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Targeting mitochondria against aging

Background: Mitochondria are essential for cellular energy metabolism, but their function declines with age, contributing to age-related diseases. The exact mechanisms behind this decline are still not fully understood but involve impaired ATP production and oxidative stress that damages mitochondrial components[1]. Aging also affects inter-organelle communication and Ca^{2+} signaling, making senescent cells vulnerable to mitochondrial Ca^{2+} overload[2], which leads to increased production of reactive oxygen species. However, these cells have developed protective mechanisms, such as desensitized mitochondrial Ca^{2+} uptake machinery[3] and the utilization of hexokinase 1 as an energy stress sensor to regulate mitochondrial shape, connectivity, and metabolic activity[4].

Hypothesis and Objectives: We recently discovered a key process of mitochondrial aging, which we hypothesize to serve as a potential target for the development of *senolytics* - compounds that selectively kill senescent cells. AI-based structure-functions prediction (e.g., with AlphaFold, Schrödinger) will be used to develop lead substances that interact selectively with key processes of mitochondrial bioenergetics in senescent cells (Aim 1). Subsequently, these lead substances will be tested for their potency against cellular and animal aging (Aim 2). In addition, we will search for natural compounds with comparable lead motifs in corresponding databases (e.g., NERDD) (AIM 3), and test their potency against aging (AIM 4).

Methodology: Human cells/organoids and non-mammalian animal models of aging will be used. In addition to state-of-the-art biochemical and molecular biology techniques, we will employ biosensor-based multi-channel (sub-)cellular, multicellular, and intravital recordings of, cell metabolism & function, transcription, and signaling using super-/high-resolution microscopes (SIM, LSM, LS).

Specific position requirements: The ideal candidate holds a PhD in molecular biology, structural chemistry, or similar. The candidate ideally has experience in drug discovery using AI-based structural prediction algorithms (e.g., AlphaFold, Schrödinger) and the analysis of cellular processes and single-cell-based transcription.

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.