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Senate committee opposes Trump's NIH cuts, proposes $400M budget increase

By **Gabrielle Masson** · Aug 4, 2025 11:30am

Aging research articles

Comprehensive human proteome profiles across a 50-year lifespan reveal aging trajectories and signatures

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Proteins are the cornerstone of life. However, the proteomic blueprint of aging across human tissues remains uncharted. Here, we present a comprehensive proteomic and histological analysis of 516 samples from 13 human tissues spanning five decades. This dynamic atlas reveals widespread transcriptome-proteome decoupling and proteostasis decline, characterized by amyloid accumulation. Based on aging-associated protein changes, we developed tissue-specific proteomic age clocks and characterized organ-level aging trajectories. Temporal analysis revealed an aging inflection around age 50, with blood vessels being a tissue that ages early and is markedly susceptible to aging. We further defined a plasma proteomic signature of aging that matches its tissue origins and identified candidate senoproteins, including GAS6, driving vascular and systemic aging. Together, our findings lay the groundwork for a systems-level understanding of human aging through the lens of proteins.

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Proteomic aging signatures across mouse organs and life stages

Enzo Scifo, Sarah Morsy, Ting Liu, Kan Xie, Kristina Schaaf, Daniele Bano, and Dan Ehninger | AUTHOR INFORMATION

Aging is associated with the accumulation of molecular damage, functional decline, increasing disease prevalence, and ultimately mortality. Although our system-wide understanding of aging has significantly progressed at the genomic and transcriptomic levels, the availability of large-scale proteomic datasets remains limited. To address this gap, we have conducted an unbiased quantitative proteomic analysis in male C57BL/6J mice, examining eight key organs (brain, heart, lung, liver, kidney, spleen, skeletal muscle, and testis) across six life stages (3, 5, 8, 14, 20, and 26-month-old animals). Our results reveal age-associated organ-specific as well as systemic proteomic alterations, with the earliest and most extensive changes observed in the kidney and spleen, followed by liver and lung, while the proteomic profiles of brain, heart, testis, and skeletal muscle remain more stable. Isolation of the non-blood-associated proteome allowed us to identify organ-specific aging processes, including oxidative phosphorylation in the kidney and lipid metabolism in the liver, alongside shared aging signatures. Trajectory and network analyses further reveal key protein hubs linked to age-related proteomic shifts. These results provide a system-level resource of protein changes during aging in mice, and identify potential molecular regulators of age-related decline.

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Developing a novel aging assessment model to uncover heterogeneity in organ aging and screening of aging-related drugs

Background: The decline in organ function due to aging significantly impacts the health and quality of life of the elderly. Assessing and delaying aging has become a major societal concern. Previous studies have largely focused on differences between young and old individuals, often overlooking the complexity and gradual nature of aging.

Methods: In this study, we constructed a comprehensive multi-organ aging atlas in mice and systematically analyzed the aging trajectories of 16 organs to elucidate their functional specificity and identify organ-specific aging trend genes. Cross-organ association analysis was employed to identify global aging regulatory genes, leading to the development of a multi-organ aging assessment model, hereafter referred to as the 2A model. The model's validity was confirmed using single-cell RNA sequencing data from aging mouse lungs, cross-species gene expression profiles, and pharmacogenomic data. Furthermore, a random walk algorithm and a weighted integration approach combining gene set enrichment analysis were implemented to systematically screen potential drugs for mitigating multi-organ aging.

Results: The 2A model effectively assessed aging states in both human and mouse tissues and demonstrated predictive capability for senescent cell clearance rates. Compared to the sc-ImmuAging and SCALE clocks, the 2A model exhibited superior predictive accuracy at the single-cell level. Organ-specific analyses identified the lungs and kidneys as particularly susceptible to aging, with immune dysfunction and programmed cell death emerging as key contributors. Notably, single-cell data confirmed that plasma cell accumulation and naive-like cell reduction showed linear changes during organ aging. Aging trend genes identified in each organ were significantly enriched in aging-related functional pathways, enabling precise assessment of the aging process and determination of organ-specific aging milestones. Additionally, drug screening identified Fostamatinib, Ranolazine, and Metformin as potential modulators of multi-organ aging, with mechanisms involving key pathways such as longevity regulation and circadian rhythm.

Conclusions: The 2A model represents a significant advancement in aging assessment by integrating multi-dimensional validation strategies, enhancing its accuracy and applicability. The identification of organ-specific aging pathways and candidate pharmacological interventions provides a theoretical foundation and translational framework for precision anti-aging therapies.

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PREPRINT

Pan-tissue Transcriptome Analysis Reveals Sex-dimorphic Human Aging

Siqi Wang, Danyue Dong, Xin Li, Zefeng Wang

Complex diseases often exhibit sex-dimorphism in morbidity and prognosis, many of which are age-related. However, the underlying mechanisms of sex-dimorphic aging remain foggy, with limited studies across multiple tissues. We systematically analyzed ~17,000 transcriptomes from 35 human tissues to quantitatively evaluate the individual and combined contributions of sex and age to transcriptomic variations. We discovered extensive sex-dimorphisms during aging with distinct patterns of change in gene expression and alternative splicing (AS). Intriguingly, the male-biased age-associated AS events have a stronger association with Alzheimer's disease, and the female-biased events are often regulated by several sex-biased splicing factors that may be controlled by estrogen receptors. Breakpoint analysis showed that sex-dimorphic aging rates are significantly associated with decline of sex hormones, with males having a larger and earlier transcriptome change. Collectively, this study uncovered an essential role of sex during aging at the molecular and multi-tissue levels, providing insight into sex-dimorphic regulatory patterns.

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EnsembleAge: enhancing epigenetic age assessment with a multi-clock framework

Several widely used epigenetic clocks have been developed for mice and other species, but a persistent challenge remains: different mouse clocks often yield inconsistent results. To address this limitation in robustness, we present EnsembleAge, a suite of ensemble-based epigenetic clocks. Leveraging data from over 200 perturbation experiments across multiple tissues, EnsembleAge integrates predictions from multiple penalized models. Empirical evaluations demonstrate that EnsembleAge outperforms existing clocks in detecting both pro-aging and rejuvenating interventions. Furthermore, we introduce EnsembleAge HumanMouse, an extension that enables cross-species analyses, facilitating translational research between mouse models and human studies. Together, these advances underscore the potential of EnsembleAge as a robust tool for identifying and validating interventions that modulate biological aging.

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An unbiased comparison of 14 epigenetic clocks in relation to 10-year onset of 174 disease outcomes in 18,859 individuals

Christos Mavrommatis, Daniel W Belsky, Kejun Ying, Mahdi Moqri, Archie Campbell, Anne Richmond, Vadim N Gladyshev, Tamir Chandra, Daniel L McCartney, Riccardo E Marioni

Epigenetic Clocks have been trained to predict chronological age, healthspan and lifespan. Such clocks are often analysed in relation to disease outcomes – typically using small datasets and a limited number of clocks. Here, we present the first large-scale (n=18,849), unbiased comparison of 14 widely used clocks as predictors of 174 incident disease outcomes and all-cause mortality. Second-generation clocks significantly outperformed first-generation clocks, which have limited applications in disease settings. Of the 176 Bonferroni significant ($P<0.05/174$) associations, there were 27 diseases (including primary lung cancer and diabetes) where the hazard ratio for the clock exceeded the clock's association with all-cause mortality. Furthermore, there were 35 instances where adding a clock to a null classification model with traditional risk factors increased the classification accuracy by >1% with an AUC_{full} > 0.80. Second-generation epigenetic clocks show promise for disease risk prediction, particularly in relation to respiratory and liver-based conditions.

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Dying occurs as a defined molecular progression in *Drosophila* rather than as nonspecific physiological collapse

Andrew W Scott [1], Andrew P K Wodrich [1 2 3], Hitesh S Chaouhan [1], Arvind K Shukla [1], Kory Johnson [1], Philip G McQueen [1], Edward Giniger [1 4]

While we know much about aging, dying remains mysterious. Here, we show that old-age death in *Drosophila* is an orderly process that follows, but is distinguishable from, aging itself. We apply pseudotime trajectory analysis to transcriptomic data from individual flies as they approach death. This uncovers a reproducible progression of molecular events that accompany dying, as revealed by systematic changes in gene expression, including both continuation of some processes of early- and mid-life aging, but also activation of processes that are not associated with aging but instead define progression toward death. Finally, we reanalyze an existing *Caenorhabditis elegans* dataset and find that many processes we observe in dying flies also vary among dying worms, suggesting that features of dying have been maintained across 600 Myr of evolution. These data challenge the idea that dying is simply a collapse of physiology that is the inherent conclusion to the dysfunctions of aging.

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Lithium deficiency and the onset of Alzheimer's disease

The earliest molecular changes in Alzheimer's disease (AD) are poorly understood[1,2,3,4,5]. Here we show that endogenous lithium (Li) is dynamically regulated in the brain and contributes to cognitive preservation during ageing. Of the metals we analysed, Li was the only one that was significantly reduced in the brain in individuals with mild cognitive impairment (MCI), a precursor to AD. Li bioavailability was further reduced in AD by amyloid sequestration. We explored the role of endogenous Li in the brain by depleting it from the diet of wild-type and AD mouse models. Reducing endogenous cortical Li by approximately 50% markedly increased the deposition of amyloid-β and the accumulation of phospho-tau, and led to pro-inflammatory microglial activation, the loss of synapses, axons and myelin, and accelerated cognitive decline. These effects were mediated, at least in part, through activation of the kinase GSK3β. Single-nucleus RNA-seq showed that Li deficiency gives rise to transcriptome changes in multiple brain cell types that overlap with transcriptome changes in AD. Replacement therapy with lithium orotate, which is a Li salt with reduced amyloid binding, prevents pathological changes and memory loss in AD mouse models and ageing wild-type mice. These findings reveal physiological effects of endogenous Li in the brain and indicate that disruption of Li homeostasis may be an early event in the pathogenesis of AD. Li replacement with amyloid-evading salts is a potential approach to the prevention and treatment of AD.

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Accelerated brain ageing during the COVID-19 pandemic

The impact of SARS-CoV-2 and the COVID-19 pandemic on brain health is recognised, yet specific effects remain understudied. We investigate the pandemic's impact on brain ageing using longitudinal neuroimaging data from the UK Biobank. Brain age prediction models are trained from hundreds of multi-modal imaging features using a cohort of 15,334 healthy participants. These models are then applied to an independent cohort of 996 healthy participants with two magnetic resonance imaging scans: either both collected before the pandemic (Control groups), or one before and one after the pandemic onset (Pandemic group). Our findings reveal that, even with initially matched brain age gaps (predicted brain age vs. chronological age) and matched for a range of health markers, the pandemic significantly accelerates brain ageing. The Pandemic group shows on average 5.5-month higher deviation of brain age gap at the second time point compared with controls. Accelerated brain ageing is more pronounced in males and those from deprived socio-demographic backgrounds and these deviations exist regardless of SARS-CoV-2 infection. However, accelerated brain ageing correlates with reduced cognitive performance only in COVID-infected participants. Our study highlights the pandemic's significant impact on brain health, beyond direct infection effects, emphasising the need to consider broader social and health inequalities.

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PREPRINT

Normal aging increases white matter microglial reaction and perivascular macrophages in the microcebe primate

As populations age, the incidence of neurodegenerative disorders is rising. Early age-related neuropathological changes are the breeding ground for the development of these disorders. Microglia are the resident macrophages of the central nervous system. They play crucial roles in maintaining brain homeostasis, yet their age-related changes remain not fully understood. While age-related microglia changes have been strongly characterized in rodents, studies in non-human primates are scarce. The microcebe primate (mouse lemur (*Microcebus murinus*)) is widely used as a model for cerebral aging and to investigate age-related neurodegenerative processes. HLA-DR is a major histocompatibility class II cell surface receptor which presents antigens to cells of the immune response. It is a major marker of microglia reaction. In this study, we explored microglia in the whole brains of middle-aged and old microcebes using HLA-DR immunolabeling. We analyzed microglial morphology and quantified HLA-DR+ cell density and protein expression. A wide range of microglial morphologies was observed in the white matter, including thin processes microglia, "rod-like" elongated and polarized shape, hypertrophic, and amoeboid microglia. Aging was associated with increased HLA-DR+ microglial expression in the white matter while very few HLA-DR+ microglia were observed in the parenchyma of cortical gray matter regions. A second finding was the higher number of HLA-DR+ perivascular macrophages in old animals. This study in a primate outlines that, in the absence of neurodegenerative processes, the most prominent signs of age-related microglia/macrophage changes are region-specific and concern white matter and perivascular regions. This emphasizes the need to target these regions to prevent cerebral aging.

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High-Throughput Screening of Potent Drug-like Molecules Targeting 17β-HSD10 for the Treatment of Alzheimer's Disease and Cancer

Laura Aitken, Gemma Baillie, Andrew Pannifer, Angus Morrison, Louise L. Major, Magnus S. Alphey, Ritika Sethi, Martin Timmerman, John Robinson, Jennifer Riley, Yoko Shishikura, Lizbe Koekemoer, Frank Von Delft, Helma Rutjes, Kevin D. Read, Philip S. Jones, Stuart P. McElroy, Terry K. Smith, and Frank J. Gunn-Moore*

In this study, the first industrial-scale high-throughput screening of nearly 350,000 drug-like molecules targeting the enzyme 17β-HSD10, a promising therapeutic target for Alzheimer's disease and cancers, is presented. Two novel series of potent 17β-HSD10 inhibitors that demonstrate low nanomolar potency against both the enzyme and *in vivo* cellular assays with minimal cytotoxicity were identified. These inhibitors were characterized further through a series of assays demonstrating ligand–protein interactions and co-crystallography, revealing un-/non-competitive inhibition with respect to the cofactor NADH, unlike previously published inhibitors. This work significantly advances the development of 17β-HSD10-targeting therapeutics, offering new potential leads for treating Alzheimer's disease and cancers.

Acyl-CoA-binding protein as a driver of pathological aging

The tissue hormone acyl coenzyme A–binding protein (ACBP, encoded by the gene *diazepam-binding inhibitor*, DBI) has been implicated in various facets of pathological aging. Here, we show that ACBP plasma concentrations are elevated in (close-to-)centenarians (mean ± SD age 99.5 ± 4.5 y) commensurate with their health deterioration, correlating with a reduced glomerular filtration rate and a surge in senescence-associated cytokines. ACBP neutralization by means of a monoclonal antibody (mAb) improved health span in a strain of progeroid mice. In a mouse model of chronic kidney injury induced by cisplatin, anti-ACBP mAb administration counteracted both histopathological and functional signs of organ failure. ACBP inhibition also prevented the senescence of tubular epithelial cells and glomerular podocytes induced by cisplatin or doxorubicin, respectively, as measurable by the immunohistochemical detection of cyclin-dependent kinase inhibitor 1A (CDKN1A, best known as p21). Senescence was also prevented by anti-ACBP mAb treatment in additional mouse models of accelerated aging. This applied to liver damage induced by a combination of high-fat diet and carbon tetrachloride, where hepatic cells become senescent. Moreover, administration of anti-ACBP mAb prevented natural and doxorubicin-accelerated cardiomyocyte senescence. We performed single-nucleus RNA sequencing to study the transcriptome of hearts that had been exposed to doxorubicin and/or anti-ACBP in vivo. In cardiomyocytes, doxorubicin caused an anti-ACBP-reversible dysregulation of mRNAs coding for cardioprotective proteins involved in autophagy, fatty acid oxidation, mitochondrial homeostasis, and oxidative phosphorylation. Altogether, these findings plead in favor of a broad age-promoting effect of ACBP across different organ systems.

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Rapamycin Does Not Compromise Exercise-Induced Muscular Adaptations in Female Mice

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An increasing number of physically active adults are taking the mTOR inhibitor rapamycin off label with the goal of extending healthspan. However, frequent rapamycin dosing disrupts metabolic health during sedentary conditions and abates the anabolic response to exercise. Intermittent once-weekly rapamycin dosing minimizes many negative metabolic side effects of frequent rapamycin in sedentary mice. However, it remains unknown how different rapamycin dosing schedules impact metabolic, physical, and skeletal muscle adaptations to voluntary exercise training. Therefore, we tested the hypothesis that intermittent rapamycin (2 mg/kg; 1×/week) would avoid detrimental effects on adaptations to 8 weeks of progressive weighted wheel running (PoWeR) in adult female mice (5-month-old) by evading the sustained inhibitory effects on mTOR signaling by more frequent dosing schedules (2 mg/kg; 3×/week). PoWeR improved maximal exercise capacity, absolute grip strength, and myofiber hypertrophy with no differences between vehicle or rapamycin-treated mice despite greater voluntary running volume with intermittent rapamycin treatment. Conversely, frequent and intermittent rapamycin-treated mice had impaired glucose tolerance and insulin sensitivity compared to vehicle-treated mice after PoWeR; however, intermittent rapamycin reduced the impact on glucose intolerance versus frequent rapamycin. Collectively, these data in adult female mice suggest that (1) rapamycin is largely compatible with the physical and skeletal muscle benefits of PoWeR and (2) the detrimental effects of rapamycin on glucose metabolism in the context of voluntary exercise may be reduced by intermittent dosing.

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Associations between sarcopenia (defined by low muscle mass), inflammatory markers, and all-cause mortality in older adults: mediation analyses in a large U.S. NHANES community sample, 1999–2006

Background: Sarcopenia is linked to increased mortality, but the specific role of inflammation in sarcopenia-related mortality remains poorly understood. This study aims to integrate various inflammatory biomarkers to develop an inflammation prognostic score (IPS) within the large, representative NHANES cohort. It also explores the association between sarcopenia, inflammatory markers, and mortality, and investigates whether inflammation mediates this relationship.

Methods: This study analyzed data from NHANES (1999-2006) on 3,544 participants aged 65 and older, with mortality follow-up through December 31, 2019, using death records from the National Death Index (NDI). Statistical analyses accounted for complex survey design and multiple imputation for missing data. Sarcopenia was defined using appendicular skeletal mass (ASM) adjusted for body mass index (BMI). Cox regression assessed the association between sarcopenia, inflammatory markers, and all-cause mortality. The IPS was developed using LASSO regression, and mediation analysis was conducted to assess whether inflammatory markers mediate the relationship between sarcopenia and mortality.

Results: Among 3,544 elderly participants, sarcopenia was present in 25.4%, with a 66.6% overall mortality rate during the follow-up period. Multivariate Cox regression confirmed that sarcopenia is an independent risk factor for mortality [Hazard ratio (HR) = 1.235-1.281, $P < 0.001$]. Inflammatory markers were significantly associated with all-cause mortality. The IPS showed a clear trend of increasing mortality risk across quartiles, with HR reaching 2.044 in Q4 ($P < 0.001$). Mediation analysis showed that IPS mediated 20.8% of the relationship between sarcopenia and mortality, with the mediating effect remaining significant after adjusting for confounders.

Conclusion: This study confirms the association between sarcopenia and increased mortality risk, with inflammation as a key mediating factor, highlighting its role in sarcopenia-related mortality.

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Interactions between bone density and muscle mass in predicting all-cause mortality: a 10-year prospective cohort study of 1388 older men (aged 77–101 years)

Main Outcome Measure

All-cause mortality by death certificates and International Classification of Diseases-Ninth Revision codes measured from 2014 to 2016 through August 2024. Data analysis was performed during December 2024. Cox hazards models were used to model the relationship between the exposures and outcomes, unadjusted and adjusted for covariates.

Results

A total of 1388 men with a mean age of 84.2 ± 4.1 years (77–101 years, 91.6% white) were followed for 6.58 ± 2.61 years. A total of 663 (47.8%) men died. In unadjusted analyses using continuous exposures, interaction terms were significant between bone and muscle variables for all-cause mortality ($P < 0.001$ to 0.039). In men with low muscle mass or low muscle volume (≤50th percentile), each SD decrease in bone density increased all-cause mortality by a respective 19% (HR = 1.19 95% CI 1.07–1.34) and 29% (HR = 1.29 95% CI 1.11–1.49) in multivariable-adjusted models. Likewise, in men with low muscle mass or low muscle volume (≤50th percentile), each SD decrease in bone strength increased all-cause mortality by a respective 19% (HR = 1.19 95% CI 1.06–1.33) and 29% (HR = 1.29 95% CI 1.12–1.48) in multivariable-adjusted models.

Conclusions

We found consistent evidence for a combined association of bone and muscle health on all-cause mortality. Randomised controlled trials are now needed to confirm if increasing or preserving bone and muscle mass in old age reduces mortality risk.

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Early-life exercise extends healthspan but not lifespan in mice

Mengya Feng, Min Li, Jing Lou, Guiling Wu, Tian Gao, Fangqin Wu, Yanzhen Tan, Nini Zhang, Yong Zhao, Lin Zhao, Jia Li, Changhong Shi, Xing Zhang ✉, Jiankang Liu ✉ & Feng Gao ✉

It is well-known that physical activity exerts health benefits, yet the potential impacts of early-life regular exercise on later-life health and lifespan remains poorly understood. Here, we demonstrate that 3 months of early-life exercise in mice results in lasting health benefits, extending healthspan, but not lifespan. C57BL/6J mice underwent swimming exercise from 1 to 4 months of age, followed by detraining for the remainder of their lives. While early-life exercise did not extend the overall lifespan, it significantly improved healthspan in both male and female mice, as evidenced by enhanced systemic metabolism, cardiovascular function, and muscle strength, as well as reduced systemic inflammation and frailty in aged mice. Multiple-organ transcriptome analyses identified enhanced fatty acid metabolism in skeletal muscles as a major feature in aged mice that underwent early-life exercise. These findings reveal the enduring long-term health benefits of early-life exercise, highlighting its pivotal role in improving healthspan.

Daily steps and health outcomes in adults: a systematic review and dose-response meta-analysis

Findings

57 studies from 35 cohorts were included in the systematic review and 31 studies from 24 cohorts were included in meta-analyses. For all-cause mortality, cardiovascular disease incidence, dementia, and falls, an inverse non-linear dose-response association was found, with inflection points at around 5000–7000 steps per day. An inverse linear association was found for cardiovascular disease mortality, cancer incidence, cancer mortality, type 2 diabetes incidence, and depressive symptoms. Based on our meta-analyses, compared with 2000 steps per day, 7000 steps per day was associated with a 47% lower risk of all-cause mortality (HR 0·53 [95% CI 0·46–0·60]; I^2=36·3; 14 studies), a 25% lower risk of cardiovascular disease incidence (HR 0·75 [0·67–0·85]; I^2=38·3%; six studies), a 47% lower risk of cardiovascular disease mortality (HR 0·53 [0·37–0·77]; I^2=78·2%; three studies), a non-significant 6% lower risk of cancer incidence (HR 0·94 [0·87–1·01]; I^2=73·7%; two studies), a 37% lower risk of cancer mortality (HR 0·63 [0·55–0·72]; I^2=64·5%; three studies), a 14% lower risk of type 2 diabetes (HR 0·86 [0·74–0·99]; I^2=48·5%; four studies), a 38% lower risk of dementia (HR 0·62 [0·53–0·73]; I^2=0%; two studies), a 22% lower risk of depressive symptoms (HR 0·78 [0·73–0·83]; I^2=36·2%; three studies), and a 28% lower risk of falls (HR 0·72 [0·65–0·81]; I^2=47·5%; four studies). Studies on physical function (not based on meta-analysis) reported similar inverse associations. The evidence certainty was moderate for all outcomes except for cardiovascular disease mortality (low), cancer incidence (low), physical function (low), and falls (very low).

Interpretation

Although 10 000 steps per day can still be a viable target for those who are more active, 7000 steps per day is associated with clinically meaningful improvements in health outcomes and might be a more realistic and achievable target for some. The findings of the study should be interpreted in light of limitations, such as the small number of studies available for most outcomes, a lack of age-specific analysis and biases at the individual study level, including residual confounding.

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A pilot study evaluating differences in muscle tissue saturation and blood flow between older adults with and without sarcopenia

Provisionally accepted

To optimize skeletal muscle function, adequate oxygen transport and nutrient delivery to the muscle is needed. Decreased blood flow with aging may result in reduced nutritive flow to muscle, which may be compounded by those with less muscle mass. The purpose of this study was to examine differences in muscle oxygen utilization and muscle blood flow between non-sarcopenic and sarcopenic adults during pre-and post-prandial periods and during aerobic and anaerobic exercise.Methods: Ten older adults (mean±SD; age=72.4±4.9y; stature=167.5±7.6cm; body mass=71.6±12.2kg) were categorized as non-sarcopenic, and eight (age=82.9±11.4y; stature=165.7±4.5cm; body mass=70.3±8.0kg) were categorized as sarcopenic based on handgrip strength, body composition, and physical performance. Near-infrared spectroscopy (NIRS) was recorded pre-and-post consumption of a rapidly-digesting carbohydrate meal and during aerobic and anaerobic exercise. Deoxygenated hemoglobin (Hb)+myoglobin (Mb) (deoxyHb), Total Hb+Mb (THb) and muscle tissue oxygen saturation index (TSI) was measured using NIRS. Changes from baseline were calculated for deoxyHb and THb normalized to adipose tissue thickness (ΔdeoxyHbATT and ΔTHbATT).Results: Post-prandial, non-sarcopenic individuals had 224% greater ΔTHbATT at 90 min (p=0.034) compared to sarcopenic and higher levels at 150 mins compared to baseline (p=0.004). Non-sarcopenia demonstrated greater ΔTHbATT at 90-120 mins than 15-60 min (p=0.018-0.047). During aerobic exercise, non-sarcopenic reported approximately 9% greater TSI compared to sarcopenic individuals (p=0.023-0.046). For anaerobic exercise, non-sarcopenic individuals saw 18%-49% lower values for ΔTHbATT at 80 and 100% compared to 60% and a 4% lower value at 100% compared to 80% of the exercise bout (p=0.034-0.043), while sarcopenic individuals experienced no change (p=0.122-0.512). Non-sarcopenia had 13% greater TSI than those with sarcopenia at 40% (p=0.026) and saw significant decreases over the anaerobic exercise bout (p=0.011-0.049) while TSI in the sarcopenic group remained unchanged (p=0.084-0.529).Discussion: Sarcopenia demonstrated decreased oxidative capacity and blood flow detectable by NIRS, potentially contributing to metabolic dysfunction. While more research is needed, NIRS responses were distinct between sarcopenic and non-sarcopenic individuals post-prandial and during exercise. Nutrition and exercise interventions focusing on strategies to improve blood flow to promote muscle health are necessary to reduce sarcopenia and related-metabolic dysfunction progression with aging.

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Multiomics and cellular senescence profiling of aging human skeletal muscle uncovers Maraviroc as a senotherapeutic approach for sarcopenia

Cellular senescence is a hallmark of organismal aging but how it drives aging in human tissues is not fully understood. Here we leverage single nucleus multiomics to profile senescence in mononucleated cells of human skeletal muscle and provide the first senescence atlas. We demonstrate the intra- and inter-populational transcriptomic and epigenomic heterogeneity and dynamics of cellular senescence. We also identify commonalities and variations in senescence-associated secretory phenotypes (SASPs) among the cells and elucidate SASP mediated cellular interactions and niche deregulation. Furthermore, we identify targetable SASPs and demonstrate the possibility of using Maraviroc as a pharmacological senotherapeutic for treating age-associated sarcopenia. Lastly, we define transcription factors that govern senescence state and SASP induction in aging muscle and elucidate the key function and mechanism of JUNB in SASP activation. Altogether, our findings demonstrate the prevalence and function of cellular senescence in skeletal muscle and identify a novel pharmacological intervention for sarcopenia.

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Senescent macrophages induce ferroptosis in skeletal muscle and accelerate osteoarthritis-related muscle atrophy

Muscle atrophy around joints is a common issue for people with osteoarthritis (OA), but its causes are poorly understood. Here we demonstrate that chronic inflammation in quadriceps muscle coincides with OA in mice, characterized by an increase in macrophages, activation of inflammatory pathways and tissue vascularization. We show that, during OA progression, macrophages progressively exhibit increasing phenotypes of senescence and promote muscle atrophy through paracrine induction of ferroptosis. Mechanistically, iron overload-induced mitochondrial damage results in reduced asparagine metabolites, impairing coenzyme Q10 (CoQ10) synthesis by inhibiting mTORC1–HMGCR signaling. Ultimately, this cascade enhances lipid peroxidation and promotes ferroptosis in skeletal muscle cells. We show that the cardiac medication CoQ10 can attenuate muscle atrophy by inhibiting ferroptosis, thereby reducing pathological damage to OA joints. Our findings offer insights for the potential management of muscle atrophy in patients with OA.

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PREPRINT

NAD⁺ Replenishment Mitigates Cardiomyocyte Senescence and Corrects Heart Failure with Preserved Ejection Fraction in Aged Mice

Cardiomyocyte senescence, characterized by elevated cell cycle inhibitor expression, persistent DNA damage response, and mitochondrial dysfunction, contributes to myocardial stiffness and the progression of heart failure with preserved ejection fraction (HFpEF), the most common form of heart failure affecting individuals over 65. In this study, we investigated the role of NAD⁺ metabolism in cardiomyocyte senescence and cardiac function. Aged mice exhibited reduced cardiac NAD⁺ levels, impaired NAD⁺ biosynthesis and mobilization, and increased consumption, leading to suppressed SIRT1/6 activity and accumulation of senescent cardiomyocytes. This was accompanied by diastolic dysfunction consistent with HFpEF. In senescent AC16 cardiomyocytes, NAD⁺ depletion promoted senescence, which was reversed by the NAD⁺ precursors nicotinamide riboside (NR) and dihydronicotinamide riboside (NRH). In aged mice, two months of NR or NRH treatment improved diastolic function and reduced cardiomyocyte senescence. While NR primarily activated SIRT1 to suppress cell cycle arrest markers, NRH more robustly activated both SIRT1 and SIRT6, enhancing DNA damage repair. Acetylated H2AX, a SIRT6 substrate elevated in aged hearts and senescent cells, was selectively deacetylated by NRH. These findings identify NAD⁺ availability as a critical regulator of cardiac senescence and support NAD⁺ precursors, particularly NRH, as promising senescence-reducing therapies for treating aging-associated HFpEF.

CD38-Targeting Peptide Vaccine Ameliorates Aging-Associated Phenotypes in Mice

Shangcheng Yu [1], Zhiqiang Li [1], Yuxiang Tang [1], Yuling Chen [1], Yingying Ma [1], Kunlin Du [1], Zhaoyun Zong [1], Kangze Feng [1], Yali Wei [2], Limeng Chen [3], Haiteng Deng [1 4]

Antiaging vaccines have recently been found to elicit long-term benefits in slowing the aging process. Meanwhile, high CD38 expression in organs is an aging characteristic contributing to a decreased NAD^+/NADH ratio. Thus, in the current study, we systematically investigate the effects of a CD38-targeting peptide vaccine (CD38-vaccine) on aging-associated phenotypes in mice. The CD38-vaccine induces a robust T-cell immune response, selectively depletes $CD38^+$ myeloid cells in the spleen, and ameliorates age-related physical and cognitive function decline. Metabolically, vaccination improves glucose tolerance, enhances oxygen consumption, and decreases the number of senescent cells and mRNA levels of senescence-related genes in liver tissues. Vaccination also increases the NAD^+/NADH ratio in the liver tissues, enhances oxidative metabolism, and reduces glycolysis. These findings indicate that targeting CD38 via vaccination is a promising strategy for ameliorating aging-associated phenotypes.

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Genetic association of intelligence with longevity in *Drosophila melanogaster*

Mousumee Khan, Enkhchimeg Lkhagva, Hae-mi Kim, Chongkai Zhai, Sharif Hasan Siddiqui, Seong-Tshool Hong

Epidemiological studies in different populations, in different countries, and in different epochs consistently showed that high intelligence is positively correlated with longevity. The link between high intelligence and longevity has remained unknown, only to be assumed as a consequence of the socioeconomic difference associated with intelligence in human population. Here, we report that genome stability contributes both to lifespan and intelligence in *Drosophila melanogaster*. The intelligence of the genetically heterogenous flies was determined by T-maze olfactory memory assay, and the flies moving to the right direction defined as intelligent flies (INT) were separated from the flies moving to the wrong direction defined as non-intelligent flies (NINT). INT male and female lived 26.40% and 21.35% longer than NINT male and female, respectively, suggesting a possible genetic linkage between intelligence and longevity. The bidirectional selective breeding based on intelligence extended lifespans gradually generation by generation in INT breeding contrast to the reversed pattern in NINT breeding. INT of F12 generation lived longer than NINT of F12 generation, 63.91% for male and 67.88% for female, as a result from slower aging. The whole-genome transcriptome analysis showed the activation of the genes in ribosome and autophagy in INT and the pathways of genome stability and immune reaction in NINT. Especially, the genetic pathway associated with genome stability was most noticeable, indicating that genome stability contributes both to lifespan and intelligence in *D. melanogaster*.

Profiling Epigenetic Aging at Cell-Type Resolution Through Long-Read Sequencing

Alec Eames, Mahdi Moqri, Jesse R. Poganik, Vadim N. Gladyshev

DNA methylation can give rise to robust biomarkers of aging, yet most studies profile it at the bulk tissue level, which masks cell type-specific alterations that may follow distinct aging trajectories. Long-read sequencing technology enables methylation profiling of extended DNA fragments, enabling mapping to their cell type of origin. In this study, we introduce a framework for evaluating cell type-specific aging using long-read sequencing data, without the need for cell sorting. Leveraging cell type-specific methylation patterns, we map long-read fragments to individual cell types and generate cell type-specific methylation profiles, which are used as input to a newly developed probabilistic aging model, LongReadAge, capable of predicting epigenetic age at the cell type level. We use LongReadAge to track aging of myeloid cells and lymphocytes from bulk leukocyte data as well as circulating cell-free DNA, demonstrating robust performance in predicting age despite limited shared features across samples. This approach provides a novel method for profiling the dynamics of epigenetic aging at cell type resolution.

Identification of Functional Cellular Markers Related to Human Health, Frailty and Chronological Age

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Aging leads to a decline in physiological reserves, an increase in age-related diseases, reduced functional ability and a shortened healthspan. While molecular markers of chronological aging exist, their link to general health and intrinsic capacity (IC), a composite measure of physical and mental capacities, remains unclear. This study integrates the WHO's Healthy Aging framework with geroscience to explore fibroblasts as indicators of health. We assessed primary skin fibroblasts from 133 individuals aged 20–96, evaluating their ability to maintain tissue structure, modulate immune responses and regulate metabolism (SIM functions). By combining functional and molecular analyses, we investigated the relationship between fibroblast performance, chronological age and IC. Our results demonstrate that fibroblast SIM functions are modified with stressors and age, correlating with IC rather than just chronological age. Notably, fibroblasts from pre-frail and frail individuals exhibited reduced mitochondrial respiration and lower extracellular periostin levels, with periostin being able to capture IC status, irrespective of age and sex, reflecting a cellular 'health memory'. The SIM paradigm provides a complementary framework to the established hallmarks of aging, advancing our understanding of how cellular aging impacts functional decline. These findings suggest that fibroblast-derived markers could serve as indicators of frailty and reduced IC, enabling early detection of individuals at risk for health deterioration and laying the foundation for early identification of functional decline.

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Single-cell and spatial transcriptomics map senescent vascular cells in arterial remodeling during atherosclerosis in mice

Growing evidence suggests that the induction of cellular senescence in vascular cells is causally linked to the etiology of cardiovascular diseases. To investigate systematically the heterogeneity of senescent vascular cells in atherosclerosis, we used a high-fat diet and PCSK9 overexpression to induce atherosclerosis in a senescence reporter mouse model (*p16-tdTomato*$^{+/-}$) and performed single-cell RNA sequencing on whole aortas. Using the SenMayo and CellAge gene sets, we identified four clusters of vascular smooth muscle cells (VSMCs), fibroblasts and T cells enriched in features of senescence, which were reduced upon treatment with the senolytic agent ABT-737. We then derived a global senescence signature of atherosclerosis including *Spp1*, *Ctsb* and *Tnfrsf11b* mRNAs. We validated the enrichment of these mRNAs in senescence by using spatial transcriptomics in a second mouse model of atherosclerosis and senolysis (*Ldlr*$^{-/-}$; *p16-3MR*), as well as by analyzing in vitro models of human VSMC senescence. Our results uncover a vascular-specific transcriptomic signature of senescence that may be exploited for tracking and treating age-related vascular diseases.

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The exposome of healthy and accelerated aging across 40 countries

Protective and risk factors can drive healthy or accelerated aging, with distinct environments modulating their effects. The impact of the exposome—the combined physical and social exposures experienced throughout life—on accelerated aging remains unknown. We assessed delayed and accelerated aging in 161,981 participants from 40 countries (45.09% female; mean age, 67.06; s.d., 9.85) by measuring biobehavioral age gaps (BBAGs), defined as the difference between estimated age from protective and risk factors and chronological age, in cross-sectional and longitudinal designs. BBAGs predicted chronological age, followed by regional and exposomal factor analyses, linked to accelerated aging. Europe led in healthy aging, while Egypt and South Africa showed the greatest acceleration; Asia and Latin America fell in between (Cliff's delta (δd) = 0.15–0.52; all $P < 0.0001$). Accelerated aging was more evident in eastern and southern Europe; globally, it was also associated with lower income ($\delta d = 0.48–0.56$, $P < 1 \times 10^{-15}$). Exposomal factors of accelerated aging include physical (air quality), social (socioeconomic and gender inequality, migration) and sociopolitical (representation, party freedom, suffrage, elections and democracy) determinants (all Cohen's d (d) > 0.37, $P < 0.0001$). BBAGs predicted future functional (r (Pearson correlation) = −0.33, $P < 1 \times 10^{-15}$, $d = 0.70$) and cognitive declines ($r = -0.22$, $P < 1 \times 10^{-15}$, $d = 0.44$), and larger BBAGs ($P < 0.0001$, $d = 1.55$). Healthy and accelerated aging are influenced by physical, social and sociopolitical exposomes, with considerable disparities across nations.

Cross-omics risk scores of inflammation markers are associated with all-cause mortality: The Canadian Longitudinal Study on Aging

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Inflammation is a critical component of chronic diseases, aging progression, and lifespan. Omics signatures may characterize inflammation status beyond blood biomarkers. We leveraged genetics (polygenic risk score [PRS]), metabolomics (metabolomic risk score [MRS]), and epigenetics (epigenetic risk score [ERS]) to build multi-omics-multi-marker risk scores for inflammation status represented by the level of circulating C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α). We found that multi-omics risk scores generally outperformed single-omics risk scores in predicting all-cause mortality in the Canadian Longitudinal Study on Aging. Compared with circulating inflammation biomarkers, some multi-omics risk scores had a higher hazard ratio (HR) for all-cause mortality when including both score and circulating IL-6 in the same model (1-SD IL-6 MRS-ERS: HR = 2.20 [1.55–3.13] vs. 1-SD circulating IL-6 HR = 0.94 [0.67,1.32]. 1-SD IL-6 PRS-MRS: HR = 1.47 [1.35,1.59] vs. 1-SD circulating IL-6 HR = 1.33 [1.18, 1.51]. 1-SD PRS-MRS-ERS: HR = 1.95 [1.40, 2.70] vs. 1-SD circulating IL-6: HR = 0.99 [0.71, 1.39]). In the Nurses' Health Study (NHS), NHS II, and Health Professional Follow-up Study with available omics, 1 SD of IL-6 PRS and 1-SD IL-6 PRS-MRS had HR = 1.12 [1.00,1.26] and HR = 1.13 [1.01,1.26] among individuals >65 years old without mutual adjustment of the score and circulating IL-6. Our study demonstrates that some multi-omics scores for inflammation markers may characterize important inflammation burden for an individual beyond those represented by blood biomarkers and improve our prediction capability for the aging process and lifespan.

Even at 100+: Acute Exercise Modulates Inflammatory Pathways in Centenarians

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Centenarians exhibit remarkable disease resilience despite chronic low-grade inflammation. We investigated the inflammation-related proteome response to acute exercise in seven centenarians (100–104 years). Exercise downregulated 52 proteins (e.g., TNF, IL10, IL1RN, CCL family members) involved in immune cell trafficking, apoptosis, and cytokine regulation. Even at the extreme end of the lifespan, humans retain molecular responsiveness to exercise, with modulation of inflammation-related pathways.

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PREPRINT

sTelomere replication stress-induced DNA damage response triggers inflammatory signaling via canonical and non-canonical STING pathways

Wei Zhu, Yi Gong, Yunong Wang, Myriam Gorospe, Yie Liu

Telomeres are protected by the shelterin complex, but they are also common fragile sites and are particularly susceptible to replicative stress. We found that depletion of telomeric repeat-binding factor 1 (TRF1), a key shelterin component essential for telomere replication, in mouse embryonic fibroblasts (MEFs) activated ATR- and subsequent ATM-dependent DNA damage responses. TRF1 loss increased the formation of micronuclei and cytosolic DNA, leading to ATR-dependent micronuclear rupture and activation of the cGAS/STING pathway. ATM activation enhanced STING K63 modification, thereby boosting the STING/NFκB pathway. Inhibition of ATM or cGAS reduced the expression of the pro-inflammatory cytokine IL6, with combined inhibition further suppressing IL6 levels. Depletion or inhibition of STING alone decreased production of IL6 and IFNβ, with no major reduction by combined ATM and/or cGAS inhibitors. These findings indicate that STING acts epistatically with ATM- and cGAS-mediated inflammatory responses. Overall, the telomere replication stress and dysfunction triggered by loss of TRF1 promotes inflammation through the ATR/cGAS/STING and ATM/STING pathways.

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PREPRINT

A multi-omics analysis of human fibroblasts overexpressing an *Alu* transposon reveals widespread disruptions in aging-associated pathways

During aging and cellular senescence, repetitive elements are frequently transcriptionally derepressed across species and cell types. Among these, the most abundant repeats by copy number in the human genome are *Alu* retrotransposons. Though *Alu* elements are often studied for their mutagenic potential, there is increasing appreciation for their contributions to other biological functions, including pro-inflammatory signaling and mitochondrial dysfunction. However, a comprehensive analysis of *Alu*-driven molecular changes remains to be conducted, and *Alu*'s potential contributions to aging features remain incompletely characterized. Here, we show that overexpression of an *AluJb* transposon in human primary IMR-90 fibroblasts leads to large-scale alterations across the transcriptome, cellular proteome, and secretome. Functional genomics analyses reveal alterations in aging/senescence pathways, broadly, and mitochondrial metabolism, proteostasis, cell cycle, and extracellular matrix pathways, more specifically. Our results demonstrate that *Alu* transcriptional upregulation is sufficient to drive widespread disruptions to cellular homeostasis that mirror aging-associated alterations.

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A Trade-Off between Body Mass and Cancer Resistance in Cetaceans Is Mediated by Cell Cycle-Related Gene Evolution

Linxia Sun , Yi Li , Huijie Zhang , Xinrui Chen , Guang Yang , Shixia Xu ✉ Author Not

Cetaceans, well-known for their exceptionally long lifespans and substantial body masses, demonstrate a lower risk of cancer mortality compared to other mammals, consistent with Peto's paradox. Yet, the underlying mechanisms of cancer resistance, possibly evolved due to large body size, remain largely unclear. Here, we conducted an evolutionary analysis of 50 cell cycle-related genes, which play crucial role in both cancer progression and organismal body mass modulation, to investigate the mechanisms underlying the trade-off between body size and cancer resistance in cetaceans. We found that 66.7% (4/6) rapidly evolving genes (i.e. *CDK2*, *CDT1*, *ORC3*, and *DBF4*) and 50% (2/4) positively selected genes (*ORC2* and *ORC3*) identified in cetaceans are involved in regulating cell cycle checkpoints, which halt the cell cycle in response to damage to allow repair and prevent cancer induction. Additionally, we identified four-body mass-associated genes (*CCNE1*, *ORC5*, *E2F3*, and *DBF4*) known to regulate cell growth; mutations or dysregulation of these genes can drive uncontrolled proliferation and cancer development. Interestingly, convergent evolution was observed in the African elephant and the bowhead whale at the tumor suppressor gene *MYT1*, potentially revealing a convergent mechanism of cancer resistance in large-bodied species. Notably, in vitro assays revealed that a cetacean-specific mutation M155T in the rapidly evolving gene *CCND1* more effectively suppressed tumor cell proliferation and migration. Overall, our study has provided new insights into how the evolution of cell cycle-related genes balances body mass and cancer resistance in cetaceans, offering molecular support for Peto's paradox.

The SG90 cohort of the oldest-old in Singapore

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The global population is ageing rapidly. While genetics, lifestyle, and environment are known contributors to healthspan, most insights are drawn from Western cohorts, leaving Asian populations underrepresented despite unique biological, lifestyle, and cultural factors. The SG90 cohort study aimed to fill knowledge gaps in healthy ageing by identifying modifiable medical, biological, lifestyle, psychological, behavioural, and social factors that contribute to longevity in the oldest-old. The study recruited 1,158 participants aged 85 and above from the Singapore Chinese Health Study (SCHS) and Singapore Longitudinal Aging Study (SLAS) between 2015 and 2021. Data collection involved face-to-face interviews to obtain sociodemographic, lifestyle, sleep, functional status, quality of life, medical conditions and healthcare economics information, along with clinical assessments covering physical examinations, anthropometry, physical performance, cognition, and mental health. Biospecimens, including blood, saliva, stool, urine, toenails, hair, and skin tape strips were collected to support extensive multi-omic and cellular analyses. Participants, primarily female (64.5%) and Chinese (97.5%) with a median age of 87 years [interquartile range (IQR): 86-89], were mostly non-smokers (72.1%) and infrequent alcohol consumers (94.9%), with 66.5% exercising regularly. Functional assessments indicate high independence, with median Basic activities of daily living (BADL) and Instrumental ADL (IADL) scores of 20 (IQR: 19-20) and 14 (IQR: 11-16), respectively. 36% of participants rated their self-reported health as good to excellent. The SG90 cohort study offers a comprehensive clinical and biological data resource on healthy ageing among Asia's oldest-old, laying a foundation for targeted interventions to promote healthy longevity and quality of life.

Structure-based machine learning screening identifies natural product candidates as potential geroprotectors

Age-related diseases and syndromes result in poor quality of life and adverse outcomes, representing a challenge to healthcare systems worldwide. Several pharmacological interventions have been proposed to target the aging process to slow its adverse effects. The so-called *geroprotectors* have been proposed as novel molecules that could maintain the organism's homeostasis, targeting specific aspects linked to the hallmarks of aging and delaying the adverse outcomes associated with age. On the other hand, machine learning (ML) is revolutionising drug design by making the process faster, cheaper, and more efficient.

Psilocybin treatment extends cellular lifespan and improves survival of aged mice

Kosuke Kato, Jennifer M. Kleinhenz, Yoon-Joo Shin, Cristian Coarfa, Ali J. Zarrabi & Louise Hecker

Psilocybin, the naturally occurring psychedelic compound produced by hallucinogenic mushrooms, has received attention due to considerable clinical evidence for its therapeutic potential to treat various psychiatric and neurodegenerative indications. However, the underlying molecular mechanisms remain enigmatic, and few studies have explored its systemic impacts. We provide the first experimental evidence that psilocin (the active metabolite of psilocybin) treatment extends cellular lifespan and psilocybin treatment promotes increased longevity in aged mice, suggesting that psilocybin may be a potent geroprotective agent.

Long-term effects of s-KL treatment in wild-type mice: Enhancing longevity, physical well-being, and neurological resilience

Aging is a major risk factor for pathologies including sarcopenia, osteoporosis, and cognitive decline, which bring suffering, disability, and elevated economic and social costs. Therefore, new therapies are needed to achieve healthy aging. The protein Klotho (KL) has emerged as a promising anti-aging molecule due to its pleiotropic actions modulating insulin, insulin-like growth factor-1, and Wnt signaling pathways and reducing inflammatory and oxidative stress. Here, we explored the anti-aging potential of the secreted isoform of this protein on the non-pathological aging progression of wild-type mice. The delivery of an adeno-associated virus serotype 9 (AAV9) coding for secreted KL (s-KL) efficiently increased the concentration of s-KL in serum, resulting in a 20% increase in lifespan. Notably, KL treatment improved physical fitness, related to a reduction in muscle fibrosis and an increase in muscular regenerative capacity. KL treatment also improved bone microstructural parameters associated with osteoporosis. Finally, s-KL-treated mice exhibited increased cellular markers of adult neurogenesis and immune response, with transcriptomic analysis revealing induced phagocytosis and immune cell activity in the aged hippocampus. These results show the potential of elevating s-KL expression to simultaneously reduce the age-associated degeneration in multiple organs, increasing both life and health span.

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PREPRINT

Inflammaging in aged tissues drives remodeling of the CD8$^+$T cell compartment

Aging profoundly reshapes the immune cell landscape, with particularly strong effects on CD8$^+$ T cells, including a marked decline in naïve cells and the emergence of age-associated GZMK$^+$ CD8$^+$ T cells (T_{AA} cells). Although T_{AA} cells make up a significant fraction of the aged CD8$^+$ T cell compartment, the pathway underlying their development remains unknown. In this study, we demonstrate that T_{AA} cell development is cell-extrinsic and requires antigen exposure within aged non-lymphoid tissues. Using a novel TNF$^{\Delta 69AU/+}$ mouse model, we show that systemic low-grade inflammation, characteristic of inflammaging, accelerates CD8$^+$ T cell aging and promotes early accumulation of T_{AA} cells. Through detailed analysis of T_{AA} cell heterogeneity, we identified a progenitor subpopulation enriched in the aged adipose tissue. Using heterochronic transplantation, we show that adipose tissue acts as a functional niche, supporting progenitor maintenance and driving the conversion of young CD8$^+$ T cells into the aged phenotype. Taken together, our findings reveal how aging of non-lymphoid tissues orchestrates the reorganization of the CD8$^+$ T cell compartment and highlight adipose tissue as a promising target for therapeutic strategies aimed at modulating immune aging.

Multiorgan transcriptomics in mice identifies immunoglobulin heavy constant mu (*Ighm*) as a tissue-level aging biomarker

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Identifying aging-associated biomarkers applicable for multiple tissues is challenging but crucial for assessing tissue aging. Here, we obtained and analyzed 456 transcriptomes on 17 organs from 30 C57BL/6 J mice with different ages, revealing the consistently upregulated mRNAs of *Ighm*, *C4b*, and *Ccl8* in most aged organs. This finding received support from independent transcriptomic and proteomic datasets and was further validated through western blot, enzyme-linked immunosorbent assay (ELISA), and immunofluorescence, arguing for both *Ighm* mRNA and protein as tissue-level aging biomarkers, at least in mice. Its sensitivity to antiaging interventions further emphasizes the significance of *Ighm* in assessing tissue aging in mice.

SIRT2 and NAD$^+$ Boosting Broadly Suppress Aging-Associated Inflammation

Marine Barthez, Zehan Song, Yufan Feng, Yifei Wang, Chih-ling Wang, Danica Chen

Aging leads to chronic inflammation that is linked to aging-associated conditions and diseases. Multiple immune pathways become activated during aging, posing a challenge to effectively reduce aging-associated inflammation. SIRT2, an NAD$^+$-dependent deacetylase, suppresses several immune pathways that become activated during aging and may represent an attractive target to broadly dampen aging-associated inflammation. Here, we show that SIRT2 deficiency leads to increased inflammation governed by multiple immune pathways and tissue function decline at an old age, while NAD$^+$ boosting with 78c suppresses aging-associated inflammation and improves tissue function. These findings highlight SIRT2 as a master regulator of aging-associated inflammation and support NAD$^+$ boosting as an effective strategy to counteract aging-associated inflammation and tissue function decline.

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PREPRINT

Multi-omics analysis highlights the link of aging-related cognitive decline with systemic inflammation and alterations of tissue-maintenance

Aging-related cognitive decline is associated with changes across different tissues and the gut microbiome, including dysfunction of the gut-brain axis. However, only few studies have linked multi-organ alterations to cognitive decline during aging. Here we report a multi-omics analysis integrating metabolomics, transcriptomics, DNA methylation, and metagenomics data from hippocampus, liver, colon, and fecal samples of mice, correlated with cognitive performance in the Barnes Maze spatial learning task across different age groups. We identified 734 molecular features associated with cognitive rank within individual data layers, of which 227 features remain when integrating all data layers with each other. Among the single-layer predictors, several host and microbial features were highlighted, with host-associated markers being predominant. Host features associated with cognitive function mainly belong to innate and adaptive inflammatory activity (inflammaging) and developmental processes. Our findings suggest that cognitive decline in aging is tightly coupled to systemic, age-associated inflammation, potentially initiated by microbiome-driven gastrointestinal inflammatory activity, emphasizing a link between peripheral tissue alterations and brain function.

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Microglia promote inflammatory cell death upon neuronal mitochondrial impairment during neurodegeneration

The failure to clear dysfunctional mitochondria, cell death and inflammation have been linked in neurodegenerative disease, but their relationship and role in these conditions is not fully understood. Loss of *Vps13d* prevents clearance of mitochondria, and mutations in human *VPS13D* have been associated with neurological movement disorders. To investigate the relationship between mitochondrial health, inflammation and neurodegeneration, we created a conditional *Vps13d*-knockout mouse. Loss of *Vps13d* in excitatory neurons resulted in behavioral changes and neurodegeneration. Vacuolar protein sorting 13D (VPS13D) deficiency also caused mitochondrial ultrastructural defects and dysfunction in neurons followed by gasdermin E processing, cyclic GMP–AMP synthase (cGAS)–stimulator of interferon response cGAMP interactor (STING) signaling, microglial activation and cell death. Gasdermin E localization with mitochondria in *Vps13d*-mutant neurons was required for elevated extracellular mitochondrial DNA that promoted activation of microglia. Depletion of microglia suppressed cell death and behavioral phenotypes but not mitochondrial changes in the neuron-specific *Vps13d*-knockout model, indicating that microglia promote cell death in this model of neurodegenerative disease.

Loss of insulin signaling in microglia impairs cellular uptake of Aβ and neuroinflammatory response exacerbating AD-like neuropathology

Insulin receptors are present on cells throughout the body, including the brain. Dysregulation of insulin signaling in neurons and astrocytes has been implicated in altered mood, cognition, and the pathogenesis of Alzheimer's disease (AD). To define the role of insulin signaling in microglia, the primary phagocytes in the brain critical for maintenance and damage repair, we created mice with an inducible microglia-specific insulin receptor knockout (MG-IRKO). RiboTag profiling of microglial mRNAs revealed that loss of insulin signaling results in alterations of gene expression in pathways related to innate immunity and cellular metabolism. In vitro, loss of insulin signaling in microglia results in metabolic reprogramming with an increase in glycolysis and impaired uptake of Aβ. In vivo, MG-IRKO mice exhibit alterations in mood and social behavior, and when crossed with the 5xFAD mouse model of AD, the resultant mice exhibit increased levels of Aβ plaque and elevated neuroinflammation. Thus, insulin signaling in microglia plays a key role in microglial cellular metabolism and the ability of the cells to take up Aβ, such that reduced insulin signaling in microglia alters mood and social behavior and accelerates AD pathogenesis. Together, these data indicate key roles of insulin action in microglia and the potential of targeting insulin signaling in microglia in treatment of AD.

A Frailty-Based Plasma Proteomic Signature Capturing Overall Health and Well-Being in Older Adults

Frailty is an age-related syndrome characterized by an increased vulnerability to adverse health outcomes in the face of stressors. By deriving a blood-based proteomic signature for frailty, the current study aimed to enhance the understanding of frailty biology and created a person-specific predictor for the risk of frailty and other adverse age-related health outcomes. A 25-protein signature (proteomic frailty index [pFI]) predictive of the cumulative frailty index (FI) in the LonGenity cohort was derived using a penalized regression method. The pFI was significantly correlated with the FI at baseline (Pearson r = 0.58) and showed significant associations with age-related chronic conditions, incident mortality, and clinical measures. In an independent cohort of 5195 participants in the Atherosclerosis Risk in Communities study, pFI was successfully validated with measured FI ($r = 0.61$, $p < 0.001$) and was associated with physical frailty at baseline ($p < 0.001$). The pFI was significantly associated with physical, clinical, and cognitive measures, as well as incident mortality (HR [95% CI] = 1.13 [1.12-1.14]) and dementia (HR [95% CI] = 1.07 [1.05-1.09]) after accounting for demographic factors. The pFI was further validated against FI ($r = 0.45$, $p < 0.001$) in a second independent study in 654 participants from the Baltimore Longitudinal Study of Aging. In conclusion, we identified and validated a 25-protein signature as an index of frailty that also captures overall well-being, health, and risk for key age-related diseases.

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Long-Term Obesity and Biological Aging in Young Adults

Paulina Correa-Burrows, PhD[1,2]; Raquel Burrows, MD[1]; Cecilia Albala, MD[1,2]; et al

Exposure Body mass index (BMI) trajectory across the life course, recorded multiple times since birth. Group 1 had healthy BMI across the life course, group 2 had persistent obesity since adolescence, and group 3 had persistent obesity since childhood.

Main Outcomes and Measures Smoothed BMI trajectories (cubic polynomials) were used to estimate obesity duration. Primary outcomes were DNA methylation–based age and telomere length (TL). Secondary outcomes included levels of aging-related cytokines, growth factors, and adipomyokines.

Results In the sample of 205 adults (mean [SD] age, 28.9 [0.6] years; 100 females [49%]), 89 (43%) were in group 1, 43 (21%) in group 2, and 73 (36%) in group 3. Mean (SD) obesity duration was 12.9 (4.8) years in group 2 and 26.6 (2.3) years in group 3. Long-term obesity was associated with adulthood expression of biomarkers denoting antagonistic and integrative aging hallmarks, including mean (SD) hs-CRP (1.69 [2.1] vs 3.67 vs 4.24 [2.4] mg/L; $P < .001$; $f = 0.57$ [95% CI, 0.44-0.70]) and IL-6 (log, 0.69 [0.5] vs 1.03 [0.4] vs 0.99 [0.4]; $P < .001$; $f = 0.53$ [95% CI, 0.41-0.62]), as well as FGF-21, IGF-1, IGF-2, apelin, and irisin. Cohen f coefficient indicated a large effect size for the association of long-term obesity with adulthood expression of these markers.

Conclusions and Relevance In this multiple-events case-control study, long-term obesity was associated with the expression of biochemical aging markers in adults aged 28 to 31 years, consistent with epigenetic alterations, telomere attrition, chronic inflammation, impaired nutrient sensing, mitochondrial stress, and compromised intercellular communication. In young adults, chronic health issues may emerge from accelerated biological aging associated with long-term obesity.

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PREPRINT

Restriction of individual branched-chain amino acids has distinct effects on the development and progression of Alzheimer's disease in 3xTg mice

Dietary protein is a critical regulator of metabolic health and aging in diverse species. Recent discoveries have determined that many benefits of a low protein diet are the result of reduced consumption of the three branched-chain amino acids (BCAAs), leucine, isoleucine, and valine. Intriguingly, each BCAA has distinct physiological and molecular effects, with restriction of isoleucine alone being sufficient to improve metabolic health and extend the lifespan of mice. While restriction of protein or all three BCAAs improves cognition in mouse models of Alzheimer's disease (AD), the impact of restricting each individual BCAA on the progression and development of AD is unknown. Here, we investigate the effect of restricting each individual BCAA on metabolic health, AD pathology, molecular signaling, and cognition in the 3xTg mouse model. We find that restriction of isoleucine and valine, but not leucine, promotes metabolic health. Restriction of each BCAA had distinct effects on AD pathology and molecular signaling, with transcriptomic analysis of the brain revealing both distinct and shared, and highly sex-specific, molecular impacts of restricting each BCAA. Restricting any of the three BCAAs improved short-term memory in males, with isoleucine restriction having the strongest effect, while restricting valine had the greatest cognitive benefits in females. We identify a set of significantly altered pathways strongly associated with reduced AD pathology and improved cognitive performance in males. Our findings suggest that restricting any of the BCAAs, particularly isoleucine or valine, may form the basis of a novel sex-specific approach to prevent or delay the progression of AD.

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A comparative study of the effects of high protein diets of soy and dairy on healthy aging by integrating multi-omics approaches

The global aging population necessitates optimal dietary protein strategies to mitigate age-related decline. However, few studies have linked soy and dairy protein intake to aging. This study investigated soy and dairy protein impacts on aging through epidemiological and animal analysis. Epidemiological data linked higher soy (not dairy) protein intake with slower biological aging. In animal experiments, the effects of 15% and 30% (protein energy supply ratios) casein diet (CPD) and soy protein diet (SPD) on aging-related health outcomes, aging phenotypes and its molecular mechanisms in middle-aged rats were explored. After 27 weeks feeding, compared to 15% SPD, 30% SPD significantly reduced adiposity, improved lipid profiles, enhanced memory and muscle performance, while 30% CPD failed to demonstrate comparable improvements. Also, 30% SPD alleviated liver and kidney impairment, decreased aging markers (p53, p16, p21) levels and SASP factors. Mechanically, 30% SPD suppressed mTORC1 activation via decreased serum branched-chain amino acids. Furthermore, gut microbiota analysis revealed that SPD reshaped gut microbiota composition, enriched beneficial taxa such as *Akkermansia* and *Duncaniella*, and decreased pathogenic bacteria *Fusobacterium*, compared with CPD. Metabolomics further found that SPD specifically reduced phospholipid metabolites such as LPC 22:4-SN1, O-phosphatecholine, which were strongly correlated with behavioral index and SASP factors. Integrative analysis identified significant associations between SPD-enriched microbiota (*Prevotellaceae_UCG-001* and *Defluviitaleaceae_UCG-011*) and metabolites and aging phenotypes. Collectively, soy protein exerts superior anti-aging effects over casein through coordinated suppression of mTORC1 driven senescence and modulation of gut microbiota-metabolite. This study provides a basis for prioritizing soy protein in healthy aging dietary strategies.

C. elegans aging research

Sesn-1 is required for lifespan extension during caloric deprivation in *C. elegans* through inhibition of mTORC1 and activation of autophagy

Sestrins, evolutionarily conserved stress-responsive proteins, are increasingly recognized for their potential role in lifespan regulation. This study aimed to elucidate the influence of the *sesn-1* gene on lifespan modulation during caloric deprivation (CD) in the model organism *C. elegans*. Our findings reveal that *sesn-1* mediates lifespan extension under CD, primarily through the repression of mTORC1 kinase and activation of autophagy. Moreover, we identified an essential role for *sesn-1* in enhancing stress resilience in nematodes, particularly in the context of nutrient sensing. Further investigations demonstrated *sesn-1*'s interaction with the GATOR2 protein complex, its role in maintaining muscle integrity and a potential synergy between *sesn-1* and the FOXO pathway. Overall, our research underscores the profound implications of Sestrins in aging and stress resistance, shedding light on possible therapeutic avenues for prevention and treatment of age-associated disorders.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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EDITORIAL

Editorial | Open access | Published: 08 July 2025

Escaping ageing through Cell Annealing—a phenomenological model

Sebastian Memczak, Juan Carlos Izpisua Belmonte & Thore Graepel

Cellular rejuvenation shows great promise for treating age-related diseases and disabilities. However, the underlying molecular mechanisms and how and where information for youthful, healthy cells might be stored remain poorly understood. This is largely due to the complexity of ageing which involves numerous molecular modalities, their interactions, and a wide array of phenotypes, making it challenging to model or even conceptualise these processes.[1] Here, we introduce "Cell Annealing", a phenomenological model that builds on the Waddington Landscape and features of Hopfield Networks. It provides a novel perspective on ageing, aims to deepen our understanding of cell state information storage and retrieval, and offers a framework for cell rejuvenation and therapeutic interventions.

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Open problems in ageing science: A roadmap for biogerontology

Angelo Talay, Aleksey V. Belikov, Paul Ka Po To, Hamid H. Alfatemi, Uri Alon, Joris Deelen, Collin Y. Ewald, David Gems, Vera Gorbunova, Jan Gruber, Sara Hägg, John Hemming, Steve Horvath, Alaattin Kaya, Caitlin J. Lewis, Andrea Maier, Maria B Marinova, Graham Pawelec, Shahaf Peleg, Suresh Rattan, Morten Scheibye-Knudsen, Tomas Schmauck-Medina, Vardan Saroyan, Andrei Seluanov, Alexandra Stolzing, Emma Teeling, Robert W. Williams, Todd White, Maximilian Unfried, João Pedro de Magalhães

The field of ageing science has gone through remarkable progress in recent decades, yet many fundamental questions remain unanswered or unexplored. Here we present a curated list of 100 open problems in ageing and longevity science. These questions were collected through community engagement and further analysed using Natural Language Processing to assess their prevalence in the literature and to identify both well-established and emerging research gaps. The final list is categorized into different topics, including molecular and cellular mechanisms of ageing, comparative biology and the use of model organisms, biomarkers, and the development of therapeutic interventions. Both long-standing questions and more recent and specific questions are featured. Our comprehensive compilation is available to the biogerontology community on our website (this http URL). Overall, this work highlights current key research questions in ageing biology and offers a roadmap for fostering future progress in biogerontology.

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PERSPECTIVE

Methylation clocks for evaluation of anti-aging interventions

Josh Mitteldorf[1]

Methylation clocks have found their way into the community of aging research as a way to test anti-aging interventions without having to wait for mortality statistics. But methylation is a primary means of epigenetic control, and presumably has evolved under strong selection. Hence, if methylation patterns change consistently at late ages it must mean one of two things. Either (1) the body is evolved to destroy itself (with inflammation, autoimmunity, etc.), and the observed methylation changes are a means to this end; or (2) the body detects accumulated damage, and is ramping up repair mechanisms in a campaign to rescue itself. My thesis herein is that both Type 1 and Type 2 changes are occurring, but that only Type 1 changes are useful in constructing methylation clocks to evaluate anti-aging interventions. This is because a therapy that sets back Type 1 changes to an earlier age state has stopped the body from destroying itself; but a therapy that sets back Type 2 changes has stopped the body from repairing itself. Thus, a major challenge before the community of epigenetic clock developers is to distinguish Type 2 from Type 1. The existence of Type 1 epigenetic changes is in conflict with conventional Darwinian thinking, and this has prompted some researchers to explore the possibility that Type 1 changes might be a form of stochastic epigenetic drift. I argue herein that what seems like directed epigenetic change really is directed epigenetic change. Of five recent articles on "stochastic methylation clocks," only one (from the Conboy lab) is based on truly stochastic changes. Using the Conboy methodology and a methylation database, I construct a measure of true methylation drift, and show that its correlation with age is too low to be useful.

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The emerging role of multiomics in aging research

Douglas M. Ruden

Aging is a complex biological process involving coordinated changes across multiple molecular systems. Traditional reductionist approaches, while valuable, are insufficient to capture the full scope of aging's systemic nature. Multiomics – integrating data from genomics, transcriptomics, epigenomic proteomics, and metabolomics – provides a comprehensive framework to study aging as an interconnected network. In this Perspective, I explore how multiomic strategies, particularly those leveraging epigenomic and single-cell data, are reshaping our understanding of aging biology. Epigenetic alterations, including DNA methylation and histone modifications, are not only hallmarks but also powerful biomarkers of biological age. I discuss advances in multiomic aging clocks, cross-tissue atlases, and single-cell spatial technologies that decode aging at unprecedented resolution. I also build on a prior review I wrote with colleagues, Epigenomics. 2023;15(14):741–754, which introduced the concept of pathological epigenetic events that are reversible (PEERs) – epigenetic alterations linked to early-life exposures that predispose to aging and disease but may be therapeutically modifiable. This Perspective examines how PEERs and multiomics intersect to inform biomarkers, geroprotective interventions, and personalized aging medicine. Finally, I highlight integration challenges, ethical concerns, and the need for standardization to accelerate clinical translation. Together, these insights position multiomics as a central pillar in the future of aging research.

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Cellular senescence—from solid organs to vascularized composite allotransplants

Vascularized composite allotransplantation (VCA) has emerged as a novel therapy approach to restore form and function in patients with severe tissue defects of the face, hand, and abdominal wall, among other anatomical regions. The composite allografts comprise different tissues such as skin, muscle, or bone. Clinical data demonstrate promising mid- and long-term outcomes following VCA surgery, but our understanding of the cellular interactions and molecular pathways in VCA surgery is oftentimes deduced from solid organ transplantation (SOT). In SOT, the concept of cellular senescence has grown increasingly popular which is characterized by a permanent cellular proliferation arrest in response to endogenous and exogenous stimuli. Senescent cells, through the release of mitochondrial DNA and secretion of proinflammatory proteins, can amplify the immunogenicity of transplants, hindering graft acceptance and longevity. This understanding has paved the way for novel interventions, including the use of senolytics—agents that selectively eliminate senescent cells—to modulate immune responses and mediate immunotolerance. There is a body of evidence that underlines the therapeutic potential of senescence to improve SOT outcomes; however, the relevance of senescence to VCA outcomes remains elusive. In this review, we aim to summarize the current literature on senescence in different solid organ transplants and outline the potential impact of senescence on VCA outcomes. This knowledge may help providers develop a broader understanding of the cellular and molecular landscape in VCA to develop targeted therapies and advance VCA patient care.

Beyond classical collagen: basement membrane collagen IV in age-associated lung diseases

Chronic lung diseases such as COPD, asthma, idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension are characterised by aberrant remodelling and degradation of the extracellular matrix. This is particularly evident within the basement membrane. Collagen IV, a major component of the basement membrane, is essential for maintaining structural support and regulating cell behaviour. However, disruptions in collagen IV metabolism and basement membrane integrity have been implicated in the pathogenesis of chronic lung diseases, especially in ageing populations where basement membrane turnover is compromised. Cleavage of collagen IV during basement membrane remodelling generates bioactive fragments known as matrikines, which serve as markers of tissue remodelling and potential diagnostic biomarkers. Despite the prominence of collagen IV in the basement membrane, its role in chronic lung diseases remains understudied compared to other collagen types. This review provides a comprehensive exploration of the roles of basement membrane collagen IV and its matrikines in COPD, asthma, IPF and pulmonary hypertension, emphasising their significance beyond classical matrix components. Through an analysis of clinical studies, animal models and *in vitro* experiments, the contributions of collagen IV to disease pathogenesis and progression are discussed. Furthermore, potential diagnostic and therapeutic implications of targeting collagen IV are outlined. By providing insights into the relationship between collagen IV and chronic lung diseases, this review aims to guide future research and clinical interventions in the field.

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Mitochondria dysfunction: cause or consequence of physiologic aging?

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Affiliations + expand

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Abstract

Mitochondria are no longer viewed solely as ATP- or metabolite-generating organelles but as key regulators of cellular signaling that shape physiologic aging. Contrary to earlier theories linking aging to mitochondrial DNA mutations and oxidative damage, current evidence shows that these factors do not causally limit physiologic aging. Instead, an evolving literature links age-related loss of mitochondrial signaling and function to important physiologic changes of aging. Moreover, mild inhibition of mitochondrial respiratory function with drugs like metformin promote health span. These findings open new paths for pharmacologically reprogramming mitochondrial signaling to extend healthy aging.

Caenorhabditis elegans as an emerging high throughput chronotherapeutic drug screening platform for human neurodegenerative disorders

Mrutyunjaya Panda [1], Maria Fakitsa [2], Maria Markaki [3], Nektarios Tavernarakis [4]

An increase in the aging population is accompanied by increased susceptibility to age-associated neurodegeneration, with currently no cure. Despite the diversity of symptoms and etiologies, neurodegenerative disorders share mechanistic commonalities and many pathophysiological features. These include disruptions in circadian rhythms that affect neuronal physiology. Systematic investigations in several animal models have advanced our understanding of the molecular processes that link circadian rhythms and neurodegenerative disease states. These models have also been used to screen and validate promising chronotherapeutic drug candidates that target the circadian clock to ameliorate neurodegeneration. With the emergence of robust and reliable methodologies to measure daily rhythms, the nematode model Caenorhabditis elegans has become a versatile tool for high throughput chronotherapeutic drug screening against neurodegenerative disorders. In this review, we discuss the unique features and advantages of C. elegans as an enabling platform for chronotherapeutic drug discovery, towards the development of innovative strategies for the treatment of human neurodegenerative conditions.

Apheresis for Senescence: Targeting the Senescence-associated Secretory Phenotype to Delay Aging and Age-Related Diseases

Aging is driven by cellular senescence and chronic inflammation, largely mediated by the senescence-associated secretory phenotype (SASP). SASP factors promote inflammaging, impair tissue homeostasis, and contribute to age-related diseases such as cardiovascular disease, neurodegeneration, and cancer. Current anti-aging strategies focus on senolytics or SASP inhibitors, yet these approaches have limitations. We discuss therapeutic plasma exchange (TPE) and selective apheresis, as interventions to mitigate SASP-driven aging. TPE removes inflammatory cytokines, metabolic waste, and senescence-associated proteins, while replenishing rejuvenating factors. Selective apheresis could enhance precision by targeting specific SASP components. By reducing systemic inflammation and restoring a youthful proteomic environment, these strategies may improve immune function, tissue regeneration, and overall healthspan. This review explores the mechanistic basis of SASP in aging and evaluates the potential of apheresis-based therapies as viable interventions to delay aging and age-related disease progression.

Position paper: leveraging non-human primate (NHP) specificities to accelerate Parkinson's disease and ageing research

The PD-AGE international task force underscores the pivotal role that non-human primate (NHP) models play in advancing our understanding of Parkinson's disease (PD) and ageing. Due to their close genetic, anatomical, and behavioural similarity to humans, NHPs uniquely enable translational research to bridge basic science towards clinical application. They are indispensable for modelling the complex motor and non-motor symptoms of PD, as well as age-related neurodegeneration. This paper outlines the scientific rationale, methodological strengths, and ethical considerations surrounding NHP use in PD research. We highlight the need for standardised models, innovative tools, and long-term collaborative infrastructure to enhance the translational value of NHP studies. We propose a three-phase roadmap to develop a global research consortium to optimise resource use, improve model fidelity, and accelerate therapeutic development for PD and related neurodegenerative disorders.

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Next-generation CRISPR gene editing tools in the precision treatment of Alzheimer's and Parkinson's disease

Harsh Kumar Meshram [1], Sanjay Kumar Gupta [2], Akash Gupta [1], Kushagra Nagori [3], Ajazuddin [4]

Emerging gene-editing technologies, such as the CRISPR system, represent a potential pathway for precision medicine targeting the genetic and molecular causes of diseases. Second-generation CRISPR technologies, including base editing, prime editing, and engineered Cas variants, have improved fidelity and offer alternative strategies for precise gene correction, transcriptional repression or activation, and modulation of pathological pathways in neurodegeneration. These tools can correct single-nucleotide mutations, reduce pathological protein accumulation, and modulate neuroinflammatory responses, all integral to the pathogenesis of Alzheimer's disease (AD) and Parkinson's disease (PD), both chronic, progressive neurodegenerative disorders. Unfortunately, currently available treatments are limited and primarily palliative. Preclinical studies have shown promising results, with improvements in cognitive and motor deficits in animal models. However, significant challenges must be addressed to ensure safe and effective delivery to the CNS, minimize off-target effects, and address ethical concerns. Current clinical investigations aim to translate these findings into available therapeutic options. This review also identifies the biological mechanisms, therapeutic use cases, and current limitations of next-generation CRISPR systems as tools in the context of AD and PD, providing both therapeutic and research capabilities through their unique strengths. Ultimately, the future of transactional neurogenomics will determine the clinical possibilities of CRISPR-based strategies for advancing neurodegenerative disease management beyond palliative and symptomatic treatment, toward a feasible mechanistic form of disease modification.

CTAD taskforce: genetic therapies in Alzheimer's disease

D. Jakabek [a], A.M. Isaacs [a], B. De Strooper [b], M. Tuszynski [c], R. Lane [d], O. Uspenskaya [e], E. McDade [f], M.S. Rafii [g], C.J. Mummery [a]

There are an increasing number of genetic approaches to treating Alzheimer's disease and other dementias, with some promising results from early-phase trials. This prompted the convention of the first EU-US CTAD Task Force on genetic therapies in Alzheimer's disease in October 2024. Preclinical studies and clinical trials of genetic therapies in Alzheimer's disease and other dementias are presented here with key lessons for the field. Importantly, there are several challenges and opportunities unique to neurogenetic therapies which were reviewed and discussed, including means of genetic manipulation, adverse events, monitoring, timing of therapy, and the importance of patient involvement in trial design. Continued collaboration across disciplines will accelerate development of neurogenetic therapeutics.

Markers of biological age in dogs

Polina Zemko [a], Marco Canevelli [b c], Sofia Pavanello [d e f], Matteo Cesari [g], Federico Bonsembiante [a], Manuela Campisi [d], Luana Cannella [d], Simona Buscarnera [b], Alessandro Zotti [a], Tommaso Banzato [a]

As human life expectancy continues to rise, ageing and age-related diseases have become critical societal challenges, driving extensive research across genetics, molecular biology, biochemistry, and behavioral sciences. In this context, domestic dogs (*Canis lupus familiaris*) offer a unique model for ageing research due to their shared environmental exposures with humans, diverse genetic profiles, and relatively short lifespans. This review aims to identify potential biomarkers of ageing in dogs, facilitating a deeper understanding of age-related mechanisms and supporting the evaluation of interventions designed to promote healthy ageing. We present a research of peer-reviewed literature on age-related variations of various parameters across multiple biological systems, including epigenetic, telomere, immune, metabolic, and cognitive markers in dogs. Our findings highlight several robust biomarkers, such as DNA methylation-based epigenetic clocks, telomere attrition, CD4+/CD8+ T-cell ratio, hematological markers (e.g., globulin levels), and cognitive function scores. These biomarkers demonstrate strong parallels with human ageing processes, particularly concerning genomic and epigenetic alterations. However, challenges remain, including breed-specific variability, body size differences, and inconsistent evidence regarding inflammageing markers, such as pro-inflammatory cytokines. Despite these limitations, indicators of chronic inflammation (e.g., anemia of chronic disease and elevated globulins) are evident in older dogs. Future research directions include the standardization of biomarker protocols for dogs, the development of longitudinal studies to track dynamic age-related changes, and further exploration of emerging biomarkers, such as those related to microbiome composition and oxidative stress.

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Microglia–neuron crosstalk in Alzheimer's disease: an exploration of molecular mechanisms and pathological implications

Microglia, the resident immune sentinels of the central nervous system (CNS), engage in dynamic crosstalk with neurons, the principal units of information transmission, to maintain CNS homeostasis. Emerging research has established that dysregulation of this intricate communication network critically contributes to Alzheimer's disease (AD) pathogenesis, offering novel insights for therapeutic development. In this review, we dissect the molecular mechanisms underlying multifaceted microglia-neuron interactions in AD. Bidirectional communication occurs through neurotransmitter transmission, synaptic elimination, the secretion of signaling molecules and extracellular vesicles, and direct membrane contact. Disrupted crosstalk in AD triggers pathogenic cascades: cholinergic dysfunction induces microglial hyperactivation and oxidative stress; aberrant synaptic elimination accelerates memory loss; and neuron-derived pathological vesicles propagate neuroinflammation. Elucidating these interactions reveals promising therapeutic insights for AD. Targeting crosstalk pathways-such as activating TREM2, selectively inhibiting the complement cascade, or modulating inflammasome activity-may halt neurodegeneration while preserving essential immune surveillance. Moreover, integrating spatiotemporal omics with live imaging could dynamically track microglia-neuron crosstalk, revealing critical transition points from neuroprotection to neurodegeneration.

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Beyond the usual suspects: expanding aging research from classic models to really cool critters

Amy Walker

Model organisms such as yeast, worms, flies, and mice were key to discovering genes and other factors controlling life span and directly improved our understanding of human aging. Today, genomic tools allow study of a broader range of species, including those with short or long life spans, closely related species with different aging rates, or differences in interspecies aging. Models such as killifish, bats, and ants have much to teach us about human aging. They also reveal a flexible biological toolkit that species can use when evolutionary pressures drive rebalancing of growth, reproduction, or resilience with age-related decline.

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Telomeres at the nexus of aging, tumor suppression, and inflammation: toward an understanding beyond senescence

Samuel I. Bloom and Jan Karlseder

Aging is the greatest risk factor for most diseases. We propose that aging manifests as disease as a function of tumor-suppressive capabilities. Adequate tumor suppression results in cell death or an accumulation of damaged cells leading to inflammation and tissue dysfunction that underlies diseases such as cardiovascular disease, neurodegenerative diseases, or type 2 diabetes. Conversely, inadequate tumor suppression leads to cancer. Telomeres are central to this process because they oppose hyperproliferation that is required for cancer initiation by enforcing two potent tumor suppressor mechanisms: senescence and crisis. Although senescent cells promote age-related diseases via inflammatory signaling, crisis cells have lost the p53 and RB pathways, have more unstable genomes, and harbor shorter telomeres, all of which could increase inflammation to a greater degree than is seen in senescence. This model emphasizes the intimate relationship between aging, telomeres, tumor suppression, and inflammation and suggests that crisis cells may represent an unexplored driver of inflammation in advanced age.

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The interplay between senescence, inflammation, and the immune system

Jesús Gil

The past 40 years have witnessed significant progress in aging research. Although aging was once considered a stochastic process, it is now understood to be regulated by pathways and processes that can be dissected with modern cellular and molecular biology approaches. The aberrant accumulation of cells undergoing cellular senescence and an increase in chronic, sterile inflammation are two of those aging hallmarks. Here we discuss how these processes are connected and how the relationship between senescent cells and the immune system dictates the extent of inflammatory processes contributing to age-related dysfunction and disease.

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Studying ovarian aging and its health impacts: modern tools and approaches

Bérénice A. Benayoun[1,2,3,4,5], Alison Kochersberger[6] and Jennifer L. Garrison[1,6,7,8,9]

Ovarian aging is a critical yet understudied driver of systemic aging in female bodies, with profound implications for female health and longevity. Despite its significance, we still know little about ovarian aging and its systemic effects on aging trajectories. With new efforts over the past few years, interest in the field has been growing and there is momentum to address these questions. This review highlights the importance of leveraging modern tools and approaches to better understand ovarian aging and its impact on health span. Specifically, we believe it will be useful for both aging researchers looking to go into research on ovarian aging and reproductive researchers looking to adopt more modern toolkit. We focus on menopause—a key marker of ovarian aging—as a lens through which to examine the current state of the field, identify limitations in existing research, and outline goals for future progress. By emphasizing cutting-edge techniques and emerging models, we seek to illuminate new pathways for research that could lead to improved strategies for managing ovarian aging and enhancing overall female health.

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From telomeres and senescence to integrated longevity medicine: redefining the path to extended healthspan

Despite significant advances in aging research, translating these findings into clinical practice remains a challenge. Aging is a complex, multifactorial process shaped by many factors including genetic, metabolic, and environmental factors. While medical advancements have extended lifespan, healthspan remains constrained by cellular senescence, telomere attrition, and systemic inflammation—core hallmarks of biological aging. However, emerging evidence suggests that telomere dynamic is not inevitable but can be influenced by oxidative stress, lifestyle choices, and metabolic regulation. This review examines how telomere-based biomarkers and metabolic interventions can drive personalized longevity medicine, enabling targeted strategies to delay aging. Furthermore, it highlights the integration of geroscience into clinical practice—integrated longevity medicine leveraging biomarker tracking, metabolic therapies, and preventive interventions—to redefine aging as a modifiable process, ultimately extending both lifespan and healthspan.

Cardiac Cachexia: A Comprehensive Review

Julia S Szinte [1], Manish A Parikh [1 2], William H Frishman [3], Stephen J Peterson [1 2]

Cardiac cachexia remains a phenomenon seen more particularly in New York Heart Association Classification class III or IV heart failure patients. This is frequently missed and written off as "old age." It has a mortality rate of 50% within 18 months of diagnosis, so it is imperative to diagnose cardiac cachexia promptly. It remains elusive in the complexity of its underlying pathophysiology, from cytokine release from both the endocardium and the gut, with systemic implications. This review provides an analysis of cardiac cachexia: (1) definition and diagnostic criteria; (2) prevalence and mortality outcomes; (3) pathophysiology: biomarkers, neurohormonal activation, inflammatory cytokines, involvement of the gut, and iron deficiency anemia; (4) potential of reversibility; (5) differentiating cardiac cachexia from sarcopenia and frailty; (6) treatment: both pharmacologic and nonpharmacologic. This complex disease remains underrecognized.

The *APOE* Gene Cluster in Normal Aging

Aging is a multifaceted biological process characterized by numerous physiological and molecular alterations that profoundly impact health and susceptibility to disease. Among the genetic determinants influencing aging, the apolipoprotein E (*APOE*) gene cluster has emerged as a critical focus of research. This study explored the diverse roles of *APOE* in both normal and pathological aging, with particular emphasis on its involvement in Alzheimer's disease (AD). We first examined the "physiological" aspects of aging, highlighting cellular and systemic adaptations that support organismal homeostasis. This was followed by an analysis of the pathophysiological deviations underlying neurodegenerative disorders, with AD as a key example. The role of *APOE* in normative aging was then discussed, including its contributions to lipid metabolism, synaptic plasticity, and neuroprotection-functions essential for maintaining both cerebral and systemic health. However, the pathological implications of *APOE* genetic variants, particularly the ε4 allele, were considered in relation to the increased risk of AD and other age-related diseases. Additionally, the *APOE* gene cluster, which includes adjacent regulatory and interactive genes, was examined for its potential to modulate *APOE* expression and function, thereby influencing the aging process. This synthesis underscores the pivotal role of the *APOE* gene cluster in elucidating the genetic and molecular mechanisms underlying aging and age-related diseases, providing a foundation for the development of targeted therapeutic interventions.

Roles of RNA modifications in aging and age-related diseases

Eunseok Kang, Rosa Haque, Hanseul Lee, Seung-Jae V Lee [1]

RNA modifications are key epigenetic alterations that play regulatory functions in RNA biology, including RNA stability and translation. Emerging evidence indicates that RNA modification is crucial for various physiological and pathological processes, including aging. This review describes functions of key RNA modifications, including N6-methyladenosine (m6A), 5-methylcytosine (m5C), N7-methylguanosine (m7G), 2'-O-methylation (Nm), N1-methyladenosine (m1A), adenosine-to-inosine (A-to-I) RNA editing, pseudouridylation (ψ), and N4-acetylcytidine (ac4C), highlighting their roles in aging and age-associated diseases. We also discuss dynamics of RNA modifications and associated protein factors during aging. This review provides important information on molecular mechanisms underlying aging regulation, focusing on effects of RNA modifications, which can help us understand healthy longevity in humans.

OTHER RESEARCH & REVIEWS

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The mutagenic forces shaping the genomes of lung cancer in never smokers

Lung cancer in never smokers (LCINS) accounts for around 25% of all lung cancers[1,2] and has been associated with exposure to second-hand tobacco smoke and air pollution in observational studies[3,4,5]. Here we use data from the Sherlock-*Lung* study to evaluate mutagenic exposures in LCINS by examining the cancer genomes of 871 treatment-naive individuals with lung cancer who had never smoked, from 28 geographical locations. *KRAS* mutations were 3.8 times more common in adenocarcinomas of never smokers from North America and Europe than in those from East Asia, whereas a higher prevalence of *EGFR* and *TP53* mutations was observed in adenocarcinomas of never smokers from East Asia. Signature SBS40a, with unknown cause[6], contributed the largest proportion of single base substitutions in adenocarcinomas, and was enriched in cases with *EGFR* mutations. Signature SBS22a, which is associated with exposure to aristolochic acid[7,8], was observed almost exclusively in patients from Taiwan. Exposure to secondhand smoke was not associated with individual driver mutations or mutational signatures. By contrast, patients from regions with high levels of air pollution were more likely to have *TP53* mutations and shorter telomeres. They also exhibited an increase in most types of mutations, including a 3.9-fold increase in signature SBS4, which has previously been linked with tobacco smoking[9], and a 76% increase in the clock-like[10] signature SBS5. A positive dose–response effect was observed with air-pollution levels, correlating with both a decrease in telomere length and an increase in somatic mutations, mainly attributed to signatures SBS4 and SBS5. Our results elucidate the diversity of mutational processes shaping the genomic landscape of lung cancer in never smokers.

Association between ultra-processed food consumption and lung cancer risk: a population-based cohort study

Background The evidence on associations between ultra-processed foods (UPF) and lung cancer risk is limited and inconsistent.

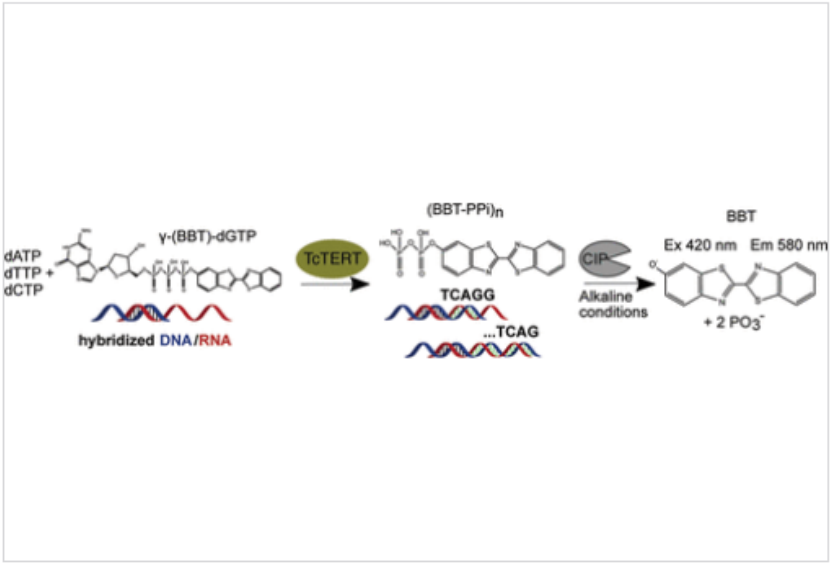
Research question Are UPF associated with an increased risk of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)?

Methods Data of participants in this study were collected from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Dietary intakes were assessed through a validated diet history questionnaire. These foods were categorised using the NOVA classification according to the degree of processing in the PLCO Cancer Screening Cohort. All cases of incident lung cancer were pathologically verified. Multivariable Cox regression was used to assess the association between consumption of UPF and lung cancer after adjustment for various potential confounders, including key risk factors related to lung cancer and overall diet quality.

Results A total of 1706 cases of lung cancer cases, including 1473 NSCLC and 233 SCLC, were identified during a mean follow-up of 12.2 years among 101 732 adults (mean age 62.5 years). After multivariable adjustments, individuals in the highest quarters for UPF consumption had a higher risk of lung cancer (HR=1.41, 95% CI 1.22 to 1.60), NSCLC (HR=1.37, 95% CI 1.20 to 1.58) and SCLC (HR=1.44, 95% CI 1.03 to 2.10) compared with those in the lowest quarter. These results remained statistically significant after a large range of subgroup and sensitivity analyses.

Conclusions Higher consumption of UPF is associated with an increased risk of lung cancer, NSCLC and SCLC. Although additional research in other populations and settings is warranted, these findings suggest the healthy benefits of limiting UPF.

High-Throughput Screening Tool to Identify Small Molecule Inhibitors of Telomerase



Telomerase reverse transcriptase is a ribonucleoprotein complex that maintains telomere length in rapidly dividing cells, thus enabling cellular immortality. Despite being recognized as an important cancer target for decades, no small molecule telomerase inhibitors have been approved as anticancer therapeutics to date. Several limitations, including the absence of high-throughput screening tools, have posed challenges to the telomerase drug discovery field. Here, we describe a high-throughput, fluorescently coupled screening method employing a chemically modified reporter nucleotide. We utilize the *Tribolium castaneum* telomerase as a surrogate model as it shares a high degree of active site homology with the human enzyme. We piloted this tool by screening a chemical library of ~3600 nucleoside mimetics to demonstrate excellent assay quality, and identified 2 compounds with inhibitory activity that were further validated in a direct enzymatic assay. Our work introduces a method that has the potential to uncover novel telomerase inhibitors for further drug discovery efforts.

Circulating Klotho and mortality patterns among US cancer survivors: A cohort study

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Klotho, a longevity hormone, exerts diverse anticancer activities. However, evidence regarding the association between serum Klotho and mortalities among cancer survivors is lacking. We examined the association between serum Klotho and the risks of all-cause and cancer mortalities among 1602 cancer adults from the National Health and Nutrition Examination Survey (NHANES) (2007–2016) using multivariate Cox proportional hazard models. The nonlinear relationship was determined using the likelihood ratios test, and the inflection points and 2-piecewise Cox proportional hazards regression models were computed. After a median follow-up period of 84.0 months, U-shaped associations between circulating Klotho and all-cause and cancer mortality were observed (*P* for nonlinear = .04, .02, respectively), with identified inflection points (pg/mL) of 765.5 for all-cause and 767.6 for cancer mortality. Klotho below these thresholds was inversely associated with all-cause mortality (Hazard ratio, HR, 95% confidence interval, CI) (0.72, 0.53–0.98) and cancer mortality (0.61, 0.39–0.96); Klotho above the threshold showed a trend of positive associated with cancer mortality (1.22, 0.99–1.50). Effect modification of age was apparent (*P* interaction .007); Klotho was associated positively with cancer mortality risk among participants aged under 60 (1.50, 1.09–2.05). The U-shaped associations between serum Klotho and all-cause and cancer mortality indicate that maintaining an ideal Klotho level in cancer patients could reduce mortality risks. This provides insight into the knowledge of nonlinearity relationship between serum Klotho, a longevity hormone, and survival outcomes in cancer populations.

Effect of HEPA Filtration Air Purifiers on Blood Pressure: A Pragmatic Randomized Crossover Trial

Results

A total of 154 participants were analyzed. The mean age was 41.1 years, 59.7% were women, 68.2% were non-Hispanic White, and a majority were of higher socioeconomic status. The mean baseline brachial systolic blood pressure (SBP)/diastolic BP was 118.8/76.5 mm Hg. HEPA filtration significantly reduced PM in comparison to both indoor sham and outdoor levels. Participants' SBP at the start of the intervention period moderated the efficacy of the intervention (*P* = 0.03). Participants who had elevated brachial SBP (≥120 mm Hg) had a significant 2.8-mm Hg mean reduction in SBP after HEPA filtration (*P* = 0.03) and a 0.2-mm Hg mean increase in SBP after sham filtration (*P* = 0.85). The net result was a significant 3.0-mm Hg mean difference in favor of HEPA filtration (*P* = 0.04). There was no significant benefit on diastolic BP or for participants with normal SBP (<120 mm Hg).

Conclusions

The use of in-home HEPA air purifiers resulted in clinically important reductions in SBP for people with elevated SBP in environments with relatively low $PM_{2.5}$ concentrations.