NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

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2021 UW NSC Pilot Award

Investigate the functional and mechanistic differential effects of SHLP2 and K4R SHLP2 on cellular protection

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How did you become interested in aging?

During my PhD, I studied the role of mitochondrial gene mutation in Parkinson's disease (PD). Although studying genetic mutation of PD provides us insights on the pathology of the disease, it only contributes 5-10% of PD patients. The most significant risk of sporadic PD is aging. Since then, I became interested in aging and why aging contributes to PD and other age-related diseases. Now, I am studying the role of mitochondria and mitochondrial microprotein during aging and age-related diseases.

Briefly describe your project in non-scientific terms. What questions are you trying to answer?

My research aims to uncover the functional effect of mtSNPs in age-related diseases. I am particularly interested in how mtSNPs affect mitochondrial derived peptide (MDP) and contribute to aging and age-related diseases. I first identified a PD protective mtSNP that alters the amino acid of a MDP called SHLP2. The SHLP2 variant had superior protection against mitochondrial dysfunction in vitro and in vivo models of PD. Particularly, in the funded project, I investigated the molecular mechanism of how SHLP2 and its variant protect against mitochondria dysfunction by measuring NAD+ and its metabolites.

What previous research or experience informed the development of this proposal?

My PhD and postdoctoral training in the field of PD and mitochondrial derived peptides (MDPs) allowed me to explore the function of PD-associated mtSNP in the form of MDPs.

What's exciting about your project's potential impact?

A personalized approach based on genomic analysis has been proposed to be beneficial in delaying or preventing aging and age-associated diseases. There is substantial sequence variability in mitochondrial DNA, and we theorized that this might affect the function of mitochondrial-derived peptides (MDPs), which play essential roles in the aging process. My studies will identify the functional effect of PD associated mtDNA SNP in PD and cognitive decline. This project's insight can be rapidly translated into clinical and population research and possibly position SHLP2 analogs as potential neuroprotective interventions and personalized medicine.

If your project is successful, what is the next step?

If successful, the next step would be to investigate therapeutic potential of the MDP using PD mice models.

How has support from and collaboration with the NSCs helped further this project and/or your research overall?

The Nathan Shock Center has not only provided me with the funding to run metabolomics analysis, but also provided me with consistent guidance to design the experiments and analysis. The NSC-funded project results are included in the manuscript that will be submitted soon. Furthermore, the results provided me with important preliminary data for my R01 application to study further the role of the MDPs in PD and cognitive decline.