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The ethics case for longevity science

Zhuang Zhuang Han [1], João Pedro de Magalhães [2]

Recent advances in biogerontology show that ageing is malleable, opening the possibility of delaying chronic disease and extending healthspan. Ethical debate has been dominated by consequentialist framings, balancing potential benefits against fears of overpopulation, inequality, or loss of meaning. We seek to further this discussion by grounding the case for longevity research not only in outcomes but also in respect for autonomy, self-ownership, and the intrinsic value of life itself. On this basis, we address three kinds of critiques: philosophical appeals to "naturalness", societal concerns about resources, justice and stagnation, and individual worries about meaning and boredom, showing that none provide decisive objections. Beyond rebuttal, we highlight neglected benefits: longevity research drives technological integration like the Apollo program, affirms the priority of existing persons over abstractions, and liberates individuals from rigid age-based expectations. The moral baseline must flip: the burden now falls on defenders of forced ageing to explain why preventable suffering should continue.

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PREPRINT

The Demographic and GDP Impacts of Slowing Biological Aging

Raiany Romanni-Klein, Nathaniel Hendrix, Richard W. Evans, Jason DeBacker

Biological aging imposes significant socio-economic costs, increasing health expenses, reducing productivity, stalling population growth and straining social systems, culminating in reduced economic activity. We draw insights from interviews with 102 scientists working on aging biology and develop four macroeconomic simulations: slowing brain aging, slowing reproductive aging, and an overall delay in biological aging (including the novel concept of "replacing aging"). Our model is calibrated to represent how slowing biological aging manifests in the US economy and population through the channels of mortality, fertility, and productivity rates by age. We simulate the economic and demographic impacts of near-future advancements in aging science. We find that a one-year delay in brain aging alone could add $201 billion annually to US GDP. A one-year delay in overall biological aging could boost GDP by $408 billion annually, yielding $27.1 trillion in net present value in the long run.

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European cancer mortality predictions for the year 2026: the levelling of female lung cancer mortality

Background: We provided updated cancer mortality estimates for 2026 in the European Union (EU) and its five most populous countries, with a focus on lung cancer.

Methods: Cancer death certifications and population data were obtained from the World Health Organization and United Nations databases. For the EU, France, Germany, Italy, Poland, Spain and the UK we derived data for all cancers combined and major cancer sites since 1970. Linear regression models, based on the most recent age-specific trends identified by Poisson joinpoint regression, were used to estimate deaths in 2026. The number of averted deaths between 1989 and 2026 was computed by applying the 1988 peak rate to subsequent populations.

Results: For 2026, we estimated about 1,230,000 EU cancer deaths, corresponding to age-standardised rates of 114.1/100,000 males (-7.8% vs 2020-2022) and 74.7/100,000 females (-5.9%). In the EU countries and the whole EU, favourable trends are predicted for most major cancers, except female pancreatic cancer. In the UK, predicted rates are also favourable, except female colorectal cancer. Lung cancer mortality continues to decrease markedly among males, while we predicted a levelling off of rates - around 12.5/100,000 - among females in all considered countries and the whole EU, except for Spain (+2.4%). Among females, lung cancer mortality declines are confined to those <65 years, while unfavourable trends continued in older age groups. Around 7.3 million total cancer deaths have been avoided in the EU since the peak observed in 1988. The corresponding figure for lung cancer is 1.8 million among males, while no averted deaths were recorded among females.

Conclusion: Lung cancer mortality predictions for 2026 indicate a levelling off among EU females, with age- and country-specific differences. Mortality trends in ASRs for most cancers remain favourable in the EU and the UK, though the absolute number of cancer deaths is not declining due to population ageing.

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Global and regional cancer burden attributable to modifiable risk factors to inform prevention

Cancer remains a leading cause of morbidity globally, largely attributable to modifiable risks. We estimated the 2022 global and national cancer burden attributable to 30 such factors, including tobacco smoking, alcohol consumption, high body mass index, insufficient physical activity, smokeless tobacco and areca nut, suboptimal breastfeeding, air pollution, ultraviolet radiation, 9 infectious agents and 13 occupational exposures, to inform prevention efforts. Using GLOBOCAN data for 36 cancer sites in 185 countries, we applied prevalence data from around 2012 to reflect exposure–cancer latency and estimated Levin-based or Miettinen-based population-attributable fractions (PAFs) or direct estimates where applicable. Combined PAFs accounting for overlapping exposures were derived by cancer, sex, country and region. In 2022, an estimated 7.1 million of 18.7 million new cancer cases (37.8%) were attributable to 30 modifiable risk factors—2.7 million (29.7%) in women and 4.3 million (45.4%) in men. The proportion of preventable cancers ranged from 24.6% to 38.2% in women and from 28.1% to 57.2% in men across regions. Smoking (15.1%), infections (10.2%) and alcohol consumption (3.2%) were the leading contributors to cancer burden. Lung, stomach and cervical cancers represented nearly half of preventable cancers. Strengthening efforts to reduce modifiable exposures remains central to global cancer prevention.

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AI tools boost individual scientists but could limit research as a whole

Analyses of hundreds of thousands of papers in the natural sciences reveal a paradox: scientists who use AI tools produce more research but on a more confined set of topics.

By Veda C. Storey

Artificial intelligence is influencing many aspects of society, including science. Writing in *Nature*, Hao *et al.*[1] report a paradox: the adoption of AI tools in the natural sciences expands scientists' impact but narrows the set of domains that research is carried out in. The authors examined more than 41 million papers, roughly 311,000 of which had been augmented by AI in some way — through the use of machine-learning methods or generative AI, for example. They find that scientists who conduct AI-augmented research publish more papers, are cited more often and progress faster in their careers than those who do not, but that AI automates established fields rather than supporting the exploration of new ones. This raises questions

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IDEAS

America's next moonshot: Ultra-healthy 60-somethings

Keeping people well for longer may be the fastest way to boost our workforce — and our families.

By Raiany Romanni-Klein Updated February 6, 2026, 3:00 a.m.

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US Congress set to reject Trump's sweeping science budget cuts

Lawmakers have announced legislation that would increase funding for basic research by more than 2%.

By Jeff Tollefson & Max Kozlov

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Cell Symposia

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Heritability of intrinsic human life span is about 50% when confounding factors are addressed

BEN SHENHAR, GLEN PRIDHAM, THAÍS LOPES DE OLIVEIRA, NAVEH RAZ, YIFAN YANG, JORIS DEELEN, SARA HÄGG, AND URI ALON

How heritable is human life span? If genetic heritability is high, longevity genes can reveal aging mechanisms and inform medicine and public health. However, current estimates of heritability are low—twin studies show heritability of only 20 to 25%, and recent large pedigree studies suggest it is as low as 6%. Here we show that these estimates are confounded by extrinsic mortality—deaths caused by extrinsic factors such as accidents or infections. We use mathematical modeling and analyses of twin cohorts raised together and apart to correct for this factor, revealing that heritability of human life span due to intrinsic mortality is above 50%. Such high heritability is similar to that of most other complex human traits and to life-span heritability in other species.

Cellular survivorship bias as a mechanistic driver of muscle stem cell aging

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Aging is characterized by a decline in the ability of tissue repair and regeneration after injury. In skeletal muscle, this decline is largely driven by impaired function of muscle stem cells (MuSCs) to efficiently contribute to muscle regeneration. We uncovered a cause of this aging-associated dysfunction: a cellular survivorship bias that prioritizes stem cell persistence at the expense of functionality. With age, MuSCs increased expression of a tumor suppressor, N-myc down-regulated gene 1 (NDRG1), which, by suppressing the mammalian target of rapamycin (mTOR) pathway, increased their long-term survival potential but at the cost of their ability to promptly activate and contribute to muscle regeneration. This delayed muscle regeneration with age may result from a trade-off that favors long-term stem cell survival over immediate regenerative capacity.

Molecular and phenotypic blueprint of human hematopoiesis links proliferation stress to stem cell aging

Hematopoietic stem/progenitor cells (HSPC) aging has long been associated with myeloid skewing, reduced clonal output, and impaired regenerative capacity, but quantitative immunophenotypic and functional analysis across the human lifespan has been lacking. Here, we provide a comprehensive phenotypic, transcriptional, and functional dissection of human hematopoiesis from youth to advanced age. Although primitive hematopoietic stem cell (HSC) numbers were stable during aging, overall cellularity declined, especially for erythroid and lymphoid lineages. HSPCs from older individuals exhibited repopulating frequencies comparable with those from younger donors in both primary and secondary xenografts; however, aged HSCs displayed impaired differentiation, chromatin and cell cycle dysregulation, and poor tolerance to activation-induced proliferative stress, resulting in DNA damage and senescence-like features after xenotransplantation. Importantly, imposing proliferative stress on young human HSPCs *in vivo* recapitulated key aging-associated phenotypic and functional declines. Together, our findings identify dysregulated activation responses as a defining feature of HSPC aging and establish proliferative stress–based xenotransplantation models as powerful platforms for investigating age-related hematopoietic dysfunctions.

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Mutation in IR or IGF1R produces features of long-lived mice while maintaining metabolic health

Insulin/insulin growth factor signaling is a conserved pathway that regulates lifespan. However, long-lived loss-of-function mutants often produce insulin resistance, slow growth, and impair reproduction. Recently, a gain-of-function mutation in the kinase insert domain (KID) of the *Drosophila* insulin/IGF receptor was seen to dominantly extend lifespan without impairing insulin sensitivity, growth, or reproduction. This substitution occurs within residues conserved in mammalian insulin receptor (IR) and insulin growth factor-1 receptor (IGF-1R). We produced 2 knock-in mouse strains that carry the homologous KID Arg/Cys substitution in murine IR or IGF-1R, and we replicated these genotypes in human cells. Cells with heterodimer receptors of IR or IGF-1R induce receptor phosphorylation and phospho-Akt when stimulated with insulin or IGF. Heterodimer receptors of IR fully induce pERK, but ERK was less phosphorylated in cells with IGF-1R heterodimers. Adults with a single KID allele (producing heterodimer receptors) have normal growth and glucose regulation. At 4 months, these mice variably display hormonal markers that associate with successful aging counteraction, including elevated adiponectin and FGF21, as well as reduced leptin and IGF-1. Livers of IGF-1R females show decreased transcriptome-based biological age, which may point toward delayed aging and warrants an actual lifespan experiment. These data suggest that KID mutants may slow mammalian aging while they avoid the complications of insulin resistance.

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PREPRINT

Cellular Aging Signatures in the Plasma Proteome Record Human Health and Disease

Aging is asynchronous across cells and organs, but whether plasma proteins can capture cell type-specific aging and predict disease and mortality remains unknown. We developed machine learning models to estimate the biological age of more than 40 distinct cell types spanning neuronal, immune, glial, endocrine, epithelial, and musculoskeletal origins using over 7,000 plasma proteins measured in 60,000 individuals across three cohorts, comprising the largest human plasma proteomics aging study to date. Individuals showed heterogeneous aging profiles, with 20-25% exhibiting accelerated aging in a single cell type and 1-3% across ten or more cell types. APOE genotype showed antagonistic aging effects in different cell types: APOE4 carriers exhibited older astrocytes but younger macrophages, while APOE2 carriers showed the inverse. Cellular aging signatures were uniquely associated with disease status and predicted incident disease and mortality over 15 years of follow-up. Amyotrophic lateral sclerosis (ALS) showed the strongest association with skeletal myocyte aging (hazard ratio = 12.7 for extreme accelerated versus youthful aging). In Alzheimer's disease (AD), prevalent cases showed accelerated aging across multiple neural and peripheral cell types, with extreme astrocyte aging conferring AD risk comparable to APOE4 carrier status. Moreover, extreme astrocyte aging increased AD risk in APOE4/4 carriers threefold, while youthful astrocytes strikingly reduced risk. Beyond neurodegeneration, respiratory cell aging identified smokers at 58% higher lung cancer risk, and myeloid aging identified normoglycemic individuals at higher diabetes risk. Both specific cellular vulnerabilities and cumulative aging burden influenced survival, wherein youthful immune or neuronal profiles were protective. A polycellular aging risk score provided robust mortality risk stratification across platforms and cohorts. These findings establish a framework for quantifying biological aging at the cellular resolution using plasma proteomics, revealing heterogeneity in aging trajectories and their impact on disease susceptibility and resilience.

PATENT

Organ aging biomarkers derived from the plasma proteome

Abstract

Provided herein are minimally invasive compositions, methods, systems, kits and uses for biomarkers derived from the plasma proteome that identify, predict, and monitor organ health, aging, dysfunction and disease in humans. Said methods comprise a) obtaining a sample from said subject; b) measuring the concentrations of two or more proteins from said organ in said sample from said subject wherein said concentrations of said two or more proteins provides a biological age of said organ in health and/or disease; and c) comparing said biological age of said organ to a chronological age of said subject, wherein a gap between said biological age of said organ and said chronological age of said subject identifies accelerated and slowed aging of said organ.

Plasma Proteome Profiling of Centenarian Across Switzerland Reveals Key Youth-Associated Proteins

Flavien Delhaes [1], Justine Falciola [1], Adar Hoffman [2 3], Stéphanie Carnesecchi [4], Stefano Cavalli [5], Armin von Gunten [6], Daniela S Jopp [2 3], François R Herrmann [1], Karl-Heinz Krause [7]

Centenarians exhibit remarkable longevity and compression of morbidity making them an ideal population for uncovering proteins associated with successful aging. Using proteomics, we characterized the immune and cardiometabolic profiles of centenarians' plasma from the SWISS100 cohort. We identified 583 differentially expressed proteins (DEPs) by centenarians when compared with hospitalized geriatric patients (age 80-90 years) and younger healthy participants (age 30-60 years). We replicated the association of 23 proteins with a standard set of aging proteins (APs) developed by the Targeting Aging with Metformin (TAME) consortium. By comparing the centenarian signature to an independent centenarian proteomics study, we identified 135 DEPs in both studies with identical aging directions, establishing a robust set of APs in centenarians. Applying fractional polynomial regressions, we uncovered proteins with linear and non-linear profiles associated with age and identified a subgroup of 37 proteins with a younger signature in centenarians. Protein-protein interaction and pathway enrichment analyses of 37 proteins point to programmed cell death, metabolic enzyme pathways, regulation of extracellular matrix stability, immune and inflammatory responses, and neurotrophic signaling pathways. This novel approach to aging research has uncovered new proteins and pathways, which may present promising targets to understand processes associated with longevity and healthy aging.

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A combination of differential expression and network connectivity analyses identifies a common set of RNA splicing and processing genes altered with age across human tissues

Although transcriptomic changes are known to occur with age, the extent to which these are conserved across tissues is unclear. Previous studies have identified little conservation in age-modulated genes in different tissues. Here, we sought to identify common transcriptional changes with age in humans (aged 20 to 70) across tissues using differential network analysis, assuming that differential expression analysis alone cannot detect all changes in the transcriptional landscape that occur in tissues with age. Our results demonstrate that differential connectivity analysis reveals significant transcriptional alterations that are not detected by differential expression analysis. Combining the two analyses, we identified gene sets modulated by age across all tissues that are highly enriched in terms related to "RNA splicing" and "RNA processing". The identified genes are also highly interconnected in protein-protein interaction networks. Co-expression module analyses demonstrated that other genes that show tissue-specific variations with age are enriched in pathways that combat the accumulation of aberrant RNAs and proteins, likely caused by defective splicing. Additionally, with convergent connectivity patterns, most tissues significantly reorganized their gene connectivity with age. Our results identified genes and processes whose age-associated transcriptional changes are conserved across tissues, demonstrating a central role for RNA splicing and processing genes and highlighting the importance of differential network analysis for understanding the ageing transcriptome.

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PREPRINT

Transcriptome-wide association study and fly experiments uncover the role of *CoA synthase* in ageing across species

While significant progress has been made in understanding the genetic architecture of ageing in model organisms, our understanding of human ageing remains limited. We performed a multi-tissue Transcriptome-wide association study (TWAS) on human lifespan, integrating GWAS data from >1 million parental lifespans with gene expression prediction models derived from reference transcriptomic datasets; followed by replication using healthspan and longevity phenotypes as additional readouts of ageing. The TWAS uncovered 563 significant gene associations, of which 139 replicated. *TOMM40*, encoding a component of the mitochondrial outer membrane translocase that is fundamental for mitochondrial function, had the strongest association with parental lifespan and longevity and was fine-mapped as a putatively causal lifespan gene at the *APOE-TOMM40* region. Uniquely in our study, we identified fly orthologues of replicating genes and examined if modulating their expression impacts *Drosophila* longevity. The nine novel associations with all three ageing outcomes included *COASY*, encoding Coenzyme A synthase. Knocking down its fly orthologue, *Ppat-dpck*, resulted in significant lifespan extension in flies. Hence, in addition to discovering new genes associated with human ageing, by combining human TWAS with experimental *Drosophila* work, we provide evidence for the role of *COASY* (*Ppat-dpck*) in ageing across species.

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Integrative epigenetics and transcriptomics identify aging genes in human blood

Recent epigenome-wide studies have identified a large number of genomic regions that consistently exhibit changes in their methylation status with aging across diverse populations, but the functional consequences of these changes are largely unknown. On the other hand, transcriptomic changes are more easily interpreted than epigenetic alterations, but previously identified age-related gene expression changes have shown limited replicability across populations. Here, we develop an approach that leverages high-resolution multi-omic data for an integrative analysis of epigenetic and transcriptomic age-related changes and identify genomic regions associated with both epigenetic and transcriptomic age-dependent changes in blood. Our results show that these multi-omic aging genes in blood are enriched for adaptive immune functions, replicate more robustly across diverse populations and are more strongly associated with aging-related outcomes compared to the genes identified using epigenetic or transcriptomic data alone. These multi-omic aging genes may serve as targets for epigenetic editing to facilitate cellular rejuvenation.

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Genetic links between multimorbidity and human aging

The growing epidemiological burden of multimorbidity among older adults underscores an urgent need to develop interventions that can address multiple age-related diseases (ARDs) at once. Yet, the biological mechanisms driving their co-occurrence remain poorly understood. In this study, we conducted a multivariate genome-wide association analysis to dissect the shared genetic architecture of five common ARDs: heart attack, high cholesterol, hypertension, stroke, and type 2 diabetes. We defined this shared genetic component as the multivariate age-related disease factor (mvARD) and identified 263 independent variants across 180 genomic loci associated with mvARD. These variants were significantly enriched for associations with extreme human longevity, lending empirical support for the geroscience hypothesis in humans. Integrative gene prioritization using transcriptome-wide association studies, colocalization analysis, and Mendelian randomization identified four high-confidence genes in blood—*DCAF16*, *PHF13*, *MGA*, and *GTF2B*—with putative causal roles on mvARD. Using two-sample Mendelian randomization, we also found several modifiable lifestyle factors, including body mass index and dietary intake, that causally influenced the risk for multiple ARDs. Together, our findings revealed a shared genetic basis for common ARDs that overlapped with the biology of human aging and pointed to potential molecular and behavioral targets for delaying disease onset and promoting healthy aging.

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Comprehensive integration of multi-omics data identifies novel immunological biomarkers and repurposable drug targets for human aging and frailty

Aging and frailty are complex biological processes characterized by a gradual decline in physiological functions and increased vulnerability to stressors. Although immunological dysregulation is recognized as a key feature of both, studies identifying shared biomarkers and therapies are limited. We conducted a detailed multi-omics analysis combining data from Gerontome (2347 aging-related genes), a significant frailty GWAS, and transcriptome data from aging immune cells (2843 DEGs). We employed advanced bioinformatics tools, including WGCNA, machine learning, immune cell deconvolution, and drug repurposing. We identified 28 core genes common across all datasets, including TP53, APOE, IL6, FOXO3, and SIRT1. The turquoise module, comprising 1872 genes, showed the strongest correlation with frailty ($r = 0.78$, $p = 2.1e-16$) among the 23 modules identified via WGCNA. Using a 12-gene panel, our machine learning model achieved an AUC of 0.91 for frailty prediction. Immune cell analysis revealed that frail patients had significantly higher levels of senescent T cells ($p = 1e-06$) and M1 macrophages ($p = 7e-04$) compared to healthy controls. Drug repurposing identified 47 FDA-approved drugs targeting 18 key genes, with metformin, rapamycin, and tocilizumab showing particular promise.

This research provides a comprehensive catalog of biomarkers for frailty and aging, highlighting immune pathways and opportunities for drug repurposing. Our findings emphasize the role of immunosenescence and inflammation in frailty and offer a foundation for targeted therapies.

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Chronic stress and the mitochondria–telomere axis: human evidence for a bioenergetic-debt model of early aging

Chronic stress has been linked to mitochondrial dysfunction and impaired telomere maintenance, yet the mechanistic relationships connecting these pathways in humans remain poorly resolved. Using longitudinal findings from the Guillén-Parra cohort as a motivating human example, this Perspective offers a reinterpreted framework that proposes a unifying energetic interpretation in which bioenergetic insufficiency—defined as a mismatch between stress-induced energetic demand and mitochondrial throughout—rather than accumulated molecular damage, forms the upstream constraint linking stress physiology, mitochondrial performance, and telomerase regulation. In this cohort, lower baseline mitochondrial energetic capacity predicted greater longitudinal declines in telomerase activity, while telomere length remained stable across the short observation window, supporting the view that telomerase activity represents an early, energy-sensitive marker of unresolved stress adaptation, whereas telomere shortening is a delayed structural consequence. Interpreted within the Exposure-Related Malnutrition (ERM) framework, these patterns suggest that repeated activation of stress-response pathways without adequate metabolic recovery limits mitochondrial throughput and progressively compromises genome maintenance. In contrast, repeated exposure to mild stressors followed by sufficient recovery promotes adaptive strengthening of mitochondrial function and telomeric maintenance, consistent with physiological hormesis. We outline a roadmap integrating telomerase activity with dynamic indices of mitochondrial and redox function, including NAD^+ availability, and emerging biomarkers of systemic energetic strain, such as circulating cell-free mitochondrial DNA and GDF15. By reframing aging phenotypes as early-stage failures of energetic resolution, this model highlights modifiable windows of vulnerability and hormesis-informed strategies—including exercise-induced adaptive stress, circadian alignment, and nutritional sufficiency—as actionable pathways for preserving mitochondrial resilience and telomere maintenance.

Lifetime non-relational traumatic experiences are associated with biological ageing

Exposure to non-relational trauma, such as serious accidents, war or life-threatening illness, is linked to poor mental and physical health. Its relationship with biological ageing markers, however, remains underexplored. This study's aim was to examine associations between non-relational trauma and multiple biological ageing markers, and to assess whether associations vary by trauma burden, trauma type and sex. We analysed UK Biobank data from 152,863 participants (mean age = 56.4 years; 56.5% female). Lifetime exposure to six non-relational traumatic experiences was assessed. Biological ageing markers included metabolomic age (MileAge) delta, a metabolomic mortality profile score, frailty, leukocyte telomere length and grip strength. Regression models, adjusted for demographic and socioeconomic confounders, estimated associations between trauma and biological ageing markers. We also examined trauma burden, trauma type-specific and sex-specific associations. Non-relational trauma was associated with a metabolite-predicted age exceeding chronological age (MileAge delta; β = 0.047, 95% CI 0.032-0.062), elevated metabolomic mortality scores (β = 0.102, 95% CI 0.051-0.153) and greater frailty (β = 0.298, 95% CI 0.290-0.307), with a graded, approximately linear pattern for frailty (i.e., higher non-relational trauma sum scores were associated with higher frailty scores). All trauma types were associated with greater frailty, with the strongest association for life-threatening illness. There was no evidence of associations with telomere length, and mixed findings for grip strength. Several associations differed by sex, for example overall trauma burden was more strongly associated with greater frailty in females compared to males. Lifetime non-relational trauma was associated with older biological ageing profiles, with the strongest associations with frailty. These findings support the notion that non-relational trauma exposure is associated with long-term health status, underscoring the need for mitigating ageing-related health decline in trauma-exposed populations.

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Sex Differences in Associations Between Adversity and Biological Ageing

Adverse events across the life course have been linked to older biological ageing profiles. Whether these associations differ between males and females, and whether such differences depend on adversity occurring in childhood, adulthood or both periods, remains unclear. In 153,557 UK Biobank participants aged 40–69 years, we assessed associations of childhood and/or adulthood adversity with metabolomic ageing, frailty, telomere length and grip strength. Sex differences were evaluated using stratified analyses and sex-by-adversity interaction tests. Exposure to adversity in childhood and/or adulthood was reported by 64.6% of males and 69.6% of females. Childhood adversity was associated with multiple ageing markers primarily in females, including a metabolite-predicted age exceeding chronological age, greater frailty, shorter telomeres and weaker grip strength. Adulthood adversity was more strongly associated with certain ageing markers in males, particularly greater frailty and weaker grip strength. This divergence in sex-specific associations between childhood and adulthood exposure was consistent across several markers, with statistically significant sex-by-adversity interactions for frailty and grip strength. In this large, population-based sample, the timing of adversity, distinguishing childhood from adulthood, shaped whether females or males showed stronger associations with biological ageing markers. These findings suggest that sex differences in biological ageing profiles may partly reflect distinct sensitive periods of vulnerability, highlighting the importance of considering both sex and timing of exposure to adversity when examining links between adversity and biological ageing.

Epigenetic age deceleration reflects exercise-induced cardiorespiratory fitness improvements

Epigenetic clocks are emerging as promising biomarkers of biological aging, yet their sensitivity to short-term interventions remains unclear. This pilot study investigates whether the GrimAge clock can capture the effects of a 6-month cycling-based endurance exercise training intervention, with cardiorespiratory fitness (VO_2 max) and body composition as primary outcomes. We enrolled 42 adults aged 35-65, of whom 38 completed the study and 33 adhered to the protocol (> 66% adherence). Participants demonstrated significant improvements in VO_2 max (+ 20%, $P < 0.001$) and body composition ($P < 0.001$). High-quality epigenetic data preprocessing yielded highly reproducible GrimAge estimates (< 2 months measurement error), which strongly correlated with chronological age ($R^2 = 0.86$, $P < 0.001$). On average, GrimAge decreased by 7.44 months relative to the expected trajectory ($P = 0.012$), reflecting improvements in VO_2 max ($R^2 = 0.27$, $P = 0.002$) but not body composition changes. Notably, GrimAge changes strongly correlated with fluctuations in leukocyte composition, particularly neutrophil fraction ($R^2 = 0.74$, $P < 0.001$). Adjusting for leukocyte composition improved consistency in GrimAge changes, aligning them with additional intervention outcomes and explaining up to 81% of variance. These findings demonstrate that GrimAge is responsive to short-term endurance training, serving as a meaningful biomarker of improved cardiorespiratory fitness, while also capturing immune system variability. This study supports the use of GrimAge in evaluating longevity interventions and highlights the importance of accounting for leukocyte composition in epigenetic aging research.

DNA-protein cross-links promote cGAS-STING–driven premature aging and embryonic lethality

DNA-protein cross-links (DPCs) are highly toxic DNA lesions that block replication and transcription, but their impact on organismal physiology is unclear. We identified a role for the metalloprotease SPRTN in preventing DPC-driven immunity and its pathological consequences. Loss of SPRTN activity during replication and mitosis lead to unresolved DNA damage, chromosome segregation errors, micronuclei formation, and cytosolic DNA release that activates the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway. In a *Sprtn* knock-in mouse model of Ruijs-Aalfs progeria syndrome, chronic cGas-Sting signaling caused embryonic lethality through inflammation and innate immune responses. Surviving mice displayed aging phenotypes beginning in embryogenesis, which persisted into adulthood. Genetic or pharmacological inhibition of cGas-Sting rescued embryonic lethality and alleviated progeroid phenotypes.

ER remodelling is a feature of ageing and depends on ER-phagy

The endoplasmic reticulum (ER) comprises an array of subdomains, each defined by a characteristic structure and function. Although altered ER processes are linked to age-onset pathogenesis, it is unclear whether shifts in ER structure or dynamics underlie these functional changes. Here we establish ER structural and functional remodelling as a conserved feature of ageing across yeast, Caenorhabditis elegans and mammals. Focusing on C. elegans as the exemplar of metazoan ageing, we reveal striking age-related reductions in ER volume across diverse tissues and a morphological shift from rough sheets to tubular ER. This morphological transition corresponds with large-scale shifts in ER proteome composition from protein synthesis to lipid metabolism, a phenomenon conserved in mammalian tissues. We show that Atg8 and ULK1-dependent ER-phagy drives age-associated ER remodelling through tissue-specific factors, including the previously uncharacterized ER-phagy regulator TMEM-131 and the IRE-1-XBP-1 branch of the unfolded protein response. Providing support for a model where ER remodelling is adaptive, diverse lifespan-extending paradigms downscale and remodel ER morphology throughout life. Furthermore, mTOR-dependent lifespan extension in yeast and worms requires ER-phagy, indicating that ER remodelling is a proactive and protective response during ageing. These results reveal ER-phagy and ER dynamics as pronounced, underappreciated mechanisms of both normal ageing and age-delaying interventions.

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PREPRINT

LongevityBench: Are SotA LLMs ready for aging research?

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Aging is a core biological process observed in most species and tissues, which is studied with a vast array of technologies. We argue that the abilities of AI systems to emulate aging and to accurately interpret biodata in its context are the key criteria to judge an LLM's utility in biomedical research. Here, we present LongevityBench — a collection of tasks designed to assess whether foundation models grasp the fundamental principles of aging biology and can use low-level biodata to arrive at phenotype-level conclusions. The benchmark covers a variety of prediction targets including human time-to-death, mutations' effect on lifespan, and age-dependent omics patterns. It spans all common biodata types used in longevity research: transcriptomes, DNA methylation profiles, proteomes, genomes, clinical blood tests and biometrics, as well as natural language annotations. After ranking state-of-the-art foundation models using LongevityBench, we highlight their weaknesses and outline procedures to maximize their utility in aging research and life sciences.

The human pathome shows sex and tissue specific aging patterns

Little is known about tissue-specific changes that occur with aging in humans. Using the description of 33 million histological samples we extract thousands of age- and mortality-associated features from text narratives that we call The Human Pathome (pathoage.com). Notably, we can broadly determine when post-development aging starts at the organism and tissue level, indicating a sexual dimorphism with females aging earlier but slower and males aging later but faster. We employ unsupervised topic-modeling to identify terms and themes that predict age and mortality. As a proof of principle, we cross-reference these terms in PubMed to identify nintedanib as a potential aging intervention and show that nintedanib reduces markers of cellular senescence, reduces pro-fibrotic gene pathways in senescent cells and extends the lifespan of fruit flies. Our findings pave the way for expanded exploitation of population text datasets towards discovery of novel aging interventions.

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In Vivo Chemical Reprogramming Is Associated With a Toxic Accumulation of Lipid Droplets Hindering Rejuvenation

Partial reprogramming has emerged as a promising strategy to reset the epigenetic landscape of aged cells towards more youthful profiles. Recent advancements have included the development of chemical reprogramming cocktails that can lower the epigenetic and transcriptomic age of cells and upregulate mitochondrial biogenesis and oxidative phosphorylation. However, the ability of these cocktails to affect biological age in a mammalian aging model has yet to be tested. Here, we have characterized the effects of partial chemical reprogramming on mitochondrial structure and function in aged mouse fibroblasts and tested its in vivo efficacy in genetically diverse male UM-HET3 mice. This approach increases the size of mitochondria, alters cristae morphology, causes an increased fusing of mitochondrial networks, and speeds up movement velocity. At lower doses, the chemical reprogramming cocktail can be safely administered to middle-aged mice using implantable osmotic pumps, albeit with no effect on the transcriptomic age of kidney or liver tissues and only a modest effect on the expression of OXPHOS complexes. However, at higher doses, the cocktail causes a drastic reduction in body weight necessitating euthanasia. In the livers and kidneys of these animals, we observe significant increases in lipid droplet accumulation, as well as changes in mitochondrial morphology in the livers that are associated with mitochondrial stress. Thus, partial chemical reprogramming may induce mitochondrial stress and lead to significant lipid accumulation, which may cause toxicity and hinder the rejuvenation of cells and tissues in aged mammals.

Hyperactivation of mTORC1 blocks stem cell fate transitions through TFE3–NuRD association

Mechanistic target of rapamycin complex 1 (mTORC1) integrates signals from nutrients, growth factors, and cellular stress to regulate biosynthesis and maintain homeostasis. Dysregulated mTORC1 disrupts stem cell homeostasis and impairs cell fate transitions in vivo and in vitro. Previous studies have shown that mTORC1 hyperactivation promotes nuclear translocation of TFE3, blocking pluripotency exit in both mouse and human naïve embryonic stem cells. Similarly, our earlier work has demonstrated that sustained mTORC1 activation impedes somatic cell reprogramming via the transcriptional coactivator PGC1α. This raises the question of how mTORC1 coordinates gene transcription across distinct transitions in pluripotent cells. Here, we show that TFE3 mediates the transcriptional blockade induced by mTORC1 hyperactivation during reprogramming. Notably, during both pluripotency exit and reprogramming, TFE3 recruits the NuRD corepressor complex to repress genes essential for cell fate transitions. These findings uncover a shared mechanism by which mTORC1 and TFE3 regulate stem cell identity, highlighting the dual regulatory role of TFE3 and its potential implications in development, aging, and tumorigenesis.

Cognitive rejuvenation through partial reprogramming of engram cells

Counteracting cognitive decline is a declared goal of regenerative medicine. Recently, partial cellular reprogramming has emerged as a promising strategy to promote tissue regeneration and restore cellular function, but whether this approach bears fruit when targeted to cell populations underlying cognitive processes remains unknown. Here, we report that partial reprogramming of engram neurons—*bona fide* memory trace cells—by OSK-mediated gene therapy reversed the expression of senescence- and disease-related cellular hallmarks in aged mice and models of Alzheimer's disease (AD), re-established aberrant epigenetic-transcriptional patterns pertaining to synaptic plasticity, and counteracted AD-typical neuronal hyperexcitability. Importantly, irrespective of the brain area targeted or the behavioral paradigm employed, engram reprogramming also recovered learning and memory capacities to levels of healthy young animals, suggesting cognitive rejuvenation. These results posit that partial reprogramming of specific cell populations in the brain can be exploited for cognitive restoration in aging and disease.

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PREPRINT

COUNTERING AGE-ASSOCIATED ALTERATIONS IN OLIGODENDROCYTE-DERIVED EXTRACELLULAR MATRIX REJUVENATES COGNITION

Efforts to rejuvenate age-related cognitive decline have predominantly targeted neurons, often overlooking non-neuronal cell types in the aging brain. Here, we show that countering alterations in oligodendrocyte-derived extracellular matrix (ECM) in the aging hippocampus restores cognition. We identify broad age-associated transcriptional and proteomic changes in oligodendrocytes, including dysregulation of the matrisome, with marked upregulation of ECM components and associated regulators with age. Among these, we detect an increase in Hyaluronan and proteoglycan link protein 2 (HAPLN2), an oligodendrocyte-derived core matrisome protein that locates specifically at the nodes of Ranvier, in the hippocampus of aged mice and older humans. Hapln2 overexpression in oligodendrocytes of young mice recapitulated age-related memory impairments. Conversely, abrogating the age-related increase in Hapln2 induced synaptic plasticity-related hippocampal transcriptional signatures and improved memory in aged mice. Together, these data define oligodendrocyte-derived ECM remodeling as a hallmark of brain aging that can be targeted to rescue cognitive decline.

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PREPRINT

Characterizing the SASP-Dependent Paracrine Spreading of Senescence Between Human Brain Cell Types

One of the defining phenotypes of a senescent cell is the senescence-associated secretory phenotype (SASP), which can propagate senescence in neighboring cells both in vitro and in vivo. Importantly, this paracrine spreading of senescence can act in a cell non-autonomous manner, influencing neighboring cell populations and contributing to immune cell recruitment. As cellular senescence has recently been linked to both age-related neurodegenerative phenotypes and local inflammation and is more clearly defined across brain cell types in a cell-type-dependent manner, an urgent question remains regarding how a cell-type-specific paracrine spreading of senescence occurs in the brain. Here, we set out to profile the cell-type-specific features of the SASP and characterize the directionality of paracrine senescence-spreading between major brain cell types. Through this analysis, we identified key SASP ligand-receptor pairs involved in this paracrine dissemination. Targeting these factors with specific inhibitors, we prevented the paracrine spreading of senescence in a brain cell-type-dependent manner. Taken together, we identified specific SASP targets for therapeutic intervention in the context of human brain cells and thereby informed the SASP-dependent reaction of immune cells and age-related tissue dysfunction across both normal aging and models of neurodegenerative disease.

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PREPRINT

Reproducible *in vivo* applications of the p16-3MR model in senescence research

The p16-3MR mouse model has been widely used to visualize and conditionally eliminate p16-expressing senescent cells *in vivo* and has been applied across diverse biological contexts, including tissue repair, fibrosis, cancer, therapy response, and aging. Despite the development of multiple senescence reporter and ablation systems, p16-3MR stands out for its broad and sustained adoption across independent laboratories. Here, we review the extensive published literature supporting the reproducibility and utility of the p16-3MR system and present new validation data across acute and chronic senescence-inducing conditions. We demonstrate reproducible induction of p16-associated bioluminescence during wound healing, chemotherapy, and aging, as well as partial but consistent reduction following ganciclovir treatment. We further delineate the strengths and limitations of the individual components of the 3MR construct, including HSV-thymidine kinase–mediated clearance, Renilla luciferase– based bioluminescence, and monomeric red fluorescent protein, and discuss how factors such as cell abundance, tissue context, pigmentation, and substrate chemistry influence detection sensitivity.

Together, these data confirm that the p16-3MR model is a functional and versatile tool for studying senescent cells *in vivo* when used with appropriate experimental design and interpretation, and they provide support for its continued application alongside emerging senescence models.

AKG-TET axis is central to senescence plasticity

Shin Akakura · Siamak Tabibzadeh [2]

Cellular senescence, a state of stable cell-cycle arrest associated with aging, is characterized by a distinct pro-inflammatory secretome. This study systematically interrogates the critical role of the α-ketoglutarate (AKG)-Ten-eleven translocation (TET) axis in regulating senescence in human somatic cells. Downregulating *TET* expression and activity, either genetically (siRNA) or pharmacologically (via C35), or limiting AKG bioavailability through a targeting peptide, trigger widespread epigenetic reprogramming, amplify pro-inflammatory signaling, and enhance the senescence-associated secretory phenotype (SASP), ultimately driving cells toward replicative senescence. Conversely, augmenting AKG bioavailability or *TET* expression and activity significantly enhances cellular resilience to stress, effectively preventing and reversing senescent phenotypes. These findings not only position the AKG-TET axis as a critical regulatory nexus of cellular senescence but also challenge the traditional view of senescence as a fixed endpoint, revealing its dynamic and plastic nature susceptible to therapeutic intervention.

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Age-independent and targetable transcription factor networks regulating $CD8^+$ T cell senescence in aging humans

The age-related decline in immunity is accompanied by the accumulation of senescent $CD8^+$ T cells. Using senescent cell isolation coupled with multi-omics profiling, we reveal the transition to senescence to be controlled by chromatin state-specific transcription factor (TF) networks in younger and older donors independent of age. These TF networks mediate widespread enhancer remodeling, repressing cell identity genes while upregulating inflammatory and secretory pathways. Inhibition or downregulation of AP1, KLF5, or RUNX2 modulates the transcriptional output and partially restores the blunted response to stimulation of senescent $CD8^+$ T cells. Senescent $CD8^+$ T cell gene signatures also predict responsiveness to chimeric antigen receptor (CAR)-T cell therapy in diffuse large B cell lymphomas. Overall, our study defines the gene-regulatory mechanisms underlying human $CD8^+$ T cell senescence, highlights TF network perturbation as a viable strategy to manipulate the senescence state, and identifies senescent $CD8^+$ T cell gene signatures as prognostic tools for immunotherapy outcome.

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Senotoxins target senescence via lipid binding specificity, ion imbalance and lipidome remodeling

Senescence is a driver of aging and a barrier to tumor progression, but its persistent accumulation drives inflammation and relapse. Thus, the success of chemotherapy could be jeopardized when senescence emerges in the tumor microenvironment. Here we identified the senolytic properties of a pore-forming toxin, sticholysin I (StnI). StnI and our engineered improved form, StnIG, selectively hampers viability of chemotherapy-induced senescent cancer cells, as well as senescent primary cells. We show that its selectivity is mediated by specific binding and lipid ratios associated with senescence, including compromised membrane bilayer asymmetry. Mechanistically, StnIG triggers sodium and calcium influx and an enduring potassium efflux in senescent cells. Calcium triggers the opening of calcium-activated potassium channels, leading to cell death by apoptosis and pyroptosis. Finally we show that StnIG synergizes with senescence-inducing chemotherapy to drive remission of solid tumors in mice. Our findings define StnI and StnIG as senotoxins with translational potential for cancer therapy.

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The Secretome of Human Trophoblast Stem Cells Attenuates Senescence-Associated Traits

Senescent cells display indefinite growth arrest and a pro-inflammatory, senescence-associated secretory phenotype (SASP). As the accumulation of senescent cells in tissues with age plays detrimental roles in age-related pathologies, there is much interest in finding therapeutic strategies to eliminate them or suppress the SASP. In this study, we investigated the impact of the secretome and extracellular vesicles (EVs) derived from human trophoblast stem cells (hTSCs) on senescent human fibroblasts. We found that the hTSC conditioned medium (hTSC-CM), and in particular the EVs (hTSC-EVs), significantly reduced the levels of mRNAs encoding SASP factors and the secretion of SASP factors including CXCL1, IL8, and GDF15. Proteomic analysis of hTSC-CM and EVs indicated an enrichment in proteins involved in cell adhesion, tissue repair, and remodeling of the extracellular matrix (ECM). Furthermore, incubation of senescent cells with hTSC-EVs attenuated DNA damage and inflammatory signaling, at least in part by suppressing the function of NF-κB, a major transcriptional regulator of the SASP program. Our findings underscore the value of hTSC-CM and EVs therein in therapeutic approaches directed at senescent cells.

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Comparing Functional Consequences of Human iPSC-Microglia and Neural Stem Cell-Derived Extracellular Vesicles in Mitigating Cognitive Decline in Alzheimer's Disease

Stem cell-derived extracellular vesicles (EVs) show promise as a therapeutic approach for neurodegenerative diseases, particularly Alzheimer's Disease (AD), where traditional regenerative interventions have achieved limited success. Our previous research demonstrated the neuroprotective benefits of human neural stem cell (hNSC)-derived EVs in 2- and 6-month-old AD mice (5xFAD) that exibited improved cognitive function and reduced AD-related neuropathology. This study aimed to compare the neuroprotective efficacy of EVs derived from two human cell lines: hNSCs from H9 embryonic stem cells and human iPSC-derived microglia (iMGLs). Additionally, we investigated the efficacy of an expanded EV treatment paradigm at subsequently longer time points. Three-month-old 5xFAD mice received weekly retro-orbital vein injections of either hNSC- or iMGL-derived EVs for 4 weeks. Cognitive function testing revealed comparable cognitive improvements in both EV treatment groups compared to vehicle-injected AD mice. Both iMGL- and hNSC-derived EVs significantly reduced amyloid beta plaques, astrogliosis, and microglial activation, while restoring synaptophysin and postsynaptic density protein PSD-95 to control levels in AD brains. Gene expression analysis revealed significantly reduced neuroinflammation and elevated neuroprotective signatures following both EV treatments. MicroRNA analysis of the EV-derived cargo revealed unique and shared miRNA signatures associated with differentially expressed genes in both cell lines. These findings demonstrate the feasibility and neuroprotective benefits of recurrent systemic injections of EVs derived from human NSCs and differentiated human microglia lines in alleviating cognitive dysfunction and neuropathology in Alzheimer's disease.

Valacyclovir Treatment of Early Symptomatic Alzheimer Disease
The VALAD Randomized Clinical Trial

Results Of the 120 participants (mean age, 71.4 [SD, 8.6] years; 55% were female), 93 (77.5%) completed the trial. At 78 weeks, the LSM change in the 11-item ADAS-Cognitive Subscale score was 10.86 (95% CI, 8.80 to 12.91) in the valacyclovir group vs 6.92 (95% CI, 4.88 to 8.97) in the placebo group, indicating greater cognitive worsening with valacyclovir than placebo (between-group difference, 3.93 [95% CI, 1.03 to 6.83]; $P = .01$). The LSM change in the ADCS-ADL Scale score at 78 weeks was −13.78 (95% CI, −17.00 to −10.56) in the valacyclovir group vs −10.16 (95% CI, −13.37 to −6.96) in the placebo group (between-group difference, −3.62 [95% CI, −8.16 to 0.93]). At 78 weeks, the LSM change in the ^{18}F-florbetapir amyloid PET SUVR was 0.03 (95% CI, −0.04 to 0.10) in the valacyclovir group vs 0.01 (95% CI, −0.06 to 0.08) in the placebo group (between-group difference, 0.02 [95% CI, −0.08 to 0.12]). The LSM change in the ^{18}F-MK-6240 tau PET medial temporal SUVR at 78 weeks was 0.07 (95% CI, −0.06 to 0.19) in the valacyclovir group vs −0.04 (95% CI, −0.15 to 0.07) in the placebo group (between-group difference, 0.11 [95% CI, −0.06 to 0.28]). The most common adverse events were elevated serum creatinine level (5 participants [8.3%] in the valacyclovir group vs 2 participants [3.3%] in the placebo group) and COVID-19 infection (3 [5%] vs 2 [3.3%], respectively).

Conclusions and Relevance Valacyclovir was not efficacious with cognitive worsening for the primary outcome and it is not recommended to treat individuals with early symptomatic AD and HSV seropositivity.

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PREPRINT

Punctuated memory change: The temporal dynamics and brain basis of memory stability in aging

Are there individuals who resist episodic memory decline into older age? Analyzing 728,000 memory tests from 80,000 participants with at least 4 assessments, we introduce a simulation-calibrated framework to identify genuine memory stability. Across cohorts and models, ~10% of adults ≥70 years showed stable performance over a decade. In an MRI subgroup (n≈2,000), stable performers exhibited lower rates of brain atrophy across widespread regions, anchoring cognitive stability in structural brain maintenance. However, stability was often transient rather than trait-like: many individuals followed trajectories with extended plateaus of stable performance punctuated by episodes of accelerated decline. Accordingly, 54% showed at least one period of observed stability, averaging 10 years, whereas only 0.4% upheld stable performance over 24 years under the strictest definition. These findings are consistent with a complex-systems model of cognitive aging in which decline often reflects critical transitions rather than continuous erosion.

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PREPRINT

Single-cell, multi-region profiling of the macaque brain across the lifespan

Brain aging is a complex process with profound health and societal consequences. However, the molecular and cellular pathways that govern its temporal progression-along with any cell type-, region-, and sex-specific heterogeneity in such progression-remain poorly defined. Here, we present a transcriptomic atlas of 5.3 million cells from 582 samples spanning 11 brain regions of 55 rhesus macaques (29 female, 26 male), aged 5 months (early life) to 21 years (late adulthood). We annotate 12 major cell classes and 225 subclusters, including region-specific subtypes of excitatory and inhibitory neurons, astrocytes, and ependymal cells. We identify a vulnerable excitatory neuron population in the superficial cortical lamina and a cortical interneuron population that are less abundant later in life, along with subtle, region-specific, age-associated compositional differences in subpopulations of microglia and oligodendrocytes, whose detection required single-cell resolution. Finally, we chart convergent and divergent age-associated molecular signatures across brain regions and cell classes-where some of these signatures are sex-specific and could underlie sex biases in neurological disorders. We find that age-associated transcriptional programs not only overlap substantially with those seen in Alzheimer's disease (AD), but also unfold along distinct temporal trajectories across brain regions, suggesting that aging and AD may share molecular roots that emerge at different life stages and in region-specific, sex-specific windows of vulnerability. This work provides a temporal, regional, and sex-stratified atlas of the aging primate brain, offering insights into cell type-specific vulnerabilities and regional heterogeneity with translational human relevance.

Selective degradation of DAPK1 via a novel hydrophobic tagging attenuates tau pathology in Alzheimer's disease

Methods

A library of HyT-based bifunctional molecules was synthesized and systematically screened for their ability to degrade DAPK1 *in vitro*. CJ1 emerged as the most potent candidate degrader of DAPK1, and its capacity to induce DAPK1 degradation via the proteasome system was further evaluated. Its effects on tau phosphorylation and neuronal viability were evaluated in multiple cellular models. The *in vivo* efficacy of systemic CJ1 administration was assessed in two tau-related pathology (tauopathy) mouse models, AAV-hTau-P301L and hTau transgenic mice. Behavioral, biochemical, and histological analyses were performed to evaluate cognitive function, tau pathology, neuroinflammation, neurodegeneration, and safety.

Results

CJ1 selectively promoted the posttranslational degradation of DAPK1 by the proteasome system without affecting DAPK1 mRNA expression. *In vitro* studies demonstrated that CJ1 significantly reduced tau phosphorylation at multiple AD-related sites. *In vivo*, CJ1 effectively penetrated the blood–brain barrier, decreased the levels of both the soluble and insoluble forms of hyperphosphorylated tau, and suppressed the formation of neurofibrillary tangles. Additionally, CJ1 treatment restored synaptic and dendritic structures, enhanced spatial learning and memory, attenuated neuroinflammatory responses, preserved neuronal populations, and produced no evidence of systemic toxicity.

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Molecular features of human pathological tau distinguish tauopathy-associated dementias

In Alzheimer's disease (AD), pathological tau protein shows a progressive accumulation of post-translational modifications (PTMs), reflecting disease severity, progression, and prion-like activity. Although many neurodegenerative diseases with dementia display tau aggregates, the pathological proteoforms of tau protein from each disease type remain unknown. Here, using a quantitative mass spectrometry-based proteomics platform, FLEXITau, deep characterization of pathological tau protein isolated from the brains of 203 human subjects with AD, familial AD (fAD), chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Pick's disease (PiD), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB)—a non-tauopathy symptomatic control—and healthy controls (CTR) is performed. Unsupervised data analyses and supervised machine learning identify distinct molecular features of pathological tau for each disease, enabling molecular disease stratification. This study identifies potential disease-specific biomarkers and therapeutic targets for tauopathies and provides critical quantitative information for pharmacokinetic modeling required for therapeutic and disease mechanism studies.

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CRISPR screens in iPSC-derived neurons reveal principles of tau proteostasis

Aggregation of the protein tau defines tauopathies, the most common age-related neurodegenerative diseases, which include Alzheimer's disease and frontotemporal dementia. Specific neuronal subtypes are selectively vulnerable to tau aggregation, dysfunction, and death. However, molecular mechanisms underlying cell-type-selective vulnerability are unknown. To systematically uncover the cellular factors controlling the accumulation of tau aggregates in human neurons, we conducted a genome-wide CRISPRi screen in induced pluripotent stem cell (iPSC)-derived neurons. The screen uncovered both known and unexpected pathways, including UFMylation and GPI anchor biosynthesis, which control tau oligomer levels. We discovered that the E3 ubiquitin ligase $CRL5^{SOCS4}$ controls tau levels in human neurons, ubiquitinates tau, and is correlated with resilience to tauopathies in human disease. Disruption of mitochondrial function promotes proteasomal misprocessing of tau, generating disease-relevant tau proteolytic fragments and changing tau aggregation *in vitro*. These results systematically reveal principles of tau proteostasis in human neurons and suggest potential therapeutic targets for tauopathies.

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Aging clocks delineate neuron types vulnerable or resilient to neurodegeneration and identify neuroprotective interventions

Different neuron types show distinct susceptibility to age-dependent degeneration, yet the underlying mechanisms are poorly understood. Here we applied aging clocks to single neuron types in Caenorhabditis elegans and found that distinct neurons differ in their biological age. Ciliated sensory neurons with high neuropeptide and protein biosynthesis gene expression show accelerated aging and degeneration, correlating with loss of function, which could be prevented by pharmacological inhibition of translation. We show that the C. elegans neuronal aging transcriptomes correlate with human brain aging patterns and anticorrelate with geroprotective interventions. We performed an in silico drug screen to identify potentially neuroprotective small molecules. We show that the natural occurring plant metabolite syringic acid and the piperazine derivative vanoxerine delay neuronal degeneration, and propose these compounds as neuroprotective interventions. Furthermore, we identify neurotoxins that accelerate neurodegeneration, indicating that distinguishing aging trajectories between neuron types can inform on protective interventions as well as risk factors.

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Peripheral cancer attenuates amyloid pathology in Alzheimer's disease via cystatin-c activation of TREM2

Alzheimer's disease (AD) and cancer are among the most devastating diseases worldwide. Epidemiological data indicate that the incidence of AD significantly decreases in patients with a history of cancer. However, whether and how peripheral cancer may affect AD progression is yet to be studied. Here, we find that peripheral cancer inhibits amyloid pathology and rescues cognition via secretion of cystatin-c (Cyst-C), which binds amyloid oligomers and activates triggering receptor expressed on myeloid cells 2 (TREM2) in microglia, enabling microglia to degrade the pre-existing amyloid plaques in AD mice. These effects of Cyst-C are abolished by a cell-type-specific deletion (*Cx3cr1*$^{TREM2^{-/-}}$) or mutation of TREM2 (TREM2^{R47H}) or Cyst-C (Cyst-C^{L68Q}) in microglia. Together, these findings provide significant conceptual advances into cancer neuroscience and establish therapeutic avenues that are distinct from the present amyloid-lowering strategies, aiming at degrading the existing amyloid plaques for precision-targeted AD therapy.

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PREPRINT

Mitochondrial double-stranded RNA accumulation in brain aging and Alzheimer's disease

Mitochondria and inflammation are tightly linked in aging and Alzheimer's disease (AD), and recent evidence implicates mitochondrial double-stranded RNA (mt-dsRNA) as a potential trigger of inflammation. We examined mt-dsRNA accumulation and dsRNA signaling in brain aging and AD using human brain tissue and complementary *in vitro* transcriptomic datasets, quantifying mitochondrial transcripts and dsRNA editing. We found that mt-dsRNA accumulated after midlife and coincided with reduced expression of mitochondrial RNA processing and translation machinery, along with increased expression of dsRNA antiviral signaling proteins, consistent with cytoplasmic mt-dsRNA-driven inflammation. In AD brains, mt-dsRNA accumulation was further increased and correlated with cognitive impairment, neuropathological severity, and AD risk genotypes. Genes associated with these measures reflected altered ubiquitin-dependent regulation of antiviral signaling, potentially indicating altered sensitivity to mt-dsRNA. Together, these findings highlight mitochondrial RNA homeostasis as an unrecognized contributor to age- and AD-related neurodegeneration by identifying mt-dsRNA as a potential driver of chronic inflammation.

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Targeting immune cells in the aged brain reveals that engineered cytokine IL-10 enhances neurogenesis and improves cognition

The immune system could play an important role in the age-related decline in brain function, yet specific immune-based strategies to enhance brain resilience in older individuals are lacking. Here, we combined engineered proteins and direct brain delivery to target immune cell populations within the old brain. We detected T cells with an exhaustion signature in the old brain and targeted them with a potent engineered checkpoint inhibitor (RIPR-PD1). This led to T cell expansion and strong pro-inflammatory responses in many brain cell types, notably microglia. To rescue age-related inflammatory imbalances in microglia, we used the anti-inflammatory cytokine interleukin (IL)-10. IL-10 boosted anti-inflammatory responses in old microglia, but it also triggered pro-inflammatory signaling. An engineered IL-10 variant that uncouples pro- and anti-inflammatory responses positively impacted the transcriptome of multiple cell types, enhanced neurogenesis, and improved cognition in aged mice. Our findings pave the way for immunotherapies for the aged brain.

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Interleukin-10 expressing B lineage cells in visceral adipose tissue protect against aging-related insulin resistance and extend lifespan

Visceral adipose tissue (VAT) inflammation is considered as an important contributor of aging, however, whether there is endogenous factor(s) in VAT that counteract this process remains obscure. Here we reported that interleukin (IL)-10 expressing B lineage (B-10) cells are greatly expanded in aged VAT in human and mouse. In aged VAT, B-10 cells are the primary source of IL-10. B cell-specific knockout of IL-10 exaggerated aging-related inflammation and insulin resistance (IR) and reduced lifespan, which could be partially recovered via adoptive transfer of B-10 cells from wild-type mice. Aged VAT microenvironment enhanced IL-10 secretion and proliferation of B-10 cells. The proliferation of B-10 cells was mediated by increases in BAFF in aged VAT. Knock-down of BAFF in VAT compromised aging-related expansion of B-10 cells. On the contrary, VAT-specific overexpression of BAFF promoted B-10 cells expansion, improved aging-related inflammation and IR, and prolonged lifespan.

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The visual system of the longest-living vertebrate, the Greenland shark

The Greenland shark (*Somniosus microcephalus*) is the longest-living vertebrate and inhabits the exceptionally dim and cold waters of the Arctic deep sea. Due to its extreme lifespan, harsh environmental conditions, and prevalent corneal parasitisation, the Greenland shark has previously been thought to have impaired or degenerated vision. Here, we present genomic, transcriptomic, histological and functional evidence that the Greenland shark retains an intact visual system well-adapted for life in dim light. Histology and in vitro opsin expression revealed visual adaptations typical of deep-sea species, including densely packed, elongated rods and a short-wavelength shift in rod visual pigment sensitivity compared to shallow-water sharks. In situ hybridisation confirmed the presence of essential visual cell types: rods, Müller glia, and bipolar, amacrine, and ganglion cells. Moreover, despite being over a century old, the examined specimens showed no obvious signs of retinal degeneration. Using whole genome and retinal RNA-sequencing, we further show that dim-light (rod-based) vision genes are intact and robustly expressed, while many bright-light (cone-based) vision genes have become pseudogenized and/or are no longer expressed. Finally, we identify robust expression of DNA repair-associated genes in the retina, which may help support long-term maintenance of retinal integrity over the Greenland shark's extreme lifespan.

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Is Thymic Involution Truly a Deterioration or an Adaptation?

In mammals, the immune system recognizes and combats pathogens while retaining a memory of prior encounters. In the thymus, naïve T cells capable of recognizing specific antigens are generated through random gene rearrangement, ensuring a diverse immune repertoire. However, the production rate of naïve T cells declines with age, typically following an exponential or power-law function—a phenomenon known as thymic involution, which is often regarded as a deterioration of biological function (immunosenescence). In this paper, we propose a novel theory suggesting that thymic involution may represent an adaptive strategy. As individuals age, repeated exposure to diverse pathogens leads to the accumulation of memory T cells, thereby reducing the need for newly generated naïve T cells to combat infections. Moreover, naïve T cells can persist in the periphery and retain the capacity to initiate immune responses against novel antigens. Using Pontryagin's Maximum Principle, we calculate the optimal schedule of naïve T cell production. The results show that the production rate peaks during a brief period shortly after birth, followed by an exponential decline throughout life, eventually reaching a phase in which naïve T cell production ceases. If peripheral naïve T cells decay very slowly, the optimal strategy may consist of producing all cohorts at birth, with no subsequent production.

Metformin hijacks AMPK-ERK1/2 signaling to trigger a pathogenic “selection trap” and thymic atrophy

Metformin shows clinical promise beyond diabetes, yet its immunological safety in non-diabetic contexts remains uncertain. We found that metformin induces apoptosis in double-positive thymocytes across various mouse models and, importantly, creates a “selection trap” by promoting phenotypic maturation ($TCR\beta^{+}CD69^{+}$) while simultaneously triggering their elimination. Mechanistically, this trap is sprung via mitochondrial dysfunction initiated by complex I inhibition, which causes ATP depletion and elevated mitochondrial reactive oxygen species. This metabolic stress drives sustained AMP-activated protein kinase (AMPK) activation, repurposing extracellular signal-regulated kinase 1/2 signaling to expose the BH3 domain of B cell lymphoma-2 (Bcl-2), thereby neutralizing its anti-apoptotic function. Transcriptomics further reveal that AMPK remodels metabolic pathways to augment oxidative injury and energy crisis, facilitating apoptosis. Notably, thymotoxicity persists even at subtherapeutic doses (25 mg/kg), challenging metformin’s indiscriminate use in non-diabetic populations due to risks to central immune homeostasis.

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Disease tolerance and infection pathogenesis age-related tradeoffs in mice

Disease tolerance is a defence strategy essential for survival of infections, limiting physiological damage without killing the pathogen[1,2]. The disease course and pathology an infection may cause can change over the lifespan of a host due to the structural and functional physiological changes that accumulate with age. Because successful disease tolerance responses require the host to engage mechanisms that are compatible with the disease course and pathology caused by an infection, we predicted that this defence strategy would change with age. Animals infected with a 50% lethal dose (LD_{50}) of a pathogen often show distinct health and sickness trajectories due to differences in disease tolerance[1,3] and can be used to define tolerance mechanisms. Here, using a polymicrobial sepsis model, we found that, despite having the same LD_{50}, aged and young susceptible mice showed distinct disease courses. In young survivors, cardiac *Foxo1* and its downstream effector *Trim63* (MuRF1) protected from sepsis-induced cardiac remodelling, multi-organ injury and mortality. Conversely, in aged hosts, *Foxo1* and *Trim63* acted as drivers of sepsis pathogenesis and death. Our findings have implications for the tailoring of therapy to the age of an infected individual and indicate that disease tolerance genes show antagonistic pleiotropy.

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Association between shingles vaccination and slower biological aging: Evidence from a U.S. population-based cohort study

Jung Ki Kim, PhD ✉, Eileen M Crimmins, PhD

There is growing interest in whether adult vaccines such as shingles vaccine may slow biological aging beyond preventing acute infections. Using data from the nationally representative U.S. Health and Retirement Study, we examined whether shingles vaccination is associated with more favorable profiles across seven biological aging domains: inflammation, innate and adaptive immunity, cardiovascular hemodynamics, neurodegeneration, and epigenetic and transcriptomic aging, as well as a composite biological aging score. Analyses included adults aged 70+ in 2016 (n = 3,884), with biological measures drawn from venous blood, flow cytometry, and physical assessments. Weighted linear regressions adjusted for sociodemographic, and health covariates. Shingles vaccination was significantly associated with lower inflammation scores (b=−0.14, p = 0.0027), slower epigenetic (b=−0.17, p = 0.0001) and transcriptomic aging (b=−0.19, p < .0001), and a lower composite biological aging score (b=−0.18, p = 0.0002), suggesting potential benefits for systemic inflammation, molecular and overall biological aging. In contrast, vaccination was linked to higher adaptive immunity scores (b = 0.09, p = 0.0133), an unexpected finding warranting further investigation. Timing analyses indicated that epigenetic, transcriptomic and overall composite biological aging improvements were most pronounced within three years post-vaccination, with slower aging persisting beyond this window. The results support the hypothesis that shingles vaccination may influence key biological systems relevant to aging, though effects appear domain-specific and vary over time. Longitudinal studies are needed to confirm these patterns and explore implications for long-term health. This study adds to emerging evidence that vaccines could play a role in strategies to promote healthy aging by modulating biological systems beyond infection prevention.

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Cholesterol Lowering Alone Fails to Reverse Atherosclerotic Plaque Necrosis, Granulopoiesis, and Neurovascular Neutrophils in Middle-Aged Mice

Cholesterol lowering through diet, lifestyle, and pharmacologic therapy remains central for limiting atherosclerosis and prevention of major adverse cardiovascular events. Yet, 33%-50% of individuals on lipid-lowering therapy continue to exhibit elevated inflammation. Middle age (MA) represents a critical window for disease acceleration, underscoring a need to better understand nonresolving inflammation in this time frame. Here, we rendered young (2 months) and MA mice (10 months) hypercholesterolemic with an AAV8-PCSK9 virus and western diet (WD). Following 20 weeks on WD, mice were switched to a chow diet for 6 weeks to induce lipid lowering. This design models dietary cholesterol reduction to dissect lipid-driven versus inflammation-driven pathways in atherosclerosis. At baseline atherosclerosis, we found that MA mice had increased plaque necrosis as well as increased circulating and bone marrow PMN compared to young mice. After chow switch, unlike in young mice, MA mice had increased plaque necrosis and reduced remodeling, as well as increased circulating white blood cells and bone marrow hematopoietic stem cell progenitors (HSPCs). In MA chow-switched mice, circulating neutrophils correlated with necrosis whereas young mice exhibited no correlation. Furthermore, MA atherosclerotic mice had bone marrow HSPCs and neutrophils that exhibited a more activated phenotype relative to young after chow switch. In addition, we observed elevated neutrophil-endothelial contacts in the hippocampal vasculature of MA mice after chow switch. While dietary intervention and lowered plasma cholesterol restrained atheroprogression in young, it was inadequate in MA mice, failing to reduce systemic inflammation and indicating the need for complementary therapies during this time frame.

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Rapamycin Exerts Its Geroprotective Effects in the Ageing Human Immune System by Enhancing Resilience Against DNA Damage

mTOR inhibitors such as rapamycin are among the most robust life-extending interventions known, yet the mechanisms underlying their geroprotective effects in humans remain incompletely understood. At non-immunosuppressive doses, these drugs are senomorphic, that is, they mitigate cellular senescence, but whether they protect genome stability itself has been unclear. Given that DNA damage is a major driver of immune ageing, and immune decline accelerates whole-organism ageing, we tested whether mTOR inhibition enhances genome stability. In human T cells exposed to acute genotoxic stress, we found that rapamycin and other mTOR inhibitors suppressed senescence not by slowing protein synthesis, halting cell division, or stimulating autophagy, but by directly reducing DNA lesional burden and improving cell survival. Ex vivo analysis of aged immune cells from healthy donors revealed a stark enrichment of markers for DNA damage, senescence, and mTORC hyperactivation, suggesting that human immune ageing may be amenable to intervention by low-dose mTOR inhibition. To test this in vivo, we conducted a placebo-controlled experimental medicine study in older adults administered with low-dose rapamycin. p21, a marker of DNA damage-induced senescence, was significantly reduced in immune cells from the rapamycin compared to placebo group. These findings reveal a previously unrecognised role for mTOR inhibition: direct genoprotection. This mechanism may help explain rapamycin's exceptional geroprotective profile and opens new avenues for its use in contexts where genome instability drives pathology, ranging from healthy ageing, clinical radiation exposure and even the hazards of cosmic radiation in space travel.

Rapamycin Reverses the Hepatic Response to Diet–Induced Metabolic Stress That Is Amplified by Aging

Aging is associated with increased susceptibility to metabolic stress and chronic liver disease, yet the interactions between age and metabolic stressors and the potential for ameliorating interventions remain incompletely understood. Here, we examined the hepatic response of young (7-month-old) and old (25-month-old) C57BL/6 male mice to a 9-week high-fat diet (HFD) and assessed whether rapamycin, a well-established pro-longevity intervention, could mitigate age-exacerbated effects. While both age groups developed metabolic-associated steatohepatitis (MASH), older mice displayed more severe hepatic steatosis, inflammation, and transcriptional dysregulation. Transcriptomic profiling of whole livers and purified hepatocytes revealed that aging amplifies HFD-induced inflammatory and metabolic gene expression changes, including activation of immune pathways and suppression of metabolic pathways. Notably, treatment of aging mice with rapamycin reversed the majority of HFD-driven transcriptional alterations, including upregulation of pro-inflammatory regulators such as Stat1, and dysregulation of metabolic gene networks. Rapamycin also reduced hepatosteatosis, total body weight, and a tumorigenic transcriptomic signature associated with hepatocellular carcinoma risk. These findings demonstrate that aging intensifies hepatic sensitivity to dietary metabolic stress and identify rapamycin as a promising therapeutic to counteract age-related liver dysfunction and metabolic dysfunction-associated steatotic liver disease (MASLD) progression.

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PREPRINT

The gerotherapeutic drugs rapamycin, acarbose, and phenylbutyrate extend lifespan and enhance healthy aging in house crickets

The house cricket (Acheta domesticus) is a promising preclinical geroscience model due to its short lifespan, low maintenance, age-associated functional decline, and responsiveness to geroprotective drugs. Continuous dosing with rapamycin, acarbose, and phenylbutyrate extends lifespan; whether intermittent dosing offers similar benefits remains unknown. We tested 274 sex-matched crickets given 2-week intermittent dosing of each drug starting at mid-age (8-weeks), followed by behavioral testing at 10-weeks (geriatric stage). Assays included Y-maze olfactory discrimination, open-field exploration, and treadmill performance. Locomotor gaits were identified by velocity-based K-means clustering (silhouette > 0.5). A subset was monitored for post-treatment survival using Kaplan-Meier analysis. Olfactory preference was preserved by all drugs (d's = -1.82 to -1.28, P's < 0.01), with strongest effects in rapamycin-treated individuals. Rapamycin-treated males matched or exceeded juvenile locomotor activity; phenylbutyrate reduced male activity (d = 1.49, P < 0.05) and acarbose increased walking-to-running ratios (d = -0.75, P < 0.05). Rapamycin increased central exploration and freezing (d = -1.55, P < 0.0001), while acarbose and phenylbutyrate increased peripheral freezing (d = -0.76, P < 0.05). Rapamycin and phenylbutyrate extended maximum running time (d's = -2.30 to -1.32, P's < 0.0001), with sex-specific jumping gains in rapamycin-treated females and acarbose-treated males. Post-treatment lifespan was prolonged by rapamycin (HR = 0.42, P < 0.001) and reduced by acarbose in females (HR's = 2.92 to 3.03, P's < 0.05). Intermittent rapamycin preserved survival, cognition, and locomotion, while acarbose and phenylbutyrate produced selective benefits, supporting A. domesticus as a scalable model for geroprotective drug discovery.

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Metformin inhibits nuclear egress of chromatin fragments in senescence and aging

Chronic inflammation promotes aging and age-associated diseases. While metabolic interventions can modulate inflammation, how metabolism and inflammation are connected remains unclear. Cytoplasmic chromatin fragments (CCFs) drive chronic inflammation through the cGAS-STING pathway in senescence and aging. However, CCFs are larger than nuclear pores, and how they translocate from the nucleus to the cytoplasm remains uncharacterized. Here we report that chromatin fragments exit the nucleus via nuclear egress, a membrane trafficking process that shuttles large complexes across the nuclear envelope. Inactivating critical nuclear egress proteins, the ESCRT-III or Torsin complex, traps chromatin fragments at the nuclear membrane and suppresses cGAS-STING activation and senescence-associated inflammation. Glucose limitation or metformin inhibits CCF formation through AMPK-dependent phosphorylation and autophagic degradation of ALIX, an ESCRT-III component. In aged mice, metformin reduces ALIX, CCFs, and cGAS-mediated inflammation in the intestine. Our study identifies a mechanism linking metabolism and inflammation and suggests targeting the nuclear egress of chromatin fragments as a strategy to suppress age-associated inflammation.

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Reserpine prolongs lifespan but compromises locomotion and heat-stress resilience in *Drosophila melanogaster*

Pharmacological modulation of monoaminergic signaling, a process targeted by many therapeutic and recreational drugs via receptors, transporters, degradation enzymes, or reuptake mechanisms, is emerging as a promising aging intervention and as a strategy to treat various maladies. Monoamines (including dopamine, serotonin, and norepinephrine) are central to the regulation of mood, movement, sleep, memory, and systemic physiology. Here, we demonstrate that Reserpine, chronic inhibitor of the vesicular monoamine transporter (VMAT), robustly extends lifespan in *Drosophila melanogaster* in a dose-dependent manner. However, reserpine-treated flies also exhibit reduced locomotor activity and impaired survival under acute heat-stress, indicating a context-dependent trade-off between lifespan extension and stress resilience. Transcriptomic profiling revealed that reserpine induces a transcriptionally repressed, low-energy state characterized by downregulation of metabolic, immune, and stress-response genes in treated aged animals. Notably, under heat-stress, reserpine blunts the induction of canonical protective genes, including heat shock proteins and antioxidant genes, resulting in increased proteotoxic vulnerability. These findings highlight the potential trade-offs of monoaminergic modulation and support further investigation of VMAT inhibitors, monoamine modulators and other hypertension drugs as geroprotective agents.

Silkworm as a model for NAD⁺–dependent lifespan regulation: Functional insights into BmNmnat1 and nicotinic acid

Nicotinamide adenine dinucleotide (NAD^+) is a central metabolic coenzyme that regulates redox homeostasis, DNA repair, and cellular longevity. While the role of NAD^+ metabolism in mammalian aging has been well studied, its significance in invertebrate systems remains underexplored. Here, we establish the silkworm (Bombyx mori) as a novel model for investigating NAD^+-dependent lifespan regulation. Through phenotypic comparisons among silkworm strains, we found that longer-lived strains exhibit higher levels of NAD^+ and elevated expression of BmNmnat1, a key enzyme in NAD^+ biosynthesis. CRISPR/Cas9-mediated knockout and RNAi knockdown of BmNmnat1 led to embryonic lethality, increased DNA damage, disrupted cell cycle progression, and morphological aging phenotypes. Supplementation with nicotinic acid (NA) significantly reversed these aging-associated changes both in vitro and in vivo, including improved redox balance, reduced oxidative stress markers, and prolonged adult lifespan. Our results highlight the evolutionarily conserved role of BmNmnat1-mediated NAD^+ metabolism in aging and establish the silkworm as a valuable invertebrate model for mechanistic studies and antiaging intervention screening.

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PREPRINT

Balance between DNA repair, LINE1 suppression and lifespan in mice with SIRT6 Serine 10 phosphorylation site mutations

Sirtuin 6 (SIRT6) is an important regulator of DNA repair, metabolism, chromatin maintenance and longevity. SIRT6 Serine 10 phosphorylation controls SIRT6 recruitment to the sites of DNA damage. To explore the effect of SIRT6 Serine 10 phosphorylation on lifespan, we generated two SIRT6 mutant mouse strains: phospho-null S10A and phosphomimetic S10E. The S10E mutant mice demonstrated enhanced DNA repair capacity, elevated LINE1 expression and reduced lifespan in male mice compared to the wild-type and S10A mice. This result suggests that SIRT6 S10E mutation enhances DNA repair capacity at the expense of reduced LINE1 silencing leading to shorter lifespan. While both SIRT6 functions in DNA repair and chromatin maintenance are important for longevity, our results suggest that when the balance between these functions is shifted, diminished of LINE1 control has a stronger impact on lifespan than enhanced DNA repair.

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PREPRINT

The aging mouse lipidome

Aging is associated with widespread metabolic changes that contribute to functional decline and disease. While prior studies have characterized age-associated changes in lipids, it still remains incompletely understood how the lipidome changes across tissues and between sexes during aging. Here, we performed targeted lipidomics across 10 organs collected from male and female mice at five ages spanning adolescence to old age. We analyzed 775 lipids across multiple lipid classes and found that aging affects the lipidome in an organ-specific manner. The thymus and quadriceps muscle had the most age-associated lipid changes, whereas lipid levels in organs such as the kidney and lung remained more stable. In quadriceps muscle, aging was associated with a decrease in specific phosphatidylcholine and phosphatidylethanolamine lipids, particularly those containing adrenic acid. We also identified sex-dependent differences in lipid composition, with the spleen showing differences throughout life. Spleens from female mice had lower levels of lysophosphatidylcholine and lysophosphatidylethanolamine compared to males. Together, these data provide a comprehensive atlas of age- and sex-associated lipid changes across mouse organs and complement existing metabolic and transcriptomic resources to support studies of mouse aging.

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PREPRINT

SenCat: Cataloging human cell senescence through multiomic profiling of multiple senescent primary cell types

There is an urgent need to comprehensively catalog senescence markers across cell types in an organism in order to characterize 'senotypes' and senescent cell heterogeneity. Here, we profiled the transcriptomes and proteomes in 14 different primary human cell types undergoing over 30 senescence paradigms to create a senescence catalog we termed 'SenCat'. We found that, while senescent cells from all primary tissue types did not share a single unique marker, they did activate shared specific metabolic and damage-response pathways implicated in tissue repair. Machine learning analysis of the SenCat transcriptomic and proteomic datasets successfully identified independent sets of senescent human cells, and senescent-like cells in mouse lung and kidney. In sum, SenCat represents a much-needed resource to identify senescent cells across tissues in the body.

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PREPRINT

SenNet Portal: Build, Optimization and Usage

Cellular senescence is a hallmark of aging and a driver of functional decline across tissues, yet its heterogeneity and context dependence have limited systematic study. The Common Fund Cellular Senescence Network (SenNet) Program addresses this challenge by generating multimodal, multi-tissue datasets that profile senescent cells across the human lifespan and complementary mouse models. The SenNet Data Portal (https://data.sennetconsortium.org) serves as the public gateway to these resources, providing open access to harmonized single-cell, spatial, imaging, transcriptomic, and proteomic data; senescence biomarker catalogs; and standardized protocols that can be used to comprehensively identify and characterize senescent cells in mouse and human tissue. As of January 2026, the portal hosts 1,753 publicly available human and mouse datasets across 15 organs using 6 general assay types. Experts from 13 Tissue Mapping Centers (TMCs) and 12 Technology Development and Application (TDAs) components contribute tissue data, analyze data, identify senescent biomarkers, and agree on panels for cross-tissue antibody harmonization. They also register human tissue data into the Human Reference Atlas (HRA) and develop user interfaces for the multiscale and multimodal exploration of this data. Built on a scalable hybrid cloud microservices architecture by the Consortium Organization and Data Coordinating Center (CODCC), the Portal enables data submission, management, integrated analysis, spatial context mapping, and cross-species senescence mapping critical for aging research. This paper presents user needs, the Portal architecture, data processing workflows, and senescence-focused analytical tools. The paper also presents usage scenarios illustrating applications in biomarker discovery, quality benchmarking, hypothesis generation, spatial analysis, cost-efficient profiling, and cell distance distribution analysis. Current limitations and planned extensions, including expanded spatial-omics releases and improved tools for senotype characterization, are discussed. SenNet protocols, code, and user interfaces are freely available on https://docs.sennetconsortium.org/apis.

C. elegans aging research

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Nematode extracellular protein interactome expands connections between signaling pathways

The nematode Caenorhabditis elegans is a favorable model for studying cell-surface protein interactomes, given its well-defined and stereotyped intercellular contacts. Here, we report an extracellular interactome dataset for C. elegans. Most of these interactions were unknown, despite recent datasets for flies and humans, as our collection contains a larger selection of protein families. We uncover interactions for all four major axon guidance pathways, including ectodomain interactions between three of them. We demonstrate that a protein family, previously known for maintaining axon positioning, functions as secreted binders for insulins and that their overexpression in vivo extends lifespan, consistent with inhibition of insulin signaling. We reveal interactions of cystine-knot proteins with putative signaling receptors, which may extend the study of neurotrophins and growth factors to nematodes. Finally, our dataset constitutes a resource for uncovering the logic of neuronal connectivity, intercellular communication and adhesion, and signaling pathways involved in aging and disease.

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The aggregate proteome of *Caenorhabditis elegans* mitochondria implicates shared mechanisms of aging and Alzheimer's disease

Background: Mitochondrial dysfunction and protein aggregation are central features of brain aging and Alzheimer's disease (AD). To define how AD seed proteins modulate these processes, we applied quantitative proteomics to sarkosyl-insoluble aggregates from *C. elegans* models of normal aging and from worms expressing human Aβ or Tau transgenes.

Results: Normal aging produced a late-onset accrual of mitochondrial proteins within aggregates, implicating impaired energy metabolism and proteostasis collapse. Aβ expression caused a striking expansion and included glycolytic enzymes, tricarboxylic acid cycle components, ribosomal proteins, and trafficking factors, consistent with broad proteostatic and bioenergetic stress, largely overlapping with aging-associated species, yet advanced in onset. Tau expression yielded a smaller set enriched for cytoskeletal, vesicular, and nuclear pore components. Post-translational modifications (4-HNE adducts, phosphorylation, acetylation, methionine oxidation) revealed distinct trajectories: Aβ imposed early oxidative and phosphorylation burden, whereas Tau and aging showed midlife PTM peaks consistent with delayed proteostasis collapse. Cross-species comparison revealed 68 insoluble proteins shared between worm models and human AD brain aggregates. From these, 17 conserved metabolic, chaperone, and trafficking proteins were prioritized by network metrics and validated functionally: RNAi knockdowns aggravated paralysis or impaired chemotaxis, confirming their functional importance.

Conclusion: These findings place mitochondrial proteome collapse at the center of aging and AD-seeded pathology, distinguish Aβ- and Tau-driven proteotoxic routes, and nominate a conserved panel of aggregation-prone proteins as mechanistic drivers and candidate biomarkers for early detection and intervention in AD.

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Different gametogenesis states uniquely impact longevity in *Caenorhabditis elegans*

Reproduction affects lifespan and fat metabolism across species, suggesting a shared regulatory axis. In *Caenorhabditis elegans*, ablation of germline stem cells leads to extended lifespan and increased fat storage. While many studies focus on germline-less *glp-1(e2144)* mutants, the hermaphroditic germline of *C. elegans* provides an excellent opportunity to study how distinct germline anomalies affect lifespan and fat metabolism. We compare metabolomic, transcriptomic, and genetic pathway differences among three sterile mutants: germline-less *glp-1*, feminized *fem-3*, and masculinized *mog-3*. All three accumulate excess fat and share expression changes in stress response and metabolism genes. However, *glp-1* mutants exhibit the most robust lifespan extension, *fem-3* mutants live longer only at certain temperatures, and *mog-3* mutants are markedly short-lived. The extended lifespan in *fem-3* mutants require *daf-16/FOXO*, as in *glp-1* mutants. In contrast, *daf-16* is dispensable for the already shortened lifespan of *mog-3* mutants. Interestingly, *mog-3* partially mimics male/mating-induced demise, offering a simplified model to study metabolic and reproductive trade-offs underlying this phenomenon. Our data indicate that disrupting specific germ cell populations leads to distinct and complex physiological and longevity outcomes. These findings highlight the importance of investigating sex-dependent differences and underlying mechanisms to fully understand and potentially modulate these relationships.

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PREPRINT

Temporally controlled nervous system-to-gut signaling bidirectionally regulates longevity in *C. elegans*

Lingxiu Xu, Chengxuan Han, Lei Chun, X.Z. Shawn Xu, Jianfeng Liu

The nervous system modulates aging by secreting signaling molecules to cell-nonautonomously regulate the physiological state of distal tissues such as the gut. However, the underlying mechanisms are not well understood. Here, using *C. elegans* as a model, we identified two distinct neuroendocrine signaling circuits through which motor neurons signal the gut in early life to shorten lifespan but in mid-late life to extend lifespan. Both circuits employ the same neurotransmitter acetylcholine (ACh), while recruiting two different gut ACh receptors ACR-6 and GAR-3 to regulate the transcription factor DAF-16 and HSF-1 in early and mid-late life, respectively. Strikingly, the gut expression of ACR-6 is restricted to early life, whereas that of GAR-3 is confined to mid-late life, providing a potential mechanism for the temporal control of the two circuits. These results identify a novel mechanism that empowers the nervous system to bidirectionally regulate longevity by differentially signaling the gut at different life stages.

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PREPRINT

ATG-18 drives longevity in an HLH-30—dependent manner

Enhancing autophagy increases lifespan and healthspan in animal models, yet the precise molecular mechanisms underlying these effects are not fully understood. Here we show that overexpression of the essential autophagic gene *atg-18* extends the lifespan of *C. elegans*. We describe a previously unknown, pleiotropic mechanism by which *atg-18* impacts lysosomes and extends lifespan through the transcription factor *hlh-30*, the master regulator of lysosomal biogenesis. We show that, under stress conditions, HLH-30 requires *atg-18* for nuclear translocation. Furthermore, *atg-18* overexpression broadly improves health and stress resilience yet paradoxically increases early-life susceptibility to lethal heat stress. In contrast, enhances heat-stress survival a loss-of-function of function mutation in *atg-18* enhances heat-stress survival, uncovering a temporal-specific effect of *atg-18*. These finding suggest an ATG-18—HLH-30 autophagy—lysosome pathway that plays a key role in lifespan and healthspan.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Insights from Brazilian supercentenarians

Supercentenarians provide a rare human model of exceptional longevity, marked by unique immune, genetic, and metabolic profiles that support resilience against age-related decline. Brazil's highly admixed population offers unparalleled opportunities to uncover protective mechanisms often missed in more homogeneous cohorts. Here, we describe ongoing genomic and cellular studies of a nationwide Brazilian cohort, featuring individuals who remained highly functional and survived COVID-19 unvaccinated. These individuals allow us to investigate molecular, immunological, and systemic pathways of resilience, offering insights that may inform strategies to extend health span.

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Q&A

Past, present and future perspectives on the science of aging

As *Nature Aging* celebrates its fifth anniversary, the journal asks some of the researchers who contributed to the journal early on to reflect on the past and the future of aging and age-related disease research, the impact of the field on human health now and in the future, and what challenges need to be addressed to ensure sustained progress.

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Beyond the hallmarks of aging: Rethinking what aging is and how we measure it

Maryam Keshavarz and Dan Ehninger

Aging is frequently assessed through lifespan extension and proxy biomarkers, yet these approaches may not fully capture the complexity of biological aging. Here, we propose refinements to discovery and evaluation strategies in aging research. Drawing on cross-species data, from humans to invertebrate models, we show mortality is often driven by a narrow set of life-limiting pathologies rather than a uniform systemic decline. This suggests lifespan extension can result from delayed disease onset without broadly slowing aging. Similarly, while tools like DNA methylation clocks and frailty indices offer value for stratification and prediction, their largely correlational nature limits mechanistic insight. Our systematic review exposes a key limitation in the widely cited "hallmarks of aging" framework: many supporting studies conflate baseline physiological shifts with genuine changes in aging rate. We advocate for study designs that enable differentiation of symptomatic effects from alterations to the trajectory of age-related phenotypic change. By integrating these refinements, the field can move toward a more mechanistic, nuanced understanding of aging, one that supports identifying causal regulators and developing interventions that truly modify aging trajectories.

Senogenic–senolytic treatment strategies enhance tumor control and can improve survival in murine cancer models: a systematic review

Results: The initial search identified 1,262 articles, of which 36 fulfilled the inclusion criteria after screening. All included studies were therapeutic mechanistic in vivo investigations. Across cancer types including colorectal, breast, ovarian, lung, melanoma, meningioma, prostate, head and neck, bladder, pancreatic, and hepatocellular carcinoma, senolytic co-treatment consistently reduced tumor burden compared with senogenic alone. Senescence markers such as SA-β-gal, p21, p53 and $p16^{INK4a}$ were decreased in the majority of combination groups, confirming attenuation of senescence-associated cell-cycle arrest. IL-6 was the most consistently suppressed SASP cytokine. Ki-67 was decreased and Caspase-3 activation increased across most models, supporting reduced proliferation and enhanced apoptosis. BCL2 downregulation and γ-H2AX elevation were observed in several studies, further suggesting increased apoptotic activity and DNA damage.

Conclusion: Senolytic plus senogenic combinations demonstrate robust preclinical efficacy in reducing tumor growth and senescent burden while promoting apoptosis across diverse in vivo models. These findings highlight senotherapy as a promising adjunct to conventional senescence-inducing anticancer therapies and underscore the need for standardized in vivo methodologies and translational studies to guide clinical application. This review protocol was prospectively registered on PROSPERO (registration number: CRD420251161998).

The m⁶A epitranscriptome: A regulatory nexus linking cellular senescence and oncogenesis

N⁶-methyladenosine (m⁶A) orchestrates RNA fate decisions through a dynamic interplay of writers, erasers, and readers, modulating splicing, stability, and translation. This review unveils how m⁶A fine-tunes senescence-associated pathways (p53/p21, p16-RB) with cancer-context-dependent duality-either as a tumor suppressor or promoter of progression/resistance. Leveraging single-cell and spatial omics, we dissect m⁶A's spatiotemporal heterogeneity in tumor-immune ecosystems. We consolidate diagnostic/prognostic biomarker advances and critically evaluate emerging therapeutics (small-molecule inhibitors, allosteric modulators, nanodelivery systems), addressing clinical barriers like selectivity and safety. Finally, we propose precision strategies targeting m⁶A-senescence networks for combined anti-cancer/anti-aging interventions.

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A comprehensive review of artificial intelligence as a catalyst in aging research: insights, gaps and future perspectives

Tasnuva Binte Mahbub [1], Parsa Safaeian [1], Salman Sohrabi [1]

Aging is driven by interconnected genetic, epigenetic, molecular, and physiological processes spanning from unicellular to organismal levels. The surge in high-throughput data, from clinical and imaging to multi-omics, has outpaced traditional analysis methods; driving the integration of artificial intelligence (AI) into aging research. This comprehensive review examines the application of machine learning, deep learning, and computer vision across four canonical aging models (yeast, *Caenorhabditis elegans*, *Drosophila melanogaster*, and mice), highlighting AI's role in lifespan prediction, biomarker and gene discovery, aging-clock construction, and assay automation via automated animal counting and imaging. However, only 3% of the reviewed studies incorporated *in vivo* biological validation with common issues including small and imbalanced datasets, dataset bias, prediction noise, lack of cross-species analyses, absence of cytotoxicity testing, and overreliance on synthetic data. These drawbacks pose AI as just an aiding tool rather than a standalone solution, and without improvements in these sectors, AI-derived findings should be considered hypothesis generating rather than definitive conclusions. To address these issues, we propose the development of a standardized scoring system, AI Quality Assessment Metric (AI-QAM), for aging research that will evaluate studies on six criteria: (1) dataset size, (2) feature dimensionality, (3) biological validation type, (4) species diversity, (5) model generalizability, and (6) interpretability. Moreover, to mitigate the problem of lacking a unifying of a framework integrating AI approaches with biological mechanisms of aging, we present a conceptual framework, mapping AI applications across biological levels and aging hallmarks. AI will fulfill its potential in aging research only when it is firmly grounded in biological principles, systematically benchmarked, and rigorously validated through experimental studies.

Exercise and the hallmarks of cardiovascular aging

Cardiovascular diseases (CVDs), including hypertension, heart failure, atherosclerosis and myocardial infarction, remain the leading cause of morbidity and mortality worldwide. Aging is a predominant risk factor for CVD. Cardiovascular aging is characterized by progressive structural changes at the cellular level and functional decline within the cardiovascular system, ultimately contributing to the onset and progression of CVD. These changes include alterations in left ventricular (LV) systolic and diastolic function, an increased incidence of sinus node dysfunction, myocardial hypertrophy, arterial stiffness, and fibrosis. Therefore, understanding the molecular mechanisms underlying cardiovascular aging and identifying interventions that can slow or mitigate its progression holds significant promise for CVD prevention and treatment. Numerous epidemiological and experimental studies have consistently demonstrated that physical activity or exercise training exerts protective effects against cardiovascular aging. However, the molecular mediators and underlying mechanisms of these benefits are not completely understood. Therefore, further investigation is warranted to elucidate these mechanisms, given their potential as novel therapeutic targets. In this review, we comprehensively synthesize molecular, preclinical, clinical, and epidemiological evidence to underscore the positive effects of exercise on cardiovascular aging. This review systematically investigates how exercise modulates the key biological hallmarks of cardiovascular aging, including deterioration of protein homeostasis (proteostasis), genomic instability, epigenetic disturbances, mitochondrial dysfunction, cellular senescence, chronic inflammation, and dysregulated neurohormonal signaling. The mechanistic insights of exercise-induced adaptations presented in this review may provide a valuable foundation for future investigations, paving the design of tailored exercise regimens aimed at mitigating the progression of cardiovascular aging.

Cellular Senescence, Inflammaging and Cardiovascular Disease

Aging is the most important yet unmodifiable risk factor for cardiovascular disease (CVD). As a result, targeting cardiovascular aging has emerged as a promising strategy to promote long-term cardiovascular health. This review summarizes current knowledge on the effects of aging within the cardiovascular system as well as systemic processes that modulate them. We highlight the roles of cellular senescence and the senescence-associated secretory phenotype (SASP), emphasizing their heterogeneous contributions to chronic low-grade inflammation and tissue remodeling-collectively termed inflammaging. Advances in biomarkers, animal models, and systems biology approaches have deepened our understanding of the interplay between senescence, inflammaging, and cardiovascular dysfunction, including the pivotal role of macrophages in senescent cell clearance. Therapeutic strategies are diverse, ranging from senolytic approaches designed to selectively eliminate senescent cells, to SASP modulation, and interventions targeting chronic inflammation and metabolic dysregulation. Of particular interest, drugs already in clinical use-such as metformin and other anti-diabetic agents-show beneficial effects on aging-related pathways, suggesting that their cardiovascular protection may in part reflect anti-aging properties. Despite these advances, therapies directly targeting senescence and inflammaging to reduce the global burden of CVD remain an urgent unmet need.

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Clonal Hematopoiesis and Its Cardiovascular Implications: A Scientific Statement From the American Heart Association

Clonal hematopoiesis (CH), the benign clonal expansion of hematopoietic stem cells, is often caused by somatic sequence variations in genes associated with hematologic malignancies. Over the past decade, CH has emerged as a risk factor for a wide range of cardiovascular diseases (CVDs), including atherosclerosis, heart failure, atrial fibrillation, and thrombosis. The cardiovascular risk associated with CH is heterogeneous; it varies on the basis of specific genes and variants, clone size, and various extrinsic features. Mechanistic studies suggest that CH contributes to CVDs through both gene-specific pathways and broader inflammatory processes. These include aberrant cytokine production, inflammasome activation, and other proinflammatory mechanisms, which can accelerate atherosclerosis, promote thrombogenesis, and impair vascular or myocardial function. These findings underscore the importance of addressing CH as a potential contributor to CVDs. CH is predominantly considered an age-related phenomenon, but lifelong influences on the fitness of genetic variants, including germline predispositions, obesity, chronic inflammation, and exposure to environmental toxins (eg, tobacco, certain cancer treatments), influence CH. A greater understanding of CH risk factors is therefore important for both individual and population-level risk assessments. Incorporating CH-associated risk into existing CVD risk prediction models may inform new personalized preventive or therapeutic approaches. No CH-specific therapies have proven efficacy in CVD treatment or prevention, but multiple molecular-based therapeutic hypotheses are beginning to be tested.

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Aging of the Hematopoietic System: Mechanisms, Consequences, and Systemic Interactions

Masashi Miyawaki, Seiji Hashimoto, Sumito Ogawa, Yoshitaka Kase

The aging of the hematopoietic system is central to physiological aging, with profound consequences for immune competence, tissue regeneration, and systemic health. Age-related changes manifest as altered blood cell composition, functional decline in hematopoietic stem cells (HSCs), and deterioration of the bone marrow niche. Beyond hematologic dysfunction, hematopoietic aging acts as a systemic amplifier of age-related diseases through clonal hematopoiesis and inflammatory remodeling. This review integrates recent insights into the mechanisms and systemic impacts of hematopoietic aging, reframing it as a modifiable axis of systemic aging. We highlight emerging rejuvenation strategies—senolytics, metabolic reprogramming, and microbiota-targeted therapies—that aim to restore hematopoietic and immune function, offering promising avenues to improve healthspan and reduce age-related multimorbidity.

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Natural senotherapeutics in respiratory health: Addressing cellular senescence, inflammaging, and immunosenescence in the aging lung

Aging is a major risk factor for respiratory diseases, with the respiratory system demonstrating a particular vulnerability to age-related decline. This review explores the intersection between aging biology and respiratory pathophysiology, focusing on three interconnected hallmarks: cellular senescence, inflammaging, and immunosenescence. Senescent cells accumulate in aging lungs, releasing a senescence-associated secretory phenotype (SASP) that perpetuates chronic inflammation and tissue dysfunction. Natural Senotherapeutics, compounds that target senescent cells or modulate their effects, offer promising strategies to address these fundamental mechanisms. We examined the latest findings on key natural compounds (rapamycin, berberine, resveratrol, pterostilbene, quercetin, EGCG, fisetin, apigenin and curcumin) that demonstrate senomorphic and/or senolytic properties in respiratory contexts. These compounds function through diverse but overlapping molecular pathways, mainly modulating inflammation, immune dysfunction and oxidative stress. Preclinical evidence consistently supports their potential in models of chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), and respiratory infections, although their clinical translation remains limited. The challenges include bioavailability, optimal dosing regimens, and delivery methods. As global demographics shift toward an aging population, developing interventions that target fundamental aging mechanisms in the respiratory system is becoming increasingly urgent. Natural senotherapeutics may offer a paradigm shift in maintaining respiratory health in older adults, with potentially fewer adverse effects than synthetic alternatives.

Premature aging in serious mental illness

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Serious mental illnesses (SMIs), including major depressive disorder, bipolar disorder, and schizophrenia, have long been linked to cognitive decline, multiple chronic medical conditions, and premature mortality. These factors significantly contribute to the severe disability seen in SMIs, extending beyond the severity of psychopathology and indicating a premature aging phenotype associated with these conditions. The mechanisms that underlie the relationship between SMIs and the premature aging phenotype are not well understood, but recent evidence suggests that individuals with SMIs may exhibit accelerated biological aging. In this review, we present a comprehensive analysis of the current literature, demonstrating the potential association of SMIs (focusing on mood disorders and schizophrenia spectrum disorders) with abnormalities across various hallmarks of biological aging. We further evaluate how these abnormalities result in more severe psychopathology, poorer treatment outcomes, and a premature aging phenotype in SMIs. We also explore how the hallmarks of biological aging can be affected by behavioral and lifestyle factors, their interconnectedness, and whether they can be considered novel treatment targets for SMIs. In summary, we present robust evidence that accelerated biological aging is a significant biological characteristic of SMIs, contributing to the multiple adverse outcomes observed in these conditions.

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Single-cell aging clocks: A precision tool for dissecting and targeting the aging process

Biological age, an indicator of an individual's health status, was initially measured using bulk tissue aging clocks. However, by averaging molecular signals across thousands of cells, these tools mask the cellular heterogeneity that characterizes aging. Recent single-cell aging clocks, enabled by high-resolution omics technologies, address this limitation. In this review, we provide a systematic overview of these tools, covering their computational foundations and the key biological insights they enable. These clocks have transformed "mosaic aging" from a hypothesis into a quantifiable phenomenon. They also highlight the plasticity of aging by tracking cell-type-specific age acceleration in disease and its reversal after interventions. Furthermore, they are opening new biological frontiers, including the "age reset" during embryogenesis, the role of the tissue microenvironment, and the molecular underpinnings of extreme longevity. Collectively, these findings recast aging not as passive decline but as a regulated, potentially malleable biological program. Single-cell aging clocks provide the foundational tools for developing the next generation of precision interventions aimed at extending human healthspan.

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Telomerase and chronic inflammation as central molecular links in aging

Unraveling complex mechanisms of telomere biology is central to understanding the close link between aging and inflammation. Telomeres are repetitive heterochromatin DNA structures at the ends of eukaryotic chromosomes, and their length is universally accepted as a marker of biological aging. Telomeres progressively shorten with every cell division until they ultimately trigger cellular senescence and apoptosis. Telomere shortening is also promoted by chronic inflammation and oxidative stress. Chronic inflammation and oxidative stress have been shown to be key drivers of age-related diseases, including neurodegeneration, cardiovascular disease, and cancer. Telomerase is central regulator at the intersection of genomic stability, mitochondrial function, epigenetic integrity, and proteostasis. Through its direct and indirect actions, telomerase modulates inflammatory pathways that drive aging and age-related diseases, highlighting its potential as a therapeutic target to mitigate inflammaging and extend healthspan.

Aligning Intrinsic Capacity and Geroscience: Linking Function with Biology

As population ages globally, the agenda of healthy aging has emerged as a critical priority. For addressing the evolving needs of the aging population, the World Health Organization (WHO) introduced the concept of Intrinsic Capacity (IC), which is defined as the composite of all physical and mental capacities. IC brings a major paradigm change, shifting the focus from disease to function and optimization of IC through life has been suggested to be required for achieving healthy aging. In parallel, geroscience is an emerging discipline aiming to understand the biology of aging and developing strategies to slow the aging process and thus prevent age-related functional decline and chronic diseases. This narrative review explores the conceptual and translational connection between IC and geroscience, proposing that IC may serve not only as a measurable indicator of global function but also as a potential target for geroscience interventions. We discuss how the hallmarks of aging underlie declines in the domains of IC and summarize emerging gerotherapeutic approaches that may potentially optimize IC. We further discuss the possibility of integrating IC into geroscience-informed clinical and public health frameworks, emphasizing its value in guiding preventive and personalized strategies for healthy aging.

Nucleotide salvage, genome instability, and potential therapeutic applications

Nucleotide salvage is crucial for maintaining DNA replication when de novo nucleotide synthesis is limited, but this metabolic flexibility poses potential threats to genome stability. Salvage kinases phosphorylate nucleosides broadly, allowing for oxidized and alkylated 2'-deoxynucleosides as well as posttranscriptionally modified ribonucleosides to enter the 2'-deoxynucleoside triphosphate (dNTP) pool. The ensuing contamination of the dNTP pool and the subsequent incorporation of modified nucleotides into genomic DNA promote mutagenesis, induce replication stress, elicit double-strand breaks, and disrupt epigenetic signaling. Although only a small subset of modified nucleosides have been assessed for salvage and genomic incorporation, the scope of salvageable substrates is probably much wider, with significant implications in mutational burden, chromatin instability, and epigenetic regulation. This overlooked aspect of genome instability is especially relevant in biological contexts of high salvage activity or elevated nucleoside damage, including chronic inflammation, cancer, aging, and dietary/microbiome exposures. Emerging evidence links salvage metabolism to tumor progression, where incorporation of salvage-derived nucleotides may contribute to unexplainable mutational signatures detected in cancers, such as gastrointestinal cancer. Recognizing salvage as a hidden source of mutagenesis reshapes our understanding of genome instability and provides potential opportunities for disease prevention, diagnosis, and therapeutic intervention.

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Non–B DNA structures and their contributions to genetic diversity, aging, and disease

DNA is most often found in its canonical B-form double-helical structure, but can also adopt alternative conformations, known as non-B DNA structures. Numerous non-B structures have been characterized, including G-quadruplexes, i-motifs, Z-DNA, hairpins, cruciforms, slipped structures, R-loops, and H-DNA. Non-B DNA motifs are enriched in functional regions, including near transcription start and end sites, topologically associated domains, and replication origins, suggesting their importance in gene regulation, genome organization, and replication. However, these structures are intrinsically prone to error-generating processing, leading to genomic instability and hence have been implicated in the development of human diseases. Here, we discuss recent advances in understanding the biological roles of non-B DNA structures and their contribution to genomic instability in somatic and germline contexts. We highlight how they promote replication stress, transcription stalling, and DNA breaks, resulting in the formation of mutational hotspots. Emerging technologies have enabled the detailed mapping of previously challenging repetitive regions that harbor potential non-B DNA-forming sequences, and are poised to unravel additional contributions in human disease and evolution. Furthermore, we explore the dual role of non-B DNA as a driver of genetic variation that facilitates evolutionary adaptation and as a source of mutations that contribute to tissue dysfunction and aging.

Strategies for blood–brain barrier rejuvenation and repair

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Blood–brain barrier (BBB) dysfunction is a hallmark of many diseases of the brain, including those that represent the largest healthcare burden (for example, Alzheimer disease and stroke). Despite this, rejuvenation and repair of the BBB is not a mainstream concept. During life, the BBB is subjected to perturbations and stresses from a wide range of endogenous or exogenous sources, which can promote brain health or can lead to brain pathologies. The BBB supports many functions that are critical for central nervous system homeostasis and so there are many mechanisms of dysfunction, and hence many targets for intervention. Furthermore, many mechanisms are shared among diseases and disease subtypes, resulting in the potential for common strategies for BBB repair. In this Review, we consider the BBB as a therapeutic target and discuss approaches to its repair and protection in specific disease states and during normal ageing.

Cellular plasticity and regenerative mechanisms in the lung

The adult lung is continuously exposed to environmental insults such as pathogens, pollutants and toxins, necessitating robust regenerative mechanisms to maintain tissue integrity and function. Epithelial regeneration relies on the activity and plasticity of resident stem and progenitor cell populations that are spatially distributed across airway and alveolar compartments. Basal cells in the conducting airways and alveolar type (AT) 2 cells in the alveoli act as regional stem cells, capable of self-renewal and multilineage differentiation. Additionally, variant club cells, bronchioalveolar stem cells (BASCs) and newly identified secretory and transitional cell types such as respiratory airway secretory and AT0 cells have emerged as critical players in lung repair. Cellular plasticity, the ability of differentiated cells to dedifferentiate or transdifferentiate, enables rapid adaptation to injury but may also contribute to chronic lung disease when dysregulated. Ageing and chronic injury reduce regenerative capacities, leading to failed repair, fibrotic remodelling or epithelial simplification, as seen in diseases such as idiopathic pulmonary fibrosis and COPD. Recent advances in single-cell and spatial transcriptomics have revealed cellular heterogeneity, novel progenitor states and transitional intermediates that underpin both normal repair and disease pathogenesis. In this review, we integrate findings from animal models and human lung studies to highlight conserved and divergent mechanisms governing cell fate decisions. We discuss how niche signals, transcriptional programmes and extrinsic cues shape epithelial regeneration and explore the therapeutic implications of targeting epithelial plasticity in chronic lung disease.

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The mTOR Pathway in Hearing Disorders: Mechanistic Links to Aging, Regeneration, and Neurodegeneration

Hearing loss is a prevalent global health problem that most often arises from aging, noise exposure, ototoxic insults, or genetic defects. In addition to its well-recognized social and economic burden, mounting evidence links hearing loss to neurological disorders such as Alzheimer's disease and dementia, underscoring the urgent need for effective curative strategies. Progress in regenerative therapies has been hindered by the limited capacity of mammalian auditory hair cells to regenerate, making a deep understanding of the underlying molecular pathology essential. The mechanistic target of rapamycin (mTOR), a master regulator of cell growth, metabolism, autophagy, and aging, has recently emerged as a key player in both auditory and neurological disorders. In this review, we summarize the current knowledge on how mTOR signaling shapes auditory cellular physiology, contributes to hearing disorder pathogenesis, and offers novel therapeutic entry points. We further explored the possibility that dysregulated mTOR activity may represent a missing mechanistic link between hearing loss and broader neurological disease processes.

Lifespan-Extending Endogenous Metabolites

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Aging is a multifactorial process influenced by genetic, environmental, and metabolic factors. Dysregulated nutrient sensing and metabolic dysfunction are hallmarks of aging, and reduction of insulin/IGF-1 signaling or metabolic interventions such as caloric restriction extend lifespan across species. Endogenous metabolites reflect and mediate these metabolic cues, linking nutrient status to epigenetic and transcriptional programs by serving as cofactors for chromatin-modifying enzymes or as allosteric modulators of transcription factors. Some metabolites have emerged as key regulators of longevity, integrating into networks to concurrently influence multiple aging-related pathways. In this review, we summarize evidence supporting the lifespan-extending effects of key endogenous metabolites across diverse model organisms and discuss their mechanisms of action. These insights underscore the potential of targeting metabolic networks as a multifaceted strategy to delay aging. Finally, we consider the translational promise of metabolite-based interventions to extend healthspan while minimizing adverse effects, and we note remaining challenges such as optimal dosing, context-specific effects, and demonstrating efficacy in humans.

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