Title: Cellular Metabolism Signaling Mechanisms in Aging and Disease

Project Description: Harnessing cellular metabolism allows scientists and physicians to interface with physiology and modulate longevity. Exercise, fasting, and dietary restriction all work to promote healthspan by activating specific cellular signaling pathways. Many of these pathways involve ordinary metabolites like acetyl-CoA and NAD, which have "secret" lives regulating cellular physiology. An emerging signaling metabolite, the ketone body beta-hydroxybutyrate (BHB), can elicit epigenetic effects, modulate inflammation, and regulate protein homeostasis, all while controlling metabolism by inhibiting enzymes, directing gene expression, and activating receptors. As novel signaling effects of ketone bodies continue to be uncovered, a mechanistic understanding of how ketone bodies regulate physiology to promote health has not been fully clarified. Geriatric clinical practice has shown that multidomain interventions can become successful treatments for complex medical issues in aging. A geroscience approach to multidomain interventions would access and manage many targets at once, like the dual signaling and metabolic roles of ketone bodies and other signaling metabolites. One of our goals is to develop targeted therapies that enhance the resilience of older adults to diseases like Alzheimer's and geriatric syndromes like delirium. The lab previously showed that a ketogenic diet can extend healthy lifespan and improve memory in aging mice, and now focuses on mechanisms of ketone bodies in dementia, delirium, and the aging brain. We are seeking researchers who are passionate about bridging the gap between cellular metabolism and physiology to solve issues in aging and disease.

Current and planned projects include:

- Understanding how signaling metabolites can influence cellular protein homeostasis to remove toxic aggregates, such as amyloid-beta and tau oligomers, in models of Alzheimer's disease and aging.
- Investigating age-related changes in ketone body metabolism and how ketosis can help maintain energy homeostasis in aging. This will help us understand how a ketogenic diet or exogenous ketones can be useful therapies in older adults, and the importance of BHB as an important metabolite and epigenetic regulator in aging.
- Investigating tissue and cell-specific metabolism of endogenous and exogenous ketone bodies in aging.
- Utilize polypharmacy models to understand the influence on ketone body metabolism in normal aging, AD, and delirium models.
- Understanding ketogenic capacity in ketolytic tissues across ages using Seahorse to assess oxygen consumption rate.

Skills Expected: Coursework foundations in biology, biochemistry, neuroscience, and chemistry desired but not necessary. Previous research experience techniques may include but are not limited to: gel electrophoresis, immunoblotting, cell culture, PCR, microscopy, and mass spectrometry. Non-negotiables are a good attitude and a commitment to participating in lab potlucks!

To learn more about the Newman lab, click HERE.
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