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Alphabet's Calico stitches $596M deal for Mabwell's anti-aging asset

By **Gabrielle Masson** · Jun 26, 2025 4:52pm

Nonuniversality of inflammaging across human populations

Inflammaging, an age-associated increase in chronic inflammation, is considered a hallmark of aging. However, there is no consensus approach to measuring inflammaging based on circulating cytokines. Here we assessed whether an inflammaging axis detected in the Italian InCHIANTI dataset comprising 19 cytokines could be generalized to a different industrialized population (Singapore Longitudinal Aging Study) or to two indigenous, nonindustrialized populations: the Tsimane from the Bolivian Amazon and the Orang Asli from Peninsular Malaysia. We assessed cytokine axis structure similarity and whether the inflammaging axis replicating the InCHIANTI result increased with age or was associated with health outcomes. The Singapore Longitudinal Aging Study was similar to InCHIANTI except for IL-6 and IL-1RA. The Tsimane and Orang Asli showed markedly different axis structures with little to no association with age and no association with age-related diseases. Inflammaging, as measured in this manner in these cohorts, thus appears to be largely a byproduct of industrialized lifestyles, with major variation across environments and populations.

Senescence-Associated Chromatin Rewiring Promotes Inflammation and Transposable Element Activation

Cellular senescence is a stable form of cell cycle arrest that contributes to aging and age-associated diseases through the secretion of inflammatory factors collectively known as the senescence-associated secretory phenotype (SASP). While senescence is driven by transcriptional and epigenetic changes, the contribution of higher-order genome organization remains poorly defined. Here, we present the highest-resolution Hi-C maps (~3 kb) to date of proliferating, quiescent, and replicative senescent (RS) human fibroblasts, enabling a comprehensive analysis of 3D genome architecture during senescence. Our analyses reveal widespread senescence-associated remodeling of chromatin architecture, including extensive compartment and subcompartment switching toward transcriptionally active states, and a dramatic increase in unique chromatin loops. These structural features correlate with local DNA hypomethylation and are largely independent of canonical CTCF binding. The altered 3D genome landscape supports expression of SASP genes, inflammation-related pathways, and neuronal gene signatures consistent with age-associated epigenetic drift. We further demonstrate that architectural changes at multiple levels, including compartments, subcompartments, and loops, facilitate the derepression of LINE-1 retrotransposons, linking 3D chromatin structure to activation of proinflammatory transposable elements. Interestingly, quiescent cells, commonly used as senescence controls, exhibited substantial overlap in inflammatory gene expression with senescent cells, raising important considerations for experimental design. Structural analysis of cell cycle genes showed distinct chromatin configurations in senescence versus quiescence, despite similar transcriptional repression. Together, our results establish a high-resolution framework for understanding how genome architecture contributes to the senescent state.

The 'autoimmunome' of centenarians

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Objective: To identify signature proteins potentially linked to resistance to autoimmunity in the blood of centenarians.

Methods: We conducted *in silico* data mining of previously published proteomic results using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) and PHENOPEDIA databases.

Results: Sixteen autoimmune disease-related proteins were identified within the proteomic signatures of centenarians. Albumin was the most connected hub protein, notably elevated in centenarians compared to younger controls, suggesting a protective role. Eight of the identified autoimmunity-related proteins-ADIPOQ, C1S, C5, C7, C9, CFD, MASP1, and SERPING1-were associated with the complement system.

Conclusion: Elevated albumin levels and a prominent complement system presence in centenarians' blood proteome may contribute to resistance to autoimmunity, highlighting potential protective mechanisms against autoimmune diseases in extreme longevity.

Biological aging is a complex non-linear process, with markedly distinct starting and end points, yet the biomarkers of its progression remain elusive. A key assumption of most machine learning (ML) approaches for age clocks is that predictive biomedical features can be identified via mathematical transformations of data to favor a linear transition from start to end, even if they erase any natural biological pattern. It is given that expected correlations, e.g., time lived (age) and time left to live (mortality), would persist in such mathematically optimized models, biologically meaningful or not. Here, we further clarify the workings of the clocks, explain the trade-off between mathematical optimization and biological interpretability, and discuss a hallmark of aging, inflammaging, that age clocks struggle to detect. We expand on the negative consequences of incoherence in linear models where some DNA methylation (DNAm) features increase with aging and disease, while others correspondingly decrease, yet positive weights are assigned to both. We quantify the misalignment between major DNAm clocks and actual changes in DNAm, providing an interactive visualization of these errors for each model. We demonstrate that major conventional age clocks are both incoherent and skewed toward leukocyte fractions and that rectifying incoherence makes the model balanced and *not* skewed toward neutrophils and better detects inflammaging. We briefly outline non-linear ML age clocks and the advantages of identifying a natural trajectory of aging directly from the primary data.

A proteomic signature of healthspan

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The focus of aging research has shifted from increasing lifespan to enhancing healthspan to reduce the time spent living with disability. Despite significant efforts to develop biomarkers of aging, few studies have focused on biomarkers of healthspan. We developed a proteomics-based signature of healthspan [healthspan proteomic score (HPS)] using proteomic data from the Olink Explore 3072 assay in the UK Biobank Pharma Proteomics Project (53,018 individuals and 2,920 proteins). A lower HPS was associated with higher mortality risk and several age-related conditions, such as chronic obstructive pulmonary disease, diabetes, heart failure, cancer, myocardial infarction, dementia, and stroke. HPS showed superior predictive accuracy for these outcomes compared to other biological age measures. Proteins associated with HPS were enriched in hallmark pathways such as immune response, inflammation, cellular signaling, and metabolic regulation. The external validity was evaluated using the Essential Hypertension Epigenetics study with proteomic data also from the Olink Explore 3072 and complementary epigenetic data, making it a valuable tool for assessing healthspan and as a potential surrogate marker to complement existing proteomic and epigenetic biological age measures in geroscience-guided studies.

LinAge2: providing actionable insights and benchmarking with epigenetic clocks

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Biological aging is marked by a decline in resilience at the cellular and systemic levels, driving an exponential increase in mortality risk. Here, we evaluate several clinical and epigenetic clocks for their ability to predict mortality, demonstrating that clocks trained on survival and functional aging outperform those trained on chronological age. We present an enhanced clinical clock that predicts mortality more accurately and provides actionable insights for guiding personalized interventions. These findings highlight the potential of mortality-predicting clocks to inform clinical decision-making and promote strategies for healthy longevity.

Pace of Aging analysis of healthspan and lifespan in older adults in the US and UK

As societies age, policy makers need tools to understand how demographic aging will affect population health and to develop programs to increase healthspan. The current metrics used for policy do not distinguish differences caused by early-life factors, like prenatal care and nutrition, from those caused by ongoing changes in people's bodies that are due to aging and that may be modifiable. Here we introduce an adapted Pace of Aging method designed to quantify differences between individuals and populations in the speed of aging-related health declines. The adapted Pace of Aging method, implemented in parallel in data from the US Health and Retirement Study and in the English Longitudinal Study of Aging (combined n = 19,045), integrates longitudinal data on blood biomarkers, physical measurements and functional tests. It reveals stark differences in rates of aging between population subgroups and demonstrates strong and consistent prospective associations with incident morbidity, disability and mortality. This adapted and generalizable method to measure Pace of Aging can advance the population science of healthy longevity.

Overexpression of the *Dicer* family genes influences lifespan and stress resistance in a tissue-, sex-, and stressor-specific manner in *Drosophila melanogaster*

Small non-coding RNAs coordinate essential cellular processes, including gene expression regulation, genome stability maintenance, and transposon suppression. These processes determine aging, lifespan, and resistance of cells and organisms to stress. In this work, we conducted a comprehensive study of the geroprotective effects of overexpression of two *Dicer* family genes (*Dcr-1* and *Dcr-2*, which are responsible for the biogenesis of miRNAs and siRNAs) in different tissues of *Drosophila melanogaster* (nervous system, fat body, intestine, muscles). Activation of the *Dicer* genes affected the lifespan in a tissue- and sex-depending manner. Females with *Dcr-1* overexpression in the nervous system exhibited a significant and reproducible increase in both median (10.0−13.4%, $p < 0.001$) and maximum lifespan (10.0−13.4%, $p < 0.01$). However, in other cases, the effect was insignificant or negative. Additionally, flies with neuronal *Dcr-1* activation had increased expression of several longevity genes (*Sirt1, bsk, tgo, Gadd45, Xpc, Azot, foxo, Hsf, Tsc1*) and significantly increased survival after acute exposure to 700 Gy γ-radiation (40−200%, $p < 0.05$). But they had reduced resistance to starvation. This indicates a crucial role of the miRNA machinery and the *Dicer* family in providing protection against genotoxic effects and coordinating metabolic processes.

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Metabolic adaptations direct cell fate during tissue regeneration

Although cell-fate specification is generally attributed to transcriptional regulation, emerging data also indicate a role for molecules linked with intermediary metabolism. For example, α-ketoglutarate (αKG), which fuels energy production and biosynthetic pathways in the tricarboxylic acid (TCA) cycle, is also a co-factor for chromatin-modifying enzymes[1,2,3]. Nevertheless, whether TCA-cycle metabolites regulate cell fate during tissue homeostasis and regeneration remains unclear. Here we show that TCA-cycle enzymes are expressed in the intestine in a heterogeneous manner, with components of the αKG dehydrogenase complex[4,5,6] upregulated in the absorptive lineage and downregulated in the secretory lineage. Using genetically modified mouse models and organoids, we reveal that 2-oxoglutarate dehydrogenase (OGDH), the enzymatic subunit of the αKG dehydrogenase complex, has a dual, lineage-specific role. In the absorptive lineage, OGDH is upregulated by HNF4 transcription factors to maintain the bioenergetic and biosynthetic needs of enterocytes. In the secretory lineage, OGDH is downregulated through a process that, when modelled, increases the levels of αKG and stimulates the differentiation of secretory cells. Consistent with this, in mouse models of colitis with impaired differentiation and maturation of secretory cells, inhibition of OGDH or supplementation with αKG reversed these impairments and promoted tissue healing. Hence, OGDH dependency is lineage-specific, and its regulation helps to direct cell fate, offering insights for targeted therapies in regenerative medicine.

Time-Restricted Feeding Promotes Longevity and Gut Health Without Fitness Trade-Offs

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Time-restricted feeding (TRF), a dietary intervention involving daily fasting periods, has been associated with metabolic benefits; however, its long-term physiological impact remains unclear. Using *Drosophila melanogaster* as a model, we investigated the effects of a 16:8 TRF regimen on lifespan, reproductive output, gut health, and microbiota composition. TRF significantly extended lifespan, even when applied only during early adulthood. Notably, this longevity benefit occurred without compromising reproductive fitness, as measured by female fecundity in life's most crucial reproductive phase. TRF promoted gut homeostasis in aged flies by reducing intestinal stem cell proliferation and enhancing epithelial barrier integrity. Furthermore, TRF induced a shift in microbiota composition, increasing the prevalence of gram-negative bacterial taxa. These results show that even short-term TRF interventions at a young age can have long-term physiological benefits. Metabolic reprogramming or increased autophagy are the most likely mechanisms mediating the health-promoting effects of this type of nutritional intervention. TRF is an effective, non-invasive strategy for promoting healthy longevity without significant adverse effects on other aspects of life.

Protection against *APOE4*-associated phenotypes with the longevity-promoting intervention 17α-estradiol in middle-aged male mice

Background

The apolipoprotein ε4 allele (*APOE4*) is associated with decreased longevity and increased vulnerability to age-related declines and disorders across multiple systems. Interventions that promote healthspan and lifespan represent a promising strategy to attenuate the development of *APOE4*-associated aging phenotypes. Here, we studied the ability of the longevity-promoting intervention 17α-estradiol (17αE2) to protect against impairments in *APOE4* versus the predominant *APOE3* genotype using early middle-aged mice with knock-in of human *APOE* alleles.

Methods

Beginning at age 10 months, male *APOE3* or *APOE4* mice were treated for 20 weeks with 17αE2 or vehicle then compared body-wide for indices of middle-aged phenotypes.

Results

Across peripheral and neural measures, *APOE4* associates with poorer outcomes. Notably, 17αE2 treatment generally improves outcomes in a genotype-dependent manner, favoring *APOE4* mice, including reductions in body weight, plasma leptin, hepatic steatosis, learning and memory, and oxidative damage in the brain. Plasma lipidomics and microglial transcriptomics show reductions in genotype-specific differences with 17αE2 treatment.

Conclusions

These findings demonstrate that *APOE4* promotes systemic and neural aging phenotypes linked to AD and that 17αE2-mediated healthspan actions show a positive *APOE4* bias. Collectively, the findings suggest that longevity-promoting interventions may be useful in mitigating deleterious age-related risks associated with the *APOE4* genotype.

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Nicotinamide Riboside Supplementation Benefits in Patients With Werner Syndrome: A Double-Blind Randomized Crossover Placebo-Controlled Trial

Werner syndrome (WS) is a rare hereditary progeroid syndrome caused by mutations in the *WRN* gene. Patients frequently develop various age-associated diseases prematurely, often leading to early mortality (≤ 60 years of age). Depletion of nicotinamide adenine dinucleotide (NAD)$^+$ has been reported in patients with WS, suggesting a key role in the pathogenesis of WS. NAD$^+$ supplementation may improve the condition of WS and other accelerated aging diseases. Therefore, we conducted a double-blind, randomized, crossover, placebo-controlled trial in patients with WS to evaluate the safety and efficacy of the NAD$^+$ precursor, nicotinamide riboside (NR). NR (1000 mg) or placebo capsules were self-administered once daily for 26 weeks, followed by a crossover to the opposite arm for another 26 weeks. The primary endpoint was the safety of NR. Secondary endpoints included NAD$^+$ levels in plasma, number, and size of skin ulcers, blood examinations, sarcopenia, heel pad thickness, cardio–ankle vascular index (CAVI), and ankle–brachial index. The exploratory endpoints involved metabolome profiles of plasma. No serious adverse events were observed during NR treatment. Importantly, CAVI improved, the skin ulcer area decreased, and heel pad thinning showed a declining trend. Metabolomic analysis revealed a significant decrease in blood creatinine. NR treatment significantly improved arterial stiffness, as indicated by CAVI, and likely suppressed renal functional decline in patients with WS. Therefore, NR may be beneficial for preventing atherosclerosis, skin ulcers, and kidney dysfunction in patients with WS.

Sustained Lysosomal Delivery of Enhanced Cy3-Labeled Acid Nanoparticles Restores Lysosomal pH in Retinal Pigment Epithelial Cells and Astrocytes

Lysosomal pH is frequently elevated in age-dependent neurodegenerations like Age-related Macular Degeneration (AMD), Alzheimer's Disease (AD), and Parkinson's Disease (PD). Tools that restore lysosomal pH to an optimal acidic range could enhance enzymatic degradation and reduce waste accumulation. Acidic nanoparticles offer a promising strategy for restoring lysosomal function, but accurate tracking of organelle delivery and long-term retention is needed to optimize dosage. To improve detection and enhance delivery, nanoparticles were synthesized from Poly(D,L-lactide-co-glycolide) (PLGA) polymers covalently linked to the fluorescent Cyanine3 amine (Cy3) probe. Nanoparticle concentration and loading times were optimized to achieve >90% delivery to lysosomes in cultured induced pluripotent stem cell-derived retinal pigment epithelial (iPS-RPE) cells. Uptake was heterogeneous, varying between adjacent cells. Once loaded into lysosomes, the nanoparticles were stably retained, with no detectable changes in concentration, distribution, or size for at least 28 days. iPS-RPE cells internalized more nanoparticles than the ARPE-19 cell line or mouse optic nerve head astrocyte cultures. Functionally, PLGA nanoparticles restored an acidic pH and cathepsin D levels in compromised lysosomes. In summary, Cy3-PLGA nanoparticles enabled improved tracking and long-term delivery to lysosomes, supporting future in vivo applications to restore lysosomal pH in aging and degenerating tissues.

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Accumulation of Epigenetic Noise in the Aging Corneal Epithelium and Its Possible Mechanism

The cornea is the eye's "window" and plays an important role in vision. Aging has a substantial impact on corneal function by reducing the ability of corneal cells to protect the eye, refract light, and repair itself. In this study, we investigated DNA methylation patterns and the activity of the DNMT and TET families, which are responsible for shaping these patterns, in the aging corneal epithelium. To this end, we used corneal epithelial cell sheets detached from the corneas of 2- and 14-month-old mice to study gene expression, DNA methylation, and DNA hydroxymethylation. We detected significant changes in gene expression in aging corneal epithelial cells. Our data indicate that aging leads to significant changes in the methylation of individual cytosines and large DNA regions, which were similar to those shown for other aging tissues. We observed reduced expression of genes from the DNMT and TET families and reduced DNA hydroxymethylation levels in the corneal epithelium of 14-month-old mice compared to 2-month-old mice. These data indicate that the activity of TET enzymes is reduced in the corneal epithelium during aging. Thus, we found an accumulation of epigenetic noise in the aging corneal epithelium, manifested by increases and decreases in DNA methylation levels, which may be caused by decreased activity of TET enzymes. We propose that the observed age-related changes in the corneal epithelium reflect epigenetic changes occurring in the limbal epithelial stem cells.

Single-cell profiling identifies hair cell SLC35F1 deficiency as a signature of primate cochlear aging

Cochlear aging causes substantial hearing impairment in older adults, yet primate-specific mechanisms remain poorly characterized. Our comprehensive analysis combining single-cell and histopathological profiling in aging *Macaca fascicularis* demonstrates progressive cochlear degeneration featuring accelerated sensory hair cell loss, senescent spiral ganglion neurons with elevated neuroinflammation, and marked stria vascularis atrophy. We discovered that downregulation of transmembrane transport proteins, particularly SLC35F1, serves as a critical biomarker of hair cell aging. Functional validation through *Slc35f1* knockdown in adult mice successfully recapitulated key aspects of age-related hearing loss, including hair cell degeneration and auditory function decline. Notably, we showed that long-term metformin administration at clinically relevant doses effectively delays cochlear aging in primates. These findings provide fundamental insights into the cellular and molecular basis of primate cochlear aging while establishing a foundation for developing targeted interventions against age-related hearing loss.

Aggregation of HAPLN2, a component of the perinodal extracellular matrix, is a hallmark of physiological brain aging in mice

Protein aggregation is a hallmark of neurodegenerative diseases and is also observed in the brains of elderly individuals without such conditions, suggesting that aging drives the accumulation of protein aggregates. However, the comprehensive understanding of age-dependent protein aggregates involved in brain aging remains unclear. Here, we investigated proteins that become sarkosyl-insoluble with age and identified hyaluronan and proteoglycan link protein 2 (HAPLN2), a hyaluronic acid-binding protein of the extracellular matrix at the nodes of Ranvier, as an age-dependent aggregating protein in mouse brains. Elevated hyaluronic acid levels and impaired microglial function reduced the clearance of HAPLN2, leading to its accumulation. HAPLN2 oligomers induced microglial inflammatory responses both in vitro and in vivo. Furthermore, age-associated HAPLN2 aggregation was also observed in the human cerebellum. These findings suggest that HAPLN2 aggregation results from age-related decline in brain homeostasis and may exacerbate the brain environment by activating microglia. This study provides new insights into the mechanisms underlying cerebellar aging and highlights the role of HAPLN2 in age-associated changes in the brain.

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 for these cocktails to affect biological age in a mammalian aging model has yet to be tested. Here, we have analyzed the effects of partial chemical reprogramming on mitochondrial structure 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. We also discover that partial chemical reprogramming upregulates the formation of intracellular lipid droplets. 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 and body condition scores. In the livers and kidneys of these animals, we observe significant increases in oil red o staining indicative of excessive lipid droplet accumulation in these organs. Thus, the upregulation of lipid droplet formation during partial chemical reprogramming may cause toxicity hindering the rejuvenation of cells and tissues in aged mammals.

Avian Lifespan Network Reveals Shared Mechanisms and New Key Players in Animal Longevity

Lifespan is a highly variable life trait across the Tree of Life, governed by complex and multifactorial mechanisms. While some conserved pathways regulating longevity have been identified in various species, the molecular basis of this phenotype is far from being understood. In this context, the adoption of new model species and methods of investigation may offer opportunities to explore the molecular underpinnings of longevity in animals. In this study, we investigated the genomic resources of 141 birds to analyze the molecular evolution underlying extremely long- and short lifespans. We show that birds with similar lifespans exhibit convergent evolution in specific genes regardless of body mass and phylogenetic relationship, enabling the construction of a "lifespan network" of protein–protein interactions. This network highlights the interplay between metabolism and cell cycle control as key processes in avian lifespan regulation. This lifespan network not only provides evidence for shared mechanisms of lifespan regulation across different organisms but also enables the identification of new candidates for studying aging, particularly in humans. By integrating multiple evolutionary signals from both extremes of the lifespan distribution, our results show the power of evolutionary and comparative approaches in studying complex traits like longevity, providing new insights into aging research.

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

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

Systematic profiling reveals betaine as an exercise mimetic for geroprotection

Summary

Exercise has well-established health benefits, yet its molecular underpinnings remain incompletely understood. We conducted an integrated multi-omics analysis to compare the effects of acute vs. long-term exercise in healthy males. Acute exercise induced transient responses, whereas repeated exercise triggered adaptive changes, notably reducing cellular senescence and inflammation and enhancing betaine metabolism. Exercise-driven betaine enrichment, partly mediated by renal biosynthesis, exerts geroprotective effects and rescues age-related health decline in mice. Betaine binds to and inhibits TANK-binding kinase 1 (TBK1), retarding the kinetics of aging. These findings systematically elucidate the molecular benefits of exercise and position betaine as an exercise mimetic for healthy aging.

Molecular signatures of longevity identify compounds that extend mouse lifespan and healthspan

Longevity interventions in mammals are typically discovered on a case-by-case basis, hindering systematic geroprotector development. We developed a platform for the identification of longevity interventions integrating longevity gene expression biomarkers within and across species, in silico chemical screening, analyses of selected compounds in cell culture, short-term dietary interventions coupled with omics profiling, and ultimately lifespan studies in mice. This approach identified compounds (selumetinib, vorinostat, celastrol, AZD-8055, LY-294002) that extended lifespan and/or healthspan in aged C57BL/6JN male mice, with limited effects in females. In addition, selumetinib and vorinostat increased lifespan when administered to young, genetically heterogeneous UM-HET3 mice. Our biomarker-driven platform accelerates geroprotector discovery, offering a scalable approach to target conserved longevity pathways.

An Antagonistically Pleiotropic Gene Regulates Vertebrate Growth, Maturity and Aging

The antagonistic pleiotropy theory of aging predicts functional trade-offs between early-life and late-life fitness. However, empirical evidence for these trade-offs in vertebrates remains scarce, particularly in the context of ecologically relevant life histories. Here, we identify *vestigial-like 3* (*vgll3*), a transcription cofactor previously linked with age at maturity in humans and Atlantic salmon through GWAS studies, as an antagonistically pleiotropic gene in turquoise killifish (*Nothobranchius furzeri*). By disrupting two conserved *vgll3* isoforms, we show that reduction of *vgll3*, in an isoform- or dose-dependent manner, accelerated male growth and reproductive development. This indicates that *vgll3* regulates sexual maturity. However, early-life benefits come at a late-life cost, as older mutant males with a disrupted long isoform develop melanoma-like tumors, validated via transplantation into immunodeficient *rag2* models, and exhibit increased age-related mortality rate. These findings highlight *vgll3* as a key regulator of vertebrate life-history trade-offs, balancing early-life fitness with late-life disease risks.

Measuring frailty: a comparison of the cumulative deficit model of frailty in survey and routine data

Purpose: Frailty, a state of increased vulnerability to adverse health outcomes, impacts individuals and healthcare systems. The cumulative deficit model provides a flexible frailty measure but its application across diverse data remains underexplored. This study compares frailty indices derived from survey and routine data.

Methods: Frailty indices in the Clinical Practice Research Datalink (CPRD) Aurum (N = 1,625,677) and the English Longitudinal Study of Ageing (ELSA) (N = 5190) were compared for adults aged 65 + in England. Deficits were categorised as "one-to-one", "one-to-many", and "one-to-none". Age-sex-standardised deficit prevalence, frailty distribution and associations with demographics were analysed using summary statistics and regression.

Results: Mean frailty index scores were similar (CPRD: 0.13 ± 0.10; ELSA: 0.13 ± 0.12) but differences were observed in the capture of specific deficits. The majority of deficits had a "one-to-none" or "one-to-many" mapping. Among 14 comparable deficits, visual impairment, fractures and heart failure were more common in CPRD, while falls, sleep disturbance and arthritis were more frequent in ELSA. Severe frailty and greater fitness were more prevalent in ELSA than CPRD. Sex and age influenced frailty similarly in both datasets, with frailty index scores increasing more rapidly with age in CPRD.

Conclusion: Differences in the number and types of deficits measured offset each other overall, supporting the cumulative deficit model's premise that including a sufficient range of deficits does not significantly alter population-level frailty measures. This interchangeability may alleviate concerns about deficit selection, supporting more flexible approaches to population frailty assessment across both survey and routine data.

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The Combination of Two Small Molecules Improves Neurological Parameters and Extends the Lifespan of C3H Strain Female Mice

Objectives

Targeting partial cellular reprogramming pathways through specific small molecule combinations holds promise for lifespan extension in model organisms. Chemical cocktails like RepSox and tranylcypromine (TCP) may induce beneficial age-related changes without the risks of full reprogramming. This study investigated the effects of RepSox and TCP on neurological markers, physical activity, skeletal health, and survival in aging C3H female mice.

Methods

Female C3H mice were divided into two age groups: "old" (16–20 months) and "senior" (10–13 months). They received intraperitoneal injections of RepSox (5 mg/kg) and TCP (3 mg/kg) or DMSO (control) every 72 h for 30 days. Physiological state, neurological scores, open field test performance, skeletal deformation, and survival were assessed. Histological analyses of organs (brain, liver, heart, kidneys, lungs, muscles) were performed post-treatment. Statistical analyses included Mann-Whitney tests, mixed-effects linear regression, Kaplan-Meier survival analysis, and the Gao-Allison test.

Findings

In the "old" group, treated mice showed enhanced neurological status, fur and skeletal health, and increased cortical angiogenesis, though with some adverse histological changes in the liver and brain. In the "senior" group, treated mice displayed a plateau in mortality after month seven, while deaths continued in controls. Although overall survival was not significantly different, maximum lifespan significantly increased in treated mice ($p = 0.039$, Gao-Allison test). Histological findings revealed localized adaptive changes rather than major toxic effects. These results suggest that the combination of RepSox and TCP exerts protective effects on aging phenotypes and may potentially slow systemic aging processes in C3H mice.

Selective removal of 7-ketocholesterol by a novel atherosclerosis therapeutic candidate reverts foam cells to a macrophage-like phenotype

Methods

This research aims to elucidate the molecular mechanisms of UDP-003, a novel therapeutic compound, in mitigating the harmful effects of 7KC in mouse and human monocyte and macrophage cell lines.

Results

Experimental evidence demonstrates that administration of UDP-003 can reverse the foam cell phenotype, rejuvenating these cells by returning phagocytic function, preventing loss in efferocytosis ability, and decreasing both reactive oxygen species (ROS) and intracellular lipid droplet accumulation. We further demonstrate that UDP-003 drives urinary excretion of 7KC *in vivo* and has a safety/toxicity profile compatible with initiation of human clinical trials.

Conclusions

Our data suggest that the targeted removal of 7KC from foam cells with UDP-003 can potentially prevent and reverse atherosclerotic plaque formation. UDP-003 has the potential to be the first disease-modifying therapeutic approach to treating atherosclerotic disease.

Cell-Surface LAMP1 is a Senescence Marker in Aging and Idiopathic Pulmonary Fibrosis

The accumulation of senescent cells (SEN) with aging produces a chronic inflammatory state that accelerates age-related diseases. Eliminating SEN has been shown to delay, prevent, and in some cases reverse aging in animal disease models and extend lifespan. There is thus an unmet clinical need to identify and target SEN while sparing healthy cells. Here, we show that Lysosomal-Associated Membrane Protein 1 (LAMP1) is a membrane-specific biomarker of cellular senescence. We have validated selective LAMP1 upregulation in SEN in human and mouse cells. $Lamp1^+$ cells express high levels of the prototypical senescence markers p16, p21, Glb1, and have low Lmnb1 expression as compared to $Lamp1^-$ cells. The percentage of $Lamp1^+$ cells is increased with age and in mice with fibrotic lungs due to bleomycin (BLM) instillation. The RNA-Sequencing analysis of the Lamp1-enriched populations in sham and BLM mice lung tissue revealed enrichment of several senescence-related genes in both groups when compared to the SenMayo gene set derived from transcriptomic profiling of senescence markers in Mayo Clinic research datasets. Finally, we use a dual antibody-drug conjugate (ADC) strategy to eliminate SEN in cell culture assay.

Hypertension, Diabetes, and High Cholesterol Awareness Among US Adults

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Cardiovascular mortality has plateaued in the US, likely reflecting a rising burden of cardiovascular risk factors.[1] Although screening for risk factors such as hypertension, diabetes, and high cholesterol level is important, some adults are unaware they have these conditions.[2] The COVID-19 pandemic may have worsened awareness given disruptions in preventive screenings.[3] We evaluated changes in the proportion of US adults who were unaware they had hypertension, diabetes, or high total cholesterol level from 2013 to 2023.

Deep and Quantitative Proteomic Profiling of Low Volume Mouse Serum Across the Lifespan

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Assessing and validating circulating biomarkers is essential for the development of pre-clinical biomarkers that predict biological aging and aging-phenotypes in mice. However, comprehensive proteomics of serum, especially in longitudinal mouse studies, is limited by low volumes of samples. In this study, we develop a workflow for comprehensive and quantitative proteomic analysis of low volume mouse serum and demonstrate its utility and performance in identifying and evaluating key associations with aging phenotypes. Notably, a nanoparticle (NP)-based serum processing workflow coupled to mass spectrometry (MS) increases proteomic coverage by 2 to 4-fold across a range of volumes and provides a quantitative and reproducible (CV < 10%) pipeline for NP-based studies. In a study of 30 mice (aged 12, 24, and 30 months), we uncovered 3992 protein groups across all samples (2235 on average) in 20 µL of serum and highlight novel insights into aging-associated changes in serum and associations with glucose and body composition. With 1 µL additional serum, a 48-cytokine assay quantified 39 additional proteins not identified by MS. This study establishes a powerful workflow that enables deep quantitative proteomics of biologically relevant proteins in volumes feasibly obtained from mice (20 µL of serum) and presents fundamental insights into the aging serum proteome.

Aging murine peritoneal macrophages undergo female-specific remodeling driven by hormone-dependent and independent mechanisms

Aging is a complex process characterized by a progressive decline in physiological functions driven by both biological and environmental factors, with notable differences between sexes. Immune function is strongly influenced by biological sex, affecting both innate and adaptive immune responses, including macrophage behavior. In this study, we investigated the effects of age and sex on the immune cell composition within the peritoneal cavity niche and identified macrophages as the most affected cell type. Macrophages, as central components of the innate immune system, play critical roles in maintaining tissue homeostasis and responding to infections. Here, we find that aging induces sex-specific remodeling of murine peritoneal macrophage transcriptomic and epigenomic landscapes. Consistently, peritoneal macrophages undergo sex-specific functional remodeling with aging (*i.e.* female-specific phagocytic decline and metabolic rewiring). Modulation of gonadal hormone signaling showed that changes in circulating estrogen levels likely contribute to aspects of female-specific macrophage age-related changes. Importantly, multi-omic analysis identified candidate transcription factors whose sex-specific age-regulated expression may drive aspects of sex-specific 'omic' remodeling with aging. Specifically, Irf2 downregulation in female macrophages recapitulates distinct transcriptomic and metabolic aspects of macrophage female aging phenotypes. These findings suggest that female-specific age-related functional remodeling arises through hormone-dependent and -independent mechanisms in peritoneal macrophages.

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CMV reshapes lymphoid immunity in aging: a single-cell atlas with predictive modeling

Cytomegalovirus (CMV), a common herpesvirus, establishes lifelong latency and increases in prevalence with age; yet its systemic impact on the aging immune system remains incompletely understood. We profiled circulating immune cells from healthy older adults (median age: 73) who were CMV(+) or CMV(-) using single-cell RNA-sequencing and validated key findings by flow cytometry. CMV(+) individuals exhibited significant expansion of adaptive immune cells: CD4$^+$ and CD8$^+$ TEMRA T, GZMK$^+$ CD8$^+$ T, γδ T, and atypical B cells. Among innate immune cells, monocytes and dendritic cells remained largely unchanged while *KLRC2*$^+$ (adaptive) NK cells increased and CD56^{dim} NK cells decreased. To facilitate CMV assessment in datasets with unknown CM serostatus, we developed *CMVerify*, a machine learning classifier that accurately predicts CMV serostatus from single-cell data across platforms and age groups (97% accuracy). These findings reveal extensive CMV-associated immune remodeling in older adults and underscore the importance of incorporating CMV status in studies of immune aging.

Red-wine gene networks associated with exceptional longevity in humans

Moderate consumption of red wine has been associated with healthy aging and longevity, defined as one drink per day for women and two drinks per day for men (approximately 142 ml or 5 oz per drink). Previous research has revealed the health benefits of red wine, particularly in relation to cardiovascular disease. However, the influence of genetic factors on these benefits remains to be elucidated. In this study, we explored genes linked to red wine and created a curated gene set that intersects with those related to centenarians, who are markers of exceptional longevity. Utilizing over 190 databases, we identified and validated a curated list of genes, and conducted gene set enrichment analysis as well as enrichment analysis of annotations and diseases. Our findings highlighted 43 genes connected to centenarians, suggesting that these genes play a crucial role in stress response and apoptosis, which are essential for cell survival and renewal. Additionally, we noted that these genes were enriched in pathways associated with smooth muscle cell proliferation, neuroinflammation, nucleotide excision repair, and lipoprotein metabolism (false discovery rate, FDR $< 3 \times 10^{-07}$). Gene set enrichment analysis indicated significant tissue expression in the gastrointestinal, cardiovascular, and respiratory systems. Furthermore, the disease-gene enrichment analysis pointed to associations with the diseases related to the tissues, including cardiovascular disease (heart disease and stroke), type 2 diabetes, gastrointestinal diseases and metabolic diseases, immune diseases, and cancer (FDR $< 9.37 \times 10^{-6}$); notably, cardiovascular diseases, diabetes, and cancer are leading causes of death, suggesting that the genes may be protective against those diseases. Although further research is necessary to uncover additional genes, this study provides the first genetic overview of the health benefits of red wine, emphasizing its potential in supporting healthy aging and longevity.

Abstract Th0030: Impact of Atherosclerosis-Induced Cellular Senescence on Vascular Cognitive Impairment and Dementia

Vascular Cognitive Impairment Disease (VCID) ranks as the second most prevalent form of dementia, after Alzheimer's disease, and is closely linked to cardiovascular diseases (CVDs). Recent research has identified the abnormal accumulation of senescent cells as a novel mechanism linking cellular senescence with atherosclerosis. Conditions such as hypertension, heart disease, and specifically atherosclerosis are major risk factors for VCID. Atherosclerosis induces cellular senescence within the aorta, characterized by heightened senescence-associated beta-galactosidase in vascular smooth muscle cells, endothelial cells, and immune cells. Given that atherosclerosis affects the body's largest artery and can broadly impact organs, including the brain, we hypothesize that atherosclerosis may induce senescence via remote plaque formation or activation of the senescence-associated secretory phenotype (SASP). To examine this hypothesis, we utilized mice susceptible to developing atherosclerosis when fed a high-fat diet (HFD). A subset of HFD mice then received ABT-737, a senolytic drug that selectively kills senescent cells. Pulse wave velocity measurements revealed a significant increase in arterial stiffness in HFD mice, while ABT-737 treatment led to a substantial reduction in stiffness. Interestingly, in male atherosclerotic mice, we observed an increase in anxiety, although senolytic ABT-737 did not appear to rescue this effect. Surprisingly, ABT-737 alone improved spatial long-term memory, independent of disease. In a measure of locomotor activity, atherosclerosis significantly reduced nocturnal activity levels which were subsequently increased by ABT-737. Using mass spectrometry on brain tissue, we found that a subset of differentially expressed proteins have an inverse relationship in HFD compared to HFD + ABT-737. Proteins involved with cholesterol transport and cell signaling were significantly increased in HFD; while proteins involved in the initiation of translation were significantly decreased. When compared to HFD + ABT-737 mice, significantly expressed proteins in both directions returned to baseline. Our findings suggest that disease-driven (atherosclerosis) secondary senescence promotes VCID, impairing specific areas of brain function (amygdala and hippocampus) which is potentially mediated by immune cell recruitment, translation, and cholesterol homeostasis.

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Cross-National Evidence on Risk of Death Associated with Loneliness: A Survival Analysis of 1-Year All-Cause Mortality among Older Adult Home Care Recipients in Canada, Finland, and Aotearoa | New Zealand

Settings and Participants

Home care recipients in 3 countries—Canada, Finland, and Aotearoa | New Zealand (ANZ) —who were 65 years and older were selected for this retrospective analysis.

Methods

We fit a multivariable Cox regression model to obtain the adjusted proportional hazards of 1-year mortality among home care recipients for each of the 3 countries.

Results

A total of 178,610, 35,073, and 169,703 home care recipients in Canada, Finland, and ANZ respectively, were included in the study. The respective baseline rates of loneliness in the 3 countries were 15.9%, 20.5%, and 24.4% of recipients. In multivariate Cox regression analysis, being lonely was independently associated with a lower likelihood of mortality among home care recipients, with hazard ratios of 0.82 (95% CI 0.78-0.86) in Canada, 0.85 (95% CI 0.79-0.92) in Finland, and 0.77 (95% CI 0.74-0.81) in ANZ.

Conclusions and Implications

Loneliness is pervasive in home care settings across the 3 countries; however, its association with mortality differs from reports for the general population. Loneliness was not associated with an increased risk of death after adjusting for health-related covariates. The causal order between changes in health, loneliness, and mortality is unclear. For example, loneliness may be a consequence of those health changes rather than their cause. Hence, temporal order needs better delineation. Health care systems should treat loneliness as an important mental health priority irrespective of a possible relationship with physical health.

C. elegans aging research

Metabolic analysis of sarcopenic muscle identifies positive modulators of longevity and healthspan in C. elegans

Sarcopenia is the age-related degeneration of skeletal muscle, resulting in loss of skeletal muscle tone, mass, and quality. Skeletal muscle is a source of systemic metabolites and macromolecules important for neuronal health, function, and healthy neuronal aging. Age-related loss of skeletal muscle might result in decreased metabolite and macromolecule availability, resulting in reduced neuronal function or increased susceptibility to unhealthy aging and neurodegenerative diseases. We aimed to identify muscle metabolite candidates that regulate healthy aging. C57BL/6J mice were aged to young adult (4 months) and old age (25 months) and skeletal muscle was collected. Age-related muscle loss was confirmed by reduced muscle mass, muscle fiber degeneration, reduced myosin intensity, in addition to a metabolic shift and increased DNA damage in skeletal muscle. Using a low molecular weight enriched metabolomics protocol, we assessed the metabolic profile of skeletal muscle from young adult and old age mice and identified 20 metabolites that were significantly changed in aged muscle. These metabolite candidates were tested in C. elegans assays of lifespan, healthspan, muscle, and mitochondrial morphology under normal and stressed conditions. We identified four metabolite candidates (beta-alanine, 4-guanidinobutanoic acid, 4-hydroxyproline, pantothenic acid) that, when supplemented in C. elegans provided robust gero- and mitochondrial protection. These candidates also affected life-, and health- span in C. elegans models of amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy (DMD). Our findings support that aging muscle can be used to identify novel metabolite modulators of lifespan and health and may show promise for future treatments of neurodegenerative and neuromuscular disorders.

Heat shock proteins function as signaling molecules to mediate neuron–glia communication in C. elegans during aging

The nervous system is primarily composed of neurons and glia, and the communication between them has profound roles in regulating the development and function of the brain. Neuron-glia signal transduction is known to be mediated by secreted signals through ligand-receptor interactions on the cell membrane. Here we show a new mechanism for neuron-glia signal transduction, wherein neurons transmit proteins to glia through extracellular vesicles, activating glial signaling pathways. We find that in the amphid sensory organ of Caenorhabditis elegans, different sensory neurons exhibit varying aging rates. This discrepancy in aging is governed by the cross-talk between neurons and glia. We demonstrate that early aged neurons can transmit heat shock proteins to glia via extracellular vesicles. These neuronal heat shock proteins activate the glial IRE1-XBP1 pathway, leading to the transcriptional regulation of chondroitin synthases to protect glia-embedded neurons from aging-associated functional decline. Therefore, our studies unveil a new mechanism for neuron-glia communication in the nervous system and provide new insights into our understanding of brain aging.

Pro-longevity compounds extend Caenorhabditis elegans male lifespan and reproductive healthspan

Sex differences in aging are robust and ubiquitous. Demographic differences in aging generated by sex have long been recognized, but the underlying biological basis for these differences and the potential for sex-specific interventions remain understudied. To explore sex differences in the response to pro-longevity interventions, we utilized the C. elegans aging model and asked whether male lifespan and reproductive healthspan can be extended via compounds known to have pro-longevity effects in hermaphrodites. We tested seven different compounds at two concentrations each and found that lifespan was extended under all tested conditions. However, reproductive healthspan measured by mating success in late life improved under only two tested conditions, sulforaphane and metformin. These results demonstrate that lifespan and healthspan can be decoupled in C. elegans males and offer a new framework for screening pro-longevity compounds and for studying sex differences in aging in a classical aging model.

Genetic mapping of lifespan and mitochondrial stress response in *C. elegans*

The mitochondrial unfolded protein response (UPR^{mt}) is one of the mito-nuclear regulatory circuits that restores mitochondrial function upon stress conditions, promoting metabolic health and longevity. However, the complex gene interactions that govern this pathway and its role in aging and healthspan remain to be fully elucidated. Here, we activated the UPR^{mt} using doxycycline (Dox) in a genetically diverse *C. elegans* population comprising 85 strains and observed large variation in Dox-induced lifespan extension across these strains. Through multi-omic data integration, we identified an aging-related molecular signature that was partially reversed by Dox. To identify the mechanisms underlying Dox-induced lifespan extension, we applied quantitative trait locus (QTL) mapping analyses and found one UPR^{mt} modulator, *fipp-1/FIP1L1*, which was functionally validated in *C. elegans* and humans. In the human UK Biobank, *FIP1L1* was associated with metabolic homeostasis, underscoring its translational relevance. Overall, our findings demonstrate a novel UPR^{mt} modulator across species and provide insights into potential translational research.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Senolytics under scrutiny in the quest to slow aging

João Pedro de Magalhães ✉

As the world's population continues to age, the ability to slow human aging pharmacologically would bring enormous health and medical benefits. It would also offer extraordinary financial rewards to any enterprise that was capable of delivering longevity in a pill. Because the major causes of mortality worldwide are age-related diseases (such as cancer, cardiovascular disease, type 2 diabetes and neurodegenerative disorders), delaying the onset of aging and age-related diseases is a dream as old as time. The discovery that aging can be delayed in animal models (including in mice) using genetic, dietary and pharmacological interventions has given rise to a growing longevity biotechnology industry[1], which is keen to translate these preclinical discoveries into human applications.

An overview of contemporary theories of ageing

João Pedro de Magalhães ✉

Ageing is a complex biological process whose underlying mechanisms remain contentious. Nonetheless, due to an ageing global population and the rising incidence of age-related diseases, understanding why we age is one of the most important scientific questions of our time, with profound medical implications. Here, I explore the fundamental nature of the ageing process and provide an overview of modern mechanistic theories. I critically examine two main groups of ageing theories: error-based and program-based theories. I discuss the relevance of these theories in the context of ageing patterns, genetic manipulations and longevity drugs, highlighting how experimental challenges and technological limitations have hindered progress. Overall, there is a pressing and unmet need for a robust theoretical framework in ageing research. Elucidating the cellular and molecular mechanisms of ageing would be crucial for developing effective interventions that slow the ageing process and prevent its associated diseases.

Beyond genes and environment: mapping biological stochasticity in aging

Aging is characterized by extensive variability in the onset of morbidity and mortality, even in genetically identical populations with carefully controlled environments. This points to the important role stochasticity plays in shaping the divergent aging process between individual organisms. Here, we survey how stochastic factors at the level of molecules, cells, tissues, and organisms manifest in and impact the aging process, with a focus on the nematode *Caenorhabditis elegans*. Findings of stochasticity in *C. elegans* give additional insights for aspects of aging in the more complex settings of mammals with parallels drawn between organisms when appropriate. The emerging understanding of the stochastic contributors to longevity will enhance research strategies and medical interventions for personalized medicine.

Emerging uncertainty on the anti-aging potential of metformin

Metformin is the most commonly prescribed glucose-lowering agent worldwide for the treatment of type II diabetes. Due to evidence of improvements in healthspan and lifespan in model organisms, and mechanistic data relevant to the hallmarks of aging, it has been considered a promising candidate in the search for pharmacological interventions that may attenuate the ageing process in humans. Various epidemiological studies have been influential in generating support for this hypothesis. These include pronounced anticancer and cardioprotective benefits compared to other antidiabetic treatments, and an observation of metformin use in type II diabetes being associated with better survival than that of the general population. Here we discuss recent developments in the evidence underlying the rationale for using metformin to target ageing. We describe the methodological limitations of some of the early and most influential findings and critically assess their scientific follow-up, including replication attempts of key experimental and observational findings, and a range of clinical trials of metformin in individuals without type II diabetes. These developments generally illustrate an emerging uncertainty in the anti-aging potential of metformin.

In-silico evaluation of aging-related interventions using omics data and predictive modeling

A major challenge in aging research is identifying interventions that can improve lifespan and health and minimize toxicity. Clinical studies cannot usually consider decades-long follow-up periods, and therefore, in-silico evaluations using omics-based surrogate biomarkers are emerging as key tools. However, many current approaches train predictive models on observational data, rather than on intervention data, which can lead to biased conclusions. Yet, the first classifiers for lifespan extension by compounds are now available, learned on intervention data. Here, we review evaluation methodologies and we prioritize training on intervention data whenever available, highlight the importance of safety and toxicity assessments, discuss the role of standardized benchmarks, and present a range of feature processing and predictive modeling approaches. We consider linear and non-linear methods, automated machine learning workflows, and use of AI. We conclude by emphasizing the need for explainable and reproducible strategies, the integration of safety metrics, and the careful validation of predictors based on interventional benchmarks.

Factors involved in human healthy aging: insights from longevity individuals

The quest to decipher the determinants of human longevity has intensified with the rise in global life expectancy. Long-lived individuals (LLIs), who exceed the average life expectancy while delaying age-related diseases, serve as a unique model for studying human healthy aging and longevity. Longevity is a complex phenotype influenced by both genetic and non-genetic factors. This review paper delves into the genetic, epigenetic, metabolic, immune, and environmental factors underpinning the phenomenon of human longevity, with a particular focus on LLIs, such as centenarians. By integrating findings from human longevity studies, this review highlights a diverse array of factors influencing longevity, ranging from genetic polymorphisms and epigenetic modifications to the impacts of diet and physical activity. As life expectancy grows, understanding these factors is crucial for developing strategies that promote a healthier and longer life.

Aerobic Capacity Beyond Cardiorespiratory Fitness Linking Mitochondrial Function, Disease Resilience and Healthy Aging

Tian Gao, Yang Hu, Huifeng Zhang, Rongpei Shi, Yang Song, Mingge Ding ✉, Feng Gao

Aerobic capacity is conventionally equated with cardiorespiratory fitness (CRF), but its physiological essence extends far beyond cardiopulmonary performance. Aerobic capacity is an integrative physiological indicator reflecting the entire process from oxygen uptake and transport to mitochondrial energy conversion, with mitochondrial function constituting its molecular core. Emerging evidence reveals robust associations between diminished aerobic capacity and increased risks of non-communicable chronic diseases and age-related functional decline. However, its potential as a valuable tool for early disease detection and intervention remains undervalued in clinical practice. By synthesizing recent clinical and experimental studies, we highlight the crucial role of aerobic capacity, particularly its mechanistic links to impaired mitochondrial function, which drives disease progression through impaired energy metabolism and chronic inflammation. Furthermore, exercise interventions designed to enhance aerobic capacity have shown promise in improving mitochondrial efficiency, promoting cardiometabolic adaptation, and boosting overall health, thus offering an effective strategy for chronic disease prevention. We advocate for inclusion of aerobic capacity assessments in routine health evaluations and emphasize the need to integrate aerobic capacity optimization into public health frameworks to advance preventive strategies against chronic diseases and promote healthy aging.

Time-Restricted Feeding Promotes Longevity and Gut Health Without Fitness Trade-Offs

Ann-Cathrin Hofacker, Mirjam Knop, Susanne Krauss-Etschmann, Thomas Roeder ✉

Time-restricted feeding (TRF), a dietary intervention involving daily fasting periods, has been associated with metabolic benefits; however, its long-term physiological impact remains unclear. Using *Drosophila melanogaster* as a model, we investigated the effects of a 16:8 TRF regimen on lifespan, reproductive output, gut health, and microbiota composition. TRF significantly extended lifespan, even when applied only during early adulthood. Notably, this longevity benefit occurred without compromising reproductive fitness, as measured by female fecundity in life's most crucial reproductive phase. TRF promoted gut homeostasis in aged flies by reducing intestinal stem cell proliferation and enhancing epithelial barrier integrity. Furthermore, TRF induced a shift in microbiota composition, increasing the prevalence of gram-negative bacterial taxa. These results show that even short-term TRF interventions at a young age can have long-term physiological benefits. Metabolic reprogramming or increased autophagy are the most likely mechanisms mediating the health-promoting effects of this type of nutritional intervention. TRF is an effective, non-invasive strategy for promoting healthy longevity without significant adverse effects on other aspects of life.

Myelin dysfunction in aging and brain disorders: mechanisms and therapeutic opportunities

Zhihai Huang [1] [2], Yulan Zhang [1], Peibin Zou [1] [2], Xuemei Zong [3] [4], Quanguang Zhang [5] [6]

Affiliations + expand

Abstract

Myelin is a multilamellar membrane that surrounds axons in the vertebrate nervous system. Properly functioning myelin is essential for the rapid conduction of nerve impulses, and it metabolically supports axonal integrity. Emerging evidence indicates that myelin is also involved in various aspects of cognition, with adaptive myelination playing a critical role in memory consolidation and motor learning. However, these physiological processes can be disrupted in various diseases. Understanding the mechanisms underlying myelin pathology is therefore essential for the development of targeted therapies for associated medical conditions. This review provides a comprehensive overview of the role of myelin in neural function, with a particular focus on adaptive myelination in cognition. We also highlight myelin dysfunction and the underlying mechanisms in the aging brain, as well as in diverse brain disorders and neurological conditions, including neurodegenerative diseases, psychiatric conditions, brain injuries, chemotherapy-related cognitive impairment, and neurological symptoms associated with COVID-19. Furthermore, we discuss the therapeutic potential of recently identified pro-myelinating compounds in aging-associated cognitive decline and brain disorders, as well as the future of remyelination therapies. Current evidence suggests that restoring functional myelin may serve as a therapeutic strategy for various medical conditions associated with myelin dysfunction.

Malnutrition in Older Adults

Authors: Alfonso J. Cruz-Jentoft, M.D., Ph.D., and Dorothee Volkert, Ph.D.   Author Info & Affiliations

Abstract

Malnutrition in older adults is common, underrecognized, and contributes to poor health and risk of death. Guidelines are available to facilitate prevention and treatment of malnutrition.

Dietary ingredients inducing cellular senescence in animals and humans: A systematic review

Lihuan Guan [a b 1], Kristina Zdantsevich [c 1], Elena Sandalova [a], Karen C. Crasta [a d e f g], Andrea B. Maier [a b h] 👤 ✉

Background

Cellular senescence (CS) is a hallmark of ageing and age-related diseases. While dietary interventions are often explored to reduce CS, less is known about dietary ingredients that induce it. This study systematically reviews the evidence on dietary ingredients that promote CS in animal models and humans.

Methods

Following PRISMA guidelines (PROSPERO: CRD42022338885), PubMed and Embase were searched for studies on dietary ingredients administered via the gastrointestinal tract affecting CS markers in animal models or adults. Risk of bias was assessed using SYRCLE's and Cochrane's tools.

Results

From 10,806 articles, 80 studies (77 animal, 3 human) were included. In animals, high-fat diets commonly induced CS across tissues. The plant extract Teng Long Bu Zhong Tang and certain bioactives promoted CS in tumor tissues, potentially offering anti-cancer benefits. Excessive ethanol intake caused CS in the liver and other organs. In humans, increased CS load was linked to red meat-based meals, high protein intake, and DHA-enriched fish oil. Most studies showed unclear risk of bias.

Conclusions

High-fat diets and anti-cancer natural products promote CS in animal models. Preliminary human evidence suggests similar effects from high-protein, red meat-based diets, or DHA-enriched fish oil. Further research is needed to clarify mechanisms and guide dietary and public health recommendations.

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Factors involved in human healthy aging: insights from longevity individuals

The quest to decipher the determinants of human longevity has intensified with the rise in global life expectancy. Long-lived individuals (LLIs), who exceed the average life expectancy while delaying age-related diseases, serve as a unique model for studying human healthy aging and longevity. Longevity is a complex phenotype influenced by both genetic and non-genetic factors. This review paper delves into the genetic, epigenetic, metabolic, immune, and environmental factors underpinning the phenomenon of human longevity, with a particular focus on LLIs, such as centenarians. By integrating findings from human longevity studies, this review highlights a diverse array of factors influencing longevity, ranging from genetic polymorphisms and epigenetic modifications to the impacts of diet and physical activity. As life expectancy grows, understanding these factors is crucial for developing strategies that promote a healthier and longer life.

Amino acid neurotransmitters in sarcopenia and healthy aging

Steffi M Jonk [1], James R Tribble [1], Peter Swoboda [2], Pete A Williams [3]

Affiliations + expand

Abstract

Sarcopenia is the age-related degeneration of skeletal muscle. Healthy skeletal muscle secretes metabolites and macromolecules that are systemically important for the immune system and central nervous system function and health. Exercise interventions to stimulate skeletal muscle are therapeutic for sarcopenia and limit risk and/or provide neuroprotection in neurodegenerative disease models. Metabolic analysis of aged skeletal muscle has identified altered skeletal muscle metabolomes at an old age. Many of the molecules identified are amino acids that also act as neurotransmitters. In this review, we summarize how 13 amino acids act as neurotransmitters or as precursor to neurotransmitters, and how these are involved in the skeletal muscle secretome, sarcopenia, and aging.

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Photoaging: UV radiation-induced cGAS-STING signaling promotes the aging process in skin by remodeling the immune network

Excessive exposure of the skin to UV radiaton (UVR) accelerates the aging process and leads to a photoaging state which involves similar pathological alterations to those occurring in chronological aging. UVR exposure, containing both UVA and UVB radiation, triggers cellular senescence and a chronic inflammatory state in skin. UVR promotes oxidative stress and a leakage of double-stranded DNA (dsDNA) from nuclei and mitochondria into the cytoplasm of keratinocytes and fibroblasts. It is recognized that cytosolic dsDNA is a specific danger signal which stimulates cytoplasmic DNA sensors. The activation of the signaling through the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) is a major defence and survival mechanism combatting against tissue injuries. There is abundant evidence that UVR exposure of skin stimulates cGAS-STING signaling which promotes cellular senescence and remodels both the local and systemic immune network. cGAS-STING signaling activates the IRF3 and NF-κB signaling pathways which trigger both pro-inflammatory and immunosuppressive responses. Moreover, cGAS-STING signaling stimulates inflammatory responses by activating the NLRP3 inflammasomes. Senescent fibroblasts secrete not only cytokines but also chemokines and colony-stimulating factors which induce myeloid differentiation and recruitment of immune cells into inflamed skin. Photoaging is associated with an immunosuppressive state in skin which is attributed to an expansion of immunosuppressive cells, such as Tregs. UVR-induced cGAS-STING signaling also stimulates the expression of PD-L1, a ligand for inhibitory immune checkpoint receptor, which evokes an exhaustion of effector immune cells. There is clear evidence that cGAS-STING signaling can also accelerate chronological aging by remodeling the immune network.

Digital biomarkers of ageing for monitoring physiological systems in community-dwelling adults

Digital health technologies are transforming health care and personal health management by providing quantifiable data on physiological, behavioural, and environmental health parameters using digital biomarkers. This narrative review classified, characterised, and evaluated digital biomarkers of ageing across ten physiological systems to explore the applications of these biomarkers in research and clinical practice. The systematic search identified minimally invasive or non-invasively measured digital biomarkers suitable for longitudinal studies and practical use by community-dwelling adults. The digital biomarkers were classified according to their physiological system, characterised by their capture methods, and evaluated based on the following criteria: validity (age-associated, function-associated, and mortality-associated), generalisability, responsiveness to interventions, associations with clinical outcomes, and cost-effectiveness in large-scale settings. Digital biomarkers of ageing were found across eight physiological systems. Registered clinical trials that used these digital biomarkers as outcomes were also identified. Continued research and technological advancements are crucial for maximising the potential of digital biomarkers in promoting healthy ageing and longevity.

When therapy-induced senescence meets tumors: A double-edged sword: A review

Liu, Kang MM[a]; Huang, Haijin PhD[b]; Zhang, Minhong MM[b]; Chen, Siming MM[b]; Yang, Yitao MB[b]; Fang, Chunyun PhD[b]; Zhong, Xiaojuan PhD[b,*]

The tumor microenvironment (TME) significantly influences tumor development, progression, and clinical outcomes. Therapy-induced cellular senescence is a fundamental process affecting the microenvironment. This review summarizes the characteristics of therapy-induced cellular senescence, its beneficial and detrimental effects on the TME, and the underlying mechanisms contributing to its dual effects. It further elaborates on optimizing the beneficial aspects of therapy-induced cellular senescence while concomitantly mitigating its adverse effects in the treatment of tumors and prevention of recurrence. Finally, potential interventions, including antiaging drug therapies, senescence inducers, senescence clearance agents, and inhibition of adverse senescence-associated secretory phenotype (SASP) production were explored to inhibit the harmful SASP induced by therapy, with the aim of limiting the production of detrimental SASP in the TME, thereby reducing the risk of tumor recurrence.

An evolutionary medicine and life history perspective on aging and disease: Trade-offs, hyperfunction, and mismatch 🔓

Jacob E Aronoff ✉ , Benjamin C Trumble

The rise in chronic diseases over the last century presents a significant health and economic burden globally. Here, we apply evolutionary medicine and life history theory to better understand their development. We highlight an imbalanced metabolic axis of growth and proliferation (anabolic) versus maintenance and dormancy (catabolic), focusing on major mechanisms including IGF-1, mTOR, AMPK, and Klotho. We also relate this axis to the hyperfunction theory of aging, which similarly implicates anabolic mechanisms such as mTOR in aging and disease. Next, we highlight the Brain–Body Energy Conservation model, which connects the hyperfunction theory with energetic trade-offs that induce hypofunction and catabolic health risks such as impaired immunity. Finally, we discuss how modern environmental mismatches exacerbate this process. Following our review, we discuss future research directions to better understand health risk. This includes studying IGF-1, mTOR, AMPK, and Klotho and how they relate to health and aging in human subsistence populations, including with lifestyle shifts. It also includes understanding their role in the developmental origins of health and disease as well as the social determinants of health disparities. Furthermore, we discuss the need for future studies on exceptionally long-lived species to understand potentially underappreciated trade-offs and costs that come with their longevity. We close with considering possible implications for therapeutics, including (i) compensatory pathways counteracting treatments, (ii) a "Goldilocks zone," in which suppressing anabolic metabolism too far introduces catabolic health risks, and (iii) species constraints, in which therapeutics tested in shorter lived species with greater anabolic imbalance will be less effective in humans.

OTHER RESEARCH & REVIEWS

IL-7 armed binary CART cell strategy to augment potency against solid tumors

Alejandro G Torres Chavez, Mary K McKenna, Anmol Gupta, Neha Daga, Juan Vera, Ann M Leen, Pradip Bajgain

Clinical studies of T cells engineered with chimeric antigen receptor (CAR) targeting CD19 in B-cell malignancies have demonstrated that relapse due to target antigen (CD19) loss or limited CAR T cell persistence is a common occurrence. The possibility of such events is greater in solid tumors, which typically display more heterogeneous antigen expression patterns and are known to directly suppress effector cell proliferation and persistence. T cell engineering strategies to overcome these barriers are being explored. However, strategies to simultaneously address both antigen heterogeneity and T cell longevity, while localizing anti-tumor effects at disease sites, remain limited. In this study we explore a dual antigen targeting strategy by directing independent CARs against the solid tumor targets PSCA and MUC1. To enhance functional persistence in a tumor-localized manner, we expressed the transgenic IL-7 cytokine and receptor (IL-7Rα) in respective CAR products. We now demonstrate the potency and durable antitumor effects of this binary strategy in a pancreatic tumor model.