

**BIOGRAPHICAL SKETCH**

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NAME: Yang Liu

eRA COMMONS USER NAME (credential, e.g., agency login): YANGLIU123

POSITION TITLE: Graduate Student Research Assistant

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<br>(if applicable) | Start Date<br>MM/YYYY | Completion<br>Date<br>MM/YYYY | FIELD OF STUDY                        |
|---------------------------------|---------------------------|-----------------------|-------------------------------|---------------------------------------|
| Tongji University               | BS                        | 09/2015               | 07/2019                       | Biotechnology                         |
| Johns Hopkins University        | MS                        | 09/2019               | 05/2021                       | Biochemistry and<br>Molecular Biology |
| University of Wisconsin Madison | PHD                       | 09/2022               | 05/2027<br>(Expected)         | Endocrinology                         |

**A. Personal Statement**

As an undergrad I knew I was interested in aging research, and at seminars for freshmen in our department, Dr. Lei Xue said that it was also his initial motivation to get into the field of biomedical research. I was excited to join his lab studying drosophila signaling pathways. During my over two years in the lab, I learned basic fly handling, fly genetics, fly phenotype and behavioral characterization. I also had the chance to complete my undergrad thesis project. We found two genes *mle* and *mor* were required in JNK pathway over activation induced cell death in various fly organs and they work downstream of *bsk*. Through the process, I was able to learn the basic logic behind genetic pathways and experiments design, giving me more confidence to explore diverse research directions.

Knowing techniques limited to flies would not be enough to fulfill my research interests, I started to pursue my master's in Dr. Jiou Wang's lab in Johns Hopkins University. I thought it would be helpful for me to learn more about brain aging in this ALS lab. During my time in the lab, I mostly used cell culture models to study mechanisms that could rescue disrupted cellular protein turnover and cell death phenotype under the stress of lysosomal inhibition. We found downregulation of two genes, NDST3 and PDZD8 promotes V-ATPase assembly and lysosomal acidification through different mechanisms, allowing for better protein degradation function and cell survival under Baf-A1 treatment. Also disruption of these proteins was found in spinal cords of familial ALS patient samples, indicating dysregulation of lysosomal acidity and disrupted autophagy of disease-prone proteins might be one of the underlying mechanisms in these patients. These projects lead to my first coauthor publication.

In my master's I learned cell and molecular experiment techniques and explored how to study a specific mechanism question related to just one gene in a specific disease background. Then I realized that I would want a chance to study aging in whole organisms in a more general way. So for my PhD I joined Dr. Lamming's lab for molecular physiology of aging using mice as our main experiment model. Most of my research topics for now are on dietary Isoleucine restriction. Besides that, I'm still looking forward to exploring other anti-aging interventions or aging-related research topics during my time in the lab and beyond. I believe that my current research mentoring environment with my proposed training plan will provide a solid foundation for my future research.

1. Tang Q, Liu M, **Liu Y**, Hwang RD, Zhang T, Wang J. NDST3 deacetylates  $\alpha$ -tubulin and suppresses V-ATPase assembly and lysosomal acidification. EMBO J. 2021;40(19):e107204.

## **B. Positions, Scientific Appointments and Honors**

### **Positions and Scientific Appointments**

|                       |                                                   |
|-----------------------|---------------------------------------------------|
| <b>2020– 2021</b>     | <b>Graduate Research Assistant, Johns Hopkins</b> |
| <b>2021 – 2022</b>    | <b>Research Technician, Johns Hopkins</b>         |
| <b>2022 – Present</b> | <b>Graduate Research Assistant, UW-Madison</b>    |

### **C. Contributions to Science**

#### **Undergrad research:**

For my undergrad thesis project, I used fly genetics experiments to study where two required genes work on JNK pathway in JNK signaling overactivation driven cell death. The lab previously found RNAi of either *mle* or *mor* gene could rescue the cell death phenotype of overexpressing JNK upstream activator *Egr* in fly eyes, scutes and wing veins. I then confirmed these two genes were required using different RNAi and dominant negative lines. In my project we found downregulation of these genes could rescue the cell death phenotype induced by overexpressing different kinase components on JNK pathway to various degrees. And we concluded these two genes work downstream of or work with *bsk*, the transcriptional cofactor that translocate from cytosol into the nucleus when phosphorylated. This project would help future researchers understand basic mechanisms of cell death induced by *Egr*/TNF pathway activation in various health and disease related conditions including cancer.

Besides this project, I also had a chance to dissect and image larval motor neurons. We found either up or downregulation of Hippo pathway genes *Wts* or *Yki* in fly neurons could disrupt cargo transport in larval motor neurons adjacent to VNC, shown as accumulated vesicles labeled with GFP. Besides, I participated in a screen for drugs that could possibly improve motor behaviors of an Alzheimer's Disease fly model. These projects set a background for future researchers to start investigating from.

#### **Graduate research:**

In my master's, in my first project we found that a protein, NDST3 deacetylates  $\alpha$ -tubulin and suppresses V-ATPase assembly and lysosome acidification in cultured cells. The protein decreased in spinal cord samples of familial ALS patients, indicating increased acetylated  $\alpha$ -tubulin and over acidification of lysosome might play a role in this type of familial ALS. I was included as a coauthor in this paper (Tang Q, Liu M, Liu Y, Hwang RD, Zhang T, Wang J. NDST3 deacetylates  $\alpha$ -tubulin and suppresses V-ATPase assembly and lysosomal acidification. EMBO J. 2021;40(19):e107204).

For my master's thesis project, I focused on a protein, PDZD8, found in the same screen as NDST3. Both of their downregulation could make the cells survive better under the stress of V-ATPase inhibitor, Baf-A1 treatment. I found though downregulation of PDZD8 changed cellular levels of some proteasome components and accelerated overall K-48 ubiquitin linked protein degradation, the proteasome substrate activity didn't change, measured by commercial kits and chase experiments of tagged proteasome substrates. And later I found in PDZD8 KO cells, there's also lysosome over acidification and increased V-ATPase assembly, which explains their better survival under Baf-A1. As an ER protein, PDZD8 was found to be required for organelle contact and was reported to share structure traits with endo lysosomal membrane protein Rab7. PDZD8 and Rab7 both physically interact with a cytosol component of V-ATPase, so our hypothesis is that downregulation of PDZD8 allows Rab7 to recruit more V-ATPase V1 subunit onto lysosome membrane and cause downstream over acidification. While the hypothesis and further mechanisms still need validation.

These projects helped broaden our understanding of basic lysosomal function control under stress and our findings were in accordance with the idea that lysosomal and autophagy dysfunction was usually found in familial ALS patients. Finding of these two genes also provided possible inhibition therapeutic targets to treat neurodegenerative diseases with elevated lysosomal pH.

In my PhD I studied dietary amino acids' role in metabolic health and aging. Protein and some amino acid restriction diets promote metabolic health and longevity in diverse species. Our lab has previously found in young male C57BL/6J mice, the beneficial metabolic effects of low protein diet are principally mediated by

Isoleucine. And switching to a diet with 67% Isoleucine restriction at 6-month-old was able to extend lifespan of both male and female HET3 mice. Part of my research would be on finding the possibly translational-friendly degree of Isoleucine restriction to maximize metabolic health improvement in both lean and obese backgrounds. We're also collaborating with other labs and different cores at UW-Madison to characterize metabolites, transcription, epigenetics and microbiota change in Isoleucine restricted mice to gain a better understanding of the whole picture and look for possible mechanisms. As different mouse strains with different genetic backgrounds respond to nutritional cues differently, I'm also participating in a lifespan study using various strains and sexes of mice with different physiological response to short term Isoleucine restriction to explore the lifespan extending effect of lifelong Isoleucine restriction starting at 6-month-old. These projects would lead to publications and findings indicating whether if and how populations with different genetic backgrounds would benefit from dietary Isoleucine restriction.