compared with a non-WD (healthy diet), accelerates declines in physical function over the adult lifespan, and whether regular voluntary exercise attenuates age- and WD-associated declines in function. To determine this, we studied 4 cohorts of male C57BL/6 mice that consumed either normal chow [NC] or WD with or without access to voluntary running [VR] wheels beginning at 3 mo of age and assessed strength (grip strength normalized to body mass) and endurance (rota-rod distance) every 3 mo throughout life. WD decreased average lifespan by 30% (WD: 18.6±0.5 vs. NC: 26.7±0.8 mo); therefore, function was compared from 3-18 mo of age in all groups. Age-related declines (% change over 3-18 mo) in physical function were accelerated by WD (strength: WD -61.2±10.1%, NC -43.2±10.2%; endurance: WD -97.4±5.1%, NC -65.1±6.3%; all $p<0.05$ WD vs. NC). VR attenuated declines in physical function within the same diet group (strength: WDVR -34.7±5.1%, NCVR -18.6±5.2%; endurance: WDVR -48.5±5.2%, NCVR -41.4±4.7%; all $p<0.05$ versus same diet non-VR group). These unique data obtained from a lifelong study of aging in mice, indicate that: 1) consuming a WD reduces lifespan and accelerates age-related declines in physical function by 40-50% vs. a non-WD; regular voluntary exercise (wheel running) prevents this effect of WD on physical function; and 2) regular voluntary exercise also attenuates the age-associated decline in physical function by ~60-130% when consuming a healthy diet.

METABOLIC FLEXIBILITY IN CLASSICAL MONOCYTES IS NOT AFFECTED BY AGE

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Inflammaging is the chronic low-grade inflammation that occurs with age that contributes to the pathology of age-related diseases. Monocytes are innate immune cells that become dysregulated with age and which can contribute to inflammaging. Metabolism plays a key role in determining immune cell functions, with anti-inflammatory cells primarily relying on fatty acid oxidation and pro-inflammatory cells primarily relying on glycolysis. It was recently shown that lipopolysaccharide (LPS)-stimulated monocytes can compensate for a lack of glucose by utilizing fatty acid oxidation. Given that mitochondrial function decreases with age, we hypothesized that monocytes taken from aged individuals would have an impaired ability to upregulate oxidative metabolism and would have impaired effector functions. Aging did not impair LPS-induced oxygen consumption rate during glucose starvation as measured on a Seahorse XFp system. Additionally, aged monocytes maintained inflammatory gene expression responses and phagocytic capacity during LPS stimulation in the absence of glucose. In conclusion, aged monocytes maintain effector and metabolic functions during glucose starvation, at least in an ex vivo context.

EFFECT OF TLR4 INHIBITION IN FAT-INDUCED INSULIN RESISTANCE IN HUMAN SUBJECTS

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Older and obese subjects have increased levels of free fatty acids (FFA) in plasma that may mediate the inflammation and insulin resistance seen in these individuals. Data generated mostly in cells and rodents suggest that toll like receptor 4 (TLR4) mediates the inflammatory and insulin resistant states induced by FFA. In the present study, we tested the hypothesis that pharmacologic blockade of TLR4 would prevent lipid-induced insulin resistance. We recruited 10 lean, healthy subjects (Age: 51 ± 1 y, Sex: 6M/4F, BMI: 23.8 ± 0.7 kg/m2, Fasting plasma glucose (FPG): 5.5 ± 0.1 mmol/l). They were randomized to receive the following 72 h long i.v. treatments on separate occasions: saline (30 ml/h)+placebo (12 mg every 12 h); Intralipid (30 ml/h)+placebo; Intralipid (30 ml/h)+eritoran (12 mg every 12 h). After these infusions, insulin sensitivity was measured with an hyperinsulinemic clamp. Infusion of Intralipid significantly decreased insulin sensitivity (M value) by 14%. FPG and fasting plasma insulin concentrations increased with Intralipid infusion by 7% and 22%, respectively. Intralipid also caused a low-grade inflammatory state, evidenced by increases in plasma levels of TNFa (32%), lipopolysaccharide (14%), LPS binding protein (21%), and blood monocytes counts (15%). However, metabolic and inflammatory outcomes were not different between the Intralipid+placebo and the Intralipid+eritoran groups. We conclude that short-term TLR4 inhibition with eritoran fails to prevent lipid-induced inflammation and insulin resistance. Studies with longer acting TLR4 inhibitors may be needed to clarify the role of TLR4 on the pro-inflammatory and insulin resistant states seen with aging and obesity.

CLONAL HEMATOPOIESIS IN A CENTENARIAN COHORT

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Mosaicism, the presence of two or more genotypically or karyotypically distinct populations of cells in a single individual, plays an important role in human disease. Mosaicism can result in mutations and/or chromosomal alterations such as loss, gain, or copy-number neutral loss of heterozygosity. Clonal mosaicism and its relationship to aging and cancer, has been previously studied, and earlier work suggests that clonal mosaicism tends to increase with age. The aim of our research is to use genotype data of centenarians to explore the relationship between extreme longevity and mosaic chromosomal alterations (mCAs). To this end, we analyzed genome-wide genotypes from blood-derived DNA of 338 individuals from the New England Centenarian Study. The participants in this dataset ranged from 45 to 112 years of age. For the detection of mCA events, we used MoChA (https://github.com/freeseek/mocha), a bcftools extension, that predicts mCAs based on B-allele frequency (BAF) and log2 intensity(R) ratio (LRR), and uses long-range phase information to increase sensitivity. Chromosomal alteration

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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