Mitophagy Regulation in Alzheimer’s Disease

Qian Cai

Department of Cell Biology and Neuroscience
Rutgers University
Mitochondria are essential for neuronal survival and function

Mitochondrial dysfunction and impaired transport associate with major neurodegenerative diseases (AD, PD, ALS, HD).

Manji et al., *Nat Rev Neurosci.*, 2012

Autophagy is the major cellular quality control system

Deliver and degrade dysfunctional intracellular components or damaged organelles in the lysosome

Defective autophagy has been indicated in major neurodegenerative diseases
Mitochondrial quality control

Sheng and Cai, Nat Rev Neurosci., 2012
Cortical Neuron Imaging Showing Dynamic and Spatial Parkin Translocation and Degradation of Depolarized Mitochondria (Mitophagy and Impact on Mitochondrial Motility)

Parkin-Targeted Mitochondria Accumulate in the Somatodendritic Regions

The PINK1/Parkin pathway mediates mitophagy, ensuring mitochondrial integrity and function. (Narendra and Youle, 2011)
Dynamic Degradation of Parkin-Targeted Dysfunctional Mitochondria in the Soma of Live Cortical Neurons

The first neuronal imaging evidence showing dynamic Parkin translocation onto depolarized mitochondria for their degradation within the autophagy-lysosomal system.

Cai et al., *Current Biology*, 2012
Parkin-mediated mitophagy in healthy neurons

Cai et al., Autophagy, 2012
Cai et al., Current Biology, 2012
Pathogenic hallmarks of Alzheimer’s disease

Amyloid-β (Aβ)

Amyloid Plaques
Toxic effects of Aβ on mitochondria

- Mechanisms underlying mitochondrial defects in AD neurons

Mitochondrial quality control is altered in Alzheimer’s disease

Damaged or dysfunctional mitochondria

- Reduced PreP proteolytic activity
  - Aβ
- Increased Drp1-mediated fission

Mitochondrial toxicity and dysfunction

Increased mitochondrial fragmentation

Mitophagy?
Parkin-mediated mitophagy is induced in mutant hAPP Tg neurons.
Accumulation of mitochondria within autophagic vacuoles in the hippocampus of AD patient brains

Mitophagy is induced in AD patient brains.

Aberrant accumulation of defective mitochondria in AD patient brains.

Ye et al., *Human Molecular Genetics*, 2015
Depletion of cytosolic Parkin over disease progression in AD patient brains

Mitophagy induction is coupled with enhanced Parkin degradation.

Parkin depletion leads to defects in the elimination of defective mitochondria, resulting in their aberrant accumulation in AD neurons.

Ye et al., *Human Molecular Genetics*, 2015
Lysosomal deficits contribute to mitochondrial pathology in AD neurons

Tammineni et al., Human Molecular Genetics, 2017
Abnormal mitochondrial quality control in AD

Damaged or dysfunctional mitochondria

- Reduced PreP proteolytic activity
- Increased Drp1-mediated fission
- Enhanced mitophagy induction

- Mitochondrial toxicity and dysfunction
- Increased mitochondrial fragmentation
- Accumulation of mitophagosomes

Decreased lysosomal proteolysis

Potential fields for collaboration

• Molecular and cellular mechanisms underlying normal aging and age-related neurodegenerative diseases
  – Autophagy-lysosomal regulation in aging and neurodegeneration
  – Axonal transport and membrane trafficking and their impacts on axonal homeostasis
  – Mitophagy and mitochondrial quality control in healthy, aged and diseased neurons
Acknowledgements

Lab Members
Yu Young Jeong
Mingyang Zhang
Preethi Sheshadri
Sinsuk Han
Elaine Gavin
Xiao Su
Jasmine Cheung
Priyanka Tiwari
Prasad Tammineni
Tuancheng Feng
Xuan Ye
Xiaqin Sun
Daniyal Aikal
Chanchal Agrawal
Yesha Parekh
Joyce Lam
Jeffrey Shu
Angela Yao
John Filtes
Rashmi Pillai
Carolyn Zhu
Venkatraman Thulasi
Daijun Ling

Funding support
R01 (NINDS, NIH)
R21 (NINDS, NIH)
K99/R00 (NIA, NIH)
NIRG Award (Alzheimer’s Association)
Charles & Johanna Busch Biomedical Award

Collaborations
Zu-Hang Sheng (NINDS, NIH)
Huaibin Cai (NIA, NIH)
Alexander Kusnecov (Rutgers)
Barth Grant (Rutgers)
Christopher Rongo (Rutgers)
Ronald Hart (Rutgers)
David J. Margolis (Rutgers)
Susan Cheng (NINDS, NIH)
Rajesh Patel (Rutgers)
Valentin Starovoytov (Rutgers)