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±312 [2,350-5,140] vs. 5,352±384 [3,560-6,590] µm2, p=0.01) than men. Type I CSA did not differ by sex (4,918±228 [3,740-5,600] vs. 5,630±440 [3,640-7,670] µm2, 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