events, including whole chromosome events, were detected in 180 out of the 338 individuals. A total of 165 duplications, 97 deletions, and 9 copy-number neutral loss of heterozygosity were detected. Additionally, there were 42 events whose copy number state could not be determined with high confidence. 236 events out of the 313 were detected in individuals aged 100 and older. Our analysis of chromosomal alteration frequency by age indicates that, within centenarians, the proportion of individuals with mCAs significantly decreases with increased age ($p < 0.05$, correlation -0.73).

INCREASED BETA2-ADRENERGIC RECEPTOR SIGNALING ENHANCES PROGRESSION OF HEPATOCELLULAR CARCINOMA

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We investigated whether increased signaling by beta2-adrenergic receptors (β2-ARs), which mediate the action of catecholamines, enhances the progression of hepatocellular carcinoma (HCC). Mean age of patients with HCC, the most prolific form of liver cancer, has progressively increased over the last decade. Beta2-AR-mediated signaling in liver increases with age. We also observed increased β2-AR levels in liver tissues of patients with HCC compared to control subjects. We, therefore, hypothesized that increased β2-AR signaling enhances HCC progression while inhibition of β2-AR signaling by treatment with beta blockers suppresses its progression. To test this hypothesis, we used N-nitrosodiethylamine (DEN) to induce HCC in liver-specific β2-AR knockout (LKO) and control mice in the absence or presence of beta blocker propranolol. At the end of 25 weeks, we observed increased numbers of visible tumors, disarray of liver architecture, and mortality in DEN-induced control mice which was reduced by propranolol treatment. We also observed that DEN-treated LKO mice demonstrated reduced mortality, disarray of architecture, and phosphorylation of oncogene Src compared to DEN-treated control mice. Taken together, these results indicate that decreased β2-AR signaling because of a lack of receptors in the liver or inhibition of receptor action with propranolol reduces HCC progression. Studies are in progress to determine the β2-AR-mediated mechanisms involved in HCC progression. Our studies suggest that beta blocker propranolol, used to treat cardiovascular diseases, may be repurposed as a potential therapeutic option for treatment of HCC.

LEFT VENTRICULAR REMODELING PROCEEDS FROM YOUNG ADULTHOOD INTO MIDLIFE IN INTRAUTERINE GROWTH RESTRICTION BABOONS

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Previous cross-sectional studies have shown young adult baboons (~5-6 y.o.), subjected to intrauterine growth restriction (IUGR) by maternal calorie restriction during pregnancy and lactation, exhibit ventricular remodeling with mildly impaired heart function relative to age/sex-matched controls (CTL). METHODS: In this longitudinal study cardiac MRI was performed on male IUGR baboons (n=7). A 3 Tesla, Siemens TIM Trio MRI system was used with phase-array coils with parallel imaging acquisition and breath-holding during the scan. Studies of IUGR animals occurred at 4.7 + 0.1 yr. intervals; the first scan (scan1) at 5.8 + 1.2 y (human equivalent - HE ~24 years) and the second (scan2) at 10.4 + 1.2 yr (HE~40 y). Scans on the CTL animals (N=4) occurred at 5.3 + 1.4 years and 10 + 1.4 years. RESULTS: Change in body weight over 4.7 years was less in the IUGR group (Δwt=6.3 + 6.1 kg) than in the control group (Δwt =11.5 + 8.2 kg). Left ventricular (LV) ejection fraction (EF) was significantly greater in IUGR animals for scan2 (+10.7%, p=0.03) but not in normal controls (+1.8%, p=0.75). Stroke volume and end-diastolic LV volume were normalized to body surface area (BSA). SV/BSA (17.6 + 4.9, 31.5 + 12.3 mL/sq.m; p=0.016) and EDV/BSA (47.3 + 13.6, 64.5 + 18.8 mL/sq.m; p=0.045) were also significantly increased in IUGR animals but not controls. In IUGR subjects, Δweight was significantly and positively correlated with ΔEF (r=0.86, p=0.01). CONCLUSIONS: In IUGR, but not in CTL baboons, cardiac function adaptations continue into midlife and are related to increases in body weight with aging. We conclude that IUGR programs cardiovascular function and that programmed changes continue into midlife.

AGING INDUCES NLRP3 INFLAMMASOME DEPENDENT ADIPOSE B CELL EXPANSION TO IMPAIR METABOLIC HOMEOSTASIS

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Visceral adiposity in elderly is associated with alterations in adipose tissue immune cells leading to inflammation and metabolic dysfunction. The Nlrp3 inflammasome is a critical regulator of macrophage activation, inflammation, and immunometabolism in visceral adipose tissue during aging; however, the potential contribution of adipose tissue B cells is unexplored. Here, we show that aging expands adipose-resident B cells and fat-associated lymphoid clusters (FALCs) in visceral white adipose tissue of female mice. Adipose tissue B cells exhibit a memory-like B cell profile similar to the phenotype of aged B cells that are increased in spleen of old mice. Mechanistically, the age-induced FALC formation and adipose B cell expansion, but not B cell transcriptional program, is dependent on the Nlrp3 inflammasome. Furthermore, B cell depletion in aged mice improves insulin sensitivity and metabolic capacity of adipose tissue. These data reveal that inhibiting Nlrp3-dependent B cell accumulation can be targeted to reverse metabolic impairment in aging adipose tissue.

METABOLIC CONSEQUENCES OF METHIONINE REDOX IN METHIONINE RESTRICTION

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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