aeruginosa. C. elegans subjected to select lifespan-extending kynurenine pathway interventions fared better when challenged with P. aeruginosa at older ages. Additionally, fluorescent infection tracking has displayed decreased infection rates in worms with elevated 3HAA. Our data suggests pro-immune activity is facilitated by 3HAA acting downstream of the dbl-1 pathway in addition to directly inhibiting bacterial growth. Our goal is to discover the mechanism(s) through which the kynurenine pathway interacts with immune function in animals and identify potential targets for clinical therapy in aging populations.

EARLY LIFE THYMECTOMY INDUCES GLUCOSE INTOLERANCE IN MIDDLE-AGED MICE

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Previously we have found that T cells contribute to age-related glucose intolerance. The purpose of this study was to test the hypothesis that early life thymectomy at 3wks of age induces T cell aging and subsequent impairments in glucose homeostasis in otherwise young animals. Male C57BL6 mice underwent thymectomy (thymex; n=7) or sham surgery (control; n=7) at 3wks of age. A glucose (2g/kg) tolerance test (GTT) was performed at 6 and 9mo via intraperitoneal injection. Following euthanasia at 9mo of age, splenic T cell phenotype was assessed by flow cytometry. Group differences were assessed by independent samples t-test or repeated measures ANOVA and Bonferroni post-hoc test. Data are presented as mean±SEM. At 6mo, the thymex animals had a significantly lower fasting glucose compared to controls (156.8±7.9mg/dl,174.1±5.8mg/dl, p=0.06). During the GTT, 6mo old thymex mice had a greater area under the curve (AUC) compared to controls (31893.8±612.3mg/dl, 28020.9±1112.9mg/dl, p=0.03). At 9mo, the thymex mice had greater fasting glucose compared to controls (215.6±11.6mg/dl, 176.3±7.9mg/dl, p=0.016), as well as a greater GTT AUC (61445.4±1949.2mg/dl, 41527.5±2530.3mg/dl, p=0.0001). The thymex group also had increased fasting and glucose stimulated insulin levels compared to controls (0=1.3±0.2ng/ml 0.3±0.1ng/ml, p=0.01; 15=1.7±0.2ng/ml,0.44±0.1ng/ml, p=0.0014). Thymex mice exhibited a blunted splenic CD4:CD8 ratio (0.5±0.2, 1.1±0.2, p=0.04) compared to controls and a trend toward a memory CD8+ T cell phenotype (23.1±11.6%, 7.1±2.6, p=0.08), both consistent with aging. This data indicates that early life thymectomy may accelerate T cell aging, resulting in impairments in glucose tolerance in otherwise young and middle aged mice.

EXPERIENCING A NATURAL DISASTER ACCELERATES AGING OF THE IMMUNE SYSTEM

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Extreme adverse events such as natural disasters can accelerate disease progression and promote chronic inflammation. These phenotypes also increase in prevalence with age, suggesting that experiencing adversity might accelerate aging of the immune system. Adversity can induce persistent gene regulatory changes which may mechanistically explain the immune similarities between aging and adversity. To test how immune system aging is accelerated following a natural disaster, we measured the impact of Hurricane Maria on peripheral blood immune cell gene expression in a population of free-ranging rhesus macaques (Macaca mulatta) from before (n=435) versus after (n=108) Hurricane Maria. Experiencing Hurricane Maria altered the expression of 260 genes (FDR<10%), which were primarily involved in the inflammatory response. There was significant overlap in these hurricane-affected and age-associated genes with 40% (n=104) being associated with both the hurricane and aging, more than double the expected amount (Fisher's Exact Test OR=3.7, p=4.06 x 10–21). The effects of the hurricane and aging on gene expression were also significantly correlated (rho=0.23, p=1.33 x 10-84), suggesting that they alter similar molecular pathways in the immune system. Further, we found that animals that experienced the hurricane had a gene expression profile that was, on average, 1.6 years older than animals that did not experience the hurricane (the equivalent of 6–7 years in a human lifespan, p=0.003). Together, our results provide some of the first evidence that extreme natural disasters mechanistically accelerates aging in the immune system.

HEMATOPOIETIC MOSAIC CHROMOSOMAL ALTERATIONS IN THE NEW ENGLAND CENTENARIAN STUDY.

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Mosaic chromosomal alterations (mCAs) are structural alterations that include deletions, duplications, or copy-neutral loss of heterozygosity. mCAs are reported to be associated with survival, age, cancer, and cardiovascular disease. Previous studies of mCAs in large population-based cohorts (UK Biobank, MGBB, BioBank Japan, and FinnGen) have demonstrated a steady increase of mCAs as people age. The distribution of mCAs in centenarians and their offspring is not well characterized. We applied MOsaic CHromosomal Alteration (MoChA) caller on 2298 genome-wide genotype samples of 1582 centenarians, 443 centenarians' offspring, and 273 unrelated controls from the New England Centenarian Study (NECS). Integrating Log R ratio and B-allele frequency (BAF) intensities with genotype phase information, MoChA employs a Hidden Markov Model to detect mCA-induced deviations in allelic balance at heterozygous sites consistent with genotype phase in the DNA microarray data. We analyzed mCAs spanning over 100 k base pairs, with an estimated cell fraction less than 50%, within samples with genome-wide BAF phase concordance across phased heterozygous sites less than 0.51, and with LOD score of more than 10 for the model based on BAF and