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Scientific News
2nd of November 2024
Sven Bulterijs

Business/Conferences/ General news

Nobel prize for aging researcher Gary Ruvkun

Nobel Prize in Physiology or Medicine

The 2024 medicine laureates

The Nobel Assembly at the Karolinska Institutet has decided to award the 2024 Nobel Prize in Physiology or Medicine jointly to Victor Ambros and Gary Ruvkun "for the discovery of microRNA and its role in post-transcriptional gene regulation."

In 1993, they published unexpected findings describing a new level of gene regulation, which turned out to be highly significant and conserved throughout evolution.

Ill. Niklas Elmehed © Nobel Prize Outreach

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Roche tosses out tau prospect, returning rights to UCB 4 years after placing $120M bet

By **Nick Paul Taylor** · Oct 22, 2024 8:30am

Roche sees rapid amyloid clearing in Alzheimer's study, adjusts protocol after patient death

By **Gabrielle Masson** · Oct 30, 2024 11:40am

Free Webinar

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Free webinar

Unlocking Longevity: Aging Hallmarks and Innovative Anti-Aging Strategies

ACS Webinars | November 14, 2024 @ 2:00 PM EST

Aging is marked by a gradual decline of physiological fitness and the accumulation of cellular damage, resulting in reduced function and increased vulnerability to diseases. Over the past 20 years, research and development in the field of aging and anti-aging strategies have rapidly expanded and diversified.

ACS Webinars

MEET THE EXPERTS

Janet Sasso
Information Scientist, CAS, a division of the American Chemical Society

David Sinclair
Professor, Department of Genetics
Paul F. Glenn Center for Biology of Aging Research, Harvard Medical School

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Clinical Scientist-Dentist, Procter & Gamble

Tamara Tchkonia

Upcoming conferences

Aging research articles

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Implausibility of radical life extension in humans in the twenty-first century

S. Jay Olshansky, Bradley J. Willcox, Lloyd Demetrius & Hiram Beltrán-Sánchez

Over the course of the twentieth century, human life expectancy at birth rose in high-income nations by approximately 30 years, largely driven by advances in public health and medicine. Mortality reduction was observed initially at an early age and continued into middle and older ages. However, it was unclear whether this phenomenon and the resulting accelerated rise in life expectancy would continue into the twenty-first century. Here using demographic survivorship metrics from national vital statistics in the eight countries with the longest-lived populations (Australia, France, Italy, Japan, South Korea, Spain, Sweden and Switzerland) and in Hong Kong and the United States from 1990 to 2019, we explored recent trends in death rates and life expectancy. We found that, since 1990, improvements overall in life expectancy have decelerated. Our analysis also revealed that resistance to improvements in life expectancy increased while lifespan inequality declined and mortality compression occurred. Our analysis suggests that survival to age 100 years is unlikely to exceed 15% for females and 5% for males, altogether suggesting that, unless the processes of biological aging can be markedly slowed, radical human life extension is implausible in this century.

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Trends in Healthy Life Years Between 2005 and 2019 in 31 European Countries: The Compression or Expansion of Morbidity?

Jakub Straka [1], Luděk Šídlo [1], Ivana Kulhánová [1 2]

Affiliations + expand

PMID: 39479338 PMCID: PMC11521812 DOI: 10.3389/ijph.2024.1607574

Abstract

Objectives: Our objective was to assess morbidity trends in Europe and to classify European countries based on population ageing theories: the compression, expansion and dynamic equilibrium of morbidity.

Methods: The proportions of healthy life years were calculated for 31 European countries for the period 2005-2019 based on life expectancy values and healthy life years at age 65 years adopted from the Eurostat database. European countries were classified according to morbidity patterns applying the standard deviation distance from the average of relative change method between the selected years.

Results: A large degree of variation in terms of life expectancy and healthy life years at age 65 years was determined between 2005 and 2019. While the life expectancy differences between men and women were consistent across all the European countries, the gender gap concerning healthy life years was more diverse. Approximately one-third of the countries fell into the expansion, compression and dynamic equilibrium categories, respectively.

Conclusion: Significant variations were identified in healthy life year trends across European countries, which underscores the need for preventive strategies.

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PREPRINT

DNAm aging biomarkers are responsive: Insights from 51 longevity interventional studies in humans

Raghav Sehgal, Daniel Borrus, Jessica Kasamato, Jenel F. Armstrong, John Gonzalez, Yaroslav Markov, Ahana Priyanka, Ryan Smith, Natàlia Carreras, Varun B. Dwaraka, DNAm aging biomarkers community, community Longevity interventional studies, Albert Higgins-Chen

Aging biomarkers can potentially allow researchers to rapidly monitor the impact of an aging intervention, without the need for decade-spanning trials, by acting as surrogate endpoints. Prior to testing whether aging biomarkers may be useful as surrogate endpoints, it is first necessary to determine whether they are responsive to interventions that target aging. Epigenetic clocks are aging biomarkers based on DNA methylation with prognostic value for many aging outcomes. Many individual studies are beginning to explore whether epigenetic clocks are responsive to interventions. However, the diversity of both interventions and epigenetic clocks in different studies make them difficult to compare systematically. Here, we curate TranslAGE-Response, a harmonized database of 51 public and private longitudinal interventional studies and calculate a consistent set of 16 prominent epigenetic clocks for each study, along with 95 other DNAm biomarkers that help explain changes in each clock. With this database, we discover patterns of responsiveness across a variety of interventions and DNAm biomarkers. For example, clocks trained to predict mortality or pace of aging have the strongest response across all interventions and show consistent agreement with each other, pharmacological and lifestyle interventions drive the strongest response from DNAm biomarkers, and study population and study duration are key factors in driving responsiveness of DNAm biomarkers in an intervention. Some classes of interventions such as TNF-alpha inhibitors have strong, consistent effects across multiple studies, while others such as senolytic drugs have inconsistent effects. Clocks with multiple sub-scores (i.e. "explainable clocks") provide specificity and greater mechanistic insight into responsiveness of interventions than single-score clocks. Our work can help the geroscience field design future clinical trials, by guiding the choice of interventions, specific subsets of epigenetic clocks to minimize multiple testing, study duration, study population, and sample size, with the eventual aim of determining whether epigenetic clocks can be used as surrogate endpoints.

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PREPRINT

When to Trust Epigenetic Clocks: Avoiding False Positives in Aging Interventions

Daniel S. Borrus, Raghav Sehgal, Jenel Fraij Armstrong, Jessica Kasamoto, John Gonzalez, Albert Higgins-Chen

Recent human studies have suggested that aging interventions can reduce aging biomarkers related to morbidity and mortality risk. Such biomarkers may potentially serve as early, rapid indicators of effects on healthspan. An increasing number of studies are measuring intervention effects on epigenetic clocks, commonly used aging biomarkers based on DNA methylation profiles. However, with dozens of clocks to choose from, different clocks may not agree on the effect of an intervention. Furthermore, changes in some clocks may simply be the result of technical noise causing a false positive result. To address these issues, we measured the variability between 6 popular epigenetic clocks across a range of longitudinal datasets containing either an aging intervention or an age-accelerating event. We further compared them to the same clocks re-trained to have high test-retest reliability. We find the newer generation of clocks, trained on mortality or rate-of-aging, capture aging events more reliably than those clocks trained on chronological age, as these show consistent effects (or lack thereof) across multiple clocks including high-reliability versions, and including after multiple testing correction. In contrast, clocks trained on chronological age frequently show sporadic changes that are not replicable when using high-reliability versions of those same clocks, or when using newer generations of clocks and these results do not survive multiple-testing correction. These are likely false positive results, and we note that some of these clock changes were previously published, suggesting the literature should be re-examined. This work lays the foundation for future clinical trials that aim to measure aging interventions with epigenetic clocks, by establishing when to attribute a given change in biological age to a bona fide change in the aging process.

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PREPRINT

Methylation Clocks Do Not Predict Age or Alzheimer's Disease Risk Across Genetically Admixed Individuals

Sebastián Cruz-González, Esther Gu, Lissette Gomez, Makaela Mews, Jeffery M. Vance, Michael L. Cuccaro, Mario R. Cornejo-Olivas, Briseida E. Feliciano-Astacio, Goldie S. Byrd, Jonathan L. Haines, Margaret A. Pericak-Vance, Anthony J. Griswold, William S. Bush, John A. Capra

Epigenetic clocks that quantify rates of aging from DNA methylation patterns across the genome have emerged as a potential biomarker for risk of age-related diseases, like Alzheimer's disease (AD), and environmental and social stressors. However, methylation clocks have not been validated in genetically diverse cohorts. Here we evaluate a set of methylation clocks in 621 AD patients and matched controls from African American, Hispanic, and white cohorts. The clocks are less accurate at predicting age in genetically admixed individuals, especially those with substantial African ancestry, than in the white cohort. The clocks also do not consistently identify age acceleration in admixed AD cases compared to controls. Methylation QTL (meQTL) commonly influence CpGs in clocks, and these meQTL have significantly higher frequencies in African genetic ancestries. Our results demonstrate that methylation clocks often fail to predict age and AD risk beyond their training populations and suggest avenues for improving their portability.

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PREPRINT

AgeML:Age modeling with Machine Learning

Jorge Garcia Condado, Iñigo Tellaetxe Elorriaga, Jesus M. Cortes, Asier Erramuzpe

An approach to age modeling involves the supervised prediction of age using machine learning from subject features. The derived age metrics are used to study the relationship between healthy and pathological aging in multiple body systems, as well as the interactions between them. We lack a standard for this type of age modeling. In this work we developed AgeML, an OpenSource software for age-prediction from any type of tabular clinical data following well-established and tested methodologies. The objective is to set standards for reproducibility and standardization of reporting in supervised age modeling tasks. AgeML does age modeling, calculates age deltas, the difference between predicted and chronological age, measures correlations between age deltas and factors, visualizes differences in age deltas of different clinical populations and classifies clinical populations based on age deltas. With this software we are able to reproduce published work and unveil novel relationships between body organs and polygenetic risk scores. AgeML is age modeling made easy for standardization and reproducibility.

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A hematology-based clock derived from the Study of Longitudinal Aging in Mice to estimate biological age

Biological clocks and other molecular biomarkers of aging are difficult to implement widely in a clinical setting. In this study, we used routinely collected hematological markers to develop an aging clock to predict blood age and determine whether the difference between predicted age and chronologic age (aging gap) is associated with advanced aging in mice. Data from 2,562 mice of both sexes and three strains were drawn from two longitudinal studies of aging. Eight hematological variables and two metabolic indices were collected longitudinally (12,010 observations). Blood age was predicted using a deep neural network. Blood age was significantly correlated with chronological age, and aging gap was positively associated with mortality risk and frailty. Platelets were identified as the strongest age predictor by the deep neural network. An aging clock based on routinely collected blood measures has the potential to provide a practical clinical tool to better understand individual variability in the aging process.

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A metabolomic profile of biological aging in 250,341 individuals from the UK Biobank

Shiyu Zhang, Zheng Wang, Yijing Wang, Yixiao Zhu, Qiao Zhou, Xingxing Jian, Guihu Zhao, Jian Qiu, Kun Xia, Beisha Tang, Julian Mutz ✉, Jinchen Li ✉ & Bin Li ✉

The metabolomic profile of aging is complex. Here, we analyse 325 nuclear magnetic resonance (NMR) biomarkers from 250,341 UK Biobank participants, identifying 54 representative aging-related biomarkers associated with all-cause mortality. We conduct genome-wide association studies (GWAS) for these 325 biomarkers using whole-genome sequencing (WGS) data from 95,372 individuals and perform multivariable Mendelian randomization (MVMR) analyses, discovering 439 candidate "biomarker - disease" causal pairs at the nominal significance level. We develop a metabolomic aging score that outperforms other aging metrics in predicting short-term mortality risk and exhibits strong potential for discriminating aging-accelerated populations and improving disease risk prediction. A longitudinal analysis of 13,263 individuals enables us to calculate a metabolomic aging rate which provides more refined aging assessments and to identify candidate anti-aging and pro-aging NMR biomarkers. Taken together, our study has presented a comprehensive aging-related metabolomic profile and highlighted its potential for personalized aging monitoring and early disease intervention.

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Effects of testosterone and metformin on the GlycanAge index of biological age and the composition of the IgG glycome

Martina Vinicki [1], Tea Pribić [1], Frano Vučković [1], Azra Frkatović-Hodžić [1], Isaac Plaza-Andrades [2], Francisco Tinahones [3 4], Joseph Raffaele [5 6], José Carlos Fernández-García [# 7 8], Gordan Lauc [# 9 10]

With aging, the body's ability to maintain regular functions declines, increasing susceptibility to age-related diseases. Therapeutic interventions targeting the underlying biological changes of aging hold promise for preventing or delaying multiple age-related diseases. Metformin, a drug commonly used for diabetes treatment, has emerged as a potential gerotherapeutic agent due to its established safety record and preclinical and clinical data on its anti-aging effects. Glycosylation, one of the most common and complex co- and post-translational protein modifications, plays a crucial role in regulating protein function and has been linked to aging and various diseases. Changes in immunoglobulin G (IgG) glycosylation patterns have been observed with age, and these alterations may serve as valuable biomarkers for disease predisposition, diagnosis, treatment monitoring, and overall health assessment. In this study, we analyzed the IgG glycosylation patterns of white men from Europe, aged 29-45 years, under treatment with metformin, testosterone, metformin plus testosterone, and placebo (trial registration number NCT02514629, 2013/07/04), and investigated the longitudinal changes in glycosylation over time. We observed statistically significant differences in the IgG glycome composition between participants on testosterone therapy and placebo, with decreased agalactosylation and increased galactosylation and sialylation. However, metformin therapy did not result in statistically significant changes in glycosylation patterns. These findings contribute to our understanding of the impact of therapeutic interventions on IgG glycosylation and confirm the value of IgG glycosylation as a significant biomarker, capable of assessing biological age using the GlycanAge index and providing insight into overall health compared to chronological age.

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PREPRINT

Systemic extracellular acidification is a hallmark of aging

Eliano dos Santos, Yining Xie, Enyuan Cao, Andrea Foley, Max E. Taylor, Ivan Andrew, George Young, Natalie L. Trevaskis, Helena M. Cochemé

Understanding the critical pathophysiological processes that promote age-related disease is needed to uncover effective targets for preventive medicine. Here, we investigate how extracellular pH changes with age and its impact on longevity, using fly and mouse models. We find that extracellular acidification occurs in flies during aging and correlates to mortality rate. With age, flies also become more susceptible to die from acidotic stress, which can be prevented by alkalotic treatment. Acidification is caused by insufficient acid elimination, linked to downregulation of genes in the fly excretory tract that control pH and ATP production, essential for active secretion initiation. In mice, we show that lymph-drained interstitial fluids acidify with age. Expression of genes, whose pathogenic loss-of-function variants cause tubular acidosis in humans, is decreased in the kidneys of aging mice. Overall, this study sheds light on dysregulated systemic acid-base balance as a conserved pathophysiological mechanism of aging.

Aging by autodigestion

Frank A. DeLano, Geert W. Schmid-Schönbein

The mechanism that triggers the progressive dysregulation of cell functions, inflammation, and breakdown of tissues during aging is currently unknown. We propose here a previously unknown mechanism due to tissue autodigestion by the digestive enzymes. After synthesis in the pancreas, these powerful enzymes are activated and transported inside the lumen of the small intestine to which they are compartmentalized by the mucin/epithelial barrier. We hypothesize that this barrier leaks active digestive enzymes (e.g. during meals) and leads to their accumulation in tissues outside the gastrointestinal tract. Using immune-histochemistry we provide evidence in young (4 months) and old (24 months) rats for significant accumulation of pancreatic trypsin, elastase, lipase, and amylase in peripheral organs, including liver, lung, heart, kidney, brain, and skin. The mucin layer density on the small intestine barrier is attenuated in the old and trypsin leaks across the tip region of intestinal villi with depleted mucin. The accumulation of digestive enzymes is accompanied in the same tissues of the old by damage to collagen, as detected with collagen fragment hybridizing peptides. We provide evidence that the hyperglycemia in the old is accompanied by proteolytic cleavage of the extracellular domain of the insulin receptor. Blockade of pancreatic trypsin in the old by a two-week oral treatment with a serine protease inhibitor (tranexamic acid) serves to significantly reduce trypsin accumulation in organs outside the intestine, collagen damage, as well as hyperglycemia and insulin receptor cleavage. These results support the hypothesis that the breakdown of tissues in aging is due to autodigestion and a side-effect of the fundamental requirement for digestion.

Association between prescription drugs and all-cause mortality risk in the UK population

Jonas Morin [1], Yves Rolland [2], Heike A Bischoff-Ferrari [2 3], Alejandro Ocampo [1 4], Kevin Perez [1]

Although most drugs currently approved are meant to treat specific diseases or symptoms, it has been hypothesized that some might bear a beneficial effect on lifespan in healthy older individuals, outside of their specific disease indication. Such drugs include, among others, metformin, SGLT2 inhibitors and rapamycin. Since 2006, the UK biobank has recorded prescription medication and mortality data for over 500'000 participants, aged between 40 and 70 years old. In this work, we examined the impact of the top 406 prescribed medications on overall mortality rates within the general population of the UK. As expected, most drugs were linked to a shorter lifespan, likely due to the life-limiting nature of the diseases they are prescribed to treat. Importantly, a few drugs were associated with increased lifespans, including notably Sildenafil, Atorvastatin, Naproxen and Estradiol. These retrospective results warrant further investigation in randomized controlled trials.

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Mifepristone and rapamycin have non-additive benefits for life span in mated female *Drosophila*

Gary N. Landis, Britta Baybutt, Shoham Das, Yijie Fan, Kate Olsen, Karissa Yan & ...show all

The drugs mifepristone and rapamycin were compared for their relative ability to increase the life span of mated female *Drosophila melanogaster*. Titration of rapamycin indicated an optimal concentration of approximately 50 μM, which increased median life span here by average +81%. Meta-analysis of previous mifepristone titrations indicated an optimal concentration of approximately 466 μM, which increased median life span here by average +114%. Combining mifepristone with various concentrations of rapamycin did not produce further increases in life span, and instead reduced life span relative to either drug alone. Assay of maximum midgut diameter indicated that rapamycin was equally efficacious as mifepristone in reducing mating-induced midgut hypertrophy. The mito-QC mitophagy reporter is a previously described green fluorescent protein (GFP)–mCherry fusion protein targeted to the outer mitochondrial membrane. Inhibition of GFP fluorescence by the acidic environment of the autophagolysosome yields an increased red/green fluorescence ratio indicative of increased mitophagy. Creation of a multi-copy mito-QC reporter strain facilitated assay in live adult flies, as well as in dissected midgut tissue. Mifepristone was equally efficacious as rapamycin in activating the mito-QC mitophagy reporter in the adult female fat-body and midgut. The data suggest that mifepristone and rapamycin act through a common pathway to increase mated female *Drosophila* life span, and implicate increased mitophagy and decreased midgut hypertrophy in that pathway.

Senescent cell transplantation into the skin induces age-related peripheral dysfunction and cognitive decline

Cellular senescence is an established cause of cell and tissue aging. Senescent cells have been shown to increase in multiple organs during aging, including the skin. Here we hypothesized that senescent cells residing in the skin can spread senescence to distant organs, thereby accelerating systemic aging processes. To explore this hypothesis, we initially observed an increase in several markers of senescence in the skin of aging mice. Subsequently, we conducted experiments wherein senescent fibroblasts were transplanted into the dermis of young mice and assessed various age-associated parameters. Our findings reveal that the presence of senescent cells in the dermal layer of young mice leads to increased senescence in both proximal and distal host tissues, alongside increased frailty, and impaired musculoskeletal function. Additionally, there was a significant decline in cognitive function, concomitant with increased expression of senescence-associated markers within the hippocampus brain area. These results support the concept that the accumulation of senescent cells in the skin can exert remote effects on other organs including the brain, potentially explaining links between skin and brain disorders and diseases and, contributing to physical and cognitive decline associated with aging.

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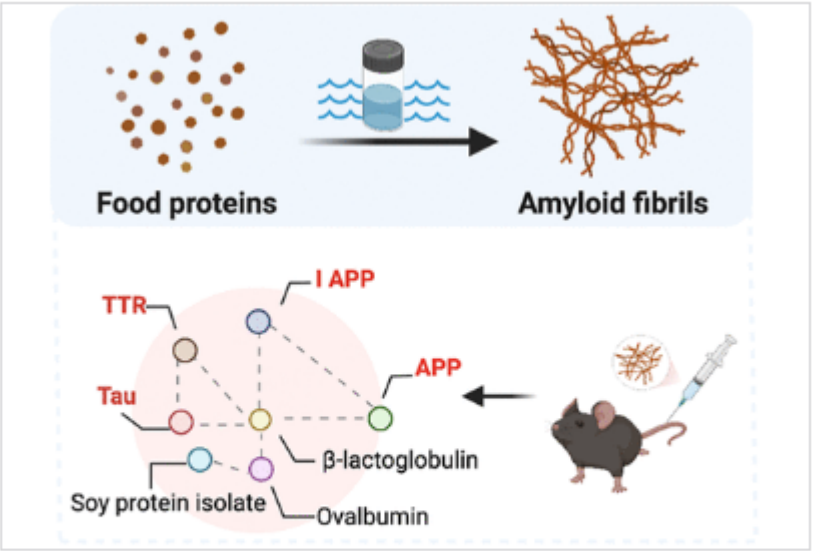
Exogenous Amyloid Fibrils Can Cause Significant Upregulation of Neurodegenerative Disease Proteins

Xihua Liu, Wenzhe Jia, Yapeng Fang*, and Yiping Cao*

Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, are associated with the formation of amyloid fibrils. In familial cases, the mutant causative genes accentuate disease progression through overexpression or misfolding of amyloidogenic proteins. Besides, considerable amyloidosis cases arise from external factors, but their origin and mechanisms are not yet fully understood. Herein, we found that amyloid fibrils generated from egg and milk proteins, in addition to their nutritional effects to intestinal cells, can selectively reduce the viability of nervous cells as well as pancreatic islet cells. In contrast, soy protein amyloid fibrils lacked cytotoxicity to the aforementioned cells. This protein source and cell type-dependent cytotoxicity are demonstrated to be associated with the significant upregulation of amyloidogenic proteins. The finding was also confirmed by the vein injection of beta-lactoglobulin fibrils to mice, exhibiting the pronounced upregulations of amyloid beta$_{1-42}$ (Aβ_{1-42}) and islet amyloid polypeptide in vivo. The study therefore provides insight into the health implications of exogenous amyloid fibrils.



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PREPRINT

Endogenous neuronal DNA double-strand breaks are not sufficient to drive brain aging and neurodegeneration

Sarah Cohen, Laura Cheradame, Karishma J. B. Pratt, Sarah Collins, Ashlie Barillas, Annika Carlson, Vijay Ramani, Gaëlle Legube, Saul A. Villeda, R. Dyche Mullins, Bjoern Schwer

Loss of genomic information due to the accumulation of somatic DNA damage has been implicated in aging and neurodegeneration. Somatic mutations in human neurons increase with age, but it is unclear whether this is a cause or a consequence of brain aging. Here, we clarify the role of endogenous, neuronal DNA double-strand breaks (DSBs) in brain aging and neurodegeneration by generating mice with post-developmental inactivation of the classical non-homologous end-joining (C-NHEJ) core factor Xrcc4 in forebrain neurons. Xrcc4 is critical for the ligation step of C-NHEJ and has no known function outside of DSB repair. We find that, unlike their wild-type counterparts, C-NHEJ-deficient neurons accumulate high levels of DSB foci with age, indicating that neurons undergo frequent DSBs that are typically efficiently repaired by C-NHEJ across their lifespan. Genome-wide mapping reveals that endogenous neuronal DSBs preferentially occur in promoter regions and other genic features. Analysis of 3-D genome organization shows intra-chromosomal clustering and loop extrusion of neuronal DSB regions. Strikingly, however, DSB accumulation caused by loss of C-NHEJ induces only minor epigenetic alterations and does not significantly affect gene expression, 3-D genome organization, or mutational outcomes at neuronal DSBs. Despite extensive aging-associated accumulation of neuronal DSBs, mice with neuronal Xrcc4 inactivation do not show neurodegeneration, neuroinflammation, reduced lifespan, or impaired memory and learning behavior. We conclude that the formation of spontaneous neuronal DSBs caused by normal cellular processes is insufficient to cause brain aging and neurodegeneration, even in the absence of C-NHEJ, the principal neuronal DSB repair pathway.

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PREPRINT

Mosaic Regulation of Stress Pathways Underlies Senescent Cell Heterogeneity

Roberto A. Avelar, Thomas Duffield, Cyril Lagger, Nikita Krstevska, Marian Breuer, João Pedro de Magalhães

Cellular senescence (CS) and quiescence (CQ) are stress responses characterised by persistent and reversible cell cycle arrest, respectively. These phenotypes are heterogeneous, dependent on the cell type arrested and the insult inciting arrest. Because a universal biomarker for CS has yet to be identified, combinations of senescence-associated biomarkers linked to various biological stress responses including lysosomal activity (β-galactosidase staining), inflammation (senescence-associated secretory phenotypes, SASPs), and apoptosis (senescent cell anti-apoptotic pathways) are used to identify senescent cells.

Using in vitro human bulk RNA-seq datasets, we find that senescent states enrich for various stress responses in a cell-type, temporal, and insult-dependent manner. We further demonstrate that various gene signatures used to identify senescent cells in the literature also enrich for stress responses, and are inadequate for universally and exclusively identifying senescent samples.

Genes regulating stress responses – including transcription factors and genes controlling chromatin accessibility – are contextually differentially expressed, along with key enzymes involved in metabolism across arrest phenotypes. Additionally, significant numbers of SASP proteins can be predicted from senescent cell transcriptomes and also heterogeneously enrich for various stress responses in a context-dependent manner.

We propose that 'senescence' cannot be meaningfully defined due to the lack of underlying preserved biology across senescent states, and CS is instead a mosaic of stress-induced phenotypes regulated by various factors, including metabolism, TFs, and chromatin accessibility. We introduce the concept of Stress Response Modules, clusters of genes modulating stress responses, and present a new model of CS and CQ induction conceptualised as the differential activation of these clusters.

Mitochondrial fatty acid oxidation drives senescence

Shota Yamauchi [1 2], Yuki Sugiura [3], Junji Yamaguchi [4 5], Xiangyu Zhou [1 2], Satoshi Takenaka [1 6], Takeru Odawara [1], Shunsuke Fukaya [1], Takao Fujisawa [1 6], Isao Naguro [1], Yasuo Uchiyama [5], Akiko Takahashi [2], Hidenori Ichijo [1 6]

Cellular senescence is a stress-induced irreversible cell cycle arrest involved in tumor suppression and aging. Many stresses, such as telomere shortening and oncogene activation, induce senescence by damaging nuclear DNA. However, the mechanisms linking DNA damage to senescence remain unclear. Here, we show that DNA damage response (DDR) signaling to mitochondria triggers senescence. A genome-wide small interfering RNA screen implicated the outer mitochondrial transmembrane protein BNIP3 in senescence induction. We found that BNIP3 is phosphorylated by the DDR kinase ataxia telangiectasia mutated (ATM) and contributes to an increase in the number of mitochondrial cristae. Stable isotope labeling metabolomics indicated that the increase in cristae enhances fatty acid oxidation (FAO) to acetyl-coenzyme A (acetyl-CoA). This promotes histone acetylation and expression of the cyclin-dependent kinase inhibitor $p16^{INK4a}$. Notably, pharmacological activation of FAO alone induced senescence both in vitro and in vivo. Thus, mitochondrial energy metabolism plays a critical role in senescence induction and is a potential intervention target to control senescence.

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PREPRINT

Comparable anti-ageing efficacies of a multi-ingredient nutraceutical and a senolytic intervention in old mice

Charlotte Brookes, Edward Fielder, Evon Low, Diogo Barardo, Thomas von Zglinicki, Satomi Miwa

Single-ingredient dietary supplements have demonstrated some potential to extend lifespan and improve healthspan; however, the efficacy of defined multi-ingredient nutraceuticals remains underexplored. Senolytic interventions have been successful in reducing multi-morbidity, frailty, and cognitive decline in animal models and are seen as promising anti-ageing interventions in mammals. We compared the effects of a 12-ingredient nutraceutical on mice lifespan and healthspan markers with that of a high efficacy senolytic intervention consisting of a low dose of Navitoclax combined with the specific mitochondrial uncoupler BAM15. Both interventions were started at old age (20 months). The supplement was given daily until the end of the experiment (30 months of age), but the senolytic intervention consisted of two short (5 days each) rounds of treatment at 20 and 23 months of age. Despite late onset, both interventions increased median lifespan similarly by around 20% over controls. The senolytic intervention significantly reduced frailty progression and improved cognitive function after the second round of treatment, but without subsequent treatment, these effects appeared to wane at later ages. The multi-ingredient supplement tended to reduce frailty progression steadily with time, albeit not significant, and maintained cognitive function. Mechanistically, *in vitro*, there was no evidence of senolytic activity of the multi-ingredient nutraceutical as a whole nor of its individual ingredients. Continuous multi-ingredient dietary supplementation shows promise in achieving comparable anti-ageing efficacy as a senolytic intervention.

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Aging at scale:Younger dogs and larger breeds from the Dog Aging Project show accelerated epigenetic aging

Dogs exhibit striking within-species variability in lifespan, with smaller breeds often living more than twice as long as larger breeds. This longevity discrepancy also extends to health and aging–larger dogs show higher rates of age-related diseases. Despite this well-established phenomenon, we still know little about the biomarkers and molecular mechanisms that might underlie breed differences in aging and survival. To address this gap, we generated an epigenetic clock using DNA methylation from over 3 million CpG sites in a deeply phenotyped cohort of 864 companion dogs from the Dog Aging Project, including some dogs sampled annually for 2-3 years. We found that the largest breed size tends to have epigenomes that are, on average, 0.37 years older per chronological year compared to the smallest breed size. We also found that higher residual epigenetic age was significantly associated with increased mortality risk, with dogs experiencing a 34% higher risk of death for each year increase in residual epigenetic age. These findings not only broaden our understanding of how aging manifests within a diverse species but also highlight the significant role that demographic factors play in modulating the biological mechanisms underlying aging. Additionally, they highlight the utility of DNA methylation as both a biomarker for healthspan-extending interventions, a mortality predictor, and a mechanism for understanding inter-individual variation in aging in dogs.

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The companion dog as a model for inflammaging: a cross-sectional pilot study

Inflammaging, the chronic, progressive proinflammatory state associated with aging, has been associated with multiple negative health outcomes in humans. The pathophysiology of inflammaging is complex; however, it is often characterized by high serum concentrations of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and C-reactive protein (CRP). Few studies have evaluated the effects of age on inflammatory cytokines in companion dogs, and most of these studies included dogs of a single breed. In this cross-sectional study, we measured multiple circulating inflammatory markers and hematological parameters in banked serum samples from 47 healthy companion dogs of various breeds enrolled in the Dog Aging Project. Using univariate linear models, we investigated the association of each of these markers with age, sex, body weight, and body condition score (BCS), a measure of obesity in the dog. Serum IL-6, IL-8, and TNF-α concentrations were all positively associated with age. Lymphocyte count was negatively associated with age. Platelet count had a negative association with body weight. IL-2, albumin, cholesterol, triglyceride, bilirubin, S100A12, and NMH concentrations were not associated with age, weight, BCS, or sex after adjustment for multiple comparisons. Our findings replicate previous findings in humans, including increases in IL-6 and TNF-α with age, giving more evidence to the strength of the companion dog as a model for human aging.

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Cancer Prevalence across Vertebrates

Zachary T. Compton; Walker Mellon; Valerie K. Harris; Shawn Rupp; Diego Mallo; Stefania E. Kapsetaki; Mallory Wilmot; Ryan Kennington; Kathleen Noble; Cristina Baciu; Lucia N. Ramirez; Ashley Peraza; Brian Martins; Sushil Sudhakar; Selin Aksoy; Gabriela Furukawa; Orsolya Vincze; Mathieu Giraudeau; Elizabeth G. Duke; Simon Spiro; Edmund Flach; Hannah Davidson; Christopher I. Li; Ashley Zehnder; Trevor A. Graham; Brigid V. Troan; Tara M. Harrison; Marc Tollis; Joshua D. Schiffman; C. Athena Aktipis; Lisa M. Abegglen; Carlo C. Maley; Amy M. Boddy

Cancer is pervasive across multicellular species, but what explains the differences in cancer prevalence across species? Using 16,049 necropsy records for 292 species spanning three clades of tetrapods (amphibians, sauropsids, and mammals), we found that neoplasia and malignancy prevalence increases with adult mass (contrary to Peto's paradox) and somatic mutation rate but decreases with gestation time. The relationship between adult mass and malignancy prevalence was only apparent when we controlled for gestation time. Evolution of cancer susceptibility appears to have undergone sudden shifts followed by stabilizing selection. Outliers for neoplasia prevalence include the common porpoise (<1.3%), the Rodrigues fruit bat (<1.6%), the black-footed penguin (<0.4%), ferrets (63%), and opossums (35%). Discovering why some species have particularly high or low levels of cancer may lead to a better understanding of cancer syndromes and novel strategies for the management and prevention of cancer.

Significance: Evolution has discovered mechanisms for suppressing cancer in a wide variety of species. By analyzing veterinary necropsy records, we can identify species with exceptionally high or low cancer prevalence. Discovering the mechanisms of cancer susceptibility and resistance may help improve cancer prevention and explain cancer syndromes.

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Dietary restriction impacts health and lifespan of genetically diverse mice

Caloric restriction extends healthy lifespan in multiple species[1]. Intermittent fasting, an alternative form of dietary restriction, is potentially more sustainable in humans, but its effectiveness remains largely unexplored[2,3,4,5,6,7,8]. Identifying the most efficacious forms of dietary restriction is key for developing interventions to improve human health and longevity[9]. Here we performed an extensive assessment of graded levels of caloric restriction (20% and 40%) and intermittent fasting (1 and 2 days fasting per week) on the health and survival of 960 genetically diverse female mice. We show that caloric restriction and intermittent fasting both resulted in lifespan extension in proportion to the degree of restriction. Lifespan was heritable and genetics had a larger influence on lifespan than dietary restriction. The strongest trait associations with lifespan included retention of body weight through periods of handling—an indicator of stress resilience, high lymphocyte proportion, low red blood cell distribution width and high adiposity in late life. Health effects differed between interventions and exhibited inconsistent relationships with lifespan extension. 40% caloric restriction had the strongest lifespan extension effect but led to a loss of lean mass and changes in the immune repertoire that could confer susceptibility to infections. Intermittent fasting did not extend the lifespan of mice with high pre-intervention body weight, and two-day intermittent fasting was associated with disruption of erythroid cell populations. Metabolic responses to dietary restriction, including reduced adiposity and lower fasting glucose, were not associated with increased lifespan, suggesting that dietary restriction does more than just counteract the negative effects of obesity. Our findings indicate that improving health and extending lifespan are not synonymous and raise questions about which end points are the most relevant for evaluating aging interventions in preclinical models and clinical trials.

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Plant and Animal Fat Intake and Overall and Cardiovascular Disease Mortality

Bin Zhao, PhD[1,6,7]; Lu Gan, MSc[1,6,7]; Barry I. Graubard, PhD[2]; et al

The analysis included 407 531 men and women (231 881 [56.9%] male; the mean [SD] age of the cohort was 61.2 [5.4] years). During 8 107 711 person-years of follow-up, 185 111 deaths were ascertained, including 58 526 CVD deaths. After multivariable adjustment (including adjustment for the relevant food sources), a greater intake of plant fat (HRs, 0.91 and 0.86; adjusted ARDs, −1.10% and −0.73%; *P* for trend < .001), particularly fat from grains (HRs, 0.92 and 0.86; adjusted ARDs, −0.98% and −0.71%; *P* for trend < .001) and vegetable oils (HRs, 0.88 and 0.85; adjusted ARDs, −1.40% and −0.71%; *P* for trend < .001), was associated with a lower risk for overall and CVD mortality, respectively, comparing the highest to the lowest quintile. In contrast, a higher intake of total animal fat (HRs, 1.16 and 1.14; adjusted ARDs, 0.78% and 0.32%; *P* for trend < .001), dairy fat (HRs, 1.09 and 1.07; adjusted ARDs, 0.86% and 0.24%; *P* for trend < .001), or egg fat (HRs, 1.13 and 1.16; adjusted ARDs, 1.40% and 0.82%; *P* for trend < .001) was associated with an increased risk for mortality for overall and CVD mortality, respectively, comparing the highest to the lowest quintile. Replacement of 5% energy from animal fat with 5% energy from plant fat, particularly fat from grains or vegetable oils, was associated with a lower risk for mortality: 4% to 24% reduction in overall mortality, and 5% to 30% reduction in CVD mortality.

The findings from this prospective cohort study demonstrated consistent but small inverse associations between a higher intake of plant fat, particularly fat from grains and vegetable oils, and a lower risk for both overall and CVD mortality. A diet with a high intake of animal-based fat, including fat from dairy foods and eggs, was also shown to be associated with an elevated risk for both overall and CVD mortality.

Optimal lifestyle patterns for delaying ageing and reducing all-cause mortality: insights from the UK Biobank

Ce Liu, Zhaoru Yang, Li He, Ya Xiao, Hao Zhao, Ling Zhang, Tong Liu, Rentong Chen, Kai Zhang & Bin Luo

Methods

A prospective cohort study was conducted using data from over half a million UK Biobank participants. Two datasets were created by subjective and objective measurements of physical activity: the Subjective Physical Activity (SPA) and Objective Physical Activity (OPA) datasets. Lifestyle patterns, including diet habits, exercise levels, and sleep quality, were assessed within these datasets. Biological aging was quantified using validated methods, including Homeostatic Dysregulation, Klemera-Doubal Method Biological Age, Phenotypic Age, and Telomere Length. All-cause mortality data were obtained from the National Health Service. Statistical analyses included weighted linear regression and Cox proportional hazard models, adjusted for a range of covariates.

Results

The findings indicate that, in most cases, maintaining an anti-inflammatory diet, engaging in at least moderate physical activity, and ensuring healthy sleep conditions are associated with delayed physiological aging (Cohen's d ranging from 0.274 to 0.633) and significantly reduced risk of all-cause mortality (HR-SPA: 0.690, 95% CI: 0.538, 0.884; HR-OPA: 0.493, 95% CI: 0.293, 0.828). These effects are particularly pronounced in individuals under 60 years of age and in women. However, it was observed that the level of physical activity recommended by the World Health Organization (600 MET-minutes/week) does not achieve the optimal effect in delaying biological aging. The best effect in decelerating biological aging was seen in the high-level physical activity group (≥ 3000 MET-minutes/week). The study also highlights the potential of biological age acceleration and telomere length as biomarkers for predicting the risk of mortality.

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Reproduction has immediate effects on female mortality, but no discernible lasting physiological impacts: A test of the disposable soma theory

Sharon E Mitchell [# 1], Megan Simpson [# 1], Lena Coulet [1 2], Solenn Gouedard [1 2], Catherine Hambly [1], Juliano Morimoto [3 4], David B Allison [5], John R Speakman [1 6 7 8]

The disposable soma theory (DST) posits that organisms age and die because of a direct trade-off in resource allocation between reproduction and somatic maintenance. DST predicts that investments in reproduction accentuate somatic damage which increase senescence and shortens lifespan. Here, we directly tested DST predictions in breeding and nonbreeding female C57BL/6J mice. We measured reproductive outputs, body composition, daily energy expenditure, and oxidative stress at peak lactation and over lifetime. We found that reproduction had an immediate and negative effect on survival due to problems encountered during parturition for some females. However, there was no statistically significant residual effect on survival once breeding had ceased, indicating no trade-off with somatic maintenance. Instead, higher mortality appeared to be a direct consequence of reproduction without long-term physiological consequences. Reproduction did not elevate oxidative stress. Our findings do not provide support for the predictions of the DST.

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The opposite aging effect to single cell transcriptome profile among cell subsets

Comparing transcriptome profiling between younger and older samples reveals genes related to aging and provides insight into the biological functions affected by aging. Recent research has identified sex, tissue, and cell type-specific age-related changes in gene expression. This study reports the overall picture of the opposite aging effect, in which aging increases gene expression in one cell subset and decreases it in another cell subset. Using the Tabula Muris Senis dataset, a large public single-cell RNA sequencing dataset from mice, we compared the effects of aging in different cell subsets. As a result, the opposite aging effect was observed widely in the genes, particularly enriched in genes related to ribosomal function and translation. The opposite aging effect was observed in the known aging-related genes. Furthermore, the opposite aging effect was observed in the transcriptome diversity quantified by the number of expressed genes and the Shannon entropy. This study highlights the importance of considering the cell subset when intervening with aging-related genes.

C. elegans aging research

High-content phenotypic analysis of a *C. elegans* recombinant inbred population identifies genetic and molecular regulators of lifespan

Arwen W. Gao [1,2,8] · Gaby El Alam [1,8] · Yunyun Zhu [3,8.] … · Riekelt H. Houtkooper [2] · Joshua J. Coon [3,4,5,6] · Johan Auwerx [1,10] … Show more

Lifespan is influenced by complex interactions between genetic and environmental factors. Studying those factors in model organisms of a single genetic background limits their translational value for humans. Here, we mapped lifespan determinants in 85 *C. elegans* recombinant inbred advanced intercross lines (RIAILs). We assessed molecular profiles—transcriptome, proteome, and lipidome—and life-history traits, including lifespan, development, growth dynamics, and reproduction. RIAILs exhibited large variations in lifespan, which correlated positively with developmental time. We validated three longevity modulators, including *rict-1*, *gfm-1*, and *mltn-1*, among the top candidates obtained from multiomics data integration and quantitative trait locus (QTL) mapping. We translated their relevance to humans using UK Biobank data and showed that variants in *GFM1* are associated with an elevated risk of age-related heart failure. We organized our dataset as a resource that allows interactive explorations for new longevity targets.

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PREPRINT

Computer prediction and genetic analysis identifies retinoic acid modulation as a driver of conserved longevity pathways in genetically-diverse *Caenorhabditis* nematodes

Stephen A. Banse, Christine A. Sedore, Anna L. Coleman-Hulbert, Erik Johnson, Brian Onken, David Hall, Erik Segerdell, E. Grace Jones, Yuhua Song, Hadley Osman, Jian Xue, Elena Battistoni, Suzhen Guo, Anna C. Foulger, Madhuri Achanta, Mustafa Sheikh, Theresa Fitzgibbon, John H. Willis, Gavin C. Woodruff, Monica Driscoll, Gordon J. Lithgow, Patrick C. Phillips

Aging is a pan-metazoan process with significant consequences for human health and society—discovery of new compounds that ameliorate the negative health impacts of aging promise to be of tremendous benefit across a number of age-based co-morbidities. One method to prioritize a testable subset of the nearly infinite universe of potential compounds is to use computational prediction of their likely anti-aging capacity. Here we present a survey of longevity effects for 16 compounds suggested by a previously published computational prediction set, capitalizing upon the comprehensive, multi-species approach utilized by the *Caenorhabditis* Intervention Testing Program (CITP). While eleven compounds (aldosterone, arecoline, bortezomib, dasatinib, decitabine, dexamethasone, erlotinib, everolimus, gefitinib, temsirolimus, and thalidomide) either had no effect on median lifespan or were toxic, five compounds (all-trans retinoic acid, berberine, fisetin, propranolol, and ritonavir) extended lifespan in *Caenorhabditis elegans*. These computer predictions yield a remarkable positive hit rate of 30%. Deeper genetic characterization of the longevity effects of one of the most efficacious compounds, the endogenous signaling ligand all-trans retinoic acid (atRA, designated tretinoin in medical products), which is widely prescribed for treatment of acne, skin photoaging and acute promyelocytic leukemia, demonstrated a requirement for the regulatory kinases AKT-1 and AKT-2. While the canonical Akt-target FOXO/DAF-16 was largely dispensable, other conserved Akt-targets (Nrf2/SKN-1 and HSF1/HSF-1), as well as the conserved catalytic subunit of AMPK AAK-2, were all necessary for longevity extension by atRA. Evolutionary conservation of retinoic acid as a signaling ligand and the structure of the downstream effector network of retinoic acid combine to suggest that the all-trans retinoic acid pathway is an ancient metabolic regulatory system that can modulate lifespan. Our results highlight the potential of combining computational prediction of longevity interventions with the power of nematode functional genetics and underscore that the manipulation of a conserved metabolic regulatory circuit by co-opting endogenous signaling molecules is a powerful approach for discovering aging interventions.

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PREPRINT

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

Steffi M Jonk, Alan Nicol, Vicki Chrysostomou, Emma Lardner, Shu-Che Yu, Gustav Stålhammar, Jonathan G Crowston, James R Tribble, Peter Swoboda, Pete A Williams

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

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Longevity biotechnology: bridging AI, biomarkers, geroscience and clinical applications for healthy longevity

The recent unprecedented progress in ageing research and drug discovery brings together fundamental research and clinical applications to advance the goal of promoting healthy longevity in the human population. We, from the gathering at the Aging Research and Drug Discovery Meeting in 2023, summarised the latest developments in healthspan biotechnology, with a particular emphasis on artificial intelligence (AI), biomarkers and clocks, geroscience, and clinical trials and interventions for healthy longevity. Moreover, we provide an overview of academic research and the biotech industry focused on targeting ageing as the root of age-related diseases to combat multimorbidity and extend healthspan. We propose that the integration of generative AI, cutting-edge biological technology, and longevity medicine is essential for extending the productive and healthy human lifespan.

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PREPRINT

Conserved Biological Processes in Partial Cellular Reprogramming: A Comprehensive Review

Roberto A. Avelar , Daniel Palmer , Anton Y. Kulaga , Georg Fuellen *

Partial or transient cellular reprogramming is defined by the limited induction of pluripotency factors without fully de-differentiating cells into a pluripotent state. Comparing in vitro and in vivo mouse studies, and in vitro studies in humans, supported by visualizations of the interconnections among the data, we show consistent patterns in how such reprogramming modulates key biological processes. Generally, it leads to enhanced chromatin accessibility, upregulation of chromatin modifiers, and improved mitochondrial activity. These changes are accompanied by shifts in stress response programs, such as inflammation, autophagy, and cellular senescence, as well as dysregulation of extracellular matrix pathways. We also underscore the challenges in evaluating complex processes like aging and cellular senescence, given the variability in biomarkers used across studies. Overall, we highlight biological processes consistently influenced by reprogramming while noting that some effects are context-dependent, varying according to cell type, species, sex, and the reprogramming method employed. These insights inform future research and therapeutic applications in aging and regenerative medicine.

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The Power of a Complex Systems Perspective to Elucidate Aging

Alan A Cohen, PhD, Marcel G M Olde Rikkert, MD, PhD

It is becoming highly accepted that aging, age-related diseases, and geriatric healthcare can move forward if reductionist research is complemented by integrative research uniting knowledge on specific aging mechanisms, multiple biomedical, social, psychological, lifestyle, and environmental factors and their interactions. In this special issue, we present exciting papers that illustrate how complexity science theory and practice can be applied to aging research and provide a better understanding and quantification of healthy aging and vulnerability to disease. Recent insights on biomarkers, clocks of aging, frailty, and resilience are covered and studied in interaction with a dynamic multiscale perspective. The editorial and closing viewpoint guide you through basic principles of gerontological complexity science and shed light on new research horizons, including innovative systems-based interventions.

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Contextualizing aging clocks and properly describing biological age

Adiv A. Johnson ✉, Maxim N. Shokhirev

Usage of the phrase “biological age” has picked up considerably since the advent of aging clocks and it has become commonplace to describe an aging clock's output as biological age. In contrast to this labeling, biological age is also often depicted as a more abstract concept that helps explain how individuals are aging internally, externally, and functionally. Given that the bulk of molecular aging is tissue-specific and aging itself is a remarkably complex, multifarious process, it is unsurprising that most surveyed scientists agree that aging cannot be quantified via a single metric. We share this sentiment and argue that, just like it would not be reasonable to assume that an individual with an ideal grip strength, VO_2 max, or any other aging biomarker is biologically young, we should be careful not to conflate an aging clock with whole-body biological aging. To address this, we recommend that researchers describe the output of an aging clock based on the type of input data used or the name of the clock itself. Epigenetic aging clocks produce epigenetic age, transcriptomic aging clocks produce transcriptomic age, and so forth. If a clock has a unique name, such as our recently developed epigenetic aging clock CheekAge, the name of the clock can double as the output. As a compromise solution, aging biomarkers can be described as indicators of biological age. We feel that these recommendations will help scientists and the public differentiate between aging biomarkers and the much more elusive concept of biological age.

Bats as instructive animal models for studying longevity and aging

Lisa Noelle Cooper [1], Mohammad Y Ansari [1], Grace Capshaw [2], Alex Galazyuk [1], Amanda M Lauer [3], Cynthia F Moss [2], Karen E Sears [4], Mark Stewart [5], Emma C Teeling [6], Gerald S Wilkinson [7], Rachel C Wilson [8], Thomas P Zwaka [9], Rena Orman [5]

Bats (order Chiroptera) are emerging as instructive animal models for aging studies. Unlike some common laboratory species, they meet a central criterion for aging studies: they live for a long time in the wild or in captivity, for 20, 30, and even >40 years. Healthy aging (i.e., healthspan) in bats has drawn attention to their potential to improve the lives of aging humans due to bat imperviousness to viral infections, apparent low rate of tumorigenesis, and unique ability to repair DNA. At the same time, bat longevity also permits the accumulation of age-associated systemic pathologies that can be examined in detail and manipulated, especially in captive animals. Research has uncovered additional and critical advantages of bats. In multiple ways, bats are better analogs to humans than are rodents. In this review, we highlight eight diverse areas of bat research with relevance to aging: genome sequencing, telomeres, and DNA repair; immunity and inflammation; hearing; menstruation and menopause; skeletal system and fragility; neurobiology and neurodegeneration; stem cells; and senescence and mortality. These examples demonstrate the broad relevance of the bat as an animal model and point to directions that are particularly important for human aging studies.

Experimental models as a tool for research on sarcopenia: A narrative review

Janire Alonso-Puyo [1], Oihane Izagirre-Fernandez [1], Olatz Crende [2], Asier Valdivia [2], Patricia García-Gallastegui [3], Begoña Sanz [4]

Sarcopenia is a musculoskeletal disorder related to muscle mass and function; as the worldwide population ages, its growing prevalence means a decline in quality of life and an increased burden for public health systems. As sarcopenia is a reversible condition, its early diagnosis is of utmost importance. Consensus definitions and diagnosis protocols for sarcopenia have been evolving for a long time, and the identification of molecular pathways subjacent to sarcopenia is a growing research area. The use of liquid biopsies to identify circulating molecules does not provide information about specific regulatory pathways or biomarkers in relevant tissue, and the use of skeletal muscle biopsies from older people has many limitations. Complementary tools are therefore necessary to advance the knowledge of relevant molecular aspects. The development of experimental models, such as animal, cellular, or bioengineered tissue, together with knock-in or knock-out strategies, could therefore be of great interest. This narrative review will explore experimental models of healthy muscle and aged muscle cells as a tool for research on sarcopenia. We will summarize the literature and present relevant experimental models in terms of their advantages and disadvantages. All of the presented approaches could potentially contribute to the accurate and early diagnosis, follow-up, and possible treatment of sarcopenia.

Unraveling aging from transcriptomics

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Research into aging constitutes a pivotal endeavor aimed at elucidating the underlying biological mechanisms governing aging and age-associated diseases, as well as promoting healthy longevity. Recent advances in transcriptomic technologies, such as bulk RNA sequencing (RNA-seq), single-cell transcriptomics, and spatial transcriptomics, have revolutionized our ability to study aging at unprecedented resolution and scale. These technologies present novel opportunities for the discovery of biomarkers, elucidation of molecular pathways, and development of targeted therapeutic strategies for age-related disorders. This review surveys recent breakthroughs in different types of transcripts on aging, such as mRNA, long noncoding (lnc)RNA, tRNA, and miRNA, highlighting key findings and discussing their potential implications for future studies in this field.

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Improving understanding of ferroptosis: Molecular mechanisms, connection with cellular senescence and implications for aging

In the face of cell damage, cells can initiate a response ranging from survival to death, the balance being crucial for tissue homeostasis and overall health. Cell death, in both accidental and regulated forms, plays a fundamental role in maintaining tissue homeostasis. Among the regulated mechanisms of cell death, ferroptosis has garnered attention for its iron-dependent phospholipid (PL) peroxidation and its implications in aging and age-related disorders, as well as for its therapeutic relevance. In this review, we provide an overview of the mechanisms, regulation, and physiological and pathological roles of ferroptosis. We present new insights into the relationship between ferroptosis, cellular senescence and aging, emphasizing how alterations in ferroptosis pathways contribute to aging-related tissue dysfunction. In addition, we examine the therapeutic potential of ferroptosis in aging-related diseases, offering innovative insights into future interventions aimed at mitigating the effects of aging and promoting longevity.

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Oxidative stress and cell senescence as drivers of ageing: Chicken and egg

Thomas von Zglinicki

Oxidative stress and cell senescence are both important drivers of ageing and age-associated disease and disability. In vitro, they are closely interconnected in a chicken-and-egg relationship: Not only is oxidative stress an important cause of cell senescence, but senescent cells are also sources of oxidative stress, obscuring cause-effect relationships during the ageing process. We hypothesize that cell senescence is a significant cause of tissue and systemic oxidative stress during ageing. This review aims to critically summarize the available evidence for this hypothesis. After summarizing the cellular feedback mechanisms that make oxidative stress an integral part of the senescent phenotype, it critically reviews the existing evidence for a role of senescent cells as causes of oxidative stress during mammalian ageing in vivo, focussing on results from intervention experiments. It is concluded that while the available data are in agreement with this hypothesis, they are still too scarce to support a robust conclusion.

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Mouse models used to test the role of reactive oxygen species in aging and age-related chronic diseases ★

Hoang Van M. Nguyen [a], Qitao Ran [c e], Adam B. Salmon [d e], Ahn Bumsoo [f], Ying Ann Chiao [g], Shylesh Bhaskaran [g], Arlan Richardson [b h]

With the development of the technology to generate transgenic and knockout mice in the 1990s, investigators had a powerful tool to directly test the impact of altering a specific gene on a biological process or disease. Over the past three decades, investigators have used transgenic and knockout mouse models, which have altered expression of antioxidant genes, to test the role of oxidative stress/damage in aging and age-related diseases. In this comprehensive review, we describe the studies using transgenic and knockout mouse models to test the role of oxidative stress/damage in aging (longevity) and three age-related diseases, e.g., sarcopenia, cardiac aging, and Alzheimer's Disease. While longevity was consistently altered only by one transgenic and one knockout mouse model as predicted by the Oxidative Stress Theory of Aging, the incidence/progression of the three age-related diseases (especially Alzheimer's disease) were robustly impacted when the expression of various antioxidant genes was altered using transgenic and knockout mouse models.

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Cell senescence in cardiometabolic diseases

Mandy O. J. Grootaert

Cellular senescence has been implicated in many age-related pathologies including atherosclerosis, heart failure, age-related cardiac remodeling, diabetic cardiomyopathy and the metabolic syndrome. Here, we will review the characteristics of senescent cells and their endogenous regulators, and summarize the metabolic stressors that induce cell senescence. We will discuss the evidence of cell senescence in the onset and progression of several cardiometabolic diseases and the therapeutic potential of anti-senescence therapies.

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Ovarian Aging and Fertility

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Women in their late 30s to early 40s who have difficulty conceiving are often unaware that success rates of fertility treatment decline with age, most commonly due to declining ovarian function. Counseling about the high prevalence of infertility and miscarriage may be met with surprise and sadness. Reports of children born to high-profile women older than 50 years may contribute to misconceptions, but these births highlighted in the media were likely achieved with donor oocytes from a younger woman or with oocytes or embryos that were previously cryopreserved. Consistent with declining fertility rates worldwide,[1] the fertility rate in the US has declined from 70.9 births per 1000 women in 1990 to 56.1 per 1000 in 2022.[2] Simultaneously, the 2019 US Census reported that age at first birth had risen from 27 years in 1990 to 30 years in 2019 as more women postponed first birth.

OTHER RESEARCH & REVIEWS

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The FlyWire connectome: neuronal wiring diagram of a complete fly brain

Artificial intelligence and human expertise meet to generate a map of all the connections in the fly brain. The resource is already being used by experimentalists and theoreticians to further our understanding of neural circuits in the fly and beyond.