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Sven Bulterijs

Business/Conferences/ General news

Biomedical researchers' perspectives on the reproducibility of research

Kelly D. Cobey, Sanam Ebrahimzadeh, Matthew J. Page, Robert T. Thibault, Phi-Yen Nguyen, Farah Abu-Dalfa, David Moher

We conducted an international cross-sectional survey of biomedical researchers' perspectives on the reproducibility of research. This study builds on a widely cited 2016 survey on reproducibility and provides a biomedical-specific and contemporary perspective on reproducibility. To sample the community, we randomly selected 400 journals indexed in MEDLINE, from which we extracted the author names and emails from all articles published between October 1, 2020 and October 1, 2021. We invited participants to complete an anonymous online survey which collected basic demographic information, perceptions about a reproducibility crisis, perceived causes of irreproducibility of research results, experience conducting reproducibility studies, and knowledge of funding and training for research on reproducibility. A total of 1,924 participants accessed our survey, of which 1,630 provided useable responses (response rate 7% of 23,234). Key findings include that 72% of participants agreed there was a reproducibility crisis in biomedicine, with 27% of participants indicating the crisis was "significant." The leading perceived cause of irreproducibility was a "pressure to publish" with 62% of participants indicating it "always" or "very often" contributes. About half of the participants (54%) had run a replication of their own previously published study while slightly more (57%) had run a replication of another researcher's study. Just 16% of participants indicated their institution had established procedures to enhance the reproducibility of biomedical research and 67% felt their institution valued new research over replication studies. Participants also reported few opportunities to obtain funding to attempt to reproduce a study and 83% perceived it would be harder to do so than to get funding to do a novel study. Our results may be used to guide training and interventions to improve research reproducibility and to monitor rates of reproducibility over time. The findings are also relevant to policy makers and academic leadership looking to create incentives and research cultures that support reproducibility and value research quality.

Empowering biomedical discovery with AI agents

Shanghua Gao [1] · Ada Fang [1,2,8,11] · Yepeng Huang [1,3,11.] ... · Yasha Ektefaie [1,6] · Jovana Kondic [7] · Marinka Zitnik [1,8,9,10]

We envision “AI scientists” as systems capable of skeptical learning and reasoning that empower biomedical research through collaborative agents that integrate AI models and biomedical tools with experimental platforms. Rather than taking humans out of the discovery process, biomedical AI agents combine human creativity and expertise with AI’s ability to analyze large datasets, navigate hypothesis spaces, and execute repetitive tasks. AI agents are poised to be proficient in various tasks, planning discovery workflows and performing self-assessment to identify and mitigate gaps in their knowledge. These agents use large language models and generative models to feature structured memory for continual learning and use machine learning tools to incorporate scientific knowledge, biological principles, and theories. AI agents can impact areas ranging from virtual cell simulation, programmable control of phenotypes, and the design of cellular circuits to developing new therapies.

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Protecting scientific integrity in an age of generative AI

Wolfgang Blau, Vinton G. Cerf, Juan Enriquez, +20, and Michael Witherell Authors Info & Affiliations

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Revolutionary advances in AI have brought us to a transformative moment for science. AI is accelerating scientific discoveries and analyses. At the same time, its tools and processes challenge core norms and values in the conduct of science, including accountability, transparency, replicability, and human responsibility (1–3). These difficulties are particularly apparent in recent advances with *generative AI*. Future innovations with AI may mitigate some of these or raise new concerns and challenges.

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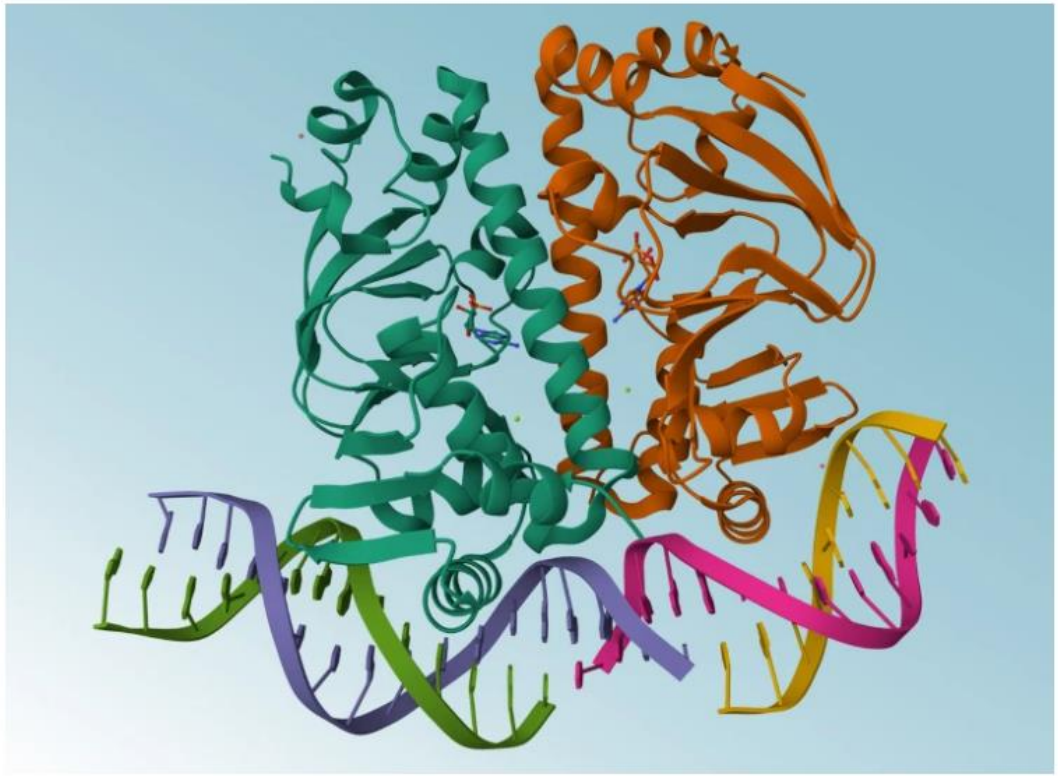
AI protein-prediction tool AlphaFold3 is now open source

The code underlying the Nobel-prize-winning tool for modelling protein structures can now be downloaded by academics.

By Ewen Callaway



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Retirement Age Then and Now: A Biologist's Perspective

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Steven N Austad, PhD

The National Institute on Aging (NIA) was officially established in October 1974 as a consequence of the Research on Aging Act (Public Law 93-296) passed earlier that same year. Its official purpose was (and remains) the "conduct and support of biomedical, social, and behavioral research and training related to the aging process and the diseases and other special problems and needs of the aged," although today we would say "older adults" rather than "the aged." This year, we are celebrating 50 years of the NIA's existence, which makes this a convenient time to ask the question, "what has changed for older adults between 1974 and now?"

"Now," for the purposes of this article will mean 2019 rather than 2024, both because 2019 census data are available whereas 2024 data are not and also because it is the last available year in which United States mortality data are not influenced by the large but apparently temporary demographic impact of COVID-19 deaths. That impact saw life expectancy at birth in the United States fall by 2.4 years between 2019 and 2021, the largest drop in life expectancy since the 1918 influenza pandemic caused an almost 12-year drop (Noymer & Garenne, 2000). Like the 1918 pandemic, demographic recovery from COVID-19 appears to be relatively quick. By 2022, the latest year census data are available, about half of the COVID life expectancy decrease had been recovered, so life expectancy in 2024 should likely have recovered to its prepandemic level (Arias et al., 2023).

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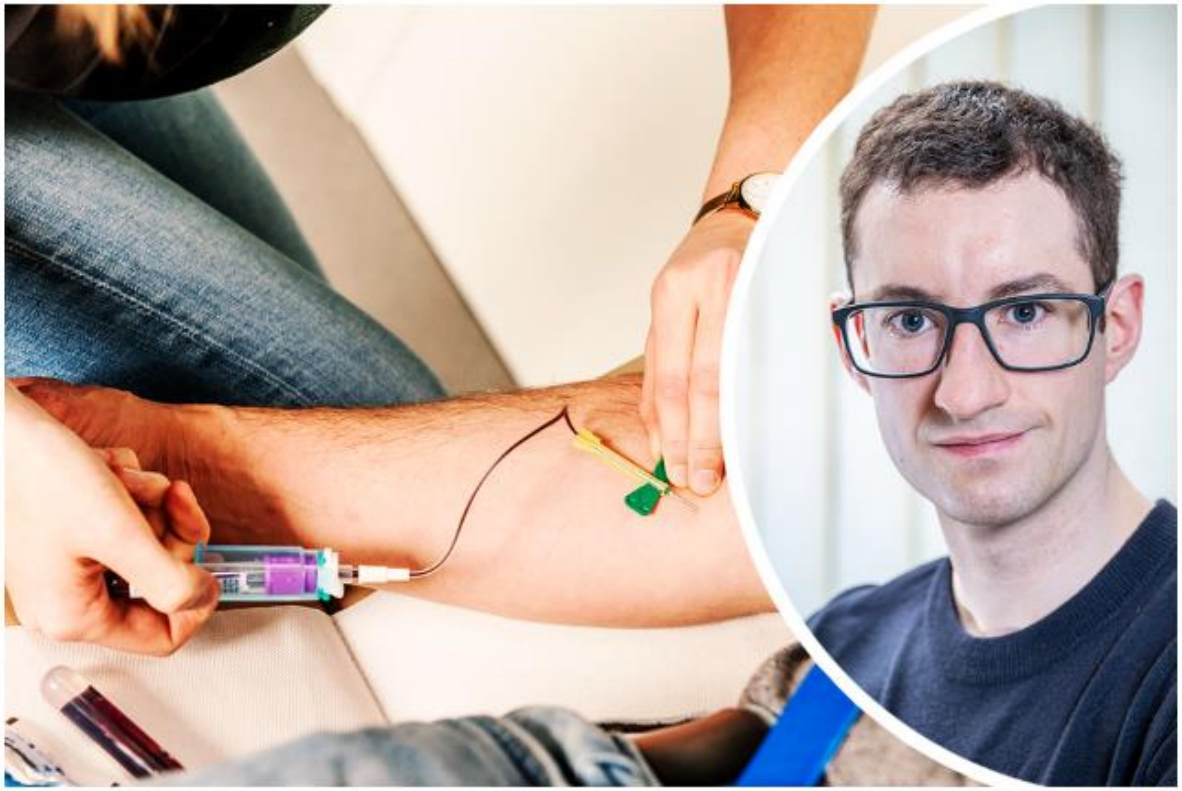
Met één bloedprikje weten we binnenkort welke organen van ons lichaam het snelst verouderen



"Via een bloedafname probeert men in te schatten hoe sterk elk orgaan afzonderlijk al verouderd is", zegt expert Sven Bulterijs. — © DVH

EHA2024

Upcoming conferences

Aging research articles

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A panoramic view of cell population dynamics in mammalian aging

ZEHAO ZHANG, CHLOE SCHAEFER, WEIRONG JIANG, ZIYU LU, JASPER LEE, ANDRAS SZIRAKI, ABDULRAOUF ABDULRAOUF, BRITTNEY WICK, MAXIMILIAN HAEUSSLER, [...], AND JUNYUE CAO +4 authors Authors Info & Affiliations

To elucidate aging-associated cellular population dynamics, we present *PanSci*, a single-cell transcriptome atlas profiling over 20 million cells from 623 mouse tissues across different life stages, sexes, and genotypes. This comprehensive dataset reveals more than 3,000 unique cellular states and over 200 aging-associated cell populations. Our panoramic analysis uncovered organ-, lineage-, and sex-specific shifts of cellular dynamics during lifespan progression. Moreover, we identify both systematic and organ-specific alterations in immune cell populations associated with aging. We further explored the regulatory roles of the immune system on aging and pinpointed specific age-related cell population expansions that are lymphocyte dependent. Our "cell-omics" strategy enhances comprehension of cellular aging and lays the groundwork for exploring the complex cellular regulatory networks in aging and aging-associated diseases.

Association of Muscle Strength With All-Cause Mortality in the Oldest Old: Prospective Cohort Study From 28 Countries

Lars Louis Andersen, Rubén López-Bueno ✉, Rodrigo Núñez-Cortés, Eduardo Lusa Cadore, Ana Polo-López, Joaquín Calatayud

Methods

We included 1890 adults aged ≥ 90 years (61.6% women, mean age 91.0 ± 1.5 years) from 27 European countries and Israel participating in the Survey of Health, Ageing and Retirement in Europe (SHARE) study. Muscle strength was assessed using handgrip dynamometry (unit: kilogram). Using time-varying Cox regression with restricted cubic splines, we determined the prospective association of muscle strength with mortality, controlling for age, sex, smoking, BMI, marital status, education, geographical region and self-perceived health.

Results

Over a mean follow-up of 4.2 ± 2.4 years, more than half of the participants died (n = 971, 51.4%). The mean handgrip strength was 20.4 ± 8.0 kg for all participants, with men (26.7 ± 7.5 kg) showing significantly higher strength than women (16.4 ± 5.4 kg) ($p < 0.001$). Using the median level of muscle strength as reference (18 kg), lower and higher levels were associated in a gradual and curvilinear fashion with higher and lower mortality risk, respectively. The 10th percentile of muscle strength (10 kg) showed a hazard ratio (HR) of 1.27 (95% CI 1.13–1.43, $p < 0.001$). The 90th percentile (31 kg) showed an HR of 0.69 (95% CI 0.58–0.82, $p < 0.001$). Stratified for sex, the median levels of muscle strength were 26 kg for men and 16 kg for women. The 10th percentile of muscle strength showed HRs of 1.33 (95% CI 1.10–1.61, $p < 0.001$) at 15 kg for men and 1.19 (95% CI 1.05–1.35, $p < 0.01$) at 10 kg for women. The 90th percentile of muscle strength showed HRs of 0.75 (95% CI 0.59–0.95, $p < 0.01$) at 35 kg for men and 0.75 (95% CI 0.62–0.90, $p < 0.001$) at 23 kg for women. Sensitivity analyses, which excluded individuals who died within the first 2 years of follow-up, confirmed the main findings.

Conclusion

Rather than a specific threshold, muscle strength is gradually and inversely associated with mortality risk in the oldest old. As muscle strength at all ages is highly adaptive to resistance training, these findings highlight the importance of improving muscle strength in both men and women among the oldest old.

Negative effects of lifespan extending intervention on resilience in mice

Katelynn M. Corder, Jessica M. Hoffman, Anamarija Sogorovic, Youfeng Yang, Anisha Banerjee, Yi Sun, Michael B. Stout, Steven N. Austad

One key goal of basic aging research is the development of reliable assays of both current and future health. These assays could dramatically accelerate progress toward developing health-extending interventions by obviating the need for full lifespan studies, especially if they were informative relatively early in life. One potential approach is the assessment of physiological resilience, defined as the ability to recover from an adverse event. Here, using CB6F1 mice, we evaluated four potential resilience assays, each quantifying recovery from a physiological challenge with clear relevance to humans. The challenges were: (1) anesthesia recovery, (2) restoration of hemoglobin levels after a blood draw, (3) speed of wound healing, and (4) survival after pathogen exposure. We evaluated how each changed with age and with interventions known to extend health in males only (17α-estradiol) or both sexes (calorie restriction). We found that three of the four (recovery from anesthesia, blood draw, and pathogen exposure) showed significant and expected age effects, but wound healing did not. None of the three age-sensitive assays responded to the health-extending interventions in the way we expected, and for some assays, including anesthesia response, interventions actually worsened outcomes. Possible explanations are: (1) our interventions were too brief, (2) the ages we evaluated were too young, (3) our assays did not capture important features of organismal resilience, or (4) organismal resilience is not as clearly related to current or future health as hypothesized. Future studies are needed to determine which of these interpretations is valid and to determine whether other resilience metrics may be more informative about current and future health.

Chronic social stress induces p16-mediated senescent cell accumulation in mice

Carey E. Lyons, Jean Pierre Pallais, Seth McGonigle, Rachel P. Mansk, Charles W. Collinge, Matthew J. Yousefzadeh, Darren J. Baker, Patricia R. Schrank, Jesse W. Williams, Laura J. Niedernhofer, Jan M. van Deursen, Maria Razzoli & Alessandro Bartolomucci

Life stress can shorten lifespan and increase risk for aging-related diseases, but the biology underlying this phenomenon remains unclear. Here we assessed the effect of chronic stress on cellular senescence—a hallmark of aging. Exposure to restraint stress, a psychological non-social stress model, increased $p21^{Cip1}$ exclusively in the brains of male, but not female mice, and in a $p16^{Ink4a}$-independent manner. Conversely, exposure to chronic subordination stress (only males were tested) increased key senescent cell markers in peripheral blood mononuclear cells, adipose tissue and brain, in a $p16^{Ink4a}$-dependent manner. $p16^{Ink4a}$-positive cells in the brain of chronic subordination stress-exposed mice were primarily hippocampal and cortical neurons with evidence of DNA damage that could be reduced by $p16^{Ink4a}$ cell clearance. Clearance of $p16^{Ink4a}$-positive cells was not sufficient to ameliorate the adverse effects of social stress on measured metrics of healthspan. Overall, our findings indicate that social stress induces an organ-specific and $p16^{Ink4a}$-dependent accumulation of senescent cells, illuminating a fundamental way by which the social environment can contribute to aging.

Clearance of p21 highly expressing senescent cells accelerates cutaneous wound healing

Nathan S Gasek [# 1 2], Pengyi Yan [# 1 2], Junyu Zhu [# 1 2], K-Raman Purushothaman [3], Taewan Kim [1 2], Lichao Wang [1 2], Binsheng Wang [1 2], William F Flynn [4], Mingda Sun [1], Chun Guo [1], Billy Huggins [1 2], Roshanak Sharafieh [5], Yueying Zhou [1 6], Vojtech Parizek [1], Tamar Tchkonia [7 8], James L Kirkland [7 8 9], Saranya P Wyles [3], Ming Xu [10 11]

While senescent cells have detrimental roles in several contexts, they are highly heterogeneous. p16 highly expressing senescent cells have been reported to exert beneficial functions in wound healing. Here we use Xenium spatial transcriptomics to identify a distinct p21 highly expressing senescent population induced on wounding, with a pro-inflammatory profile. We find that clearing p21 highly expressing cells expedites wound closure and is partially mediated by NF-κB inhibition, thus enhancing our understanding of the multifaceted functions of senescence in tissue remodeling.

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PREPRINT

An Open Competition for Biomarkers of Aging

Kejun Ying, Seth Paulson, Julian Reinhard, Lucas Paulo de Lima Camillo, Jakob Träuble, Stefan Jokiel, Biomarkers of Aging Consortium, Dane Gobel, Chiara Herzog, Jesse R. Poganik, Mahdi Moqri, Vadim N. Gladyshev

Open scientific competitions have successfully driven biomedical advances but remain underutilized in aging research, where biological complexity and heterogeneity require methodological innovations. Here, we present the results from Phase I of the Biomarkers of Aging Challenge, an open competition designed to drive innovation in aging biomarker development and validation. The challenge leverages a unique DNA methylation dataset and aging outcomes from 500 individuals, aged 18 to 99. Participants are asked to develop novel models to predict chronological age, mortality, and multi-morbidity. Results from the chronological age prediction phase show important advances in biomarker accuracy and innovation compared to existing models. The winning models feature improved predictive power and employ advanced machine learning techniques, innovative data preprocessing, and the integration of biological knowledge. These approaches have led to the identification of novel age-associated methylation sites and patterns. This challenge establishes a paradigm for collaborative aging biomarker development, potentially accelerating the discovery of clinically relevant predictors of aging-related outcomes. This supports personalized medicine, clinical trial design, and the broader field of geroscience, paving the way for more targeted and effective longevity interventions.

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PREPRINT

Cell-type specific epigenetic clocks to quantify biological age at cell-type resolution

Huige Tong, Xiaolong Guo, Macsue Jacques, Qi Luo, Nir Eynon, Andrew E. Teschendorff

The ability to accurately quantify biological age could help monitor and control healthy aging. Epigenetic clocks have emerged as promising tools for estimating biological age, yet they have been developed from heterogeneous bulk tissues, and are thus composites of two aging processes, one reflecting the change of cell-type composition with age and another reflecting the aging of individual cell-types. There is thus a need to dissect and quantify these two components of epigenetic clocks, and to develop epigenetic clocks that can yield biological age estimates at cell-type resolution. Here we demonstrate that in blood and brain, approximately 39% and 12% of an epigenetic clock's accuracy is driven by underlying shifts in lymphocyte and neuronal subsets, respectively. Using brain and liver tissue as prototypes, we build and validate neuron and hepatocyte specific DNA methylation clocks, and demonstrate that these cell-type specific clocks yield improved estimates of chronological age in the corresponding cell and tissue-types. We find that neuron and glia specific clocks display biological age acceleration in Alzheimer's Disease with the effect being strongest for glia in the temporal lobe. Moreover, CpGs from these clocks display a small but significant overlap with the causal DamAge-clock, mapping to key genes implicated in neurodegeneration. The hepatocyte clock is found accelerated in liver under various pathological conditions. In contrast, non-cell-type specific clocks do not display biological age-acceleration, or only do so marginally. In summary, this work highlights the importance of dissecting epigenetic clocks and quantifying biological age at cell-type resolution.

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PREPRINT

Profiling Epigenetic Aging at Cell-Type Resolution Through Long-Read Sequencing

Alec Eames, Mahdi Moqri, Jesse R. Poganik, Vadim N. Gladyshev

DNA methylation can give rise to robust biomarkers of aging, yet most studies profile it at the bulk tissue level, which masks cell type-specific alterations that may follow distinct aging trajectories. Long-read sequencing technology enables methylation profiling of extended DNA fragments, which allows mapping to their cell type of origin. In this study, we introduce a framework for evaluating cell type-specific aging using long-read sequencing data, without the need for cell sorting. Leveraging cell type-specific methylation patterns, we map long-read fragments to individual cell types and generate cell type-specific methylation profiles, which are used as input to a newly developed probabilistic aging model, LongReadAge, capable of predicting epigenetic age at the cell-type level. We apply LongReadAge to track aging of myeloid cells and lymphocytes from bulk leukocyte data as well as circulating cell-free DNA, demonstrating robust performance in predicting age despite limited shared features across samples. This approach provides a novel method for profiling the dynamics of epigenetic aging at cell-type resolution.

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PREPRINT

Leveraging Single-Cell RNA-Seq to Generate Robust Microglia Aging Clocks

Natalie Stanley, Luvna Dhawka, Sneha Jaikumar, Yu-Chen Huang, Anthony S Zannas

'Biological aging clocks' - composite molecular markers thought to capture an individual's biological age - have been traditionally developed through bulk-level analyses of mixed cells and tissues. However, recent evidence highlights the importance of gaining single-cell-level insights into the aging process. Microglia are key immune cells in the brain shown to adapt functionally in aging and disease. Recent studies have generated single-cell RNA sequencing (scRNA-seq) datasets that transcriptionally profile microglia during aging and development. Leveraging such datasets, we develop and compare computational approaches for generating transcriptome-wide summaries to establish robust microglia aging clocks. Our results reveal that unsupervised, frequency-based featurization approaches strike a balance in accuracy, interpretability, and computational efficiency. We further extrapolate and demonstrate applicability of such microglia clocks to readily available bulk RNA-seq data with environmental inputs. Single-cell-derived clocks can yield insights into the determinants of brain aging, ultimately promoting interventions that beneficially modulate health and disease trajectories.

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PREPRINT

Devising reliable and accurate epigenetic predictors: choosing the optimal computational solution

Charlotte D.Vavourakis, Chiara M. Herzog, Martin Widschwendter

Illumina DNA methylation arrays are frequently used for the discovery of methylation signatures associated with aging and disease. One of the major hurdles to overcome when training trait prediction models is the high dimensionality of the data, with the number of features (CpGs) greatly exceeding the typical number of samples assessed. In addition, most large-scale DNA methylation-based studies do not include replicate measurements for a given sample, making it impossible to estimate the degree of measurement uncertainty or the reliability of the prediction models. A recent study proposed that training penalized regression models on derived principal components (PCs) rather than on the original features (CpGs) results in more reliable age predictions, as estimated from technical replication. Moreover, the same method could be applied for predicting other phenotypes more reliably. Here, we aimed at validating the proposed PC method. We found that although dimension reduction with PCA consistently led to small improvements in the reliability of age prediction models, it severely compromised their accuracy. PC-based models needed far larger training set sizes to be similarly accurate as CpG-based models, whereas reliability did not depend on the sample size of the training set data for either approach. Finally, the PC version of a novel multiclass predictor for breast, ovarian and endometrial cancer we trained using weighted ensembles of deep-learning models also had a markedly lower predictive accuracy compared to a CpG version, suggesting limited applicability of the proposed PC method for predicting phenotypes beyond age.

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Transform the Information Landscape Applying Waddington Landscape to Information Theory of Aging and Epigenetic Rejuvenation

Yue Wu

The Information Theory of Aging (ITOA) provides a framework for understanding aging and rejuvenation via changes in epigenetic information. These changes are visualized using Waddington landscape — a 3D topology that represents cell trajectories during changes in cell identity — constructed from field decomposition of scRNA velocity data. Studies have demonstrated that the Waddington landscape can serve as a mechanistic model of epigenetic information. It explains how age-driven decline in cellular function and reprogramming-induced rejuvenation can be understood by studying the transformations in the Waddington landscape. This study provides insights into the representation of epigenetic information and discusses how it can be reprogrammed to restore a younger cellular state.

Characterising developmental dynamics of adult epigenetic clock sites

Rosa H. Mulder [a,b] · Alexander Neumann [a,b] · Janine F. Felix [b,c] · Matthew Suderman [d] · Charlotte A.M. Cecil [a,e,f]

Background

DNA methylation (DNAm), an epigenetic mechanism that regulates gene activity in response to genetic and environmental influences, changes as we age. DNAm at specific sites on the genome can be used to calculate 'epigenetic clocks', which are powerful biomarkers of age, as well as of ageing. However, little is known about how these clock sites 'behave' during development and what factors influence their variability in early life. This knowledge could be used to optimise healthy ageing well before the onset of age-related conditions.

Methods

We leveraged results from two longitudinal population-based cohorts (N = 5019 samples from 2348 individuals) to characterise trajectories of adult clock sites from birth to early adulthood. To explore what factors may drive early individual differences at these clock sites, we also tested for enrichment of genetic factors and prenatal exposures based on existing epigenome-wide association meta-analyses.

Findings

We find that clock sites (i) diverge widely in their developmental trajectories, often showing non-linear change over time; (ii) are substantially more likely than non-clock sites to vary between individuals already from birth, differences that are predictive of DNAm variation at later ages; and (iii) show enrichment for genetic influences and prenatal environmental exposures, including prenatal smoking, diet and maternal physical health conditions.

Interpretation

These results suggests that age(ing)-related epigenetic processes might originate—and differ between individuals—already very early in development. Understanding what drives these differences may in future help us to devise better strategies to promote healthy ageing.

Age-Dependent DNA Methylation Variability on the X-Chromosome in Male and Female Twins

by Qihua Tan [1,2,*], Hikmat Alo [1], Marianne Nygaard [1], Mette Sørensen [1], Alisa Saleh [1], Jonas Mengel-From [1] and Kaare Christensen [1]

We aimed to explore the age-dependent epigenetic variability on the X-chromosome with consideration of X-chromosome inactivation by applying a sex-stratified regression analysis to DNA methylation array data on X-linked CpGs in aging identical twins. We found 13 X-linked CpGs showing age-related significant increase in variability in males (FDR < 0.05) but none in females. In females, we found a significantly higher proportion of CpGs showing increased variability with age among nominally significant ($p < 0.05$) CpGs under inactivation, but not among CpGs escaping inactivation. Survival analysis showed a slight trend of correlation by directional change in the variable CpGs with mortality in males. Compared with females, the male X-chromosome can be more vulnerable to epigenetic instability during aging.

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CircAge: A Comprehensive Resource for Aging-Associated Circular RNAs Across Species and Tissues

Xin Dong, Zhen Zhou, Yanan Wang, Ayesha Nisar, Shaoyan Pu, Longbao Lv, Yijiang Li, Xuemei Lu, Yonghan He

Circular RNAs (circRNAs) represent a novel class of RNA molecules characterized by a circular structure and enhanced stability. Emerging evidence indicates that circRNAs play pivotal regulatory roles in the aging process. Despite this, there is a lack of a systematic resource that integrates aging-associated circRNA data. Therefore, we developed a comprehensive database named circAge, which encompasses 689 aging-related samples from 7 species and 21 tissue types. We also generated 47 new tissue samples from mice and rhesus monkeys through high-throughput sequencing. Integrating predictions from multiple bioinformatics tools, we identified over 413,378 unique circRNAs. Our data analysis revealed a general increase in circRNA expression levels with age, with approximately 22% of circRNAs demonstrating sequence conservation across species. The circAge database systematically predicts potential interactions between circRNAs and miRNAs, RNA-binding proteins, and assesses the coding potential of circRNAs. This resource lays a foundation for elucidating the regulatory mechanisms of circRNAs in aging. As a comprehensive repository of aging-associated circRNAs, circAge will significantly accelerate research in this field, facilitating the discovery of novel biomarkers and therapeutic targets for aging biology and developing diagnostic and therapeutic strategies for aging and age-related diseases. CircAge is publicly available at https://circage.kiz.ac.cn.

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Analysis of lifespan across Diversity Outbred mouse studies identifies multiple longevity-associated loci

Martin N. Mullis, Kevin M. Wright, Anil Raj, Daniel M. Gatti, Peter C. Reifsnyder, Kevin Flurkey, Jonathan R. Archer, Laura Robinson, Andrea Di Francesco, Karen L. Svenson, Ron Korstanje, David E. Harrison, J. Graham Ruby, Gary A. Churchill

Lifespan is an integrative phenotype whose genetic architecture is likely to highlight multiple processes with high impact on health and aging. Here, we conduct a genetic meta-analysis of longevity in Diversity Outbred (DO) mice that includes 2,444 animals from three independently conducted lifespan studies. We identify six loci that contribute significantly to lifespan independently of diet and drug treatment, one of which also influences lifespan in a sex-dependent manner, as well as an additional locus with a diet-specific effect on lifespan. Collectively, these loci explain over half of the estimated heritable variation in lifespan across these studies and provide insight into the genetic architecture of lifespan in DO mice.

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PREPRINT

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

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

Diminished signaling via insulin/insulin-like growth factor-1 (IGF-1) axis is associated with longevity in different model organisms. IGF-1 gene is highly conserved across species, with only few evolutionary changes identified in it. Despite its potential role in regulating life span, no coding variants in IGF-1 have been reported in human longevity cohorts to date. This study investigated the whole exome sequencing data from 2,487 individuals in a cohort of Ashkenazi Jewish centenarians, their offspring, and controls without familial longevity to identify functional IGF-1 coding variants. We identified two likely functional coding variants *IGF-1*:p.Ile91Leu and *IGF-1*:p.Ala118Thr in our longevity cohort. Notably, a centenarian specific novel variant *IGF-1*:*p*.Ile91Leu was located at the binding interface of IGF-1 – IGF-1R, whereas *IGF-1*:p.Ala118Thr was significantly associated with lower circulating levels of IGF-1. We performed extended all-atom molecular dynamics simulations to evaluate the impact of Ile91Leu on stability, binding dynamics and energetics of IGF-1 bound to IGF-1R. The *IGF-1*:p.Ile91Leu formed less stable interactions with IGF-1R's critical binding pocket residues and demonstrated lower binding affinity at the extracellular binding site compared to wild-type IGF-1. Our findings suggest that *IGF-1*:p.Ile91Leu and *IGF-1*:p.Ala118Thr variants attenuate IGF-1R activity by impairing IGF-1 binding and diminishing the circulatory levels of IGF-1, respectively. Consequently, diminished IGF-1 signaling resulting from these variants may contribute to exceptional longevity in humans.

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An updated reference genome sequence and annotation reveals gene losses and gains underlying naked mole-rat biology

The naked mole-rat (NMR; *Heterocephalus glaber*) is a eusocial subterranean rodent with a highly unusual set of physiological traits that has attracted great interest amongst the scientific community. However, the genetic basis of most of these traits has not been elucidated. To facilitate our understanding of the molecular mechanisms underlying NMR physiology and behaviour, we generated a long-read chromosomal-level genome assembly of the NMR. This genome was subsequently annotated and incorporated into multiple whole genome alignments in the Ensembl database. Our long-read assembly identified thousands of repeats and genes that were previously unassembled in the NMR and improved the results of routinely used short-read sequencing-based experiments such as RNA-seq, snRNA-seq, and ATAC-seq. We identified several spermatozoa related gene losses that may underlie the unique degenerative sperm phenotype in NMRs (*IRGC*, *FSCB*, *AKAP3*, *MROH2B*, *CATSPER1*, *DCDC2C*, *ATP1A4*, *TEKT5, and ZAN*), and an additional gene loss related to the established NK-cell absence in NMRs (*PILRB*). We resolved several tandem duplications in genes related to pathways underlying unique NMR adaptations including hypoxia tolerance, oxidative stress, and nervous system protection (*TINF2*, *TCP1*, *KYAT1*). Lastly, we describe our ongoing efforts to generate a reference telomere-to-telomere assembly in the NMR which includes the resolution of complex gene families. This new reference genome should accelerate the discovery of the genetic underpinnings of NMR physiology and adaptation.

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Extensive longevity and DNA virus-driven adaptation in nearctic *Myotis* bats

The genus *Myotis* is one of the largest clades of bats, and exhibits some of the most extreme variation in lifespans among mammals alongside unique adaptations to viral tolerance and immune defense. To study the evolution of longevity-associated traits and infectious disease, we generated near-complete genome assemblies and cell lines for 8 closely related species of *Myotis*. Using genome-wide screens of positive selection, analyses of structural variation, and functional experiments in primary cell lines, we identify new patterns of adaptation contributing to longevity, cancer resistance, and viral interactions in bats. We find that *Myotis* bats have some of the most significant variation in cancer risk across mammals and demonstrate a unique DNA damage response in primary cells of the long-lived *M. lucifugus*. We also find evidence of abundant adaptation in response to DNA viruses - but not RNA viruses - in *Myotis* and other bats in sharp contrast with other mammals, potentially contributing to the role of bats as reservoirs of zoonoses. Together, our results demonstrate how genomics and primary cells derived from diverse taxa uncover the molecular bases of extreme adaptations in non-model organisms.

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PREPRINT

DNA repair and anti-cancer mechanisms in the long-lived bowhead whale

At over 200 years, the maximum lifespan of the bowhead whale exceeds that of all other mammals. The bowhead is also the second-largest animal on Earth, reaching over 80,000 kg[1]. Despite its very large number of cells and long lifespan, the bowhead is not highly cancer-prone, an incongruity termed Peto's Paradox[2]. This phenomenon has been explained by the evolution of additional tumor suppressor genes in other larger animals, supported by research on elephants demonstrating expansion of the p53 gene[3–5]. Here we show that bowhead whale fibroblasts undergo oncogenic transformation after disruption of fewer tumor suppressors than required for human fibroblasts. However, analysis of DNA repair revealed that bowhead cells repair double strand breaks (DSBs) and mismatches with uniquely high efficiency and accuracy compared to other mammals. The protein CIRBP, implicated in protection from genotoxic stress, was present in very high abundance in the bowhead whale relative to other mammals. We show that CIRBP and its downstream protein RPA2, also present at high levels in bowhead cells, increase the efficiency and fidelity of DNA repair in human cells. These results indicate that rather than possessing additional tumor suppressor genes as barriers to oncogenesis, the bowhead whale relies on more accurate and efficient DNA repair to preserve genome integrity. This strategy which does not eliminate damaged cells but repairs them may be critical for the long and cancer-free lifespan of the bowhead whale.

Heales
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PREPRINT

DNA methylation of transposons pattern aging differences across a diverse cohort of dogs from the Dog Aging Project

Within a species, larger individuals often have shorter lives and higher rates of age-related disease. Despite this well-known link, we still know little about underlying age-related epigenetic differences, which could help us better understand inter-individual variation in aging and the etiology, onset, and progression of age-associated disease. Dogs exhibit this negative correlation between size, health, and longevity and thus represent an excellent system in which to test the underlying mechanisms. Here, we quantified genome-wide DNA methylation in a cohort of 864 dogs in the Dog Aging Project. Age strongly patterned the dog epigenome, with the majority (66% of age-associated loci) of regions associating age-related loss of methylation. These age effects were non-randomly distributed in the genome and differed depending on genomic context. We found the LINE1 (long interspersed elements) class of TEs (transposable elements) were the most frequently hypomethylated with age (FDR < 0.05, 40% of all LINE1 regions). This LINE1 pattern differed in magnitude across breeds of different sizes– the largest dogs lost 0.26% more LINE1 methylation per year than the smallest dogs. This suggests that epigenetic regulation of TEs, particularly LINE1s, may contribute to accelerated age and disease phenotypes within a species. Since our study focused on the methylome of immune cells, we looked at LINE1 methylation changes in golden retrievers, a breed highly susceptible to hematopoietic cancers, and found they have accelerated age-related LINE1 hypomethylation compared to other breeds. We also found many of the LINE1s hypomethylated with age are located on the X chromosome and are, when considering X chromosome inactivation, counter-intuitively more methylated in males. These results have revealed the demethylation of LINE1 transposons as a potential driver of inter-species, demographic-dependent aging variation.

Genome-Wide Statistical Evidence Elucidates Candidate Factors of Life Expectancy in Dogs

Won Hee Ko [1], Sangil Kim [2], Alix Catry [3], Je-Yoel Cho [4], Seunggwan Shin [5]

It is well-established that large and heavy dogs tend to live shorter lives. In this study, we aimed to determine whether traits other than body size are associated with the life expectancy of dogs. We compiled a dataset of 20 phenotypes, including body size, lifespan, snout ratio, and shedding, into a single matrix for 149 dog breeds using data from the American Kennel Club (AKC) and other peer-reviewed sources. The analysis revealed that drooling might be associated with both the lifespan and BMI of dogs. Furthermore, a genome-wide association study (GWAS) with adjusted phenotypes and statistical verification methods, such as Mendelian randomization (MR). Additionally, conducting differentially expressed gene (DEG) analysis with the salivary gland for the two cases, hypersalivation/less drooling versus various body sizes, we could observe the hypersalivation-related proteins. This genetic analysis suggests that body size and drooling might be candidate factors influencing lifespan. Consequently, we identified several candidate genes, including IGSF1, PACSIN2, PIK3R1, and MCCC2, as potential genetic factors influencing longevity-related phenotypes.

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Is castration leading to biological aging in dogs? Assessment of lipid peroxidation, inflammation, telomere length, mitochondrial DNA copy number, and expression of telomerase and age-related genes

Background

Biological aging is a complex process influenced by various factors, including reproductive status and castration. This study aimed to evaluate the impact of castration on biological aging in dogs.

Method

Fifteen male crossbred dogs were randomly divided into a sham-operation control group (n = 5) and a castrated group (n = 10). Blood samples were collected at weeks 0, 4, 8, 12, 16, and 18 post-surgery. Malondialdehyde (MDA as indicator of Lipid peroxidation), C-reactive protein (as an indicator of inflammation), telomere length, mitochondrial DNA (mtDNA) copy number, and the expression of age-related (P16, P21, TBX2) and telomerase-related (TERT) genes were assessed in blood samples.

Results

Plasma MDA levels were higher in the control group at weeks 16 and 18, while CRP levels were higher only at week 18. Telomere length and mtDNA copy number were lower in the control group at week 18. Gene expression analysis showed that P16 was lower in the control group at weeks 8 and 12, P21 and TERT were lower at weeks 16 and 18, and TBX2 was lower at weeks 16 and 18. The TBX2/P16 ratio was lower in the control group at weeks 16 and 18 but higher at week 12, while the TBX2/P21 ratio did not differ between groups.

Conclusion

Castration appears to have a protective effect against biological aging in dogs, as evidenced by lower lipid peroxidation, inflammation, and age-related changes in telomere length, mtDNA copy number, and gene expression.

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Reverse development in the ctenophore *Mnemiopsis leidyi*

Joan J. Soto-Angel and Pawel Burkhardt Authors Info & Affiliations

Reverse development, or the ability to rejuvenate by morphological reorganization into the preceding life cycle stage is thought to be restricted to a few species within Cnidaria. To date, *Turritopsis dohrnii* is the only known species capable of undergoing reverse development after the onset of sexual reproduction. Here, we demonstrate that the ctenophore *Mnemiopsis leidyi* is capable of reversal from mature lobate to early cydippid when fed following a period of stress. Our findings illuminate central aspects of ctenophore development, ecology, and evolution and show the high potential of *M. leidyi* as a unique model system to study reverse development and rejuvenation. Besides shedding light on the plasticity of developmental programs, these results raise fundamental questions about early animal development, body plans, and life cycles.

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Discovering geroprotectors through the explainable artificial intelligence-based platform AgeXtend

Aging involves metabolic changes that lead to reduced cellular fitness, yet the role of many metabolites in aging is unclear. Understanding the mechanisms of known geroprotective molecules reveals insights into metabolic networks regulating aging and aids in identifying additional geroprotectors. Here we present AgeXtend, an artificial intelligence (AI)-based multimodal geroprotector prediction platform that leverages bioactivity data of known geroprotectors. AgeXtend encompasses modules that predict geroprotective potential, assess toxicity and identify target proteins and potential mechanisms. We found that AgeXtend accurately identified the pro-longevity effects of known geroprotectors excluded from training data, such as metformin and taurine. Using AgeXtend, we screened ~1.1 billion compounds and identified numerous potential geroprotectors, which we validated using yeast and *Caenorhabditis elegans* lifespan assays, as well as exploring microbiome-derived metabolites. Finally, we evaluated endogenous metabolites predicted as senomodulators using senescence assays in human fibroblasts, highlighting AgeXtend's potential to reveal unidentified geroprotectors and provide insights into aging mechanisms.

Exceptional longevity of mammalian ovarian and oocyte macromolecules throughout the reproductive lifespan

The mechanisms contributing to age-related deterioration of the female reproductive system are complex, however aberrant protein homeostasis is a major contributor. We elucidated exceptionally stable proteins, structures, and macromolecules that persist in mammalian ovaries and gametes across the reproductive lifespan. Ovaries exhibit localized structural and cell-type-specific enrichment of stable macromolecules in both the follicular and extrafollicular environments. Moreover, ovaries and oocytes both harbor a panel of exceptionally long-lived proteins, including cytoskeletal, mitochondrial, and oocyte-derived proteins. The exceptional persistence of these long-lived molecules suggest a critical role in lifelong maintenance and age-dependent deterioration of reproductive tissues.

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Molecular and genetic insights into human ovarian aging from single-nuclei multi-omics analyses

Chen Jin ✉, Xizhe Wang, Jiping Yang, Seungsoo Kim, Adam D. Hudgins, Amir Gamliel, Mingzhuo Pei, Daniela Contreras, Melody Devos, Qinghua Guo, Jan Vijg, Marco Conti, Jan Hoeijmakers, Judith Campisi, Rogerio Lobo, Zev Williams, Michael G. Rosenfeld & Yousin Suh ✉

The ovary is the first organ to age in the human body, affecting both fertility and overall health. However, the biological mechanisms underlying human ovarian aging remain poorly understood. Here we present a comprehensive single-nuclei multi-omics atlas of four young (ages 23–29 years) and four reproductively aged (ages 49–54 years) human ovaries. Our analyses reveal coordinated changes in transcriptomes and chromatin accessibilities across cell types in the ovary during aging, notably mTOR signaling being a prominent ovary-specific aging pathway. Cell-type-specific regulatory networks reveal enhanced activity of the transcription factor CEBPD across cell types in the aged ovary. Integration of our multi-omics data with genetic variants associated with age at natural menopause demonstrates a global impact of functional variants on gene regulatory networks across ovarian cell types. We nominate functional non-coding regulatory variants, their target genes and ovarian cell types and regulatory mechanisms. This atlas provides a valuable resource for understanding the cellular, molecular and genetic basis of human ovarian aging.

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Late-life protein or isoleucine restriction impacts physiological and molecular signatures of aging

Restricting the intake of protein or the branched-chain amino acid isoleucine promotes healthspan and extends lifespan in young or adult mice. However, their effects when initiated in aged animals are unknown. Here we investigate the consequences of consuming a diet with 67% reduction of all amino acids (low AA) or of isoleucine alone (low Ile), in male and female C57BL/6J.Nia mice starting at 20 months of age. Both dietary regimens effectively promote overall metabolic health without reducing calorie intake. Both low AA and low Ile diets improve aspects of frailty and slow multiple molecular indicators of aging rate; however, the low Ile diet reduces grip strength in both sexes and has mixed, sexually dimorphic effects on the heart. These results demonstrate that low AA and low Ile diets can promote aspects of healthy aging in aged mice and suggest that similar interventions might promote healthy aging in older adults.

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Post hoc analysis of ADAMANT, a phase 2 clinical trial of active tau immunotherapy with AADvac1 in patients with Alzheimer's disease, positive for plasma p-tau217

Background: The spread of tau pathology closely correlates with the disease course and cognitive decline in Alzheimer's disease (AD). Tau-targeting immunotherapies are being developed to stop the spread of tau pathology and thus halt disease progression. In this post hoc analysis of the ADAMANT clinical trial, we examined the performance of AADvac1, an active immunotherapy targeting the microtubule-binding region (MTBR) of tau, in a subgroup of participants with elevated plasma p-tau217, indicating AD-related neuropathological changes.

Methods: ADAMANT was a 24-month, randomized, placebo-controlled, parallel-group, double-blinded, multicenter, phase 2 clinical trial in subjects with mild AD. The trial participants were randomized 3:2 to receive six doses of AADvac1 or placebo at 4-week intervals, followed by five booster doses at 14-week intervals. The primary outcome was safety. The secondary outcomes were the Clinical Dementia Rating-Sum of Boxes (CDR-SB), the Alzheimer's Disease Cooperative Study - Activities of Daily Living score for Mild Cognitive Impairment 18-item version (ADCS-ADL-MCI-18), and immunogenicity. Volumetric MRI, plasma neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) were exploratory outcomes. The inclusion criterion for this post-hoc analysis was a baseline plasma p-tau217 level above the cutoff for AD.

Results: Among 196 ADAMANT participants, 137 were positive for plasma p-tau217 (mean age 71.4 years, 59% women). AADvac1 was safe and well tolerated in this subgroup. AADvac1 reduced the rate of accumulation of log-plasma NfL by 56% and that of GFAP by 73%. The treatment differences in the CDR-SB and ADCS-ADL-MCI-18 scores favored AADvac1 but were not statistically significant. AADvac1 had no effect on whole-brain volume but nonsignificantly reduced the loss of brain cortical tissue in several regions. Importantly, the impact on the study outcomes was more pronounced in participants with higher anti-tau antibody levels.

Conclusions: These results suggest that AADvac1 tau immunotherapy can reduce plasma biomarkers of neurodegeneration and neuroinflammation. These findings and possible observations on brain atrophy and cognition are hypothesis-generating and warrant further evaluation in a larger clinical trial.

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PREPRINT

Cannabis smoke and oral Δ9THC enhance working memory in aged but not young adult subjects

With increased legalization of recreational and medical cannabis, use of this drug is growing rapidly among older adults. As cannabis use can impair cognition in young adults, it is critically important to understand how consumption interacts with the cognitive profile of aged individuals, who are already at increased risk of decline. The current study was designed to determine how cannabis influences multiple forms of cognition in young adult and aged rats of both sexes when delivered via two translationally-relevant routes of administration. Acute exposure to cannabis smoke enhanced prefrontal cortex-dependent working memory accuracy in aged males, but impaired accuracy in aged females, while having no effects in young adults of either sex. In contrast, the same cannabis smoke exposure regimen had minimal effects on a hippocampus-dependent trial-unique non-matching to location mnemonic task, irrespective of age or sex. In a second set of experiments, chronic oral consumption of Δ9-tetrahydrocannabinol (Δ9THC) enhanced working memory in aged rats of both sexes, while having no effects in young adults. In contrast, the same oral Δ9THC regimen did not affect spatial learning and memory in either age group. Minimal age differences were observed in Δ9THC pharmacokinetics with either route of administration. Together, these results show that cannabis and Δ9THC can attenuate working memory impairments that emerge in aging. While these enhancing effects do not extend to hippocampus-dependent cognition, cannabis does not appear to exacerbate age-associated impairments in this cognitive domain.

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PREPRINT

IMMClock reveals immune aging and T cell function at single-cell resolution

Yael Gurevich Schmidt, Di Wu, Sanna Madan, Sanju Sinha, Sahil Sahni, Vishaka Gopalan, Binbin Wang, Saugato Rahman Dhruba, Alejandro A. Schäffer, Nan-ping Weng, Nicholas P. Restifo, Kun Wang, Eytan Ruppin

The aging of the immune system substantially impacts individual immune responses, yet accurately quantifying immune age remains a complex challenge. Here we developed **IMMClock**, a novel immune aging clock that uses gene expression data to predict the biological age of individual $CD8^+$ T cells, $CD4^+$ T cells, and NK cells. The accuracy of IMMClock is first validated across multiple independent datasets, demonstrating its robustness. Second, utilizing the IMMClock, we find that intrinsic cellular aging processes are more strongly altered during immune aging than differentiation processes. Thirdly, our analysis confirms the strong associations between immune aging and established processes such as cellular senescence, exhaustion, and telomere length at the single cell level. Furthermore, immune aging is accelerated under several disease conditions such as type 2 diabetes, heart disease, and cancer. Finally, we apply IMMClock to analyze a perturb-seq gene activation screen of T cell functionality. We find that the post-perturbation immune age of individual T cells is strongly correlated with their pre-perturbation immune age. Furthermore, the immune age at resting state of individual T cells is strongly predictive of their post-stimulation activation state. Overall, IMMClock advances our understanding of immune aging by providing precise, single-cell level age estimations. Its future applications hold promise for identifying interventions that concomitantly rejuvenate and activate T cells, potentially enhancing efforts to counteract age-related immune decline.

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Age-related loss of intestinal barrier integrity plays an integral role in thymic involution and T cell ageing

Jessica Conway, Erica N. De Jong, Andrea J. White, Ben Dugan, Nia Paddison Rees, Sonia M. Parnell, Lisa E. Lamberte, Archana Sharma-Oates, Jack Sullivan, Claudio Mauro ... See all authors

The intestinal epithelium serves as a physical and functional barrier against harmful substances, preventing their entry into the circulation and subsequent induction of a systemic immune response. Gut barrier dysfunction has recently emerged as a feature of ageing linked to declining health, and increased intestinal membrane permeability has been shown to promote heightened systemic inflammation in aged hosts. Concurrent with age-related changes in the gut microbiome, the thymic microenvironment undergoes a series of morphological, phenotypical and architectural alterations with age, including disorganisation of the corticomedullary junction, increased fibrosis, increased thymic adiposity and the accumulation of senescent cells. However, a direct link between gut barrier dysbiosis and thymic involution leading to features of immune ageing has not been explored thus far. Herein, we reveal strong associations between enhanced microbial translocation and the peripheral accumulation of terminally differentiated, senescent and exhausted T cells and the compensatory expansion of regulatory T cells in older adults. Crucially, we demonstrate that aged germ-free mice are protected from age-related increases in intestinal permeability, highlighting the direct impact of mucosal permeability on thymic ageing. Together, these findings establish a novel mechanism by which gut barrier dysfunction drives systemic activation of the immune system during ageing through thymic involution. This enhances our understanding of drivers of T cell ageing and opens up the possibility for the use of microbiome-based interventions to restore immune homeostasis and promote healthy ageing in older adults.

Spatial transcriptomic landscape unveils immunoglobin-associated senescence as a hallmark of aging

Shuai Ma [1,5,6,8,24,25,26] · Zhejun Ji [2,5,6,25] · Bin Zhang [1,8,25] · … · Weiqi Zhang [3,4,8,24] ✉ · Ying Gu [9,12,23] ✉ · Guang-Hui Liu [1,5,6,7,8,24,27] ✉ … Show more

To systematically characterize the loss of tissue integrity and organ dysfunction resulting from aging, we produced an in-depth spatial transcriptomic profile of nine tissues in male mice during aging. We showed that senescence-sensitive spots (SSSs) colocalized with elevated entropy in organizational structure and that the aggregation of immunoglobulin-expressing cells is a characteristic feature of the microenvironment surrounding SSSs. Immunoglobulin G (IgG) accumulated across the aged tissues in both male and female mice, and a similar phenomenon was observed in human tissues, suggesting the potential of the abnormal elevation of immunoglobulins as an evolutionarily conserved feature in aging. Furthermore, we observed that IgG could induce a pro-senescent state in macrophages and microglia, thereby exacerbating tissue aging, and that targeted reduction of IgG mitigated aging across various tissues in male mice. This study provides a high-resolution spatial depiction of aging and indicates the pivotal role of immunoglobulin-associated senescence during the aging process.

Immunosenescence Inventory—a multi-omics database for immune aging research

Hao Li, Wei Zhao, Fei Yang, Qin Qiao, Shuai Ma, Kuan Yang, Shuhui Song, Si Wang, Jing Qu ✉, Guang-Hui Liu ... Show more

The immune system is intricately interconnected with all other bodily systems. As individuals age, the immune system undergoes changes known as immunosenescence, increasing susceptibility to disease, and contributing significantly to the morbidity and mortality observed in older populations. Immunosenescence drives systemic aging and therefore represents a key therapeutic target to extend healthy aging. In recent years, the extensive application of omics technologies has broadened our understanding of aging and immunity, necessitating a comprehensive database to encapsulate these advancements and deepen our insights into immune aging in the era of artificial intelligence. The Immunosenescence Inventory is a pioneering database designed to provide a multidimensional and integrative view of the aging immune system. By leveraging cutting-edge omics technologies and analytical tools, Immunosenescence Inventory offers a comprehensive resource for researchers to explore the intricate relationship between immunosenescence and age-related health outcomes. Furthermore, the database, which aids in the creation of diagnostic tools for immune aging conditions, is now publicly available at https://ngdc.cncb.ac.cn/iaa/home.

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PREPRINT

Proliferative events ameliorate DNA damage accumulation without affecting function in hematopoietic stem cells

Shubham Haribhau Mehatre, Harsh Agrawal, Irene Mariam Roy, Sarah Schouteden, Satish Khurana

Upon aging, HSCs show functional decline with increased proliferation, myeloid skewing, and poor engraftment efficiency. Accumulation of DNA damage has been causally linked with this phenomenon, with the debatable role of proliferative events. In this study, we sought to enquire the effect of increased hematopoietic stem cell (HSC) proliferation during the lifetime on the hematopoietic aging in mice. Multiple rounds of blood withdrawals were performed between two to twelve months of adult life to maintain higher proliferation rate in HSC population. Our experiments showed little effect of increased proliferation rate on age-associated functional decline in hematopoietic system. However, we noted a decrease in the double strand breaks (DSBs) accumulated with age in mice that underwent serial bleeding regimen. Analysis of single-cell sequencing data from mouse and human HSPCs showed enrichment of DNA damage response pathways confirmed by increased expression of the genes involved. Importantly, we demonstrate that the induction of HSC proliferation in aged mice is sufficient to decrease the load of DSBs. Hence, our results show that proliferative events during lifetime might aid in clearing age-associated DSBs. While these DNA damages might not be directly linked with the functional decline, proliferation induced clearance can have clinical implications.

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PREPRINT

Reducing functionally defective old HSCs alleviates aging-related phenotypes in old recipient mice

Yuting Wang, Wenhao Zhang, Chao Zhang, Hoang Tran Van, Takashi Seino, Yi Zhang

Aging is a process accompanied by functional decline in tissues and organs with great social and medical consequences. Developing effective anti-aging strategies is of great significance. In this study, we demonstrated that transplantation of young hematopoietic stem cells (HSCs) into old mice can mitigate aging phenotypes, underscoring the crucial role of HSCs in the aging process. Through comprehensive molecular and functional analyses, we identified a subset of HSCs in aged mice that exhibit "younger" molecular profiles and functions, marked by low levels of CD150 expression. Mechanistically, $CD150^{low}$ HSCs from old mice can effectively differentiate into downstream lineage cells but not their $CD150^{high}$ counterparts. Notably, transplantation of old $CD150^{low}$ HSCs attenuates aging phenotypes and prolongs lifespan of elderly mice compared to those transplanted with unselected or $CD150^{high}$ HSCs. Importantly, reducing the dysfunctional $CD150^{high}$ HSCs can alleviate aging phenotypes in old recipient mice. Thus, our study demonstrates the presence of "younger" HSCs in old mice, and aging-associated functional decline can be mitigated by reducing dysfunctional HSCs.

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PREPRINT

Human skin rejuvenation via mRNA

Aging is characterized by a gradual decline in function, partly due to accumulated molecular damage. Human skin undergoes both chronological aging and environmental degradation, particularly UV-induced photoaging. Detrimental structural and physiological changes caused by aging include epidermal thinning due to stem cell depletion and dermal atrophy associated with decreased collagen production. Here, we present a comprehensive single-cell atlas of skin aging, analyzing samples from young, middle-aged, and elderly individuals, including both sun-exposed and sun-protected areas. This atlas reveals age-related cellular composition and function changes across various skin cell types, including epidermal stem cells, fibroblasts, hair follicles, and endothelial cells. Using our atlas, we have identified basal stem cells as a highly variable population across aging, more so than other skin cell populations such as fibroblasts. In basal stem cells, we identified ATF3 as a novel regulator of skin aging. ATF3 is a transcriptional factor for genes involved in the aging process, with its expression reduced by 20% during aging. Based on this discovery, we have developed an innovative mRNA-based treatment to mitigate the effects of skin aging. Cell senescence decreased 25% in skin cells treated with ATF3 mRNA, and we observed an over 20% increase in proliferation in treated basal stem cells. Importantly, we also found crosstalk between keratinocytes and fibroblasts as a critical component of therapeutic interventions, with ATF3 rescue of basal cells significantly enhancing fibroblast collagen production by approximately 200%. We conclude that ATF3-targeted mRNA treatment effectively reverses the effects of skin aging by modulating specific cellular mechanisms, offering a novel, targeted approach to human skin rejuvenation.

C. elegans aging research

A small-molecule screen identifies novel aging modulators by targeting 5-HT/DA signaling pathway

Shi-Wei Ye [1,2], Shuang-Di Song [1,2], Xi-Juan Liu [1], Yun Luo [1], Shi-Qing Cai [1]

The risk of many human diseases including cardiovascular diseases, cancer, neurodegenerative diseases, and musculoskeletal disorders rises significantly in the elderly. With the increase in the aging population, it is becoming increasingly important to understand the biology of healthy aging and develop interventions that slow down the aging process or prevent age-related diseases. In this study, by a high-throughput screen in Caenorhabditis elegans (C. elegans), we identified 11 small molecules that promote healthy aging. Among them, Carbamazepine (a voltage-gated channels inhibitor) and Calmagite (a calcium and magnesium indicator) enhanced serotonin (5-HT) and dopamine (DA) levels, extended lifespan, and preserved several important behaviors in aging C. elegans. These behaviors include slowing responses to food, pharyngeal pumping, locomotion, and male mating. Interestingly, we further found that administration of Carbamazepine or Calmagite alleviated hyperexcitability of aging male diagonal muscles and improved behavioral performance by ameliorating Ca^{2+} homeostasis. Mechanistically, administration of Carbamazepine or Calmagite induced nuclear translocation of the transcription factor DAF-16 and thus up-regulated its downstream genes numr-1/-2, which are known to promote resistance to metal-induced stresses and longevity. Taken together, our study offers a way for the discovery of drugs that promote healthy aging, and provides potential interventions for preventing behavioral deterioration in the elderly.

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PREPRINT

A nucleic acid prodrug activates mitochondrial respiration and extends lifespan

Takahisa Anada, Michiharu Kawahara, Taisei Shimada, Ryotaro Kuroda, Eriko Kage-Nakadai, Shingo Kobayashi, Masaru Tanaka

Mitochondrial dysfunction caused by aging leads to decreased energy metabolism, resulting in functional decline and increased frailty in multiple tissues. Strategies for protecting and activating mitochondria under stressful conditions are required to suppress aging and age-related diseases. However, it is challenging to develop drugs capable of boosting mitochondrial respiration and compensating for the reduced intracellular adenosine triphosphate (ATP) levels. In this study, we developed a prodrug that stimulates the metabolism of intracellular adenine nucleotides (AXP: adenosine monophosphate (AMP), adenosine diphosphate (ADP), and ATP). It enhances AMP-activated protein kinase activity, fatty acid oxidation, oxidative stress resistance, and mitochondrial respiration, thereby increasing the intracellular ATP levels. Furthermore, this prodrug markedly extended the lifespan of *Caenorhabditis elegans*. The stimulation of the AXP energy metabolism (AXP stimulation) proposed in this study is expected to offer a new strategy against aging and pave the way for a novel approach in the bioenergetic molecules drug discovery.

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ELO-6 expression predicts longevity in isogenic populations of *Caenorhabditis elegans*

Weilin Kong, Guoli Gu, Tong Dai, Beibei Chen, Yanli Wang, Zheng Zeng & Mintie Pu

Variations of individual lifespans within genetically identical populations in homogenous environments are remarkable, with the cause largely unknown. Here, we show the expression dynamic of the *Caenorhabditis elegans* fatty acid elongase ELO-6 during aging predicts individual longevity in isogenic populations. *elo-6* expression is reduced with age. ELO-6 expression level exhibits obvious variation between individuals in mid-aged worms and is positively correlated with lifespan and health span. Interventions that prolong longevity enhance ELO-6 expression stability during aging, indicating ELO-6 is also a populational lifespan predictor. Differentially expressed genes between short-lived and long-lived isogenic worms regulate lifespan and are enriched for PQM-1 binding sites. *pqm-1* in young to mid-aged adults causes individual ELO-6 expression heterogeneity and restricts health span and life span. Thus, our study identifies ELO-6 as a predictor of individual and populational lifespan and reveals the role of *pqm-1* in causing individual health span variation in the mid-aged *C. elegans*.

Endogenous mitochondrial NAD(P)H fluorescence can predict lifespan

Christopher S. Morrow, Pallas Yao, Carlos A. Vergani-Junior, Praju Vikas Anekal, Paula Montero Llopis, Jeffrey W. Miller, Bérénice A. Benayoun & William B. Mair

Many aging clocks have recently been developed to predict health outcomes and deconvolve heterogeneity in aging. However, existing clocks are limited by technical constraints, such as low spatial resolution, long processing time, sample destruction, and a bias towards specific aging phenotypes. Therefore, here we present a non-destructive, label-free and subcellular resolution approach for quantifying aging through optically resolving age-dependent changes to the biophysical properties of NAD(P)H in mitochondria through fluorescence lifetime imaging (FLIM) of endogenous NAD(P)H fluorescence. We uncover age-dependent changes to mitochondrial NAD(P)H across tissues in *C. elegans* that are associated with a decline in physiological function and construct non-destructive, label-free and cellular resolution models for prediction of age, which we refer to as "mito-NAD(P)H age clocks." Mito-NAD(P)H age clocks can resolve heterogeneity in the rate of aging across individuals and predict remaining lifespan. Moreover, we spatiotemporally resolve age-dependent changes to mitochondria across and within tissues, revealing multiple modes of asynchrony in aging and show that longevity is associated with a ubiquitous attenuation of these changes. Our data present a high-resolution view of mitochondrial NAD(P)H across aging, providing insights that broaden our understanding of how mitochondria change during aging and approaches which expand the toolkit to quantify aging.

Full-length direct RNA sequencing reveals extensive remodeling of RNA expression, processing and modification in aging Caenorhabditis elegans

Erin C Schiksnis [1], Ian A Nicastro [1], Amy E Pasquinelli [1]

Organismal aging is marked by decline in cellular function and anatomy, ultimately resulting in death. To inform our understanding of the mechanisms underlying this degeneration, we performed standard RNA sequencing (RNA-seq) and Oxford Nanopore Technologies direct RNA-seq over an adult time course in Caenorhabditis elegans. Long reads allowed for identification of hundreds of novel isoforms and age-associated differential isoform accumulation, resulting from alternative splicing and terminal exon choice. Genome-wide analysis reveals a decline in RNA processing fidelity. Finally, we identify thousands of inosine and hundreds of pseudouridine edits genome-wide. In this first map of pseudouridine modifications for C. elegans, we find that they largely reside in coding sequences and that the number of genes with this modification increases with age. Collectively, this analysis discovers transcriptomic signatures associated with age and is a valuable resource to understand the many processes that dictate altered gene expression patterns and post-transcriptional regulation in aging.

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The abundance change of age-regulated secreted proteins affects lifespan of C. elegans

Prasun Kumar Bhunia [1], Vishwajeet Raj [1], Prasad Kasturi [2]

Affiliations + expand

PMID: 39505117 DOI: 10.1016/j.mad.2024.112003

Abstract

Proteome integrity is vital for survival and failure to maintain it results in uncontrolled protein abundances, misfolding and aggregation which cause proteotoxicity. In multicellular organisms, proteotoxic stress is communicated among tissues to maintain proteome integrity for organismal stress resistance and survival. However, the nature of these signalling molecules and their regulation in extracellular space is largely unknown. Secreted proteins are induced in response to various stresses and aging, indicating their roles in inter-tissue communication. To study the fates of age-regulated proteins with potential localization to extracellular, we analysed publicly available age-related proteome data of C. elegans. We found that abundance of majority of the proteins with signal peptides (SP) increases with age, which might result in their supersaturation and subsequent aggregation. Intriguingly, these changes are differentially regulated in the lifespan mutants. A subset of these SP proteins is also found in the cargo of extracellular vesicles. Many of these proteins are novel and functionally uncharacterized. Reducing levels of a few extracellular proteins results in increasing lifespan. This suggests that uncontrolled levels of extracellular proteins might disturb proteostasis and limit the lifespan. Overall, our findings suggest that the age-induced secreted proteins might be the potential candidates to be considered as biomarkers or for mitigating age-related pathological conditions.

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A clustering-based survival comparison procedure designed to study the *Caenorhabditis elegans* model

Paul-Marie Grollemund, Cyril Poupet, Élise Comte, Muriel Bonnet, Philippe Veisseire & Stéphanie Bornes

Caenorhabditis elegans is highly important in current research, serving as a pivotal model organism that has greatly advanced the understanding of fundamental biological processes such as development, cellular biology, and neurobiology, helping to promote major advances in various fields of science. In this context, the survival of a nematode under various conditions is commonly investigated via statistical survival analysis, which is typically based on hypothesis testing, providing valuable insights into the factors influencing its longevity and response to various environmental factors. The extensive reliance on hypothesis testing is acknowledged as a concern in the scientific analysis process, emphasizing the need for a comprehensive evaluation of alternative statistical approaches to ensure a rigorous and unbiased interpretation of research findings. In this work, we propose an alternative method to hypothesis testing for evaluating differences in nematode survival. Our approach relies on a clustering technique that takes into account the complete structure of survival curves, enabling a more comprehensive assessment of survival dynamics. The proposed methodology helps to identify complex effects on nematode survival and enables us to derive the probability that treatment induces a specific effect. To highlight the application and benefits of the proposed methodology, it is applied to two different datasets, one simple and one more complex.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Disagreement on foundational principles of biological aging

Vadim N Gladyshev ✉, Benjamin Anderson, Hanna Barlit, Benjamin Barré, Samuel Beck, Bahareh Behrouz, Daniel W Belsky, Amandine Chaix, Manish Chamoli, Brian H Chen ...

To gain insight into how researchers of aging perceive the process they study, we conducted a survey among experts in the field. While highlighting some common features of aging, the survey exposed broad disagreement on the foundational issues. What is aging? What causes it? When does it begin? What constitutes rejuvenation? Not only was there no consensus on these and other core questions, but none of the questions received a majority opinion—even regarding the need for consensus itself. Despite many researchers believing they understand aging, their understanding diverges considerably. Importantly, as different processes are labeled as "aging" by researchers, different experimental approaches are prioritized. The survey shed light on the need to better define which aging processes this field should target and what its goals are. It also allowed us to categorize contemporary views on aging and rejuvenation, revealing critical, yet largely unanswered, questions that appear disconnected from the current research focus. Finally, we discuss ways to address the disagreement, which we hope will ultimately aid progress in the field.

Climbing the longevity pyramid: overview of evidence-driven healthcare prevention strategies for human longevity

Longevity medicine is an emerging and iterative healthcare discipline focusing on early detection, preventive measures, and personalized approaches that aim to extend healthy lifespan and promote healthy aging. This comprehensive review introduces the innovative concept of the "*Longevity Pyramid*." This conceptual framework delineates progressive intervention levels, providing a structured approach to understanding the diverse strategies available in longevity medicine. At the base of the Longevity Pyramid lies the level of prevention, emphasizing early detection strategies and advanced diagnostics or timely identification of potential health issues. Moving upwards, the next step involves lifestyle modifications, health-promoting behaviors, and proactive measures to delay the onset of age-related conditions. The Longevity Pyramid further explores the vast range of personalized interventions, highlighting the importance of tailoring medical approaches based on genetic predispositions, lifestyle factors, and unique health profiles, thereby optimizing interventions for maximal efficacy. These interventions aim to extend lifespan and reduce the impact and severity of age-related conditions, ensuring that additional years are characterized by vitality and wellbeing. By outlining these progressive levels of intervention, this review offers valuable insights into the evolving field of longevity medicine. This structured framework guides researchers and practitioners toward a nuanced strategic approach to advancing the science and practice of healthy aging.

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The catabolic - anabolic cycling hormesis model of health and resilience

Edward J. Calabrese [a], Mark P. Mattson [b]

A major goal of aging research is to identify ways of extending productive and disease-free lifespans. Here we present the catabolic – anabolic cycling hormesis (CACH) model for optimizing health. The CACH model is based on the concept that cells and organ systems respond to catabolic challenges in ways that bolster their resilience and that an anabolic recovery period is required to effectuate the benefits of the catabolic challenge. As two prominent real-world examples we highlight the literature on the molecular and cellular mechanisms by which physical exercise and intermittent fasting bolster cellular and organismal performance and resilience, and suppress disease processes. Over periods of weeks and months the CACH of exercise and fasting promote optimal health. The hormesis concept is integral to the CACH model and predicts an upper limit to the beneficial effects of catabolic – anabolic cycling that reflects a limit of biological plasticity. This paper extends the hormesis model of health by proposing that 1) it is comprised of two complementary phases: catabolic (adaptive stress responses and conservation of resources) and anabolic (growth and plasticity) and, 2) that CACH is metabolically integrated, quantitatively flexible and dynamically regulated. This model has important implications for future basic and translational research in the fields of aging and related disease processes.

Pro-Aging Metabolic Reprogramming: A Unified Theory of Aging

Zhiguo Wang [a b], Baofeng Yang [c]

Despite recent advances in understanding the biology of aging, the field remains fragmented due to the lack of a central organizing hypothesis. Although there are ongoing debates on whether the aging process is programmed or stochastic, it is now evident that neither perspective alone can fully explain the complexity of aging. Here, we propose the pro-aging metabolic reprogramming (PAMRP) theory, which integrates and unifies the genetic-program and stochastic hypotheses. This theory posits that aging is driven by degenerative metabolic reprogramming (MRP) over time, requiring the emergence of pro-aging substrates and triggers (PASs and PATs) to predispose cells to cellular and genetic reprogramming (CRP and GRP).

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The evolution of ageing: classic theories and emerging ideas

Ageing is generally regarded as a non-adaptive by-product of evolution. Based on this premise three classic evolutionary theories of ageing have been proposed. These theories have dominated the literature for several decades. Despite their individual nuances, the common thread which unites them is that they posit that ageing results from a decline in the intensity of natural selection with chronological age. Empirical evidence has been identified which supports each theory. However, a consensus remains to be fully established as to which theory best accounts for the evolution of ageing. A consequence of this uncertainty are counter arguments which advocate for alternative theoretical frameworks, such as those which propose an adaptive origin for ageing, senescence, or death. Given this backdrop, this review has several aims. Firstly, to briefly discuss the classic evolutionary theories. Secondly, to evaluate how evolutionary forces beyond a monotonic decrease in natural selection can affect the evolution of ageing. Thirdly, to examine alternatives to the classic theories. Finally, to introduce a pluralistic interpretation of the evolution of ageing. The basis of this pluralistic theoretical framework is the recognition that certain evolutionary ideas will be more appropriate depending on the organism, its ecological context, and its life history.

The Quest for Eternal Youth: Hallmarks of Aging and Rejuvenating Therapeutic Strategies

by Vharoon Sharma Nunkoo [1], Alexander Cristian [2,*], Anamaria Jurcau [2,*], Razvan Gabriel Diaconu [3] and Maria Carolina Jurcau [3]

The impressive achievements made in the last century in extending the lifespan have led to a significant growth rate of elderly individuals in populations across the world and an exponential increase in the incidence of age-related conditions such as cardiovascular diseases, diabetes mellitus type 2, and neurodegenerative diseases. To date, geroscientists have identified 12 hallmarks of aging (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired macroautophagy, mitochondrial dysfunction, impaired nutrient sensing, cellular senescence, stem cell exhaustion, defective intercellular communication, chronic inflammation, and gut dysbiosis), intricately linked among each other, which can be targeted with senolytic or senomorphic drugs, as well as with more aggressive approaches such as cell-based therapies. To date, side effects seriously limit the use of these drugs. However, since rejuvenation is a dream of mankind, future research is expected to improve the tolerability of the available drugs and highlight novel strategies. In the meantime, the medical community, healthcare providers, and society should decide when to start these treatments and how to tailor them individually.

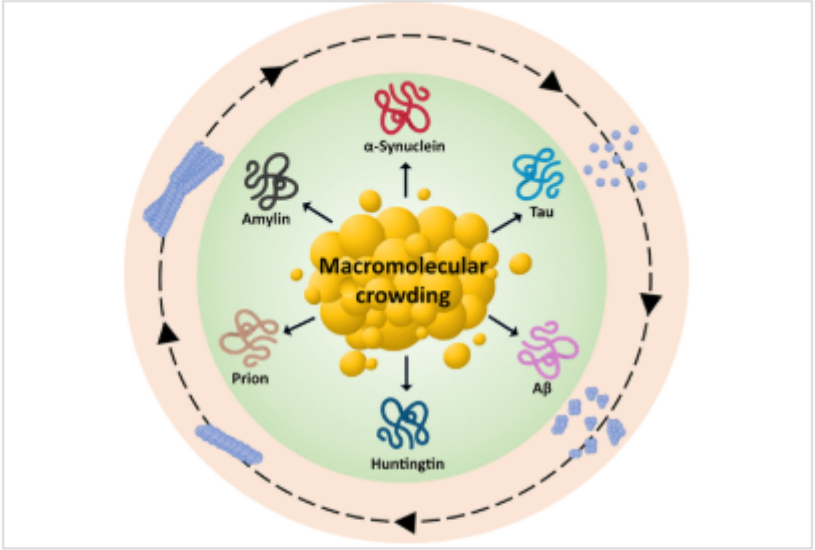
Central role of the ER proteostasis network in healthy aging

Claudio Hetz [1,2,3,4,7] · Andrew Dillin [5,6,8]

Aging trajectories vary among individuals, characterized by progressive functional decline, often leading to disease states. One of the central hallmarks of aging is the deterioration of proteostasis, where the function of the endoplasmic reticulum (ER) is dramatically affected. ER stress is monitored and adjusted by the unfolded protein response (UPR); a signaling pathway that mediates adaptive processes to restore proteostasis. Studies in multiple model organisms (yeast, worms, flies, and mice) in addition to human tissue indicates that adaptive UPR signaling contributes to healthy aging. Strategies to improve ER proteostasis using small molecules and gene therapy reduce the decline of organ function during normal aging in mammals. This article reviews recent advances in understanding the significance of the ER proteostasis network to normal aging and its relationship with other hallmarks of aging such as senescence.

Unraveling the Molecular Jam: How Crowding Shapes Protein Aggregation in Neurodegenerative Disorders

Shashi Prakash Patel, Tejas Nikam, Bhargavi Sreepathi, Vijayshree S. Karankar, Ankita Jaiswal, Salumuri Vamsi Vardhan, Anika Rana, Vanshu Toga, Nidhi Srivastava, Shubhini A Saraf, and Saurabh Awasthi*



Protein misfolding and aggregation are the hallmarks of neurodegenerative diseases including Huntington's disease, Parkinson's disease, Alzheimer's disease, and prion diseases. A crowded cellular environment plays a crucial role in modulating protein aggregation processes *in vivo* and the pathological aggregation of proteins linked to different neurodegenerative disorders. Here, we review recent studies examining the effects of various crowding agents, such as polysaccharides, polyethylene glycol, and proteins like BSA and lysozyme on the behaviors of aggregation of several amyloidogenic peptides and proteins, including amylin, huntingtin, tau, α-synuclein, prion, and amyloid-β. We also summarize how the aggregation kinetics, thermodynamic stability, and morphology of amyloid fibrils are altered significantly in the presence of crowding agents. In addition, we also discuss the molecular basis underlying the modulation of amyloidogenic aggregation, focusing on changes in the protein conformation, and the nucleation mechanism. The molecular understanding of the effects of macromolecular crowding on amyloid aggregation is essential for revealing disease pathologies and identifying possible therapeutic targets. Thus, this review offers a perspective on the complex interplay between protein aggregation and the crowded cellular environment *in vivo* and explains the relevance of crowding in the context of neurodegenerative disorders.

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The dichotomic role of cytokines in aging

Rafael Cardoso Maciel Costa Silva [1]

Affiliations + expand

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Abstract

The chronic inflammation present in aged individuals is generally depicted as a detrimental player for longevity. Here, it is discussed several beneficial effects associated with the cytokines that are chronically elevated in inflammaging. These cytokines, such as IL-1β, type I interferons, IL-6 and TNF positively regulate macroautophagy, mitochondrial function, anti-tumor immune responses and skeletal muscle biogenesis, possibly contributing to longevity. On the other side, the detrimental and antagonistic role of these cytokines including the induction of sarcopenia, tissue damage and promotion of tumorigenesis are also discussed, underscoring the dichotomy associated with inflammaging and its players. In addition, it is discussed the role of the anti-inflammatory cytokine IL-10 and other cytokines that affect aging in a more linear way, such as IL-11, which promotes senescence, and IL-4 and IL-15, which promotes longevity. It is also discussed more specific regulators of aging that are downstream cytokines-mediated signaling.

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Cellular senescence in acute human infectious disease: a systematic review

Introduction: *Acute infectious disease represents a significant cause of mortality and morbidity in elderly individuals admitted to the hospital. In its extreme, it presents as sepsis, a systematic inflammatory and immunologic response responsible for self-injurious organ injury. As individuals age, a unique set of factors including immunosenescence predispose them to acquiring an infection and a worse clinical prognosis.* This systematic review explores the relationship between cellular senescence, an age-related inflammatory phenomenon, with acute human infectious disease.

Methods: Embase via OVID, Scopus, Web of Science, Global Index Medicus, Cochrane Library via Wiley, and ClinicalTrials.gov were queried. Included studies must have compared at least one of the following measures of cellular senescence between patients with an infection and without an infection: cell cycle inhibition measured via levels of $p16^{INK4a}$ and/or $p21^{CIP1}$, short telomere length, DNA damage via ɣH2AX, high senescence-associated β galactosidase activity, and inflammation via the detection of senescence associated secretory phenotype (SASP). Manuscripts were screened and data collected via two independent reviewers.

Results: A total of 15,828 studies were screened after duplicates were removed. One hundred and fifty-three full-text articles were assessed for eligibility and a total of 16 original articles were included in analysis. Of the 16 original articles included, 12 (75%) articles were centered on SARS-CoV-2, 2 (12.5%) articles utilized patients infected with *Leishmania braziliensis*, 1 (6.25%) with *Plasmodium falciparum*, and 1 (6.25%) with Hepatitis C.

Conclusion: Current literature demonstrates robust upregulation of markers of cellular senescence in the setting of acute SARS-CoV-2, *P. falciparum*, *L. braziliensis*, and hepatitis C virus, and that markers of senescence correlate with disease severity and persist for months after resolution. Limitations in the number and types of infectious organisms studied, low sample sizes, modest longitudinal sampling, and a lack of consistency in markers measured, the method of measurement, and the definition of normal values represent ongoing gaps in the literature.

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Cellular senescence: mechanisms and relevance to cancer and aging

Shota Yamauchi, Akiko Takahashi

Cellular senescence is an irreversible cell cycle arrest induced by stresses such as telomere shortening and oncogene activation. It acts as a tumor suppressor mechanism that prevents the proliferation of potentially tumorigenic cells. Paradoxically, senescent stromal cells that arise in the tumor microenvironment have been shown to promote tumor progression. In addition, senescent cells that accumulate *in vivo* over time are thought to contribute to aging and age-related diseases. These deleterious effects of senescent cells involve the secretion of bioactive molecules such as inflammatory cytokines and chemokines, a phenomenon known as the senescence-associated secretory phenotype (SASP). While the role of cellular senescence *in vivo* is becoming increasingly clear, the intracellular signaling pathways that induce the expression of senescent phenotypes are not fully understood. In this review, we outline senescence-associated signaling pathways and their relevance to cancer and aging.

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Immunosenescence: A new direction in anti-aging research

Hanzhou Li [a b 1], Shan lin [a 1], Yuming Wang [a 1], Yuexuan Shi [a], Xixing Fang [c], Jida Wang [a], Huantian Cui [d] ✉, Yuhong Bian [a] ✉, Xin Qi [a b] ✉

The immune system is a major regulatory system of the body, that is composed of immune cells, immune organs, and related signaling factors. As an organism ages, observable age-related changes in the function of the immune system accumulate in a process described as 'immune aging. Research has shown that the impact of aging on immunity is detrimental, with various dysregulated responses that affect the function of immune cells at the cellular level. For example, increased aging has been shown to result in the abnormal chemotaxis of neutrophils and decreased phagocytosis of macrophages. Age-related diminished functionality of immune cell types has direct effects on host fitness, leading to poorer responses to vaccination, more inflammation and tissue damage, as well as autoimmune disorders and the inability to control infections. Similarly, age impacts the function of the immune system at the organ level, resulting in decreased hematopoietic function in the bone marrow, a gradual deficiency of catalase in the thymus, and thymic atrophy, resulting in reduced production of related immune cells such as B cells and T cells, further increasing the risk of autoimmune disorders in the elderly. As the immune function of the body weakens, aging cells and inflammatory factors cannot be cleared, resulting in a cycle of increased inflammation that accumulates over time. Cumulatively, the consequences of immune aging increase the likelihood of developing age-related diseases, such as Alzheimer's disease, atherosclerosis, and osteoporosis, among others. Therefore, targeting the age-related changes that occur within cells of the immune system might be an effective anti-aging strategy. In this article, we summarize the relevant literature on immune aging research, focusing on its impact on aging, in hopes of providing new directions for anti-aging research.

Regulating translation in aging: from global to gene-specific mechanisms

Mathilde Solyga, Amitabha Majumdar, and Florence Besse | AUTHOR INFORMATION

Aging is characterized by a decline in various biological functions that is associated with changes in gene expression programs. Recent transcriptome-wide integrative studies in diverse organisms and tissues have revealed a gradual uncoupling between RNA and protein levels with aging, which highlights the importance of post-transcriptional regulatory processes. Here, we provide an overview of multi-omics analyses that show the progressive uncorrelation of transcriptomes and proteomes during the course of healthy aging. We then describe the molecular changes leading to global downregulation of protein synthesis with age and review recent work dissecting the mechanisms involved in gene-specific translational regulation in complementary model organisms. These mechanisms include the recognition of regulated mRNAs by *trans*-acting factors such as miRNA and RNA-binding proteins, the condensation of mRNAs into repressive cytoplasmic RNP granules, and the pausing of ribosomes at specific residues. Lastly, we mention future challenges of this emerging field, possible buffering functions as well as potential links with disease.

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Promising tools into oxidative stress: A review of non-rodent model organisms

Yuhao Zhang [1], Yun Li [1], Tianyi Ren [1], Jin-Ao Duan [2], Ping Xiao [3]

Affiliations + expand

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Abstract

Oxidative stress is a crucial concept in redox biology, and significant progress has been made in recent years. Excessive levels of reactive oxygen species (ROS) can lead to oxidative damage, heightening vulnerability to various diseases. By contrast, ROS maintained within a moderate range plays a role in regulating normal physiological metabolism. Choosing suitable animal models in a complex research context is critical for enhancing research efficacy. While rodents are frequently utilized in medical experiments, they pose challenges such as high costs and ethical considerations. Alternatively, non-rodent model organisms like zebrafish, Drosophila, and C. elegans offer promising avenues into oxidative stress research. These organisms boast advantages such as their small size, high reproduction rate, availability for live imaging, and ease of gene manipulation. This review highlights advancements in the detection of oxidative stress using non-rodent models. The oxidative homeostasis regulatory pathway, Kelch-like ECH-associated protein 1-Nuclear factor erythroid 2-related factor 2 (Keap1-Nrf2), is systematically reviewed alongside multiple regulation of Nrf2-centered pathways in different organisms. Ultimately, this review conducts a comprehensive comparative analysis of different model organisms and further explores the combination of novel techniques with non-rodents. This review aims to summarize state-of-the-art findings in oxidative stress research using non-rodents and to delineate future directions.

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The impact of cysteine on lifespan in three model organisms: A systematic review and meta-analysis

Yue Ma, Mengqi Chen, Kaiyao Huang, Wakam Chang

Cysteine is an amino acid present in thiol proteins and often dictates their secondary structures. Although considered nonessential, cysteine may be essential for patients with certain metabolic diseases and can reduce the requirement for dietary methionine. Cysteine and some of its derivatives, such as N-acetylcysteine, are considered antioxidants and widely used in animal aging studies. To provide insights into the potential anti-aging effects of cysteine, we systematically reviewed and performed a meta-analysis to investigate the impact of cysteine supplementation on lifespan using three model organisms: mice, nematodes, and fruit flies. A total of 13 mouse studies, 13 *C. elegans* studies, and 5 *Drosophila* studies were included in the analysis. The findings revealed that cysteine supplementation significantly reduced the risk of mortality in mice and *C. elegans*. Subgroup analysis showed consistent results across different starting times and administration methods and revealed adverse effects of high doses on worms and a lack of effect in nondisease mouse models. Similar to mice, the effects of cysteine supplementation on *Drosophila* were not statistically significant, except in transgenic flies. The study identified certain limitations, including the quality of the included studies and the potential for publication bias. We also discussed uncertainties in the underlying molecular mechanisms and the clinical application of dietary cysteine.

Probiotics as a targeted intervention in anti-ageing: a review

Fengcui Shi, Jingwen Peng, Haojin Li, Denghai Liu, Li Han, Ying Wang, ...show all

Context

The age-induced disruption of gut flora, termed gut dysbiosis, is intimately tied to compromised immune function, augmented oxidative stress and a spectrum of age-linked disorders.

Objective

This review examines the fundamental mechanisms employed by probiotic strains to modulate gut microbiota composition and metabolic profiles, mitigate cognitive decline *via* the gut-brain axis (GBA), modulate gene transcription and alleviate inflammatory responses and oxidative stress.

Conclusion

We elucidate the capacity of probiotics as a precision intervention to restore gut microbiome homeostasis and alleviate age-related conditions, thereby offering a theoretical framework for probiotics to decelerate ageing, manage age-related diseases, and elevate quality of life.

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Overlooked histories in ageing research: Pioneering women at the foundation of our field

Marina Ezcurra, Colin Selman, Jennifer Tullet, Nathan Woodling

A list of this decade's most prominent names in ageing research would undoubtedly include many women who have led the field in recent years. While the field, and science in general, still have far to go in achieving gender parity in opportunities and recognition, we can celebrate the progress made to date. However, the longer 'history of the field' that many of us present in our classrooms, conference halls and writings often tends to be dominated by men. Although numerous men have made fundamental observations that have shaped our understanding of ageing from both a mechanistic and evolutionary perspective, the unfortunate reality is that women making similar contributions have not received equal recognition throughout much of our field's history. As a starting point for wider representation and further conversations in this area, we present here a short list of women—Marjory Warren, Lillian Jane Martin, Margaret Alexander Ohlson, Rebeca Gerschman and Marion J. Lamb—whose contributions were foundational to ageing research in the 20th century. Their work spanned theoretical, experimental and clinical insight into the biology of ageing—and yet their names are too seldom mentioned when introducing our field. We hope this list can be a starting point for a more inclusive recognition of the diverse scientists who helped pave the way for our field today.

OTHER RESEARCH & REVIEWS

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An "off-on" fluorescent probe for imaging pyruvic acid in living systems

Man Li [1], Xiang Li [2], Linfeng Chen [3], Xiaohong Li [3], Chunrong Liu [4]

Affiliations + expand

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Abstract

Pyruvic acid (PA) is an α-keto acid which exert important biological and pathological functions. The current PA profiling assays are mainly based on the ultraviolet spectroscopy and electrochemical biosensor, requiring killing cells and destroying tissues which limit their application in living cells. Optical imaging provides nondestructive powerful and detective tools to better understand the physiological and pathological role of PA in living systems. However, as far as we know, none of"off - on" PA fluorescent sensor has been developed. Herein, we reported a PA recognition reaction that arylhydroxylamine group could be selectively reduced to acetylamide group by PA. With this recognition reaction, a fluorescence probe (FPA) based on the photoinduced electron transfer (PET) pathway was designed, synthesized and could release strong fluorescence at 447 nm. We proved that FPA could detect PA in aqueous solution, living cells, Caenorhabditis elegans and the roots of Arabidopsis thaliana with good selectivity and sensitivity as low as 0.42 μM. In addition, we successfully using probe FPA to study the intracellular PA production pathway in cells and evaluated its physiological level in Arabidopsis roots at different growth stages. The results show that the physiological level of PA in Arabidopsis thaliana roots is closely associated with their growth stages, which indicated that PA might act as a carbon source and related growth signaling molecule to promote plant growth and root elongation. Therefore, we expect probe FPA to be a powerful tool to better understand the physiological and pathological role of PA.

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Small-Molecule Probe for Imaging Oxidative Stress–Induced Carbonylation in Live Cells

OD Ozlem Dilek DT Dilek Telci HE Hazel Erkan-Candag

Protein carbonylation has been known as the major form of irreversible protein modifications and is also widely used as an indicator of oxidative stress in the biological environment. In the presence of oxidative stress, biological systems tend to produce large amounts of carbonyl moieties; these carbonyl groups do not have particular UV-Vis and fluorescence spectroscopic characteristics that we can differentiate, observe, and detect. Thus, their detection and quantification can only be performed using specific chemical probes. Commercially available fluorescent probes to detect specific carbonylation in biological systems have been used, but their chemical portfolio is still very limited. This protocol outlines the methods and procedures employed to synthesize a probe, (E,Z)-2-(2-(2-hydroxybenzylidene)hydrazonyl)-5-nitrophenol (2Hzin5NP), and assess its impact on carbonylation in human cells. The synthesis involves several steps, including the preparation of its hydrazone compounds mimicking cell carbonyls, 2-Hydrazinyl 5-nitrophenol, (E,Z)-2-(2-ethylidenehydrazonyl)-5-nitrophenol, and the final product (E,Z)-2-(2-(2-hydroxybenzylidene)hydrazonyl)-5-nitrophenol. The evaluation of fluorescence quantum yield and subsequent cell culture experiments are detailed for the investigation of 2Hzin5NP effects on cell proliferation and carbonylation.