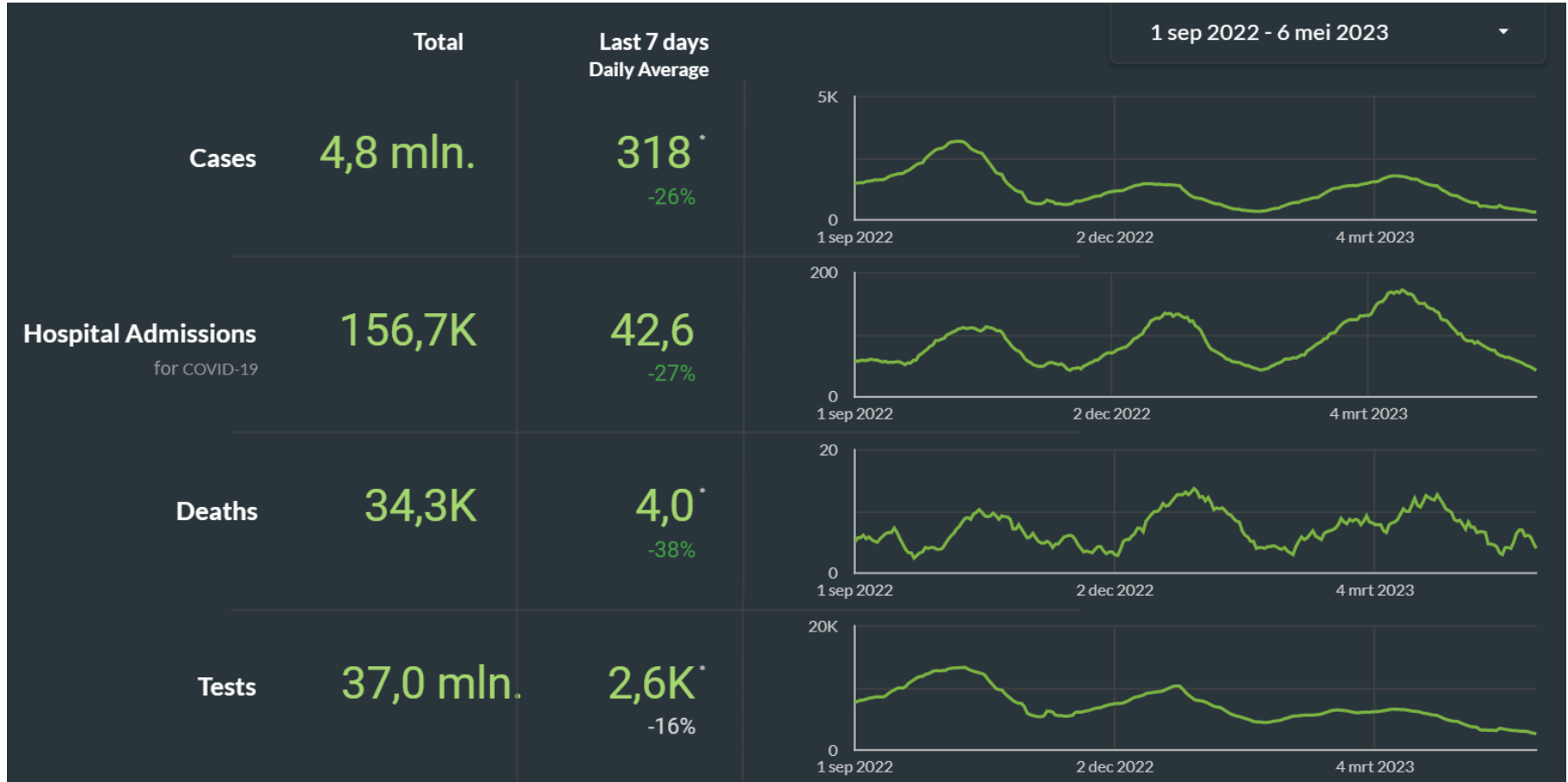




Heales
**HEALTHY LIFE EXTENSION
SOCIETY**

Scientific News
6th of May 2023
Sven Bulterijs

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General news

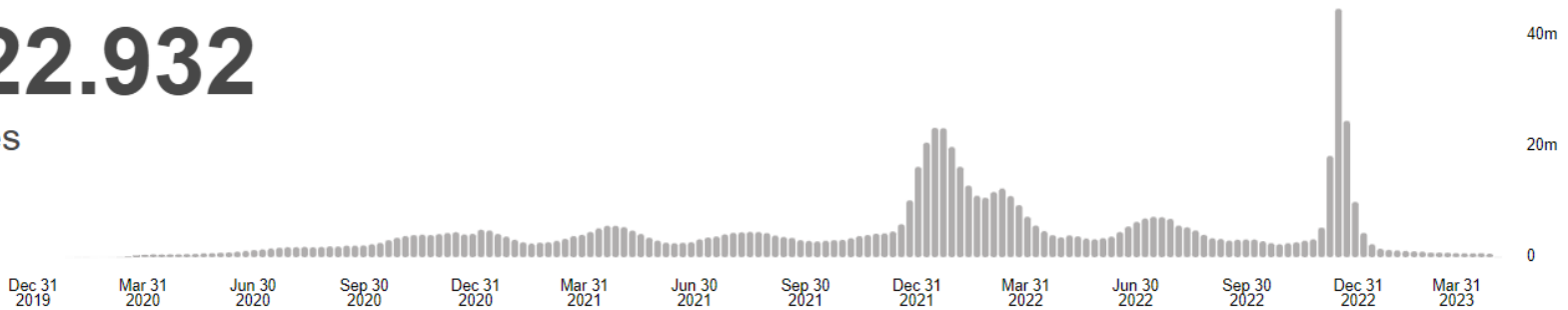


Global Situation



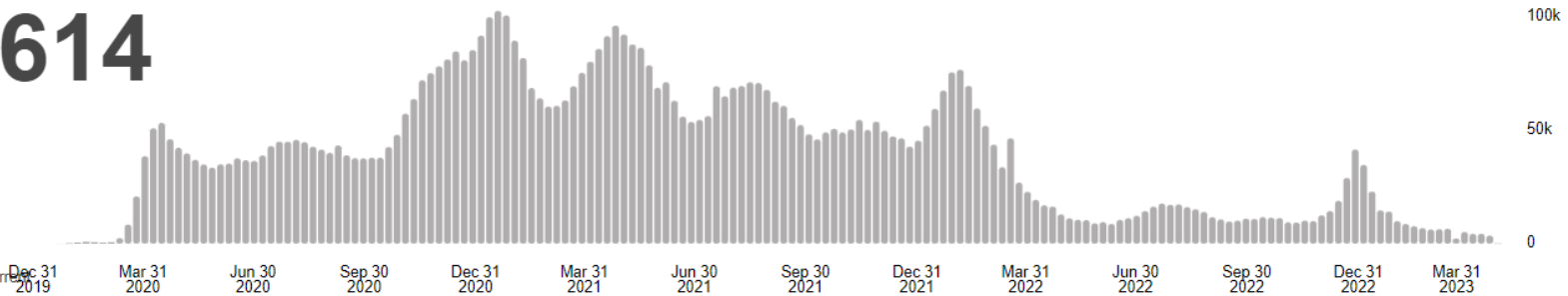
765.222.932

confirmed cases




6.921.614

deaths



Source: World Health Organization

 Data may be incomplete for the current day or week.



‘De oplossing voor de demografische tijdbom? Draai de biologische leeftijd terug’

Reginald Deschepper

28-04-2023, 15:00 •

Deel dit
artikel:



Een manier om de demografische tijdbom te ontmantelen, is om mensen biologisch te verjongen. ‘De wetenschap zet op dat vlak rasse schreden vooruit’, schrijft medisch antropoloog Reginald Deschepper.

HEALTH & WELLNESS

Longevity Seekers Embraced This Drug. But Does It Actually Fight Aging?

An antiaging crowd latched onto the diabetes drug metformin hoping it would extend their lifespan. Studies give conflicting results.



TIME

ACCELERATING TALENT IN AGING BIOLOGY



American Federation for Aging Research

5 April · 🌐

AFAR is pleased to announce the Time Initiative, a program aimed at accelerating talent in aging biology. The pilot program is uniquely designed to engage current and recent undergraduate students, providing them with knowledge, resources, and mentors to become the next generation of leaders in the field.

The centerpiece of the initiative is the Time Fellowship, which offers selected students the opportunity to attend an annual retreat, apply for special project funding, and receive direct mentorship from leaders in the field. In addition to the fellowship, the program includes in-person and virtual events and a range of online resources such as curated reading materials, online lectures, and ways to connect with peers and the larger aging research community.

A future where we all are living healthier, longer will be shaped by the next generation of innovative scientists, entrepreneurs, and policymakers, and more: connect with us at www.timeinitiative.org to get involved.

Hevolution/AFAR New Investigator Awards in Aging Biology and Geroscience Recipients Announced

Eighteen Three-Year Grants of \$375,000 Each Awarded, for a Total of \$6.75 Million

April 18, 2023 10:30 AM Eastern Daylight Time

RIYADH, Saudi Arabia & NEW YORK--(BUSINESS WIRE)--Hevolution Foundation and the American Federation for Aging Research (AFAR) are pleased to announce the inaugural Hevolution/AFAR [New Investigator Awards](#) in Aging Biology and Geroscience Research recipients. Eighteen three-year awards of \$375,000 each, for a total of \$6.75 Million, have been granted support research projects in the basic biology of aging or geroscience, a research paradigm based on addressing the biology of aging and age-related disease to promote healthy aging.

“In partnership with AFAR, Hevolution Foundation is excited to strengthen the international pipeline of aging researchers through the New Investigator Awards”

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The awards support talented early career investigators. The recipients:

- **Samuel Beck, PhD**, Associate Professor, Boston University School of Medicine: *Big data-guided anti-aging drug discovery and its validation.*
- **Charlotte Cecil, PhD**, Associate Professor, Erasmus University Medical Center: *What makes clocks tick? Mapping determinants of epigenetic age acceleration in early life*
- **Marco Demaria, PhD**, Associate Professor, European Research Institute for the Biology of Ageing (ERIBA): *Targeting altered Ca²⁺ signaling in cellular senescence to extend healthy longevity*

Alzheimer's Drug Discovery Foundation gets \$200M from family of Estée Lauder

By **Gabrielle Masson** • Apr 5, 2023 11:16am

Alzheimer's Drug Discovery Foundation



Alzheimer's disease

amyloid plaque

neurodegenerative diseases

Aging research articles

Heterogeneous aging across multiple organ systems and prediction of chronic disease and mortality

[Ye Ella Tian](#) , [Vanessa Cropley](#), [Andrea B. Maier](#), [Nicola T. Lautenschlager](#), [Michael Breakspear](#) & [Andrew Zalesky](#) 

[Nature Medicine](#) (2023) | [Cite this article](#)

19k Accesses | 600 Altmetric | [Metrics](#)

Abstract

Biological aging of human organ systems reflects the interplay of age, chronic disease, lifestyle and genetic risk. Using longitudinal brain imaging and physiological phenotypes from the UK Biobank, we establish normative models of biological age for three brain and seven body systems. Here we find that an organ's biological age selectively influences the aging of other organ systems, revealing a multiorgan aging network. We report organ age profiles for 16 chronic diseases, where advanced biological aging extends from the organ of primary disease to multiple systems. Advanced body age associates with several lifestyle and environmental factors, leukocyte telomere lengths and mortality risk, and predicts survival time (area under the curve of 0.77) and premature death (area under the curve of 0.86). Our work reveals the multisystem nature of human aging in health and chronic disease. It may enable early identification of individuals at increased risk of aging-related morbidity and inform new strategies to potentially limit organ-specific aging in such individuals.

Ageing-associated changes in transcriptional elongation influence longevity

Physiological homeostasis becomes compromised during ageing, as a result of impairment of cellular processes, including transcription and RNA splicing^{1,2,3,4}. However, the molecular mechanisms leading to the loss of transcriptional fidelity are so far elusive, as are ways of preventing it. Here we profiled and analysed genome-wide, ageing-related changes in transcriptional processes across different organisms: nematodes, fruitflies, mice, rats and humans. The average transcriptional elongation speed (RNA polymerase II speed) increased with age in all five species. Along with these changes in elongation speed, we observed changes in splicing, including a reduction of unspliced transcripts and the formation of more circular RNAs. Two lifespan-extending interventions, dietary restriction and lowered insulin-IGF signalling, both reversed most of these ageing-related changes. Genetic variants in RNA polymerase II that reduced its speed in worms⁵ and flies⁶ increased their lifespan. Similarly, reducing the speed of RNA polymerase II by overexpressing histone components, to counter age-associated changes in nucleosome positioning, also extended lifespan in flies and the division potential of human cells. Our findings uncover fundamental molecular mechanisms underlying animal ageing and lifespan-extending interventions, and point to possible preventive measures.

Engineering longevity—design of a synthetic gene oscillator to slow cellular aging

ZHEN ZHOU , YUTING LIU , YUSHEN FENG , STEPHEN KLEPIN , LEV S. TSIMRING , LORRAINE PILLUS , JEFF HASTY , AND NAN HAO  [Authors](#)













[Info & Affiliations](#)

Synthetic biology enables the design of gene networks to confer specific biological functions, yet it remains a challenge to rationally engineer a biological trait as complex as longevity. A naturally occurring toggle switch underlies fate decisions toward either nucleolar or mitochondrial decline during the aging of yeast cells. We rewired this endogenous toggle to engineer an autonomous genetic clock that generates sustained oscillations between the nucleolar and mitochondrial aging processes in individual cells. These oscillations increased cellular life span through the delay of the commitment to aging that resulted from either the loss of chromatin silencing or the depletion of heme. Our results establish a connection between gene network architecture and cellular longevity that could lead to rationally designed gene circuits that slow aging.

m⁶A epitranscriptomic regulation of tissue homeostasis during primate aging





How N⁶-methyladenosine (m⁶A), the most abundant mRNA modification, contributes to primate tissue homeostasis and physiological aging remains elusive. Here, we characterize the m⁶A epitranscriptome across the liver, heart and skeletal muscle in young and old nonhuman primates. Our data reveal a positive correlation between m⁶A modifications and gene expression homeostasis across tissues as well as tissue-type-specific aging-associated m⁶A dynamics. Among these tissues, skeletal muscle is the most susceptible to m⁶A loss in aging and shows a reduction in the m⁶A methyltransferase METTL3. We further show that METTL3 deficiency in human pluripotent stem cell-derived myotubes leads to senescence and apoptosis, and identify NPNT as a key element downstream of METTL3 involved in myotube homeostasis, whose expression and m⁶A levels are both decreased in senescent myotubes. Our study provides a resource for elucidating m⁶A-mediated mechanisms of tissue aging and reveals a METTL3-m⁶A-NPNT axis counteracting aging-associated skeletal muscle degeneration.

The Human Extracellular Matrix Diseaseome Reveals Genotype–Phenotype Associations with Clinical Implications for Age-Related Diseases

by  Cyril Statzer ¹ ,  Karan Luthria ² ,  Arastu Sharma ¹ ,  Maricel G. Kann ^{2,*}   and  Collin Y. Ewald ^{1,*}  

The extracellular matrix (ECM) is earning an increasingly relevant role in many disease states and aging. The analysis of these disease states is possible with the GWAS and PheWAS methodologies, and through our analysis, we aimed to explore the relationships between polymorphisms in the compendium of ECM genes (i.e., matrisome genes) in various disease states. A significant contribution on the part of ECM polymorphisms is evident in various types of disease, particularly those in the core-matrisome genes. Our results confirm previous links to connective-tissue disorders but also unearth new and underexplored relationships with neurological, psychiatric, and age-related disease states. Through our analysis of the drug indications for gene–disease relationships, we identify numerous targets that may be repurposed for age-related pathologies. The identification of ECM polymorphisms and their contributions to disease will play an integral role in future therapeutic developments, drug repurposing, precision medicine, and personalized care.

Telomouse – a mouse model with human-length telomeres generated by a single amino acid change in RTEL1

 Riham Smoom, Catherine Lee May, Vivian Ortiz, Mark Tigue, Hannah M. Kolev, Melissa Rowe, Yitzhak Reizel, Ashleigh Morgan, Nachshon Egyes, Dan Lichtental,  Emmanuel Skordalakes,  Klaus H. Kaestner,  Yehuda Tzfati

doi: <https://doi.org/10.1101/2021.06.06.447246>

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Abstract

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ABSTRACT

Telomeres, the ends of eukaryotic chromosomes, protect genome integrity and enable cell proliferation. Maintaining optimal telomere length in the germline and throughout life limits the risk of cancer and enables healthy aging. Telomeres in the house mouse, *Mus musculus*, are about five times longer than human telomeres, limiting the use of this common laboratory animal for studying the contribution of telomere biology to aging and cancer. We identified a key amino acid variation in the helicase RTEL1, naturally occurring in the short-telomere mouse species *M. spretus*. Introducing this variation into *M. musculus* is sufficient to reduce the telomere length set point in the germline and generate mice with human-length telomeres. While these mice are fertile and appear healthy, the regenerative capacity of their colonic epithelium is compromised. The engineered Telomouse reported here demonstrates a dominant role of RTEL1 in telomere length regulation and provides a unique model for aging and cancer.

Chaotic aging: Intrinsically disordered proteins in aging-related processes

 Vladimir D. Manyilov,  Nikolay S. Ilyinsky, Semen V. Nesterov, Baraa M.G.A. Saqr, Guy W. Dayhoff II, Egor V. Zinovev, Simon S. Matrenok, Alexander V. Fonin, Irina M. Kuznetsova,  Konstantin K. Turoverov,  Valentin Ivanovich,  Vladimir N. Uversky

The development of aging is associated with the disruption of key cellular processes manifested as well-established hallmarks of aging. Intrinsically disordered proteins (IDPs) and intrinsically disordered regions (IDRs) have no stable tertiary structure that provide them a power to be configurable hubs in signaling cascades and regulate many processes, potentially including those related to aging. There is a need to clarify the roles of IDPs/IDRs in aging. The dataset of 1624 aging-related proteins was collected from established aging databases and experimental studies. There is a noticeable presence of IDPs/IDRs, accounting for about 36% of the aging-related dataset, which is comparable to the disorder content of the whole human proteome (about 40%). A Gene Ontology analysis of the our Aging proteome reveals an abundance of IDPs/IDRs in one-third of aging-associated processes, especially in genome regulation. Signaling pathways associated with aging also contain IDPs/IDRs on different hierarchical levels. Protein-protein interaction network analysis showed that IDPs present in different clusters associated with different aging hallmarks. Protein cluster with IDPs enrichment and high liquid-liquid phase separation (LLPS) probability has “nuclear” localization and DNA-associated functions, related to aging hallmarks: genomic instability, telomere attrition, epigenetic alterations, stem cells exhaustion. Some IDPs related to aging with high LLPS propensity were identified as “dangerous” based on the prediction of their propensity to aggregation. Overall, our analyses indicate that IDPs/IDRs play significant roles in aging-associated processes, particularly in the regulation of DNA functioning. IDP aggregation, which can lead to loss-of-function and toxicity, could be critically harmful to the cell. A structure-based analysis of aging and the identification of proteins that are particularly susceptible to disturbances can enhance our understanding of the molecular mechanisms of aging and open up new avenues for slowing it down.

NFκB nuclear dynamics orchestrate inflammatory aging

Sho Tabata, Keita Matsuda, Kenshiro Nagai, Yoshihiro Izumi, Masatomo Takahashi, Yasutaka Motomura, Ayaka Ichikawa Nagasato, Shuichi Shimma, Kazuyo Moro, Takeshi Bamba, Mariko Okada

doi: <https://doi.org/10.1101/2023.04.18.536673>

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Abstract

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Abstract

Upregulation of nuclear factor κB (NFκB) signaling is a hallmark of aging and a major cause of age-related chronic inflammation. NFκB activity plays a critical role in transcriptional regulation and cell fate determination; however, its physiological function in inflammatory aging remains unclear. Here, we demonstrate that dysfunction of negative feedback regulators of NFκB, IκBα and A20, alters the NFκB nuclear dynamics from oscillatory to sustained, thereby promoting cellular senescence. Sustained NFκB activity by IκBα downregulation enhances inflammatory gene expression through increased NFκB-DNA binding, promotes purine catabolism by downregulating hypoxanthine phosphoribosyltransferase, and arrests the cell cycle. This regulatory mechanism was confirmed in aged mice heart tissues, suggesting that prolonged nuclear localization of NFκB drives chronic inflammation and metabolic rewiring associated with aging.

Physical activity is associated with slower epigenetic ageing— Findings from the Rhineland study

Fabienne A. U. Fox, Dan Liu, Monique M. B. Breteler, Nasir Ahmad Aziz 

Epigenetic ageing, i.e., age-associated changes in DNA methylation patterns, is a sensitive marker of biological ageing, a major determinant of morbidity and functional decline. We examined the association of physical activity with epigenetic ageing and the role of immune function and cardiovascular risk factors in mediating this relation. Moreover, we aimed to identify novel molecular processes underlying the association between physical activity and epigenetic ageing. We analysed cross-sectional data from 3567 eligible participants (mean age: 55.5 years, range: 30–94 years, 54.8% women) of the Rhineland Study, a community-based cohort study in Bonn, Germany. Physical activity components (metabolic equivalent (MET)-Hours, step counts, sedentary, light-intensity and moderate-to-vigorous intensity activities) were recorded with accelerometers. DNA methylation was measured with the Illumina HumanMethylationEPIC BeadChip. Epigenetic age acceleration (Hannum's age, Horvath's age, PhenoAge and GrimAge) was calculated based on published algorithms. The relation between physical activity and epigenetic ageing was examined with multivariable regression, while structural equation modeling was used for mediation analysis. Moreover, we conducted an epigenome-wide association study of physical activity across 850,000 CpG sites. After adjustment for age, sex, season, education, smoking, cell proportions and batch effects, physical activity (step counts, MET-Hours and %time spend in moderate-to-vigorous activities) was non-linearly associated with slower epigenetic ageing, in part through its beneficial effects on immune function and cardiovascular health. Additionally, we identified 12 and 7 CpGs associated with MET-Hours and %time spent in moderate-to-vigorous activities, respectively ($p < 1 \times 10^{-5}$). Our findings suggest that regular physical activity slows epigenetic ageing by counteracting immunosenescence and lowering cardiovascular risk.


Evidence of a pan-tissue decline in stemness during human aging

Gabriel Arantes dos Santos, Gustavo Daniel Vega Magdaleno,  João Pedro de Magalhães

doi: <https://doi.org/10.1101/2023.04.13.536766>

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Abstract

Despite their biological importance, the role of stem cells in human aging remains to be elucidated. In this work, we applied a machine learning methodology to GTEx transcriptome data and assigned stemness scores to 17,382 healthy samples from 30 human tissues aged between 20 and 79 years. We found that ~60% of the studied tissues present a significant negative correlation between the subject's age and stemness score. The only significant exception to this pattern was the uterus, where we observed an increased stemness with age. Moreover, we observed a global trend of positive correlations between cell proliferation and stemness. When analyzing the tissues individually, we found that ~50% of human tissues present a positive correlation between stemness and proliferation and 20% a negative correlation. Furthermore, all our analyses show negative correlations between stemness and cellular senescence, with significant results in ~80% of the tissues analyzed. Finally, we also observed a trend that hematopoietic stem cells derived from old patients might have more stemness. In short, we assigned stemness scores to human samples and show evidence of a pan-tissue loss of stemness during human aging, which adds weight to the idea that stem cell deterioration contributes to human ageing.

Spurious intragenic transcription is a feature of mammalian cellular senescence and tissue aging

[Payel Sen](#) , [Greg Donahue](#), [Catherine Li](#), [Gabor Egervari](#), [Na Yang](#), [Yemin Lan](#), [Neil Robertson](#), [Parisha P. Shah](#), [Erik Kerkhoven](#), [David C. Schultz](#), [Peter D. Adams](#) & [Shelley L. Berger](#) 















Mammalian aging is characterized by the progressive loss of tissue function and increased risk for disease. Accumulation of senescent cells in aging tissues partly contributes to this decline, and targeted depletion of senescent cells in vivo ameliorates many age-related phenotypes. The fundamental molecular mechanisms responsible for the decline of cellular health and fitness during senescence and aging are largely unknown. In this study, we investigated whether chromatin-mediated loss of transcriptional fidelity, known to contribute to fitness and survival in yeast and worms, also occurs during human cellular senescence and mouse aging. Our findings reveal aberrant transcription initiation inside genes during senescence and aging that co-occurs with changes in the chromatin landscape. Interventions that alter these spurious transcripts have profound consequences on cellular health, primarily affecting intracellular signal transduction pathways. We propose that age-related spurious transcription promotes a noisy transcriptome and degradation of coherent transcriptional networks.

Navitoclax (ABT-263) Rejuvenates Human Skin by Eliminating Senescent Dermal Fibroblasts in a Mouse/Human Chimeric Model

Kento Takaya , Tatsuyuki Ishii, Toru Asou, and Kazuo Kishi

Chronic senescence, such as aging, contributes to age-related tissue dysfunction and disease development. The accumulation of senescent fibroblasts and the senescence-associated secretory phenotype is particularly implicated in this process. Removal of senescent cells has been reported to prevent tissue dysfunction and to extend the life span during aging. ABT-263 (navitoclax), which inhibits antiapoptotic proteins, is a leading antiaging drug; however, its role in human skin aging is unclear. This study aimed to determine the rejuvenating effects of ABT-263 on aging skin using a human skin graft mouse model. We assessed the viability of ABT-263-treated skin fibroblasts after inducing senescence. Aged human skin was transplanted under the back skin of nude mice and injected intraperitoneally with the drug or control. Analysis of the skin specimens revealed that ABT-263 induced selective elimination of senescent dermal fibroblasts. Senescent human skin treated with ABT-263 exhibited a decrease in the number of senescent cells and in the expression of aging-related secretory phenotype molecules, such as matrix metalloproteinases and interleukins and an increase in collagen density. Our results indicate that selective removal of senescent skin cells with ABT-263 can improve the aging phenotype of human skin without side effects. ABT-263 is, thus, a novel potential therapeutic agent for skin aging.

Human Metabolome Reference Database in a Biracial Cohort across the Adult Lifespan



by  Qu Tian ^{1,*}  ,  M. Gordian Adam ^{2,†},  Enrique Ozcariz ² ,  Giovanna Fantoni ³,
 Nader M. Shehadeh ³,  Lisa M. Turek ⁴,  Victoria L. Collingham ⁴,  Mary Kaileh ⁵ ,
 Ruin Moaddel ³ and  Luigi Ferrucci ¹

As one of the OMICS in systems biology, metabolomics defines the metabolome and simultaneously quantifies numerous metabolites that are final or intermediate products and effectors of upstream biological processes. Metabolomics provides accurate information that helps determine the physiological steady state and biochemical changes during the aging process. To date, reference values of metabolites across the adult lifespan, especially among ethnicity groups, are lacking. The “normal” reference values according to age, sex, and race allow the characterization of whether an individual or a group deviates metabolically from normal aging, encompass a fundamental element in any study aimed at understanding mechanisms at the interface between aging and diseases. In this study, we established a metabolomics reference database from 20–100 years of age from a biracial sample of community-dwelling healthy men and women and examined metabolite associations with age, sex, and race. Reference values from well-selected healthy individuals can contribute to clinical decision-making processes of metabolic or related diseases.

Necroptosis inhibition counteracts neurodegeneration, memory decline, and key hallmarks of aging, promoting brain rejuvenation

Age is the main risk factor for the development of neurodegenerative diseases. In the aged brain, axonal degeneration is an early pathological event, preceding neuronal dysfunction, and cognitive disabilities in humans, primates, rodents, and invertebrates. Necroptosis mediates degeneration of injured axons, but whether necroptosis triggers neurodegeneration and cognitive impairment along aging is unknown. Here, we show that the loss of the necroptotic effector *Mkl1* was sufficient to delay age-associated axonal degeneration and neuroinflammation, protecting against decreased synaptic transmission and memory decline in aged mice. Moreover, short-term pharmacologic inhibition of necroptosis targeting RIPK3 in aged mice, reverted structural and functional hippocampal impairment, both at the electrophysiological and behavioral level. Finally, a quantitative proteomic analysis revealed that necroptosis inhibition leads to an overall improvement of the aged hippocampal proteome, including a subclass of molecular biofunctions associated with brain rejuvenation, such as long-term potentiation and synaptic plasticity. Our results demonstrate that necroptosis contributes to age-dependent brain degeneration, disturbing hippocampal neuronal connectivity, and cognitive function. Therefore, necroptosis inhibition constitutes a potential geroprotective strategy to treat age-related disabilities associated with memory impairment and cognitive decline.




Whole organism aging: Parabiosis, inflammaging, epigenetics, and peripheral and central aging clocks. The ARS of aging

[Reinald Pamplona](#)^a, [Mariona Jové](#)^a, [José Gómez](#)^b, [Gustavo Barja](#)^c  

The strong interest shown in the study of the causes of aging in recent decades has uncovered many mechanisms that could contribute to the rate of aging. These include mitochondrial ROS production, DNA modification and repair, lipid peroxidation-induced membrane fatty acid unsaturation, autophagy, telomere shortening rate, apoptosis, proteostasis, senescent cells, and most likely there are many others waiting to be discovered. However, all these well-known mechanisms work only or mainly at the cellular level. Although it is known that organs within a single individual do not age at exactly the same rate, there is a well-defined species longevity. Therefore, loose coordination of aging rate among the different cells and tissues is needed to ensure species lifespan. In this article we focus on less known extracellular, systemic, and whole organism level mechanisms that could loosely coordinate aging of the whole individual to keep it within the margins of its species longevity. We discuss heterochronic parabiosis experiments, systemic factors distributed through the vascular system like DAMPs, mitochondrial DNA and its fragments, TF-like vascular proteins, and inflammaging, as well as epigenetic and proposed aging clocks situated at different levels of organization from individual cells to the brain. These interorgan systems can help to determine species longevity as a further adaptation to the ecosystem.

C. elegans aging research

A megaprotein brake for aging and insulin-mTOR signaling

Taruna Pandey, Bingying Wang, Changnan Wang, Jenny Zu, Huichao Deng,  Kang Shen, Goncalo Dias do Vale,  Jeffrey G. McDonald,  Dengke K. Ma

doi: <https://doi.org/10.1101/2023.02.14.528431>

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Abstract

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Abstract

Insulin-mTOR signaling drives anabolic growth in organismal development, while its late-life antagonistic pleiotropy affects aging and compromises lifespan across animal phylogeny. Here we identify LPD-3 as a megaprotein that orchestrates the tempo of insulin-mTOR signaling during *C. elegans* aging. We find that an agonist insulin INS-7 is drastically over-produced and shortens lifespan in *lpd-3* mutants, a *C. elegans* model of human Alkuraya-Kučinskas syndrome. LPD-3 forms a bridge-like tunnel megaprotein to facilitate phospholipid trafficking to plasma membrane. Lipidomic profiling reveals increased abundance of hexaceramide species in *lpd-3* mutants, accompanied by up-regulation of hexaceramide biosynthetic enzymes, including HYL-1 (Homolog of Yeast Longevity). Reducing HYL-1 activity decreases INS-7 levels and rescues the shortened lifespan of *lpd-3* mutants through insulin receptor/DAF-2 and mTOR/LET-363. LPD-3 antagonizes SINH-1, a key mTORC2 component, and reduces protein abundance with age in wild type animals. We propose that LPD-3 acts as a megaprotein brake for aging and its age-dependent decline restricts lifespan through the sphingolipid-hexaceramide and insulin-mTOR pathways.

Automated recognition and analysis of body bending behavior in *C. elegans*


Hui Zhang^{1 2}, Weiyang Chen^{3 4}

Background: Locomotion behaviors of *Caenorhabditis elegans* play an important role in drug activity screening, anti-aging research, and toxicological assessment. Previous studies have provided important insights into drug activity screening, anti-aging, and toxicological research by manually counting the number of body bends. However, manual counting is often low-throughput and takes a lot of time and manpower. And it is easy to cause artificial bias and error in counting results.

Results: In this paper, an algorithm is proposed for automatic counting and analysis of the body bending behavior of nematodes. First of all, the numerical coordinate regression method with convolutional neural network is used to obtain the head and tail coordinates. Next, curvature-based feature point extraction algorithm is used to calculate the feature points of the nematode centerline. Then the maximum distance between the peak point and the straight line between the pharynx and the tail is calculated. The number of body bends is counted according to the change in the maximum distance per frame.

Conclusion: Experiments are performed to prove the effectiveness of the proposed algorithm. The accuracy of head coordinate prediction is 0.993, and the accuracy of tail coordinate prediction is 0.990. The Pearson correlation coefficient between the results of the automatic count and manual count of the number of body bends is 0.998 and the mean absolute error is 1.931. Different strains of nematodes are selected to analyze differences in body bending behavior, demonstrating a relationship between nematode vitality and lifespan. The code is freely available at <https://github.com/hthana/Body-Bend-Count>.

CRISPR-activated expression of collagen *col-120* increases lifespan and heat tolerance

Anita Goyal¹, and Collin Y. Ewald^{1§} 

¹Laboratory of Extracellular Matrix Regeneration, Institute of Translational Medicine, Department of Health Sciences and Technology, ETH Zürich, Schwerzenbach CH-8603, Switzerland

§Correspondence to: Collin Y. Ewald (collin-ewald@ethz.ch)

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Abstract

Transgenic overexpression of collagen *col-120* increases the lifespan of *C. elegans*. However, whether post-developmental enhancement of collagen expression could also increase the lifespan is unknown. Recently, we described a method to induce the expression of a target gene using catalytically dead Cas9 (dCas9)-engineered *C. elegans* via ingestion of bacteria expressing a pair of promoter-specific single guide RNAs (sgRNA). Here, we cloned *col-120* promoter-specific sgRNA oligo pair into L4440-Biobrick-sgRNA and fed these bacteria to dCas9::VP64 transgenic *C. elegans*. We observed a similar percentage of lifespan extension by post-developmentally dCas9-induced expression of *col-120*, as previously reported through transgenic overexpression of *col-120*. Consistent with this result is that induction of another previously shown longevity-promoting collagen, *col-10*, also increased lifespan. Furthermore, we found an enhanced resilience to heat stress and increased expression of *hsp-16.2* upon dCas9-activated *col-120* expression. Together, these results provide an orthogonal method to validate longevity by enhancing *col-120* expression and point towards a potential role of collagen enhancement in thermotolerance.

REVIEWS/COMMENTS/
METHODS/EDITORIALS

Programmed versus non-programmed evolution of aging. What is the evidence?

Reinald Pamplona ¹, Mariona Jové ¹, José Gómez ², Gustavo Barja ³

Affiliations [+ expand](#)

PMID: 37004927 DOI: [10.1016/j.exger.2023.112162](https://doi.org/10.1016/j.exger.2023.112162)

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Abstract

The evolutionary meaning and basic molecular mechanisms involved in the determination of longevity remain an unresolved problem. Currently, different theories are on offer in response to these biological traits and to explain the enormous range of longevities observed in the animal kingdom. These theories may be grouped into those that defend non-programmed aging (non-PA) and those that propose the existence of programmed aging (PA). In the present article we examine many observational and experimental data from both the field and from the laboratory and sound reasoning accumulated in recent decades both compatible and not with PA and non-PA evolutionary theories of aging. These analyses are briefly summarized and discussed. Our conclusion is that most of the data favour programmed aging with a possible contribution of non-PA antagonist pleiotropy in various cases.

Rapamycin, the only drug that has been consistently demonstrated to increase mammalian longevity. An update

Zelton Dave Sharp ¹, Randy Strong ²

Affiliations + expand

PMID: 37011714 DOI: [10.1016/j.exger.2023.112166](https://doi.org/10.1016/j.exger.2023.112166)

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Conflict of interest statement

Declaration of competing interest The University of Texas Health Science Center at San Antonio has been awarded a patent, U.S. Patent Application No. 13/128,800, by inventors Zelton Dave Sharp and Randy Strong, for an encapsulated rapamycin formulation used in this paper. Under a licensing agreement between Emtora Biosciences and the University of Texas Health Science Center San Antonio, R. Strong and Z.D. Sharp, the University is entitled to milestone payments and royalty on sales of microencapsulated rapamycin. The university has a plan for managing conflicts of interest under its "Policy and Procedures for Promoting Objectivity in Research by Managing, Reducing or Eliminating Conflicts of Interest."

Morphochemicals: Perspectives for discovery of drugs targeting anatomical control mechanisms in regenerative medicine, cancer and aging

[Léo Pio-Lopez](#)¹, [Michael Levin](#)^{1 2}  

Morphochemicals are a new class of interventions that target the setpoints of anatomical homeostasis for efficient, modular control of growth and form. Here, we focus on a subclass: electrochemicals, which specifically target the cellular bioelectrical interface. Cellular collectives in all tissues form bioelectrical networks via ion channels and gap junctions that process morphogenetic information, controlling gene expression and allowing cell networks to adaptively and dynamically control growth and pattern formation. Recent progress in understanding this physiological control system, including predictive computational models, suggests that targeting bioelectrical interfaces can control embryogenesis and maintain shape against injury, senescence and tumorigenesis. We propose a roadmap for drug discovery focused on manipulating endogenous bioelectric signaling for regenerative medicine, cancer suppression and antiaging therapeutics.

Cellular senescence and neurodegeneration

[Kristopher Holloway](#), [Kashfia Neherin](#), [Kha Uyen Dam](#) & [Hong Zhang](#) 

Advancing age is a major risk factor of Alzheimer's disease (AD). The worldwide prevalence of AD is approximately 50 million people, and this number is projected to increase substantially. The molecular mechanisms underlying the aging-associated susceptibility to cognitive impairment in AD are largely unknown. As a hallmark of aging, cellular senescence is a significant contributor to aging and age-related diseases including AD. Senescent neurons and glial cells have been detected to accumulate in the brains of AD patients and mouse models. Importantly, selective elimination of senescent cells ameliorates amyloid beta and tau pathologies and improves cognition in AD mouse models, indicating a critical role of cellular senescence in AD pathogenesis. Nonetheless, the mechanisms underlying when and how cellular senescence contributes to AD pathogenesis remain unclear. This review provides an overview of cellular senescence and discusses recent advances in the understanding of the impact of cellular senescence on AD pathogenesis, with brief discussions of the possible role of cellular senescence in other neurodegenerative diseases including Down syndrome, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis.

Mitophagy regulation in aging and neurodegenerative disease

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PMID: 37124925 PMCID: PMC10133433 (available on 2024-04-04)

DOI: [10.1007/s12551-023-01057-6](https://doi.org/10.1007/s12551-023-01057-6)

Abstract

Mitochondria are the primary cellular energy generators, supplying the majority of adenosine triphosphate through oxidative phosphorylation, which is necessary for neuron function and survival. Mitophagy is the metabolic process of eliminating dysfunctional or redundant mitochondria. It is a type of autophagy and it is crucial for maintaining mitochondrial and neuronal health. Impaired mitophagy leads to an accumulation of damaged mitochondria and proteins leading to the dysregulation of mitochondrial quality control processes. Recent research shows the vital role of mitophagy in neurons and the pathogenesis of major neurodegenerative diseases. Mitophagy also plays a major role in the process of aging. This review describes the alterations that are being caused in the mitophagy process at the molecular level in aging and in neurodegenerative diseases, particularly Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis, also looks at how mitophagy can be exploited as a therapeutic target for these diseases.

Energizing Mitochondria to Prevent Mobility Loss in Aging: Rationale and Hypotheses

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PMID: 37057904 DOI: [10.1249/JES.0000000000000315](https://doi.org/10.1249/JES.0000000000000315)

Abstract

Based on recent studies from our group and others, we hypothesize that mitochondrial dysfunction during aging may be the root cause of mobility decline through deficits in the musculoskeletal and central nervous systems. Mitochondrial dysfunction could be a therapeutic target to prevent mobility decline in aging.

Annual Review of Biomedical Data Science

Vol. 6- (Volume publication date August 2023)



Review in Advance first posted online on April 26, 2023. (Changes may still occur before final publication.)

<https://doi.org/10.1146/annurev-biodatasci-020722-120642>

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Organismal aging exhibits wide-ranging hallmarks in divergent cell types across tissues, organs, and systems. The advancement of single-cell technologies and generation of rich datasets have afforded the scientific community the opportunity to decode these hallmarks of aging at an unprecedented scope and resolution. In this review, we describe the technological advancements and bioinformatic methodologies enabling data interpretation at the cellular level. Then, we outline the application of such technologies for decoding aging hallmarks and potential intervention targets and summarize common themes and context-specific molecular features in representative organ systems across the body. Finally, we provide a brief summary of available databases relevant for aging research and present an outlook on the opportunities in this emerging field.

Biological resilience and aging: Activation of stress response pathways contributes to lifespan extension

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While aging was traditionally viewed as a stochastic process of damage accumulation, it is now clear that aging is strongly influenced by genetics. The identification and characterization of long-lived genetic mutants in model organisms has provided insights into the genetic pathways and molecular mechanisms involved in extending longevity. Long-lived genetic mutants exhibit activation of multiple stress response pathways leading to enhanced resistance to exogenous stressors. As a result, lifespan exhibits a significant, positive correlation with resistance to stress. Disruption of stress response pathways inhibits lifespan extension in multiple long-lived mutants representing different pathways of lifespan extension and can also reduce the lifespan of wild-type animals. Combined, this suggests that activation of stress response pathways is a key mechanism by which long-lived mutants achieve their extended longevity and that many of these pathways are also required for normal lifespan. These results highlight an important role for stress response pathways in determining the lifespan of an organism.

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The restriction of calories, branched-chain amino acids, and methionine have all been shown to extend lifespan in model organisms. Recently, glycine was found to boost longevity in genetically heterogenous mice. This simple amino acid similarly extends lifespan in rats and improves health in mammalian models of age-related disease. While compelling data indicate that glycine is a pro-longevity molecule, divergent mechanisms may underlie its effects on aging. Glycine is abundant in collagen, a building block for glutathione, a precursor to creatine, and an acceptor for the enzyme glycine N-methyltransferase (GNMT). A review of the literature strongly implicates GNMT, which clears methionine from the body by taking a methyl group from S-adenosyl-L-methionine and methylating glycine to form sarcosine. In flies, *Gnmt* is required for reduced insulin/insulin-like growth factor 1 signaling and dietary restriction to fully extend lifespan. The geroprotector spermidine requires *Gnmt* to upregulate autophagy genes and boost longevity. Moreover, the overexpression of *Gnmt* is sufficient to extend lifespan and reduce methionine levels. Sarcosine, or methylglycine, declines with age in multiple species and is capable of inducing autophagy both in vitro and in vivo. Taken all together, existing evidence suggests that glycine prolongs life by mimicking methionine restriction and activating autophagy.

Ageing is a phenomenon in which cells, tissues and organs undergo systemic pathological changes as individuals age, leading to the occurrence of ageing-related diseases and the end of life. It is associated with many phenotypes known as ageing characteristics, such as genomic instability, nutritional imbalance, mitochondrial dysfunction, cell senescence, stem cell depletion, and an altered microenvironment. The sirtuin family (SIRT), known as longevity proteins, is thought to delay ageing and prolong life, and mammals, including humans, have seven family members (SIRT1-7). SIRT4 has been studied less among the sirtuin family thus far, but it has been reported that it has important physiological functions in organisms, such as promoting DNA damage repair, participating in the energy metabolism of three substances, inhibiting inflammatory reactions and apoptosis, and regulating mitochondrial function. Recently, some studies have demonstrated the involvement of SIRT4 in age-related processes, but knowledge in this field is still scarce. Therefore, this review aims to analyse the relationship between SIRT4 and ageing characteristics as well as some age-related diseases (e.g., cardiovascular diseases, metabolic diseases, neurodegenerative diseases and cancer).

OTHER RESEARCH & REVIEWS

An excavate root for the eukaryote tree of life

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SCIENCE ADVANCES • 28 Apr 2023 • Vol 9, Issue 17 • DOI: 10.1126/sciadv.ade4973

↓ 7.294



Abstract

Much of the higher-order phylogeny of eukaryotes is well resolved, but the root remains elusive. We assembled a dataset of 183 eukaryotic proteins of archaeal ancestry to test this root. The resulting phylogeny identifies four lineages of eukaryotes currently classified as “Excavata” branching separately at the base of the tree. Thus, Parabasalia appear as the first major branch of eukaryotes followed sequentially by Fornicata, Preaxostyla, and Discoba. All four excavate branch points receive full statistical support from analyses with commonly used evolutionary models, a protein structure partition model that we introduce here, and various controls for deep phylogeny artifacts. The absence of aerobic mitochondria in Parabasalia, Fornicata, and Preaxostyla suggests that modern eukaryotes arose under anoxic conditions, probably much earlier than expected, and without the benefit of mitochondrial respiration.