Mitochondria are the primary source of reactive oxygen species (ROS) within cells, mainly produced as byproducts of the electron transport chain (ETC) during ATP synthesis. Moderate and controlled synthesis of ROS is responsible for signaling, and mitochondria are crucial organelles acting as signaling hubs in the most important cellular processes. ROS serve as critical signaling molecules in various cellular processes, including the regulation of metabolic pathways, adaptation to hypoxia, and cellular defense mechanisms. For instance, low to moderate levels of ROS can activate signaling pathways that promote cell proliferation, differentiation, and survival. On the other hand excessive or uncontrolled synthesis of ROS by mitochondria is responsible, among other things, for inducing cell death during ischemia-reperfusion, the activation of inflammatory processes, and cellular senescence and aging related processes.

Redox signaling is based on a signaling loop, which includes several key elements ensuring signal transmission. The input signal, which can be an extracellular or intracellular impulse, in many cases induces a change in mitochondrial function what leads to changes in ROS synthesis. This results in the regulation of plethora of mitochondrial and cellular processes, including mitochondrial biogenesis and mitochondrial metabolism. Finally, as a consequence, these changes can directly or indirectly influence ROS synthesis by affecting the activity of the respiratory chain, thus closing the loop. Research conducted in recent years, including by our research teams, indicates that one of the most important regulatory elements of the described redox loop are mitochondrial potassium channels. However, limitations related to the molecular structure of these proteins, as well as the lack of appropriate research models, have so far prevented systematic studies regarding the role of these proteins and the redox signaling mechanisms for which they are responsible. However, breakthrough studies in recent years identifying the pore forming subunits of several mitochondrial potassium channels and developing new research models have opened the possibility for effective conduct of these studies and understanding the underlying mechanisms.

Mitochondrial potassium channels play critical roles in maintaining mitochondrial and cellular homeostasis. The first mitoK channel, namely, the ATP-sensitive potassium (mitoK$_{ATP}$) channel was identified in inner mitochondrial membrane of liver, and later in other tissues including heart and brain. Later, other mitoK channels including mitochondrial large-conductance calcium-activated potassium (mitoBK$_{Ca}$) channels have been identified.

The activity of mitoK channels affects mitochondrial function, the mitochondrial network and ultrastructure. In cardiac and brain tissue, activation of potassium channels during ischemia-reperfusion induces cytoprotective pathways and prevents excessive ROS synthesis. We also know that proteins are regulated by the redox state of mitochondria and mitochondrial ROS. However, there are no precise studies describing the mechanisms of this regulation. Therefore, due to the significant role of these proteins in regulating mitochondrial function, and their involvement in cytoprotective processes, we are undertaking studies on the regulation of these proteins by redox state. We aim to understand how ROS generated by mitochondria affect the activity of mitochondrial channels, and how and why these channels influence mitochondrial redox state and mitochondrial and cellular function.

The project’s findings can be helpful in the development of cytoprotective and anti-aging therapies. This can result in new interventions that enhance cell survival and function in conditions of oxidative stress, potentially leading to treatments that slow aging and prevent age-related diseases, improving overall healthspan and lifespan.