NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

Robert Musci, PhD

Associate Professor
Loyola Marymount University

2023 Oklahoma NSC Pilot Awardee

Investigating the turnover dynamics of mtDNA with stable isotope deuterium oxide

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How did you become interested in aging?
When I was younger, I was an EMT for a convalescent team that transported patients who were too sick to travel without medical support. Most of these patients were older with multiple diseases. This experience really shaped my view that aging presents significant challenge to quality of life. I decided to work with Drs. Karyn Hamilton and Benjamin Miller who study aging and chronic diseases for my graduate degree. Working for them really affirmed my interest in the field. From a scientific perspective, investigating the mechanisms of aging is fascinating. From a personal perspective, developing interventions to improve the quality of life and healthspan of people is a worthwhile and important endeavor.

Briefly describe your project in non-scientific terms. What questions are you trying to answer?
Mitochondria are responsible for important cellular activities. (e.g. ATP production, steroid synthesis, and calcium regulation). The mitochondrial DNA (mtDNA) is the blueprint to build parts of mitochondria. With age, mtDNA mutations accumulate and it's as if the blueprint gets smudges or errors. These errors prevent us from properly constructing the mitochondria. These mtDNA mutations are associated with age-related diseases like sarcopenia, cardiovascular disease, and Alzheimer's disease. The challenge is understanding how these mutations develop. We think the rate that mtDNA turnover affects the risk of mutations developing. The problems we are trying to solve is to first optimize a method that allows to assess mtDNA turnover and the second is to understand what happens to mtDNA turnover with age, disease, and exercise.

What previous research or experience informed the development of this proposal?
Researchers first studied mtDNA turnover in the 1960s. Their approach assessed turnover for a short period of time and found that mtDNA turnover quickly: half of the mtDNA turned over every 10 days. About 20 years ago, though, Dr. Marc Hellerstein's group revisited this question with a different approach and measured turnover for a longer period. They found that mtDNA half-life is much longer than originally thought: 200 – 300 days.

A couple years ago, Drs. Jon Wanagat of UCLA and Benjamin Miller of OMRF began collaborating to revisit this question of mtDNA turnover. They involved me and decided we also wanted to understand if the rate of mtDNA turnover changes with age. We just published that mtDNA half-life is much longer (~130 days) and that aging increased half-life (~215 days). We also found that as half-life increased, mtDNA mutations increased. This suggests that changes in mtDNA turnover with age could explain some of the mutation burden.

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

A significant hurdle to measuring mtDNA turnover is that we currently need a lot of fresh tissue. This means we are limited to what kinds of tissue we can sample and the number of tissues we can assess. The first aim of the project is to optimize our method so that we can reduce the amount of tissue needed. In addition, we also want to modify our method so we can use frozen tissue instead of fresh tissue. This will enable us to accomplish second aim. We want to use tissues already collected and assess mtDNA turnover during different scenarios. The second aim is to investigate how exercise training and heart failure affects mtDNA turnover. Exercise is a potent intervention to improve mitochondrial function. However, we don't understand how it affects mtDNA turnover.

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

Mitochondria are dynamic and complex organelles. If we are successful, we will have developed a novel approach to better assess mitochondrial dynamics. We will better understand how mtDNA turnover is related to health. We also want to understand how mtDNA turnover is related to mitochondrial protein and membrane turnover. We want to investigate how these dynamic processes change in concert with one another and how they collectively impact mitochondrial function to affect health.

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

As faculty at a Primarily Undergraduate Institution, access to state-of-the-art equipment is limited. This project requires expensive equipment we don't have. The Multiplexing Protein Analysis Core at the Oklahoma Nathan Shock Center has been instrumental in expanding my lab's research horizon. Dr. Benjamin Miller and his lab have provided the capacity to do the downstream analyses we need as well as expertise to help troubleshoot. This means I can provide research opportunities to students who wouldn't otherwise get them.

Faculty at Loyola Marymount University are dedicated to providing undergraduate students research opportunities. LMU just received a grant from the Howard Hughes Medical Institute to support undergraduate research. The goal is to get more students involved in research, especially those from underrepresented groups. This Nathan Shock Center pilot grant helped me generate preliminary data for an R15 grant I submitted to the National Institute of Aging. If funded, more students at LMU, especially those supported by the HHMI grant, will have an opportunity to participate in impactful aging research. Working with the Oklahoma NSC has expanded not only my research horizon, but also the horizons of aspiring scientists.