters even worse, we are still lacking effective therapeutic strategies against those disorders.

The main cellular culprits for pancreatic fibrosis are pancreatic stellate cells (PSCs), which comprise only 4-7% of the tissue mass. Although physiologically quiescent, these cells can undergo activation triggered by mechanical stress or inflammation. In their activated phenotype, they produce and deposit collagen-rich extracellular matrix within the tissue leading to fibrosis.

Given that activated and quiescent cells differ in their physiology and morphology, the main goal of this project is to compare the functions of mitochondria as well as mitophagy between the two PSC phenotypes. To achieve this, we plan to investigate structural and morphological differences of mitochondria using electron microscopy. We also plan to assess ETC proteins content and their organisation by applying molecular biology tools, such as BN-PAGE and immunofluorescence staining. This will be followed by a detailed evaluation of mitochondrial physiology. Since both calcium and redox balance are strictly linked to the functionality of mitochondria, we plan to conduct a series of real-time mitochondrial measurements of calcium and ROS signalling as well as pH alterations. We will also carry out metabolic stress tests on mitochondria of these cells to evaluate changes in ETC activity occurring in single organelles. Further, we plan to investigate mitophagy in both quiescent and activated PSCs as well as the impact of mitophagy modulation on cell metabolism, physiological mitochondrial calcium and ROS signalling as well as cell death. Using animal material from previous experiments, we also want to assess mitophagy of PSCs in mouse models of pancreatitis and pancreatic ductal adenocarcinoma.

This basic research project aims to unravel the role of mitochondrial alterations in PSC activation. Nevertheless, the results of this project might contribute to a better understanding of pathophysiological mechanisms driving fibrotic disorders, and as a result, could aid the development of new therapeutic strategies against fibrosis.