BIOGRAPHICAL SKETCH

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NAME: Zhou, Chuankai (Kai)

eRA COMMONS USER NAME (credential, e.g., agency login): ZHOU_C

POSITION TITLE: Buck Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, Beijing, China	B.S.	07/10	Biology
Stowers Institute for Medical Research & University of Kansas Medical Center	Ph.D.	08/16	Cell Biology
Stowers Institute for Medical Research	Post-doc	05/17	Biochemistry & Neuroscience

A. Personal Statement

The goal of my research is to investigate the consequence of protein homeostasis (proteostasis) defects on cellular organization during aging, as well as the process to rejuvenate these dysfunctions. The ongoing projects stem from my previous works that identified the formation and anchoring of cytosolic protein aggregates on mitochondria, which surprisingly import aggregated cytosolic proteins and mediate the dissolution of cytosolic protein aggregates induced by proteostasis stress. Through my three successful projects I have demonstrated the creativity and ability in commanding the directions of my research. These experience honed my skills in mentoring graduate students, managing collaborations, writing manuscripts, conference presentations, and grant applications. In addition, I have extensive experience in genetic screening, cutting-edge imaging technologies, bioinformatics, proteomics, biochemistry, and computer simulation that used in my three completed works that published in *Cell* and *Nature*. My lab is well-funded: as a winner of the 2017 NIH Director's Early Independence Award, I have built an efficient research team with two talented post-doctoral researchers and one visiting scientist working at the Buck Institute; the lab is already fully functioning and equipped with a sophisticated imaging platform based on LSM510 RGB confocal microscope (with ConfoCor3 and 7 different lasers), SPEX freezer mill, gel apparatus for DNA analysis, thermocycler, balances, centrifuges, Milli-Q apparatus for purified H_2O, Bio-Rad electrophoresis systems, refrigerator, –80˚C and –20˚C freezers, water baths, chemical hood, shaking incubators, and small items needed for the research projects.

B. Positions and Honors

Positions and Employment

2010-2016 Predoctoral Researcher, Stowers Institute for Medical research. Advisor: Rong Li, Ph.D.
2016-2017 Post-graduate Researcher, Stowers Institute for Medical research. Advisor: Kausik Si, Ph.D.
2017- Fellow, Buck Institute for Research on Aging, CA, USA

Other Experience and Professional Memberships

2012 - American Society for Cell Biology
2013 - American Heart Association

Honors

2013-2015 Predoctoral Fellowship, American Heart Association
2015 Norton B. Gilula Award, American Society for Cell Biology
2017-2022 NIH Director's Early Independence Award

C. Contributions to Science

1. Aging represents an inevitable loss of physiological integrity over time that is caused by the gradual accumulation of aging determinants in cells. Asymmetric partitioning of aging determinants allows the dividing cells to produce progeny cells with contrasting vitality and proliferative potential. This fundamental mechanism that enables rejuvenation from aging remains poorly understood. These publications document the mechanism of asymmetric partitioning of aging determinants, such as protein aggregates. I found that the physical diffusion barrier and confined motility of aggregates enable such damage to be retained in the aging mother cell. My findings revised a prevailing model on asymmetric segregation of protein aggregates and ignited a lasting interest in understanding how cells manage the formation and segregation of protein aggregates in various model organisms. I served as the primary investigator for these studies.

    a. **Zhou C.** et al. (2011) Motility and segregation of hsp104-associated protein aggregates in budding yeast. *Cell*. 147:1186-1196. PMCID: PMC3237388
    b. **Zhou C.** et al. (2014) "Life history: mother-specific proteins that promote aging." *Curr. Biol.* 24:24 R1162-4. PMID: 25514007

2. Formation of protein aggregates is a widespread problem underlying several aging-related and amyloid diseases. Although well-studied *in vitro*, the *in vivo* mechanism of protein aggregation is not well-appreciated. I discovered that instead of being a random process as suggested by *in vitro* studies, aggregate formation is spatiotemporally nucleated by newly translated peptides on the surface of endoplasmic reticulum and mitochondria. After formation, protein aggregates are anchored on these organelles. The asymmetric segregation of mitochondria during mitosis restricts the motility and leakage of aggregates. These discoveries, together with findings from other groups, established spatially organized aggregation and segregation of misfolded proteins as a defensive strategy to cope with cellular stresses. I served as the primary investigator for this study.

3. The dissolution of protein aggregates was attributed to the actions of several protein chaperones, whether cellular factors other than chaperones are involved remains unknown. In this study I found that, in addition to the chaperones, active mitochondrial import is also required for the dissolution of cytosolic aggregates. I also found that the association of aggregates with mitochondria allows aggregated cytosolic proteins to be imported by mitochondria and those imported non-mitochondrial proteins are degraded by the mitochondrial proteolysis system, which was thought to mostly manage mitochondria's own proteostasis. Mitochondria also import unstable cytosolic proteins under physiological condition and work in concert with Hsp70s to maintain cytosolic proteostasis, a mechanism conserved in mammalian cells. This work raises the possibility that the accumulation of aggregates during aging affects mitochondrial composition and provides an explanation for why protein aggregation and mitochondria dysfunction often go hand-in-hand in aging and degenerative diseases. I served as the primary investigator for this study.

    a. Ruan, L.***, Zhou C*** et al. (2017) Cytosolic Proteostasis via Importing of Misfolded Proteins into Mitochondria. *Nature* 543 (7645), 443-446. (*equal contribution). PMCID: PMC5793917
    b. He, C., **Zhou C.**, Kennedy, B. (2018) Aging in the single-celled eukaryote, S. cerevisiae. *BBA Molecular Basis of Disease* (in print)

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/50909926/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

DP5OD024598 (PI: Zhou) 09/01/2017-08/31/2022

NIH/NIDCR

Mechanism of organelle dysfunction during aging and the related rejuvenation process

Loss of protein homeostasis (proteostasis) and the consequent accumulation of aggregated proteins are hallmarks of aging and many age-related diseases, such as the neurodegenerative diseases. Although proteostasis dysfunction during aging has been explored in the context of protein aggregation, how proteostasis dysfunction affects organelle integrity is still beyond current knowledge. This work will investigate the biological consequences of protein aggregation on the integrity of mitochondria and other organelles during aging, as well as the related rejuvenation mechanisms using budding yeast as a model. The outcomes of this work will significantly improve our understanding of these hallmarks of aging and our ability to intervene in age-related diseases.