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Immuno-hematologic function (IHF) is increasingly being recognized as a central component of health status in older age. In this study, we sought to identify homogeneous IHF profiles regarding their relationship to all-cause mortality. We then studied the distribution of these profiles among individuals over age 65. We used data on 30,828 NHANES participants, including 10 baseline complete blood count with differential components [e.g., lymphocytes, leukocytes, red cell distribution width (RDW)] and all-cause mortality. We used latent profile analysis (LPA) to simultaneously optimize intra-cluster homogeneity on CBC components and inter-cluster survival differences. LPA (using MPlus 8.2) allowed for the empirical comparison of different solutions based on goodness-of-fit criteria. After LPA model convergence, a 9-class solution balanced goodness-of-fit criteria and interpretability of the resulting classes. The largest 3 classes accounted for 83.7% of the sample, with classes 1, 2 and 3 comprising 32.1%, 28.6% and 23.6%. Class 2 had lower lymphocytes, monocytes, neutrophils and platelets relative to classes 1 and 3. Survival rates were different between classes 1 and 2 (Cox model hazard ratio, HR=0.85; P=0.012) and 2 vs 3 (HR=1.18; P=0.001). The remaining 6 classes, which generally shared in common characteristics of higher RDW and lower hemoglobin, also were involved with significant survival differences. Multinomial logistic regression revealed that, among the subset of 7,173 participants over 65, older age was significantly associated with membership in class 1 relative to classes 2 (P<0.001) and 3 (P<0.001). These results point toward the possibility of developing immune marker profile indicative of accelerated aging.

## EARLY TIME RESTRICTED FEEDING IMPROVES HIGH DENSITY LIPOPROTEIN FUNCTION IN GERIATRIC MONKEYS

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Ageing conveys the greatest risk for cardiovascular disease (CVD) development, which is the dominant cause of mortality in developed nations. High density lipoprotein (HDL) particles mediate reverse cholesterol transport, are anti-inflammatory and their function predicts CVD. We observed lower plasma cholesterol efflux capacity in geriatric vervet monkeys (p=0.03) when consuming either healthy or Western diets. Adult (n=16) and geriatric (n=19) monkeys were stratified into groups fed Western diet on ad libitum (Ad Lib) or early time restricted feeding (eTFR) schedules. eTRF supplied excess food only between 6am to 2pm. Housing, seasonality and fasting conditions for data and sample collections were equivalent. After 6 months, cholesterol efflux to HDL was greater in eTRF monkeys (p=0.01), with no age by group interaction. Efflux media and plasma was chromatographically separated to confirm labelled cholesterol, and enzymatically measured cholesterol, respectively, was affiliated with HDL particles. eTRF monkeys had higher total plasma cholesterol levels (p=0.03) which was due to greater cholesterol amounts associated with only HDL, and resulted in HDL particles that were larger. eTRF resulted in robustly better HDL function such that measures from geriatric individuals were comparable to younger adults. Additionally, no differences in adiposity was observed in eTRF monkeys. Few interventions are known to raise HDL levels, and more importantly, are confirmed to improve HDL function. Our study is to date the largest, longest, controlled eTRF evaluation in primates and we show that positive biological effects are observable in HDL isolated from both adult and geriatric individuals independently of weight change.

## DEVELOPING THE COMMON MARMOSET AS A TRANSLATIONAL MODEL OF AGE-RELATED OSTEOARTHRITIS

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Age is a primary risk factor for osteoarthritis (OA). The mechanisms that contribute to OA are poorly understood and disease modifying treatments have not been identified. A critical shortcoming in developing therapies is the limited number of translational models available to identify the causes of naturally occurring OA. Our goal is to use the common marmoset as a non-human primate (NHP) model of age-related OA. NHP are the closest evolutionary relative to humans and share many characteristics of human aging. The marmoset has advantages over other NHP for aging research because of their relatively short maximal lifespan and small size. Micro-computed tomography (uCT) was performed on whole-knee joints obtained from young (10 yrs, n=3) marmosets at necropsy. OA was evaluated using a clinical uCT scoring system and quantitative assessments of subchondral bone structure and ossified meniscal volume. Advancing age was positively correlated to increased uCT OA score (p<0.05, r=0.59 ), mainly through increased number and size of osteophytes and progressive subchondral bone sclerosis from the medial to both medial and lateral compartments. For marmosets displaying meniscal ossification, older marmosets had greater (p<0.05) ossified meniscal volume than middle-aged and younger marmosets, respectively. Trabecular (p=0.05) and cortical bone thickness (p<0.05) were also lower in older marmosets. These data are the first to indicate that the marmoset develops naturally occurring, age-related OA and support the pursuit of additional studies using the marmoset to identify OA mechanisms and test potential interventions.

## LIFETIME EXERCISE ATTENUATES AGE- AND WESTERN DIET-RELATED DECLINES IN PHYSICAL FUNCTION IN MICE

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Aging is associated with progressive declines in physical function. However, it is unknown if consumption of a western-style diet (WD; high-fat and sucrose, low fiber),

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