

leading to deterioration at an organismal level and increases risk for disease and death. Genetic, pharmacological and nutritional interventions have been successfully used to preserve metabolic health, which leads to preserved healthspan and extended longevity. This symposium will discuss new approaches to nutrition and diet and mechanisms underlying interventions such as calorie restriction and genetic CR. We will also discuss species-specific metabolic mechanisms based on longitudinal studies in mice, monkeys and humans.

THE EFFECTS OF INDY ON FLY METABOLISM

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The Indy (I'm not dead yet) gene encodes a plasma membrane citrate transporter in *Drosophila*. INDY reduction affects metabolism and extends longevity of flies and worms. In flies, INDY is predominantly expressed in the midgut, fat body and oenocytes, tissues with a key role in metabolism. We hypothesize that INDY reduction in the midgut regulates citrate levels leading to metabolic changes that preserve intestinal stem cell (ISC) homeostasis and slows aging by modifying Insulin/Insulin-like signaling (IIS), which is a key nutrient sensing pathway. Our second goal was to examine the role of JAK/STAT signaling pathway, which activates epithelial renewal in the gut, in response to aging-related stressors. We hypothesize that Indy reduction has effects on the microbiome, preventing bacterial overgrowth and altering community diversity, leading to extended longevity in a JAK/STAT-mediated fashion. Our data suggest that effects of Indy reduction is mediated by reduced IIS and JAK/STAT pathways

SOURCES AND IMPORTANCE OF MITOCHONDRIAL NAD

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Nicotinamide adenine dinucleotide (NAD) levels fall with age or disease, and rise with exercise or caloric restriction. Moreover, the demonstration that supplemental NAD precursors drive beneficial effects in rodent models has driven a resurgence in interest in the basic biology of this molecule. Although NAD is present in the mitochondrial matrix and critical to the function of the organelle, the source of mitochondrial NAD has been debated. We recently used isotopic labeling to demonstrate that direct uptake of intact NAD is one mechanism by which mitochondria are able to obtain this nucleotide. Here, we show that this activity is sufficient to restore respiratory capacity in NAD-deficient isolated

mitochondria, and identify SLC25A51 as a carrier that can mediate the transport of NAD across mitochondrial membranes. Understanding the compartment-specific regulation of NAD will be crucial to understanding how cells and tissues adapt their metabolism to changes in NAD availability. Funding: DK098656 to J.A.B., GM126897 to L.A.C.

ROLE OF REDUCED PROTEIN INTAKE IN METABOLIC AND HEALTHSPAN BENEFITS OF PLANT-BASED DIETS

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Plant-based nutrition consisting of vegetarian/vegan dietary patterns are positively associated with metabolic fitness and inversely associated with risk of cardiovascular disease, diabetes and all-cause mortality. The nutritional and molecular basis of such benefits remains unclear. Here we considered the potential contribution of protein quality (amino acid profiles) and quantity to plant-based nutritional benefits. To this end, we investigated whether individuals adhering to plant-based diets consume a different AA profile, and used isocaloric diets in controlled rodent studies with modulation of both AA composition and total protein amount using crystalline AA vs. naturally-sourced protein ingredients. We found surprisingly few differences between AA profiles of vegans vs. omnivores, but large effects of total protein independent of source in rodent studies, strongly suggesting a major effect of total protein rather than AA composition in health benefits of plant-based diets. Mechanistically, we discuss the role of reduced protein intake on glucose and lipid homeostasis.

LONGITUDINAL FASTING BLOOD GLUCOSE TRENDS AND MORTALITY RISK IN MICE DIFFERS FROM THAT OF NON-HUMAN PRIMATES AND HUMANS

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Longitudinal studies in humans have led to the development of strong predictors of outcomes of health, disease and mortality. Translation from model organisms to human has been faced with species-specific regulation of metabolic function and challenged by the lack of longitudinal studies addressing trajectories of change that can be used, as in humans to predict outcomes. Here we compare longitudinal predictors of health and mortality of three major metabolic indices among mice, non-human primates and humans. Longitudinal fasting blood glucose, body weight and body composition over the lifespan were compared across species, mice, Rhesus monkeys and humans. Survival analysis was conducted to calculate the risk of death for subjects with highest and lowest quartiles of fasting blood glucose. We will present data highlighting species-specific mechanisms of glucose homeostasis over the lifespan and its association with mortality.