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