NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

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2021 UW NSC Pilot Award
Intergenerational effect of maternal age on offspring metabolome

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How did you become interested in aging?
I transitioned from cancer biology research to aging research a year ago when I started my position as a postdoctoral scientist at the Marine Biological Laboratory. I am generally interested in the role of autophagy, mitochondria, and metabolism on cancer metastasis and drug resistance. We know that most cancers--including breast, colorectal, and lung cancers--occur when we are older and are characterized by changes in mitochondrial metabolism and dynamics. Mitochondrial and metabolic dysfunctions are also hallmarks of aging. So, I think if we can understand the mechanisms behind healthy aging, we can decrease the incidence of cancers and other aging related diseases.

Additionally, we know that more and more families are having children at later ages. Increasing parental age is associated with lower offspring health and lifespan, however. Thus, I am worried about what happens to future generations. We need immediate solutions and a deeper understanding of what causes a decline in metabolic and mitochondrial health with age. That is why I joined Kristin Gribble's lab. We focus our attention on the role of mitochondria and metabolism in maternal age effect on offspring life and use rotifers (aquatic invertebrates) as a model.

Briefly describe your project in non-scientific terms. What questions are you trying to answer?
Advanced maternal age is associated with a decline in offspring health, lifespan, and stress resistance in a wide range of species, including humans. However, in some species and strains, older mothers produce more fit offspring. Little is known about the molecular mechanisms driving this dichotomy between beneficial and negative maternal effects. Our previous finding in the aquatic invertebrate rotifer, showed that females at late ages have an imbalance in mitochondrial homeostasis including a decline in oxidative phosphorylation and calcium signaling gene expression. Furthermore, our preliminary data shows that old-mother offspring have altered mitochondrial integrity including increased mtDNA copy number, mitochondria number, mitochondrial size, and oxidative potential, however they exhibit decreased mitochondrial intermembrane area and ATP production. Thus, we hypothesize that age-associated defects in metabolism and mitochondrial efficiency of advanced maternal age transmit and cause negative health outcomes in old-mother offspring. We anticipate that these changes will manifest as significant differences between the metabolomes of young-mother and old-mother offspring.

What previous research or experience informed the development of this proposal?
Our group has found that rotifer offspring from older mothers have a shorter lifespan and decreased health and stress resistance. With increasing age, rotifer mothers have a decline in mitochondria homeostasis while old-mother offspring have altered mitochondrial integrity. So, we speculate that these age-related changes in maternal mitochondrial homeostasis may change offspring metabolism, which may drive the observed negative effects of advanced maternal age on offspring fitness outcomes.

What's exciting about your project's potential impact?
In this pilot project, I have unexpectedly found that in a particular rotifer strain, offspring from older mothers have a longer lifespan and increased phototaxis, but a lower fecundity and lower resistance to heat stress and mitochondrial complex I inhibition. We found that these are correlated with metabolic changes such as maintaining lower methionine metabolism throughout life and high spermidine metabolites in early life. These pathways have also been reported to extend lifespan and improve physical functions in other organisms. Thus, these functional and phenotypic and metabolomic studies, have allowed us to identify potential therapeutic targets to improve rotifer offspring lifespan, with potential for translation to human health. Additionally, this project will also provide critical preliminary data for a K99/R00-scale investigation to advance the field of the biology of aging by characterizing the mitochondrially-mediated transgenerational maternal age effects on offspring health and fitness.

If your project is successful, what is the next step?
From the results of this pilot project, I now have some insight on mechanisms that may explain the positive effect on the lifespan of old-mother offspring in one rotifer strain. Using these insights, I plan to perform targeted metabolomics on another rotifer strain in which advanced maternal age has a negative effect on offspring lifespan. I hope this side-by-side comparison of this differential effect of aged mothers on offspring will provide targets for future mechanistic investigation of maternal metabolic effects and maternal age effects on offspring health and lifespan.

How has support from and collaboration with the NSCs helped further this project and/or your research overall?
The faculty and staff of the Metabolite Phenotypes of Aging Core at the University of Washington Nathan Shock Center were incredibly supportive and helpful throughout this project, including during experimental design, sample analysis, and data analysis. Before being offered a grant award, I consulted with Daniel Promislow. This helped me to refine my research question and experimental design and was a helpful interaction for me as a new researcher in the aging field. Core scientists, including Danijel Djukovic and Fausto Carnevale Neto, demonstrate a strong understanding of the field and an unwavering passion for it. Despite the rotifer model being new to them, they have helped me to optimize our sample size and collection. We were thus able to identify about 200 metabolites with the Core's targeted metabolomics technology. It is quite an impressive number of metabolites and can help to provide a more complete picture of the metabolic mechanisms of aging. With our continuous communication and structured analysis, we are now collaborating on an additional experiment, which will provide further insight on metabolic signature and maternal age's effect on offspring health and lifespan.