Heales

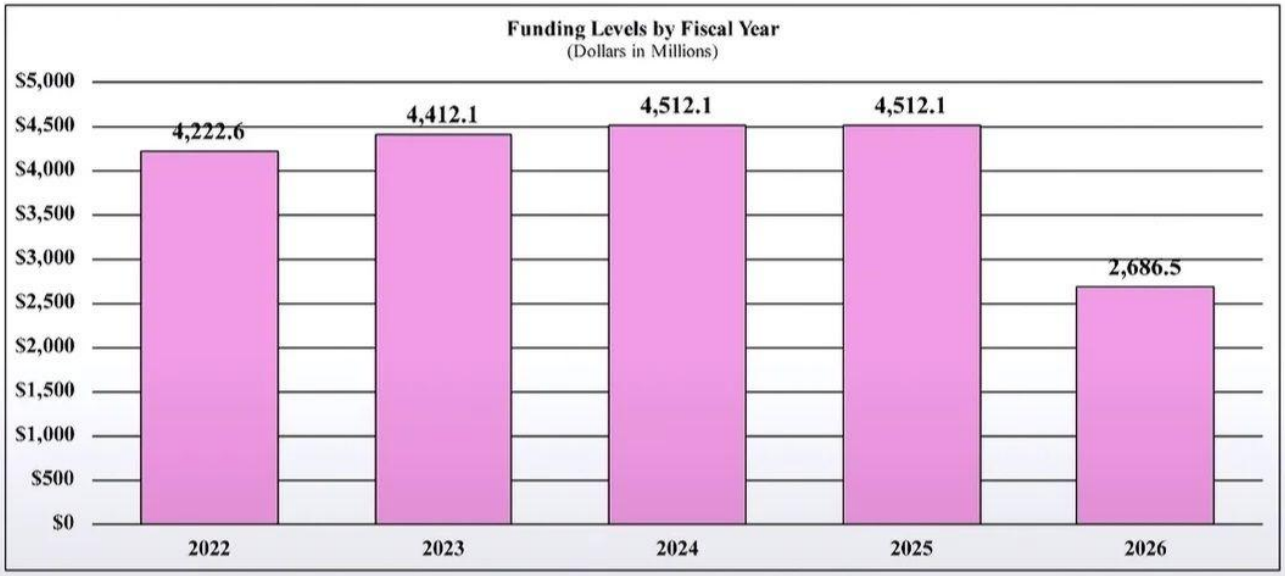
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
6th of December 2025
Sven Bulterijs

Business/Conferences/ General news

Heales
HEALTHY LIFE EXTENSION SOCIETY

While we're in a grey tsunami, Trump wants to cut the budget of the National Institute on Aging by 40%! To show how foolish this is: the economic return of slowing down aging by just one year is $38 trillion!



Heales
HEALTHY LIFE EXTENSION SOCIETY

AbbVie cuts ties with Google-backed longevity company, lays off scientists

The pharma giant's moves are a notable shift a decade after its investments in aging research

Harmful quackery

Psychedelics and immortality: *Nature* went to a health summit starring RFK and JD Vance

The Make America Healthy Again summit, attended by health secretary Robert F. Kennedy Jr and vice-president JD Vance, gave a sense of what's driving US health policy.

By Max Kozlov

Heales
HEALTHY LIFE EXTENSION SOCIETY

Patient dies after receiving Intellia's CRISPR therapy

By **Nick Paul Taylor** · Nov 7, 2025 5:25am

Aging research articles

Heales
HEALTHY LIFE EXTENSION SOCIETY

The global burden of aortic aneurysm in adults over 55: evolving trends, risk factors, and projections

Background: Aortic aneurysm (AA) is a life-threatening vascular disease and a major contributor to global cardiovascular mortality, particularly in older adults. This study aims to report global trends in mortality and disability-adjusted life years (DALYs) attributable to AA among adults aged 55 years and older from 1990 to 2021.

Methods: We conducted a comprehensive analysis of aortic aneurysm mortality and disability-adjusted life years (DALYs) from 1990 to 2021, utilizing data from the Global Burden of Disease (GBD) study. Trends were examined by sex, age group, socio-demographic index (SDI), region, and country. Joinpoint regression was used to assess annual percentage changes (APCs), and Bayesian age-period-cohort (BAPC) modeling projected AA burden to 2035. Primary risk factors were also analyzed.

Results: Between 1990 and 2021, global AA-related deaths rose by 73.9% [from 79,608 (95% UI, 74,398-84,032) to 138,450 (123,754-149,214)], while the mortality rate declined by 21.4% (from 11.86 to 9.32 per 100,000). Similar patterns were observed for DALYs, with a 62.6% increase in total DALYs but a 26.5% decrease in rates. Males and older adults experienced disproportionately higher mortality and DALY rates. Marked regional and national disparities emerged: the greatest increases in AA burden were seen in low-middle SDI regions [mortality rate EAPC, 1.49 [95% CI, 1.43-1.54]; DALY rate EAPC, 1.29 [95% CI, 1.23-1.35]], while high-income North America and Australasia achieved the largest reductions. The leading risk factor globally was smoking, particularly among males. BAPC projections indicate continued declines in age-standardized AA mortality and DALY rates through 2035, though absolute numbers will likely remain high.

Interpretation: Although rates of AA-related mortality and DALYs have declined globally, the absolute burden continues to rise, driven by population aging and persistent risk factors. Disparities across regions and SDI groups highlight the urgent need for targeted prevention, including tobacco control, risk factor management, and selective screening-especially in rapidly aging, low-resource settings. Strengthening health system capacity for both prevention and surgical intervention will be critical to curbing future AA burden.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Global, Regional and National Burden of Osteoarthritis, 1990–2021: A Decomposition and Age–Period–Cohort Analysis

Objectives: Osteoarthritis (OA) is a leading cause of disability worldwide, driven by ageing populations and lifestyle factors, such as obesity and sedentary behaviours. Understanding the global, regional and national trends in OA prevalence is crucial for public health planning and resource allocation.

Methods: This study employed data from the Global Burden of Disease (GBD) 2021 database to examine the prevalence of OA from 1990 to 2021. Age-standardised prevalence rates (ASPR) and decomposition analysis were conducted to identify key drivers, including age structure shift, population growth and epidemiological change. An age-period-cohort (APC) model was applied to assess the influence of demographic shifts on OA prevalence. Stratified analyses were conducted by socio-demographic index (SDI) regions to assess disparities in OA burden.

Results: The global number of OA cases rose from 256 million (95% CI: 227-283 million) in 1990 to 607 million (95% CI: 538-671 million) in 2021, with an ASPR of 6967.29 (95% CI: 6180.70-7686.06) per 100,000 individuals. Population growth contributed 74% of this increase, whereas age structure shift accounted for 16%. High SDI regions reported the highest ASPR, with 7897.27 (95% CI: 7067.13-8689.88) per 100,000, compared with 5605.58 (95% CI: 4967.54-6230.60) in low SDI regions.

Conclusions: The global burden of OA has escalated during the last 30 years, particularly in ageing populations. Although population growth and demographic shifts are major drivers, regional disparities highlight the need for targeted prevention strategies and improved healthcare access in lower SDI regions.

Organ-specific proteomic aging clocks predict disease and longevity across diverse populations

Aging and age-related diseases share convergent pathways at the proteome level. Here, using plasma proteomics and machine learning, we developed organismal and ten organ-specific aging clocks in the UK Biobank (n = 43,616) and validated their high accuracy in cohorts from China (n = 3,977) and the USA (n = 800; cross-cohort r = 0.98 and 0.93). Accelerated organ aging predicted disease onset, progression and mortality beyond clinical and genetic risk factors, with brain aging being most strongly linked to mortality. Organ aging reflected both genetic and environmental determinants: brain aging was associated with lifestyle, the *GABBR1* and *ECM1* genes, and brain structure. Distinct organ-specific pathogenic pathways were identified, with the brain and artery clocks linking synaptic loss, vascular dysfunction and glial activation to cognitive decline and dementia. The brain aging clock further stratified Alzheimer's disease risk across *APOE* haplotypes, and a super-youthful brain appears to confer resilience to *APOE4*. Together, proteomic organ aging clocks provide a biologically interpretable framework for tracking aging and disease risk across diverse populations.

A scalable step count–based predictor of biological age: development and validation of MoveIt! Age in community-dwelling adults and geriatric rehabilitation inpatients

Measuring biological age typically requires invasive and costly procedures. To address this, the MoveIt! Age Score was developed: a simple, scalable, and interpretable aging clock that predicts biological age using only wearable-derived steps data. MoveIt! Age was trained on steps data from the United States National Health and Nutrition Examination Survey (NHANES), using chronological age, maximum step count, and step count variability to predict PhenoAge, a blood biochemistry biological age score. MoveIt! Age performance was evaluated in two independent cohorts: Mitochondria and Muscle Health in Elderly (MitoHealth; N = 55; healthy young adults or older adults from the Netherlands) and Restoring Health of Acutely Unwell Adults (RESORT; N = 145; geriatric rehabilitation inpatients from Australia). In RESORT, MoveIt! Age was assessed and compared to SenoClock-BloodAge and PhenoAge (hematological aging clocks). Delta age was the predicted biological age minus chronological age. In the NHANES testing dataset, MoveIt! Age demonstrated high predictive accuracy of chronological age (r = 0.97, RMSE = 5.4 years) and was more significantly associated with mortality than PhenoAge. In MitoHealth, delta MoveIt! Age showed differences between young adults and older adults who were normal, healthy, or health-impaired, with MoveIt! Age more significantly associated with muscle NAD^+ levels (r = -0.37, p = 0.023) than chronological age (p = 0.416). Delta MoveIt! Age associated more strongly than other clocks with physical function outcomes, including frailty, handgrip strength, and functional performance. These findings support MoveIt! Age as a practical tool to gain insights into biological age in both clinical and community settings.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A multi-omics molecular landscape of 30 tissues in aging female rhesus macaques

A systematic investigation of aging patterns across virtually all major tissues in nonhuman primates, our evolutionarily closest relatives, can provide valuable insights into tissue aging in humans, which is still elusive largely due to the difficulty in sampling. Here, we generated and analyzed multi-omics data, including transcriptome, proteome and metabolome, from 30 tissues of 17 female rhesus macaques (*Macaca mulatta*) aged 3–27 years. We found that certain molecular features, such as increased inflammation, are consistent across tissues and align with findings in mice and humans. We further revealed that tissue aging in macaques is asynchronous and can be classified into two distinct types, with one type exhibiting more pronounced aging degree, likely associated with decreased mRNA translation efficiency, and predominantly contributing to whole-body aging. This work provides a comprehensive molecular landscape of aging in nonhuman primate tissues and links translation efficiency to tissue-specific aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Somatic mutations impose an entropic upper bound on human lifespan

Evgeniy Efimov, Vlad Fedotov, Leonid Malaev, Ekaterina E. Khrameeva, Dmitrii Kriukov

Somatic mutations accumulate with age and can cause cell death, but their quantitative contribution to limiting human lifespan remains unclear. We developed an incremental modeling framework that progressively incorporates factors contributing to aging into a model of population survival dynamics, which we used to estimate lifespan limits if all aging hallmarks were eliminated except somatic mutations. Our analysis reveals fundamental asymmetry across organs: post-mitotic cells such as neurons and cardiomyocytes act as critical longevity bottlenecks, with somatic mutations reducing median lifespan from a theoretical non-aging baseline of 430 years to 169 years. In contrast, proliferating tissues like liver maintain functionality for thousands of years through cellular replacement, effectively neutralizing mutation-driven decline. Multi-organ integration predicts median lifespans of 134-170 years — approximately twice current human longevity. This substantial yet incomplete reduction indicates that somatic mutations significantly drive aging but cannot alone account for observed mortality, implying comparable contributions from other hallmarks.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A cGAS-mediated mechanism in naked mole-rats potentiates DNA repair and delays aging

YU CHEN, ZHIXI CHEN, HAO WANG, ZHEN CUI, KAI-LE LI, ZHIWEI SONG, LINGJIANG CHEN, XIAOXIANG SUN, XIAOYU XU, [...], AND ZHIYONG MAO

In a panel of assays, we found that naked mole-rat cGAS, in contrast to human and mouse cGAS, enhanced HR repair efficiency. This functional reversal is mediated by the substitution of four specific amino acid residues within the C-terminal domain of the cGAS protein. Mechanistically, this amino acid alteration enabled naked mole-rat cGAS to prolong its retention on chromatin in the wake of DNA damage by modulating its ubiquitination status, thereby altering its interaction with the segregase P97. The prolonged presence of naked mole-rat cGAS on chromatin facilitated the formation of a complex between the canonical HR factor RAD50 and FANCI, a factor primarily associated with the Fanconi anemia pathway. We further demonstrated that FANCI promoted the chromatin recruitment of RAD50, thereby potentiating HR repair. Consequently, naked mole-rat cGAS attenuated stress-induced cellular senescence, mitigated organ degeneration, and extended life span in fruit flies. Critically, reverting these four amino acid residues abolished these protective effects. Furthermore, adeno-associated virus–mediated delivery of naked mole-rat cGAS to aged mice reduced frailty, attenuated hair graying, lowered circulating levels of immunoglobulin G and interleukin-6, and decreased cellular senescence markers in multiple tissues. Once again, these beneficial effects were dependent on the four specific amino acids.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging alters genomic instability at endogenous mutation hotspots in mice

Aging is a critical risk factor for cancer development with genetic instability presenting as a common hallmark. Alternative DNA-forming sequences are endogenous sources of genetic instability that are enriched at mutation hotspots in cancer genomes. Using a transgenic mutation-reporter mouse model containing an H-DNA-forming sequence from a mutation hotspot in Burkitt lymphoma, we demonstrate tissue-specific effects of aging on DNA structure-induced mutagenesis, with H-DNA mutation frequencies increasing in spleen and liver and decreasing in brain tissues. DNA sequencing revealed a correlation of increasing large deletions with increasing mutation frequencies. Further, we observed tissue-specific modulation of mechanisms of H-DNA processing, including decreased nucleotide excision repair activity in aged brain tissues and increased cleavage activity on H-DNA structures in aging spleen tissues. Together, these findings provide significant insights into the relationship between aging and cancer-associated genetic instability, aiding in the delineation of the underlying mechanisms of age-associated cancer development.

Click–code–seq reveals strand biases of DNA oxidation and depurination in human genome

DNA modifications drive aging, neurodegeneration, carcinogenesis and chemotherapy drug action. Accurate mapping of diverse DNA modifications with single-nucleotide precision in complex genomes remains challenging. We upgraded click-code-seq, a click-chemistry-aided DNA-modification mapping strategy, to enable its first application for sequencing oxidation and depurination in the human genome. We developed a companion fluorescence assay, click-fluoro-quant, to rapidly quantify common DNA modifications and novel adaptors to minimize false positives and assess modification frequency. We uncovered that endogenous DNA oxidation in a human cell line mirrors cancer mutational signatures linked to oxidative stress. The chemotherapy drug irofulven preferentially induces depurination in ApA dimers and promoters. Notably, oxidized guanines and apurinic sites, both irofulven induced and endogenous, are depleted in gene transcribed strands, with the strand bias increasing with gene expression. This work substantially advances click-code-seq for deciphering the impacts of key modifications in human DNA on cellular physiology and toxicological responses.

Fluorescence lifetime clocks quantify senescence and aging

Epigenetic and omics-based clocks have provided invaluable tools to quantify aging, yet these clocks do not provide direct readouts of aging in real-time in living systems. As methylation changes in nucleolar ribosomal DNA are reliably associated with aging and cellular senescence, we hypothesized that shifts in rRNA species could be leveraged to generate image-based clocks using selective dyes. Here we engineer sensitive and photostable hybrid polymethine dyes selective for rRNA. We present a fluorescence lifetime imaging strategy to visually quantify age- and cellular senescence-dependent nucleolar RNA changes that bypasses requirements for extensive sample preparation such as DNA isolation and enables in vivo, real-time age quantification. We demonstrate resolution through cellular to organismal scales and demonstrate translatability by generating clocks from cells and tissues, as well as Caenorhabditis elegans, mice and human samples. Our fluorescence lifetime imaging strategy thus enables in vivo measurements of aging and senescence and expands the toolbox for aging biology research and translation.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Multi-tissue spatial transcriptomics reveals biological age hotspots in mouse and human aging

Victor Vicente-Alvarez, Cecilia G. de Magalhaes, Dmitrii Glubokov, Adrian Molière, Alexander Tyshkovskiy, Vadim N. Gladyshev

Aging proceeds heterogeneously across tissues, yet how biological age varies within the spatial architecture of individual organs remains poorly understood. Here, we introduce stAge, a framework that quantifies localized transcriptomic age (tAge) from spatial transcriptomics data in mouse and human samples during natural aging and in response to injury, infection, neurodegeneration, and cancer. stAge captures age differences among samples and provides a single multi-tissue model for assessing aging within and across organs. Across tissues and conditions, stAge uncovers robust spatial gradients of biological age and shows that injury and neurodegeneration induce pronounced age acceleration, with stronger responses in older organisms and partial normalization during recovery. With advancing age, tissues develop pronounced hotspots of accelerated aging and coldspots of preserved resilience. Hotspots are enriched for metabolic and immune aging signatures, whereas chromatin-related signatures are associated with coldspots. These findings show that aging is spatially structured within tissues and lay a foundation for developing spatially targeted rejuvenation strategies.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Biological age measured by DNA methylation clocks and frailty: a systematic review and meta-analysis

Jian Hua Tay [1], Duarte Barros [2], Weilan Wang [1], Vanessa Kristina Wazny [1], Andrea B Maier [3]

Background: Frailty is an age-related condition characterised by multisystem physiological decline, which increases vulnerability to adverse outcomes. Biomarkers of ageing might identify individuals at risk and enable early interventions. This systematic review and meta-analysis aimed to examine cross-sectional and longitudinal associations between DNA methylation-based biological age metrics (eg, DNA methylation age, epigenetic-age acceleration [EAA], and age deviation) and frailty.

Methods: In a systematic search of six databases (Embase, Cochrane Central Register of Controlled Trials, PubMed, Ovid, Scopus, and Web of Science) from Jan 1, 2011, to June 6, 2025, we identified population-based cohort studies reporting associations between DNA methylation age, EAA, or age deviation and frailty from general or disease-specific populations with a control group. Risk of bias was assessed using an adapted Newcastle-Ottawa Scale. Random-effects meta-analyses with Hartung-Knapp adjustments were performed on standardised β coefficients and SEs. Publication bias, influence, and sensitivity analyses were conducted.

Findings: From 34 437 records screened, 24 studies met the inclusion criteria (17 cross-sectional studies, one longitudinal study, and six studies that were both cross-sectional and longitudinal), encompassing 28 325 participants (14 757 [52·1%] female; median of mean age 65·2 years [IQR 62·2-69·4]). DNA methylation age and age deviation showed no association with frailty. In cross-sectional meta-analyses, higher Hannum EAA (nine studies; n=11 162; standardised β coefficient 0·06 [95% CI 0·02-0·09], I^2=71·4%), PhenoAge EAA (eight studies; n=10 371; 0·07 [0·03-0·11], I^2=81·7%), GrimAge EAA (eight studies; n=10 371; 0·11 [0·06-0·15], I^2=90·5%), and pace of ageing (five studies; n=7895; 0·10 [0·01-0·19], I^2=91·0%) were significantly associated with higher frailty. In longitudinal meta-analyses, higher GrimAge EAA (five studies; n=6143; 0·02 [0·00-0·05], I^2=46·0%, p=0·0481) was significantly associated with increases in frailty, whereas PhenoAge EAA and pace of ageing were not significantly associated with frailty.

Interpretation: Higher GrimAge EAA is consistently associated with higher frailty. Future research should focus on developing and validating DNA methylation clocks that integrate molecular surrogates of health risk and are specifically trained to predict frailty in large, harmonised, longitudinal cohorts, enabling their translation into clinical practice.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The protein phosphatase 6 subunit SAPS3 modulates lifespan by regulating metabolism

YING YANG, DA EUN KANG, QI FAN, ERIC A. HANSE, HOSUNG BAE, ROCIO A. BARAHONA, XIYU SHEN, BRYAN I. RUIZ, SHELLY H. LEE, [...], AND MEI KONG

Aging is characterized by disruptions in metabolic homeostasis, yet the mechanisms that regulate these metabolic changes remain poorly understood. We show that the serine/threonine–protein phosphatase 6 (PP6) regulatory subunit 3, SAPS3, is a critical regulator of metabolism during aging. SAPS3 deletion significantly extends lifespan in mice and counteracts age-related impairments in metabolic health. SAPS3 deficiency improves the effects of aging on the affective behaviors, cognition, and motor functions in aged mice. We find that SAPS3 expression is increased during aging to inhibit adenosine monophosphate–activated kinase (AMPK) activity. Deletion of SAPS3 leads to AMPK activation and reverses cellular senescence and aging-induced metabolic alterations. Using in vivo U-$^{13}C_6$-D-glucose tracing and metabolomic analysis, we find that SAPS3 deficiency restores metabolic homeostasis with increased glycolysis, tricarboxylic acid (TCA) cycle, and decreased fatty acid synthesis in aged mice. These findings highlight a critical role of the SAPS3/PP6 phosphatase complex in aging and suggest that strategies targeting SAPS3 may promote longevity and healthy aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mitochondrial Respiratory Supercomplex Assembly Factor COX7RP Contributes to Lifespan Extension in Mice

COX7RP is a critical factor that assembles mitochondrial respiratory chain complexes into supercomplexes, which is considered to modulate energy production efficiency. Whether COX7RP contributes to metabolic homeostasis and lifespan remains elusive. We here observed that *COX7RP*-transgenic (*COX7RP*-Tg) mice exhibit a phenotype characterized by a significant extension of lifespan. In addition, metabolic alterations were observed in *COX7RP*-Tg mice, including lower blood glucose levels at 120 min during the glucose tolerance test (GTT) without a significant difference in the area under the curve (AUC), as well as reduced serum triglyceride (TG) and total cholesterol (TC) levels. Moreover, *COX7RP*-Tg mice exhibited elevated ATP and nicotinamide adenine dinucleotide levels, reduced ROS production, and decreased senescence-associated β-galactosidase levels. Single-nucleus RNA-sequencing (snRNA-seq) revealed that senescence-associated secretory phenotype genes were downregulated in old *COX7RP*-Tg white adipose tissue (WAT) compared with old WT WAT, particularly in adipocytes. This study provides a clue to the role of mitochondrial respiratory supercomplex assembly factor COX7RP in resistance to aging and longevity extension.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Autonomous AI Agents Discover Aging Interventions from Millions of Molecular Profiles

Decades of publicly available molecular studies have generated millions of samples testing diverse interventions, yet these datasets were rarely analyzed for their effects on aging. Aging clocks now enable biological age estimation and life outcome prediction from molecular data, creating an opportunity to systematically mine this untapped resource. We developed ClockBase Agent, a publicly accessible platform that reanalyzes millions of human and mouse methylation and RNA-seq samples by integrating them with over 40 aging clock predictions. ClockBase Agent employs specialized AI agents that autonomously generate aging-focused hypotheses, evaluate intervention effects on biological age, conduct literature reviews, and produce scientific reports across all datasets. Reanalyzing 43,602 intervention-control comparisons through multiple aging biomarkers revealed thousands of age-modifying effects missed by original investigators, including over 500 interventions that significantly reduce biological age (e.g., ouabain, KMO inhibitor, fenofibrate, and NF1 knockout). Large-scale systematic analysis reveals fundamental patterns: significantly more interventions accelerate rather than decelerate aging, disease states predominantly accelerate biological age, and loss-of-function genetic approaches systematically outperform gain-of-function strategies in decelerating aging. As validation, we show that identified interventions converge on canonical longevity pathways and with strong concordance to independent lifespan databases. We further experimentally validated ouabain, a top-scoring AI-identified candidate, demonstrating reduced frailty progression, decreased neuroinflammation, and improved cardiac function in aged mice. ClockBase Agent establishes a paradigm where specialized AI agents systematically reanalyze all prior research to identify age-modifying interventions autonomously, transforming how we extract biological insights from existing data to advance human healthspan and longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Sex-specific longitudinal reversal of aging in old frail mice

Important studies report acute rejuvenation of mammalian cells and tissues by blood heterochronicity, old plasma dilution, defined factors, and partial reprogramming. And extension of rodent lifespan via single-prong methods was tried in recent years. Here, we examined whether simultaneous calibration of pathways that change with aging in opposite directions would be more effective in increasing healthspan and lifespan. Moreover, we started with the challenging age group - frail 25-months-old mice that are equivalent to ~75-year-old people. We used an Alk5 inhibitor (A5i) of the age-elevated, pro-fibrotic transforming growth factor-beta (TGF-β) pathway that regulates inflammatory factors, including IL-11, and oxytocin (OT) that is diminished with age and controls tissue homeostasis via G-protein-coupled receptor and ERK signaling. Treatment of old frail male mice with OT+A5i resulted in a remarkable 73% life extension from that time, and a 14% increase in the overall median lifespan. Further, these animals had significantly increased healthspan, with improved physical performance, endurance, short term memory, and resilience to mortality. Intriguingly, these benefits manifested only in the male and not in the female mice, yet OT+A5i had positive effects on fertility of middle-aged female mice. Mechanistically, the bio-orthogonal metabolic proteomics on the blood serum demonstrated that the acute, 7-day, treatment of the old mice with OT+A5i youthfully restored systemic signaling determinants and reduced protein noise in old mice of both sexes. However, after 4 months of OT+A5i, only old male, but not female, mice remained responsive, showing the youthful normalization of systemic proteome. These findings establish the significant health-span extension capacity of OT+A5i and emphasize the differences in aging and in response to longevity therapeutics between the sexes.

A collagen amino acid composition supplementation reduces biological age in humans and increases health and lifespan in vivo

Collagen supplementation has gained attention with increasing claims regarding its beneficial effects on healthy aging based on clinical observations and lifespan extension in pre-clinical models; however, how and which part of an ingested collagen promotes healthy longevity is unknown. Here, we identified the minimal required unit of ingested collagen, which consists of the proper ratio of three glycine to one proline to one hydroxyproline that was sufficient to increase the motility-healthspan and lifespan of *C. elegans*, as well as collagen homeostasis in human fibroblasts in vitro. Supplementation in 20-month-old mice improved grip strength and prevented age-related fat accumulation. In a clinical observational trial (ISRCTN93189645, 03.07.2025), oral supplementation in humans demonstrated improved skin features within three months and a reduction in biological age by 1.4 years ($p = 0.04$) within 6 months. Thus, a ratio of three amino acids elicits evolutionarily conserved health benefits from ingested collagens.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Reductive death is averted by an ancient metabolic switch

Biguanides, including metformin, the world's most prescribed oral hypoglycemic, extend health-span and lifespan in vertebrates and invertebrates. Given the widespread use and apparent safety of metformin, it is assumed that its effects are not associated with toxicity, except when in marked excess. Here we determine that accumulation of damaging reducing equivalents is an unanticipated toxicity associated with biguanides, the defense against which requires post-transcriptional protection of *de novo* fatty acid biosynthesis. We demonstrate that biguanide treatment during impaired fatty acid biosynthesis drives NADPH toxicity, leading to catastrophic elevation of NADH/GSH reducing equivalents and accelerated death across metazoans. Multiple NADPH-generating interventions require fatty acid biosynthesis to prevent markedly shortened survival, indicating that this defense mechanism is broadly leveraged. We propose that fatty acid biosynthesis is a tunable rheostat which can minimize biguanide-induced reductive stress whilst maximizing its pro-longevity outcomes and serve as an exploitable vulnerability in reductive stress sensitive cancers.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Effects of Long-term low-dose intermittent rapamycin administration on glucose metabolism and immune system of SAMP8 and SAMR1 mice

Aging involves a gradual decline in physiological integrity, and rapamycin (RAPA) has demonstrated potential as an anti-aging agent. Nonetheless, its effects on glucose metabolism and immune function may vary based on dosage and administration regimen. This study investigates the impact of intermittent low-dose RAPA on glucose metabolism and immune function in Senescence-Accelerated Mouse Prone 8 (SAMP8) and Senescence-Accelerated Mouse Resistant 1 (SAMR1) mice. Twelve-week-old male SAMP8 and SAMR1 mice were treated with RAPA (0.78 μg/kg) every five days for six months. Glucose uptake, mitochondrial respiratory capacity, spleen and thymus immunophenotype, lymphoproliferation, and cytokine profiles were evaluated. Our findings indicate that RAPA reduced glucose uptake in the bladder and the percentage of $FoxP3^+$ lymphocytes in the spleen of SAMP8 mice, while enhancing mitochondrial respiratory control and ATP production in liver. In SAMR1 mice, RAPA administration led to a decrease in $CD3^+$ thymocytes and splenic lymphoproliferative capacity, while also enhanced mitochondrial performance. Comparisons between Control groups revealed that SAMP8 mice exhibited higher glucose uptake in several tissues, lower lymphocyte populations in spleen and thymus, altered $CD4^+/CD8^+$ ratios, and reduced IL-4 expression compared with SAMR1 mice. The findings reinforce the potential of RAPA to modulate aging-related processes, highlighting improvements in mitochondrial function and energy metabolism across strains with different aging processes. However, the immunosuppressive effects of RAPA remain evident, even at low doses administered intermittently, in an age- and strain-specific manner. These findings emphasize the therapeutic potential of RAPA while underscoring the need for customized dosing strategies to balance efficacy and safety. These data highlight mitochondrial metabolic improvements as the primary benefit of intermittent low-dose RAPA and suggest potential clinical relevance for conditions involving compromised mitochondrial energy metabolism.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Effect of the mitophagy inducer urolithin A on age-related immune decline: a randomized, placebo-controlled trial

Mitochondrial dysfunction and stem cell exhaustion contribute to age-related immune decline, yet clinical interventions targeting immune aging are lacking. Recently, we demonstrated that urolithin A (UA), a mitophagy inducer, expands T memory stem cells (T_{SCM}) and naive T cells in mice. In this randomized, double-blind, placebo-controlled trial, 50 healthy middle-aged adults received oral UA (1,000 mg day^{-1}) or placebo for 4 weeks; time points of analysis were baseline and day 28. Primary outcomes were phenotypical changes in peripheral $CD3^+$ T cell subsets and immune metabolic remodeling. UA expanded peripheral naive-like, less terminally exhausted $CD8^+$ cells (treatment difference 0.50 percentage points; 95% CI = 0.16 to 0.83; $P = 0.0437$) while also increasing $CD8^+$ fatty acid oxidation capacity (treatment difference = 14.72 percentage points; 95% confidence interval (CI) = 6.46 to 22.99; $P = 0.0061$). Secondary outcomes included changes in plasma cytokine levels (IL-6, TNF, IL-1β, IL-10), immune populations assessed via flow cytometry, immune cell function, and mitochondrial content. Analysis revealed augmented mitochondrial biogenesis in $CD8^+$ cells, increased peripheral $CD56^{dim}CD16^{bright}$ NK cells, and nonclassical $CD14^{lo}CD16^{hi}$ monocytes in UA-treated participants, as well as improved activation-elicited TNF secretion in T cells and bacterial uptake by monocytes. Exploratory single-cell RNA sequencing demonstrated UA-driven transcriptional shifts across immune populations, modulating pathways linked to inflammation and metabolism. These findings indicate that short-term UA supplementation modulates human immune cell composition and function, supporting its potential to counteract age-related immune decline and inflammaging. ClinicalTrials.gov registration number: NCT05735886.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Life-extending interventions do not necessarily result in compression of morbidity: a case example offering a robust statistical approach

Despite extensive research on life-extending interventions, rigorous statistical techniques to determine their impact on compression of morbidity (CoM) are rarely used. We present a case example of an analytical method for examining the effect of life-extending dietary interventions on CoM by comparing the rates of decline in vitality and survival toward the end of life. Using data from previous experimental studies in mice, we calculated the average rate of vitality decline by fitting exponential decay models to individual vitality trajectories and compared this rate with the rate of survival decline estimated from Cox proportional hazards model. The results showed that, surprisingly, the life-extending interventions failed to compress morbidity. Instead, the models suggested a potential expansion of morbidity with the interventions, particularly for chronic caloric restriction, as evidenced by a greater difference between the rates of vitality decline and survival decline in the intervention group than in the control group. The results further showed age-dependent effects, with interventions likely to demonstrate CoM at very old ages. These findings challenge the assumption that lifespan extension necessarily compresses morbidity, highlighting the need to consider lifespan, healthspan, and CoM as endpoints when evaluating anti-aging interventions. We do not claim that life-extending interventions categorically fail to achieve CoM; rather, we demonstrate how a rigorous statistical approach can be applied to test the CoM hypothesis. Our framework offers a valuable tool for future studies, and further refining this method will be crucial to determine under which circumstances lifespan extension leads to CoM. The potential to choose from multiple analyses of CoM calls for leadership in the geroscience community both to standardize the nomenclature so that different CoM analysis approaches can be communicated clearly and to establish a "default" CoM analysis for everyone to use in addition to their analyses of choice, thus facilitating comparisons and meta-analyses across studies.

Body-wide multi-omic counteraction of aging with GLP-1R agonism

Junzhe Huang [1,2,3,4,5,16] · Andrew J. Kwok [1,2,3,4,5,16] · Jason Chak Yan Li [1,2,3,4,5,16] · … · Thomas W. Leung [1,2,3] · Vincent C.T. Mok [1,2,3,4,5] · Ho Ko [1,2,3,4,5,17] … Show more

Identifying practical ways to counteract aging and associated degenerative disorders is urgently needed. We performed deep molecular profiling and functional assessments in aging male mice to show that glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment broadly counteracts age-related changes. In mice treated with a GLP-1RA from 11 months for 30 weeks, we observed strong body-wide multi-omic age-counteracting effects and improved selected physical functions. Importantly, the effects were specific to aged mice, not young adults, and were attained with a relatively low dose that minimally affected food intake or body weight. With GLP-1RA treatment beginning at 18 months for 13 weeks, the molecular age-counteracting effects were even stronger and largely dependent on hypothalamic GLP-1R, pointing to a brain-body axis of aging modulation. Comparison with mammalian target of rapamycin (mTOR) inhibition, a proven anti-aging strategy, revealed strong multi-omic similarities. Our findings have broad implications for the mechanisms behind GLP-1RAs' pleiotropic benefits, guiding clinical trials, and informing development of anti-aging-based therapeutics.

Human collagen III mRNA therapy for effective skin rejuvenation

Background: Skin photoaging leads to the deterioration of dermal collagen and overall skin integrity, resulting in visible signs of aging, particularly around the eye. Collagen III plays a pivotal role in maintaining skin elasticity and facilitating proper collagen fibril organization. Messenger RNA (mRNA)-based therapeutics present a novel alternative for addressing these limitations by enabling the localized production of full-length, biologically active proteins.

Methods: This study evaluates the therapeutic effects of human collagen III (hCOL3A1) mRNA on UVB-induced skin photoaging using in vitro and in vivo models. In vitro, human fibroblasts were used to assess oxidative stress, senescence, apoptosis, proliferation, and migration. In vivo, a UVB-induced murine photoaging model was used to assess skin barrier function, dermal thickness, collagen content, and senescence markers were analyzed post-treatment. Transcriptome analysis was conducted to explore gene expression changes and key pathways involved in photoaging and repair mechanisms.

Results: Our findings demonstrate that hCOL3A1 mRNA reduces oxidative stress, senescence, apoptosis and promotes cell proliferation and migration in a photoaging cell model. In a murine photoaging model, hCOL3A1 mRNA significantly improves skin barrier function, enhances dermal thickness, restores collagen content, improves dermal structure, and reduces cellular senescence markers without inducing systemic toxicity or immunogenicity. Transcriptome analyses reveal that hCOL3A1 mRNA reverses UVB-induced gene expression changes, reinstating critical signaling pathways for skin homeostasis and fibroblast function.

Conclusions: These results highlight hCOL3A1 mRNA as a promising therapeutic candidate for skin photoaging and underscore the potential of mRNA-based therapies in dermatology and regenerative medicine.

The *JAK2V617F* and *CALR* mutations and risk of cancer, cardiovascular diseases, and all-cause mortality

Background

Clonal hematopoiesis (CH) is associated with adverse outcomes. We hypothesized that CH (*JAK2V617F* and *CALR*) is associated with cancer, vascular disease, and all-cause mortality, even at a variant allele frequency (VAF) <1%.

Methods

We screened 19,832 individuals from the Danish General Suburban Population Study for *JAK2V617F* and *CALR* mutations by digital-droplet PCR. We used Cox regression with hazard ratio (HR) and 95% confidence interval (95%CI), stratified by CH (*JAK2V617F* and *CALR*), VAF (<1% vs. ≥1%), mutation type (*JAK2V617F* or *CALR*), and *JAK2V617F* VAF.

Results

The HR (95%CI) for any cancer was 1.71 (1.46–2.01) in CH, 1.28 (1.05–1.56) in VAF < 1%, 4.35 (3.34–5.66) in VAF ≥ 1%, and higher for *JAK2V617F* but not *CALR*. For hematological cancer, the HR (95%CI) was 8.41 (6.44–10.99) in CH, 3.53 (2.35–5.30) in VAF < 1%, and 40.01 (28.97–55.26) in VAF ≥ 1%, and also higher for *JAK2V617F* and *CALR*. For arterial diseases, the HR (95%CI) was 1.25 (1.03–1.52) in CH, 1.75 (1.18–2.59) in VAF ≥ 1%, and 1.28 (1.05–1.55) in *JAK2V617F*. The HR for venous disease was only higher in *JAK2V617F* VAF ≥ 1%. The HR (95%CI) for all-cause mortality was 1.45 (1.19–1.75) in CH, 1.36 (1.10–1.69) in VAF < 1%, 1.91 (1.26–2.88) in VAF ≥ 1%, and also higher for *JAK2V617F* and *CALR*. The population-attributable risk proportion (95%CI) for myeloproliferative neoplasms (MPNs) was 76.6% (66.8–86.4) in CH, 47.1% (29.6–64.6) in VAF < 1%, and 71.0% (59.4–82.6) in VAF ≥ 1%, with a nomogram generated.

Conclusions

CH—defined by the *JAK2V617F* and *CALR* mutations—was associated with cancer, MPN, all-cause mortality—even with VAF < 1%—and vascular diseases at VAF ≥ 1%. These are novel findings, indicating that the *JAK2V617F* and *CALR* mutations confer an oncogenic potential with a VAF below the current CH of indeterminate potential definition.

Six Drivers of Aging Identified Among Genes Differentially Expressed With Age

Ariella Coler-Reilly [1 2 3], Zachary Pincus [4 5], Erica L Scheller [1 2 4 6], Roberto Civitelli [1 2 6]

Many studies have compared gene expression in young and old samples to gain insights on aging, the primary risk factor for most chronic diseases. However, these studies only identify associations without distinguishing drivers of aging from compensatory geroprotective responses or incidental downstream effects. Here, we introduce a workflow to characterize causal effects of differentially expressed genes on lifespan. First, we performed a meta-analysis of 25 gene expression datasets comprising samples of various tissues from healthy, untreated adult mammals (humans, dogs, and rodents) at two distinct ages. Genes were ranked by the number of datasets in which they exhibited consistent differential expression with age. The top age-upregulated genes were TMEM176A, EFEMP1, CP, and HLA-A; the top age-downregulated genes were CA4, SIAH, SPARC, and UQCR10. Second, the effects of the top ranked genes on lifespan were measured by applying post-developmental RNA interference of the corresponding ortholog in Caenorhabditis elegans. Out of 10 age-upregulated and 9 age-downregulated genes that were tested, two age-upregulated genes (csp-3/CASP1 and spch-2/RSRC1) and four age-downregulated genes (C42C1.8/DIRC2, ost-1/SPARC, fzy-1/CDC20, and cah-3/CA4) produced significant and reproducible lifespan extension. Notably, the data do not suggest that the direction of differential expression with age is predictive of the effect on lifespan. Our study provides novel insight into the relationship between differential gene expression and aging phenotypes, pilots an unbiased workflow that can be easily repeated and expanded, and pinpoints six genes with evolutionarily conserved, causal roles in the aging process for further study.

Heales
HEALTHY LIFE EXTENSION SOCIETY

*HLA-DRB1*15:01* is associated with a reduced likelihood of longevity in northern European men

Methods

We conducted an initial case-control study, comparing imputed HLA alleles from a German longevity cohort with younger controls. Associations were evaluated with logistic regression, adjusting for multiple testing and population structure. Subsequently, significant associations (adjusted $P \leq 0.05$) were tested for replication in two additional populations of similar ancestry: a Danish longevity cohort and the UK Biobank. Furthermore, epitope binding and immunogenicity predictions were performed to detect potential mechanisms linking HLA alleles to longevity.

Results

Our analysis revealed a novel male-specific association of *HLA-DRB1*15:01:01* with longevity (adjusted $P = 2.80 \times 10^{-2}$, odds ratio = 0.64, 95% CI: 0.48–0.82). In Germans, *HLA-DRB1*15:01:01* was less frequent among male cases (10%) than controls (15%), whilst female cases exhibited no substantial decrease (14%), suggesting that men carrying this allele have a lower chance of becoming long-lived. This finding was replicated in the UK Biobank and found to be consistent in the Danish cohort. Computational predictions further revealed that *HLA-DRB1*15:01* is more likely to trigger an immune response against an apolipoprotein B-100 (APOB-100) epitope than other *HLA-DRB1* alleles. Furthermore, the overall predicted APOB-100 immunogenicity of all *HLA-DRB1* alleles was significantly associated with longevity (estimate −0.11, SE = 0.03, $P = 0.005$).

Heritability and shared environmental effects of brain diseases in 12,040 extended families

Brain diseases have complex patterns of genetic and environmental risk factors, and better understanding of these risks is required for more effective prevention strategies. Participants of the Dutch Brain Research Registry provided detailed information on family structure and occurrence of brain diseases. A total of 12,040 participants (73% female, aged 64.9 ± 11 years) provided information on 101,379 family members (53% female, aged 62 ± 25 years). We estimated heritability (h^2) of the nine most common brain diseases using polygenic modeling in SOLAR and assessed variations in h^2 through bootstrapping; Alzheimer's disease (AD) ($h^2 = 73$, range 53-86, $P_{fdr} < 0.001$), ALS ($h^2 = 72$, range 10-98, $P_{fdr} = 0.030$), frontotemporal dementia (FTD) ($h^2 = 48$, range 0-97, $P_{fdr} = 0.132$), vascular dementia (VaD) ($h^2 = 41$, range 7-64, $P = 0.003$), Lewy Body dementia ($h^2 = 34$, range 0-58, $P = 0.132$), iCVA ($h^2 = 27$, 6-59, $P_{fdr} = 0.013$), hCVA ($h^2 = 29$, 8-57, $P_{fdr} = 0.007$), Parkinson's disease (PD) ($h^2 = 38$, 6-66, $P_{fdr} = 0.013$), and multiple sclerosis ($h^2 = 10$, 10-97, $P_{fdr} < 0.001$). Shared environmental effects could be estimated for AD ($c^2 = 5.8\%$, $P_{fdr} = 0.011$), VaD ($c^2 = 9.0\%$, $P_{fdr} = 0.021$), FTD ($c^2 = 9.7\%$, $P_{fdr} = 0.33$), iCVA ($c^2 = 15.9\%$, $P_{fdr} < 0.001$), hCVA ($c^2 = 14.9\%$, $P_{fdr} = 0.005$), and PD ($c^2 = 7.5\%$, $P_{fdr} = 0.25$). These findings underscore the significance of genetic contribution to most brain diseases and the important role of shared environments in AD and vascular-related conditions, highlighting initiatives to mitigate modifiable risk factors.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Human Umbilical Cord Mesenchymal Stem Cells Ameliorate Cognitive Decline by Restoring Senescent Microglial Function via NF-κB-SREBP1 Pathway Inhibition

Aging is a major risk factor for neurodegenerative diseases, yet the role of senescent microglia in age-related cognitive dysfunction remains incompletely understood. Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) have been extensively studied for their significant potential in anti-aging. In this study, we demonstrated that hUC-MSCs ameliorate age-related cognitive decline and downregulate senescence-associated markers in the aged hippocampus. Furthermore, co-culture experiments showed that senescent microglia exacerbate neuronal senescence and neuroinflammation, while also suppressing the apoptosis of senescent neurons. These findings suggested that senescent microglia contribute to age-related cognitive decline by exacerbating neuronal damage and impairing senescent neurons' clearance. We also elucidated a novel mechanism by which hUC-MSCs alleviate age-related cognitive decline by targeting senescent microglia. Specifically, we showed that hUC-MSCs reduce senescence-associated markers, decrease lipid droplet accumulation, and restore phagocytic function in senescent microglia through the inhibition of the NF-κB-SREBP1 pathway. This pathway modulation attenuates neuronal damage and promotes the apoptosis of senescent neurons, facilitating the clearance of damaged neurons. These findings highlight the therapeutic potential of hUC-MSCs in age-related neurodegenerative disorders.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Stage-specific roles of clonally expanded CD8$^+$ T cells in regulating amyloid pathology in Alzheimer's disease models

Clonally expanded CD8$^+$ T cells may contribute to Alzheimer's disease (AD) pathology through interactions with brain-resident cells. However, the functional impact of AD-specific T cell receptor (TCR) clonotypes remains unclear. Here, we demonstrate that CD8$^+$ T cells undergo clonal expansion in early-stage AD mouse models, *App*$^{NL\text{-}G\text{-}F}$ and 5xFAD, and that their depletion reduces amyloid plaque accumulation. Expanded TCR-expressing CD8$^+$ T cells preferentially infiltrate the brain, exacerbating plaque deposition. Moreover, brain-infiltrating CD8$^+$ T cells impair microglial transition into disease-associated states, suppressing amyloid clearance via CCL5-CCR5 signaling. Pharmacological blockade of CCL5 attenuates amyloid deposition, whereas CCL5 administration aggravates pathology. Notably, T cell depletion at later disease stages exacerbates amyloid pathology, suggesting a temporal shift in their function. Early-stage CD8$^+$ T cells exhibit cytotoxic and effector profiles, whereas late-stage cells acquire tissue-resident and exhausted phenotypes. This temporal switch—from pathogenic to protective roles—highlights the stage-specific contribution of CD8$^+$ T cells to AD and their potential as therapeutic targets.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The Alzheimer's therapeutic Lecanemab attenuates Aβ pathology by inducing an amyloid-clearing program in microglia

Controversies over anti-amyloid immunotherapies underscore the need to elucidate their mechanisms of action. Here we demonstrate that Lecanemab, a leading anti-β-amyloid (Aβ) antibody, mediates amyloid clearance by activating microglial effector functions. Using a human microglia xenograft mouse model, we show that Lecanemab significantly reduces Aβ pathology and associated neuritic damage, while neither fragment crystallizable (Fc)-silenced Lecanemab nor microglia deficiency elicits this effect despite intact plaque binding. Single-cell RNA sequencing and spatial transcriptomic analyses reveal that Lecanemab induces a focused transcriptional program that enhances phagocytosis, lysosomal degradation, metabolic reprogramming, interferon *γ* genes and antigen presentation. Finally, we identify *SPP1*/osteopontin as a major factor induced by Lecanemab treatment and demonstrate its role in promoting Aβ clearance. These findings highlight that effective amyloid removal depends on the engagement of microglia through the Fc fragment, providing critical insights for optimizing anti-amyloid therapies in Alzheimer's disease.

Amyloid beta binding partners in the brain tissue of older adults

Introduction: The mechanism linking extracellular amyloid beta (Aβ) with intraneuronal tau tangles, pathological hallmarks of Alzheimer's disease (AD), is not understood; it was tested in the current study through Aβ binding partners.

Methods: Data were from decedents of community-based clinical-pathological studies. Of 52 Aβ binding partners, suggested by non-human studies, levels of 34 together with total Aβ protein were quantified in the dorsolateral prefrontal cortex. Post mortem pathological assessment immunohistochemically quantified Aβ load and tau tangle density.

Results: The strongest mediations between Aβ and tau tangles were observed for Ras-related C3 botulinum toxin substrate 1 (RAC1) and sodium/potassium-transporting ATPase subunit alpha-3 (ATP1A3), which collectively mediated 10.1% of the association between Aβ and tau tangles. In contrast, Aβ mediated >70% of the associations of matrix proteins with tau tangles.

Discussion: Identification of Aβ binding partners that mediate the association between Aβ and tau tangles may provide new targets for AD treatment.

Highlights: RAC1 linked Aβ with tau tangles. ATP1A3 linked Aβ with tau. RAC1 and ATP1A3 collectively mediated 10.1% of the association between Aβ and tau. Aβ mediated >70% of the associations of matrix proteins, such as APOE, with tau.

Spatial and single-cell transcriptomics reveal the reorganization of cerebellar microglia with aging

Andy P. Tsai [1,2,11] · Douglas E. Henze [3,11] · Eduardo Ramirez Lopez [1,2] · … · Alina Isakova [4] · Stephen R. Quake [3,9,10] · Tony Wyss-Coray [1,2,4,12] … Show more

The cerebellum, essential for motor coordination and increasingly recognized for its role in cognition, is typically considered more resilient to aging and largely spared from hallmark Alzheimer's disease (AD) pathology. However, transcriptomic analyses across fifteen mouse brain regions revealed that the cerebellum undergoes some of the earliest and most pronounced age-related changes. To investigate cerebellar aging, we applied single-nucleus RNA sequencing (RNA-seq), microglial bulk RNA-seq, and multiplexed error-robust fluorescence *in situ* hybridization (MERFISH)-based spatial transcriptomics. Microglia showed the most prominent changes, including elevated expression of a neuroprotective signature and reduced expression of a lipid-droplet-accumulating signature compared to hippocampal microglia. Spatial analyses further revealed that aged cerebellar microglia were positioned in close proximity to granule cells. Utilizing this relationship, we identified a proximity-dependent transcriptional state defined by the neuron-associated microglial signature. This signature reveals a region-specific microglial adaptation, highlighting cerebellar reorganization with age and potential resilience to AD.

Heales
HEALTHY LIFE EXTENSION SOCIETY

NAD^+ reverses Alzheimer's neurological deficits via regulating differential alternative RNA splicing of *EVA1C*

Dysfunctional alternative splicing events (ASEs) in RNA are markers of aging and Alzheimer's disease (AD). As a key neuronal resilience metabolite, the oxidized nicotinamide adenine dinucleotide (NAD^+) slows down AD progression in preclinical studies with several clinical trials ongoing. However, the underlying molecular mechanisms around how NAD^+ enhances neuronal resilience, especially whether it has any effect on ASEs, have remained elusive. This study shows that NAD^+ augmentation corrects the ASEs of many genes via a key protein, EVA1C (epithelial V-like antigen 1 homolog C), which is involved in neuronal development and activities. EVA1C is reduced in the hippocampus in patients with AD compared to cognitively normal ones. NAD^+-induced memory retention is partially dependent on EVA1C, as adeno-associated virus–based *Eva1c* knockdown in the hippocampal CA1 region annuls NAD^+-induced memory improvement in pathological Tau–bearing mice. We propose that NAD^+ reduces AD pathologies, at least partially, via amplification of the NAD^+-*EVA1C* splicing axis, pointing to a potential splice-switching therapy for AD.

Spermine modulation of Alzheimer's Tau and Parkinson's α−synuclein: implications for biomolecular condensation and neurodegeneration

Spermine, a pivotal player in biomolecular condensation and diverse cellular processes, has emerged as a focus of investigation in aging, neurodegeneration, and other diseases. Despite its significance, the mechanistic details of spermine remain incompletely understood. Here, we describe the distinct modulation by spermine on Alzheimer's Tau and Parkinson's α-synuclein, elucidating their condensation behaviors in vitro and in vivo. Using biophysical techniques including time-resolved SAXS and NMR, we trace electrostatically driven transitions from atomic-scale conformational changes to mesoscopic structures. Notably, spermine extends lifespan, ameliorates movement deficits, and restores mitochondrial function in C. elegans models expressing Tau and α-synuclein. Acting as a molecular glue, spermine orchestrates in vivo condensation of α-synuclein, influences condensate mobility, and promotes degradation via autophagy, specifically through autophagosome expansion. This study unveils the interplay between spermine, protein condensation, and functional outcomes, advancing our understanding of neurodegenerative diseases and paving the way for therapeutic development.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Serum Exosomes from a Uniquely Defined Early-Adult Donor Cohort Reprogram Endothelial Transcriptomes Linked to Alzheimer's Pathogenesis

Age-related changes in circulating exosomes are implicated in cerebrovascular aging and the pathogenesis of Alzheimer's disease (AD). Neurovascular dysfunction and blood-brain barrier (BBB) breakdown are recognized as early events in AD, often preceding amyloid-β deposition. Primary human brain micro endothelial cells (HBMECs) from a 38-year-old male were treated with exosomes from young (18–25 years) and old (65–72 years) donors. Whole transcriptomic RNA sequencing analysis identified 5,432 differentially expressed genes, which were organized into five transcriptional clusters. Two principal clusters demonstrated reciprocal patterns: 1) exosomes derived from serum of older adult donors (65–72 years) downregulated genes essential for mitochondrial function (e.g., oxidative phosphorylation) and protein synthesis (e.g., ribosomal biogenesis) and 2) upregulating genes linked to inflammation, junctional remodeling, and proliferative signaling. Crucially, subsequent treatment with exosomes derived from serum of young adult donors (18–25 years) reversed these detrimental transcriptomic profiles via restoration of the expression of mitochondrial and ribosomal machinery toward baseline and suppressed the inflammatory and maladaptive proliferative signaling induced by exosomes derived from serum of older adult donors. These findings demonstrate that exosomes derived from serum of young adult donors can counteract detrimental signals of aging at the transcriptional level, reinforcing the cellular architecture underlying BBB integrity. This supports the therapeutic potential of using exosomes derived from serum of young adult donors to reverse endothelial aging and interrupt the early neurovascular dysfunction that contributes to the progression of AD.

Topological turning points across the human lifespan

Alexa Mousley, Richard A. I. Bethlehem, Fang-Cheng Yeh & Duncan E. Astle

Structural topology develops non-linearly across the lifespan and is strongly related to cognitive trajectories. We gathered diffusion imaging from datasets with a collective age range of zero to 90 years old ($N = 4,216$). We analyzed how 12 graph theory metrics of organization change with age and projected these data into manifold spaces using Uniform Manifold Projection and Approximation. With these manifolds, we identified four major topological turning points across the lifespan – around nine, 32, 66, and 83 years old. These ages defined five major epochs of topological development, each with distinctive age-related changes in topology. These lifespan epochs each have a distinct direction of topological development and specific changes in the organizational properties driving the age-topology relationship. This study underscores the complex, non-linear nature of human development, with unique phases of topological maturation, which can only be illuminated with a multivariate, lifespan, population-level perspective.

Genetic Insights Into the Interplay Between Aging and Kidney Health

The aging process markedly amplifies the risk of kidney diseases, whereas kidney dysfunction also accelerates aging. However, the intricate interplay between aging and kidney diseases remains incompletely understood. In this context, we conducted a comprehensive genetic investigation by incorporating multivariate aging indicators and multiple kidney phenotypes. We explored their shared genetic architecture for each trait pair through cross-trait analyses, and two-step mediation analyses were employed to investigate the mediating role of plasma metabolites in causal relationships. Our findings revealed significant negative correlations between healthy aging and kidney diseases, kidney injury, and kidney function decline. We identified 949 pleiotropic single nucleotide polymorphisms, 85 candidate pleiotropic genes, and 8 shared causal genes across tissues, including SH2B3 and MAP2K1 as druggable genes. Notably, mediation analyses highlighted the crucial role of lipoprotein in mediating the detrimental causal effects of kidney diseases on healthy aging. These findings underscore the complex shared genetic etiology and mediators between aging and kidney phenotypes, offering novel insights into their underlying mechanisms and highlighting potential therapeutic strategies.

Age-related lung structure changes by quantitative assessment: a cross-sectional study in a Chinese male cohort

Objectives: This study aims to investigate age-related alterations of lung structure.

Methods: We retrospectively collected 928 male subjects from an annual lung nodule screening cohort. The quantitative parameters included lung volume (LV), mean lesion density (MLD), emphysema indexes (LAA-910, LAA-910%, LAA-950 and LAA-950%), number of bronchi (NB) and volume of bronchi (VB), as well as ratio of airway to the lung (ALR). The quantitative parameters were calculated for total lung, right lung, left lung, and the individual lobes.

Results: LV and VB peaked in the group of 51-60 years-old and 61-70 years-old, respectively. MLD decreased with age, while LAA-910, LAA-950, LAA-910%, LAA-950%, and ALR all showed an increasing trend with age. LV, NB, and VB of the right lung were larger than those of the left lung, while MLD, LAA-950, LAA-950%, and ALR of the right lung were lower than those of the left lung ($P < 0.05$). The LV of bilateral upper lobes increased with age, while a decline of LV of bilateral lower lobes was observed since the sixties. The MLD of the bilateral lower lobes decreased ($P < 0.05$). The LAA-910%, LAA-950%, and ALR of the 71-80 years-old in all five lobes were higher than those of the other four groups ($P < 0.05$). LAA-950 and LAA-950% of bilateral lower lobes displayed a steeper increase began at 60 years old. We also provide a computational formula, LungAge Score, for the assessment of the structural lung aging features.

Conclusion: Lung aging is not a linear process, and the lung structural alterations in the upper and lower lobes exhibit significant heterogeneity.

Long-term exposure to ultrafine particles accelerates biological aging and increases respiratory vulnerability in COPD

Long-term exposure to particulate matter is a known risk factor for chronic obstructive pulmonary disease (COPD), yet the impact of ultrafine particles (UFPs) remains poorly understood. As COPD is an age-related disease, the potential modifying role of biological age acceleration in UFP-induced respiratory effects warrants investigation. We conducted a longitudinal panel study of 47 COPD patients with three repeated clinic visits in Beijing, China. Annual exposure levels to UFPs were estimated using a land use regression model. Lung function and respiratory inflammation were assessed at each visit. Biological age was quantified using the Klemera-Doubal method (KDM-BA) and PhenoAge algorithms. Associations were estimated using linear mixed-effects models. Overall, each IQR increase in UFPs exposure was associated with a 3.0-year increase in both KDM-BA (95 % CI: 0.2-5.8) and PhenoAge acceleration (95 % CI: 0.1-5.8). Accelerated biological age was associated with reductions in large and small airway function and lung volume. Stratified analysis indicated that individuals with faster biological aging were more susceptible to UFP-related lung injury. Our study provides novel evidence linking long-term UFP exposure to accelerated biological aging and impaired respiratory function in COPD patients. Biological age may serve as a modifier in assessing air pollution-related health risks.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Genetic ablation of p16 leads to pulmonary remodeling, pro-senescence response, and immune modulation in mice exposed to low-dose, Sub-chronic, environmental tobacco smoke

Objective: Cyclin-dependent kinase inhibitor 2 A, CDKN2A/p16INK4a (p16), is a gene involved in regulating the cell cycle, cellular senescence, and inflammatory responses. The role of p16 in pulmonary immune-inflammatory and cellular senescence responses to low-dose, sub-chronic environmental tobacco smoke (ETS) is not known. We hypothesized that p16-deficient (knockout, KO) mice would exhibit adverse lung responses compared to wild-type (WT) mice, characterized by a decline in lung function, impaired immune responses, lung remodeling, and dysregulated inflammatory responses at low-level ETS exposure.

Materials and methods: C57BL/6J (WT) and p16 knockout, $p16^{-/-}$, were exposed to low dose ETS [10 mg/m^3 total particulate matter (TPM)] for 3 months. Bronchoalveolar fluid (BALF) and lung tissue were used in subsequent analyses.

Results: Histological analysis revealed mild alveolar simplification in p16 KO mice compared to WT mice. CDKN2A/p16 KO BALF did not have the same immune cell infiltration or cytokine response as the WT counterparts, where IL-17A, TNF-α, and GM-CSF were significantly elevated, indicating impaired immune response with p16 deficiency. Proteomic analysis revealed significantly elevated proteins related to inflammation, extracellular matrix remodeling, cellular metabolism, pro-senescence, and oxidative stress in p16 KO mice (Kynu, Col5a3, Lamtor3). NLRP3 and PTGS2 (COX-2) activation z-scores were lower in p16 KO mice, while IL33 and CCR5 activation z-scores were higher compared to WT mice.

Discussion: Thus, p16 deficiency amplifies ETS-induced alveolar architecture, impaired immune responses, and altered inflammatory pathways, contributing to heightened susceptibility to emphysema-like changes compared to WT mice even at low ETS levels. This study revealed that p16 deletion alters response to low-level ETS, not necessarily by amplifying the classic 'damage response' but by modifying immune and senescence signaling in the lungs.

Conclusion: Overall, p16 has a complex and nuanced protective role in lung health, and careful targeting p16-related pathways could offer therapeutic strategies for mitigating chronic lung diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Histone H4 Lysine 12 Lactylation Promotes the Senescence of Alveolar Epithelial Type II Cells in Chronic Obstructive Pulmonary Disease by Modulating the CD38–NAD^+ Signaling Pathway

In chronic obstructive pulmonary disease, the senescence of type II alveolar epithelial cells is a key driver of disease progression, severely impacting lung function and structure. Lactate accumulation, a common feature of chronic hypoxic conditions such as COPD, is increasingly recognized for its role in modulating cellular functions via epigenetic mechanisms. This study aimed to investigate the specific effects of lactate-induced histone lactylation on AEC2 senescence and its contribution to COPD progression. Our experiments revealed a significant increase in histone lactylation levels in COPD models, with site-specific screening identifying histone H4 lysine 12 lactylation as a predominant modification. Using the Cleavage Under Targets and Tagmentation technique (CUT&Tag) sequencing, we demonstrated that H4K12la modulates the CD38-nicotinamide adenine dinucleotide (NAD^+) signaling pathway, thereby promoting AEC2 senescence and exacerbating COPD progression. Further in vitro and in vivo analyses confirmed that elevated H4K12la expression was associated with increased CD38 levels and decreased NAD^+ concentrations. To interrogate this pathway, we employed the p300/CBP inhibitor A485, which specifically inhibits H4K12la levels. This intervention significantly improved AEC2 senescence and reduced COPD-related pathology. Subsequently, we explored additional therapeutic strategies using the CD38 inhibitor 78c and the NAD^+ precursor β - nicotinamide mononucleotide (NMN), both of which effectively reduced senescence markers and further ameliorated COPD symptoms. These findings highlight the critical role of lactate-induced histone lactylation, specifically H4K12la, in COPD pathogenesis. Targeting the H4K12la-CD38-NAD^+ axis, with strategies such as p300/CBP inhibition, offers promising therapeutic avenues for managing the disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Integrative Omics Reveal Female-Specific Benefits of p16^{+} Cell Clearance in Aging Mice

Yao Lin, Boshi Wang, Mengling Huang, Justina C. Wolters, Marco Demaria

Aging is marked by the accumulation of cells expressing the cyclin-dependent kinase inhibitor p16Ink4a. These p16^{+} cells, largely senescent, contribute to inflammation and tissue dysfunction. While eliminating p16^{+} cells improves healthspan, sex-specific differences in their burden and clearance remain unclear. Through combined transcriptomic, proteomic, and functional analyses, we reveal distinct sex-dependent dynamics of p16^{+} cells during aging. Female mice accumulate significantly more p16^{+} cells across multiple tissues, particularly in the liver. In the p16-3MR model, selective ablation of these cells enhances grip strength, promotes skin regeneration, and reduces liver damage exclusively in females. Multi-omics profiling shows that p16^{+} cell removal shifts female liver expression toward youthful, health-associated profiles, marked by improved mitochondrial activity and reduced inflammatory signaling—molecular patterns resembling those induced by longevity interventions such as calorie restriction, rapamycin, and acarbose. Integrative analysis of our and independent datasets identifies a conserved transcriptional network involving Srm, Cd36, and Lrrfip1, suggesting shared mitochondrial–immune regulatory mechanisms. Overall, our findings establish p16^{+} cells as critical yet heterogeneous drivers of tissue aging, uncover sex-specific differences in their abundance and senolytic responsiveness, and support the development of precision senotherapeutics that consider sex as a key biological variable in aging and rejuvenation.

Endothelial LRRC8A delays vascular ageing in natural and accelerated ageing mouse models

Aims: Vascular ageing (VA), characterised by vascular endothelial dysfunction, is a major contributor to age-related chronic conditions. Leucine-rich repeat-containing protein 8A (LRRC8A) is vital in maintaining vascular endothelial function; however, the role of endothelial LRRC8A in VA is undefined. We aimed to investigate the role and mechanism of endothelial LRRC8A in VA.

Methods and results: We found that LRRC8A expression was clearly downregulated in the aged murine aortas. Further integrated analysis of single-cell and bulk RNA-seq and experimental verification revealed that endothelial LRRC8A governed VA by counteracting cell cycle, cellular senescence and oxidative stress. Additionally, endothelial LRRC8A deletion exacerbated the D-galactose (D-gal)-induced VA progression. Mechanistically, endothelial LRRC8A phosphorylated AMPK at T172 and subsequently facilitated SIRT1 nuclear translocation, ultimately counteracting the p53-dependent senescence pathway and activating the FOXO3-dependent antioxidant pathway. Therapeutically, pharmacological agonists of AMPK and SIRT1 effectively rescued endothelial cell senescence and VA in the context of endothelial LRRC8A deficiency. Additionally, endothelial-targeted adeno-associated virus (AAV)-LRRC8A gene therapy can effectively delay the progression of VA in naturally ageing mice.

Conclusions: Our findings provide the first evidence supporting endothelial LRRC8A as a novel modulator of the AMPK-SIRT1 axis and suggest that targeting LRRC8A represents a promising therapeutic strategy for VA and age-related chronic conditions.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Electron Microscopy and Multi-Omics Reveal Mitochondrial Dysfunction and Structural Remodeling in the Hearts of Elderly Mice

Aging is a key driver of cardiac dysfunction, promoting structural remodeling, metabolic alterations, and loss of cellular resilience. In aged hearts, extracellular matrix remodeling and collagen accumulation reduce ventricular compliance, impairing both diastolic function and stress adaptability. Cardiomyocytes exhibit diminished regenerative capacity and dysregulated stress responses, with mitochondrial dysfunction emerging as a central contributor to energy imbalance, oxidative stress, and fibrosis. Traditional single-omics approaches are insufficient to capture the complexity of these interconnected changes. To address this, we employed an integrative multi-omics strategy-combining spatial transcriptomics, proteomics, and metabo-lipidomics with electron microscopy-to investigate cardiac aging in mice at three life stages: adult (12 months), middle-aged (24 months), and elderly (30 months). Electron microscopy revealed enlarged, structurally compromised mitochondria. Spatial transcriptomics showed reduced expression of cardioprotective genes (MANF, CISH, and BNP) and increased expression of profibrotic markers like CTGF. Proteomics revealed widespread mitochondrial dysregulation and impaired ATP production. Metabolic and lipidomic profiling identified reduced antioxidant metabolites and accumulation of lipotoxic species, such as ceramides and diacylglycerols. This multiscale analysis highlights key molecular and metabolic alterations driving cardiac aging, identifying potential therapeutic targets to mitigate age-related functional decline. Overall, our findings highlight the value of integrated, system-level approaches for uncovering the complex mechanisms that drive organ aging. Although our study was conducted in mice, validation in human models will be crucial to establish the translational relevance of these results and to guide future research with potential impact across diverse biomedical fields.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Viral Infections and Risk of Cardiovascular Disease: Systematic Review and Meta-Analysis

Results

We included 155 studies. HIV infection was consistently associated with an elevated risk of CHD (pooled adjusted risk ratio [RR], 1.60 [95% CI, 1.38–1.85]) and stroke (RR, 1.45 [95% CI, 1.26–1.67]). SARS-CoV-2 infection was associated with an increased risk of CHD (RR, 1.74 [95% CI, 1.44–2.11]) and stroke (RR, 1.69 [95% CI, 1.23–2.31]). In self-controlled case series studies, laboratory-confirmed influenza infection was associated with an elevated risk of acute myocardial infarction (pooled incidence rate ratio, 4.01 [95% CI, 2.66–6.05]) and stroke during the first 1 month (incidence rate ratio, 5.01 [95% CI, 3.41–7.37]). In cohort studies, hepatitis C virus infection was associated with a higher risk of CHD (RR, 1.27 [95% CI, 1.13–1.42]) and stroke (RR, 1.23 [95% CI, 1.04–1.46]). Herpes zoster was also associated with an elevated risk of CHD (RR, 1.12 [95% CI, 1.08–1.15]) and stroke (RR, 1.18 [95% CI, 1.09–1.27]). There is insufficient evidence to determine the effect of cytomegalovirus on cardiovascular disease. Although on a limited basis, hepatitis A virus, herpes simplex virus type 1, respiratory syncytial virus, human papillomavirus, dengue, and chikungunya have been linked to an increased risk of cardiovascular disease.

High Blood Pressure in Childhood and Premature Cardiovascular Disease Mortality

Results | Among 37 081 children, the mean (SD) age was 7.1 (0.6) years, mean SBP was 101.9 (10.2) mm Hg, and mean DBP was 61.2 (10.0) mm Hg at baseline (**Table**). Approximately 21% of children were classified with hypertension. During a median (IQR) follow-up through age 54 (52-55) years, there were 487 cardiovascular and 2242 noncardiovascular deaths.

A 1-SD higher SBP (unadjusted hazard ratio [HR], 1.15 [95% CI, 1.04-1.26]; adjusted HR [aHR], 1.14 [95% CI, 1.03-1.26]) and DBP (unadjusted HR, 1.17 [95% CI, 1.07-1.29]; aHR, 1.18 [95% CI, 1.07-1.29]) at age 7 years was significantly associated with premature CVD mortality. Findings were also consistent in magnitude and direction in the fixed-effects sibling analysis (359 children in 150 sibling clusters) for SBP (aHR, 1.14 [95% CI, 0.90-1.45]) and DBP (aHR, 1.18 [95% CI, 0.93-1.51]). There was a significant interaction by sex for SBP ($P < .01$), with a stronger magnitude of association in male (aHR, 1.31 [95% CI, 1.14-1.50]) vs female individuals (aHR, 0.97 [95% CI, 0.84-1.11]). Cumulative incidence functions differed by BP category for CVD mortality but not non-CVD mortality (**Figure**). Elevated BP (unadjusted HR, 1.45 [95% CI, 1.16-1.81]; aHR, 1.48 [95% CI, 1.18-1.86]) and hypertension (unadjusted HR, 1.41 [95% CI, 1.13-1.75]; aHR, 1.40 [95% CI, 1.12-1.76]) at age 7 years were associated with greater risk of CVD mortality.

Colchicine for the secondary prevention of cardiovascular events

Fahim Ebrahimi[a], Ramin Ebrahimi[a], Maximilian Beer, Christof Manuel Schönenberger, Hannah Ewald, Matthias Briel, Perrine Janiaud, Julian Hirt[a], Lars G Hemkens[a]

Included studies

We included 12 studies involving 22,983 randomised participants. The follow-up in the studies ranged from 6 to 80 months. Overall, 11,524 participants were assigned to low-dose colchicine treatment and 11,459 were assigned to a control intervention, which constituted either usual care plus placebo or usual care only. The doses of colchicine used were 0.5 mg once or twice daily. At baseline, the mean age of participants ranged from 57 to 74 years. Most participants (79.4%) were male.

Synthesis of results

There is high-certainty evidence that low-dose colchicine treatment reduces the risk of myocardial infarction, with a risk ratio (RR) of 0.74 (95% confidence interval (CI) 0.57 to 0.96; 22,153 participants, 8 studies; $I^2 = 51\%$), yielding an absolute risk reduction of 9 fewer events (95% CI 16 fewer to 2 fewer) per 1000 patients, when the myocardial infarction rate is about 4% (36 events per 1000 patients) in the control group.

There is also high-certainty evidence that low-dose colchicine reduces the risk of stroke with a RR of 0.67 (95% CI 0.47 to 0.95; 22,483 participants, 10 studies; $I^2 = 40\%$), yielding an absolute risk reduction of 8 fewer events (95% CI 12 fewer to 1 fewer) per 1000 patients, when the stroke rate is about 2% (22 events per 1000 patients) in the control group.

There is high-certainty evidence that the use of low-dose colchicine does not increase the rate of serious adverse events (RR 0.98, 95% CI 0.94 to 1.02; 15,677 participants, 4 studies; $I^2 = 0\%$). However, gastrointestinal adverse events were more common under treatment with colchicine (RR 1.68, 95% CI 1.11 to 2.57; 22,185 participants, 10 studies; $I^2 = 91\%$).

For all other outcomes assessed, the evidence is of moderate certainty. Colchicine probably results in little to no difference in all-cause mortality (RR 1.01, 95% CI 0.84 to 1.21; 22,747 participants, 10 studies; $I^2 = 1\%$; moderate-certainty evidence), in cardiovascular mortality (RR 0.94, 95% CI 0.73 to 1.22; 22,271 participants; 8 studies; $I^2 = 13\%$; moderate-certainty evidence), and coronary revascularisation (RR 0.83, 95% CI 0.64 to 1.08; 13,705 participants, 5 studies; $I^2 = 40\%$; moderate-certainty evidence).

There is no evidence about the benefits or harms of colchicine on quality-of-life or on the risk of all-cause hospitalisation.

Intrinsic changes in cell differentiation and identity drive impaired wound healing in aged female murine skin

Cellular and molecular mechanisms that drive a perturbed wound microenvironment and impaired healing in aged skin have not been fully delineated. To obtain a comprehensive understanding of cell-intrinsic changes acquired during ageing that impact early responses to injury, we performed single-cell RNA sequencing in young and aged intact female murine skin and wounds 3 days post-injury. We observed that substantial changes in the mean proportional distribution and transcriptomic state of skin resident subpopulations in aged, but not young, tissues accompany a global increase in basal inflammation. This is driven by an altered signalling environment leading to impaired keratinocyte differentiation, loss of fibroblast identity and defective macrophage function. Further, we show that ageing-induced changes in skin resident cells persist after injury, resulting in increased expression of senescence-related genes in wound fibroblasts and aberrant monocyte-to-macrophage transitioning coupled to an enhanced inflammatory signature and defective intercellular signalling in comparison to wounds in young mice. In summary, our data highlights a contribution of both cell-intrinsic changes and an altered tissue microenvironment to poor wound healing responses in aged mice.

Enhancer Rewiring Orchestrates Inflammation and Loss of Cell Identity During Muscle Stem Cell Aging

Loss of regeneration is a key feature of aging organs, often linked to stem cell exhaustion. Skeletal muscle stem cells (MuSCs) undergo age-related numerical and functional decline, contributing to reduced regenerative potential. Using low-input multi-omics, we systematically profiled the epigenome, transcriptome, and 3D genome of MuSCs from individual mice across 3 age groups (young, old, and geriatric) and both sexes. At baseline, young male MuSCs showed reduced expression of cell cycle-related mRNAs. In aged mice, particularly males, MuSCs exhibited early alterations (emerging during the transition from young to old age) including enhanced proinflammatory signaling, and loss of cell identity. Late alterations (emerging during the transition from old to geriatric age) included heightened inflammation, widespread enhancer activation, and extensive 3D genome rewiring. Proinflammatory pathways were enriched for interferon signaling and correlated with endogenous retroviral expression and NFκB activity. Late-stage epigenome and 3D genome rewiring reflected downstream degenerative changes in muscle organization, response to cytokines, and loss of myogenic identity. Thus, progressive molecular shifts may explain the aggravated proliferative deficit and functional impairment observed in MuSCs during aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Iron homeostasis and cell clonality drive cancer-associated intestinal DNA methylation drift in aging

Anna Krepelova, Mahdi Rasa, Francesco Annunziata, Jing Lu, Chiara Giannuzzi, Omid Omrani, Elisabeth Wyart, Paolo Ettore Porporato, Ihab Ansari, Dor Bilenko, Yehudit Bergman & Francesco Neri

Epigenetic drift is a key feature of aging and is associated with age-related diseases including cancer, yet the underlying molecular mechanisms remain unclear. Here, by analyzing DNA methylation and gene expression data from healthy and cancerous human colon samples, we identify an aging and colon cancer-associated DNA methylation (DNAm) drift. We find evidence that this drift is conserved in the mouse intestinal epithelium, where we demonstrate its origin within intestinal stem cells and identify its cell-intrinsic and non-mitotic characteristics, finding that its expansion is regulated via crypt clonality and fission. Mechanistically, we find that this drift is driven by age-related inflammation and reduced Wnt signaling, which dysregulate iron metabolism and impair TET activity. Despite CpG-level heterogeneity, we find that DNAm changes are consistent at the gene level, suggesting potential functionality. Our findings shed light on the epigenetic mechanisms of aging and provide a mechanistic basis for the hypermethylation observed in cancer.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Mitochondrial Dysfunction Rewires Macrophage Metabolism, Driving Pro-inflammatory Priming and Immune System Remodeling

Macrophage activation is tightly coupled to cellular metabolism: classically activated pro-inflammatory (M1) macrophages rely on glycolysis and a disrupted tricarboxylic acid cycle, whereas alternatively activated (M2) macrophages depend on oxidative phosphorylation (OXPHOS) and fatty acid oxidation. Although mitochondria are central to this metabolic plasticity, it remains unclear whether mitochondrial dysfunction itself can dictate macrophage polarization.

Using macrophage-specific OPA1 knockout mice, we investigated how mitochondrial dysfunction influences macrophage metabolism and immune homeostasis. Loss of OPA1 caused severe impairment of OXPHOS, reduced mitochondrial membrane potential, and a compensatory glycolytic shift, driving M0 and M2 macrophages toward an M1-like bioenergetic state. Integrative metabolomic and transcriptomic analyses revealed strong priming of OPA1-deficient macrophages towards classical activation, including accumulation of M1-associated metabolites (lactate, succinate, itaconate) and upregulation of NF-κB–driven and other inflammatory gene programs, resulting in increased secretion of IL-6 and TNF even in the absence of stimulation.

Functionally, this metabolic shift primed non-activated and M2 macrophages toward partial M1 polarization with enhanced bactericidal capacity, while simultaneously suppressing M2-associated processes such as proliferation, efferocytosis, and expression of Arg1, CD206, and RELMα.

In vivo, *OPA1*$^{\Delta M}$ mice displayed reduced peritoneal macrophage abundance, impaired self-renewal after IL-4 complex stimulation, and compensatory monocyte recruitment. The remaining macrophages exhibited increased MHCII and reduced RELMα expression, consistent with partial M1 skewing and loss of alternative activation. These local alterations were mirrored systemically: blood profiling revealed enhanced T-cell activation and sex-specific remodeling of immune composition during inflammation and aging.

Collectively, these findings demonstrate that mitochondrial dysfunction serves as a cell-intrinsic cue that primes macrophages toward a glycolytic, pro-inflammatory phenotype while constraining their M2 properties and proliferative capacities. This dual metabolic and functional rewiring highlights mitochondrial integrity as a pivotal determinant of macrophage immunometabolic identity and reveals how its disruption can reshape both local and systemic immune homeostasis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metabolites mediate the effects of healthy lifestyles on the risks of common age-related diseases

Background: Limited research is available on the associations between healthy lifestyles and age-related diseases, particularly those involving multiple diseases and their underlying mechanisms. We aimed to determine whether healthy lifestyles are associated with a lower likelihood of age-related diseases, and whether metabolites mediate these associations.

Methods: The UK Biobank data cohort was used in this study. Five lifestyle factors (diet, physical activity, sedentary behavior, sleep duration, and alcohol consumption) were combined to determine that composite lifestyle scores. Lifestyle-related metabolic signatures were analyzed using Cox proportional hazards models. We then conducted sequential analyses combining Cox regression, linear regression, extreme gradient boosting (XGBoost), and Shapley additive explanation (SHAP) values to identify metabolites associated with age-related diseases and healthy lifestyle scores. Mediation analysis was performed to investigate the potential mediating effects of the identified metabolites on age-related diseases.

Results: Healthy lifestyle scores contributed the most to prevention of chronic obstructive pulmonary disease (COPD) (hazard ratio [HR] [95% confidence interval (CI): 0.72 (0.71, 0.74)], followed by emphysema [HR (95% CI): 0.75 (0.71, 0.78)]. Furthermore, intermediate or healthy lifestyles significantly decreased the age-related risk of stroke, chronic liver disease, chronic kidney disease (CKD), osteoporosis, osteoarthritis, and hypertension. Age-related diseases were associated with the top 10 metabolites, and these associations were individually or jointly mediated. For example, glycoprotein acetylation contributed 14.43% to the overall association between healthy lifestyle scores and inflammatory bowel disease (IBD), whereas low-density lipoprotein (LDL) cholesterol level attenuated this association by 2.92%, the fatty acid content based on the degree of unsaturation showed a 21.64% contribution to the association between the healthy lifestyle score and type 2 diabetes, whereas cholesterol esters in large high-density lipoproteins (HDLs) accounted for 4.57%. Sensitivity analyses verified the robustness and validity of these findings.

Conclusions: These findings provide a deeper understanding of the intricate relationships among lifestyle and metabolites and the development of age-related diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Life-long behavioral screen reveals an architecture of vertebrate aging

Claire N. Bedbrook, Ravi D. Nath, Libby Zhang, Scott W. Linderman, Anne Brunet, Karl Deisseroth

Mapping behavior of individual vertebrate animals across lifespan is challenging, but if achieved, could provide an unprecedented view into the life-long process of aging. We created the first platform for high-resolution continuous behavioral tracking of a vertebrate animal across natural lifespan from adolescence to death—here, of the African killifish. This behavioral screen revealed that animals follow distinct individual aging trajectories. The behaviors of long-lived animals differed markedly from those of short-lived animals, even relatively early in life, and were linked to organ-specific transcriptomic shifts. Machine learning models accurately predicted age and even forecasted an individual's future lifespan, given only behavior at a young age. Finally, we found that animals progressed through adulthood in a sequence of stable and stereotyped behavioral stages with abrupt transitions suggesting a novel structure for the architecture of vertebrate aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

An Application for Automated Drosophila Locomotor Assay with Integrated Device Design and Computer Vision Tracking

Drosophila has long served as a powerful model for investigating locomotor behavior, and geotaxis assays have generated valuable insights into genetics, aging, and neurobiology. Nonetheless, their use can be constrained by subjective scoring, modest throughput, and challenges in reproducibility. To complement and extend these classical approaches, we developed and validated an integrated hardware–software platform that enables automated, high-resolution locomotor analysis across 12 vials in parallel. The system integrates 3D-printed mechanical components, Raspberry Pi–based video acquisition, and programmable environmental controls to ensure standardized conditions. A deep learning pipeline segments vials with near-perfect accuracy (IoU > 0.95), while computer vision algorithms quantify climbing trajectories, velocity, and positional zone occupancy at 60 frames per second. The end-to-end workflow converts raw video into time-resolved metrics, supports sex-specific aggregation, and incorporates advanced statistical analyses, including Linear Mixed Effects regression, harmonic mean p-values, and Mann–Whitney U tests. Relative to manual scoring, this automated pipeline yields 2.8-fold faster processing and nearly 800-fold higher data density. Application of the platform uncovered reproducible phenotypes of multiple genotypes. For example, a circadian mutant known as *Clock*^{out}, males displayed progressive climbing deficits with age, whereas females-maintained age-resilient trajectories. Moreover, male *Clock*^{out} exhibited a reduced performance compared to age-matched control (w^{1118}), however, female *Clock*^{out} showed subtle reduction in performance. Additionally, glial-specific knockdown of *PolG*, encoding the DNA polymerase gamma catalytic subunit, revealed striking sex-dimorphic aging patterns: females outperformed controls at older age, while males exhibited marked decline. To promote broad adoption, a user-friendly Python interface (Tkinter GUI) enables accessibility independent of computational expertise. Collectively, this standardized, high-throughput framework advances the resolution of genotype-, age-, and sex-dependent locomotor dynamics, offering new opportunities in aging, circadian biology, and neurodegeneration research.

Public Views towards Lifespan, Healthspan, and Healthy Longevity Medicine in Singapore: A Qualitative Study from the Healthy Longevity (HELO) Initiatives

Introduction: Healthy Longevity Medicine (HLM) offers a strategy to reduce the healthspan-lifespan gap, yet public perspectives remain unclear. This study refines the Healthy Longevity (HELO) framework through a qualitative exploration of public views towards lifespan, healthspan, and HLM.

Methods: Individuals living in Singapore participated in semi-structured group or individual discussions to explore (a) their understanding of lifespan and healthspan, (b) motivational factors for health behaviours, and (c) their awareness of HLM. Sampling maximised variation across age, sex, and ethnicity. Data obtained through 13 discussions were analysed with a mixed, inductive-deductive approach employing the HELO framework.

Results: Thirty-six participants (mean age = 49.4 years, SD = 15.9, 19 males, 15 ethnic Chinese) were generally familiar with the definitions of lifespan and healthspan, emphasising the importance of quality of life. Health was defined comprehensively, and autonomy over behaviours was highly valued during ageing and in adopting health behaviours. Community resources and government health initiatives were deemed useful, recognising the potential to enhance social, mental, and physical health. Singapore's busy, achievement-oriented culture was identified as a barrier to healthy behaviours. Participants expressed enthusiasm for HLM's potential to extend the healthspan yet voiced concerns about lifestyle changes and potentially losing autonomy.

Conclusion: Personal values and priorities were central to motivations towards healthy longevity. HLM should assess and align diagnostic and treatment plans with individual preferences to support sustainable health behaviours. The Singapore public's alignment with government policies presents an opportunity to promote HLM adoption.

Protein restriction reprograms the multi-organ proteomic landscape of mouse aging

Population aging is accelerating, yet the multi-organ aging process and the geroprotective effects of dietary protein restriction (PR) remain poorly understood. Here, we conducted comprehensive proteomic analyses on 41 mouse tissues during male mouse aging and PR. Our findings identified tissue-specific aging hallmarks, including widespread changes in immunoglobulins and serine protease inhibitors across multiple tissues. PR mitigated age-related tissue-specific protein expression, epigenomic states, and protein phosphorylation patterns, and it significantly improved adipose tissue functions. These findings were supported by independent reduced representation bisulfite sequencing (RRBS), phosphoproteomics, and pathological analyses. Furthermore, analysis of plasma samples from mice and humans confirmed the cardiovascular benefits of PR. We identified sexual and temporal variations in the impact of PR, with middle age being the optimal intervention period. Overall, our study depicts the multi-organ aging process and provides valuable insights into the geroprotective potential of PR.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Single-cell analysis of human thymus and peripheral blood unveils the dynamics of T cell development and aging

Age-related thymic involution increases vulnerability to cancers and infection in older adults, yet the driving mechanisms and its impact on peripheral T cells remain unclear. Using single-cell sequencing, we here analyzed 387,762 cells from human thymus and peripheral blood of young and aged individuals. Within thymus, we found aging reduced T-lineage potential in early thymic progenitors but increased innate lymphocyte lineage potential. Aged thymus were enriched in mature T cells with low *SOX4* expression and inflammatory profiles but depleted of thymic epithelial cells and expression of tissue-restricted antigens. In the periphery, we identified transcriptional features of T cell aging and established a naive T cell-based model for immune age prediction. Furthermore, we identified CD38 as a marker of recent thymic emigrants. Finally, single-cell T cell receptor (TCR) repertoire sequencing identified shifts in TCR repertoire diversity within memory/effector T cells and expanded virus-specific T cells during aging. Collectively, our data offer insights into human thymic involution and peripheral T cell aging and could inform strategies to restore compromised T cell immunity.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

Machine learning predicts lifespan and suggests underlying causes of death in aging C. elegans

Aging leads to age-related pathology that causes death, and genes affect lifespan by determining such pathology. Here we investigate how age-related pathology mediates the effect of genetic and environmental interventions on lifespan in C. elegans by means of a data-driven approach employing machine learning (ML). To this end, extensive data on how diverse determinants of lifespan (sex, nutrition, genotype, mean lifespan range: 7.5 to 40 days) affect patterns of age-related pathology was gathered. This revealed that different life-extending treatments result in distinct patterns of suppression of senescent pathology. By analysing the differential effects on mid-life pathology levels and lifespan, the ML models developed were able to predict lifespan variation, explaining 79% of the variance. Levels of pathology in the pharynx and intestine proved to be the strongest predictors of lifespan. This suggests that elderly C. elegans die predominantly from late-life disease affecting these organs. In addition, we noted profound sex differences in age-related pathology: the striking age-related pathologies in hermaphrodites affecting organs linked to reproduction are absent from males, suggesting that reproductive death may be hermaphrodite limited.

Phenotypic and metabonomics studies of FMOs in C. elegans and their roles in lifespan extension

Introduction: Flavin-Containing Monooxygenases (FMO) are widely conserved, xenobiotic-detoxifying enzymes whose additional endogenous functions have been revealed in recent studies. Those roles include the regulation of longevity in the model nematode Caenorhabditis elegans.

Objectives: The purpose of this study was to compare aspects of the phenotypes of C. elegans worms with mutations in all fmo genes, particularly focusing on the metabolome and its relationship with lifespan-extension and the worm life cycle. This is the first systematic study of the effect of fmo genetic variation on C. elegans metabolic profiles that we are aware of.

Methods: NMR Spectroscopic analysis of the extracts of metabolites from C. elegans worms of different ages and fmo genotypes was used to compare metabolite profiles of C. elegans worms and determine how these changed with genotype and ageing.

Results: Loss of both fmo-4 and fmo-3 and over-expression of fmo-2, resulted in increased levels of tryptophan in the metabolome, which correlated with an extended lifespan in these mutants. Loss of fmo-4 also led to decreased embryo hatching, along with increased sensitivity to bleach during sterilisation protocols. In contrast, in the extended lifespan fmo-1 knockout worm, the metabolome did not reveal any significant metabolite changes and therefore lifespan effects may occur through another mechanism, or hidden metabolic changes.

Conclusion: Genetic interventions coupled with metabolome profiling in C. elegans can provide insights into biological mechanisms in ageing that might lead to strategies for healthy lifespan extension in human old age.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Transcriptomic analysis of mitohormesis associated with lifespan extension in *Caenorhabditis elegans*

Non-lethal exposure to mitochondrial stress has been shown to have beneficial effects due to activation of signaling pathways, including the mitochondrial unfolded protein response (UPR^{mt}). Activation of UPR^{mt} restores the function of the mitochondria and improves general health and longevity in multiple model systems, termed mitohormesis. In *C. elegans*, mitohormesis can be accomplished by electron transport chain inhibition, a decline in mitochondrial translation, decreased mitochondrial import, and numerous other methods that activate UPR^{mt}. However, not all methods that activate UPR^{mt} promote longevity. These and other studies have started to question whether UPR^{mt} is directly correlated with longevity. Here, we attempt to address this controversy by unraveling the complex molecular regulation of longevity of the nematode under different mitochondrial stressors that induce mitochondrial stress by performing RNA sequencing to profile transcriptome changes. Using this comprehensive and unbiased approach, we aim to determine whether specific transcriptomic changes can reveal a correlation between UPR^{mt} and longevity. Altogether, this study will provide mechanistic insights on mitohormesis and how it correlates with the lifespan of *C. elegans*.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Broad Effects of Activation of Alcohol Dehydrogenase 1 on Healthspan Extension

Avery Sukienik, Samuel Berhanu, Abbas Ghaddar, Elizabeth MacPhail, Eyleen J. O'Rourke

Nutritional, genetic, and pharmacological interventions can extend lifespan; however, fewer have been shown to extend healthspan—the period of life free from chronic, debilitating diseases. In line with this, the molecular effectors that drive healthspan are even less understood than those responsible for lifespan extension. We recently reported that activation of Alcohol Dehydrogenase 1 (ADH-1) extends lifespan in yeast and *C. elegans*. In addition, *adh-1* is transcriptionally activated in yeast, worms, mice, and humans in response to caloric restriction—an intervention that extends not only lifespan but also healthspan. Therefore, we investigated whether activating *adh-1* could also extend healthspan. We demonstrate here that *adh-1* activation has broad and robust effects on health, including resistance to age-related obesity, delayed sarcopenia, and attenuated neurodegeneration. Mechanistically, ADH-1-driven healthspan extension is associated with improved proteostasis. These findings position ADH-1 as a promising target for future research aimed at promoting healthy aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Disruption of the insulin signaling pathway in *C. elegans* dramatically increases male longevity and enhances reproductive health late in life

Rose S. Al-Saadi, Hannah B. Lewack, Patrick C. Phillips

Males and females are known to have dramatically different health and lifespan trajectories, but the underlying basis for these differences is only now being fully investigated[1]. In the *Caenorhabditis elegans* nematode model system, most aging studies have been conducted with hermaphrodites, and little is known about male-specific responses to pro-longevity mutations. Several previous studies have used the auxin-inducible degron system to degrade the insulin-like DAF-2/IGF-1 receptor in hermaphrodites, finding that both ubiquitous and tissue-specific degradation can extend lifespan[2–4]. Here we show that ubiquitous degradation of DAF-2 in male *C. elegans* increases median lifespan by more than 440%, one of the longest lifespan extensions by a single intervention to date. Conversely, degrading DAF-2 in the male germline decreased lifespan, opposite of its effect in hermaphrodites[3]. Using male mating and reproductive success as a meaningful ecological and neurophysiological measure of healthspan, we found that ubiquitous degradation of DAF-2 greatly prolongs reproductive health, likely by prolonging function of the male intromittent organ in the tail. This work highlights the importance of studying sex differences in aging and highlights the utility of using *C. elegans* males to understand the underlying basis of enhanced lifespan and healthspan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The efficacy of longevity interventions in Caenorhabditis elegans is determined by the early life activity of RNA splicing factors

Geroscience aims to target the aging process to extend healthspan. However, even isogenic individuals show heterogeneity in natural aging rate and responsiveness to pro-longevity interventions, limiting translational potential. Using RNAseq analysis of young, isogenic, subpopulations of Caenorhabditis elegans selected solely on the basis of the splicing pattern of an in vivo minigene reporter that is predictive of future life expectancy, we find a strong correlation in young animals between predicted life span and alternative splicing of mRNAs related to lipid metabolism. The activity of two RNA splicing factors, Reversed Polarity-1 (REPO-1) and Splicing Factor 1 (SFA-1), early in life is necessary for C. elegans response to specific longevity interventions and leads to context-specific changes to fat content that is mirrored by knockdown of their direct target POD-2/ACC1. Moreover, POD-2/ACC1 is required for the same longevity interventions as REPO-1/SFA-1. In addition, early inhibition of REPO-1 renders animals refractory to late onset suppression of the TORC1 pathway. Together, we propose that splicing factor activity establishes a cellular landscape early in life that enables responsiveness to specific longevity interventions and may explain variance in efficacy between individuals.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Picolinic acid, a tryptophan metabolite, exhibits anabolic effects in muscle cells and improves lifespan and movement in C. elegans

Compounds promoting anabolic effects on muscle and bone may offer an ideal treatment for osteosarcopenia while potentially impacting healthspan and lifespan. We previously demonstrated the anabolic effects of picolinic acid (PIC), a tryptophan metabolite, on bone both in vitro and in vivo. However, its effects on muscle and potential additional effects on lifespan and healthspan are not yet fully understood. This study aimed to investigate PIC's effects on muscle cells in vitro and its impact on mobility and lifespan in an animal model. Murine C2C12 and human myoblasts were treated with PIC (1, 50 and 100 µM) or vehicle for 5 days. Myogenic regulatory factors (MRFs) were evaluated, and the fusion index and myotubules' length were calculated at timed intervals (Day 1, 3, and 5). In vivo, Caenorhabditis elegans were treated with increasing doses of PIC, and their lifespan and rate of movement (thrashing) were evaluated at timed intervals. PIC-treated myoblasts showed a higher and earlier expression of MRFs. On day 3, PIC-treated myotubes were significantly more fused and longer when treated with PIC than vehicle-treated controls. C. elegans treated with 1 mM of PIC showed a significantly longer lifespan. In addition, the mobility of PIC-treated C. elegans was significantly increased at all timed points. In conclusion, this study demonstrates that, besides its anabolic effect on bone, PIC has an anabolic effect on muscle, which is also associated with a longer lifespan in PIC-treated C. elegans. This evidence opens up promising avenues for further exploration of PIC as a novel therapy for osteosarcopenia with additional effects on healthspan and lifespan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Iron-deplete diet enhances *Caenorhabditis elegans* lifespan via oxidative stress response pathways

Gut microbes play a crucial role in modulating host lifespan. However, the microbial factors that influence host longevity and their mechanisms of action remain poorly understood. Using the expression of *Caenorhabditis elegans* FAT-7, a stearoyl-CoA 9-desaturase, as a proxy for lifespan modulation, we conduct a genome-wide bacterial mutant screen and identify 26 *Escherichia coli* mutants that enhance host lifespan. Transcriptomic and biochemical analyses reveal that these mutant diets induce oxidative stress and activate the mitochondrial unfolded protein response (UPRmt). Antioxidant supplementation abolishes lifespan extension, confirming that oxidative stress drives these effects. The extension of lifespan requires the oxidative stress response regulators SKN-1, SEK-1, and HLH-30. Mechanistically, these effects are linked to reduced iron availability, as iron supplementation restores FAT-7 expression, suppresses UPRmt activation, and abolishes lifespan extension. Iron chelation mimics the pro-longevity effects of the mutant diets, highlighting dietary iron as a key modulator of aging. Our findings reveal a bacterial-host metabolic axis that links oxidative stress, iron homeostasis, and longevity in *C. elegans*.

Early-Life Red Light Exposure Extends Lifespan in C. elegans through ROS-AMPK-Driven Mitochondrial Reprogramming

Specific wavelengths and intensities of light offer potential for modulating mitochondrial function to influence aging which is important for the development of non-invasive and modifiable exogenous anti-aging tools. However, the effects of exposure to different wavelengths of light during the early stages of life on health in adulthood, and the underlying mechanisms, remain poorly understood. In this study, we utilized Caenorhabditis elegans to investigate the effects of early-life (L1 to young adult stage) exposure to different light wavelengths (white, red, blue, green) on healthspan. We found that red light exposure (630 nm, 200 lx) during early life extended lifespan by 10.34% without affecting growth, movement, or reproduction, and improved late-life health indicators. Importantly, it significantly enhanced healthspan in later life, suggesting its potential as a non-invasive anti-aging strategy. Mechanistically, red light transiently suppressed mitochondrial bioenergetic activity, biogenesis, and membrane potential, and altered mitochondrial dynamics. Upon light withdrawal, mitochondrial function progressively recovered, demonstrating enhanced structure and function by day 6. Furthermore, red light stimulated ROS production, activated AMPKα phosphorylation, and triggered downstream mitochondrial quality control (MQC) programs, including the unfolded protein response (UPR^{MT}) and mitophagy. Notably, these protective effects were conserved in human dermal fibroblasts, suggesting the translational applicability of this pathway. Collectively, our study identifies a specific "photophysiological window" during early life through which red light promotes longevity via ROS-mediated activation of AMPK and enhancement of MQC, proposing a non-invasive, safe, evolutionarily conserved, and drug-free strategy to mitigate age-related mitochondrial decline. Therefore, red light can serve as a non-invasive anti-aging strategy to enhance healthspan and potentially alleviate age-related mitochondrial dysfunction.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

EDITORIAL

Editorial | Published: 12 November 2025

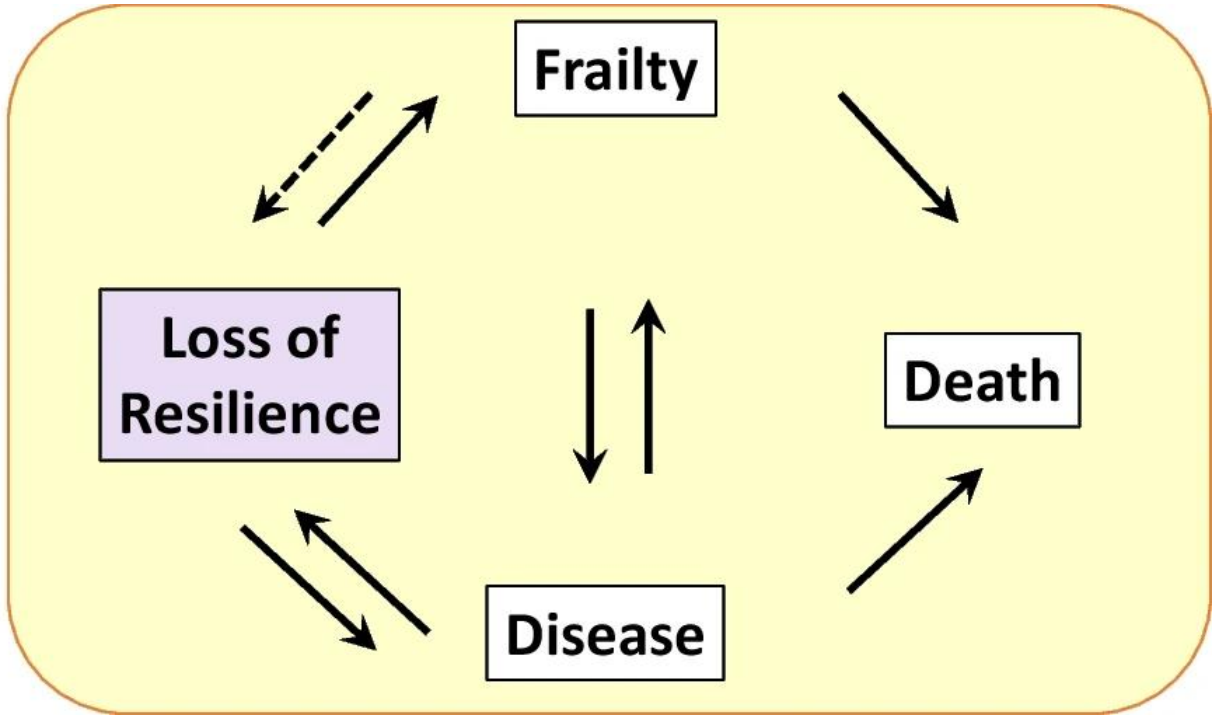
Are GLP-1s the first longevity drugs?

Nature Biotechnology **43**, 1741–1742 (2025) | Cite this article

27k Accesses | **1** Citations | **223** Altmetric | Metrics

As pharma ramps up efforts on disorders of aging, a new era of disease prevention comes into focus.

Loss of molecular resilience as the ultimate outcome of aging biology



Perspective

Entropy and Human Aging

Steven R Cummings [1] [2], Namki Hong [3], Alan A Cohen [4]

Entropy, a measure of disorder and randomness, is an essential feature of thermodynamics, chemistry, and information theory, but there has been little study of entropy in human aging. Entropy arises from random molecular interactions or other forms of damage and will manifest at all levels of human biology. It should also progress in concert across many systems and increase the risk of numerous aging-related conditions. Illustrating these principles, research by Hong in this issue of Aging Cell applies Mahalanobis distance to quantify entropy in electrocardiograms showing that entropy in one system predicts aging-related outcomes-fracture and mortality-beyond the heart. Important issues for research on entropy and human aging include the best methods for quantifying entropy and whether the development of entropy can be slowed or reversed in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging as the wound that fails to heal: a bioenergetic continuum of resolution failure

Aging may be conceptualized as a wound that fails to heal, characterized by persistent, unresolved inflammation. Building on Ogrodnik's "unhealed wound" model, this Perspective extends the Exposure-Related Malnutrition (ERM) framework to propose a bioenergetic interpretation of aging. ERM links chronic stress adaptation, nutrient misallocation, and mitochondrial insufficiency to sustained bioenergetic debt that impedes the transition from catabolic containment to anabolic repair. Across tissues, this energetic shortfall manifests as metabolic inflexibility, lipid-droplet accumulation, and a continuum of adaptive mitochondrial dysfunction that remains reversible until the threshold of senescence—the terminal stage of unresolved adaptation. Recognizing bioenergetic availability as the principal determinant of regenerative success reframes mitochondrial dysfunction and senescence not as primary causes of aging but as downstream consequences of chronic energetic exhaustion. Within this continuum, aging reflects a progressive loss of rhythmic catabolic–anabolic cycling that supports metabolic adaptation. Transient metabolic stress normally induces hormetic activation followed by anabolic recovery, but when this oscillation fails, adaptive hormesis gives way to maladaptive exhaustion. Aging thus emerges from the erosion of bioenergetic rhythm—a transition from recovery with renewal to endurance without repair.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Adapting health, economic and social policies to address population aging in China

Despite its rapid economic rise over the past four decades, China now grapples with the challenge of accommodating and supporting its expanding aging population. In 2020, 18% of its population were over age 60, and 2.5% were over age 80, projected to rise to 39% and 10%, respectively, by 2050. This demographic shift places China at the forefront of diverse individual, familial and societal challenges. Here, we review these challenges in the context of emerging breakthroughs in basic and translational research, shifts in healthcare paradigms, evolving socioeconomic and political dynamics, and policy innovations. We synthesize China's current policies toward promoting healthy longevity in the general population, focusing on social health insurance, long-term care insurance, community and home-based care and palliative care, as well as gerontological research, public health prevention, nutritional and medical interventions, while identifying strengths and gaps. Finally, we propose suggestions to promote a more inclusive, resilient and happier aging society within China's distinctive sociopolitical and cultural context.

Are Early-Onset Cancers an Example of Accelerated Biological Aging?

Jennifer L. Guida, PhD, MPH[1]; Lisa Gallicchio, PhD[1]; Paige A. Green, PhD, MPH[1]

Cancer has traditionally been considered a disease of older adults. Still, recent data have shown an increase in new cancer cases among persons younger than 50 years, referred to as early-onset cancer.[1] The increase was first described in the US yet is now considered a global phenomenon among those born in the 1980s and 1990s.[1,2] The sharpest rise in incidence has occurred among those with gastrointestinal cancers. However, similar increases in incidence have been observed in other organ systems (eg, breast, pancreas, head and neck, kidney, and reproductive organs).[1] Early-onset cancers appear to arise sporadically and are associated with substantial morbidity and mortality.[2] As such, the National Cancer Institute has established the Early-Onset Cancer Initiative to address this emerging public health issue.[3]

Heales
HEALTHY LIFE EXTENSION SOCIETY

Statistical Methods in Aging Research: Improving Current Practices and Embracing Emerging Approaches

Deependra K. Thapa[1], Erik S. Parker[1], Mounika Kandukuri[2], Xi (Rita) Wang[2], Thirupathi R. Mokalla[2], Olivia C. Robertson[2], Wasiuddin Najam[1], Andrew E. Teschendorff[3], Andrew W. Brown[4,5], John R. Speakman[6], Yisheng Peng[7], Bernard S. Gorman[8], Heping Zhang[9], Luis-Enrique Becerra-Garcia[1], Colby J. Vorland[1] and David B. Allison[1,2]

Aging research relies on varied statistical methods, and applying these methods appropriately is important for scientific rigor. However, proper use of these statistical techniques is a challenge. We discuss two categories of statistical methods in aging research: (*a*) emerging methods requiring further validation, including techniques to examine compression of morbidity, maximum lifespan, immortal time bias, molecular aging clocks, and treatment response heterogeneity, and (*b*) classic and existing methods needing reconsideration and improvement, such as stepwise regression, generalized linear models, methods for accounting for clustering and nesting effects, methods for testing for group differences, methods for mediation and moderation analyses, and nonlinear models. For each method, we review its relevance to aging research, highlight statistical issues, and suggest improvements or alternatives with examples from aging research. We urge researchers to refine traditional approaches and embrace emerging methods tailored to the unique challenges of aging research. This review will help researchers identify and apply sound statistical methods, thereby improving statistical rigor in aging research.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Predicting healthspan and disease risks through biological age

Gen Li [1,7] · Linling Cheng [2,7] · Io Nam Wong [2,7] · … · Jie Chen [1] · Li Liu [3,4] · Kang Zhang [1,2,6] … Show more

Aging is the gradual decline in physiological function essential for survival and reproduction. Unlike age-associated diseases, aging affects all individuals within a species, causing progressive impairments across multiple systems. Research shows that altering specific genes or dietary factors can extend lifespan, implicating molecular pathways in controlling senescence. Chronological age (CA) is a common measure of aging, but other hallmarks like telomere shortening better quantify functional decline. Identifying age-related hallmarks can help manipulate aging, spurring interest in aging clocks. These clocks predict biological age (BA) more precisely than CA, reflecting actual physiological health. As global life expectancy continues to rise, aging clocks hold promise for developing therapies to extend healthspan and improve life quality during aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Potential dietary geroprotectors and their impact on key mechanisms of aging

Aging involves progressive accumulation of molecular and cellular damage, leading to functional decline and increased susceptibility to age-related diseases. Natural low-molecular-weight geroprotectors are substances of plant and food origin capable of modulating key mechanisms of aging. Based on current scientific data, sixteen fundamental mechanisms of aging are analyzed, and compounds from food that demonstrate potential in slowing age-related changes are presented. Special attention is paid to the mechanisms of action of these substances at the molecular and cellular levels, as well as their availability in common food products. This review summarizes the current understanding of the interaction between natural nutrients and fundamental aging processes and opens perspectives for developing dietary strategies for healthy longevity.

Hallmarks of the Aging Skin Microenvironment: Components and Mechanisms

Skin aging is a complex biological process driven by the dynamic interplay of cellular senescence, molecular dysfunction, and microenvironmental remodeling. The aging microenvironment acts as both a consequence and a driver of skin aging, creating a vicious cycle that exacerbates inflammation, oxidative stress, and barrier dysfunction. An in-depth exploration of the aging skin microenvironment plays a revolutionary role in the field of skin anti-aging and holds promise for the discovery of novel and feasible targets for skin anti-aging. This review systematically elaborates the aging skin microenvironment through a framework of six interconnected components: (1) inflammaging and immune cell dysfunction, (2) extracellular matrix dysregulation, (3) intercellular communication and extracellular vesicles defect, (4) physical microenvironmental alterations, (5) stem cell exhaustion, and (6) microbiome dysbiosis. These components collectively establish a self-reinforcing network that perpetuates structural degradation, functional decline, and impaired regenerative capacity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Dietary interventions in skin ageing: a systematic review and meta-analysis

Background: Nutrition is a modifiable factor in skin ageing, but its effects remain inconsistently quantified. This meta-analysis assessed human studies from the Web of Science on dietary intake and skin ageing, using pooled standardised mean differences (pSMD). Interventions included carotenoids, collagen, lipids and fatty acids, polyphenols, prebiotics and probiotics, and vitamins. We included full-text English articles and excluded non-human, disease-focused, topical or in vitro studies. Publication bias was assessed using Egger's test and funnel plots. Results are shown as forest plots.

Main body: Sixty-one studies were meta-analysed. Collagen reduces wrinkles (pSMD = - 0.94 [- 1.39, - 0.49], $p = 4.82 \times 10^{-5}$). Lipids and fatty acids (pSMD = - 0.62 [- 0.92, - 0.31], $p = 7.89 \times 10^{-5}$) and polyphenols (pSMD = - 0.48 [- 0.74, - 0.21], $p = 3.96 \times 10^{-4}$) also reduce wrinkles without significant publication bias. Several interventions improve skin hydration, including collagen (pSMD = 0.66 [0.29, 1.04], $p = 5.99 \times 10^{-4}$), lipids and fatty acids (pSMD = 0.54 [0.28, 0.80], $p = 4.36 \times 10^{-5}$), polyphenols (pSMD = 0.59 [0.37, 0.80], $p = 6.43 \times 10^{-8}$), and prebiotics and probiotics (pSMD = 0.71 [0.25, 1.16], $p = 2.64 \times 10^{-3}$). Specific interventions target distinct ageing phenotypes. Carotenoids most effectively reduce redness (pSMD = - 0.53 [- 1.02, - 0.04], $p = 3.39 \times 10^{-2}$), and collagen reduces pigment spots (pSMD = - 0.16 [- 0.31, - 0.003], $p = 4.56 \times 10^{-2}$). Lipids and fatty acids improve elasticity (pSMD = 0.49 [0.14, 0.83], $p = 5.45 \times 10^{-3}$), while polyphenols strengthen barrier integrity (trans-epidermal water loss pSMD = - 0.50 [- 0.79, - 0.22], $p = 6.39 \times 10^{-4}$).

Conclusion: Dietary components target specific skin ageing phenotypes. Carotenoids, collagen, lipids and fatty acids, and polyphenols are particularly effective for redness, pigment spots, elasticity, and barrier integrity, respectively. Lipids, fatty acids, and polyphenols show broad benefits across multiple phenotypes. Shared mechanisms may contribute to overlapping effects. Evidence gaps remain, especially regarding carotenoids and vitamins. Future studies could explore combinatorial dietary interventions. This research is primarily supported by a Singapore National Medical Research Council grant.

Tretinoin for Photodamaged Facial Skin: Systematic Review and Meta-Analysis of Randomized Controlled Trials

Introduction: Randomized controlled trials have suggested that tretinoin, a topical retinoid, can improve wrinkling in photodamaged skin; however, its overall effectiveness remains subject of debate.

Objectives: This study evaluated the efficacy and safety of tretinoin in treating facial wrinkles induced by photodamage.

Method: We systematically searched the PubMed, EMBASE, and Cochrane CENTRAL databases from their inception to 16 January 2024 to identify randomized controlled trials comparing topical tretinoin with vehicle treatments. Data were synthesized using a random effects model, and sensitivity analyses were performed to evaluate the robustness of the results in the presence of potential bias.

Results: This study identified eight trials (1,361 patients; median age range 29-76 years; average follow-up duration, 16 weeks to 2 years) that met the inclusion criteria. Compared with the vehicle, topical tretinoin significantly improved clinical signs of facial photodamage. Improvements were observed in both fine wrinkles (mean difference [MD]: 0.412; 95% confidence interval [CI]: 0.233-0.590; $P<0.001$) and coarse wrinkles (MD: 0.245; 95% CI: 0.119-0.370; $P<0.001$). Sensitivity analyses confirmed the robustness of these findings.

Conclusion: Topical tretinoin is a safe and effective treatment for fine and coarse facial wrinkles resulting from photodamage.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Genetics of Aging and Life Span: Molecular Mechanisms and Intervention Prospects

The review examines modern advances in the genetics of aging and life span. The key molecular mechanisms regulating aging processes at the genetic level are analyzed, including signaling pathways and longevity genes identified in studies on model organisms and through genome analysis of long-lived species. Special attention is given to the insulin/IGF-1 signaling pathway, the role of the FOXO transcription factor, DNA repair systems, epigenetic regulation, and modulation of mTOR and AMPK kinase activity. Results of experimental studies on increasing the life span of model organisms through genetic manipulations and combined approaches are presented. Promising directions for interventions in aging processes based on the current understanding of genetic and molecular mechanisms are discussed, as well as the possibilities of developing comprehensive strategies to slow aging and prevent age-related diseases, taking into account individual genetic characteristics.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Human immune aging

Marina Terekhova · Pavla Bohacova · Maxim N. Artyomov

Aging is an essential aspect of human life, and studying its mechanisms is crucial for extending lifespan and improving quality of life. The immune system plays a central role in the onset of age-related diseases. Understanding the differences between healthy and dysfunctional aging provides key insights into the fundamental immune alternations that occur prior to the point where the system begins to fail. In this review, we explore current perspectives on human immune aging. We focus on changes in the composition of, and consequential functional effects within, the major immune compartments in both circulation and tissues. We discuss earlier findings obtained through flow cytometry, alongside more recent studies utilizing single-cell and advanced cytometry techniques. We highlight here how these methods complement each other and explore potential sources of discrepancies. Finally, we address the challenges that persist in the field of human immune aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Immunoglobulin G and Aging: Biological Functions and Its Crosstalk with the Gut Microbiota

Aging is characterized by a progressive decline in physiological integrity, often accompanied by chronic inflammation and immune dysregulation. Immunoglobulin G (IgG), a key effector of humoral immunity, undergoes substantial structural and functional remodeling with age, particularly through changes in its glycosylation profile. These modifications shift IgG toward a proinflammatory state, linking it to inflammaging and multiple age-related diseases. This review synthesizes recent advances in understanding how IgG contributes to immune aging, with a specific focus on its glycosylation-dependent functions, tissue accumulation, and bidirectional crosstalk with the gut microbiota. We also highlight the potential of IgG as a biomarker and therapeutic target in aging-related interventions. We discuss the dual functional architecture of IgG and how age-related glycan shifts-namely, increased agalactosylation, afucosylation, and bisecting N-acetylglucosamine (GlcNAc)-enhance binding to activating Fcγ receptors, amplifying proinflammatory signaling. Experimental studies demonstrate that IgG accumulation in adipose tissue contributes to metabolic dysfunction via Neonatal Fc Receptor (FcRn)-dependent pathways. Additionally, sex hormones modulate IgG glycosylation patterns, partially explaining sex-specific differences in immune aging. The concept of "glycan clocks" has emerged as a tool to assess biological age and intervention responsiveness. Moreover, the gut microbiota plays a critical role in shaping the IgG repertoire, and aging disrupts this IgG-microbiota axis, resulting in altered mucosal immunity and systemic inflammation. Interventions targeting this axis-including microbiota modulation and glycoengineering-offer promising translational avenues for immune rejuvenation. Finally, we review emerging therapeutic strategies that leverage the gut-immune interface to mitigate aging-associated cardiovascular and metabolic diseases. IgG is not merely a biomarker but an active participant in the aging process, functioning at the intersection of immune regulation, microbial symbiosis, and systemic inflammation. Its age-associated transformation reflects broader changes in host immunity and highlights new opportunities for precision interventions in immunosenescence.

Advanced immunology in aging population: unveiling the complexities of vaccine responsiveness

With the accelerating global population aging, vaccine responsiveness in older adults has emerged as an increasingly critical issue. This review systematically explores age-related changes in immune system function and their impacts on vaccine efficacy. Firstly, we outline the characteristics of immunosenescence and its regulatory effects on vaccine effectiveness from three perspectives: cellular, molecular, and signaling pathway levels. Secondly, we summarize methods for predicting vaccine immune responsiveness (such as biomarkers and advanced immunological assays) and current mainstream strategies for enhancing vaccine immune responsiveness, while enumerating several prominent novel vaccine formulations targeting the older adult population. Finally, we discuss existing controversies and future research directions regarding the study of vaccine responsiveness in older adults, and comprehensively evaluate the current research status of vaccine responsiveness in this demographic. By synthesizing extensive evidence, this review aims to provide new insights into addressing the challenges of vaccinating the older adult population and lay a theoretical foundation for developing more effective immunization strategies tailored to this vulnerable group.

Heales
HEALTHY LIFE EXTENSION SOCIETY

From gut to blood: barrier dysfunction as a driver of systemic low-grade inflammation in cardiometabolic disease

Chronic, low-grade inflammation is increasingly recognized as a fundamental driver of noncommunicable diseases-including obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), and neurodegeneration-yet the initiating events remain incompletely understood. Accumulating evidence implicates gut barrier dysfunction and bacterial translocation as pivotal mechanisms linking environmental and metabolic stressors to systemic inflammation. Mechanistically, obesity-associated depletion of typically beneficial taxa (e.g., *Faecalibacterium*, *Roseburia*, *Akkermansia muciniphila*) and enrichment of proinflammatory *Enterobacteriaceae* reduce expression of tight junction proteins-including, occludin, claudins, and zonula occludens-1 (ZO-1)-and increase the vascular permeability marker, plasmalemma vesicle-associated protein (PV-1). Combined with diminished secretion of host defense peptides (e.g., Reg3γ, lysozyme) and mucus thinning, these changes facilitate LPS-driven activation of Toll-like receptor (TLR)4 and downstream cytokines. We integrate preclinical and clinical data demonstrating how these processes propagate systemic inflammation via the gut-liver and gut-vascular axes, contributing to MASLD, insulin resistance, and vascular dysfunction. Finally, we highlight emerging interventions aimed at restoring barrier integrity-ranging from short-chain fatty acid (SCFA) supplementation and Glucagon-like peptide-2 (GLP-2) receptor agonists to host defense peptide-based therapies-and discuss methodological advances for assessing gut permeability in vivo. Understanding the gut as a dynamic interface between host and environment, and its crucial role in mediating inflammation, will be pivotal for the development of effective interventions targeting the global epidemic of obesity-related disease.

Inflammasome activation and accelerated immune aging in autoimmune disorders

Autoimmune diseases, particularly those with early onset such as systemic lupus erythematosus, juvenile idiopathic arthritis, and type 1 diabetes, are paradoxically characterized by molecular and cellular features typically associated with aging. These include telomere shortening, mitochondrial dysfunction, epigenetic alterations, and skewed immune cell phenotypes, which are considered hallmarks of immunosenescence. This perspective explores the hypothesis that aberrant inflammasome activation, particularly of the NLRP3 complex, serves as a key upstream driver of premature immune aging in autoimmunity. We examine how chronic inflammasome signaling induces senescence through pro-inflammatory cytokine production and oxidative stress, reinforces the senescence-associated secretory phenotype (SASP), and perpetuates immune dysregulation. By reframing autoimmunity as a disorder of accelerated immune aging, we highlight emerging opportunities for therapeutic intervention using senolytics, inflammasome inhibitors, and lifestyle modifications. In addition, incorporating biomarkers of immune aging into clinical assessment may enable precision immunogerontology, particularly in pediatric populations where biological and chronological age may be dissociated. Elucidating the relationship between inflammasome signaling and immune senescence provides a critical framework for understanding autoimmune pathogenesis and for developing interventions that modify disease course by targeting age-associated mechanisms.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Microvascular Health as a Key Determinant of Organismal Aging

Mattia Cenciarini, Andrea Uccelli, Francesca Mangili, Myriam Grunewald, Simone Bersini

Aging is a complex, multifaceted process affecting all organ systems, with vascular aging playing a central role in organismal health decline. Beyond its role in circulation, the vascular system acts as a dynamic interface between tissues, influencing countless physiological functions such as tissue regeneration and repair, immune responses, and metabolic balance. Importantly, age-related vascular impairment—characterized by a peculiar set of endothelial aging hallmarks—exacerbates age-related diseases (ARDs) such as cardiovascular disorders, neurodegeneration, chronic kidney disease, sarcopenia, and osteoporosis. This review combines basic concepts of angioscience and aging biology with translational interventions to devise clinical strategies promoting a functional rejuvenation of old and compromised blood vessels, fostering the prevention, delay or treatment of ARDs. Starting from the description of the cellular and molecular mechanisms driving vascular aging, a cutting-edge perspective on the organ-specific vascular impairment and its impact on tissue function is offered. Given the central role of the vasculature in aging, how targeting vascular aging through pharmacological, genetic, and lifestyle interventions holds promise for mitigating its systemic consequences and improving healthspan is discussed. Finally, how the combination of animal models (e.g., parabiosis) and novel microphysiological systems, coupled with multi-omics and artificial intelligence-driven analyses, is advancing the field toward the identification of strategies that promote vascular resilience and extend healthspan, addressing one of the most pressing biomedical challenges of a worldwide aging population is highlighted.

Senescence: An Overlooked VSMC Phenotype and Therapeutic Opportunity?

Vascular smooth muscle cells (VSMCs) modulate their phenotype from a quiescent, contractile cell to a dedifferentiated, synthetic fibroproliferative cell in response to injury and cardiovascular risk factors. Senescence is a recognized phenotypically distinct cellular state characterized by cell cycle arrest and activation of the p16 and p53 damage response pathway and expression of the senescence-associated secretory phenotype. Low levels of senescence in healthy arteries contribute to vascular homeostasis by ensuring that only healthy VSMCs compose the artery, but they are not intended to be a persistent cellular component of the artery. However, when discussing VSMC phenotype modulation into foam-like cells, macrophages, mesenchymal cells, fibroblasts, adipocytes, and other VSMC-like cells, senescence is rarely included. This raises an intriguing question: can senescence be recognized as a phenotypic state of VSMCs? As understanding SMC phenotypic switching is crucial for developing therapies that can prevent and treat cardiovascular diseases, so is understanding mechanisms of senescence, and targeting the mechanisms that regulate this modulation could be a promising approach for managing conditions such as atherosclerosis, arterial calcification, and aortic aneurysms. This review aims to summarize recent findings about the molecular mechanisms of VSMC senescence and compare similarities and contrasts with the mechanisms known to regulate VSMC phenotype plasticity. Comparison of transcriptomic databases compelled us to also raise the interesting question: if VSMC can regain their contractile phenotype, can they also be coaxed to exit the senescent state and return to the contractile VSMC phenotype? We posit that senescent VSMCs may not be an end point but rather an intermediate or inflection point in VSMC cell fate decision.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Senotherapeutics for metabolic disease and diabetic complications

Allyson K. Palmer, Rosa Spinelli, Larissa G. Langhi Prata, Selim Chaib, Masayoshi Suda, Tamar Tchkonia, Ulf Smith, James L. Kirkland

Metabolic diseases, including obesity, Type 2 diabetes (T2D), and metabolic syndrome, are increasingly prevalent worldwide, driven by sedentary lifestyles, aging populations, and complex genetic and environmental factors. Traditionally understood as disorders of glucose and lipid metabolism, a growing body of evidence now implicates cellular senescence as a central, age-related contributor to metabolic dysfunction. Senescent cells (SCs) accumulate in key metabolic tissues where they disrupt tissue function through the senescence-associated secretory phenotype (SASP), a pro-inflammatory and fibrogenic secretome. SASP factors exacerbate insulin resistance, chronic inflammation, and tissue remodeling, advancing the progression and complications of metabolic diseases. These insights have catalyzed the development of senotherapeutics, a class of interventions that includes senolytics (to eliminate SCs), senomorphics (to suppress SASP), and senosensitizers (to render resistant SCs more vulnerable to clearance). Although preclinical studies show promise, translation into clinical practice faces significant challenges, including identifying reliable biomarkers, understanding SC heterogeneity, and optimizing treatment timing and safety. As research advances, senotherapeutics may offer a transformative approach not only to managing metabolic diseases but also to mitigating associated comorbidities. The recognition that antidiabetic agents already in clinical use can modulate key features of senescence highlights a unique translational opportunity, suggesting that prevention of age-related metabolic disorders may be achievable with therapies already available in routine clinical practice. Medicine is poised to enter a new era in which targeting cellular senescence could fundamentally reshape the prevention and treatment of age-related metabolic disorders, offering the potential for improved healthspan and reduced disease burden across the lifespan.

Interplay Between Aging and Glial Cell Dysfunction: Implications for CNS Health

Aging is accompanied by complex cellular and molecular changes that compromise CNS function. Among these, glial cells (astrocytes, microglia, and oligodendrocytes) play a central role in maintaining neural homeostasis, modulating synaptic activity, and supporting metabolic demands. Emerging evidence indicates that aging disrupts glial cell physiology through processes including mitochondrial dysfunction, impaired proteostasis, chronic low-grade inflammation, and altered intercellular signaling. These alterations contribute to synaptic decline, myelin degeneration, and persistent, low-grade inflammation of the CNS. This review synthesizes current knowledge on the bidirectional relationship between aging and glial cell dysfunction, highlighting how age-related systemic and CNS-specific factors exacerbate glial impairments and, in turn, accelerate neural deterioration. Finally, this study discusses some potential therapeutic strategies aimed at preserving or restoring glial function to promote CNS resilience in aging populations. Understanding this interplay offers critical opportunities for mitigating cognitive decline and improving quality of life in older adults.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Bioenergetics and lipid metabolism in Alzheimer's disease: From cell biology to systemic health

Silvia Maioli, Ivan Nalvarte, Maria Ankarcrona, Marianne Schultzberg, Kristen L. Zuloaga, Julen Goikolea, Pieter Jelle Visser, Bart De Strooper, Bengt Winblad, Paola Pizzo, Pete A. Williams ... See all authors

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive cognitive decline. Although amyloid-β and tau pathologies remain central to our understanding of AD, growing evidence suggests that disrupted lipid metabolism and impaired bioenergetics are closely linked to these hallmark features. Genetic, lipidomic and functional studies point to alterations in cholesterol, phospholipids and polyunsaturated fatty acids, which can influence mitochondrial function, organelle communication and glial responses. These processes are further modulated by apolipoprotein E (APOE) genotype, sex differences and systemic metabolic states such as obesity and diabetes, contributing to neuroinflammation and cognitive decline. Although findings are sometimes conflicting, an emerging theme is that lipid and energy metabolisms are central to how genetic and environmental risk factors shape AD pathogenesis. This integrated perspective highlights lipid and bioenergetic pathways as promising therapeutic targets, where metabolic modulators, lipid-directed interventions and lifestyle strategies may complement amyloid-based therapies and offer opportunities for precision approaches, particularly in women and *APOE ε4* carriers.

Targeting lipid metabolism in neurodegenerative diseases: From experimental to clinical

Junpeng Long [a] · Shasha Liu [b] · Yaning Shi [a,c] · Chanjuan Zhang [a] · Li Qin [a,d] · Qidi Ai [e]

The human brain, despite accounting for only 2 % of total body weight, exhibits an exceptionally high lipid content (approximately 20 % of its mass), highlighting the critical role of lipid metabolism in maintaining neural homeostasis and function. Neurodegenerative diseases—including Alzheimer's disease (AD), Parkinson's disease (PD), stroke, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)—are characterized by progressive neuronal dysfunction and myelin degeneration. These conditions predominantly affect aging populations and represent a growing global health challenge. While aging remains the primary risk factor, compelling evidence now underscores the involvement of dysregulated lipid metabolism in their pathogenesis. However, the precise mechanisms linking dynamic lipid metabolic alterations to disease progression remain incompletely elucidated. This review systematically examines the multifaceted contributions of lipid metabolism to neurodegenerative processes and critically assesses emerging therapeutic strategies that target lipid pathways for the treatment of neurodegenerative disorders.

Lipoprotein metabolism and its impact on life expectancy

Purpose: The aim of this review is to explore the relationship between lipoprotein metabolism and life expectancy across species. The central research question addresses how different classes of lipoproteins (chylomicrons, VLDL, LDL, HDL) and their metabolic pathways influence aging processes and longevity, with a focus on both disease-related and species-specific mechanisms.

Methods: This study synthesizes data mostly from 2015 to 2024, including experimental research in animal models (rodents, primates, C. elegans, D. melanogaster), epidemiological studies in humans, and comparative analyses of lipid profiles across vertebrates and invertebrates. It also examines molecular signaling pathways and evaluates biomedical interventions.

Results: Disruptions in lipoprotein metabolism-particularly elevated LDL-C and VLDL-C levels-are strongly associated with age-related diseases and reduced lifespan in both humans and animal models. In contrast, high HDL-C levels and efficient reverse cholesterol transport are consistently linked to longevity. Species such as birds and cold-water fish exhibit unique lipid profiles that allow high cholesterol without pathological consequences, indicating evolutionary adaptations. Molecular mechanisms involving lipid-sensitive signaling pathways further modulate aging. Therapeutic and dietary interventions targeting lipoprotein metabolism show potential for lifespan extension.

Conclusion: Lipoprotein metabolism plays a central role in determining healthspan and longevity. Understanding the cross-species diversity and regulatory mechanisms of lipid transport provides critical insights into aging biology. Advances in pharmacology, nutrition, and genetic technology offer promising tools to modulate lipoprotein profiles and promote healthy aging in humans.

Ignoring the planet: A critical blind spot for research on ageing

Although research on ageing has largely concentrated on understanding the fundamental biology of the ageing process and devising pharmaceutical interventions in order to slow it down, increasing evidence has underscored the crucial role of environmental inputs across the life course and across generations, in shaping both individual and intergenerational trajectories of age-related health. These include nutrition, air pollution, social deprivation, lifestyle factors, climate change and exposure to environmental toxins, including microplastics and nanoplastics. The development of the concept of the exposome of ageing and the emergence of the new field of 'exposomics' have identified a blind spot, in particular, for geroscience. The impact of the exposome affecting human 'healthspan' (i.e., years lived in good health), extending across generations, is significant and yet under-explored in research. As such, it is under-appreciated that the declining health of the planet will have intergenerational ripple effects, epigenetically priming adverse health in future generations. We discuss the capacity to manipulate our exposome to mitigate against such effects, by addressing root causes, rather than symptoms, of both physiological and planetary dysregulation, dysfunction and decay. We propose a systems-based framework that reconnects research on ageing with exposomics and planetary ecology, creating a new field of 'ecological or exposome pharmacology', harnessing the activity of Nrf2 as a senotherapeutic intervention to improve trans- and intergenerational physiology in the face of declining planetary health.

Molecular Framework of the Onset and Progression of Skeletal Muscle Aging

by Thomas Horlem [1], Stephanie Rubianne Silva Carvalhal [2], Sandro José Ribeiro Bonatto [1,*] and Luiz Cláudio Fernandes [1,*]

Aging is a multifactorial process that progressively disrupts cellular and tissue homeostasis, affecting all organ systems at distinct rates and predisposing individuals to chronic diseases such as cancer, type II diabetes, and sarcopenia. Among these systems, skeletal muscle plays a central role in healthspan decline, yet the precise onset of its deterioration remains unclear. Most studies emphasize late-life models, overlooking the transitional phase of middle age, when initial alterations emerge. Evidence indicates that middle-aged muscle exhibits aberrant metabolism, impaired insulin sensitivity, and an early, gradual reduction in mass, suggesting that decline begins long before overt sarcopenia. This narrative review synthesizes current findings on linear and non-linear molecular biomarkers associated with the onset of skeletal muscle aging, aiming to improve early detection of muscular alterations and support the development of interventions that delay or prevent functional decline.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mitochondrial dysfunction in age-related sarcopenia: mechanistic insights, diagnostic advances, and therapeutic prospects

Sarcopenia is a progressive age-related decline in skeletal muscle mass, strength, and function, representing a significant health burden in older adults. Diagnostic criteria have been established that integrate measures of muscle mass, strength, and physical performance [e.g., European Working Group on Sarcopenia in Older People 2010 (EWGSOP1) and 2019 (EWGSOP2) criteria]. Mechanistically, sarcopenia is driven by hormonal changes, chronic inflammation, cellular senescence, and, importantly, mitochondrial dysfunction. Age-related declines in sex hormones and activation of myostatin impair muscle regeneration and metabolism, while chronic low-grade inflammation disrupts protein synthesis and accelerates proteolysis via the ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP). The accumulation of senescent cells and their secretory phenotype further exacerbates muscle degeneration and functional decline. Mitochondrial dysfunction plays a central role, characterized by impaired biogenesis, excessive reactive oxygen species (ROS) production, compromised autophagy/mitophagy, and accumulation of mitochondrial DNA (mtDNA) mutations. These defects collectively disrupt muscle energy homeostasis, promoting atrophy. The AMPK/SIRT1/PGC-1α and mTORC1 signaling pathways, along with PINK1/Parkin-mediated and receptor-dependent mitophagy, are essential for regulating mitochondrial biogenesis, protein synthesis, and mitochondrial quality control. Current and emerging therapeutic approaches include resistance and endurance exercise, nutritional and pharmacological agents targeting mitochondrial health, and hormonal modulation. Innovative treatments such as senolytics, exerkines, and gene therapies show promise but require further validation. Future advances in mechanistic understanding, diagnostics, and therapeutic strategies offer hope for mitigating sarcopenia and improving the quality of life in aging populations.

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Programmable promoter editing for precise control of transgene expression

Subtle changes in gene expression direct cells to distinct cellular states. Identifying and controlling dose-dependent transgenes require tools for precisely titrating expression. Here, we develop a highly modular, extensible framework called DIAL for building editable promoters that allow for fine-scale, heritable changes in transgene expression. Using DIAL, we increase expression by recombinase-mediated excision of spacers between the binding sites of a synthetic zinc finger transcription factor and the core promoter. By nesting varying numbers and lengths of spacers, DIAL generates a tunable range of unimodal setpoints from a single promoter. Through small-molecule control of transcription factors and recombinases, DIAL supports temporally defined, user-guided control of transgene expression that is extensible to additional transcription factors. Lentiviral delivery of DIAL generates multiple setpoints in primary cells and induced pluripotent stem cells. As promoter editing generates stable states, DIAL setpoints are heritable, facilitating mapping of transgene levels to phenotype and fate in direct conversion to induced motor neurons. The DIAL framework opens opportunities for tailoring transgene expression and improving the predictability and performance of gene circuits across diverse applications.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Nanomaterial-induced mitochondrial biogenesis enhances intercellular mitochondrial transfer efficiency

Intercellular mitochondrial transfer, the spontaneous exchange of mitochondria between cells, is a recently described phenomenon crucial for cellular repair, regeneration, and disease management. Enhancing this natural process holds promise for developing novel therapies targeting diseases associated with mitochondrial dysfunction. Here, we introduce a nanomaterial-based approach employing molybdenum disulfide (MoS_2) nanoflowers with atomic-scale vacancies to stimulate mitochondrial biogenesis in cells to make them mitochondrial biofactories. Upon cellular uptake, these nanoflowers result in a two-fold increase in mitochondrial mass and enhancing mitochondrial transfer to recipient cells by several-fold. This enhanced efficiency of transfer significantly improves mitochondrial respiratory capacity and adenosine triphosphate production in recipient cells under physiological conditions. In cellular models of mitochondrial and cellular damage, MoS_2 enhanced mitochondrial transfer achieved remarkable restoration of cell function. This proof-of-concept study demonstrates that nanomaterial-boosted intercellular mitochondrial transfer can enhance cell survivability and function under diseased conditions, offering a promising strategy for treating mitochondrial dysfunction-related diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Diverging global incidence trends of early-onset cancers: comparisons with incidence trends of later-onset cancers and mortality trends of early-onset cancers

Results: Our analysis showed that 10 early-onset cancer types (thyroid cancer, breast cancer, melanoma, uterine cancer, colorectal cancer, kidney cancer, cervical cancer, pancreatic cancer, multiple myeloma, Hodgkin lymphoma) in females and 7 early-onset cancer types (thyroid cancer, kidney cancer, testis cancer, prostate cancer, colorectal cancer, melanoma, leukemia) in males had statistically significant positive AAPCs in at least 10 countries. Among these, the following early-onset cancer types had significantly higher AAPCs than later-onset cancer types in females: colorectal cancer (6 countries; AAPC range: 1.8-3.8%), cervical cancer (6 countries; AAPC range: 1.2-3.3%), pancreatic cancer (5 countries; AAPC range: 2.3-13.0%), and multiple myeloma (5 countries; AAPC range: 3.1-9.8%); in males: prostate cancer (12 countries; AAPC range: 3.9-18.4%), colorectal cancer (8 countries; AAPC range: 1.8-3.2%), and kidney cancer (6 countries; AAPC range: 2.0-6.0%). We observed statistically significant positive AAPCs in both the incidence and mortality of the following early-onset cancer types: uterine cancer (5 countries) and colorectal cancer (3 countries in females and 5 countries in males). The steeper increases in early-onset cancers compared with later-onset cancers were mainly observed in the very high-HDI country group, including early-onset colorectal cancer (AAPC = 2.4%, 95% CI 2.1-2.6 in females; AAPC = 2.0%, 95% CI 1.7-2.4 in males) to later-onset colorectal cancer (AAPC = -0.1%, 95% CI -0.2 to 0 in females; AAPC = -0.2%, 95% CI -0.3 to 0 in males). We observed strong positive correlations between the increasing obesity prevalence and the rising incidence of early-onset obesity-related cancers in several countries, including Australia (7 cancer types), United Kingdom (7 cancer types), Canada (7 cancer types), Republic of Korea (7 cancer types), and USA (6 cancer types) in females and United Kingdom (7 cancer types), Canada (6 cancer types), Australia (5 cancer types), Sweden (5 cancer types), and Republic of Korea (4 cancer types) in males. Although we did not observe an apparent spike after 2017 in many countries, we observed continued increases in the mortality of certain cancer types, such as uterine cancer (Japan, Republic of Korea, United Kingdom, USA, and Ecuador) in females and colorectal cancer (Argentina, Canada, United Kingdom, and USA) in males.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Coevolution of cooperative lifestyles and reduced cancer prevalence in mammals

Why cancer is so prevalent among mammals, despite the fact that some species evolved resistance mechanisms, remains an open question. We hypothesized that cancer prevalence and mortality risk might have been fine-tuned by evolution. Using public databases, we show that species with cooperative habits have lower cancer prevalence and mortality risk. By developing a mathematical model, we provide a mechanistic explanation: An oncogenic variant that elicits higher cancer mortality in older and less-reproductive individuals is detrimental to cooperative mammalian societies but can lead to a counterintuitive overcompensation in population size and fitness within competitive contexts. The phenomenon of a population increasing in response to a decrease in its per capita survival rate is called the hydra effect, a process never explored in the field of cancer before. Therefore, cancer can be considered as a selected mechanism of biological obsolescence in competitive species.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Ultraprocessed Food Consumption and Risk of Early-Onset Colorectal Cancer Precursors Among Women

Importance Early-onset colorectal cancer (EOCRC) (diagnosed age <50 years) incidence is increasing globally, in parallel with increased consumption of ultraprocessed foods (UPFs). The role of UPFs in early-onset colorectal neoplasia remains underexplored.

Objective To evaluate the association between UPF consumption and risk of EOCRC precursors.

Design, Setting, and Participants This prospective cohort study included participants of the Nurses' Health Study II, an ongoing US prospective cohort of female registered nurses established in 1989. Participants were followed up from June 1, 1991, through June 1, 2015. Data were analyzed from October 2024 to July 2025. UPF intake, derived from food-frequency questionnaires administered every 4 years and classified using the Nova system, was modeled as quintiles of energy-adjusted servings per day. Of the nurses enrolled, those who had completed the baseline 1991 food-frequency questionnaire, undergone at least 1 lower endoscopy before age 50 years after baseline, had no history of cancer (except for nonmelanoma skin cancer) before endoscopy, and no colorectal polyp or inflammatory bowel disease were included.

Main Outcomes and Measures Incidence of EOCRC precursors, including conventional adenomas and serrated lesions, confirmed via medical records and pathology reports. Multivariable logistic regression models with generalized estimating equations for clustered data were used to estimate adjusted odds ratios (AORs) and 95% CIs, accounting for known and putative risk factors.

Results Among 29105 female participants (mean [SD] age, 45.2 [4.5] years) over 24 years of follow-up, 1189 cases were documented of early-onset conventional adenomas and 1598 serrated lesions. UPFs provided 34.8% of total daily calories (median, 5.7 [IQR, 4.5-7.4] servings per day). Participants with higher UPF intake had an increased risk of early-onset conventional adenomas (highest vs lowest intake: AOR,1.45; 95% CI, 1.19-1.77; overall $P<.001$) but not serrated lesions (AOR,1.04; 95% CI, 0.89-1.22; $P=.48$ for trend). Findings were consistent after further adjustment for body mass index, type 2 diabetes, dietary factors (fiber, folate, calcium, and vitamin D), and Alternative Healthy Eating Index–2010 score.

Conclusions and Relevance In this study, higher UPF intake was associated with increased risk of early-onset colorectal conventional adenomas. These data highlight the important role of UPFs in early-onset colorectal tumorigenesis and support improving dietary quality as a strategy to mitigate the increasing burden of EOCRC.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Systemic immunosuppression from ultraviolet radiation exposure inhibits cancer immunotherapy

Background: Ultraviolet radiation (UVR) affects local cutaneous and systemic immunity acutely. The wavelength, pattern and intensity of UVR exposure, individual skin phototype and immune state of individuals modulate the impact of UVR systemically. Local cutaneous immunity after UVR leads to immunosuppression that impacts melanoma. However, the effects of systemic UVR-induced changes on solid cancer therapy are not known.

Methods: We investigated the impact of repeated UVR exposure on systemic immunity and immune checkpoint blockade (ICB) tumor responses in colorectal cancer and melanoma mouse models.

Results: Animals exposed to chronic UVR exhibit decreased ICB response, which is mediated by systemic factors. Repeated UVR exposure expanded systemic lymphocyte populations and contracted total systemic myeloid cells. Specifically, UVR expanded peripheral blood $CD4^+$ regulatory T cells (Tregs), which in turn led to greater Treg infiltration and immunosuppression in colorectal and skin cancer, and colorectal ICB-resistant tumors expressed unique pathways of ICB resistance due to systemic UVR. The response to ICB was restored with systemic pharmacological depletion of Tregs. In preliminary human data, there is an association between the molecular evidence of repeated UVR exposure in dermal fibroblasts and higher systemic Tregs.

Discussion: Our data indicate that patients with melanoma and other cancers on immunotherapy should avoid repeated sun exposure.

Tumor-infiltrating bacteria disrupt cancer epithelial cell interactions and induce cell-cycle arrest

Tumor-infiltrating bacteria are increasingly recognized as modulators of cancer progression and therapy resistance. We describe a mechanism by which extracellular intratumoral bacteria, including *Fusobacterium*, modulate cancer epithelial cell behavior. Spatial imaging and single-cell spatial transcriptomics show that these bacteria predominantly localize extracellularly within tumor microniches of colorectal and oral cancers, characterized by reduced cell density, transcriptional activity, and proliferation. *In vitro*, *Fusobacterium nucleatum* disrupts epithelial contacts, inducing G0-G1 arrest and transcriptional quiescence. This state confers 5-fluorouracil resistance and remodels the tumor microenvironment. Findings were validated by live-cell imaging, spatial profiling, mouse models, and a 52-patient colorectal cancer cohort. Transcriptomics reveals downregulation of cell cycle, transcription, and antigen presentation genes in bacteria-enriched regions, consistent with a quiescent, immune-evasive phenotype. In an independent rectal cancer cohort, high *Fusobacterium* burden correlates with reduced therapy response. These results link extracellular bacteria to cancer cell quiescence and chemoresistance, highlighting microbial-tumor interactions as therapeutic targets.

Can Gene Therapy Transform the Treatment Landscape of Posterior Segment Eye Diseases? A Comprehensive Review of Recent Advancements

Posterior segment eye diseases (PSEDs) encompass a diverse group of conditions affecting the retina, choroid, optic nerve, and vitreous humor, often leading to progressive and irreversible vision loss. Age-related macular degeneration (AMD), diabetic retinopathy (DR), retinitis pigmentosa (RP), and inherited retinal diseases (IRDs) are among the most clinically significant PSEDs with a substantial global burden and economic impact. Conventional treatments for PSEDs have limitations that necessitate the development of novel therapies that address the underlying molecular drivers of the disease. Gene therapy has emerged as a promising approach, offering the potential for durable and curative outcomes through precise genetic manipulation. Advancements in gene therapy strategies, including gene augmentation, gene editing, RNA-based therapies, and optogenetics, have led to significant progress in preclinical studies and clinical trials across various PSED subtypes. US Food and Drug Administration (FDA) approval of voretigene neparvovec (Luxturna®) for RPE65-associated IRDs validated the clinical viability of ocular gene therapy, while ongoing trials for AMD, DR, and other IRDs continue to expand the therapeutic landscape. Innovations in viral and non-viral delivery systems, such as dual AAV vectors, lipid nanoparticles, and novel biomaterials, have enhanced the efficiency and specificity of gene delivery to the retina. However, challenges persist, including immune responses to viral vectors, limited transduction efficiency in certain cell types, and anatomical barriers posed by the blood-retinal barrier. Future directions in ocular gene therapy include the development of precision genome editing techniques, such as prime editing, miRNA-based regulation, and combinatorial approaches integrating gene therapy with stem cell transplantation or neuroprotective agents. As the field continues to evolve, addressing these challenges and optimizing gene therapy strategies will be crucial in translating the transformative potential of ocular gene therapy into clinical reality for patients with PSEDs.