While caloric restriction (CR) provides highly robust improvements to longevity and health, dietary restriction of the essential amino acid methionine can provide similar benefits including improved metabolic function and increased longevity. Despite these similarities between CR and methionine restriction (MR), there is growing evidence to suggest they may be mediated by different mechanisms that require further elucidation. The sulfur side-chain of methionine is highly prone to oxidation, even in vivo, with redox changes of these residues potentially altering protein function and interfering with its use as a substrate. An entire family of enzymes, methionine sulfoxide reductases, have evolved in aerobic organisms to regulate the redox status of methionine. We tested the role of methionine sulfoxide reductase A (MsrA) in the physiological and metabolic benefits of MR. After three months of MR, mice lacking MsrA (MsrA KO) showed significant loss of weight, including both fat and lean mass, in comparison to wild-type mice under MR. Both MsrA KO and wild-type mice responded to MR with improvements to both glucose and insulin tolerance. However, MR MsrA KO mice showed lower HbA1c and reduced leptin compared to MR wild-type mice. Overall, our results show mice lacking MsrA have a stronger response to MR suggesting that methionine redox may play an important role in some of the mechanisms responsible for these metabolic outcomes. Further studies clarify whether MsrA could also be a potential regulator of the longevity benefits of MR.

AGE-RELATED PRESERVATION OF MOTOR NERVE CONDUCTION VELOCITY IN NEURONAL MTORC1 KNOCKDOWN MICE

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With age, peripheral nerves undergo demyelination along with overall decrease in peripheral nerve conduction velocity in both sensory and motor nerves. Loss of innervation in muscles is thought to be a major factor in causing age-related sarcopenia including a decrease in muscle function. Dietary restriction attenuates the detrimental effects of aging in mice. Reduction of mTOR signaling is hypothesized to have overlapping mechanisms with dietary restriction. Furthermore, inhibition of mTOR via rapamycin treatment is known to extend lifespan in mice as well as improve peripheral nerve myelination. Therefore, I hypothesized that reducing mTORC1 signaling in neurons would be able to ameliorate the deleterious effects of aging in peripheral nerves. An overall decrease in nerve conduction velocity was observed in both tail sensory and sural nerves with age (15 vs. 30 months). In neuronal mTORC1 KD animals, there was an age-related preservation of both sural and sciatic nerve conduction. Rapamycin treatment produced similar effects with a trend towards increased sciatic nerve conduction velocity in rapamycin-treated wild-type mice at 19 months. The preserve sciatic nerve conduction velocity could be partially explained by preserved myelination. Neuronal mTORC1 knockdown animals had more myelin in the sciatic nerve at 30 mo. as compared to age-matched controls. Overall, these data indicate that mTORC1 signaling plays a role in the age-related decline in peripheral nerve myelination as well as nerve conduction velocity. Future therapeutics could utilize rapamycin or other rapalogs to combat the decline in peripheral nerve function associated with age and other diseases as well.

SKEWED MACROPHAGE POLARIZATION IN AGING SKELETAL MUSCLE

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Skeletal muscle aging is a major cause of disability and frailty in the elderly. The progressive impairment of skeletal muscle with aging was recently linked to a disequilibrium between damage and repair. Macrophages participate in muscle tissue repair first as pro-inflammatory M1 subtype and then as anti-inflammatory M2 subtype. However, information on the presence of macrophages in skeletal muscle is still sporadic and the effect of aging on macrophage phenotype remains unknown. In this study, we sought to characterize the polarization status of macrophages in human skeletal muscle at different ages. We found that most macrophages in human skeletal muscle are M2, and that this number increased with advancing age. On the contrary, M1 macrophages declined with aging, making the total number of macrophages invariant with older age. Notably, M2 macrophages co-localized with increasing intermuscular adipose tissue (IMAT) in aging skeletal muscle. Old BALB/c mice showed increased IMAT and regenerating myofibers in skeletal muscle, accompanied by elevated expression of adipocyte markers and M2 cytokines. Collectively, we report that polarization of macrophages to the major M2 subtype is associated with IMAT, and propose that increased M2 in aged skeletal muscle may reflect active repair of aging-associated muscle damage.

AGE-ASSOCIATED INCREASE IN KYNURENINE SUPPRESSES AUTOPHAGY AND PROMOTES APOPTOSIS IN MESENCHYMAL STEM CELLS

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The age-related increase of the tryptophan metabolite, kynurenine (KYN), has been associated with osteoporosis progression. Increased activity of by Indoleamine-(2,3)-dioxygenase(IDO), are responsible for the elevation of KYN levels in bone tissue. IDO activity is elevated with age and could be a promising therapeutic target forosteopenia and osteoporosis. Previously, our group has shown that the serum level of KYN is elevated with age and correlates with bone loss in vivo. Kynurenine suppress the expression and activity of chemokine CXCL12 essential for osteogenesis, bone marrow stem cells homing. Bone Marrow Stem Cells (BMSC) cultured in 1% FBS were treated with CXCL12

(100ng/ml) in the presence of saline control or the autophagic flux-inhibition agent chloroquine (CQ). CXCL12 treatment increased autophagy by upregulating the degree of LC3B-II by 20%. CXCL12 treatment also significantly increased co-localization of LC3B and LAMP-2 in serum starved cells. In the present study, we tested the theory that kynurenine plays an opposite role to CXCL12 by suppressing the autophagy cell survival pathway and by inducing apoptosis. Treatment of nutrient-deprived murine BMSCs with 10 or 100 μM of KYN suppresses autophagy in a dose dependent fashion while increasing cellular apoptosis. Treatment of BMSCs with KYN downregulated autophagic flux in BMSC preventing CQ-induced CL3B/LAMP-2 colocalization. KYN treatment prevented conversion of LC3B-I to LC3B-II in CQ-treated cells by 30 percent. At the same time, KYN treatment induces apoptosis, by increasing TUNEL-positive cells number by more than 50 percent. Additionally, KYN treatment significantly increased the levels of cleaved isoforms of PARP and caspase-3.

AGED MICE ARE SUSCEPTIBLE TO CARDIAC HYPERTROPHY AFTER 1 WEEK OF CONSUMING A HIGH SUGAR DIET

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Over 80% of American adults exceed their daily recommended intake of sugar (<10% kcal). While habitual sugar consumption is associated with an increased risk for diabetes and cardiovascular disease, less is known about the effects of short-term sugar consumption on metabolic health, particularly in the elderly. The purpose of this study was to test whether aged hearts are more susceptible to pathology following a short-term high sucrose (HS) diet. Specific goals were to: A) determine the effects of a 1-week HS diet exposure on the hearts of 5 month-old and 24 month-old mice; and B) test if the mitochondrial targeted peptide SS-31 can protect against HS-diet induced effects. Male CB6F1 mice were placed either on standard chow or HS diet after 1 week of receiving saline (control) or SS-31 through osmotic pumps. Heart function was assessed in vivo through echocardiography before and after treatments. One week of HS induced significant cardiac hypertrophy in the old mice compared to age-matched chow controls. Treatment with SS-31 prevented this HS induced hypertrophy. Young hearts were smaller than in the old, but size was unaffected by diet or SS-31. We observed no effect of HS (with or without SS-31) on respiration or H2O2 production in isolated mitochondria from hearts using high-resolution respirometry. These data indicate that only 1-week exposure to HS diet is enough to exacerbate cardiac hypertrophy in aging mice, but factors other than heart mitochondrial ROS may mediate this effect.

INTERVENTION WITH RAPAMYCIN TO IMPROVE HEALTHY AGING AND LONGEVITY IN A NON-HUMAN PRIMATE

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Interventions to extend lifespan and improve health with increasing age will have significant impact on a growing aged population. Several pharmaceutical interventions extend lifespan in laboratory rodent models with rapamycin, an inhibitor of mechanistic target of rapamycin (mTOR) being the most well studied. Bridging towards translation, we have an ongoing long-term study testing whether rapamycin treatment can extend lifespan and delay the progression of age-related disease in a short-lived non-human primate species, the common marmoset (Callithrix jacchus). We show that daily oral dosing of slow-releasing, encapsulated rapamycin will result in clinically effective concentrations of rapamycin in the blood and inhibit mTOR signaling. This treatment is well tolerated and does not dramatically promote known side effects of this drug, including altering clinical hematology, immune cell subsets, or promoting metabolic dysfunction including glucose intolerance in comparison to control aging marmosets. Unlike previous reports in rodents, rapamycin does not have clear effects on aging cardiovascular function in marmosets. However, in our oldest cohorts daily rapamycin treatment tends to prevent age-associated changes in body mass and composition and prevent decline in kidney function. Now more than three years after beginning treatment, we are now starting to assess the effects of rapamycin on marmoset longevity. When complete, this study will describe for the first time the potential for pharmaceutical intervention to extend longevity of a primate species with the ultimate goal of significant translational impact to human aging.

SESSION 840 (POSTER)

CAREGIVING

A HEALTHY LIFE FOR AFRICAN AMERICAN WOMEN CARING FOR OLDER ADULTS: A CONCEPT MAPPING STUDY

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Achieving optimal health and well-being among African American older adults with chronic conditions requires addressing the needs of their caregivers. This study aimed to elucidate how African American females caring for older adults view health and the factors that influence health. We identified African American women ages 24 to 64 caring for an adult 60 years or older for group concept mapping (GCM), a mixed-methods approach. Participants (N=25) first completed idea generation by providing unlimited short, free-text responses to the focus prompt, "A healthy life for a caregiver includes: ___." The 512 identified factors were reduced to 99 unique ideas. Participants then sorted the 99 ideas into clusters based on conceptual similarity and rated each idea on desirability and familiarity. Ratings were recorded on a 5-point Likert scale, ranging from very undesirable to extremely desirable and not at all familiar to extremely familiar. Data were analyzed and mapped via CS Global Max software. A cluster map with 12 outcome domains best fits the data. Identified clusters included: (1) Spirituality, (2) Maintaining relationships, (3) Good character, (4) Action to cope, (5) Preserving self, (6) Support, (7) Personal empowerment, (8) Resources, (9) Release (10) Striving for peace, (11) Wellness, (12) Self-care. Seven of the 99 ideas (representing 5 of 12 domains)