NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

Caroline Kumsta, PhD

Assistant Professor
Sanford Burnham Prebys Medical Discovery Institute

2022 San Diego NSC Pilot Awardee

Heterogeneity of autophagy during aging

How did you become interested in aging?

My interest in aging research began during my undergraduate research at the Technical University of Munich, where I learned about the process of protein folding, and the impact of protein misfolding in neurodegenerative diseases. During my PhD studies at the University of Michigan and during a short stint at Northwestern University, I began studying the roundworm C. elegans, and was mesmerized by the visualization of aggregating proteins using fluorescent proteins and their impact on cellular function. The fluorescent protein clumps became larger and more numerous with age, reflecting that aging leads to the accumulation of misfolded proteins. Usually, the cell can either repair misfolding proteins, or get rid of misfolded proteins via degradation by the proteasome or via the cellular recycling process called autophagy. With age, cells however lose the capacity to both repair and eliminate misfolded proteins, leading to the accumulation of cellular waste, further compromising cellular function. My research today is driven by the question of how these proteostatic processes fail with age and how we can prevent and counteract the effects of aging on cellular mechanisms to improve healthspan. I hope that my research will contribute to a broader understanding of aging which can have profound implications for societal health and longevity.

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

My research focuses on the cellular recycling process of autophagy which involves the breakdown of damaged and misfolded proteins and other macromolecules, and has been shown to be important for keeping our cells healthy. While several lines of evidence suggest that autophagy declines with age, the precise molecular mechanisms that underlie this, are not well understood. My research aims to further our understanding of how autophagy fails with age and how we can boost autophagy with age and in diseases with deregulated autophagy.

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

During my postdoc at Sanford Burnham Prebys Medical Discovery Institute, we found that short and mild heat stress can ameliorate protein aggregation via the induction of the cellular recycling process of autophagy. My research now investigates how heat shock leads to the induction of autophagy and improved proteostasis and whether heat treatments can be used to prevent autophagy decline with age. By understanding the heat-specific regulation of autophagy, we hope to develop strategies to boost autophagy with age also in humans.

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

The exciting part of my project lies in the development of heat therapy as a potential intervention against aging. Imagine using a simple, non-invasive treatment that might significantly enhance our healthspan by inducing autophagy to effectively clean out the cellular debris that accumulates with age. As we uncover the precise mechanisms of heat-induced autophagy, we could be paving the way for targeted therapies that could be used to prevent or delay the onset of diseases associated with aging, including neurodegenerative diseases.

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

The next step of this project will be to leverage the insights and data we have gathered to secure additional funding. This will enable us to broaden our studies and deepen our understanding of the mechanisms behind heat-induced autophagy and its implications for aging and health. The ultimate goal is to initiate intervention studies in humans to test heat therapy as a means to promote autophagy and enhance healthspan.

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

The Nathan Shock pilot grant was pivotal in establishing critical methodologies to study autophagy decline and its inducibility in humans. Moreover, the research cores enabled us access to human dermal fibroblasts of probands of different ages, and we will be able to study the heterogeneity of aging using these cell types not only in our current project but also in additional aspects of our aging-related research. In addition, the pilot grant also lead to new collaborations, thereby accelerating our progress and expanding the scope of our research.