(RAP). However, many older survivors develop chronic critical illness (CCI) with poor long-term outcomes. The etiology of CCI is multifactorial and the relative importance remains unclear. Sepsis is caused by a dysregulated immune response and biomarkers reflecting a persistent inflammation, immunosuppression and catabolism syndrome (PICS) have been observed in CCI after sepsis. Therefore, the purpose of this study was to compare serial PICS biomarkers in a) older (versus young) adults and b) older CCI (versus older RAP) patients to gain insight into underlying pathobiology of CCI in older adults. Methods: Prospective longitudinal study with young (≤ 45 years) and older (≥ 65 years) septic adults who were characterized by a) baseline predisposition, b) hospital outcomes, c) serial SOFA organ dysfunction scores over 14 days, d) Zubrod Performance status at three, six and 12-month follow-up and e) mortality over 12 months. Serial blood samples over 14 days were analyzed for selected biomarkers reflecting PICS. Results: Compared to the young, more older adults developed CCI (20% vs 42%) and had markedly worse serial SOFA scores, performance status and mortality over 12 months. Additionally, older (versus young) and older CCI (versus older RAP) patients had more persistent aberrations in biomarkers reflecting inflammation, immunosuppression, stress metabolism, lack of anabolism and anti-angiogenesis over 14 days after sepsis. Conclusion: Older (versus young) and older CCI (versus older RAP) patient subgroups demonstrate early biomarker evidence of the underlying pathobiology of PICS.

UROLITHIN A ENHANCES MUSCLE PERFORMANCE IN ELDERLY AND POSITIVELY IMPACTS BIOMARKERS LINKED TO CELLULAR HEALTH

Sophia Liu, and David Marcinek, *University of Washington, seattle, Washington, United States*

Background: Aging is associated with decline in mitochondrial function and reduced exercise capacity. Urolithin A (UA) is a natural gut metabolite shown to stimulate mitophagy and improve muscle function in aged animals, and induce mitochondrial gene expression in elderly. Purpose: Investigate if oral administration of UA improved walking distance (6MWT), muscle fatigue resistance in hand (FDI) and leg (TA) muscles, and had an impact on plasma biomarkers. Method: We conducted a randomized, double-blind, placebo-controlled study (NCT03283462) in elderly subjects (65-90 yrs.) supplemented daily with 1000mg UA or placebo for 4 months. 128 subjects were screened and 66 randomized. 6MWT and ATPmax via MRS were assessed at baseline and at 4 months. Muscle fatigue tests and plasma analysis of biomarkers were assessed at baseline, 2 and 4 months. Results: UA significantly improved muscle endurance (i.e., change in number of muscle contractions from baseline) in two different muscles (hand: PL 11.6 ±147.5, UA 95.3 ± 115.5; and leg: PL 5.7± 127.1, UA 41.4 ±65.5) compared with placebo at 2-months. Plasma levels of several acylcarnitines, ceramides and C-reactive-protein were decreased by UA at the end-of study. 6MWT distance (PL 42.5 ± 73.3 m, UA 60.8± 67.2 m) and ATPmax increased in both groups from baseline (PL 13.7±31.4%, UA19.4± 56.8%) with UA supplemented group exhibiting greater improvements, although these were not statistically different between groups. Conclusion: UA supplementation improved muscle endurance, metabolic and inflammatory plasma biomarkers after 2-months, suggesting that UA can have a positive impact on muscle and cellular health in the elderly.

Session 9095 (Poster)

Biology of Aging: Computational and Systems Approaches to Geroscience

ANALYSIS OF DGAT2 MUTATIONS REVEALS POTENTIAL LINKS BETWEEN CANCER AND LIPID DROPLET DEREGULATION

Meghan Graber, and Hayley Barta, *Xavier University, Cincinnati, Ohio, United States*

Diacylglycerol O-acyltransferase 2 is a transmembrane protein encoded by the DGAT2 gene that functions in lipid metabolism, triacylglycerol synthesis, and lipid droplet regulation. Since cancer cells exhibit altered lipid metabolism, it has been proposed that mutations in DGAT2 may contribute to this state. Using data from the Catalogue of Somatic Mutations in Cancer (COSMIC), we analyzed all reported DGAT2 mutations in human cancers. Bioinformatics analyses were performed to highlight the connections between age, pathogenicity, and cancer tissue type. Mutations are generally associated with samples from older individuals, except for those in glioblastomas which occur earlier. We also found that several DGAT2 mutations fall within the catalytic site of the enzyme and may affect enzyme function. Thus, these mutations may contribute to altered cancer metabolism. We identified D222V as a mutation hotspot neighboring a previously discovered Y223H mutation that causes Axonal Charcot-Marie-Tooth disease. Remarkably, Y223H has not been detected in cancers indicating it is inhibitory to cancer progression. Further analysis showed that most mutations do not affect DGAT2 gene expression suggesting this change is not a major contributor to cancer development. Intriguingly, although most cancers are characterized by low DGAT2 gene expression, some show high expression levels, indicating that, at least in certain cases, over-expression is not inhibitory to cellular proliferation. This work uncovers unknown roles of DGAT2 in cancers and suggests that its function may be more complex than previously appreciated.

ASSOCIATION OF GRIMAGE DNA METHYLATION COMPONENTS AND 2-YEAR MORTALITY IN THE HEALTH AND RETIREMENT STUDY

Helen Meier,[1] Colter Mitchell,[2] Eileen Crimmins,[3] Bharat Thyagarajan,[4] and Jessica Faul,[2] *1. University of Michigan, Ann Arbor, Michigan, United States, 2. University of Michigan, University of Michigan, Michigan, United States, 3. University of Southern California, Los Angeles, California, United States, 4. University of Minnesota, Minneapolis, Minnesota, United States*

DNA methylation (DNAm) patterns related to age and aging phenotypes (i.e., epigenetic clocks) are of growing interest as indicators of biological age and risk of negative health outcomes. We investigated associations between the components of GrimAge, an epigenetic clock estimated from DNAm patterns for seven blood protein levels and smoking pack years, and 2-year mortality in the Health and

Retirement Study (HRS) to determine if any of the DNAm subcomponents were driving observed associations. A representative subsample of individuals who participated in the HRS 2016 Venus Blood Study were included in this analysis (N=3430). DNAm was measured with the Infinium Methylation EPIC BeadChip. Deaths that occurred between 2016 and 2018 contributed to 2-year mortality estimates (N=159, 4.5% of the sample). Weighted logistic regression estimated the association first between GrimAge and 2-year mortality and second between the DNAm subcomponents and 2-year mortality. All models were adjusted for age, sex, race/ethnicity, education, current smoking status, smoking pack years and cell composition of the biological sample. The average GrimAge for participants with and without 2-year mortality was 77 years 68 years respectively. A one-year increase in GrimAge was associated with 17% higher odds of 2-year mortality (95% CI: 1.16, 1.17). Two of the seven DNAm blood protein subcomponents of GrimAge (TIMP metallopeptidase inhibitor 1, adrenomedullin) and DNAm smoking pack years were associated with 2-year mortality and DNAm smoking pack years appeared to drive the overall GrimAge association with 2-year mortality. GrimAge was a better predictor of 2-year mortality than the DNAm subcomponents individually.

GLOBAL PHOSPHOPROTEOMIC PROFILING OF SKELETAL MUSCLE IN OVARIAN HORMONE-DEFICIENT FEMALE MICE

Mina Peyton,[1] Tzu-Yi Yang,[1] LeeAnn Higgins,[2]
Todd Markowski,[1] Laurie Parker,[1] and Dawn Lowe,[1]
1. University of Minnesota, Minneapolis, Minnesota, United States, 2. University of Minnesota, University of Minnesota, Minnesota, United States

Dynapenia, the age-related loss of skeletal muscle strength without the loss of muscle mass, significantly impacts the activities and quality of life of the aging population. Studies have shown that dynapenia occurs earlier in females than males in both human and rodent studies. Moreover, in females, estrogen deficiency has been shown to contribute to the loss of skeletal muscle strength as well as blunted recovery of strength after injury. The maintenance of skeletal muscle contractile function is vital to the overall health of women, especially as women live 1/3 of their life in an estrogen deficient state. Reversible protein phosphorylation is an indispensable post-translational modification, playing a key role in signal transduction pathways. Phosphorylation of skeletal muscle proteins have been shown to regulate sarcomeric function, excitation-contraction coupling, energy metabolism, and fiber-type composition. To define the physiological changes in the skeletal muscle phosphoproteome associated with estrogen deficiency, we used an ovariectomy model coupled with mass spectrometry. We identified, in total, 5,424 unique phosphorylation sites and 1,177 phosphoproteins in the tibialis anterior muscle. Ingenuity Pathway Analysis show decreased phosphorylation of contractile proteins and significant predicted inhibition of the upstream kinase, CDK6 (z-score -2.0) in ovariectomized compared to control muscles. Our results suggest that estrogen deficiency remodels the skeletal muscle phosphoproteome which may alter phosphorylation signaling that might contribute to the loss of strength in females.

IN SILICO IDENTIFICATION OF ANTI-AGING PHARMACEUTICS FROM COMMUNITY KNOWLEDGE

Samuel Beck, Jun-Yeong Lee, and Jarod Rollins, *MDI Biological Laboratory, Bar Harbor, Maine, United States*

In this era of Big Data, the volume of biological data is growing exponentially. Systematic profiling and analysis of these data will provide a new insight into biology and human health. Among diverse types of biological data, gene expression data closely mirror both the static phenotypes and the dynamic changes in biological systems. Drug-to-drug or drug-to-disease comparison of gene expression signature allows repurposing/repositioning of existing pharmaceutics to treat additional diseases that, in turn, provides a rapid and cost-effective approach for drug discovery. Thanks to technological advances, gene expression profiling by mRNA-seq became a routine tool to address all aspects of the problem in modern biological research. Here, we present how drug repositioning using published mRNA-seq data can provide unbiased and applicable pharmaco-chemical intervention strategies to human diseases and aging. In specifics, we profiled over a half-million gene expression profiling data generated from various contexts, and using this, we screened conditions that can suppress age-associated gene expression changes. As a result, our analysis identified various previously validated aging intervention strategies as positive hits. Furthermore, our analysis also predicted a novel group of chemicals that has not been studied from an aging context, and this indeed significantly extended the life span in model animals. Taken together, our data demonstrate that our community knowledge-guided in silico drug-discovery pipeline provides a useful and effective tool to identify the novel aging intervention strategy.

INTERPRETABLE MACHINE LEARNING OF HIGH-DIMENSIONAL AGING HEALTH TRAJECTORIES

Spencer Farrell,[1] Arnold Mitnitski,[2] Kenneth Rockwood,[3] and Andrew Rutenberg,[1] *1. Dalhousie University, Halifax, Nova Scotia, Canada, 2. Dalhousie Unversity, Dalhousie University, Nova Scotia, Canada, 3. Dalhousie University, Dalhousie Unversity, Nova Scotia, Canada*

We have built a computational model of individual aging trajectories of health and survival, that contains physical, functional, and biological variables, and is conditioned on demographic, lifestyle, and medical background information. We combine techniques of modern machine learning with an interpretable network approach, where health variables are coupled by an explicit interaction network within a stochastic dynamical system. Our model is scalable to large longitudinal data sets, is predictive of individual high-dimensional health trajectories and survival from baseline health states, and infers an interpretable network of directed interactions between the health variables. The network identifies plausible physiological connections between health variables and clusters of strongly connected heath variables. We use English Longitudinal Study of Aging (ELSA) data to train our model and show that it performs better than traditional linear models for health outcomes and survival. Our model can also be used to generate synthetic individuals that age realistically, to impute missing data, and to simulate future aging outcomes given an arbitrary initial health state.