Public Health, Boston, Maine, United States, 5. Zafgen, Inc., Boston, Massachusetts, United States, 6. ETH Zurich, Zurich, Massachusetts, Switzerland

MetAP2 is a 67kDa protein which sits at the translation initiation complex and cleaves N-terminal methionine off of nascent peptides. Inhibitors of MetAP2 cause profound weight loss secondary to decreased food intake. These inhibitors also significantly extend longevity in mice in late-life intervention. However, the exact mechanism of action causing decreased food intake is not known. Here we investigated the molecular mechanism and target tissue of a MetAP2 inhibitor's (Zgn1062) anorectic effects. First we identified the target tissue by testing targeted Zgn1062 delivery to specific brain regions. Delivery to the medio-basal hypothalamus did not have a significant effect but delivery to the lateral ventricle resulted in significantly decrease food intake and body weight after 2 and 14 hours. When we delivered a neuron-targeted AAV encoding MetAP2 shRNA we saw decreased efficacy of MetAP2 confirming the required for neuronal MetAP2 for anorectic effects. To determine the molecular mechanisms we performed RNAseq of wildtype and MetAP2 KO HT1080 cells across a timecourse of Zgn1062 treatment. The main pathway activated across timepoints in MetAP2-dependent manner was P53 signaling. A main P53 target that was upregulated was the known anorectic peptide GDF15. We confirmed GDF15 increases in vivo at both mRNA (liver and intestines) and protein level (serum) in response to Zgn1062. We also found that Zgn1062 treatment reduces senescent cell burden in visceral adipose tissue in vivo and reduces SASP gene expression in fat explants ex vivo. We hypothesize that Zgn1062's potent P53 activation may play a role in clearance of senescent cells.

METABOLIC REGULATION OF LONGEVITY BY ONE-CARBON METABOLISM AND FLAVIN-CONTAINING MONOOXYGENASE

Christopher Choi,[1] Scott Leiser,[2] Charles Evans,[2] and Daniel Beard,[2] *1. University of Michigan Medical School, Ann Arbor, Michigan, United States, 2. University of Michigan, Ann Arbor, Michigan, United States*

Nematode flavin-containing monooxygenase-2 (fmo-2) is induced by dietary restriction and hypoxia, and is required for the longevity and health benefits of these pathways. It is also sufficient to confer these benefits when overexpressed. As FMOs are well-conserved across taxa, the fmo-2 mechanism has high translational potential. To determine the changes that occur following fmo-2 induction, we performed RNA-seq and untargeted metabolomics analyses. Our data reveal that one-carbon metabolism (OCM) is significantly altered by fmo-2 overexpression. OCM is a nexus for essential metabolic pathways, including transmethylation, transsulfuration, nucleotide synthesis, and amino acid metabolism. We hypothesized that fmo-2 confers longevity benefits by altering key metabolic processes within or downstream of OCM. To test this, we asked whether fmo-2 and OCM interact to regulate longevity by knocking down expression of genes involved with OCM and measuring lifespan and oxidative stress resistance. To understand the biological implications of these interactions, we generated a computational model using qPCR data of key OCM-related genes to predict changes in OCM metabolic flux. Our model predicts significant changes in OCM flux that are regulated by fmo-2 expression levels and are consistent with our RNAi and multi-omics results. We are now testing this model by knocking down genes downstream of OCM to determine their role in fmo-2-mediated benefits. Preliminary results support our hypothesis that changes in metabolic flux through OCM are involved downstream of fmo-2 expression, and may also implicate the UPRER in this pathway. Our future work will elucidate this mechanism and link stress perception and fmo-2-mediated longevity.

NICOTINAMIDE AND SUGAR METABOLISM ASSOCIATED WITH MUSCLE MASS LOSS DURING CALORIE RESTRICTION IN OLDER ADULTS

Ellen Quillen,[1] Jingyun Lee,[2] Cristina Furdui,[1] Daniel Beavers,[1] and Kristen Beavers,[3] *1. Wake Forest School of Medicine, Winston-Salem, North Carolina, United States, 2. Wake Forest Baptist Health, Winston-Salem, North Carolina, United States, 3. Wake Forest University, Winston-Salem, North Carolina, United States*

Weight loss among older adults remains controversial due to lean mass loss and potential exacerbation of disability risk. Using the Medifast for Seniors clinical trial (NCT02730988), which investigated high protein supplementation (≥1.0 g/kg/d) during caloric restriction to preserve lean mass among 96 older adults (>70 years, 74% women, 27% black) with obesity (BMI: 35 kg/m^2), we applied untargeted metabolomics to identify small molecules associated with the highly variable change in lean muscle mass during weight loss. Forty-seven participants were randomized to high protein weight loss, and 92% lost at least 5% body weight over 24 weeks. Across DXA-ascertained measures of lean body mass, gynoid lean mass exhibited the broadest range of change: +4% to -12%. For 38 participants, untargeted metabolomics data was generated from fasted serum samples collected before and after intervention. 121 serum metabolites were identified and change from baseline was tested for correlation with percent change in gynoid muscle mass. Increasing nicotinamide levels were associated with a greater loss of gynoid muscle mass (R^2=0.22, p=0.0027). Pathway analysis was applied to identify Kyoto Encyclopedia of Genes and Genomes (KEGG) biochemical pathways containing multiple nominally-associated metabolites. The amino sugar and nucleotide sugar metabolism pathway was significantly enriched (p=0.006), containing four sugar metabolites associated with shifts in lean muscle mass. This pathway is important in the glycosylation of polysaccharides, a ubiquitous and important regulator of energy metabolism, but has not previously been linked to muscle mass and should be further interrogated in preservation of lean muscle during weight loss.

POOR MITOCHONDRIAL HEALTH AND SYSTEMIC INFLAMMATION? TESTING OF A CLASSICAL HYPOTHESIS

Marta Zampino, Luigi Ferrucci, Richard Spencer, Kenneth Fishbein, Eleanor Simonsick, and Pei-Lun Kuo, *National Institute on Aging, Bethesda, Maryland, United States*

Chronic low-grade inflammation often occurs with aging and has been associated with negative health outcomes. Despite extensive research on the origins of "inflammaging",

the causative mechanisms remain unclear. However, a connection between poor mitochondrial health and chronic inflammation has been hypothesized, with decreasing mitochondrial function occurring with age and precipitating an increase in reactive oxygen species and other pro-inflammatory macromolecules such as mitochondrial DNA. We tested this hypothesis on a population of 619 subjects from the Baltimore Longitudinal Study of Aging, measuring muscle mitochondrial oxidative capacity in vivo by phosphorus magnetic resonance spectroscopy (P-MRS), and plasma interleukin (IL)-6, the most widely used biomarker of inflammaging. The P-MRS-derived post-exercise phosphocreatine recovery time constant tau-PCr, a measure of oxidative capacity, was expressed as a categorical variable through assignment to quintiles. Participants in the first quintile of tau-PCr (best mitochondrial function) were taken as reference and compared to the others using linear regression analysis adjusted for sex, age, lean and fat body mass, and physical activity. Those participants with the lowest oxidative capacity had significantly higher log(IL-6) levels as compared to the reference group. However, data from the other quintiles was not significantly different from the reference values. In conclusion, severe impairment of oxidative capacity is associated with increased inflammation. This study design does not provide conclusive evidence of whether increased inflammation and impaired bioenergetic recovery are both caused by underlying poor health status, or whether mitochondrial deficits lead directly to the observed inflammation; we anticipate addressing this important question with longitudinal studies.

ROLE OF INTRAMUSCULAR FAT AND LEAN MUSCLE IN SURFACE ELECTROMYOGRAPHY AMPLITUDE OF THE GLUTEUS MEDIUS IN OLDER ADULTS

Marcel Lanza,[1] Vicki Gray,[2] Alice Ryan,[3] Will Perez,[3] and Odessa Addison,[2] *1. University of Maryland, Baltimore, Baltimore, Maryland, United States, 2. University of Maryland School of Medicine, Baltimore, Maryland, United States, 3. Baltimore VA Medical Center, Baltimore, Maryland, United States*

Surface electromyography (sEMG) is frequently used to assess muscle activation in older individuals. Subcutaneous fat is one well-known factor that influences sEMG amplitude. The amount of intramuscular fat (IMAT) may negatively impact the muscles ability to produce force with aging, while high density lean tissue (HDL; fat free muscle) has an opposite effect. However, influence of IMAT or HDL on sEMG amplitude remains unclear. Thus, the aim was to investigate the influence of IMAT and HDL on sEMG amplitude of the gluteus medius (GM) muscle during a maximal voluntary isometric contraction (MVIC) in older adults. Twelve older adults (7 females; age: 71±3 y; BMI= 29±4 Kg/m2; X ± SD) underwent a CT scan to determine IMAT and HDL cross-sectional area in the GM. IMAT and HDL were normalized as a percentage of the total muscle area. Maximal hip abduction MVIC was measured at 30□ hip abduction in standing, while sEMG was recorded from the GM muscle. Spearman correlations showed a positive association between GM HDL and sEMG amplitude (r = 0.692, P = 0.013) and negative between GM IMAT and sEMG amplitude (r = -0.683, P = 0.014). This is the first study to demonstrate the amount of IMAT may limit the ability to activate the hip abductor muscle. Given that muscle activation is a determinant of strength, interventions to lower levels of IMAT and increase levels of lean muscle may be important to slowing decreases in strength with aging.

SERUM FACTORS MEDIATE THE BIOENERGETIC BENEFITS OF EXERCISE TRAINING AND CALORIC RESTRICTION

Jenny Gonzalez-Armenta,[1] Barbara Nicklas,[2] and Anthony Molina,[3] *1. Wake Forest School of Medicine, Winston-Salem, North Carolina, United States, 2. Wake Forest University, Winston-Salem, North Carolina, United States, 3. University of California San Diego, La Jolla, California, United States*

Diet and exercise interventions have been shown to improve age-related decline in mitochondrial function. While the systemic benefits of diet and exercise are apparent, the mechanisms underlying these changes are not known. Our lab and others have used blood-based bioenergetic profiling to demonstrate that systemic bioenergetic capacity is related to many aspects of healthy aging, including: gait speed, grip strength, and inflammation. This work suggests a potential role for circulating factors in mediating systemic mitochondrial function. In this study, we developed a high-throughput respirometry assay to examine the effects of circulating factors on mitochondrial function of myoblasts in vitro. We used serum from older, overweight and obese adults who participated in a clinical trial comparing resistance training (RT) and resistance training plus caloric restriction (RT+CR). When combined, both interventions significantly increased serum-mediated basal (42.08 to 50.14 pmol/min, p=0.004), ATP-linked (35.57 to 42.37 pmol/min, p=0.006), and maximal respiration (132.30 to 150.00 pmol/min, p=0.02). With RT, we found significantly increased basal (40.80 to 53.85 pmol/min, p=0.01) and ATP-linked respiration (34.36 to 46.39 pmol/min, p=0.007) and trends for increased maximal respiration (130.09 to 153.24 pmol/min, p=0.10) and spare respiratory capacity (89.30 to 101.38 pmol/min, p=0.07). With RT+CR, there were trends for increased maximal respiration (134.32 to 147.06 pmol/min, p=0.10) and spare respiratory capacity (91.06 to 100.41 pmol/min, p=0.11). Additionally, we found that post-intervention serum-mediated basal and ATP-linked respiration were significantly and positively correlated with physical ability, as reported by SPPB score. Future studies will focus on identifying circulating factors responsible for these changes.

SEX-DEPENDENT EFFECTS OF QUADRICEPS FAT CONTENT ON SINGLE MUSCLE FIBER SIZE IN OLDER ADULTS

Chad Straight,[1] Joseph Gordon III,[1] Aurora Foster,[1] Nicholas Remillard,[1] Bruce Damon,[2] Stuart Chipkin,[3] Jane Kent,[1] and Mark Miller,[1] *1. University of Massachusetts Amherst, Amherst, Massachusetts, United States, 2. Vanderbilt University, Nashville, Tennessee, United States, 3. University of Massachusetts Amherst, Amherst, United States*

Evidence suggests that ectopic fat deposition interferes with skeletal muscle structure and function, but few studies have examined underlying morphological and contractile