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Scientific News
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Sven Bulterijs

Business/Conferences/ General news

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Harvard President Says Any Move to Revoke Tax-Exempt Status Would Be 'Highly Illegal'

Alan Garber was responding to Trump's latest threat to remove the university's tax-exempt status

By Douglas Belkin Follow , *Richard Rubin* Follow *and Gareth Vipers* Follow

Updated May 2, 2025 4:51 pm ET

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Trump 2.0: an assault on science anywhere is an assault on science everywhere

US President Donald Trump is taking a wrecking ball to science and to international institutions. The global research community must take a stand against these attacks.

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Measles cases surpass 900 in US as infections confirmed in 29 states, CDC data shows

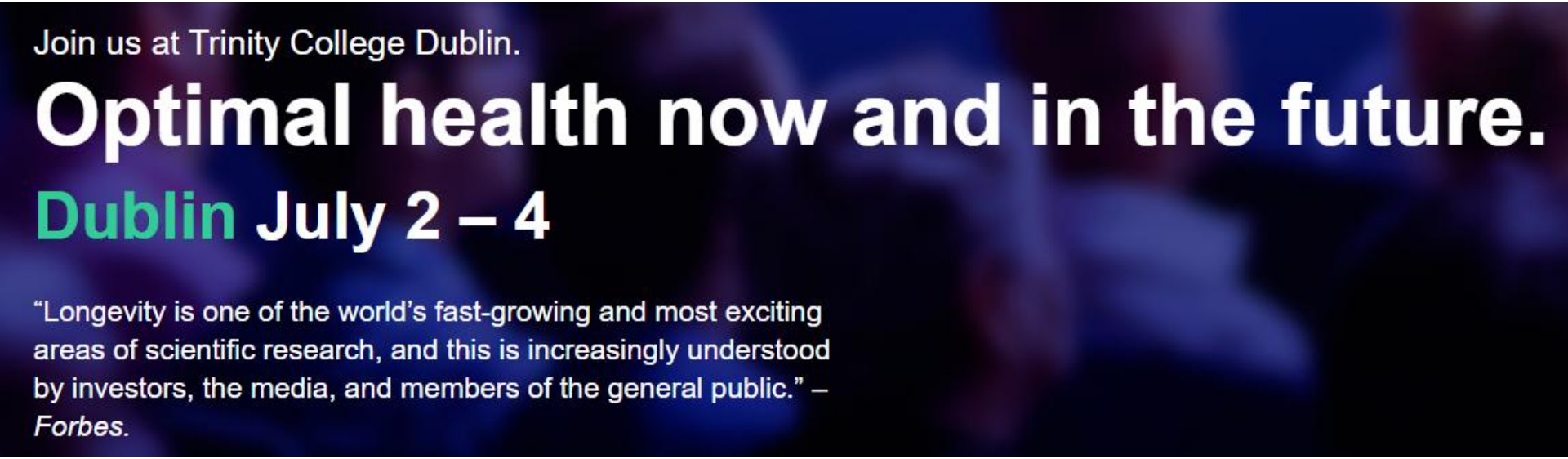
The majority of cases are among those unvaccinated or with unknown status.

By Mary Kekatos and Dr. Sarah Zubair
May 2, 2025, 6:41 PM

How contagious is measles? Measles is one of the most contagious viruses known to humans, experts say.

Upcoming conferences

I'll be there!



Aging research articles

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The mammalian longevity associated acetylome

S. Feldman-Trabelsi, N. Touitou, R. Nagar, Z. Schwartz, A. Michelson, S. Shaki, M. Y. Avivi, B. Lerrer, S. Snir & H. Y. Cohen

Despite extensive studies at the genomic, transcriptomic and metabolomic levels, the underlying mechanisms regulating longevity are incompletely understood. Post-translational protein acetylation is suggested to regulate aspects of longevity. To further explore the role of acetylation, we develop the PHARAOH computational tool based on the 100-fold differences in longevity within the mammalian class. Analyzing acetylome and proteome data across 107 mammalian species identifies 482 and 695 significant longevity-associated acetylated lysine residues in mice and humans, respectively. These sites include acetylated lysines in short-lived mammals that are replaced by permanent acetylation or deacetylation mimickers, glutamine or arginine, respectively, in long-lived mammals. Conversely, glutamine or arginine residues in short-lived mammals are replaced by reversibly acetylated lysine in long-lived mammals. Pathway analyses highlight the involvement of mitochondrial translation, cell cycle, fatty acid oxidation, transsulfuration, DNA repair and others in longevity. A validation assay shows that substituting lysine 386 with arginine in mouse cystathionine beta synthase, to attain the human sequence, increases the pro-longevity activity of this enzyme. Likewise, replacing the human ubiquitin-specific peptidase 10 acetylated lysine 714 with arginine as in short-lived mammals, reduces its anti-neoplastic function. Overall, in this work we propose a link between the conservation of protein acetylation and mammalian longevity.

Identification of functional rare coding variants in IGF-1 gene in humans with exceptional longevity

Amanat Ali, Zhengdong D. Zhang, Tina Gao, Sandra Aleksic, Evripidis Gavathiotis, Nir Barzilai & Sofiya Milman

Diminished signaling via insulin/insulin-like growth factor-1 (IGF-1) axis is associated with longevity in different model organisms. IGF-1 gene is highly conserved across species, with only few evolutionary changes identified in it. Despite its potential role in regulating lifespan, no coding variants in IGF-1 have been reported in human longevity cohorts to date. This study investigated the whole exome sequencing data from 2,108 individuals in a cohort of Ashkenazi Jewish centenarians, their offspring, and controls without familial longevity to identify functional IGF-1 coding variants. We identified two likely functional coding variants *IGF-1*:p.Ile91Leu and *IGF-1*:p.Ala118Thr in our longevity cohort. Notably, a centenarian specific novel variant *IGF-1:p.*Ile91Leu was located at the binding interface of IGF-1–IGF-1R, whereas *IGF-1*:p.Ala118Thr was significantly associated with lower circulating levels of IGF-1. We performed extended all-atom molecular dynamics simulations to evaluate the impact of Ile91Leu on stability, binding dynamics and energetics of IGF-1 bound to IGF-1R. The *IGF-1*:p.Ile91Leu formed less stable interactions with IGF-1R's critical binding pocket residues and demonstrated lower binding affinity at the extracellular binding site compared to wild-type IGF-1. Our findings suggest that *IGF-1*:p.Ile91Leu and *IGF-1*:p.Ala118Thr variants attenuate IGF-1R activity by impairing IGF-1 binding and diminishing the circulatory levels of IGF-1, respectively. Consequently, diminished IGF-1 signaling resulting from these variants may contribute to exceptional longevity in humans.

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Compression of morbidity by interventions that steepen the survival curve

Yifan Yang [1 2], Avi Mayo [3], Tomer Levy [3], Naveh Raz [3], Ben Shenhar [3], Daniel F Jarosz [4 5], Uri Alon [6]

Longevity research aims to extend the healthspan while minimizing the duration of disability and morbidity, known as the sickspan. Most longevity interventions in model organisms extend healthspan, but it is not known whether they compress sickspan relative to the lifespan. Here, we present a theory that predicts which interventions compress relative sickspan, based on the shape of the survival curve. Interventions such as caloric restriction that extend mean lifespan while preserving the shape of the survival curve, are predicted to extend the sickspan proportionally, without compressing it. Conversely, a subset of interventions that extend lifespan and steepen the shape of the survival curve are predicted to compress the relative sickspan. We explain this based on the saturating-removal mathematical model of aging, and present evidence from longitudinal health data in mice, Caenorhabditis elegans and Drosophila melanogaster. We apply this theory to identify potential interventions for compressing the sickspan in mice, and to combinations of longevity interventions. This approach offers potential strategies for compressing morbidity and extending healthspan.

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PREPRINT

Slow Gompertzian aging in long-lived *C. elegans* results from expansion of decrepitude, not decelerated aging

Bruce Zhang, David Gems

The Gompertz equation describes exponential age-increases in animal mortality rate arising from biological aging. Its parameters, α and β, are widely used to evaluate lifespan-extending interventions and human mortality patterns: it is assumed that reduction in β corresponds to deceleration of aging rate, and reduction in α to reduced aging-independent mortality. However, this view has never been empirically validated. We therefore investigated the biological basis of α and β, by simultaneous quantification of mortality and age-related health in long-lived populations of the nematode *Caenorhabditis elegans*. We show that reduction in β arises not from decelerated aging but expansion of decrepitude in longer-lived individuals, whereas reduction in α arises from decelerated aging. This empirical re-evaluation of Gompertzian aging inverts and challenges long-standing ideas in the biodemography of aging.

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PREPRINT

Tentative evidence that aging is caused by a small number of interacting processes

Axel Kowald, Thomas B L Kirkwood

Human life expectancy has increased dramatically over the past two centuries, marking a significant public health achievement. While some projections predict a future where median lifespans reach 100 years, others contend that further longevity will depend on breakthroughs targeting the biological processes of aging. Recent studies in mice have demonstrated that telomerase activation, achieved via gene therapy and transgenic approaches, can extend both median and maximum lifespans substantially without an accompanying increase in cancer risk. We analysed survival data from three such studies using the Compertz mortality model and show that these interventions reduce the slope parameter, indicative of a slower aging rate, rather than merely lowering baseline mortality. This observation challenges traditional models that assume independent, additive damage accumulation, suggesting instead that aging is driven by a limited number of interdependent processes with significant cross-talk. Mathematical modelling indicates that only three to five processes with substantial cross-talk may account for the observed deceleration. Extrapolation using Swedish survivorship data further implies that a reduction in the aging rate, similar to that seen in mice, could elevate the median human lifespan from 85 to over 100 years. These findings provide a compelling framework for developing targeted anti-aging interventions and a new perspective on the modifiability of the aging process.

Functionally enriched epigenetic clocks reveal tissue-specific discordant aging patterns in individuals with cancer

Background

Aging is a key risk factor for many diseases, including cancer, and a better understanding of its underlying molecular mechanisms may help to prevent, delay, or treat age-related pathologies. Epigenetic alterations such as DNA methylation (DNAme) changes are a hallmark of aging and form the basis of so-called epigenetic clocks, yet their functional relevance and directionality in different organs during disease development is often unclear.

Methods

Here, we link cell-specific age-related DNAme changes with three key hallmarks of aging and cancer (senescence, promoter methylation in genes associated with stem cell fate, and dysregulated proliferation) to comprehensively dissect their association with current and future cancer development, carcinogen exposure or preventive measures, and mortality using data in different organs from over 12,510 human and 105 mouse samples, benchmarking against existing epigenetic clocks.

Results

Our findings offer insights into the association of functionally enriched groups of age-related DNAme changes with cancer, identify sites perturbed earliest during carcinogenesis, as well as those distinct between cancer and reprogramming that could inform strategies to prevent teratoma formation upon in vivo reprogramming. Surprisingly, both mouse and human data reveal accelerated aging in breast cancer tissue but decelerated epigenetic aging in some non-cancer surrogate samples from breast cancer patients, in particular cervical samples.

DNAm age differences between infinium methylationEPICv1 vs EPICv2 in buffy coat, PBMC, and saliva samples

Jian Hua Tay, Yi Ern Chew, Weilan Wang, Zhi Meng Lim, Lihuan Guan, Rajkumar Dorajoo, Brian K. Kennedy, Robert Brooke, Juozas Gordevicius, Steve Horvath, Elena Sandalova & Andrea B. Maier

This study aims to evaluate differences between Infinium MethylationEPIC (EPICv1) and Infinium MethylationEPICv2 (EPICv2) arrays in estimating DNAm age with eleven DNAm clocks using buffy coat, peripheral blood mononuclear cell (PBMC), and saliva from 16 healthy middle-aged individuals. DNAm ages were estimated using six principal component-based (PC) clocks (PCHorvath1, PCHorvath2, PCHannum, PCPhenoAge, PCGrimAge, and PCDNAmTL) and five non-PC clocks (DunedinPACE, DNAmFit, YingCausAge, YingAdaptAge, and YingDamAge) across all biological samples. Agreement between arrays was assessed using Spearman correlation, Bland-Altman plots, and Wilcoxon Signed-Rank test. The 16 individuals with median age of 48 [43.5;53.8] years, were predominantly female, Chinese and non-smokers. High correlations ($\rho > 0.8$) were observed between EPICv1 and EPICv2 except for DunedinPACE, YingDamAge and YingAdaptAge. PC-based clocks showed lower systematic bias (MAPE:0.118-8.98%) compared to non-PC-based clocks (MAPE:5.31-21.2%). Saliva samples demonstrated greatest variability between arrays. EPICv2 introduces systematic biases especially in non-PC-based clocks and between different biological samples.

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Single cell–resolved cellular, transcriptional, and epigenetic changes in mouse T cell populations linked to age-associated immune decline

Jing He, Elena Burova, Chandrika Taduriyasas, +10, and David J. Glass Authors Info & Affiliations

Splenic T cells are pivotal to the immune system, yet their function deteriorates with age. To elucidate the specific aspects of T cell biology affected by aging, we conducted a comprehensive multi–time point single-cell RNA sequencing study, complemented by single-cell Assay for Transposase Accessible Chromatin (ATAC) sequencing and single-cell T cell repertoire (TCR) sequencing on splenic T cells from mice across 10 different age groups. This map of age-related changes in the distribution of T cell lineages and functional states reveals broad changes in T cell function and composition, including a prominent enrichment of Gzmk+ T cells in aged mice, encompassing both CD4+ and CD8+ T cell subsets. Notably, there is a marked decrease in TCR diversity across specific T cell populations in aged mice. We identified key pathways that may underlie the perturbation of T cell functions with aging, supporting cytotoxic T cell clonal expansion with age. This study provides insights into the aging process of splenic T cells and also highlights potential targets for therapeutic intervention to enhance immune function in the elderly. The dataset should serve as a resource for further research into age-related immune dysfunction and for identifying potential therapeutic strategies.

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Old hematopoietic stem cells retain competence to reconstitute a youthful B cell system that is highly responsive to protein–based vaccination

Background: Ageing-associated remodeling of the murine B cell system is accompanied with a reduction of $CD19^+$ B cells such as follicular B cells (FOB) and an accumulation of age-associated B cells (ABC) or activated B cell subsets. This remodeling is thought to confer an attenuated antibody response, such as to SARS-CoV-2 spike (S) vaccines in both aged mice and humans. To gain insight into the de novo development and function of an old B cell system, we reconstituted young and old immune systems by transferring hematopoietic stem cells (HSCs) from immune-competent young (2-3 months) $CD45.1^+$ donors (DY-HSC) or old (20-24 months) donors (DO-HSC) into T and B cell-deficient young recipient $CD45.2^+$ $RAG1^{-/-}$ mice, followed by protein-based vaccination.

Results: In the same environment of young $RAG1^{-/-}$ mice, transplanted DO-HSCs compared to DY-HSCs reconstituted lower numbers of $CD19^+$ B cells and $CD45.1^+$ cells, though the engraftment of donor-derived HSCs in the young bone marrow (BM) was very similar. Furthermore, indicative for youthful and unchallenged B cell systems, and in contrast to aged mice, very low levels of antigen-experienced memory B cells or age-associated B cells (ABC) developed in both DY-HSC and DO-HSC hosts. The commercially available recombinant SARS-CoV-2 S vaccine (NVX-CoV2373) induced lower IgG^+ S-antibody titers and pseudovirus neutralization activity in old compared to young mice. In contrast, very similar high IgG^+ S-antibody titers were induced in DO-HSC and DY-HSC hosts, and pseudovirus neutralization activity was even enhanced in DO-HSC compared with DY-HSC hosts.

Conclusions: Both DO-HSCs and DY-HSCs established in the young recipient BM to a similar extend, suggesting that the concomitant reduction in the de novo reconstitution of $CD19^+$ B cells in DO-HSC vs. DY-HSC transplanted animals is specifically related to old HSCs. DO-HSCs and DY-HSCs reconstitute very similar unchallenged B cell systems that efficiently elicit antigen-specific IgG antibodies by protein-based vaccination. Old HSCs thus retain competence to reconstitute a youthful and functional B cell system, at least in the young environment of transplanted $RAG1^{-/-}$ mice. This suggests that it is primarily age-related factors, and not HSCs per se, that influence the composition and functionality of the old B cell system.

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A cloaked human stem-cell-derived neural graft capable of functional integration and immune evasion in rodent models

Human pluripotent stem cell (hPSC)-derived therapies are a realistic possibility for numerous disorders, including Parkinson's disease. While generating replacement neurons is achievable, immunosuppressive drug challenges, to prevent rejection, remain. Here we adopted a hPSC line (termed H1-FS-8IM), engineered to overexpress 8 immunomodulatory transgenes, to enable transplant immune evasion. In co-cultures, H1-FS-8IM PSC-derived midbrain neurons evaded rejection by T lymphocytes, natural killer cells, macrophages, and dendritic cells. In humanized mice, allogeneic H1-FS-8IM neural grafts evaded rejection, while control hPSC-derived neural grafts evoked activation of human immune cells, elevated inflammatory cytokines in blood and cerebrospinal fluid, and caused spleen and lymph node enlargement. H1-FS-8IM neural grafts retained functionality, reversing motor deficits in Parkinsonian rats. Additional incorporation of a suicide gene into the H1-FS-8IM hPSC line enabled proliferative cell elimination within grafts. Findings demonstrate feasibility of generating a population-wide applicable, safe, off-the-shelf cell product, suitable for treating diseases for which cell-based therapies are a viable option.

Inhibition of tau neuronal internalization using anti-tau single domain antibodies

In Alzheimer's disease, tau pathology spreads across brain regions as the disease progresses. Intracellular tau can be released and taken up by nearby neurons. We evaluated single domain anti-tau antibodies, also called VHHs, as inhibitors of tau internalization. We identified three VHH inhibitors of tau uptake: A31, H3-2, and $Z70_{mut1}$. These VHHs compete with the membrane protein LRP1, a major receptor mediating neuronal uptake of tau. A31 and $Z70_{mut1}$ bind to microtubule binding domain repeats, which are involved in the interaction with LRP1. VHH H3-2 is the only VHH from our library that reduces the internalization of both monomeric tau and tau fibrils. VHH H3-2 binds a C-terminal tau epitope with high affinity. Its three-dimensional structure in complex with a tau peptide reveals a unique binding mode as a VHH-swapped dimer. These anti-tau VHHs are interesting tools to study tau prion-like propagation in tauopathies and potentially develop novel biotherapies.

Nigrostriatal iron accumulation in the progression of Parkinson's disease

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Iron deposition in the nigrostriatal system plays a pivotal role in Parkinson's disease (PD) onset and progression. This study explored the time course of nigrostriatal iron accumulation in 54 PD patients at early to moderately advanced stages and 20 age-matched healthy controls. Using multi-echo T2*-MRI and R2* relaxometry, iron content was assessed in the substantia nigra pars compacta (SNpc) and striatum. In vivo findings were contrasted with histological analyses in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism model involving six non-human primates (NHPs) and two controls using Perls' Prussian blue staining. Complementarily, dopaminergic degeneration was quantified by 6-[^{18}F]-fluoro-L-dopa PET in humans and TH immunohistochemistry in NHPs. Results showed progressive iron accumulation in the SNpc correlating with striatal dopaminergic denervation and neuronal loss. Striatal iron followed a V-shaped progression, decreasing initially and increasing later. Iron in the SNpc may serve as a marker of neurodegeneration in PD, while decreased striatal iron may indicate pathological susceptibility to dopaminergic loss.

Urolithin improves α-synuclein aggregation and DNMT1 expression in rotenone model of Parkinson's disease

α-synuclein aggregation is a key hallmark of Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). We examined the multi-targeting effects of urolithin (UA, UB, UC, UD, UE, UM5, and UM6) against α-synuclein aggregation using an *in-silico* and *in-vitro* approach. For *in-silico* analysis, several potential targets were selected like 1XQ8 (α-synuclein monomer), 1H1D (catechol-o-methyltransferase), 2BK3 (monoamine oxidase-B), 3IAM (NADH dehydrogenase), 4I5I (Sirtuin-1), and 5WVO [DNA methyltransferase-1], which play key role in α-synuclein aggregation, levodopa degradation, and mitochondrial dysfunction. In protein-protein docking analysis, 5HF9 (acetylcholinesterase, AChE) was found to interact with 1XQ8 dimer, forming a more stable complex with two additional H-bonds and one salt bridge, which indicates AChE's role as a nucleator in α-synuclein aggregation. In ligand docking and molecular dynamic studies, urolithin-A (UA) formed a more stable complex with 1XQ8, 4I5I, and 5WVO compared to specific inhibitor 1XQ8-ZPD2 and specific activator 4I5I-resveratrol. While other urolithins (UE, UM5, UC, and UD) displayed a more stable complex with 5HF9, 2BK3, 1H1D, and 3IAM compared to specific inhibitor 5HF9-physostigmine, 2BK3-selegiline, 1H1D-BIA, and specific activator 3IAM-resveratrol complexes, respectively. The blood-brain barrier permeability of UA (QPlogBB: −0.97) was predicted to be more than levodopa (QPlogBB: −1.44) and less than rotenone (QPlogBB: 0.08). DNMT1 inhibitor (5-Aza-dC) and rotenone robustly decreased the DNMT1 and α-synuclein expression in Neuro 2A cells which was significantly reversed by UA treatment at 31.25 µM concentration. These findings indicate the potential of urolithins, specifically UA, UC, UD, UE, and UM5 against α-synuclein aggregation.

Expression of anti-amyloid CARs in microglia promotes efficient and selective phagocytosis of Aβ1–42

Christina N. Heiss, Rebecca Riise, Eric Hanse, Stefanie Fruhwürth, Henrik Zetterberg & Andreas Björefeldt

Genetic engineering of microglial cells is a promising therapeutic avenue emerging with advancements in gene delivery techniques. Using a recently developed AAV capsid for efficient in vitro transduction we report the engineering of microglia with CARs (CAR-Mic) targeting phagocytosis of amyloid beta 1–42 (Aβ42). Functional screening of seven CAR constructs in human iPSC-derived microglia revealed up to 6-fold increases in internalized Aβ relative to viral control. CAR-driven phagocytic enhancement was selective for Aβ, dependent on intracellular domain signaling, and was confirmed in primary mouse microglia. These findings highlight the potential of using this approach to target dysfunctional microglia in Alzheimer's disease and other CNS disorders.

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Associations between hormone therapy use and tau accumulation in brain regions vulnerable to Alzheimer's disease

Elucidating the downstream impact of exogenous hormones on the aging brain will have far-reaching consequences for understanding why Alzheimer's disease (AD) predominates in women almost twofold over men. We tested the extent to which menopausal hormone therapy (HT) use is associated with later-life amyloid-β (Aβ) and tau accumulation using PET on $N = 146$ baseline clinically normal women, aged 51 to 89 years. Women were scanned over a 4.5-year (SD, 2.1; range, 1.3 to 10.4) and 3.5-year (SD, 1.5; range, 1.2 to 8.1) period for Aβ and tau, respectively, ~14 years after the initiation of HT. In older women (aged >70 years), HT users exhibited faster regional tau accumulation relative to non-users, localized to the entorhinal cortex and the inferior temporal and fusiform gyri, with an indirect effect of HT on cognitive decline through regional tau accumulation. In younger women (aged <70 years), HT associations with tau accumulation were negligible. Findings are relevant for optimizing menopausal treatment guidelines.

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Senescent Endothelial Cells in Cerebral Microcirculation Are Key Drivers of Age-Related Blood–Brain Barrier Disruption, Microvascular Rarefaction, and Neurovascular Coupling Impairment in Mice

With advancing age, neurovascular dysfunction manifests as impaired neurovascular coupling (NVC), microvascular rarefaction, and blood–brain barrier (BBB) disruption, contributing to vascular cognitive impairment (VCI). Our previous research established a causal link between vascular senescence induced cerebromicrovascular dysfunction and cognitive decline in accelerated aging models. The present study examines whether chronological aging promotes endothelial senescence, adversely affecting neurovascular health, and whether senolytic therapies can enhance neurovascular function and cognitive performance in aged mice. We used transgenic p16-3MR mice to identify and eliminate senescent cells and employed genetic (ganciclovir) and pharmacological (ABT263/Navitoclax) senolytic approaches. Evaluations included spatial memory performance, NVC responses, cortical microvascular density, BBB permeability, and detection of senescent endothelial cells via flow cytometry. Brain endothelial cells exhibited heightened sensitivity to aging-induced senescence, undergoing senescence at a greater rate and earlier than other brain cell types, particularly during middle age. This microvascular endothelial cell senescence was associated with NVC dysfunction, microvascular rarefaction, BBB disruption, and deteriorating cognitive performance. On the other hand, senolytic treatments in aged mice improved NVC responses, BBB integrity, microvascular density, and learning capabilities. Notably, these findings suggest that the most effective time window for senolytic treatment is in middle-aged mice, where early intervention could better prevent neurovascular dysfunction and mitigate age-related cognitive impairment.

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Evaluation of exploratory fluid biomarkers from a phase 1 senolytic trial in mild Alzheimer's disease

Senescent cell accumulation contributes to the progression of age-related disorders including Alzheimer's disease (AD). Clinical trials focused on cellular senescence are in early stages and have yet to establish reliable outcome measures reflecting senescent cell burden or response to senolytics, therapeutics that clear senescent cells. Results from the first open-label trial of senolytics, dasatinib plus quercetin (D+Q), in older adults (N=5) with early AD demonstrated central nervous system penetration of dasatinib and favorable safety and tolerability. Herein, we present exploratory analyses of senescence and AD-associated analytes in blood, cerebrospinal fluid (CSF) and urine from this study in effort to guide biomarker development for future senolytic trials. Immunoassays, mass spectrometry and transcriptomics were performed and changes in analyte levels were assessed from baseline to post-treatment using paired t-tests. Targeted cytokine and chemokine analyses revealed increases in plasma fractalkine and MMP-7 and CSF IL-6 from baseline to post-treatment. Mass spectrometry indicated stable levels of amyloid β and tau proteins in CSF, unchanged urinary metabolites, and modest treatment-associated lipid profile changes. Targeted transcriptomic analysis of peripheral blood mononuclear cells indicated downregulation of inflammatory genes including *FOS, FOSB, IL1β, IL8, JUN, JUNB, PTGS2*. The levels and treatment responses of the analytes identified here may help inform trial design and outcomes for senolytic studies. Independent validation will be necessary to develop standardized biomarker panels across senolytic trials for AD.

Identification of Senomorphic miRNAs in Embryonic Progenitor and Adult Stem Cell–Derived Extracellular Vesicles

Tianpeng Zhang [1 2], Allancer D C Nunes [1 2], Jieun Lee [3], Dana Larocca [3], Giovanni Camussi [4], Sai Kiang Lim [5], Vicky U Bascones [1 2], Luise Angelini [1 2], Ryan D O'Kelly [1 2], Xiao Dong [1 6], Laura J Niedernhofer [1 2], Paul D Robbins [1 2]

Extracellular vesicles (EVs) are secreted by most cell types, transmitting crucial signaling molecules like proteins, small RNAs, and DNA. We previously demonstrated that EVs from murine and human mesenchymal stem cells (MSCs) functioned as senomorphics to suppress markers of senescence and the inflammatory senescence-associated secretory phenotype (SASP) in cell culture and in aged mice. Here we demonstrate that EVs from additional types of human adult stem cells and embryonic progenitor cells have a senomorphic activity. Based on their miRNA profiles showing prevalence in stem cell EVs versus nonstem cell EVs and the number of age-related genes targeted, we identified eight miRNAs as potential senomorphic miRNAs. Analysis of these miRNAs by transfection into etoposide-induced senescent IMR90 human fibroblasts revealed that each of the miRNAs alone regulated specific senescence and SASP markers, but none had complete senomorphic activity. Evaluation of ~300 combinations of miRNAs for senotherapeutic activity identified a senomorphic cocktail of miR-181a-5p, miR-92a-3p, miR-21-5p, and miR-186-5p that markedly reduced the expression of $p16^{INK4a}$, $p21^{Cip1}$, IL-1β, and IL-6 and the percentage of SA-ß-gal-positive cells. Transcriptome analysis identified multiple pathways affected by the miRNA cocktail, including cellular senescence and inhibition of PCAF and HIPK2 in the p53 signaling pathway. Finally, treatment of aged mice with liposomes containing the four miRNA cocktail suppressed markers of senescence and inflammation in multiple tissues. These studies suggest that EVs derived from stem cells suppress senescence and inflammation, at least in part, through miRNAs and that a senomorphic miRNA cocktail could be used to target senescence and inflammation to extend health span.

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Targeting Senescence with Apigenin Improves Chemotherapeutic Efficacy and Ameliorates Age-Related Conditions in Mice

Cellular senescence is a cell fate triggered by stressful stimuli and displays a hypersecretory feature, the senescence-associated secretory phenotype (SASP). Senescent cell burden increases with aging and contributes to age-related organ dysfunction and multiple chronic disorders. In this study, a large scale screening of a natural product library for senotherapeutic candidates is performed. Apigenin, a dietary flavonoid previously reported with antioxidant and anti-inflammatory activities, exhibits capacity for targeting senescent cells as a senomorphic agent. This compound blocks the interactions between ATM/p38MAPK and HSPA8, preventing the transition of an acute stress-associated phenotype (ASAP) toward the SASP. Mechanistically, apigenin targets peroxiredoxin 6 (PRDX6), an intracellular redox-active molecule, suppressing the iPLA2 activity of PRDX6 and disrupting downstream reactions underlying SASP development. Apigenin reduces the severity of cancer cell malignancy promoted by senescent stromal cells in culture, while restraining chemoresistance when combined with chemotherapy in anticancer regimens. In preclinical trials, apigenin improves the physical function of animals with a premature aging-like state, alleviating physical frailty and cognitive impairment. Together, the study demonstrates the feasibility of exploiting a natural compound with senomorphic capacity to achieve geroprotective effects by modulating the SASP, thus providing a baseline for future exploration of natural agents for alleviating age-related conditions.

Senolytic treatment alleviates cochlear senescence and delays age-related hearing loss in C57BL/6J mice

Methods

The senolytic drugs dasatinib and quercetin (D + Q) were used to target senescent cells at different stages of ARHL in C57BL/6J mice. The impact of D + Q treatment on ARHL progression and cochlear degeneration was also assessed. Additionally, the protective effects of D + Q treatment were evaluated in HEI-OC1 auditory cells and cochlear explants. Transcriptomic analysis was conducted on cochlear explants subjected to different treatments.

Results

D + Q treatment at an early stage of ARHL significantly delayed ARHL progression and alleviated cochlear degeneration in male and female C57BL/6J mice. Treatment of mice with normal hearing also mitigated age-related hair cell loss. In HEI-OC1 auditory cells, D + Q treatment exerted protective effects by alleviating the senescence-associated secretory phenotype (SASP). Transcriptomic analysis of cochlear explants revealed that downregulation of inflammatory cytokines and chemokines was involved in the beneficial effects of D + Q treatment against cellular senescence. Mechanistically, D + Q treatment alleviated hair cell senescence via binding to NF-κB and inhibiting its activity.

Conclusion

Senolytics may offer a novel therapeutic strategy for attenuating cochlear senescence and slowing the progression of ARHL.

Elucidating the Role and Mechanism of Alpha-Enolase in Senescent Amelioration via Metabolic Reprogramming

Senescent cells are characterised by increased glycolysis dependence. Normalisation of glycolysis metabolism is essential for senescence amelioration. However, the mechanism of proteins involved in cellular glycolysis metabolism has not been fully elucidated. Here, we identified a candidate compound, an oxazole analogue (KB2764), that can improve senescence. To elucidate the mechanism of the KB2764, we investigated the interacting proteins. KB2764 interacted with alpha-enolase (ENO1) and pyruvate kinase M (PKM), ultimately allowing PKM to phosphorylate ENO1. KB2764 consequently increased mitochondrial ATP production and reduced reliance on glycolysis. Knockdown of the ENO1 experiment in senescent cells demonstrates that regulation of ENO1 activity is a prerequisite for recovery of mitochondrial function. Furthermore, the action of KB2764 extends its application to extend the lifespan of Caenorhabditis elegans. Taken together, our findings reveal a novel mechanism by which senescence is ameliorated through metabolic reprogramming and mitochondrial functional recovery via KB2764-mediated regulation of ENO1 protein activity.

OS-01 Peptide Topical Formulation Improves Skin Barrier Function and Reduces Systemic Inflammation Markers: A Pilot 12-Week Clinical Trial

Methods

A randomized, double-blinded clinical trial involving 60 female volunteers aged 60–90 was conducted over 12 weeks. Participants received either an OS-01 topical formulation or a commercially available moisturizer control formulation. Skin parameters, subjective perceptions, and circulating cytokine levels were assessed. Skin instrumental analysis included transepidermal water loss (TEWL), skin hydration, and pH measurements.

Results

Participants treated with the OS-01 topical formulation displayed significantly improved skin barrier function and hydration compared to the control group. Participant perceptions aligned with objective findings: after 12 weeks, 70% of participants in the OS-01 group noticed an improvement in general skin appearance versus 42% for the control group. The systemic levels of proinflammatory cytokines tended to normalize, with a significant decrease in IL-8 in the blood analysis of participants from the OS-01 group. On the other hand, the control group demonstrated an increase in a few circulating cytokines, particularly TNF-α and IFN-γ. Moreover, GlycanAge analysis measuring participants' biological age suggested the slowing of systemic aging in the group treated with the OS-01 topical formulation.

Conclusion

The study suggests that the OS-01 formulation can impact skin health by improving the skin barrier function, potentially influencing systemic inflammation and biological age. In conclusion, the study supports that targeting skin health may contribute to better longevity outcomes, underscoring the skin's pivotal role in systemic aging and supporting an integrated approach to health management.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Regeneration leads to global tissue rejuvenation in aging sexual planarians

The possibility of reversing the adverse impacts of aging could significantly reduce age-related diseases and improve quality of life in older populations. Here we report that the sexual lineage of the planarian *Schmidtea mediterranea* exhibits physiological decline within 18 months of birth, including altered tissue architecture, impaired fertility and motility, and increased oxidative stress. Single-cell profiling of young and older planarian heads uncovered loss of neurons and muscle, increase of glia, and revealed minimal changes in somatic pluripotent stem cells, along with molecular signatures of aging across tissues. Remarkably, amputation followed by regeneration of lost tissues in older planarians led to reversal of these age-associated changes in tissues both proximal and distal to the injury at physiological, cellular and molecular levels. Our work suggests mechanisms of rejuvenation in both new and old tissues concurring with planarian regeneration, which may provide valuable insights for antiaging interventions.

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SIRT5 safeguards against primate skeletal muscle ageing via desuccinylation of TBK1

Ageing-induced skeletal muscle deterioration contributes to sarcopenia and frailty, adversely impacting the quality of life in the elderly. However, the molecular mechanisms behind primate skeletal muscle ageing remain largely unexplored. Here, we show that SIRT5 expression is reduced in aged primate skeletal muscles from both genders. SIRT5 deficiency in human myotubes hastens cellular senescence and intensifies inflammation. Mechanistically, we demonstrate that TBK1 is a natural substrate for SIRT5. SIRT5 desuccinylates TBK1 at lysine 137, which leads to TBK1 dephosphorylation and the suppression of the downstream inflammatory pathway. Using SIRT5 lentiviral vectors for skeletal muscle gene therapy in male mice enhances physical performance and alleviates age-related muscle dysfunction. This study sheds light on the molecular underpinnings of skeletal muscle ageing and presents the SIRT5–TBK1 pathway as a promising target for combating age-related skeletal muscle degeneration.

Inhibition of Ferroptosis Delays Aging and Extends Healthspan Across Multiple Species

Ferroptosis, a form of iron-dependent cell death, plays a pivotal role in age-related diseases; yet, its impact on cellular senescence and healthspan in mammals remains largely unexplored. This study identifies ferroptosis as a key regulator of cellular senescence, showing that its inhibition can significantly delay aging and extend healthspan across multiple species. During cellular senescence, ferroptosis is progressively exacerbated, marked by increased lipid peroxidation, oxidative stress, and diminished glutathione peroxidase 4 (GPX4) levels. Ferroptosis inducers such as Erastin and RSL3 accelerate senescence; while, inhibitors such as liproxstatin-1 (Lip-1) and ferrostatin-1 (Fer-1) effectively mitigate both chemically and replicatively induced senescence. In vivo, Fer-1 extends lifespan and healthspan in Caenorhabditis elegans, enhances motor function, preserves tissue integrity, and mitigates cognitive decline in both prematurely and naturally aged mice. These effects are attributed to Fer-1's upregulation of GPX4 and inhibition of ferroptosis. Notably, long-term Fer-1 treatment (over 6 months) does not adversely affect body weight or induce aging-related tissue damage but rejuvenates hematological parameters. These findings establish ferroptosis as a critical player in aging dynamics and highlight its inhibition as a promising strategy to extend healthspan and lifespan, providing valuable insights for translational approaches to combat aging and age-related decline.

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PREPRINT

Boosting Cellular Longevity Through Intracellular ATP Modulation

Naci Oz, Hetian Su, Praveen Patnaik, Derek C. Prosser, Vyacheslav M. Labunskyy, Rohil Hameed, Vadim N. Gladyshev, Nan Hao, Alaattin Kaya

Aging results from the gradual accumulation of molecular damage as a result of cellular processes and is characterized by impaired functions, most notably an age-related decline in ATP production. However, the causal relationship between cellular ATP homeostasis and aging has not been established. In this study, we employed a nucleotide transporter from a eukaryotic intracellular parasite to directly alter ATP levels in budding yeast cells and exchange it with the extracellular milieu. We found that ATP depletion significantly shortens lifespan, whereas supplementation of the medium with ATP fully restores it. Analysis of gene expression showed inhibition of catabolic processes suggesting that increased ATP suppresses glucose metabolism. Our results also showed that ATP supplementation leads to lifespan extension. Overall, our study revealed the direct impact of cellular ATP homeostasis on the regulation of lifespan. This work offers new insights into the bioenergetic control of aging and positions energy metabolism as a promising target for longevity interventions.

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Influence of rapamycin on safety and healthspan metrics after one year: PEARL trial results

Design: This 48-week decentralized, double-blinded, randomized, placebo-controlled trial (NCT04488601) evaluated the long-term safety of intermittent low-dose rapamycin in a healthy, normative-aging human cohort. Participants received placebo, 5 mg or 10 mg compounded rapamycin weekly. The primary outcome measure was visceral adiposity (by DXA scan), secondary outcomes were blood biomarkers, and lean tissue and bone mineral content (by DXA scan). Established surveys were utilized to evaluate health and well-being. Safety was assessed through adverse events and blood biomarker monitoring.

Results: Adverse and serious adverse events were similar across all groups. Visceral adiposity did not change significantly ($\eta_p^2 = 0.001$, $p = 0.942$), and changes in blood biomarkers remained within normal ranges. Lean tissue mass ($\eta_p^2 = 0.202$, $p = 0.013$) and self-reported pain ($\eta_p^2 = 0.168$, $p = 0.015$) improved significantly for women using 10 mg rapamycin. Self-reported emotional well-being ($\eta_p^2 = 0.108$, $p = 0.023$) and general health ($\eta_p^2 = 0.166$, $p = 0.004$) also improved for those using 5 mg rapamycin. No other significant effects were observed.

Conclusions: Low-dose, intermittent rapamycin administration over 48 weeks is relatively safe in healthy, normative-aging adults, and was associated with significant improvements in lean tissue mass and pain in women. Future work will evaluate benefits of a broader range of rapamycin doses on healthspan metrics for longevity, and will aim to more comprehensively establish efficacy.

Heales
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PREPRINT

Rapamycin Reduces Mineral Density and Promotes Beneficial Vascular Remodeling in a Murine Model of Severe Medial Arterial Calcification

Peripheral artery disease (PAD) is the narrowing of the arteries that carry blood to the lower extremities. PAD has been traditionally associated with atherosclerosis. However, recent studies have found that thrombotic events triggered by medial arterial calcification (MAC) is the primary cause of chronic limb ischemia below the knee. MAC is localized around the elastic fibers surrounding smooth muscle cells (SMCs) in arteries. Matrix GLA protein (MGP) binds circulating calcium and prevents hydroxyapatite mineral deposition, while also modulating proosteogenic signaling by attenuating BMP-2-mediated activation of *Runx2* gene expression. $Mgp^{-/-}$ mice develop severe MAC and die around 8 weeks after birth due to aortic rupture or heart failure. We previously discovered a rare genetic disease Arterial Calcification due to Deficiency of CD73 (ACDC), in which patients present with extensive MAC in their lower extremity arteries. Using a patient-specific induced pluripotent stem cell model, we found that rapamycin inhibited calcification. Here we investigated whether rapamycin could reduce MAC in vivo using the $Mgp^{-/-}$ murine model. $Mgp^{+/+}$ and $Mgp^{-/-}$ mice received 5mg/kg rapamycin or vehicle. Calcification content was assessed via microCT, and vascular morphology and extracellular matrix content were assessed histologically. Immunostaining and western blot analysis were used to examine SMC phenotype and extracellular matrix content. Rapamycin prolonged $Mgp^{-/-}$ mice lifespan, decreased mineral density in the arteries, maintained SMC contractile phenotype, and improved vessel structure, however, calcification volume was unchanged. $Mgp^{-/-}$ mice with SMC-specific deletion of Raptor or Rictor did not recapitulate treatment with rapamycin. These findings suggest rapamycin promotes beneficial vascular remodeling in vessels with MAC.

ABSTRACT

036 - Rapamycin treatment started during adulthood protects against age-related joint tissue calcification in genetically heterogeneous male mice

Methods: UM-HET3 mice were housed and maintained at the University of Michigan, The Jackson Laboratory, and the University of Texas Health San Antonio. Starting at 9 months of age, mice were fed a diet containing eudragit-encapsulated Rapa (42ppm) or empty eudragit control (placebo) until natural death (median treatment duration: males 2.0-years, females 2.3-years). Upon death, mice were preserved in formalin. Hind limbs were dissected from mice which survived near the median lifespan (**Table 1**) of each group/sex (total sample size=72; n=18/group/sex, equal representation of each study site) and shipped to UW-Madison. MicroCT was performed to evaluate joint tissue calcification. At the time of submission, a subset of samples were processed for histopathological evaluation of cartilage degeneration via OARSI scoring (n=11-16/group/sex). Treatment effects were determined within each sex using student's t-test or Mann-Whitney test, depending on normality of data.

Results: Calcification of medial and lateral menisci, patella, and peri-patellar soft tissues were lower in Rapa-treated males versus placebo (**Figure 1**). There were no differences between placebo and Rapa for females, though females generally displayed lower calcified tissue volume than males. Preliminary OARSI scoring revealed cartilage degeneration in the medial tibia (P=0.11) and femur (P=0.16) were non-significantly lower in Rapa-treated males versus placebo (**Figure 2**). Interestingly, Rapa-treated females tended to have lower OARSI scores in the lateral femur versus placebo (P=0.07), however no treatment effects were seen in other joint compartments with more abundant cartilage degeneration.

Conclusions: We found that despite being longer-lived, male mice receiving Rapa were protected against intra-articular calcification and tended to have lower cartilage degeneration in the medial joint compartment. Interestingly, there were no major effects in female mice, which may be attributable to their low propensity to develop age-related OA compared to male mice. These findings indicate that mTOR-inhibition initiated during adulthood could be a prophylactic treatment option for age-related OA in heterogenous mice, though some of these effects may be sex-specific.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A novel inducible mtDNA mutator mouse model to study mitochondrial dysfunction with temporal and spatial control

Mitochondrial dysfunction is a hallmark of aging and numerous age-related diseases. A wealth of studies supports the accumulation of mitochondrial DNA (mtDNA) mutations as a contributing factor to mitochondrial dysfunction in aging and disease. One of the best models to study the relationship between mtDNA mutations and mitochondrial dysfunction is the mtDNA mutator mouse, which expresses a proofreading-deficient version of mtDNA polymerase-γ (PolgA). Despite its groundbreaking contributions to mitochondrial biology and aging research, this model is limited by the whole-body accumulation of mtDNA mutations, which prevents the investigation of tissue-specific differences in mitochondrial dysfunction. To overcome this limitation, we developed a novel inducible knock-in mtDNA mutator mouse model that allows spatial and temporal control of mtDNA mutations, enabling the precise study of mitochondrial dysfunction in a tissue- and time-specific manner. Here, we report the generation and validation of this novel model through whole-body induction via Cre recombinase. Our data demonstrate that, upon induction, this model recapitulates the phenotype of the original mtDNA mutator mouse manifesting the same behavioral and biochemical alterations. This work establishes the functionality of our model and highlights its value as a powerful tool for studying the impact of mtDNA mutations with enhanced specificity and control.

Heales
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AI-Driven Identification of Exceptionally Efficacious Polypharmacological Compounds That Extend the Lifespan of *Caenorhabditis elegans*

Konstantin Avchaciov, Khalyd J. Clay, Kirill A. Denisov, Olga Burmistrova, Michael Petrascheck, Peter O. Fedichev

Analysis of existing lifespan-extending geroprotective compounds suggested that polypharmacological compounds are the most effective geroprotectors, specifically those that bind multiple biogenic amine receptors. To test this hypothesis, we used graph neural networks to predict polypharmacological geroprotectors and evaluated them in *Caenorhabditis elegans*. Over 70% of the selected compounds extended lifespan, with effect sizes in the top 5% compared to all geroprotectors recorded in the DrugAge database. Thus, our study reveals that rationally designing polypharmacological compounds enables the design of geroprotectors with exceptional efficacy.

Alternate Day Fasting Enhances Intestinal Epithelial Function During Aging by Regulating Mitochondrial Metabolism

Heng Quan, Yao Lu, Yingying Lin, Peng Xue, Yuning Zhang, Yuqi Wang, Weiru Yu, Xiaoya Lin, Wuqi Yang, Cong Lv, Yafei Zhang, Fazheng Ren ✉, Huiyuan Guo ✉

With advancing age, the decline in intestinal stem cell (ISC) function can lead to a series of degenerative changes in the intestinal epithelium, a critical factor that increases the risk of intestinal diseases in the elderly. Consequently, there is an urgent imperative to devise effective dietary intervention strategies that target the alterations in senescent ISCs to alleviate senescence-related intestinal dysfunction. The 28-month-old naturally aging mouse model was utilized to discover that the primary factor contributing to the compromised barrier function and digestive absorption of the small intestine was a decrease in both the number and regenerative capacity of ISCs. The underlying mechanism involves the degeneration of mitochondrial function in ISCs, resulting in insufficient energy supply and decreased metabolic capacity. Additionally, our findings indicate that fasting-refeeding can influence the mitochondrial metabolism of ISCs, and that alternate day fasting (ADF) can facilitate the restoration of both the quantity and regenerative capabilities of ISCs, thereby exhibiting a notable antiaging effect on the small intestine. In conclusion, this study provides new insights into the potential beneficial role of ADF in ameliorating intestinal aging, thereby establishing a foundation for future investigations into dietary interventions aimed at addressing age-related intestinal dysfunction.

Prolonged fasting promotes systemic inflammation and platelet activation in humans: A medically supervised, water-only fasting and refeeding study

Methods

In this study, we investigated the effects of a medically supervised water-only fast (mean duration: 9.8 ± 3.1 days), followed by 5.3 ± 2.4 days of guided refeeding, in 20 middle-aged volunteers (mean age: 52.2 ± 11.8 years; BMI: 28.8 ± 6.4 kg/m^2).

Results

Fasting resulted in a 7.7% mean weight loss and significant increases in serum beta-hydroxybutyrate (BHB), confirming adherence. Untargeted high-dimensional plasma proteomics (SOMAScan, 1,317 proteins) revealed multiple adaptations to PF, including preservation of skeletal muscle and bone, enhanced lysosomal biogenesis, increased lipid metabolism via PPARα signaling, and reduced amyloid fiber formation. Notably, PF significantly reduced circulating amyloid beta proteins Aβ40 and Aβ42, key components of brain amyloid plaques. In addition, PF induced an acute inflammatory response, characterized by elevated plasma C-reactive protein (CRP), hepcidin, midkine, and interleukin 8 (IL-8), among others. A retrospective cohort analysis of 1,422 individuals undergoing modified fasting confirmed increased CRP levels (from 2.8 ± 0.1 to 4.3 ± 0.2 mg/L). The acute phase response, associated with transforming growth factor (TGF)-β signaling, was accompanied by increased platelet degranulation and upregulation of the complement and coagulation cascade, validated by ELISAs in blood and urine.

Conclusions

While the acute inflammatory response during PF may serve as a transient adaptive mechanism, it raises concerns regarding potential cardiometabolic effects that could persist after refeeding. Further investigation is warranted to elucidate the long-term molecular and clinical implications of PF across diverse populations.

Association between Wealth and Mortality in the United States and Europe

RESULTS

Among 73,838 adults (mean [±SD] age, 65±9.8 years), a total of 13,802 (18.7%) died during a median follow-up of 10 years. Across all participants, greater wealth was associated with lower mortality, with adjusted hazard ratios for death (quartile 2, 3, or 4 vs. quartile 1) of 0.80 (95% confidence interval [CI], 0.76 to 0.83), 0.68 (95% CI, 0.65 to 0.71), and 0.60 (95% CI, 0.57 to 0.63), respectively. The gap in survival between the top and bottom wealth quartiles was wider in the United States than in Europe. Survival among the participants in the top wealth quartiles in northern and western Europe and southern Europe appeared to be higher than that among the wealthiest Americans. Survival in the wealthiest U.S. quartile appeared to be similar to that in the poorest quartile in northern and western Europe.

CONCLUSIONS

In cohort studies conducted in the United States and Europe, greater wealth was associated with lower mortality, and the association between wealth and mortality appeared to be more pronounced in the United States than in Europe.

Butter and Plant-Based Oils Intake and Mortality

Yu Zhang, MBBS[1,2]; Katia S. Chadaideh, PhD[2,6]; Yanping Li, PhD[3,4]; et al

Results During up to 33 years of follow-up among 221 054 adults (mean [SD] age at baseline: 56.1 [7.1] years for Nurses' Health Study, 36.1 [4.7] years for Nurses' Health Study II, and 56.3 [9.3] years for Health Professionals Follow-up Study), 50 932 deaths were documented, with 12 241 due to cancer and 11 240 due to CVD. Participants were categorized into quartiles based on their butter or plant-based oil intake. After adjusting for potential confounders, the highest butter intake was associated with a 15% higher risk of total mortality compared to the lowest intake (hazard ratio [HR], 1.15; 95% CI, 1.08-1.22; *P* for trend < .001). In contrast, the highest intake of total plant-based oils compared to the lowest intake was associated with a 16% lower total mortality (HR, 0.84; 95% CI, 0.79-0.90; *P* for trend < .001). There was a statistically significant association between higher intakes of canola, soybean, and olive oils and lower total mortality, with HRs per 5-g/d increment of 0.85 (95% CI, 0.78-0.92), 0.94 (95% CI, 0.91-0.96), and 0.92 (95% CI, 0.91-0.94), respectively (all *P* for trend < .001). Every 10-g/d increment in plant-based oils intake was associated with an 11% lower risk of cancer mortality (HR, 0.89; 95% CI, 0.85-0.94; *P* for trend < .001) and a 6% lower risk of CVD mortality (HR, 0.94; 95% CI, 0.89-0.99; *P* for trend = .03), whereas a higher intake of butter was associated with higher cancer mortality (HR, 1.12; 95% CI, 1.04-1.20; *P* for trend < .001). Substituting 10-g/d intake of total butter with an equivalent amount of total plant-based oils was associated with an estimated 17% reduction in total mortality (HR, 0.83; 95% CI, 0.79-0.86; *P* < .001) and a 17% reduction in cancer mortality (HR, 0.83; 95% CI, 0.76-0.90; *P* < .001).

Conclusions and Relevance In this cohort study, higher intake of butter was associated with increased mortality, while higher plant-based oils intake was associated with lower mortality. Substituting butter with plant-based oils may confer substantial benefits for preventing premature deaths.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Ambient outdoor heat and accelerated epigenetic aging among older adults in the US

EUN YOUNG CHOI AND JENNIFER A. AILSHIRE Authors Info & Affiliations

Extreme heat is well-documented to adversely affect health and mortality, but its link to biological aging—a precursor of the morbidity and mortality process—remains unclear. This study examines the association between ambient outdoor heat and epigenetic aging in a nationally representative sample of US adults aged 56+ (N = 3686). The number of heat days in neighborhoods is calculated using the heat index, covering time windows from the day of blood collection to 6 years prior. Multilevel regression models are used to predict PCPhenoAge acceleration, PCGrimAge acceleration, and DunedinPACE. More heat days over short- and mid-term windows are associated with increased PCPhenoAge acceleration (e.g., $B_{\text{prior7-dayCaution+heat}}$: 1.07 years). Longer-term heat is associated with all clocks (e.g., $B_{\text{prior1-yearExtremecaution+heat}}$: 2.48 years for PCPhenoAge, $B_{\text{prior1-yearExtremecaution+heat}}$: 1.09 year for PCGrimAge, and $B_{\text{prior6-yearExtremecaution+heat}}$: 0.05 years for DunedinPACE). Subgroup analyses show no strong evidence for increased vulnerability by sociodemographic factors. These findings provide insights into the biological underpinnings linking heat to aging-related morbidity and mortality risks.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The impact of particulate matter exposure on global and domain-specific cognitive function: evidence from the Chinese Square Dancer Study

Results: After adjusting for basic socio-demographic factors, a 10 mg/m^3 increase in 3-year exposure to PM_{10} was significantly associated with a decrease in the DSST score by -0.05 (95% confidence interval [CI]: -0.11, 0) and an increase in the TMT-B score by 0.05 (95% CI: 0.01, 0.1). When further adjusting for gaseous pollutants (SO_2, NO_2, and O_3), even stronger associations were observed between 3-year exposure to either $PM_{2.5}$ or PM_{10} and performance in both global cognition and specific cognitive subdomains. Specifically, in the DSST subdomain, a 10 μg/m^3 increase in 1-year PM_{10} exposure was associated with a decrease in the score by -0.10 (95% CI: -0.15, -0.04). Age-stratified analyses further indicated that older participants were consistently more vulnerable to PM exposure. Notably, 3-year exposure to both $PM_{2.5}$ and PM_{10} was linked to declines in DSST scores across both middle-aged and older age groups.

Conclusion: Ambient PM exposure was significantly associated with performance in global cognitive function and specific cognitive domains among Chinese females. Female populations over 65 years old were more susceptible to the adverse effects of $PM_{2.5}$ and PM_{10}. Among the four subdomains, the DSST showed the strongest association with PM exposure, even at earlier ages, suggesting that impaired attention may serve as an early warning sign of cognitive decline.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The rodent aging interventions database (RAID): a data visualization tool for all studies reporting rodent lifespan extension

Maximus V Peto [1,2,✉], Anthony J Floyd [1], Ben Zealley [2], Aubrey D N J de Grey [2]

Numerous studies have investigated the effects of various interventions on the lifespans of mice and rats. The design of future rodent lifespan extension experiments might consider experimental parameters used in earlier investigations, but finding and reviewing all previous experiments requires a substantial resource investment. Additionally, when studied collectively, the results of previous investigations might suggest fundamental mechanisms causing age-related degeneration. Here, we report our efforts to find and aggregate data from all research reports of lifespan extension in mice or rats, which we call the "Rodent Aging Interventions Database" (RAID). We identified studies for inclusion using complex PubMed queries and by nomination from our colleagues in the field. The relevant data from each study was manually extracted and recorded in a table. A publicly available, web-based software tool was then created to enable users to visualize and filter this data in a convenient manner. Our current dataset, covering publications up to October 2022, includes 121 unique studies reporting on 212 distinct intervention protocols that extended lifespan in mice or rats. We intend to periodically update our dataset as new rodent lifespan studies are reported. RAID is publicly available at https://levf.org/raid.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Face photo-based age acceleration predicts all-cause mortality and differs among occupations

Bence Király, Iván Fejes, Csaba Kerepesi

While scientists argue what aging is and what drives aging, it is widely accepted that our face changes drastically with age and that mortality increases in late life. We hypothesize that people of the same age can be biologically older than others and that the human face may reflect accelerated molecular aging. To test this hypothesis we examine the associations of face photo-based age acceleration with mortality and lifestyle. For this purpose, we trained and tested artificial intelligence models on 442,110 photos of famous people. We found that face photo-based age predicts all-cause mortality for middle-aged and older individuals meaning that those age faster based on their face photo die sooner. We also found that, based on face photos, sport is the slowest aging occupation among famous people consistently to previous findings showing the benefits of exercise to epigenetic aging. Overall, we demonstrate that the face photo-base age model approaches biological age in some extent and provides a low-cost and fast complementary measurement for personalized medicine, as well as aging and rejuvenation studies. The model is available for demonstration and academic research purposes at https://photoage.sztaki.hu/.

C. elegans aging research

The Proprotein Convertase BLI-4 Is Required for Axenic Dietary Restriction Mediated Longevity in *Caenorhabditis elegans*

Ping Wu, Lieselot Vandemeulebroucke, Huaihan Cai, Bart P. Braeckman

Dietary restriction (DR) is a well-established method for extending lifespan across various species, including *C. elegans*. Among the different DR regimens, axenic dietary restriction (ADR), in which worms are grown in a nutrient-rich sterile liquid medium, yields the most powerful lifespan extension. However, the molecular mechanisms underlying this longevity phenotype remain largely unexplored. Through a pilot screen of candidate genes, we identified the proprotein convertase BLI-4 as a crucial factor in neurons for modulating lifespan under ADR conditions. BLI-4's role appears to be specific to ADR, as it does not significantly impact longevity under other DR regimens. We further explored the involvement of different *bli-4* isoforms and found that isoforms *b, f, i* and *j* redundantly contribute to the ADR-mediated lifespan extension, while the *bli-4d* isoform is mainly involved in development. Proteomics analysis revealed that the loss of BLI-4 function under ADR conditions specifically downregulates GOLG-2, involved in Golgi complex organization. This gene also partially mediates the longevity effects of BLI-4 under ADR conditions. Our findings highlight the importance of neuronal BLI-4 and its downstream targets in regulating lifespan extension induced by ADR in *C. elegans*.

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PREPRINT

Age deceleration and reversal gene patterns in dauer diapause

Khrystyna Totska, João C.V.V. Barata, Walter Sandt, David H. Meyer, Björn Schumacher

The aging process is characterized by a general decrease in physical functionality and poses the biggest risk factor for a variety of diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders among others. Understanding the naturally evolved mechanisms that slow aging and rejuvenate an animal could reveal important concepts how to prevent age-associated diseases and even revert aging. The *C. elegans* dauer state is a robust and long-lived alternative developmental state that after dauer exit has a normal adult lifespan with fully retained fecundity. To understand how longevity during dauer and rejuvenation following dauer exit is mediated, we characterized the gene expression changes during dauer and upon exit. We assessed how biological age, as determined via BiT Age, a transcriptome aging clock, is affected during dauer and upon dauer exit. During the dauer stage, we measured a decelerated increase in age compared to the chronological age and an age reversal following dauer exit. Transcriptomic analyses revealed major metabolic shifts and enhanced biomolecular degradation that are reversed during exit. Moreover, we show that transcription-blocking lesions can induce lasting transcription stress in dauers that is rapidly resolved by transcription-coupled nucleotide excision repair during dauer exit. Our data provide new insights into the underlying mechanisms of naturally occurring age deceleration and rejuvenation.

Kinome-wide RNAi screening in *Caenorhabditis elegans* reveals new modulators of insulin signaling and longevity

Manish Chamoli [1], Anna Foulger, Prachi Singh, Gordon Lithgow, Arnab Mukhopadhyay

The insulin/IGF-I-like signaling (IIS) pathway is a highly conserved signaling cascade that plays a crucial role in regulating longevity across species. Given its significance in aging, identifying novel kinases interacting with the IIS pathway can provide deeper insights into the mechanisms governing longevity. In this study, we performed a targeted RNAi screening of the *Caenorhabditis elegans* kinome, using dauer formation as a phenotypic readout. We identified several known and novel kinase modulators of the IIS pathway. These hits were enriched with both previously documented and undocumented lifespan regulators. Thermotolerance assays revealed mixed trends, with some kinase inhibitions increasing while others decreasing protection against thermal stress. We observed a positive correlation between thermotolerance and lifespan extension, as well as between dauer formation and lifespan extension, with thermotolerance proving to be a better predictor of longevity. Our findings offer a valuable resource for researchers exploring the IIS pathway and highlight novel, unannotated kinases as potential new therapeutic targets for aging interventions.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Transcriptomic and chromatin accessibility profiling unveils new regulators of heat hormesis in *Caenorhabditis elegans*

Hsin-Yun Chang [1], Sarah E McMurry [1], Sicheng Ma [1], Christian A Mansour [1], Sophia Marie T Schwab [1], Charles G Danko [2], Siu Sylvia Lee [1]

Heat hormesis describes the beneficial adaptations from transient exposure to mild heat stress, which enhances stress resilience and promotes healthy aging. It is thought to be the underlying basis of popular wellness practices like sauna therapy. Despite extensive documentation across species, the molecular basis of the long-term protective effects of heat hormesis remain poorly understood. This study bridges that critical gap through a comprehensive multiomic analysis, providing key insights into the transcriptomic and chromatin accessibility landscapes throughout a heat hormesis regimen adapted in *C. elegans*. We uncover highly dynamic dose-dependent molecular responses to heat stress and reveal that while most initial stress-induced changes revert to baseline, key differences in response to subsequent heat shock challenge are directly linked to physiological benefits. We identify new regulators of heat hormesis, including MARS-1/MARS1, SNPC-4/SNAPc, ELT-2/GATA4, FOS-1/c-Fos, and DPY-27/SMC4, which likely orchestrate gene expression programs that enhance stress resilience through distinct biological pathways. This study advances our understanding of stress resilience mechanisms, points to multiple new avenues of future investigations, and suggests potential strategies for promoting healthy aging through mid-life stress management.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Hyperactive 20S Proteasome Enhances Proteostasis and ERAD in *C. elegans* via degradation of Intrinsically Disordered Proteins

Age-related proteinopathies, including Alzheimer's and Parkinson's disease, are driven by the toxic accumulation of misfolded proteins, particularly intrinsically disordered proteins (IDPs), that overwhelm cellular proteostasis. The proteasome is responsible for the clearance of these proteins, but it is unclear why it fails to do so in these diseases. Here, we report a novel strategy employing a *C. elegans* model with a hyperactive 20S proteasome (α3ΔN) to achieve selective activation. This activation robustly enhances the degradation of IDPs and misfolded proteins, markedly reduces oxidative damage, and significantly improves ER-associated degradation (ERAD). Notably, aggregation-prone substrates, such as endogenous vitellogenins and human alpha-1 antitrypsin (ATZ), are efficiently cleared. Proteomic and transcriptomic reprogramming reveals systemic adaptations characterized by increased protein turnover and enhanced oxidative stress resistance, independent of superoxide dismutases. Strikingly, proteasome hyperactivation extends lifespan and enhances stress resistance independently of known proteostasis pathways including the canonical unfolded protein response mediated by xbp-1. Our findings provide substantial support for a "20S pathway" of proteostasis that alleviates protein aggregation and oxidative stress, offering a promising therapeutic strategy for neurodegenerative diseases

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Environmental NaCl affects *C. elegans* development and aging

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Sodium is an essential nutrient, but is toxic in excess. In humans, excessive dietary sodium can cause high blood pressure, which contributes to age-related diseases including stroke and heart disease. We used *C. elegans* to elucidate how sodium levels influence animal aging. Most experiments on this animal are conducted in standard culture conditions: Nematode Growth Medium (NGM) agar with a lawn of *E. coli*. Here, we report that the supplemental NaCl in standard NGM, 50 mM, accelerates aging and decreases lifespan. For comparison, we prepared NGM with reduced NaCl or excess NaCl. Considering reduced NaCl as a baseline, wild-type worms on standard NGM displayed normal development and fertility but reduced lifespan and health span, indicating toxicity in old animals. The long-lived mutants *daf-2*, *age-1*, and *nuo-6*, cultured on standard NGM, also displayed reduced lifespan. Thus, NaCl in standard NGM accelerates aging in multiple genetic backgrounds. Wild-type worms on excess NaCl displayed delayed development and reduced fertility, and reduced lifespan and health span, indicating toxicity in both young and old animals. These results suggest that young animals are relatively resistant to NaCl toxicity, but that aging causes progressive sensitivity, such that old animals display toxicity to both standard and excess NaCl. We investigated pathways that respond to NaCl. Young animals cultured with excess NaCl activated *gpdh-1*, a specific response to NaCl stress. Old animals cultured with excess NaCl activated *gpdh-1* and *hsp-6*, a reporter for the mitochondrial unfolded protein response. Thus, excess NaCl activates multiple stress response pathways in older animals.

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PREPRINT

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

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

REVIEWS/COMMENTS/ METHODS/EDITORIALS

From geroscience to precision geromedicine: Understanding and managing aging

Guido Kroemer [1,2,3] · Andrea B. Maier [4,5] · Ana Maria Cuervo [6,7,8] · … · Felipe Sierra [18] · Eric Verdin [19] · Carlos López-Otín [1,20] … Show more

Major progress has been made in elucidating the molecular, cellular, and supracellular mechanisms underlying aging. This has spurred the birth of geroscience, which aims to identify actionable hallmarks of aging. Aging can be viewed as a process that is promoted by overactivation of gerogenes, i.e., genes and molecular pathways that favor biological aging, and alternatively slowed down by gerosuppressors, much as cancers are caused by the activation of oncogenes and prevented by tumor suppressors. Such gerogenes and gerosuppressors are often associated with age-related diseases in human population studies but also offer targets for modeling age-related diseases in animal models and treating or preventing such diseases in humans. Gerogenes and gerosuppressors interact with environmental, behavioral, and psychological risk factors to determine the heterogeneous trajectory of biological aging and disease manifestation. New molecular profiling technologies enable the characterization of gerogenic and gerosuppressive pathways, which serve as biomarkers of aging, hence inaugurating the era of precision geromedicine. It is anticipated that, pending results from randomized clinical trials and regulatory approval, gerotherapeutics will be tailored to each person based on their genetic profile, high-dimensional omics-based biomarkers of aging, clinical and digital biomarkers of aging, psychosocial profile, and past or present exposures.

From biology of ageing to geroscience: where will knowledge take us?

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Aurélie Mailliez , Chantal Fradin , Éric Boulanger ✉

Healthy life expectancy is a major challenge in many countries and one of the World Health Organisation's main concerns for the current decade. With different animal models, from invertebrates to mammals, research into the biology of ageing has identified various biological and physiological processes that alter the quality of ageing. Twelve characteristics of ageing have been defined, and the aim of a growing number of studies is to find how to slow down or halt their onset. Unfortunately, the direct transposition of animal models to humans is too often disappointing, and the race to bring anti-ageing products to market is a source of misleading promises. The development of geroscience will enable the identification and validation, with more relevant clinical evidence, of pro-ageing targets to develop anti-ageing therapies and aim for healthy ageing.

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NIA Caenorhabditis Intervention Testing Program: identification of robust and reproducible pharmacological interventions that promote longevity across experimentally accessible, genetically diverse populations

A core facet of the National Institute on Aging's mission is to identify pharmacological interventions that can promote human healthy aging and long life. As part of the comprehensive effort toward that goal, the NIA Division of Biology of Aging established the Caenorhabditis Intervention Testing Program (CITP) in 2013. The C. elegans model (with an ~ 21 day lifespan) has led the field in dissection of longevity genetics and offers features that allow for relatively rapid testing and for the potential elaboration of biological mechanisms engaged by candidate geroprotectants. CITP builds on this foundation by utilizing a genetically diverse set of intervention test strains so that "subjects" represent genetic diversity akin to that that between mouse and humans. Another distinctive aspect of the CITP is a dedicated focus on reproducibility of longevity outcomes as labs at three independent test sites confirm positive outcomes. The overall goal of the Caenorhabditis Intervention Testing Program (CITP) is to identify robust and reproducible pro-longevity interventions affecting genetically diverse cohorts in the Caenorhabditis genus. A strong Data Collection Center supports data collection and dissemination. Pharmacological interventions tested by CITP can be nominated by the general public, directed by in-house screens, or supported by published scientific literature. As of December 2024, CITP tested > 75 compounds and conducted > 725,000 animal assays over 891 trials. We identified 12 compounds that confer a ≥ 20% increase in median lifespan to reproducibly and robustly extend lifespan across multiple strains and labs. Five of these interventions have pro-longevity impact reported in the mouse literature (most CITP positive interventions are not tested yet in mouse). As part of the celebration of the 50th Anniversary of the NIA, we review the development history and accomplishments of the CITP program, and we comment on translation and the promise of advancing understanding of fundamental aging biology that includes the pharmacological intervention/health interface.

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Promoting health and survival through lowered body temperature

Bruno Conti & Rafael de Cabo

Core body temperature (T_b) is a long-established determinant of longevity across species. In this Perspective, we first summarize evidence demonstrating that reducing T_b increases lifespan and that lowered T_b contributes to the antiaging effects of calorie restriction. Next, we discuss recent data that diverge from prior hypotheses on the mechanisms by which T_b affects longevity, suggesting these are limited neither to the thermodynamics of nonenzymatic chemical reactions, nor reduced formation of mitochondrial reactive oxygen species nor lowered metabolic rate. Instead, recent findings in invertebrates show that cold promotes longevity via specific pathways including nutrient sensing and proteostasis, as well as modulating the thermodynamics of proteins and nucleic acids by changing their structure and function, for example, affecting temperature-sensitive ion channels, long-lived temperature-sensitive dauer mutations, base-pair stability and stem–loop RNA structures. Temperature affects the epigenetic signature and inflammation, and lowering T_b can also induce RNA-binding cold shock proteins, activate cold-sensitive kinases and differential splicing to potentially reshape the cellular environment. Finally, we reflect on important future work and the translational potential of temperature management and temperature mimetics.

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Potential downsides of calorie restriction

Anyongqi Wang & John Roger Speakman

Although the potential benefits of calorie restriction on human lifespan remain uncertain, it is currently one of the most extensively researched non-genetic approaches to extending both lifespan and healthspan in animals. Calorie restriction offers numerous health benefits, including a reduced incidence of age-related diseases. However, calorie restriction also produces a range of negative effects, which are not fully documented and require further investigation, particularly in humans. As the viability of calorie restriction in humans will depend on the balance of benefits and detrimental effects, it is crucial to understand the nature of these negative effects and what drives them. In this Review, we summarize the effects of calorie restriction on wound healing, hunger, cold sensitivity, bone health, brain size, cognition, reproductive performance and infection, primarily based on studies of rodents with some data from other species and from humans. Overall, the detrimental effects of calorie restriction seem to stem directly from prioritization of vital functions and downregulation or suppression of energy-demanding processes, which helps preserve survival but can also lead to impaired physiological performance and increased vulnerability to stressors. The exact mechanisms underlying these effects remain unclear. Whether it might be possible to engage in calorie restriction but avoid these negative effects remains uncertain.

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Cancer-treatment-induced accelerated aging in older adult cancer survivors: A call for actions for future perspectives in geriatric oncology

Médéa Locquet [1]

Cancer treatment has significantly improved survival rates, but older adult cancer survivors remain at risk of cancer-treatment-induced late effects such as cardiac complications and second primary cancers. A new hypothesis emerged in the literature suggesting that such late effects can indeed be the manifestation of an accelerated aging process induced by cancer treatments. The cancer-treatment-induced accelerated aging could first arise from clinical and biological manifestations such as frailty, sarcopenia, cognitive impairments, cellular senescence, telomere attrition, and chronic inflammation, paralleling hallmarks of aging. Older adult cancer survivors frequently demonstrated early-onset frailty, sarcopenia, osteoporosis, cognitive impairments, diminished physical function, and increased levels of aging biomarkers compared to cancer-free age-matched older adults. However, existing studies are limited by their narrow focus on specific cancers, the use of single aging outcome measures, and short follow-up durations. A holistic research approach, incorporating comprehensive geriatric assessments and aging biomarkers, is crucial for describing the induced health burden and the mechanisms underlying these induced aging vulnerabilities. Addressing these gaps through large-scale longitudinal studies could lead to personalized interventions, improved treatment protocols, and supportive care strategies in older adult cancer survivors. Such efforts will enhance quality of life, promote healthy aging trajectories, and mitigate societal and economic burdens. To this end, concrete actions, such as establishing international consortia that include patient advocacy, are encouraged. Efforts should also include developing a centralized, registry-based repository for clinical and biological aging outcomes.

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Alpha-synuclein in Parkinson's disease: the debate that must go on

Tiago F. Outeiro [a,b,c,d]

I read with great interest and respect, the point of view by Espay and collagues entitled "The α-synuclein seed amplification assay: Interpreting a test of Parkinson's pathology" [1]. I have been working in the field of alpha-synuclein (aSyn) biology and pathobiology for quite some time now, and I am always interested in understanding the ideas circulating in the field. I admire Espay and all the other co-authors for their critical assessment of current short-comings in the field. I admit, I also share the concern that not all our current ideas fit perfectly, and that we must continue our scientific quest for understanding the role of aSyn in Parkinson's disease (PD) and related synucleinopathies. However, we also cannot disregard a wealth of evidence that implicates aSyn as a central player in PD – for the sake of fairness, I highlight the strongest evidence, from genetic studies: (i) several point mutations are linked with familial forms of the disease (for example, see Refs. [2,3]).; multiplications on the *SNCA* gene are associated with familial forms of PD [4]; several genome-wide association studies have consistently identified the *SNCA* gene as a risk factor for PD [5].

The interplay of iron, oxidative stress, and α-synuclein in Parkinson's disease progression

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The irreversible degeneration of dopamine neurons induced by α-synuclein (α-syn) aggregation in the substantia nigra is the central pathological feature of Parkinson's disease (PD). Neuroimaging and pathological autopsy studies consistently confirm significant iron accumulation in the brain of PD patients, suggesting a critical role for iron in disease progression. Current research has established that iron overload induces ferroptosis in dopaminergic neurons, evidence indicates that the impact of iron on PD pathology extends beyond ferroptosis. Iron also plays a regulatory role in modulating α-syn, affecting its aggregation, spatial conformation, post-translational modifications, and mRNA stability. Iron-induced α-syn aggregation can contribute to dopaminergic neurodegeneration through additional mechanisms, potentially creating a feedback loop in which α-syn further enhances iron accumulation, thus perpetuating a vicious cycle of neurotoxicity. Given α-syn's intrinsically disordered structure, targeting iron metabolism presents a promising therapeutic strategy for PD. Therefore, the development of iron chelators, alone or in combination with other therapeutic drugs, may offer a beneficial approach to alleviating PD symptoms and slowing disease progression.

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Biological effects of pathologies in Lewy body diseases: why timing matters

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Abstract

The emergence of promising biomarkers of α-synuclein Lewy pathology has led to new biological definitions and staging systems for Parkinson's disease and dementia with Lewy bodies. These research frameworks aim to enhance patient selection for studies of biomarkers and disease-modifying therapies. Building on approaches developed for Alzheimer's disease, these new frameworks focus on hallmark neuropathological findings in Lewy body diseases, including abnormal α-synuclein aggregates and neurodegeneration, particularly nigrostriatal dopaminergic loss. Understanding the temporal inter-relationships between Lewy pathology, Alzheimer's disease, and other co-pathologies and symptom manifestation is central to any biological staging system. Neuropathological and in vivo evidence demonstrates substantial temporal and biological heterogeneity in the progression of clinical and pathological events across Lewy body disorders, highlighting knowledge gaps. Staging systems must incorporate this evidence into a nuanced conceptual framework of biological progression. Such revision will be crucial for the appropriate selection of participants and correct timing of targeted interventions in clinical research.

NAD augmentation as a disease-modifying strategy for neurodegeneration

Christian Dölle [1], Charalampos Tzoulis [2]

Neurodegenerative diseases (NDDs) pose a significant and rapidly growing global health challenge, but there are no effective therapies to delay or halt progression. In recent years augmentation of nicotinamide adenine dinucleotide (NAD) has emerged as a promising disease-modifying strategy that targets multiple key disease pathways across multiple NDDs, such as mitochondrial dysfunction, energy deficits, proteostasis, and neuroinflammation. Several early clinical trials of NAD augmentation have been completed, and many more are currently underway, reflecting the growing optimism and urgency within the field. We discuss the rationale and evolving therapeutic landscape of NAD augmentation. We argue that, to fully realize its therapeutic potential, it is essential to determine the specific contexts in which NAD supplementation is most effective and to address crucial knowledge gaps.

A Comprehensive Review of the Role of UV Radiation in Photoaging Processes Between Different Types of Skin

Ultraviolet (UV) radiation significantly contributes to photoaging, with its effects varying among different Fitzpatrick skin types. Light skin (Types I-III) has a natural sun protection factor (SPF) of only 3.3, making it particularly vulnerable to DNA damage, collagen degradation, and skin cancer. Darker skin (Types IV-VI) has a natural SPF of 13.4, providing greater photoprotection while elevating the risk of post-inflammatory hyperpigmentation and delaying skin cancer diagnosis. UVA penetrates deep into the dermis, promoting collagen degradation, whereas UVB causes DNA mutations, increasing the risk of cancer. Eumelanin in darker skin mitigates oxidative stress, while pheomelanin in lighter skin functions as a pro-oxidant, increasing vulnerability to photoaging. Although incidence rates are lower, melanoma is identified at more advanced stages in those with darker skin, resulting in poorer outcomes. Protective measures, such as broad-spectrum sunscreens, antioxidants, and hydration, are crucial for all skin types but necessitate customized strategies. Individuals with lighter skin benefit from SPF 50+ and DNA-repairing compounds, whereas those with darker complexion necessitate SPF 30-50 and pigmentation-focused skincare. Comprehending the biological mechanisms and variations in UV damage facilitates the creation of customized photoprotection solutions, enhancing skin health and mitigating long-term UV-related issues for all skin types.

Transposon expression and repression in skeletal muscle

Matthew J Borok [1], Louai Zaidan [2], Frederic Relaix [3 4 5 6]

Transposons and their derivatives make up a major proportion of the human genome, but they are not just relics of ancient genomes. They can still be expressed, potentially affecting the transcription of adjacent genes, and can sometimes even contribute to their coding sequence. Active transposons can integrate into new sites in the genome, potentially modifying the expression of nearby loci and leading to genetic disorders. In this review, we highlight work exploring the expression of transposons in skeletal muscles and transcriptional regulation by the KRAB-ZFP/KAP1/SETDB1 complex. We next focus on specific cases of transposon insertion causing phenotypic variation and distinct muscular dystrophies, as well as the implication of transposon expression in immune myopathies. Finally, we discuss the dysregulation of transposons in facioscapulohumeral dystrophy and aging.

Promoting collagen synthesis: a viable strategy to combat skin ageing

Skin ageing is a complex physiological process primarily characterised by the deepening of wrinkles and the sagging of the skin. Collagen is essential for maintaining skin elasticity and firmness. As skin ages, it experiences structural and functional changes in collagen, including a decrease in collagen synthesis and an increase in collagen hydrolysis. Thus, promoting collagen synthesis represents a practical strategy for mitigating skin ageing. This review systematically described the functions, classifications and biosynthesis process of collagen, as well as its role in skin ageing. Additionally, the major signalling pathways and targets associated with collagen synthesis were also discussed. More importantly, the review provided a detailed summary of natural products with collagen synthesis-promoting effects and highlighted small molecule compounds with potential anti-ageing activity, especially PPARδ agonists. The relevant content offers potential targets and lead compounds for the development of anti-skin ageing therapies.

Aptamers as Diagnostic and Therapeutic Agents for Aging and Age-Related Diseases

by Tae-In Park [1], Ah Hyun Yang [1], Bashistha Kumar Kanth [2] and Seung Pil Pack [1,*]

In the 21st century, the demographic shift toward an aging population has posed a significant challenge, particularly with respect to age-related diseases, which constitute a major threat to human health. Accordingly, the detection, prevention, and treatment of aging and age-related diseases have become critical issues, and the introduction of novel molecular recognition elements, called aptamers, has been considered. Aptamers, a class of oligonucleotides, can bind to target molecules with high specificity. In addition, aptamers exhibit superior stability, biocompatibility, and applicability, rendering them promising tools for the diagnosis and treatment of human diseases. In this paper, we present a comprehensive overview of aptamers, systematic evolution of ligands by exponential enrichment (SELEX), biomarkers associated with aging, as well as aptamer-based diagnostic and therapeutic platforms. Finally, the limitations associated with predicting and preventing age-related conditions are discussed, along with potential solutions based on advanced technologies and theoretical approaches.

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Drosophila model systems reveal intestinal stem cells as key players in aging

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Affiliations + expand

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Abstract

The intestines play important roles in responding immediately and dynamically to food intake, environmental stress, and metabolic dysfunction, and they are involved in various human diseases and aging. A key part of their function is governed by intestinal stem cells (ISCs); therefore, understanding ISCs is vital. Dysregulation of ISC activity, which is influenced by various cell signaling pathways and environmental signals, can lead to inflammatory responses, tissue damage, and increased cancer susceptibility. Aging exacerbates these dynamics and affects ISC function and tissue elasticity. Additionally, proliferation and differentiation profoundly affect ISC behavior and gut health, highlighting the complex interplay between environmental factors and gut homeostasis. Drosophila models help us understand the complex regulatory networks in the gut, providing valuable insights into disease mechanisms and therapeutic strategies targeting human intestinal diseases.

Pathological and Inflammatory Consequences of Aging

by Mario García-Domínguez [1,2,3]

Aging is a complex, progressive, and irreversible biological process that entails numerous structural and functional changes in the organism. These changes affect all bodily systems, reducing their ability to respond and adapt to the environment. Chronic inflammation is one of the key factors driving the development of age-related diseases, ultimately causing a substantial decline in the functional abilities of older individuals. This persistent inflammatory state (commonly known as “inflammaging”) is characterized by elevated levels of pro-inflammatory cytokines, an increase in oxidative stress, and a perturbation of immune homeostasis. Several factors, including cellular senescence, contribute to this inflammatory milieu, thereby amplifying conditions such as cardiovascular disease, neurodegeneration, and metabolic disorders. Exploring the mechanisms of chronic inflammation in aging is essential for developing targeted interventions aimed at promoting healthy aging. This review explains the strong connection between aging and chronic inflammation, highlighting potential therapeutic approaches like pharmacological treatments, dietary strategies, and lifestyle changes.

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Extracellular Vesicles in Aging and Age-Related Diseases. How Important Are They?

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Abstract

Extracellular vesicles (EVs), lipid bilayer-bound particles secreted by cells, have attracted significant research attention for their roles in aging-related disorders, including cardiovascular disease, metabolic dysfunction, cancer, and neurodegeneration. Research shows that EV cargo and function are influenced by factors including age, disease state, exercise, nutrition and sleep, and they may modulate various aging-associated processes such as stem cell renewal, nutrient sensing, cell senescence, mitochondrial function, and insulin resistance. This perspective highlights, for a general audience, a selection of studies of EVs in aging and age-related diseases, and their diverse roles in organ crosstalk. While current evidence indicates that EVs play multiple roles in aging, there are numerous challenges including methodological challenges and limitations, heterogeneous reports of EV cargo, limited reproducibility, and apparent context-dependent effects of EVs and their cargo. Together, this limits the interpretation of these studies. This is proposed that EVs may act as fine-tuners of cellular communication within the broader aging-associated secretome and the importance of standardizing methods are emphasized. Last, future directions for EV research are suggested.

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