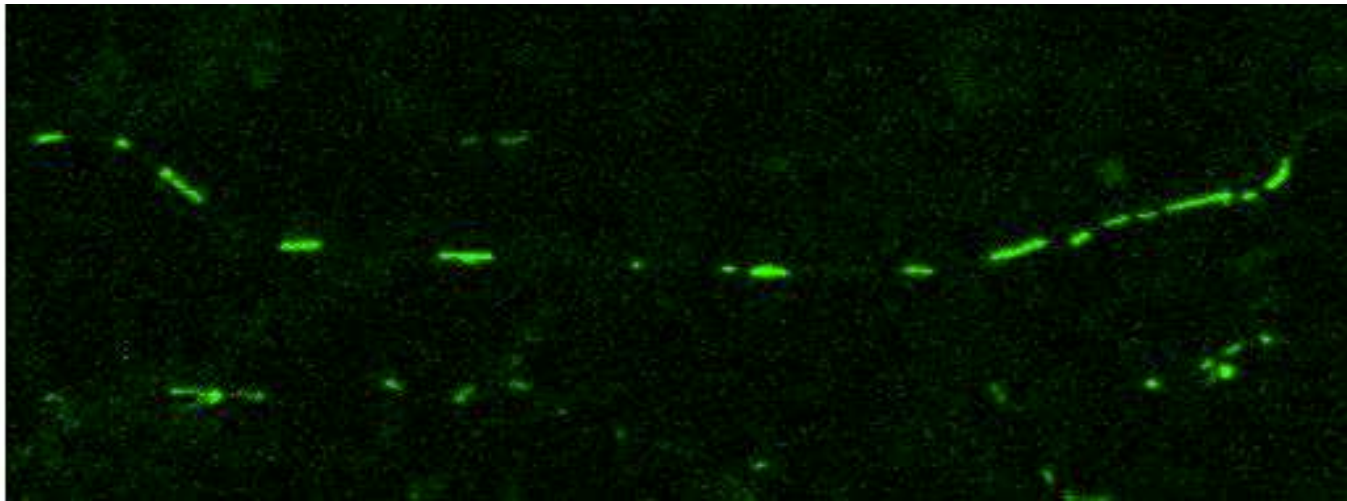


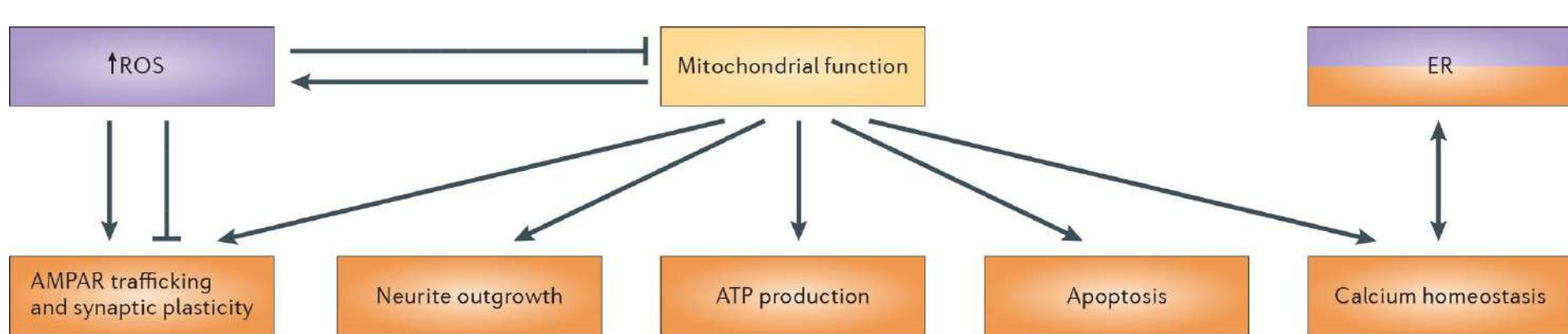
# Mitophagy Regulation in Alzheimer's Disease

Qian Cai

Department of Cell Biology and Neuroscience  
Rutgers University



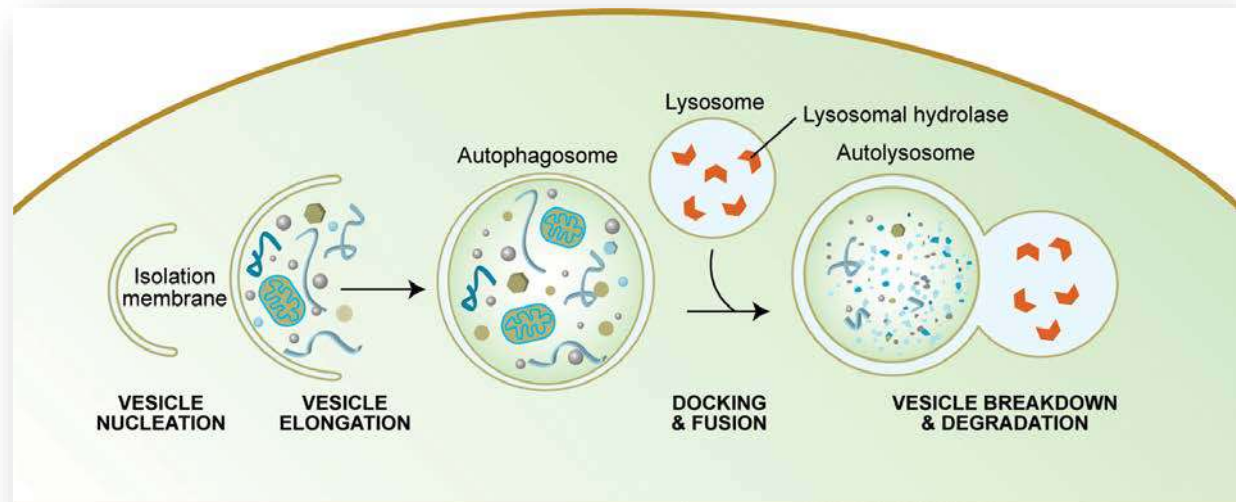
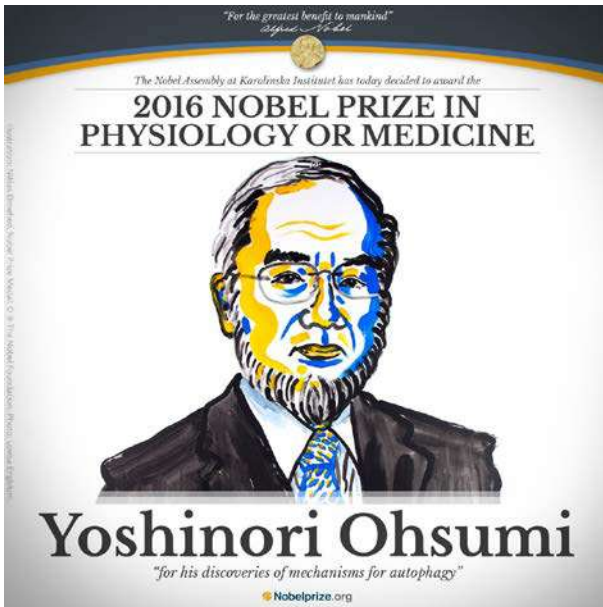
# Mitochondria are essential for neuronal survival and function



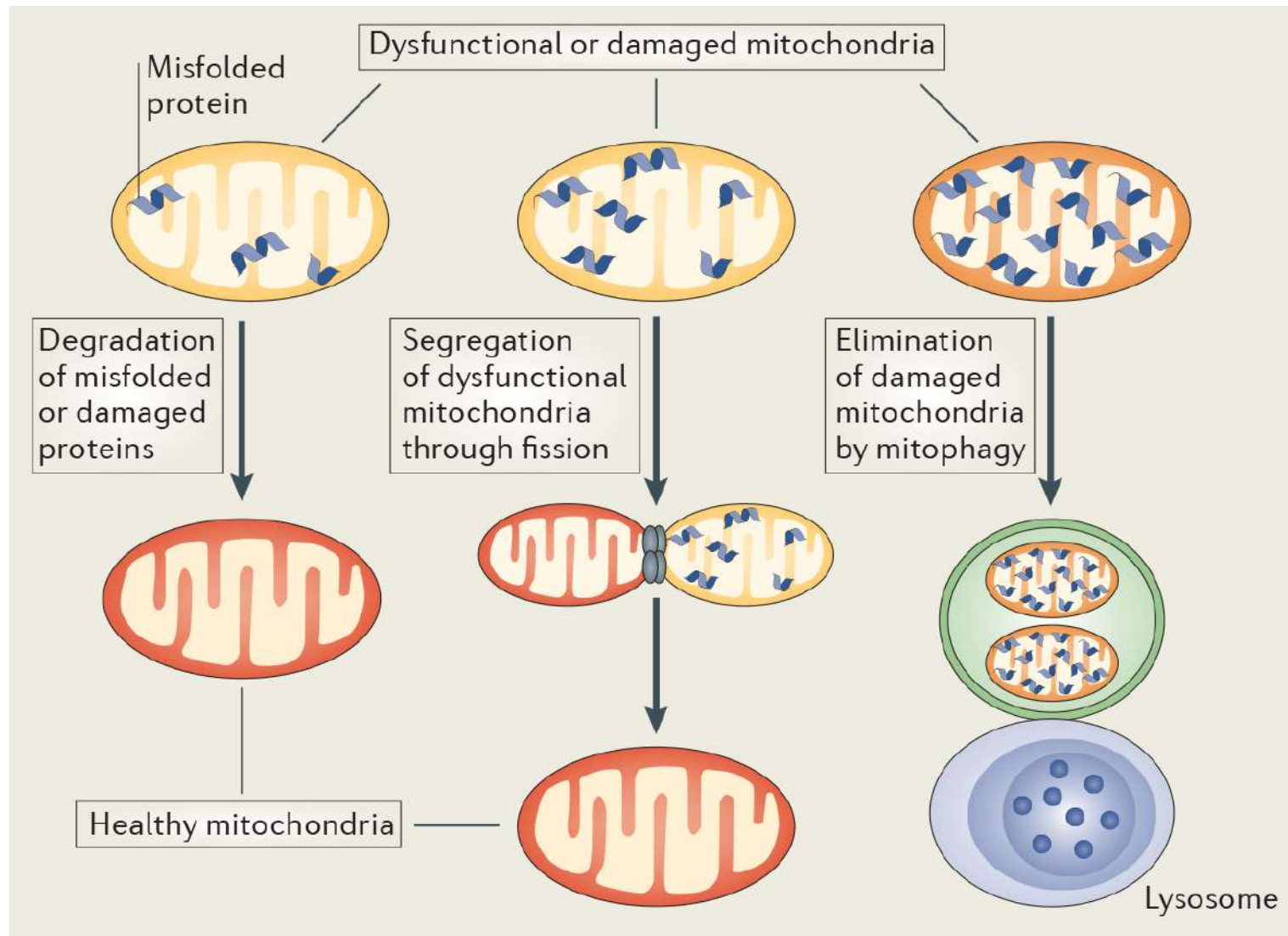
**Mitochondrial dysfunction and impaired transport associate with major neurodegenerative diseases (AD, PD, ALS, HD).**

# Autophagy-Lysosomal Pathway

- 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

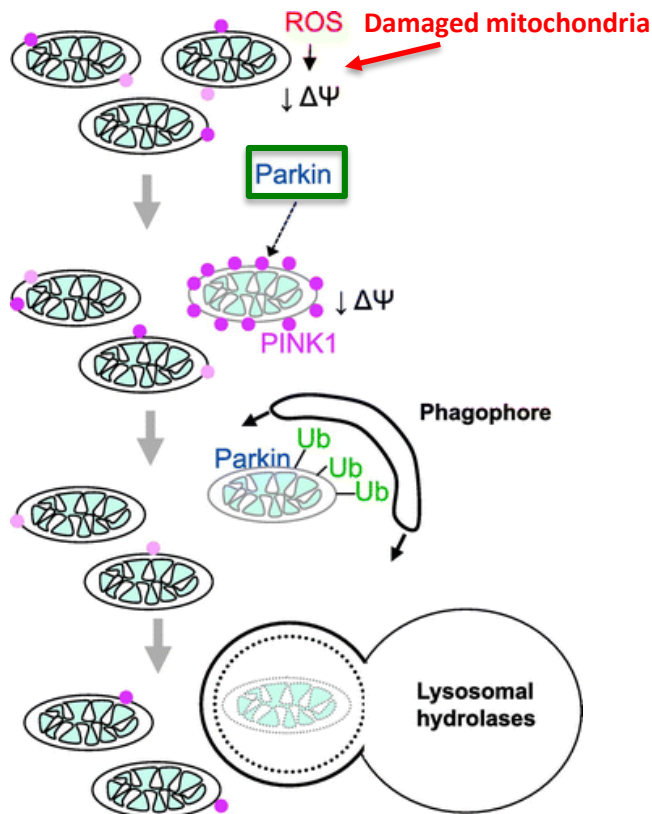


# Mitochondrial quality control

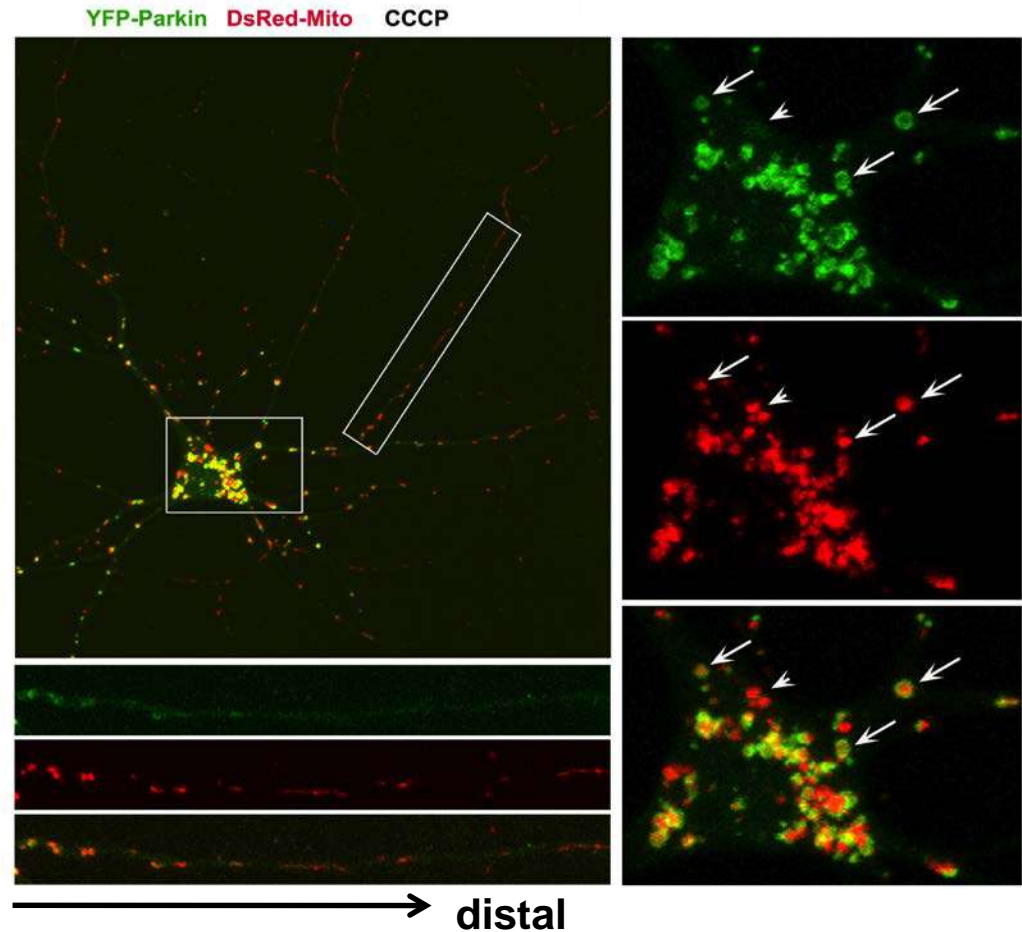


# Cortical Neuron Imaging Showing Dynamic and Spatial Parkin Translocation and Degradation of Depolarized Mitochondria (Mitophagy and Impact on Mitochondrial Motility)

## Parkin-Targeted Mitochondria Accumulate in the Somatodendritic Regions



The PINK1/Parkin pathway mediates mitophagy, ensuring mitochondrial integrity and function.  
(Narendra and Youle, 2011)

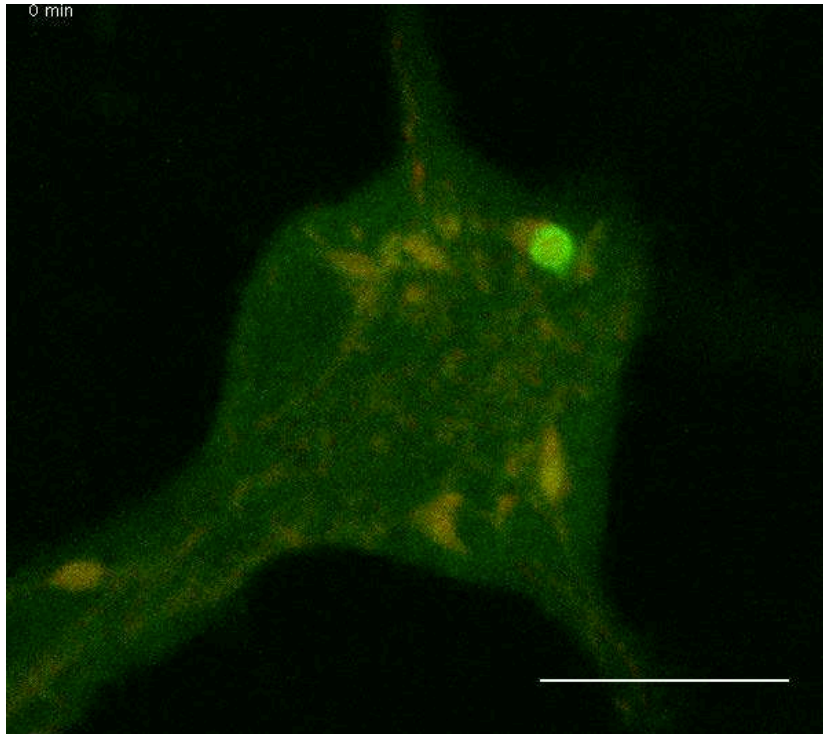


# Dynamic Degradation of Parkin-Targeted Dysfunctional Mitochondria in the Soma of Live Cortical Neurons

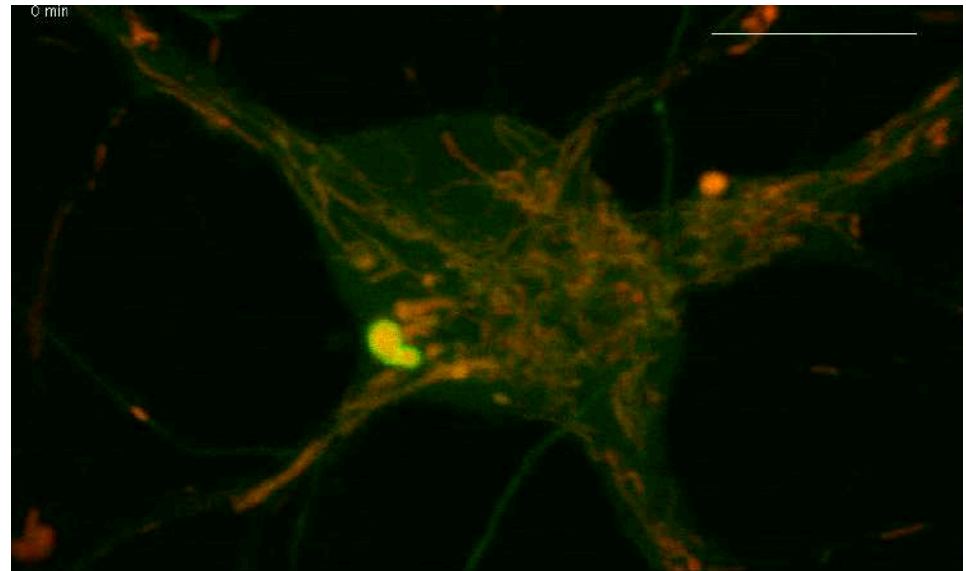


H Zakaria  
(HHMI)

YFP-Parkin DsRed-Mito



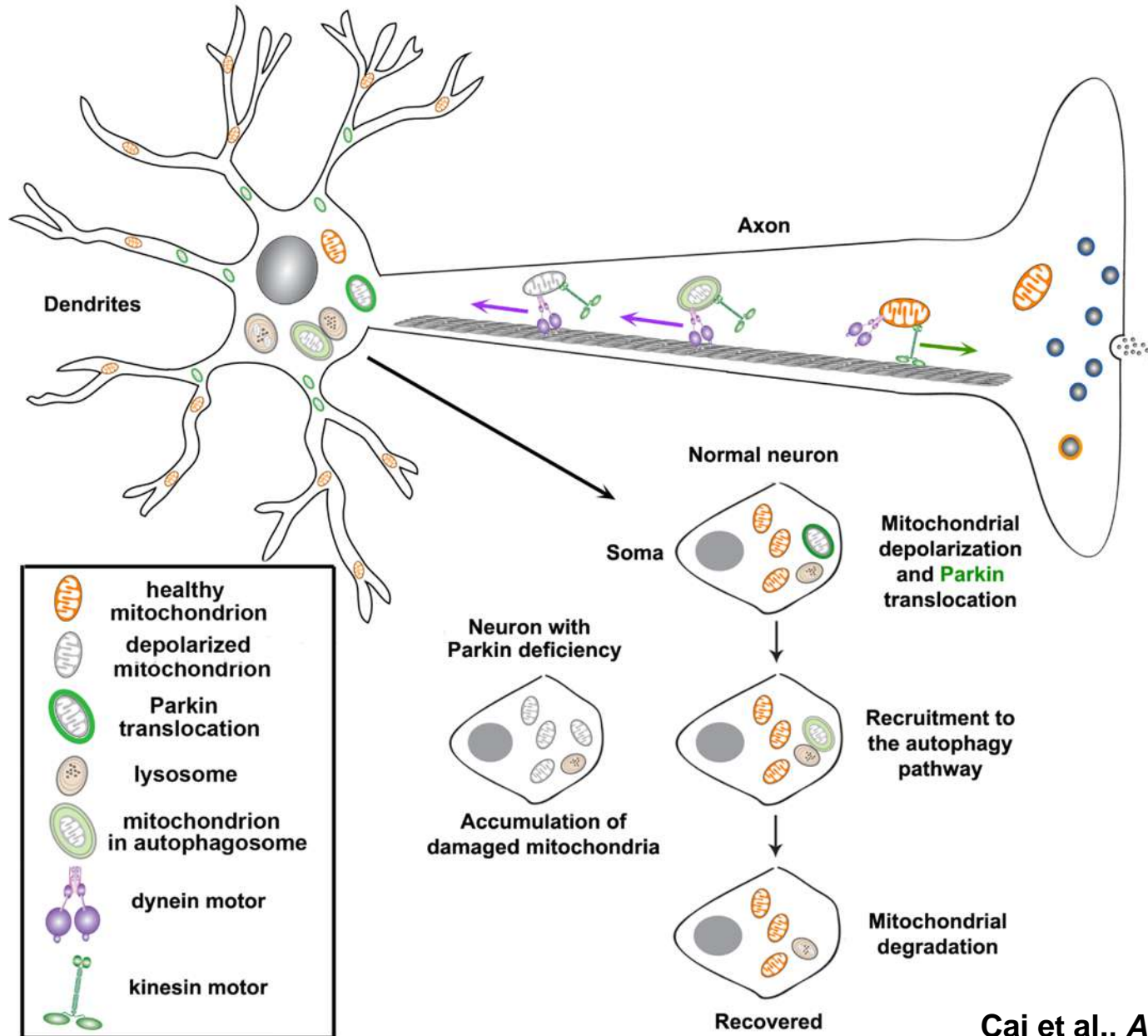
(Time-lapse for 170 min at 5 min-intervals)



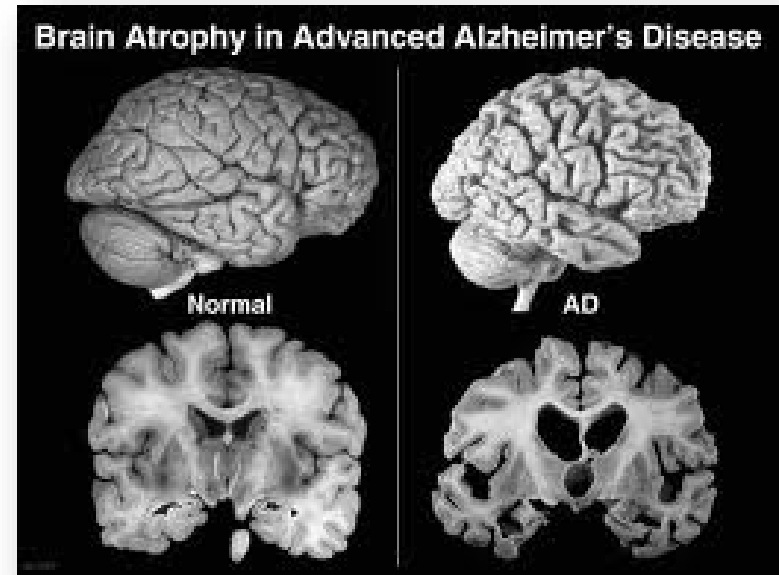
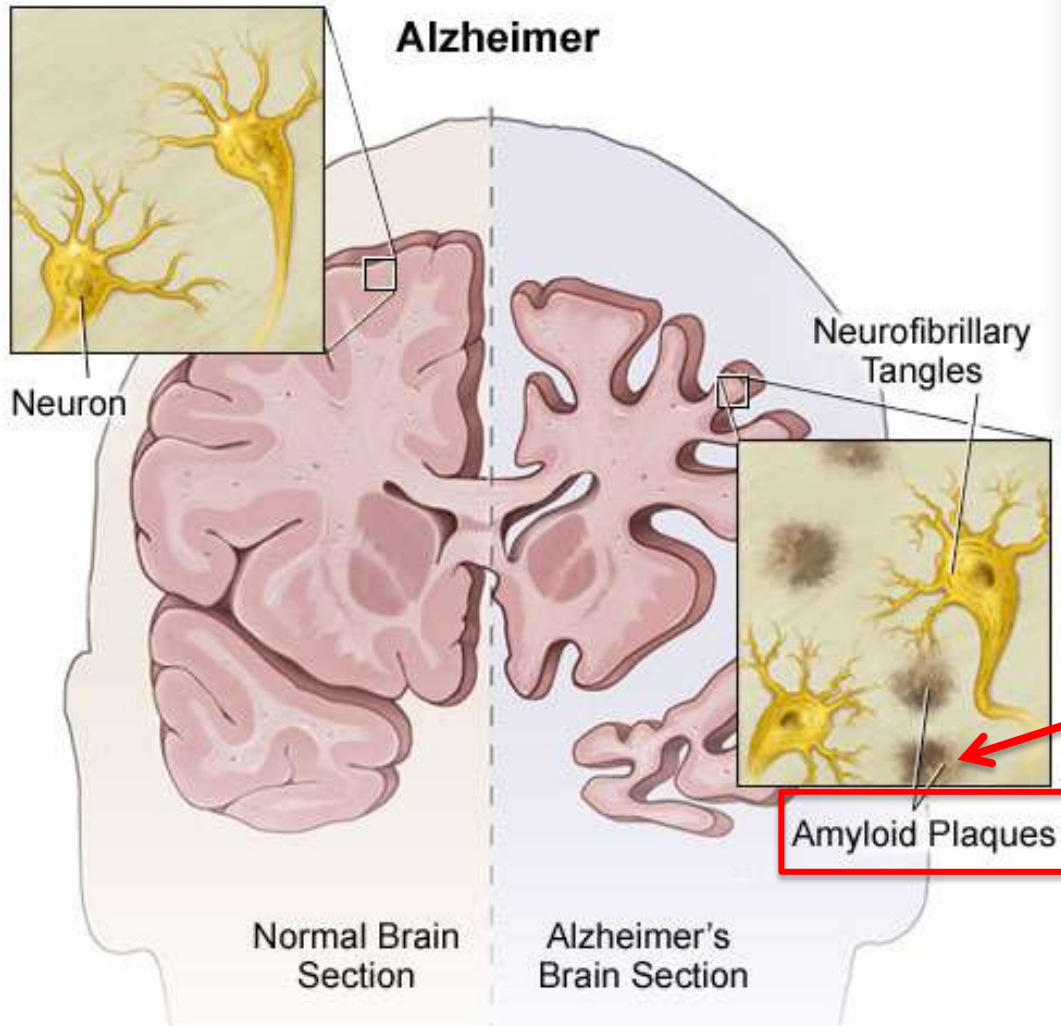
(Time-lapse for 130 min at 5 min-intervals)

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

# Parkin-mediated mitophagy in healthy neurons



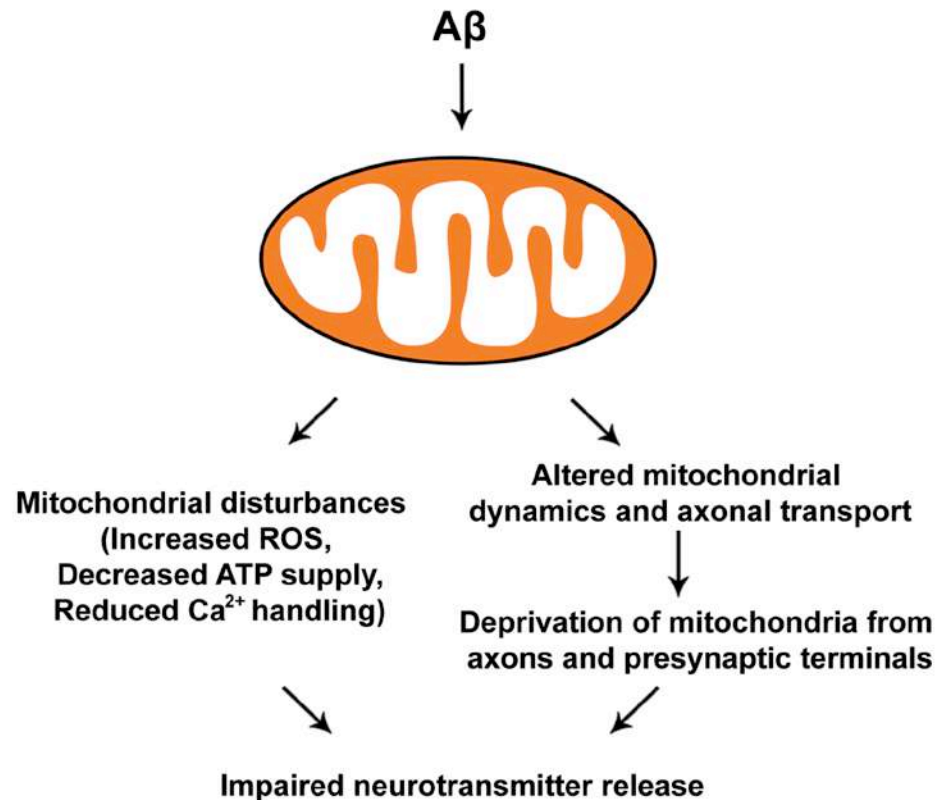
# Pathogenic hallmarks of Alzheimer's disease





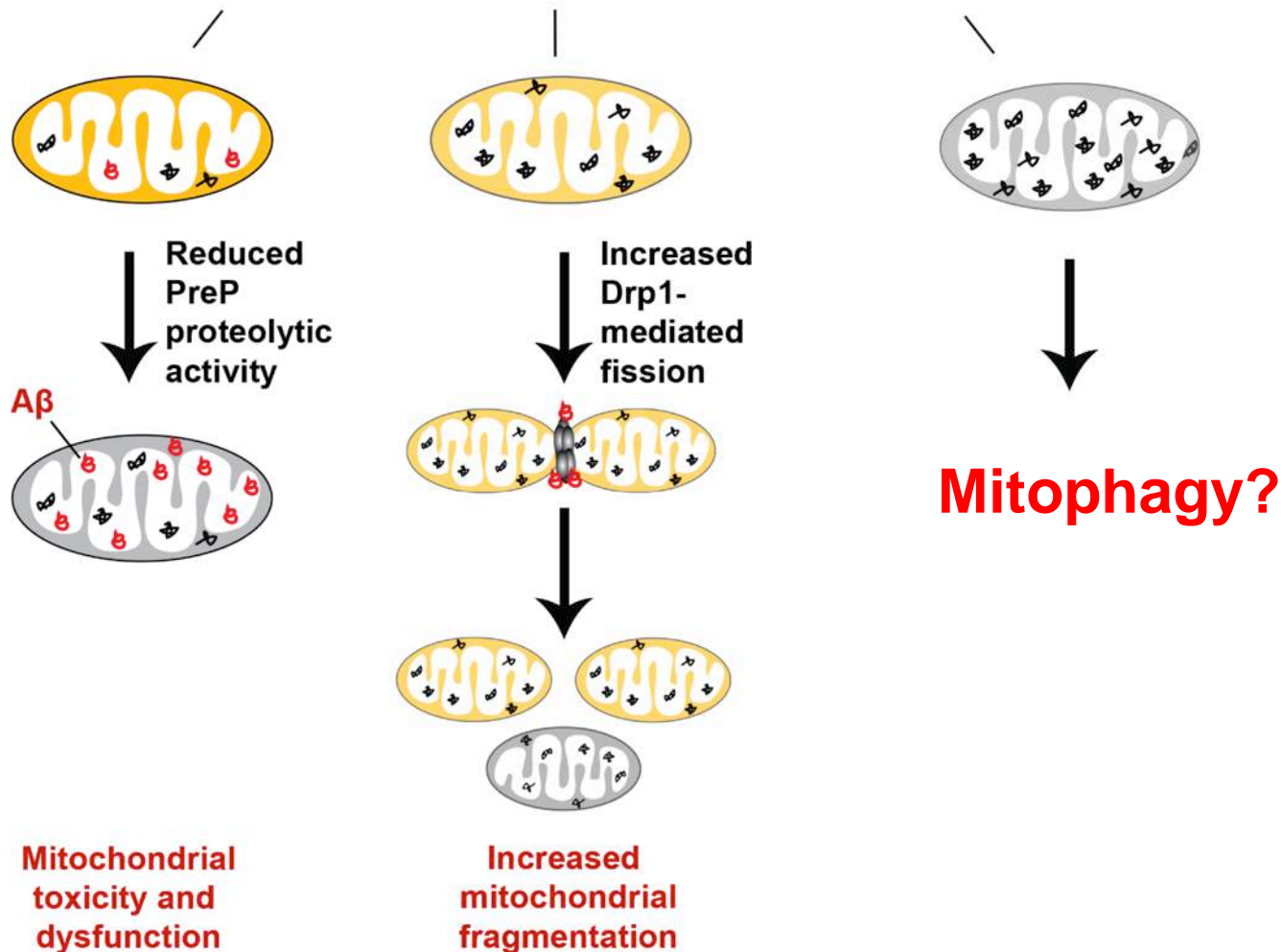
# Toxic effects of A $\beta$ on mitochondria

- Mechanisms underlying mitochondrial defects in AD neurons



# Mitochondrial quality control is altered in Alzheimer's disease

Damaged or dysfunctional mitochondria



# Parkin-mediated mitophagy is induced in mutant hAPP Tg neurons



WT neuron

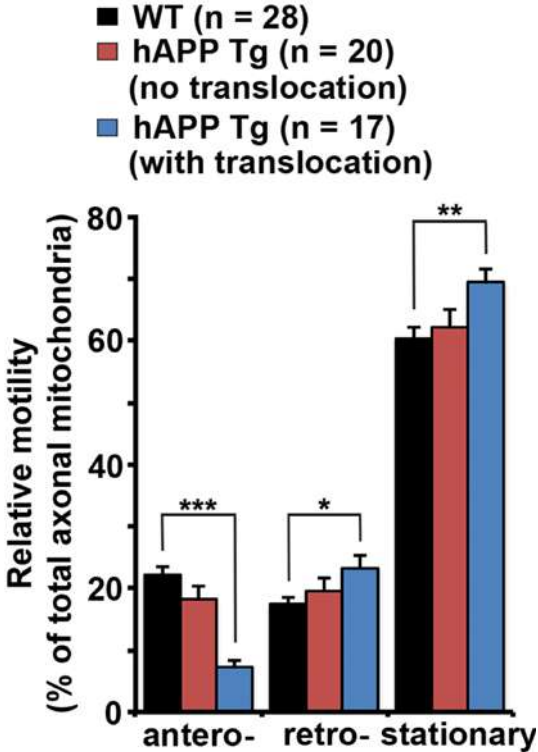
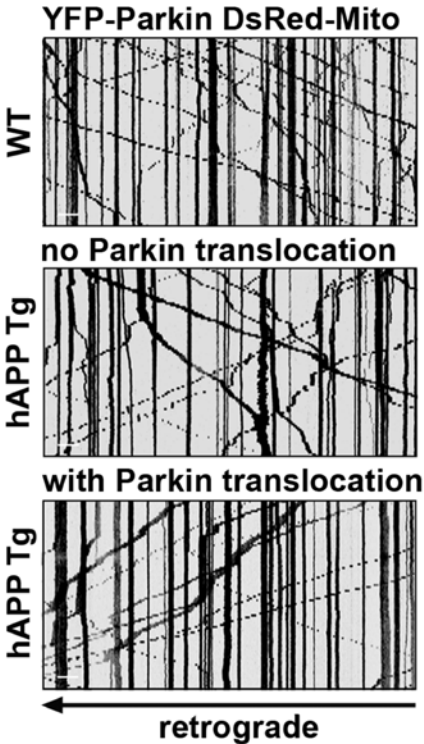
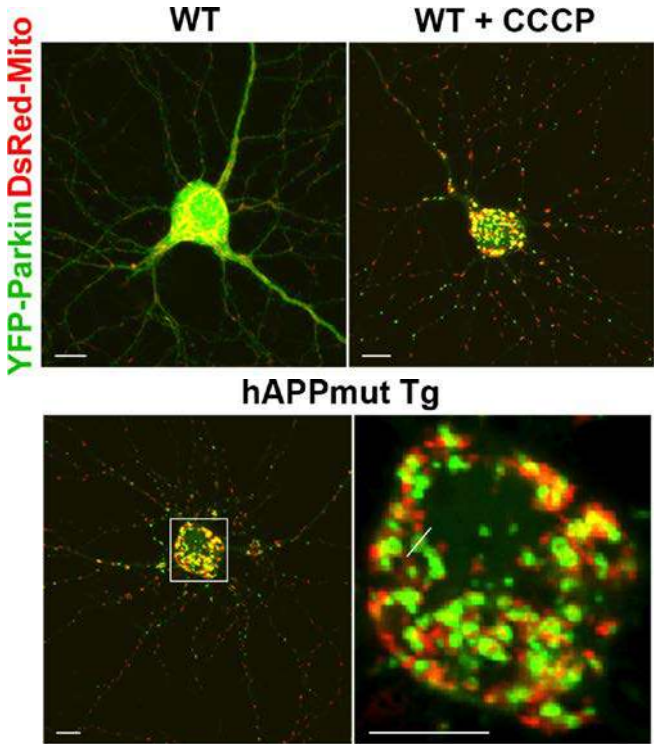


mutant hAPP Tg neuron  
without Parkin translocation

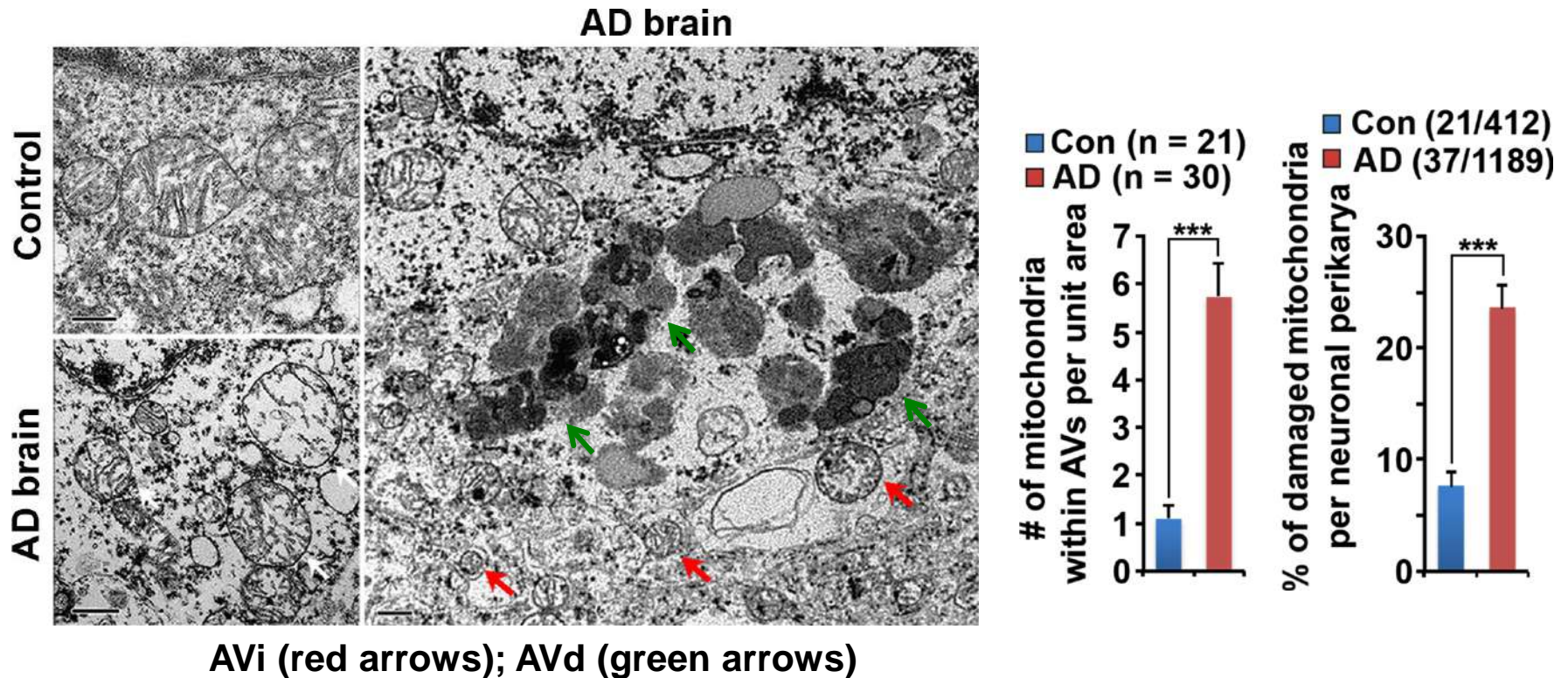


with Parkin translocation

← retrograde transport



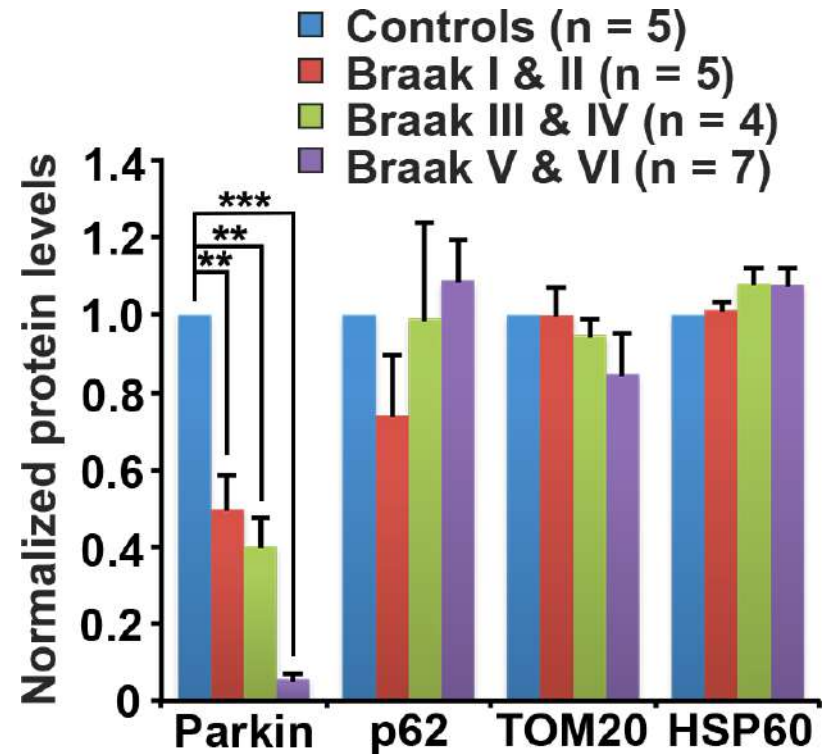
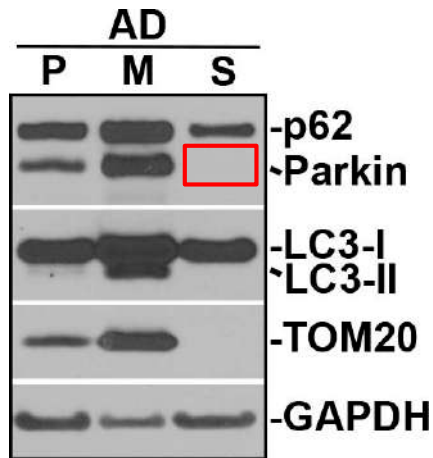
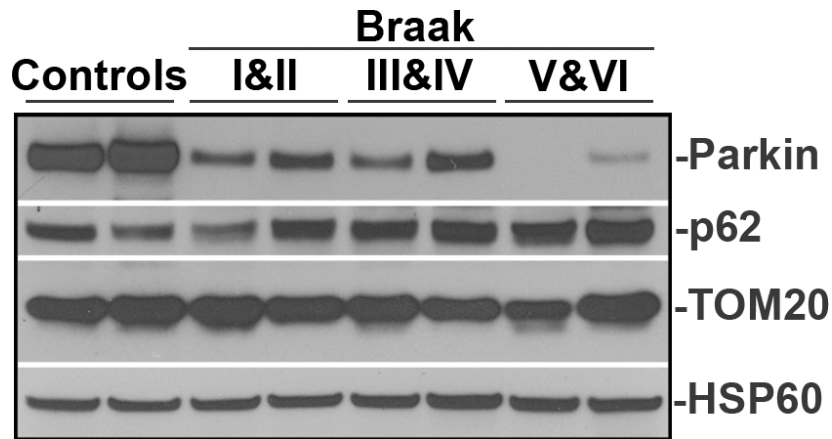
# Accumulation of mitochondria within autophagic vacuoles in the hippocampus of AD patient brains



Mitophagy is induced in AD patient brains.

Aberrant accumulation of defective mitochondria in AD patient brains.

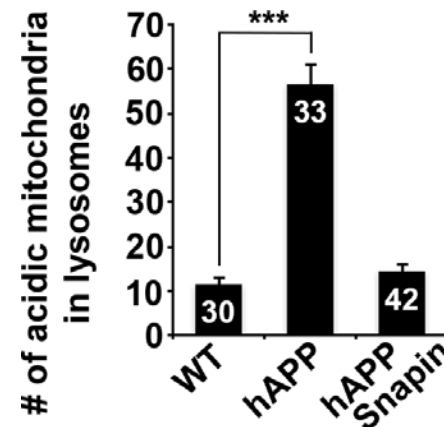
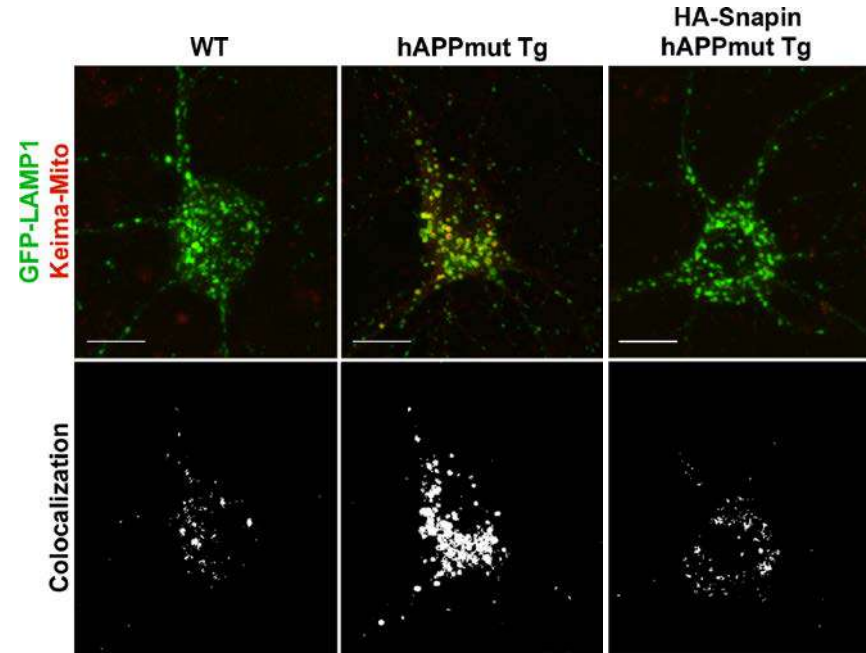
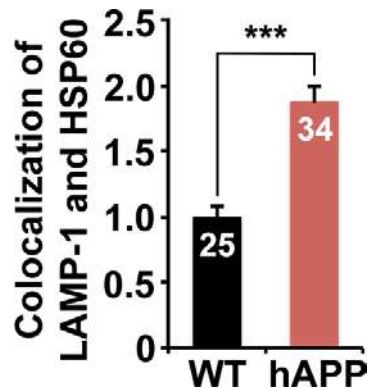
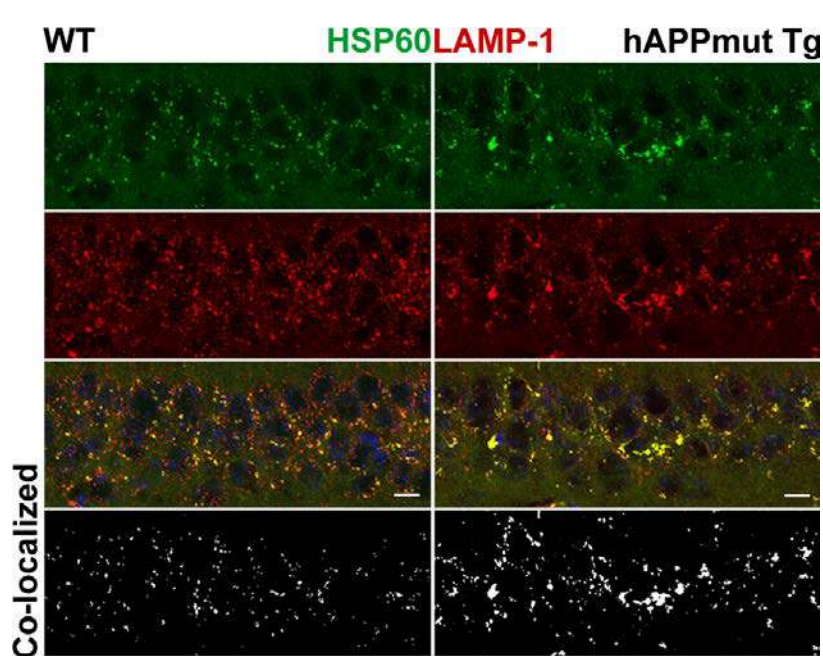
# Depletion of cytosolic Parkin over disease progression in AD patient brains



Mitophagy induction is coupled with enhanced Parkin degradation.

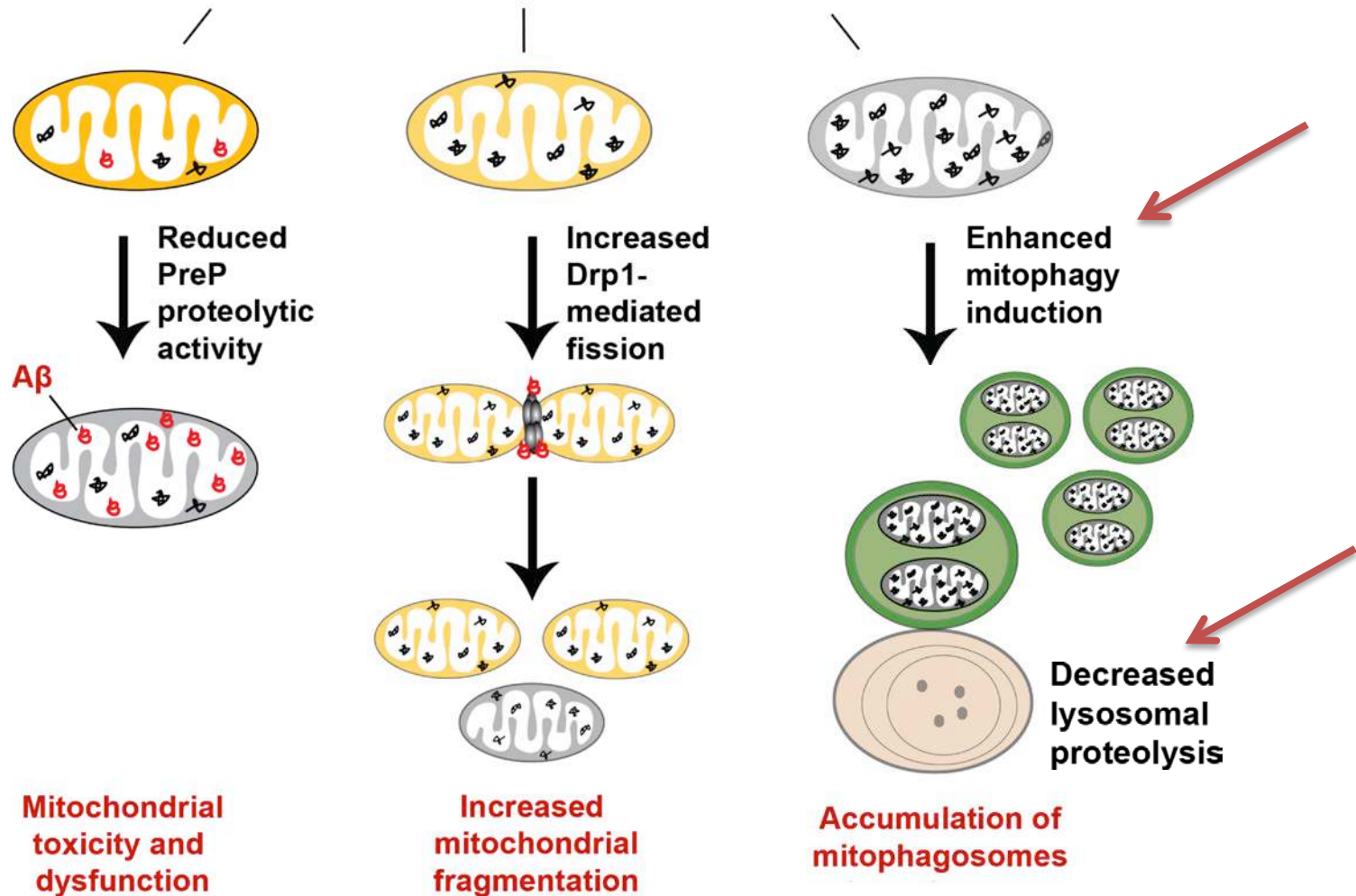
Parkin depletion leads to defects in the elimination of defective mitochondria, resulting in their aberrant accumulation in AD neurons.

# Lysosomal deficits contribute to mitochondrial pathology in AD neurons



# Abnormal mitochondrial quality control in AD

## Damaged or dysfunctional mitochondria



# 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)