DESCRIPTION FOR THE GENERAL PUBLIC

Pancreatic diseases are ruthless killers that take lives or scar for life: every year more than 400 000 people die from pancreatic cancer; there are about 3 000 000 new cases of acute pancreatitis and as many as 120 000 conclude with deaths; and even up to 50/100 000 people could be affected by chronic pancreatitis, which leads to permanent tissue fibrosis, malnutrition and type 1 diabetes. The main environmental risk factors for pancreatic diseases are alcohol abuse and cigarette smoking. Currently available therapeutic interventions against pancreatic diseases are limited and ineffective. A common feature present in pancreatic diseases is the activation of fibroblast-like pancreatic stellate cells (PSCs). Upon tissue damage or in response to inflammation, PSCs become activated, that is assume a myofibroblast-like phenotype, and start the overproduction of extracellular matrix (ECM) that replace healthy tissue leading to organ dysfunction.

Our recent discovery shows that the TRPA1 ion channel is present in PSCs, but its levels differ between quiescent and activated PSCs. The high level of TRPA1 in quiescent cells makes them prone to toxicity of ethanol metabolites and fatty acids, mediated by intracellular Ca^{2+} overload. On the contrary, the low level of TRPA1 in activated PSCs makes them substantially more resistant. Therefore, the main objective of this project is to investigate the role of TRPA1 in the physiology of PSCs, its potential role in the toxic effects of the cigarette smoke, and to understand the impact of this ion channel on the progression of pancreatic diseases.

To achieve this, a new research team will be assembled to carry out a broad range of experimental tasks. In our research, we will employ pharmacological methods and transgenic animals. First, we will investigate Ca^{2+} signals induced by the components of cigarette smoke in quiescent and activated PSCs, with the focus on the role of the TRPA1 channel. We will also investigate how TRPA1 affects parameters associated with mitochondria (including their structure and functions) and cellular metabolism. Furthermore, we intend to test whether the role of TRPA1 in PSCs is biologically relevant in pancreatic diseases. For this purpose, we will use models of acute and chronic pancreatitis induced in mice that do not have the TRPA1 channel; or in mice simultaneously undergoing pharmacological treatment with TRPA1 modulators. In addition, since excessive deposition of the ECM by PSCs and other cancer-associated fibroblasts is one of the hallmarks of pancreatic cancer, we would like to investigate the role of TRPA1 in the development of this disease. Therefore we intend to use transgenic mice and/or TRPA1 pharmacological modulators in different animal models of pancreatic cancer. We plan to carry out a very detailed investigation of the effects TRPA1 has on different cellular functions and proteins by high-throughput analyses. Finally, we intend to investigate whether certain changes in the TRPA1 gene sequence correlate with the severity of pancreatic diseases.

Although this is a typical basic research project expected to provide new information on the role of TRPA1 in pancreatic diseases, this new knowledge could contribute to the development of new therapeutic procedures or medical policies against pancreatitis or pancreatic cancer.