Universität Basel

Research Project

Understanding mitochondrial protein quality control - implications for neurodegeneration

Third-party funded project

Project title Understanding mitochondrial protein quality control - implications for neurodegeneration
Principal Investigator(s) Neutzner, Albert ;
Project Members Hemion, Charles ; Benischke, Anne-Sophie ; Fang, Lei ;
Organisation / Research unit
Departement Biomedizin / Ocular Pharmacology and Physiology (Neutzner/Meyer)
Department
Project start 01.04.2013
Probable end 31.03.2016
Status Completed
Background

Increases in life expectancy achieved during the last decades are not reflected in a comparably prolonged healthspan – the part of life not affected by serious disease. Neurodegenerative disorders such as Parkinson's or Alzheimer's disease and the associated loss of cognitive function are a major factor responsible for the observed gap between lifespan and healthspan in our aging society. At the heart of all neurodegenerative disorders lies the untimely death of neuronal cells. While the triggers for neurodegeneration are not always clear, it is accepted that mitochondrial dysfunction is the major culprit for neuronal death. Thus, maintaining mitochondrial fidelity is central to ensure neuronal function and it is an important mechanism to target in order to match healthspan to lifespan increases.

Working Hypothesis
Wholesale degradation of mitochondria via mitophagy was shown to play a major role during mitochondrial maintenance through the removal of damaged mitochondrial units. While it is now clear how irreparable mitochondria are disposed of, it is less clear how mitochondria deal with slowly accrued, below threshold damage; the kind of damage associated with aging and associated diseases such as neurodegeneration. Recently, we and others discovered an ubiquitin-mediated proteasome-dependent protein degradation pathway – dubbed outer mitochondrial membrane associated degradation or OMMAD - that might provide protein quality control to prevent runaway mitochondrial damage necessitating mitophagic destruction.

Specific Aims
We aim to further establish and explore models for oxidized and nitrosylated mitochondrial proteins to study the non-mitophagic degradation of damaged mitochondrial proteins. Special focus will be on the role of proteasomal degradation and the newly discovered OMMAD machinery in mitochondrial quality control (mitoQC). In addition, the importance of proteasome-mediated mitoQC on neuronal survival will be explored.

Experimental Design and Methods
State-of-the-art confocal microscopy, biochemical cell fractionation and specialized, quantitative Western blotting will be employed to study the turnover of proteins damaged due to oxidation or nitrosylation. In addition, stable isotope labeling with amino acids in cell culture (SILAC) will be used to characterize

substrate proteins for oxidation-induced proteasomal degradation. RNAi-based knockdown and expression of inactive mutants of OMMAD components will be used in in vitro neurodegeneration models.

Expected Value of the project
This study will provide valuable new insight into how mitochondria deal with damaged proteins and how mitochondrial function is maintained through targeted protein degradation. This will help to better understand molecular pathways leading to neuronal death connected to mitochondrial dysfunction. Ultimately, this knowledge is essential for the development of targeted treatments addressing the pressing issue of neurodegenerative processes.

Financed by
Swiss National Science Foundation (SNSF)

Add publication

Add documents

Specify cooperation partners