It is a time for us to “Honor the Past, Enrich the Future”. Not long ago the study of the biology of aging was exclusively of description of what happened with age—how do organisms, including humans, change with age at the level of proteins, cells, tissues and physiology. The identification of major genetic factors that substantially increase lifespan in model organisms ushered in the advent of a highly exploratory period focusing on the molecular, cellular and genetics mechanisms of aging. The convergence of many different streams of basic and clinical research have brought us to today, where we stand on the cusp of new environmental, molecular genetic and pharmacological breakthroughs in the biology of aging that presage new interventions that promise a healthier lifespan. The presentations in this Presidential Symposium will be from four Early Career Investigators presenting their own pioneering research in some of the most important areas of research in the biology of aging.

MECHANISMS OF LIFESPAN EXTENSION BY SIRT6 IN DROSOPHILA MELANOGASTER

Jackson Taylor, Jason Wood, Matthew Finn, Julianna Liu, Evan Mizerak, Sarah Gordon, Corinne Hutfilz, and Stephen Helfand, Brown University, Providence, Rhode Island, United States

Sirt6 is a multifunctional enzyme that regulates numerous cellular processes connected to longevity. Overexpressing Sirt6 extends lifespan in mice, but the underlying cellular mechanisms are unclear. Here, we used the powerful genetic tools and short lifespan of Drosophila melanogaster to better understand the precise mechanisms by which Sirt6 regulates longevity. Sirt6 OE in flies produces robust extension of median lifespan in both sexes. Molecular and biochemical analyses reveal that Sirt6 OE reduces expression of genes involved in protein synthesis, including many Myc target genes, via epigenetic regulation. We will further discuss our findings on the connection between Sirt6, Myc, and the molecular regulation of protein synthesis and lifespan, as well as additional Sirt6 longevity mechanisms we identified, including autophagy and silencing of transposable elements.

NEW COMPUTATIONAL APPROACHES TO AGING RESEARCH

Morgan E. Levine, Yale University School of Medicine, New Haven, Connecticut, United States

Aging is associated with numerous changes at all levels of biological organization. Harnessing this information to develop measures that accurately and reliably quantify the biological aging process will require systems biology approaches. This talk will illustrate how epigenetic data can be integrated with cellular, physiological, proteomic, and clinical data to model age-related changes that propagate up the levels—finally manifesting as age-related disease or death. I will also describe how network modeling and machine learning approaches (linear and non-linear) can be used to identify causal features in aging from which to generate novel biomarkers. Given the complexity of the biological aging process, modeling of systems dynamics over time will both lead to the development of better biomarkers of aging, and also inform our conceptualization of how alterations at the molecular level propagate up levels of organization to eventually influence morbidity and mortality risk.

EPIGENETICS, HEREDITY, AND AGING

Eric Greer, Boston Children’s Hospital/Harvard Medical School, Boston, Massachusetts, United States

Longevity has long been shown to be regulated by genetic and environmental factors. We recently showed that longevity in the nematode Caenorhabditis elegans can also be regulated by the transmission of epigenetic information. We have shown that several chromatin modifying enzymes have a transgenerational non-Mendelian effect in worms on the longevity of their descendants. I will discuss some of our recent work attempting to decipher how epigenetic modifications can regulate complex phenotypes, including longevity, and how this non-genetic information can be transmitted across generations.

SEX-DIMORPHISM IN AGING GENE REGULATION: ARE WE MISSING HALF OF THE PICTURE?

Bérénice Benayoun, Ryan Lu, Nirmal Sampathkumar, and Min Hoo Kim, University of Southern California, Los Angeles, California, United States

The existence of human supercentenarians reveals a surprising predictor for exceptional longevity: being female. Not only are 33 out of 34 living supercentenarians women, women are also more resistant to most diseases responsible for age-related morbidity in the US. However, because most molecular aging studies generally opt to use only one sex, sex-driven differences in aging remain poorly understood. A key compartment that can actively respond to sex-specific inputs throughout life is the immune system. Indeed, the majority of age-related diseases share common inflammatory mechanisms, a phenomenon described as “inflamm-aging”. Macrophages play an important role in the inflammatory response throughout life, and are considered major mediators of this phenomenon. Thus, to unbiasedly dissect sex differences in immune aging, we generated ‘omics’ data from 4 and 20 months old female and male mice. Intriguingly, we found that transcriptional aging in primary macrophage populations varies strongly between sexes, with up to 20-fold more aging changes in female vs. male cells. Pathways specifically downregulated in females with aging included lysosome, inflammation and phagolysosome. We confirmed experimentally that metabolic preferences of macrophages are indeed directly modulated in this context (e.g. glycolytic preference for male-derived cells). Our results support the notion that there are functional differences in aging trajectories in the immune system of female vs. male mice. Our research could provide new insights into the molecular underpinnings of sex-dimorphism in aging and disease.

SESSION 6505 (SYMPOSIUM)

METABOLISM AND AGING: NEW APPROACHES TO NUTRITION AND DIET IN AGING

Chair: Blanka Rogina

Aging is associated with a functional decline in metabolic, physiological, proliferative, and tissue homeostasis
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
Blanka Rogina,1 Kavitha Kannan,1 Dushyant Mishra,1 Jacob Macro,1 Danielle Lesperance,2 Nichole Broderick,2 Shivani Padhi,2 and Aaron Rosenbloom-Snow,1
1. UCOnn Health, Farmington, Connecticut, United States, 2. University of Connecticut, Storrs, Connecticut, United States

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
Joseph Baur,1 Timothy Luongo,2 Jared Eller,1 Mu-Jie Lu,4 Caroline Perry,2 and Lulu Cambonne,3 1. Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States, 2. University of Pennsylvania, Philadelphia, Pennsylvania, United States, 3. University of Texas at Austin, Austin, Texas, United States, 4. UT Austin, Austin, Texas, United States

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.

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ROLE OF REDUCED PROTEIN INTAKE IN METABOLIC AND HEALTHSPAN BENEFITS OF PLANT-BASED DIETS
James Mitchell,1 Michael MacArthur,2 and Sarah Mitchell,2 1. ETH Zurich, Zurich, Switzerland, 2. Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

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
Rafael de Cabo, Dushani Palliyaguru, Eric Shiroma, John Nam, SLAM Investigators, and Luigi Ferrucci, National Institute on Aging, Bethesda, Maryland, United States

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.