NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

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Human microglial aging modeled through mitochondrial progeria mutations

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How did you become interested in aging?
My lab is interested in how the innate immune cells of the brain, microglia, contribute to brain development and how that changes over the course of aging and contributes to disease risk. Microglia are increasingly implicated in neurodegenerative diseases such as Alzheimer's disease, and understanding how microglia and genetics are involved in aging, and how genetic disease can lead to premature aging and pediatric neurodegeneration is a major theme in my lab.

Briefly describe your project in non-scientific terms. What questions are you trying to answer?
Our project seeks to understand how mitochondria, the energy powerhouse of all cells, and mitochondrial dysfunction contribute to neurologic aging. We are studying this specifically in the immune cell of the brain, microglia, and working to understand how inflammation and mitochondrial dysfunction interact and contribute to brain aging. To do this we are using a mitochondrial disease gene called POLG, where loss of this gene is a model of progeria or premature aging. Our project uses stem cell models of immune cells with and without POLG mutations to understand how mitochondrial function leads to immune cell dysfunction and can impact the brain in an aging relevant model.

What previous research or experience informed the development of this proposal?
Our previous work characterized the transcriptome and epigenome of primary human microglia from both adults and infants has found that many mitochondrial disease genes including POLG are highly expressed in human microglia and that the level increases with increasing age. POLG mutations lead to Parkinson's disease as well as a variety of other neurodegenerative diseases. Our preliminary data found that loss of POLG led to a hyperinflammatory phenotype with mitochondrial dysfunction in stem cell derived microglia, suggesting that POLG associated aging and neurodegeneration may have an innate immune component.

What's exciting about your project's potential impact?
I'm excited about many of the implications of this model! Many of the current models of mitochondrial disease in mice do not develop neurodegeneration the same way that humans do, so human models of disease are essential, and defining how aging and neurodegeneration specifically effects human cells. Secondly, there is huge variability in the age of onset and severity among patients with POLG disease, similar to the huge differences in aging between different people. The interaction between immunity, aging, and brain function has the potential to potentially explain some of these effects, since every person has differences in their immune challenges. We are really excited to understand these differences.

If your project is successful, what is the next step?
If Some of the next steps involve understanding how mitochondrial difficulties effect innate immune function in the brain and screening for therapeutics to see if we can identify drugs or compounds that rescue the phenotype.

How has support from and collaboration with the Nathan Shock Centers helped further this project and/or your research overall?
This has been a fantastic experience for my small lab group and has really allowed this early stage project which was mostly an idea to grow and become a full fledged project. Working with the cores at the Salk Institute has been fantastic and has allowed us to try out new directions including electron microscopy and lipidomics. Lastly, the mentorship component has been wonderful, receiving mentorship from Dr. Shadel has been an honor.