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Project Title:

Metabolic rewiring as a new therapeutic approach against aging

https://www.medunigraz.at/doktoratsstudien/phd-program/phd

Background:

Mitochondria, the powerhouses of cells, play a crucial role in energy metabolism. However, their function declines with age, contributing to various age-related diseases. So far, poorly understood aging-associated processes impair the organelle's ability to generate ATP and cause oxidative stress that damages mitochondrial proteins and lipids, further compromising their function[1]. We have described aging-related changes in the inter-organelle tethering and Ca^{2+} communications making senescent cells more vulnerable to mitochondrial Ca^{2+}-overload[2]. Such settings bear danger for an increased generation of reactive oxygen species (ROS). However, senescent cells protect themselves by desensitization of the mitochondrial Ca^{2+} uptake machinery[3] and the engagement of hexokinase 1 as an energy stress sensor that regulates the shape, connectivity, and metabolic activity of this organelle[4].

Hypothesis and Objectives:

We hypothesize that by specifically manipulating mitochondrial bioenergetics, we selectively induce cell death in senescent cells (AIM 1). This will liberate the growth and differentiation of tissue-presented progenitor cells (AIM 2), ultimately leading to tissue repair (AIM 3).

Methodology:

Human cell and non-mammalian animal models of aging will be used. Besides state-of-the-art biochemical and molecular biology techniques, we will employ biosensor-based multi-channel (sub-)cellular recordings of, e.g., cell function, metabolism, transcription, and signaling using super-/high-resolution microscopes (SIM, LSM, LS). Hence, electrophysiological recordings of mitochondria, FACS, and multicell analysis recordings will be performed.

References:

1. Amorim, J. A. *et al.* Mitochondrial and metabolic dysfunction in ageing and age-related diseases. *Nat Rev Endocrinol* 1–16 (2022) doi:10.1038/s41574-021-00626-7.
2. Madreiter-Sokolowski, C. T. *et al.* Enhanced inter-compartmental Ca^{2+} flux modulates mitochondrial metabolism and apoptotic threshold during aging. *Redox biology* **20**, (2018). doi: 10.1016/j.redox.2018.11.003
3. Madreiter-Sokolowski, C. T. *et al.* PRMT1-mediated methylation of MICU1 determines the UCP2/3 dependency of mitochondrial Ca^{2+} uptake in immortalized cells. *Nat Commun* **7**, 12897 (2016). doi:10.1038/ncomms12897
4. Pilic, J. *et al.* Hexokinase 1 forms rings that regulate mitochondrial fission during energy stress. *Mol. Cell* (2024) doi:10.1016/j.molcel.2024.06.009.