

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 inflammation. The P-MRS-derived post-exercise phosphocreatine recovery time constant τ -PCr, a measure of oxidative capacity, was expressed as a categorical variable through assignment to quintiles. Participants in the first quintile of τ -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 $\log(\text{IL-6})$ 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

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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; $X \pm \text{SD}$) 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

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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

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

properties at the single fiber level. Healthy older (65-75 y) men (n=9) and women (n=9) underwent dynamometry for assessment of knee extensor maximal torque, water-fat magnetic resonance imaging to quantify quadriceps muscle cross-sectional area (CSA) and fat fraction (FF), and vastus lateralis biopsies to determine morphology and function of type I and II muscle fibers. Despite similar body mass indices (24.4 ± 1.3 vs. 24.6 ± 0.5 kg·m², $p=0.93$) and daily moderate-to-vigorous physical activity (46 ± 7 vs. 41 ± 9 min·d⁻¹, $p=0.67$), women had greater FF (9.0 ± 0.3 [range: 7.6-10.6] vs. 7.9 ± 0.4 [6.0-9.7] %, $p=0.04$) than men, indicating increased adipose tissue deposition in skeletal muscle. Women also had smaller quadriceps CSA (39.8 ± 1.8 vs. 57.9 ± 1.3 cm², $p=0.01$), specific torque (1.5 ± 0.1 vs. 1.9 ± 0.1 Nm·cm⁻², $p=0.01$) and type II fiber CSA ($3,943 \pm 312$ [2,350-5,140] vs. $5,352 \pm 384$ [3,560-6,590] μm^2 , $p=0.01$) than men. Type I CSA did not differ by sex ($4,918 \pm 228$ [3,740-5,600] vs. $5,630 \pm 440$ [3,640-7,670] μm^2 , $p=0.19$). In older women, FF was inversely associated with single fiber CSA in type I ($r = -0.81$, $p=0.02$) and II ($r = -0.76$, $p=0.03$) fibers, and tended to be associated with slower myosin-actin cross-bridge kinetics (longer myosin attachment time) in type I fibers ($r=0.65$, $p=0.08$). These relationships were not observed in men. Overall, healthy older women have greater intramuscular fat than men, which may contribute to sex-specific effects on knee extensor specific torque through differences in muscle fiber size and cross-bridge kinetics.

TIME-RESTRICTED FEEDING AND CALORIC RESTRICTION IMPACT ON SPONTANEOUS NEOPLASMS IN FEMALE MICE

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In older humans, multiple chronic diseases and increased life expectancy impose a disproportionate socioeconomic burden. Dietary interventions are valuable strategies for promoting healthy aging. Caloric restriction (CR) without malnutrition is a robust intervention able to delay disease onset and increase survival in model organisms. However, the impracticability of chronic CR outweighs the potential long-term benefits in humans. Time-restricted feeding (TRF), i.e. the limitation in the timing of food intake without necessarily reducing caloric intake, can protect against metabolic disorders through the synchronization of the circadian rhythm. This study compares whether limiting access to ad libitum (AL) food for a few hours per day mimics the beneficial effects of a CR diet. A large cohort of C57BL/6J female mice (n=250) was distributed into five feeding paradigms at midlife: AL, TRF for 8 hours, TRF for 4 hours, 20% CR and 20% CR fed twice a day (CRx2). Pathological analyses at death reveal a shift in fatal neoplasms toward an older age in TRF8 mice. AL mice had the highest prevalence of tumors (93%) and TRF4 had the lowest (77%). The highest tumor burden was observed in AL mice while CRx2 animals had the lowest number of neoplasms. Histiocytic sarcoma and lymphoma were the most represented malignancies, with CR mice exhibiting the highest rate of histiocytic sarcoma (75%) and the lowest rate of lymphoma (10%). These results indicate that time- and calorie-restricted feeding regimens can slow down malignant neoplasm progression and extend health span in female mice, even when started in adulthood.

UNCOVERING THE SPECIFIC FUNCTIONS OF MIR-33 IN REGULATION OF FEEDING AND CARDIOMETABOLIC DISEASES LINKED TO AGING.

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Heart disease and metabolic dysfunction are two of the most important age related health issues, and feeding behavior is a critical factor contributing to these conditions. miR-33 promotes the development of atherosclerosis, by impairing macrophage cholesterol efflux and reverse cholesterol transport. Specific disruption of the interaction between miR-33 and the cholesterol transporter ABCA1 protected mice from atherosclerosis in a manner similar to that observed with loss or inhibition of miR-33. However, miR-33 has also been shown to impact other cellular functions, including targeting numerous mRNAs related to bioenergetics and inflammatory response, that may also contribute to its effects on atherosclerosis. Moreover, characterization of miR-33 deficient animals has revealed a strong predisposition to the development of obesity and metabolic dysfunction. While this phenotype appears to be due to alterations in feeding behavior, it is not clear what organ or organs are primarily driving this effect or what functions of miR-33 may be responsible. To address these questions, we have generated conditional miR-33 knockout mice to selectively remove miR-33 from a number of key metabolic tissues. Using these unique mouse models, we have performed an extensive characterization of how miR-33 impacts the function of different metabolic tissues in both chow and high fat diet fed mice, and assessed what impact this has on regulation of metabolic homeostasis and atherosclerosis. This work will improve our understanding of the mechanisms regulating feeding behavior and provide critical information for the development and evaluation of novel approaches to combat cardiometabolic diseases associated with aging.

SESSION 2877 (POSTER)

SENESCENCE, EPIGENETICS, AND METFORMIN

A GENOME-WIDE INTEGRATIVE STUDY OF DNA METHYLATION, GENE EXPRESSION, AND LATER LIFE HAND GRIP STRENGTH

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Hand grip strength (HS) measures muscular strength and associates with multiple health outcomes and mortality. Studies of epigenetic and transcriptomic markers could help elucidate the biology behind HS; markers for which monozygotic (MZ) twins are excellent study populations. We performed integrated enrichment analyses (IEA) of an epigenome-wide association analysis (EWAS) and a transcriptome-wide association analysis (TWAS) of HS