Evidence for an energy conservation model of inflammaging and immunosenescence in the US Health and Retirement Study and UK Biobank

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Main text word count: 5,794

Data elements: 5 (3 tables, 2 figures)

References: 50

Abstract

The development of chronic inflammation in later life (inflammaging), alongside changes in immune cell profiles and impaired pathogen defense (immunosenescence), contribute to health risk. However, these processes have been hypothesized as adaptive remodeling of the immune system in response to accumulating somatic damage. Here we consider a recently developed theoretical framework to understand their relationship: the Brain-Body Energy Conservation model of aging. This model views immunosenescence as part of an energy conserving response to the rising energy expenditure of inflammaging. This response promotes short term survival against somatic damage at the expense of future health risk. For example, naïve T cells, which enhance defense against future infections, decline with age, while proteins that suppress the immune response to infection, including IL-10, increase. GDF-15, which is produced in response to chronic inflammation and metabolic stress, and similarly suppresses the immune response to infection, also increases with age. We find evidence consistent with this model in the US Health and Retirement Study (HRS, n = 8,184) and UK Biobank (UKB, n = 40,510). Across both cohorts, the key inflammaging marker TNFR1 partially mediated the age-related increases in IL-10 and GDF-15. In the HRS flow cytometry data, TNFR1 also mediated age-related decreases in naïve T cells. Finally, we assessed vulnerability to a novel future infection using the UKB medical records data on hospitalization or death from COVID-19 (n = 586 hospitalized or died). TNFR1, IL-10, and GDF-15, measured pre-pandemic, all partially mediated the age-related increased risk.

Keywords:

COVID-19, Inflammation, Biology of Aging, T-cells, GDF-15

Introduction

Later life is accompanied by complex changes in immune function that are implicated in health risk. There is a pronounced decline in adaptive immunity, which has been referred to as immunosenescence. This is reflected for example in the involution of the thymus and resulting decline in naïve T cells, which play an important role in defense against novel infectious exposures (1-3). Later life is also accompanied by the development of chronic, systemic, and sterile inflammation, termed inflammaging (1, 4). While these changes are often interpreted as immune dysfunction that contributes to aging and disease, some have proposed that they at least partly reflect immune remodeling that "makes the best of a bad situation" (1, 5).

A new theoretical model provides a framework to understand the relationship between inflammaging and immunosenescence from the perspective of adaptive remodeling: the Brain-Body Energy Conservation (BEC) model of aging (6). The BEC model highlights the energetic cost of inflammaging, which is progressively activated in response to accumulating somatic damage. However, total and basal energy expenditure in late life does not increase, instead decreasing after 60 years (7). The suite of functional declines and tissue atrophy observed in later life, including immunosenescence, are therefore viewed as energy conserving responses.

Current evidence suggests inflammaging is energetically costly. For example, cellular injury over time can lead to the development and accumulation of senescent cells throughout the body. These cells have arrested cell division, yet they are continually active. Their pro-inflammatory signaling, termed the senescence-associated secretory profile (SASP) (8), is a major contributor to inflammaging. These cells display markers of increased energy expenditure, such as greater mitochondrial density (6).

The BEC model draws from evolutionary life history theory (LHT), which seeks to understand how organisms allocate their finite resources, including energy, between competing functions to maximize survival and reproduction (9, 10). Central to LHT is the concept of trade-offs, as energy invested in one function comes at the expense of another. These trade-offs are often studied between three broad categories of growth, reproduction, and maintenance, with immune function considered part of maintenance (9, 11, 12). However, there is also evidence for potential trade-offs occurring within different components of the immune system, as each comes with different costs and benefits (10). Innate immunity provides non-specific and fast-acting defense against cellular damage, and its activation is a central component of inflammaging. In contrast, adaptive immunity primarily provides enhanced future protection against infections. This occurs through the proliferation and development of naïve T cells, which can respond to novel pathogens and develop memory for improved future defense (10). As a result, much of adaptive immunity provides little immediate survival benefit, suggesting it would be one of the first functions to be divested from with accumulating energy expenditure from inflammaging.

Here we test the BEC model linking inflammaging to immunosenescence using data from two large human cohorts: The US Health and Retirement Study (HRS) and the UK Biobank (UKB). The HRS is a nationally representative study of US older adults, which provides publicly available data including several thousand individuals with measured cytokines and naïve T cells. We used naïve T cell counts as a proxy for investment in the immune repertoire, which decline with thymus involution in later life. We also used the cytokines interleukin (IL)-6 and soluble tumor necrosis factor receptor 1 (TNFR1), which are important orchestrators of inflammaging and are part of the SASP signaling (13, 14). We assessed whether IL-6 and TNFR1 mediated inverse associations between age and naïve T cells. We also assessed whether these cytokines

mediated inverse associations between a collection of chronic diseases, which reflect greater somatic damage and inflammaging, and naïve T cells. This included hypertension or cardiovascular disease (CVD), diabetes, and cancer.

An expected cost of the trade-off between inflammaging and immunosenescence is impaired defense against novel infections. To assess this possibility, we relied on the UKB, which contains cytokine measures in a large sample (approximately 54,000 individuals) at baseline (years 2006-2010) as well as tracking of COVID-19 hospitalizations or deaths (years 2020-2024). This natural experiment allowed us to test whether greater inflammaging prospectively predicted greater vulnerability to a novel infection in the future. The proteomics data from the UKB contains IL-6 and TNFR1 to directly compare with the HRS as well as other central orchestrators of inflammaging: IL-1β and TNF-α. We assessed whether these cytokines mediated positive associations between age and hospitalization or death from COVID-19 over follow up. Similar to the HRS study, we also assessed whether these cytokines mediated positive associations between chronic diseases and hospitalization or death.

It has been noted previously that inflammation "activates many components of dormancy programs typically induced by nutrient scarcity" (15). Current evidence suggests GDF-15 is an important mechanism in this process. GDF-15 signals metabolic stress and plays a role in immune suppression or tolerance in response to chronic inflammation, potentially increasing vulnerability to novel viral infections like COVID-19 (6, 16-20). Measures of GDF-15 were available in both the HRS and UKB. We therefore tested whether the pro-inflammatory cytokines mediated age and disease-related increases in GDF-15, while also testing whether GDF-15 mediated associations between pro-inflammatory cytokines and COVID-19 health risk in the UKB.

Finally, while increased pro-inflammatory signaling has been observed with age, increased anti-inflammatory signaling has also been observed across diverse human populations (21, 22). There are multiple possible reasons for the development of what has been termed anti-inflammaging (13, 23). Although anti-inflammatory signaling is generally considered protective for health, there is also evidence that it reinforces inflammaging-driven immunosenescence. An experimental study in mice found that the anti-inflammatory cytokine IL-10 increased systemically in response to increasing IL-6 with age and was mechanistically involved in suppressing the immune response (24). In addition, IL-10 has been found to exert its anti-inflammatory effects through metabolic reprogramming of macrophages (25), fitting with an energy conservation framework. We therefore tested whether the pro-inflammatory cytokines mediated age and disease-related increases in IL-10, while also testing whether GDF-15 mediated associations between pro-inflammatory cytokines and COVID-19 health risk in the UKB.

Methods

US Health and Retirement Study (HRS) sample

The HRS is a nationally representative study of US older adults. Here we focus on the 2016 cross-section that included a venous blood study (26). Participants self-reported whether they had received a diagnosis of hypertension, a heart condition (cardiovascular disease), diabetes, or cancer (excluding non-melanoma skin). Participants also reported if their cancer was improving or going into remission, got worse, or stayed the same. We excluded reports of cancer improving or going into remission from the cancer designation. Measurement of cytokines and naïve T cells have been described previously (27, 28). Briefly, IL-6, TNFR1, IL-10, and GDF-15

were measured in serum with the Simple Plex assays on the ELLA System (27). Naïve T cells were measured using flow cytometry from whole blood samples collected in participants' homes. Blood samples were shipped to the University of Minnesota and processed within 48 hours of collection. Samples were centrifuged to obtain peripheral blood mononuclear cells (PBMCs), which were then cryopreserved in liquid nitrogen. Flow cytometry was performed on thawed PBMC samples using either an LSRII flow cytometer or a Fortessa X20 instrument (BD Biosciences, San Diego, CA). Immunophenotyping data were analyzed using OpenCyto and FlowAnnotator. Naïve CD4T and CD8T cells were identified using the following markers: CD3+ CD19− CD8− CD4+ CD45RA+ CCR7+ CD28+ and CD3+ CD19− CD8+ CD4− CD45RA+ CCR7+ CD28+. Counts of naïve T cells per milliliter of peripheral blood were obtained by multiplying the lymphocyte count by the percentage naïve T cells. Lymphocyte counts were obtained from a differential white blood cell count in an EDTA blood sample collected simultaneously and a Sysmex XE-2100 instrument (Sysmex America, Inc., Lincolnshire, IL) (28, 29). We also considered CMV infection as a potential confounder in the analysis, which was indicated by the detection of IgG antibodies to CMV, measured in serum with the Roche e411 immunoassay analyzer (28).

UK Biobank (UKB) sample

The UKB is a large population-based study of health that began with the recruitment of approximately 500,000 participants across the UK from 2006-2010. Participants self-reported whether they had hypertension, cardiovascular disease, diabetes, or cancer. They also self-reported the type of cancer, here we excluded non-melanoma skin cancer from the cancer designation for consistency with the US HRS. In sensitivity analyses, we also excluded UKB

participants who reported lymphoma (n = 101), given its potential influence on leukocyte profiles; however, results were similar and we therefore included them in the analysis.

Cytokines were measured in a subsample through proteomic profiling of blood plasma samples with the antibody-based Olink Explore 3072 PEA (30). This assay includes binding antibodies to measure 2,923 proteins. Measures reflect relative protein abundance in the sample, which were rank normalized by UKB researchers, resulting in approximately normal distributions. We focused on IL-6, TNFR1, IL-10, and GDF-15 to match the available HRS measures. In addition, we included IL-1β and TNF-α, which are commonly measured cytokines that play central roles initiating the inflammatory response. Hospitalization or death from COVID-19 from January 2020 through April 2024 was recorded using hospital and death records. We specifically focused on cases in which COVID-19 was recorded as the primary diagnosis or cause of death.

Analysis

To rule out potential confounding by acute infection, we excluded individuals with leukocytosis in both cohorts, using >11,000 leukocytes per microliter (μL) of blood as a cutoff. This excluded 2.87% of the HRS sample and 2.37% of the UKB. In addition, UKB participants who had died prior to January 1, 2020 (6.9%) or who were lost to follow-up (0.3%) were excluded from the analysis. This resulted in final sample sizes of n = 8,184 for the HRS and n = 40,510 for the UKB. Within the UKB sample, n = 586 were either hospitalized or died from COVID-19 (n = 524 hospitalizations, n = 169 deaths).

In the HRS, cytokines were natural log-transformed due to positive skew. Naïve CD4T and CD8T cell counts were also positively skewed and natural log-transformed after a positive

offset (+1) to adjust for zero values. UKB cytokine measures were approximately normally distributed due to previous rank normalization by UKB researchers and therefore not log-transformed. Cytokines in both cohorts, as well as naïve T cells, were then standardized (mean = 0, SD = 1).

We used linear regression models for predicting continuous outcomes, including naïve T cells in the HRS and cytokines in both cohorts, as well as logistic regression models for predicting the dichotomous outcome of hospitalization or death from COVID-19 in the UKB. Since the HRS is a nationally representative sample, we used the sample weights specific to the 2016 venous blood study. Finally, to account for potential outliers with high leverage resulting in biased regression coefficients, we used robust regression weighting. This method applies lower weights to high residual observations, limiting their influence (31). As a result, model coefficients are more robust to outliers with high leverage. The code used in the analysis can be found at: https://github.com/jakearonoff/hrs_ukb_immuneaging.

Results

The UKB sample was substantially larger, while the HRS sample was older and had a higher prevalence of disease at the time of cytokine measurement (**Table 1**). In both cohorts, there were slightly more women than men. Distributions for cytokines and naïve T cells in the HRS are shown in **Supplementary Figures S1-3**. This includes the skewed raw data and the approximately normal distribution after log-transformation. Approximately normal distributions of the UKB cytokine measures are shown in **Supplementary Figure S4**. All cytokines were positively correlated across both the HRS and UKB (**Supplementary Tables S1-2**). In both cohorts, age and disease were positively associated with pro-inflammatory cytokines, with the

exception of IL-1β in the UKB, which was not associated with diabetes or cancer (**Supplementary Table S3**).

Age, disease, cytokines, and naïve T cells in the HRS

Regression models showing associations between age, diseases, cytokines, and naïve T cells in the HRS are shown in **Table 2**. An increase of 1 year in age was associated with a 0.013 and 0.051 SD increase in IL-10 and GDF-15 respectively, as well as a 0.014 and 0.026 decrease in naïve CD4T and CD8T cells respectively. Male sex was associated with a 0.091 and 0.154 SD increase in IL-10 and GDF-15 respectively, as well as a 0.359 and 0.218 SD decrease in naïve CD4T and CD8T respectively. Having hypertension or CVD was associated with a 0.171 and 0.231 SD increase in IL-10 and GDF-15 respectively, as well as a 0.097 SD decrease in naïve CD4T cells. Having diabetes was associated with a 0.246 and 0.505 SD increase in IL-10 and GDF-15 respectively, as well as a 0.090 SD decrease in naïve CD4T cells. Having cancer was associated with a 0.074 SD increase in IL-10, as well as a 0.216 and 0.088 SD decrease in naïve CD4T and CD8T cells respectively.

IL-6 and TNFR1 were positively associated with IL-10 and GDF-15 and negatively associated with naïve CD4T cells, while TNFR1 was also negatively associated with naïve CD8T cells. Adding IL-6 and TNFR1 to the models attenuated positive associations between age and IL-10 and GDF-15, as well as negative associations between age and naïve CD4T and CD8T cells. The addition of IL-6 and TNFR1 also attenuated positive associations between cardiometabolic disease and IL-10 and GDF-15, as well as naïve CD4T cells. Finally, the addition of IL-6 and TNFR1 attenuated the positive association between cancer and IL-10 and the negative association for naïve CD4T cells, while the addition of TNFR1 attenuated the

negative association between cancer and naïve CD8T cells. In the models with all predictors, variance inflation factors indicated sufficiently low collinearity (all <2.5) to estimate the independent associations for each predictor, which included age = 1.25, sex = 1.01, hypertension or CVD = 1.17, diabetes = 1.10, cancer = 1.03, IL-6 = 1.25, and TNFR1 = 1.49.

Age, disease, cytokines, and COVID-19 health risk in the UKB

Regression models showing associations between age, diseases, cytokines, and COVID-19 hospitalization or death in the UKB are shown in **Table 3**. One year increase in age was associated with a 0.002 and 0.051 SD increase in IL-10 and GDF-15 respectively, as well as 6% increased odds of hospitalization or death from COVID-19. Male sex was not associated with IL-10; however, it was associated with a 0.159 SD increase in GDF-15 and 23% increased odds of hospitalization or death from COVID-19. Having hypertension or CVD was associated with a 0.036 and 0.192 SD increase in IL-10 and GDF-15 respectively, as well as 53% increased odds of hospitalization or death from COVID-19. Diabetes was associated with a 0.143 and 0.978 SD increase in IL-10 and GDF-15 respectively, as well as 106% increased odds of hospitalization or death from COVID-19. Cancer was associated with a 0.066 and 0.084 SD increase in IL-10 and GDF-15 respectively. While not statistically significant, cancer was associated with 14% increased odds of hospitalization or death from COVID-19.

IL-6, TNFR1, and TNF-α were all positively associated with IL-10, GDF-15, and odds of hospitalization or death from COVID-19 (cytokines measured pre-pandemic), while their addition to the models attenuated positive associations for age, cardiometabolic disease, and cancer. IL-10 and GDF-15 were positively associated with odds of hospitalization or death from COVID-19 (IL-10 at $p < 0.10$), while their addition to the model attenuated positive associations

for age, cardiometabolic disease, cancer, and pro-inflammatory cytokines. In the models with all predictors, variance inflation factors indicated sufficiently low collinearity (all <2.5) to estimate the independent associations for each predictor, which included age = 1.22, sex = 1.04, hypertension or CVD = 1.18, diabetes = 1.26, cancer = 1.01, IL-6 = 1.27, TNFR1 = 1.99, IL-1β = 1.04, TNF-α = 1.55, IL-10 = 1.11, GDF15 = 2.16.

Additional models and sensitivity analyses

We considered additional measures and models to assess potential confounding and interactions. This included weight (kg), a proxy for energy expenditure, as individual differences might confound energy conservation responses. In addition, associations for naïve T cells and COVID-19 health risk could be confounded by individual differences in cellular proliferative capacity, which declines with age and disease but is not part of a hypothesized energy conservation response. We relied on red blood cells and platelets as proxies for this possible confounding. Finally, we considered CMV infection in the HRS models as another potential confounder, since it increases pro-inflammatory cytokines and decreases naïve T cells (32). Approximately normal distributions for weight, red blood cells, and platelets in both cohorts are shown in **Supplementary Figures S5-6.** Results were very similar after adding these variables to the models, including CMV infection in the HRS models, suggesting minimal or no confounding **(Supplementary Tables S4-5)**.

Since total and basal energy expenditure have been found to decrease in later life, we considered whether the hypothesized energy conservation response intensified with age using interaction terms. These were mostly null, while significant age interaction terms were not consistent in direction. For example, in the HRS, the positive association between cancer and IL-

10 was stronger at older ages, however the negative association between cancer and naïve CD4T cells attenuated (**Supplementary Tables S6**). Further, the inverse association between TNFR1 and naïve CD8T cells attenuated with older age. In the UKB, the positive association between TNFR1 and GDF-15 strengthened with older age, while the positive association between IL-6 and GDF-15 weakened (**Supplementary Tables S7**). Associations between cytokines and COVID-19 hospitalization or death risk were not modified by age.

While GDF-15 does not directly induce thymus involution and resulting decline in naïve T cells, it serves as a proxy for metabolic stress in response to inflammation. Therefore, as an additional test of the energy conservation model, we tested associations between GDF-15 and naïve T cells in the HRS. GDF-15 was inversely associated with both naïve CD4T and CD8T cells (**Supplementary Table S8**). Further, GDF-15 attenuated inverse associations between age and naïve CD4T and CD8T cells, cardiometabolic disease and naïve CD4T cells, as well as cancer and naïve CD4T and CD8T cells.

Since risk of hospitalization or death from COVID-19 could be due to a combination of an energy conservation response as well as dysfunctional immunity, we considered a sensitivity analysis excluding individuals with diseases or conditions related to dysregulated inflammation. We excluded individuals with hypertension or CVD, diabetes, and cancer, as well as those with COPD, asthma, or allergies. This resulted in a subsample of 17,613 in which 162 were later hospitalized or died from COVID-19 (**Supplementary Table S9**). In this subsample analysis, associations for IL-6 and TNF-α attenuated, while associations for TNFR1 and IL-10 strengthened. The positive association between GDF-15 and odds of hospitalization or death was nearly identical in comparing the healthier subsample with the full sample.

HRS mediations among age and disease, cytokines, and naïve T cells

HRS mediation paths are shown in **Figure 1** and **Supplementary Table S10**, determined by the attenuation of the predictor-outcome association after adding the mediator. The positive association between age and IL-10 was mediated 81% by TNFR1. The positive association between age and GDF-15 was mediated 32% by TNFR1 and IL-6 together. However, individual mediation paths revealed this was primarily attributable to TNFR1, which mediated 28% of the age association independent of IL-6, while IL-6 only mediated 1% of the age association independent of TNFR1 (**Supplementary Table S10**). The inverse association between age and naïve CD4T cells was mediated 19% by TNFR1 and IL-6 together. However, this was mostly attributable to TNFR1, which mediated 12% of the age association independent of IL-6, while IL-6 only mediated 2% of the age association independent of TNFR1. TNFR1 mediated 4% of the inverse association between age and naïve CD8T cells.

The positive association between hypertension or CVD and IL-10 was mediated 90% by TNFR1 and IL-6 together, while for single paths TNFR1 mediated 80% of the association after adjusting for IL-6 and IL-6 mediated 66% of the association after adjusting for TNFR1 (**Supplementary Table S10**). The positive association between hypertension or CVD and GDF-15 was mediated 53% by TNFR1 and IL-6 together, while for single paths TNFR1 mediated 41% of the association after adjusting for IL-6 and IL-6 mediated 8% of the association after adjusting for TNFR1. The inverse association between hypertension or CVD and naïve CD4T cells was mediated 35% by TNFR1 and IL-6 together, while for single paths TNFR1 mediated 18% of the association after adjusting for IL-6 and IL-6 mediated 12% of the association after adjusting for TNFR1.

The positive association between diabetes and IL-10 was mediated 59% by TNFR1 and IL-6 together, while for single paths TNFR1 mediated 47% of the association after adjusting for IL-6 and IL-6 mediated 11% of the association after adjusting for TNFR1. The positive association between diabetes and GDF-15 was mediated 33% by TNFR1 and IL-6 together, while for single paths TNFR1 mediated 24% of the association after adjusting for IL-6 and IL-6 mediated 4% of the association after adjusting for TNFR1. The inverse association between diabetes and naïve CD4T cells was mediated 37% by TNFR1 and IL-6 together, while for single paths TNFR1 mediated 25% of the association after adjusting for IL-6 and IL-6 mediated 7% of the association after adjusting for TNFR1.

The positive association between cancer and IL-10 was mediated 28% by TNFR1, while the negative associations with naïve CD4T and CD8T cells were mediated 3% and 6% by TNFR1 respectively. Although cancer was positively associated with GDF-15 at $p < 0.10$ after adjusting for IL-6 and TNFR1, they did not mediate the association.

UKB mediations among age and disease, cytokines, and COVID-19 health risk

UKB mediation paths are shown in **Figure 2** and **Supplementary Tables S11-12**. The positive association between age and IL-10 was mediated 100% by TNFR1, TNF-α, and IL-6 together. It was not possible to estimate independent mediation paths due to the strong associations. For example, adding either TNFR1 or TNF-α alone into the model completely attenuated the positive association between age and IL-10. The positive association between age and GDF-15 was mediated 23% by TNFR1, TNF-α, and IL-6 together, while adjusting for each cytokine indicated single paths of 10%, 1%, and 2% for TNFR1, TNF-α, and IL-6 respectively. The positive association between age and odds of hospitalization or death from COVID-19 was

mediated 26% by TNFR1, TNF-α, and IL-6 together, while adjusting for each cytokine indicated single paths of 19%, 1%, and 5% for TNFR1, TNF-α, and IL-6 respectively.

The positive association between hypertension or CVD and IL-10 was mediated 100% by TNFR1, TNF-α, and IL-6. Similar to the age association, it was not possible to estimate independent mediation paths due to the strong associations. The positive association between hypertension or CVD and GDF-15 was mediated 52% by TNFR1, TNF-α, and IL-6 together, while adjusting for each cytokine indicated single paths of 25%, 2%, and 13% for TNFR1, TNF-α, and IL-6 respectively. The positive association between hypertension or CVD and odds of hospitalization or death from COVID-19 was mediated 34% by TNFR1 and IL-6 together, while adjusting for each cytokine indicated single paths of 24% and 5% for TNFR1 and IL-6 respectively.

The positive association between diabetes and IL-10 was mediated 56% by TNFR1, TNF-α, and IL-6 together, while adjusting for each cytokine indicated single paths of 16%, 7% and 3% for TNFR1, TNF-α, and IL-6 respectively. The positive association between diabetes and GDF-15 was mediated 15% by TNFR1, TNF-α, and IL-6 together, while adjusting for each cytokine indicated single paths of 12%, 1%, and 3% for TNFR1, TNF-α, and IL-6 respectively. The positive association between diabetes and odds of hospitalization or death from COVID-19 was mediated 32% by TNFR1 and IL-6 together, while adjusting for each cytokine indicated single paths of 27% and 3% for TNFR1 and IL-6 respectively.

TNFR1 mediated 7% of the positive association between cancer and IL-10 independent of other cytokines, while IL-6 also mediated 3% of the association independent of other cytokines. Similarly, TNFR1 mediated 35% of the positive association between cancer and GDF-15 independent of other cytokines, while IL-6 also mediated 12% of the association independent

of other cytokines. Since cancer was positively but not statistically significantly associated with odds of hospitalization or death from COVID-19, we did not consider mediation paths.

The positive association between TNFR1 and odds of hospitalization or death from COVID-19 was mediated 38% by IL-10 and GDF-15, while adjusting for each cytokine indicated single paths of 4% and 39% for IL-10 and GDF-15 respectively. The positive association between TNF-α and odds of hospitalization or death from COVID-19 was mediated 27% by IL-10 and GDF-15, while adjusting for each cytokine indicated single paths of 15% and 16% for IL-10 and GDF-15 respectively. The positive association between IL-6 and odds of hospitalization or death from COVID-19 was mediated 16% by IL-10 and GDF-15, while adjusting for each cytokine indicated single paths of 1% and 8% for IL-10 and GDF-15 respectively.

GDF-15 also mediated associations independent of the pro-inflammatory cytokines TNFR1, TNF-α, and IL-6. This included age, in which GDF-15 mediated 18% of the positive association with odds of hospitalization or death from COVID-19. In addition, GDF-15 mediated 16% and 45% of the positive associations for hypertension or CVD and diabetes respectively, independent of TNFR1, TNF-α, and IL-6.

Discussion

Here we found evidence in two large human cohorts that is consistent with an energy conservation model of inflammaging and immunosenescence. TNFR1, an indicator of inflammaging, was inversely associated with naïve T cells in the HRS, positively associated with odds of hospitalization or death from COVID-19 in the UKB, and mediated the associations between older age and these outcomes (12% for CD4T, 4% for CD8T, 19% for COVID-19). We

also found evidence consistent with the role of anti-inflammaging in augmenting immunosenescence in response to inflammaging. The anti-inflammatory cytokine IL-10 was positively associated with odds of hospitalization or death from COVID-19 and mediated 4% of the TNFR1 association. Finally, in further support of the energy conservation model of immune aging, GDF15, which is elevated in response to chronic inflammation and contributes to immune tolerance, also mediated 39% of the association between TNFR1 and increased risk of hospitalization or death, as well as 18% of the age-related increased risk independent of TNFR1.

Our findings are consistent with multiple previous studies on inflammation and immune function. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), both subclinical atherosclerosis and IL-6 were inversely associated with naïve CD4T cells (33). Another study of older individuals also found an inverse association between IL-6 and naïve T cells (34). Further, both subclinical atherosclerosis and elevated C-Reactive Protein (CRP), a marker of chronic low-grade inflammation, were found to be inversely associated with the inflammatory response to vaccination (35, 36). Further, CRP has also been found to be inversely associated with the antibody response to vaccination (37).

Adaptive remodeling in later life to promote short term survival raises the question of how this response would evolve with diminishing selection pressure. One potential explanation is that this energy conservation response evolved to function during acute periods of somatic damage in early life. An example of this is acute or transient thymus involution, which can be induced by a variety of exposures inducing somatic damage or energetic stress (e.g., chemotherapy, infection, malnutrition, pregnancy) (38, 39). There is also evidence that several cytokines play a role in acute thymus involution, including the ones examined here (38, 39). This acute response could have plausibly been co-opted for later life. Further, while selection pressure

wanes, it is not completely absent, and this could further reinforce the energy conservation response to inflammaging.

A key open question is how to empirically distinguish adaptive remodeling from maladaptive decline in late life (5). Our approach here was to assess how strong the associations were between age, cytokines, and COVID-19 health risk remained after excluding individuals with reported inflammatory diseases or conditions. While this approach is admittedly imperfect, if associations attenuated when individuals with the most dysregulated inflammatory responses were removed, it would suggest dysregulation was playing a larger role. This appeared to be the case for IL-6 and TNF-α, which were no longer predictive of COVID-19 health after removing individuals with inflammatory conditions. In the HRS, IL-6 showed stronger mediation between diseases and naïve T cells compared to age, further suggesting dysregulated inflammation was playing a larger role in the IL-6 associations. In contrast, associations for TNFR1 and GDF-15 predicting COVID-19 hospitalization or death in the UKB were very similar after removing individuals with inflammatory conditions, suggesting potential confounding by dysregulated inflammation was minimal or absent. Further, the IL-10 association strengthened after removing these individuals, suggesting that dysregulated immune function was obscuring the relationship between age-related increases in IL-10 and impaired pathogen defense. In order to assess potential confounding due to age-related functional decline separate from an expected energy conservation response, we considered models with red blood cell counts and platelets, which both decline with age due to declining proliferative capacity. Results were nearly identical in both the HRS and UKB after adding these variables, suggesting minimal or no confounding.

While here we propose that the BEC model can help explain atrophy of the immune repertoire, it is likely not a comprehensive explanation. With decreasing residual life expectancy,

the benefits of investment in the immune repertoire decline. As a result, we should expect atrophy of the immune repertoire with declining life expectancy, as is the case in later life. This might explain why we found strong inverse associations between male sex, which is associated with lower life expectancy, and naïve T cells. Relatedly, most infectious exposures have already been encountered by later life, and as a result the marginal value of further investment in the immune repertoire declines. This multifactorial process likely explains why the inflammaging markers IL-6 and TNFR1 mediated only a small proportion of the association between age and naïve T cells in the HRS.

The multifactorial process of functional decline and tissue atrophy across multiple bodily systems with age could also explain why we generally did not find evidence that the energy conservation response intensified with age. If the age-related declines in total and basal energy expenditures are due to functional declines and tissue atrophy from factors independent of an energy conservation response, this would explain our largely null age interaction terms. If future studies on other bodily systems similarly find that associations do not intensify with older age, this would further suggest the multifactorial explanation.

Our results for IL-10 are consistent with prior studies suggesting this cytokine plays a role in augmenting immunosenescence and increased vulnerability to infection in later life (24, 32). However, its influence on disease and aging is complex and context specific. Current evidence suggests that greater IL-10 is protective from the development of inflammaging and potentially some inflammatory diseases such as CVD (13, 32, 40). Further, the increase in IL-10 in response to inflammaging might serve multiple functions. In addition to energy conservation, IL-10 might also play a role in striking a balance between an excessive inflammatory response

that contributes to aging and disease and an impaired immune response to infections (41, 42). This might similarly be the case with GDF-15 (43).

While here we use the terminology of inflammaging and anti-inflammaging, consistent with pro- and anti-inflammatory, it is important to note these cytokines likely reflect a single immune response. Evidence for this can be seen for example in the positive correlations amongst cytokines with opposing functions reported here and in previous studies, as well as similar principal component loadings (14, 21, 22).

Our findings highlight TNFR1 as a particularly important marker of inflammaging. This is consistent with a recent study using a battery of cytokines to measure inflammaging across human populations. At least among industrialized populations, TNFR1 was a strong indicator of inflammaging (14). In contrast, we found that other markers often used to measure inflammaging, including IL-6, IL-1β, and TNF-α, showed weaker associations with naïve T cells or odds of hospitalization or death from COVID-19. These results highlight the importance of measuring TNFR1 in future studies.

This energy conservation model linking inflammaging to immunosenescence has important health implications. For example, it could offer an explanation of the rapamycin immune function "paradox". While rapamycin was originally used as an immunosuppressant for organ transplant patients, it has been found to improve antibody responses to vaccination as well as reduce infection risk over follow-up (44, 45). The energy conservation model of immune aging suggests this effect is likely indirect. Rapamycin can inhibit SASP signaling, thereby reducing inflammaging (46, 47). As a result, the divestment from the immune repertoire could be reversed, improving immune responses to novel infectious exposures (48). Relatedly, previous findings of transient and reversible thymus involution highlighted above further suggests the

potential for reversing immunosenescence if inflammaging can be attenuated. This could be accomplished therapeutically, such as with rapamycin, or through lifestyle changes. For example, among older adults, physical activity has been found to be inversely associated with IL-6 and positively associated with naïve CD4T cells (34). Further, non-industrialized human populations that are highly physically active with minimal excess caloric consumption, such as Tsimane forager-horticulturalists in the Bolivian Amazon, show markedly attenuated inflammaging (14, 22). Finally, a horticulture lifestyle intervention showed a reduction in IL-6 and increase in naïve CD8T cells (49). However, it is important to distinguish between interventions that might artificially dampen inflammaging such as anti-inflammatory medications and interventions that might address the causes of inflammaging, such as physical activity. Under the BEC, the former might succeed in reducing immunosenescence only at the cost of perturbing the complex energetic balance the body is attempting to maintain during aging.

Our study is not without limitations. While we assessed indicators of both investment in the immune repertoire and an outcome of vulnerability to novel infection, these were measured in different individuals across the two US and UK cohorts. The two cohorts also differed in cytokine assay methods. Cytokine measurements were cross-sectional, and as a result we cannot definitively assess causal ordering. Further, due to the complex signaling network of cytokines that results in a versatile emergent property of immune function (50), we also cannot rule out bidirectional causality amongst cytokines. Finally, we did not have direct measures of total or basal energy expenditure. However, when we assessed results before and after adding body weight to the models, a proxy for energy expenditure, results were nearly identical, suggesting this was not a major confounder.

In conclusion, here we find evidence consistent with an energy conservation model of immune aging. Immunosenescence, at least in part, can be understood as an energy conservation response to rising inflammaging in later life. This response likely promotes short term survival at the expense of greater vulnerability to novel infections in the future. Considering waning selection pressure with age, this response likely originally evolved for surviving short term stressors in early life and has been co-opted to operate chronically in later life. Finally, our study also highlights the role of anti-inflammatory signaling, or anti-inflammaging, as a contributor to immunosenescence.

Acknowledgements

This research has been conducted using the UK Biobank Resource under the approved application number 772113. The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. We are grateful to the US HRS and UKB study participants, as well as the researchers who have created and maintained these publicly available databases. Figures were created in Biorender.

Funding

This work was partially supported by the NIH/National Institute on Aging (R01AG054442).

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The US HRS data used here are considered sensitive data products and require an application and data use agreement with the HRS. UK Biobank data are available to researchers with approved project applications and payment of applicable access fees.

Author contributions

Jacob E. Aronoff: conceptualization (lead), statistical analysis, writing (original draft).

Maximilien Franck: conceptualization (supporting), writing (review and editing).

Alan A. Cohen: conceptualization (supporting), writing (review and editing).

Benjamin C. Trumble: conceptualization (supporting), writing (review and editing).

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Table 1. Descriptive statistics

	HRS (full sample)	HRS (GDF-15 subsample)	UKB
n	8,184	3,791	40,510
Mean age (SD)	68.5 (9.8)	68.4 (9.8)	56.4 (8.2)
Age range	50 – 107	50 – 100	40 – 70
% Male	46.2	45.9	45.0
% with hypertension or CVD	65.2	66.1	29.1
% with diabetes	24.6	24.9	4.8
% with cancer	10.7	9.4	6.0

Table 2. Regression models predicting IL-10, GDF-15, and Naïve T cells counts in the US HRS. Cytokines and T cell counts were standardized, with resulting regression coefficients reflecting changes in standard deviations (n = 8,184 for full sample; n = 3,791 for GDF-15 subsample). Estimates are reported as β (SE).

	IL-10	IL-10	GDF-15	GDF-15	Naïve CD4T	Naïve CD4T	Naïve CD8T	Naïve CD8T
Age	0.013***	-0.002	0.051***	0.035***	-0.014***	-0.012***	-0.026***	-0.025***
(years)	(0.001)	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)	(0.001)	(0.001)
Male	0.091***	0.095***	0.154***	0.145***	-0.359***	-0.357***	-0.218***	-0.219***
(0,1)	(0.022)	(0.019)	(0.029)	(0.025)	(0.026)	(0.026)	(0.016)	(0.016)
Hypertension or CVD (0,1)	0.171***	0.017	0.231***	0.109***	-0.097**	-0.063*	0.006	0.023
	(0.025)	(0.023)	(0.031)	(0.027)	(0.030)	(0.030)	(0.019)	(0.019)
Diabetes	0.246***	0.102***	0.505***	0.339***	-0.090**	-0.057	0.003	0.018
(0,1)	(0.025)	(0.023)	(0.041)	(0.035)	(0.029)	(0.030)	(0.017)	(0.017)
Cancer	0.074*	0.054	0.067	0.080	-0.216***	-0.210***	-0.088***	-0.083***
(0,1)	(0.037)	(0.033)	(0.057)	(0.049)	(0.042)	(0.042)	(0.022)	(0.022)
IL-6		0.158***		0.069***		-0.045***		-0.007
		(0.013)		(0.015)		(0.014)		(0.008)
TNFR1		0.336***		0.413***		-0.056***		-0.037***
		(0.015)		(0.018)		(0.014)		(0.008)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 3. Linear regression models predicting IL-10 and GDF-15, as well as logistic regression models predicting odds of hospitalization or death from COVID-19 (n = 586 out of 40,510). Cytokines were standardized, reflecting changes in standard deviations. Linear regression estimates are reported as β (SE), while logistic regression estimates are reported as odds ratios with 95% confidence intervals.

	IL-10	IL-10	GDF-15	GDF-15	COVID-19	COVID-19	COVID-19
Age (years)	0.002*** (0.0005)	-0.003*** (0.001)	0.051*** (0.0004)	0.041*** (0.0004)	1.06*** (1.04, 1.07)	1.04*** (1.02, 1.05)	1.03*** (1.02, 1.05)
Male (0,1)	0.002 (0.008)	0.0005 (0.008)	0.159*** (0.007)	0.129*** (0.006)	1.23* (1.01, 1.50)	1.21 (0.99, 1.48)	1.18 (0.96, 1.44)
Hypertension or CVD (0,1)	0.036*** (0.009)	-0.010 (0.009)	0.192*** (0.008)	0.100*** (0.007)	1.53*** (1.25, 1.87)	1.32** (1.07, 1.62)	1.26* (1.02, 1.56)
Diabetes (0,1)	0.143*** (0.020)	0.084*** (0.019)	0.978*** (0.037)	0.779*** (0.034)	2.06*** (1.54, 2.75)	1.61** (1.18, 2.19)	1.30 (0.93, 1.80)
Cancer (0,1)	0.066*** (0.016)	0.055*** (0.016)	0.084*** (0.015)	0.051*** (0.013)	1.14 (0.80, 1.62)	1.03 (0.71, 1.48)	1.02 (0.71, 1.48)

IL-6	0.021*** (0.004)	0.088*** (0.004)	1.16** (1.06, 1.27)	1.15** (1.05, 1.26)
TNFR1	0.054*** (0.005)	0.294*** (0.004)	1.33*** (1.21, 1.47)	1.18** (1.06, 1.32)
IL-1β	-0.004 (0.004)	-0.010*** (0.003)	0.94 (0.84, 1.04)	0.92 (0.83, 1.02)
TNF-α	0.165*** (0.007)	0.060*** (0.004)	1.11* (1.02, 1.20)	1.08 (0.98, 1.18)
IL-10				1.08 (0.99, 1.18)
GDF15				1.27*** (1.13, 1.42)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Figure 1. Summary of mediation results for the US Health and Retirement Study

Figure 2. Summary of mediation results for the UK Biobank

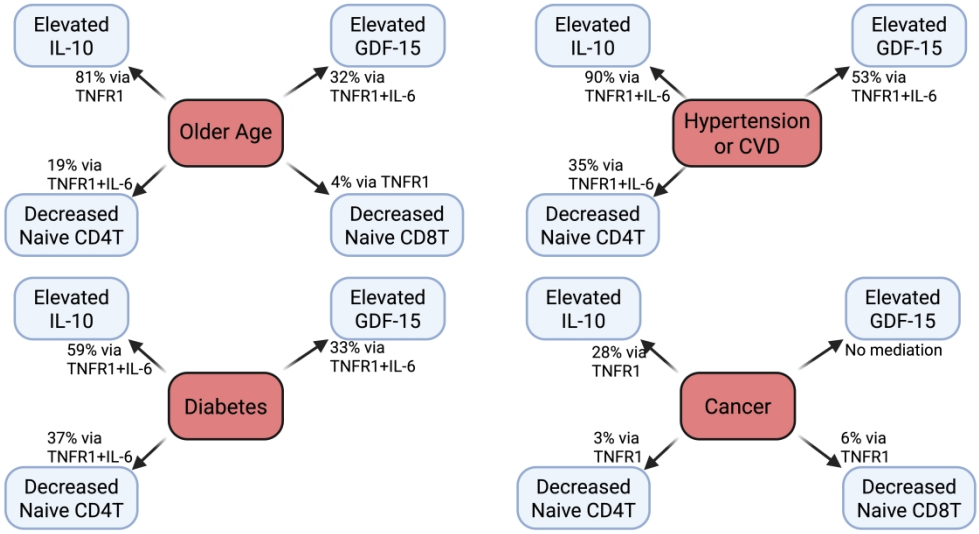

Figure 1. Summary of mediation results for the US Health and Retirement Study

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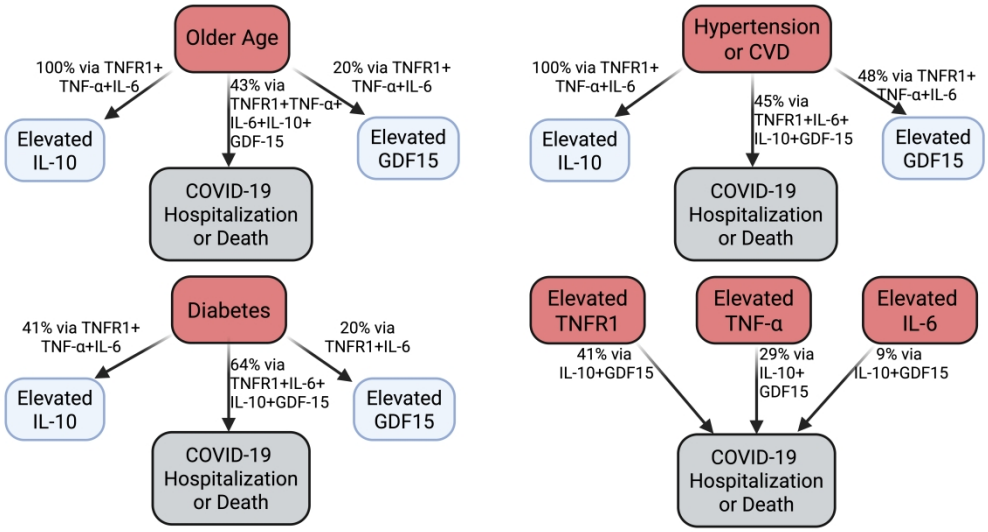
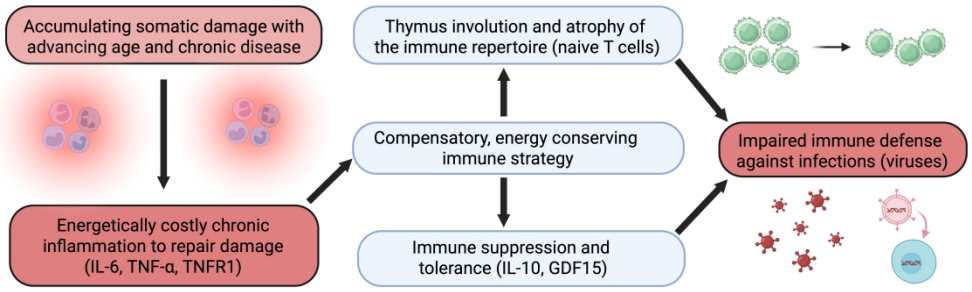


Figure 2. Summary of mediation results for the UK Biobank

714x392mm (236 x 236 DPI)



Graphical abstract

714x225mm (236 x 236 DPI)