Targeting mitochondrial potassium channels to regulate cellular senescence

Progress of knowledge in the field of health sciences and improvements in medical care increasing the number of seniors in societies of many countries. This demographic shift allow us to enjoy the presence of older members of our families longer, however it cause also new medical challenges due to the increased frequency of age-related diseases.

Harmful factors such as UV radiation, air pollution or food additives cause subsequent changes in human genetic material. At the same time, repair abilities decrease with the patient's age. Unrepaired changes in DNA can cause cancer, cell death or senescence. Senescent cells are metabolically active with while stopping cell division to prevent the transmission of mutant DNA to new cells. The current state of knowledge associates age-related diseases with the accumulation of senescent cells in suboptimally functioning organs of our bodies.

The aging of the human body is inevitable. Lifestyle and therapeutic interventions can although significantly impact both the length and quality of an individual's life. Successful aging of patients and societies has a positive impact on the psychophysical well-being, but also on the level of necessary expenditure on the health care system.

Cell division, their functional differentiation and development of senescent phenotype are regulated among others by the ionic environment of the cell, including potassium ions. Potassium channels - proteins that regulate the concentration of potassium ions in individual cells - may probably significantly influence aging and longevity.

Mitochondria are structures responsible for the energy status of cells. Moreover, they play a fundamental role in the regulation of many cellular processes. In senescent cells we observe elongated mitochondria, with a lower membrane potential and less efficient in providing energy. The current state of knowledge does not allow us to clearly determine whether changes in mitochondrial function are a sign or a cause of cell aging.

Cells change their actions depending on the type and number of signaling molecules received via receptors located in the cell membrane and intracellular membranes. Numerous ion channels located in the outer and inner mitochondrial membrane play a key role in cellular signal transduction pathways. The presence of several types of potassium channels located in the inner mitochondrial membrane has been confirmed in various human tissues. These channels directly influence the efficiency of cellular respiration, the potential of the inner mitochondrial membrane and the synthesis of reactive oxygen species. Changes in the activity of potassium channels may include, among others: protect against the negative effects of a heart attack.

We recently identified the presence of a high-conductance calcium ion-regulated mitochondrial potassium channel in smooth muscle cells derived from the human aorta. We also showed that the activity of this important potassium channel disappears in the mitochondria of senescent cells.

The aim of this project will be to explain the role of mitochondrial potassium channels in the aging process of various cell types. To achieve the project's goals, we will use human kidney cell lines that do not naturally contain mitochondrial potassium channels and, thanks to the use of genetic engineering, compare them with the same cells that have potassium channels in their mitochondria. In our previous studies, we found mitochondrial potassium channels in human brain tumor cells and human bronchial epithelial cells. Thanks to CRISPR/Cas9 technology, we will create (based on the above-mentioned) cell lines lacking mitochondrial potassium channels. In all these cells lines, we will examine the activity of mitochondria during the natural cellular aging process, as well as aging caused by stress factors.

Understanding the role of mitochondrial potassium channels in the cell senescence phenotype induction and maintenance may contribute to scientific progress in the treatment of age-related diseases and to improve preventive recommendations to support successful aging in society.