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Scientific News
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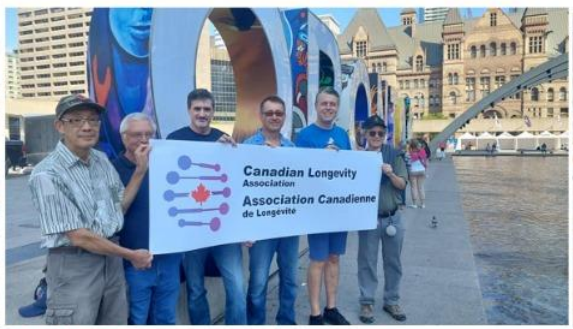
Sven Bulterijs

Business/Conferences/ General news

Longevity Day 2023



Nobel Prize in Physiology or Medicine

The 2023 medicine laureates

The Nobel Assembly at the Karolinska Institutet has decided to award the 2023 Nobel Prize in Physiology or Medicine jointly to Katalin Karikó and Drew Weissman "for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19."

Ill. Niklas Elmehed © Nobel Prize Outreach

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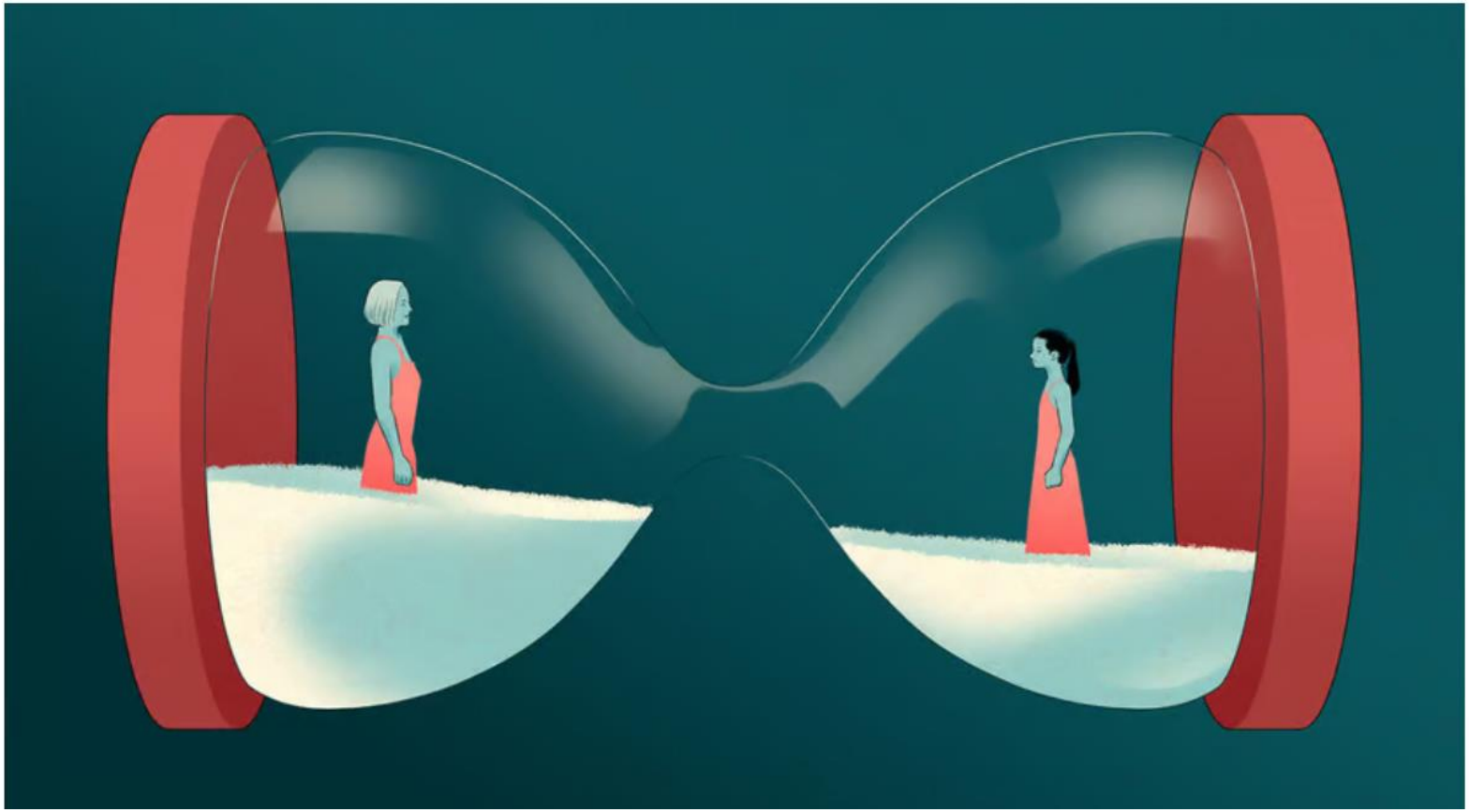
Slowing human ageing is now the subject of serious research

And some of it is making progress, writes Geoffrey Carr



Aging research articles

Nat Commun. 2023 Sep 30;14(1):6113. doi: 10.1038/s41467-023-41785-7.

Deleterious heteroplasmic mitochondrial mutations are associated with an increased risk of overall and cancer-specific mortality

Mitochondria carry their own circular genome and disruption of the mitochondrial genome is associated with various aging-related diseases. Unlike the nuclear genome, mitochondrial DNA (mtDNA) can be present at 1000 s to 10,000 s copies in somatic cells and variants may exist in a state of heteroplasmy, where only a fraction of the DNA molecules harbors a particular variant. We quantify mtDNA heteroplasmy in 194,871 participants in the UK Biobank and find that heteroplasmy is associated with a 1.5-fold increased risk of all-cause mortality. Additionally, we functionally characterize mtDNA single nucleotide variants (SNVs) using a constraint-based score, mitochondrial local constraint score sum (MSS) and find it associated with all-cause mortality, and with the prevalence and incidence of cancer and cancer-related mortality, particularly leukemia. These results indicate that mitochondria may have a functional role in certain cancers, and mitochondrial heteroplasmic SNVs may serve as a prognostic marker for cancer, especially for leukemia.

Extracellular Vesicles in Young Serum Contribute to the Restoration of Age-Related Brain Transcriptomes and Cognition in Old Mice

by Nicholas F. Fitz [1], Amrita Sahu [2], Yi Lu [1], Fabrisia Ambrosio [3,4], Iliya Lefterov [1,*] and Radosveta Koldamova [1,*]

We have previously demonstrated that circulating extracellular vesicles (EVs) are essential to the beneficial effect of young serum on the skeletal muscle regenerative cascade. Here, we show that infusions of young serum significantly improve age-associated memory deficits, and that these effects are abolished after serum depletion of EVs. RNA-seq analysis of the choroid plexus demonstrates EV-mediated effects on genes involved in barrier function and trans-barrier transport. Comparing the differentially expressed genes to recently published chronological aging clock genes reveals a reversal of transcriptomic aging in the choroid plexus. Following young serum treatment, the hippocampal transcriptome demonstrates significant upregulation of the anti-aging gene Klotho, along with an abrogated effect after EV depletion. Transcriptomic profiling of Klotho knockout and heterozygous mice shows the downregulation of genes associated with transport, exocytosis, and lipid transport, while upregulated genes are associated with activated microglia. The results of our study indicate the significance of EVs as vehicles to deliver signals from the periphery to the brain and the importance of Klotho in maintaining brain homeostasis.

No association between metformin initiation and incident dementia in older adults newly diagnosed with diabetes

Che-Yuan Wu, Christa Wang, Refik Saskin, Baiju R. Shah, Moira K. Kapral, Krista L. Lanctôt, Nathan Herrmann, Hugo Cogo-Moreira, Bradley J. MacIntosh, Jodi D. Edwards, Walter Swardfager

Methods

Residents of Ontario, Canada ≥66 years newly diagnosed with diabetes from January 1, 2008 to December 31, 2017 entered this retrospective population-based cohort. To consider the indication for metformin monotherapy initiation, people with hemoglobin A1c of 6.5%–8.0% and estimated glomerular filtration rate ≥45 mL/min/1.73 m^2 were selected. Using the landmark method to address immortal time bias, exposure was grouped into "metformin monotherapy initiation within 180 days after new diabetes diagnosis" or "no glucose-lowering medications within 180 days." To address disease latency, 1-year lag time was applied to the end of the 180-day landmark period. Incident dementia was defined using a validated algorithm for Alzheimer's disease and related dementias. Adjusted hazard ratios (aHR) and confidence intervals (CIs) were estimated from propensity-score weighted Cox proportional hazard models.

Results

Over mean follow-up of 6.77 years from cohort entry, metformin initiation within 180 days after new diabetes diagnosis (*N* = 12,331; 978 events; 65,762 person-years) showed no association with dementia risk (aHR [95% CI] = 1.05 [0.96–1.15]), compared to delayed or no glucose-lowering medication initiation (*N* = 22,369; 1768 events; 117,415 person-years).

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Geroprotective interventions converge on gene expression programs of reduced inflammation and restored fatty acid metabolism

Understanding the mechanisms of geroprotective interventions is central to aging research. We compare four prominent interventions: senolysis, caloric restriction, in vivo partial reprogramming, and heterochronic parabiosis. Using published mice transcriptomic data, we juxtapose these interventions against normal aging. We find a gene expression program common to all four interventions, in which inflammation is reduced and several metabolic processes, especially fatty acid metabolism, are increased. Normal aging exhibits the inverse of this signature across multiple organs and tissues. A similar inverse signature arises in three chronic inflammation disease models in a non-aging context, suggesting that the shift in metabolism occurs downstream of inflammation. Chronic inflammation is also shown to accelerate transcriptomic age. We conclude that a core mechanism of geroprotective interventions acts through the reduction of inflammation with downstream effects that restore fatty acid metabolism. This supports the notion of directly targeting genes associated with these pathways to mitigate age-related deterioration.

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A step toward precision gerontology: Lifespan effects of calorie and protein restriction are consistent with predicted impacts on entropy generation

Ayşe Selcen Semerciöz-Oduncuoğlu [# 1 2], Sharon E Mitchell [# 2], Mustafa Özilgen [1], Bayram Yilmaz [3], John R Speakman [2 4 5]

Understanding aging is a key biological goal. Precision gerontology aims to predict how long individuals will live under different treatment scenarios. Calorie and protein restriction (CR and PR) extend lifespan in many species. Using data from C57BL/6 male mice under graded CR or PR, we introduce a computational thermodynamic model for entropy generation, which predicted the impact of the manipulations on lifespan. Daily entropy generation decreased significantly with increasing CR level, but not PR. Our predictions indicated the lifespan of CR mice should increase by 13 to 56% with 10 to 40% CR, relative to ad libitum-fed animals. This prediction was broadly consistent with the empirical observation of the lifespan impacts of CR in rodents. Modeling entropy fluxes may be a future strategy to identify antiaging interventions.

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The biological age model for evaluating the degree of aging in centenarians

Background: Biological age (BA) has been used to assess individuals' aging conditions. However, few studies have evaluated BA models' applicability in centenarians.

Methods: Important organ function examinations were performed in 1798 cases of the longevity population (80~115 years old) in Hainan, China. Eighty indicators were selected that responded to nutritional status, cardiovascular function, liver and kidney function, bone metabolic function, endocrine system, hematological system, and immune system. BA models were constructed using multiple linear regression (MLR), principal component analysis (PCA), Klemera and Doubal method (KDM), random forest (RF), support vector machine (SVM), extreme gradient boosting (XGBoost), and light gradient boosting machine (lightGBM) methods. A tenfold crossover validate [Geen titel] cacy of models.

Results: A total of 1398 participants were enrolled, of whom centenarians accounted for 49.21%. Seven aging markers were obtained, including estimated glomerular filtration rate, albumin, pulse pressure, calf circumference, body surface area, fructosamine, and complement 4. Eight BA models were successfully constructed, namely MLR, PCA, KDM1, KDM2, RF, SVM, XGBoost and lightGBM, which had the worst R^2 of 0.45 and the best R^2 of 0.92. The best R^2 for cross-validation was KDM2 (0.89), followed by PCA (0.62).

Conclusion: In this study, we successfully applied eight methods, including traditional methods and machine learning, to construct models of biological age, and the performance varied among the models.

Proteomic architecture of frailty across the spectrum of cardiovascular disease

Andrew S. Perry, Shilin Zhao, Priya Gajjar, Venkatesh L. Murthy, Benoit Lehallier, Patricia Miller, Sangeeta Nair, Colin Neill, J. Jeffrey Carr, William Fearon, Samir Kapadia ... See all authors

While frailty is a prominent risk factor in an aging population, the underlying biology of frailty is incompletely described. Here, we integrate 979 circulating proteins across a wide range of physiologies with 12 measures of frailty in a prospective discovery cohort of 809 individuals with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation. Our aim was to characterize the proteomic architecture of frailty in a highly susceptible population and study its relation to clinical outcome and systems-wide phenotypes to define potential novel, clinically relevant frailty biology. Proteomic signatures (specifically of physical function) were related to post-intervention outcome in AS, specifying pathways of innate immunity, cell growth/senescence, fibrosis/metabolism, and a host of proteins not widely described in human aging. In published cohorts, the "frailty proteome" displayed heterogeneous trajectories across age (20–100 years, age only explaining a small fraction of variance) and were associated with cardiac and non-cardiac phenotypes and outcomes across two broad validation cohorts ($N > 35{,}000$) over ≈2–3 decades. These findings suggest the importance of precision biomarkers of underlying multi-organ health status in age-related morbidity and frailty.

Nat Commun. 2023 Sep 30;14(1):6109. doi: 10.1038/s41467-023-41683-y.

IFNγ–Stat1 axis drives aging–associated loss of intestinal tissue homeostasis and regeneration

The influence of aging on intestinal stem cells and their niche can explain underlying causes for perturbation in their function observed during aging. Molecular mechanisms for such a decrease in the functionality of intestinal stem cells during aging remain largely undetermined. Using transcriptome-wide approaches, our study demonstrates that aging intestinal stem cells strongly upregulate antigen presenting pathway genes and over-express secretory lineage marker genes resulting in lineage skewed differentiation into the secretory lineage and strong upregulation of MHC class II antigens in the aged intestinal epithelium. Mechanistically, we identified an increase in proinflammatory cells in the lamina propria as the main source of elevated interferon gamma (IFNγ) in the aged intestine, that leads to the induction of Stat1 activity in intestinal stem cells thus priming the aberrant differentiation and elevated antigen presentation in epithelial cells. Of note, systemic inhibition of IFNγ-signaling completely reverses these aging phenotypes and reinstalls regenerative capacity of the aged intestinal epithelium.

Geroscience. 2023 Sep 25. doi: 10.1007/s11357-023-00938-8. Online ahead of print.

Induction of proteasomal activity in mammalian cells by lifespan-extending tRNA synthetase inhibitors

Blaise L Mariner [1 2 3], Antonio S Rodriguez [1], Olivia C Heath [1], Mark A McCormick [4 5]

We have recently shown that multiple tRNA synthetase inhibitors can greatly increase lifespan in multiple models by acting through the conserved transcription factor ATF4. Here, we show that these compounds, and several others of the same class, can greatly upregulate mammalian ATF4 in cells in vitro, in a dose dependent manner. Further, RNASeq analysis of these cells pointed toward changes in protein turnover. In subsequent experiments here we show that multiple tRNA synthetase inhibitors can greatly upregulate activity of the ubiquitin proteasome system (UPS) in cells in an ATF4-dependent manner. The UPS plays an important role in the turnover of many damaged or dysfunctional proteins in an organism. Increasing UPS activity has been shown to enhance the survival of Huntington's disease cell models, but there are few known pharmacological enhancers of the UPS. Additionally, we see separate ATF4 dependent upregulation of macroautophagy upon treatment with tRNA synthetase inhibitors. Protein degradation is an essential cellular process linked to many important human diseases of aging such as Alzheimer's disease and Huntington's disease. These drugs' ability to enhance proteostasis more broadly could have wide-ranging implications in the treatment of important age-related neurodegenerative diseases.

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PREPRINT

ImAge: an imaging approach to quantitate aging and rejuvenation

Martin Alvarez-Kuglen, Delany Rodriguez, Haodong Qin, Kenta Ninomiya, Lorenzo Fiengo, Chen Farhy, Wei-Mien Hsu, Aaron Havas, Gen-Sheng Feng, Amanda J. Roberts, Rozalyn M. Anderson, Manuel Serrano, Peter D. Adams, Tatyana O. Sharpee, Alexey V. Terskikh

Biomarkers of biological age that predict the risk of disease and expected lifespan better than chronological age are key to efficient and cost-effective healthcare[1–3]. To advance a personalized approach to healthcare, such biomarkers must perform on the individual rather than population level, demonstrate single cell resolution, and provide scalable and cost-effective measurements. We developed a novel approach – image-based chromatin and epigenetic age (ImAge), that utilizes image texture features based on the patterns of chromatin and epigenetic marks in single nuclei. We observed the emergence of intrinsic trajectories of ImAge using dimensionality reduction without regression on chronological age. ImAge was correlated with chronological age in all tissues and organs examined and was consistent with the expected acceleration and/or deceleration of biological age in chronologically identical mice treated with chemotherapy or following a caloric restriction regimen, respectively. ImAge from chronologically identical mice inversely correlated with their locomotor activity (greater activity for younger ImAge), consistent with the essential role of locomotion as an aging biomarker. Finally, we demonstrated that ImAge is reduced upon partial reprogramming in vivo following transient expression of OSKM cassette in the liver and skeletal muscles of old mice and validated the power of ImAge to assess the heterogeneity of reprogramming. We propose that ImAge represents the first-in-class individual-level biomarker of aging and rejuvenation with single-cell resolution.

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PREPRINT

Phenformin's impact on lifespan in *C. elegans* is resilient to environmental factors that inhibit metformin-induced longevity downstream of *skn-1*/Nrf and AMP-activated protein kinase

Despite being principally prescribed to treat type 2 diabetes, biguanides, especially metformin and phenformin, have been shown to extend lifespan and healthspan in preclinical models, and to reduce the impact of aging-associated diseases such as cancer. While there have been conflicting results in studies involving rodents and humans, consistent evidence from laboratories worldwide, including our own, indicates metformin and phenformin's ability to significantly extend lifespan in *C. elegans*. However, the pro-longevity effect of metformin can vary depending on environmental conditions. Specifically, the choice of agar from different manufacturers or batches influences metformin's ability to extend lifespan in *C. elegans*. We traced ability of certain agar batches to interfere with metformin-prompted lifespan extension to the presence of a factor that acts directly in the worm, independently of the bacterial food source, that prevents longevity promoting effects downstream of longevity effectors *skn-1* and AMPK. In contrast, phenformin prompts robust lifespan extension in the face of environmental changes and exhibits broad positive effects in aging across genetically diverse *Caenorhabditis* species where the impact of metformin is highly variable. Thus metformin effects in aging are impacted by heretofore unappreciated environmental factors. Phenformin may represent a more robust agent with which to understand the longevity promoting mechanisms downstream of biguanides.

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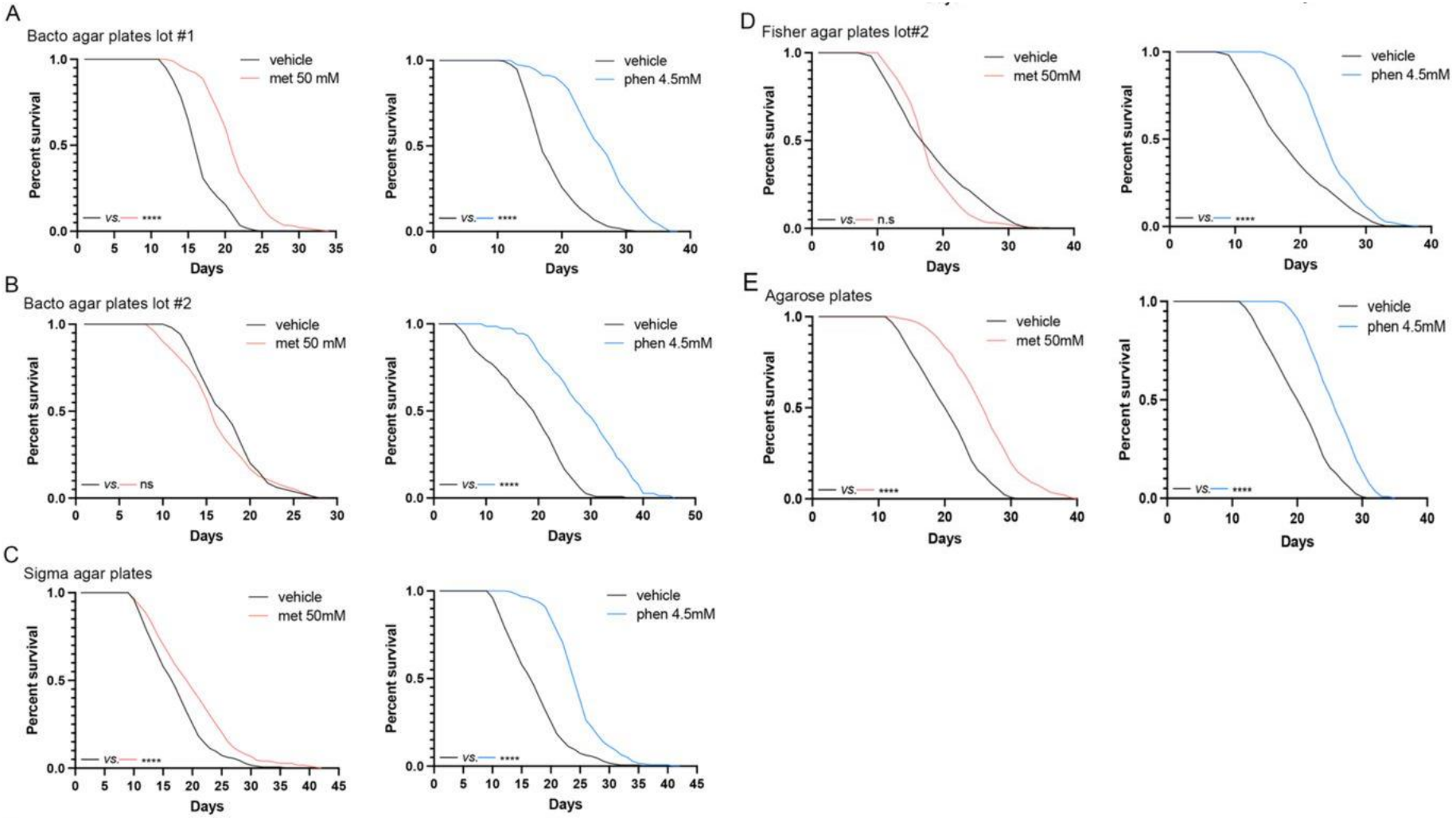
PREPRINT

Phenformin's impact on lifespan in *C. elegans* is resilient to environmental factors that inhibit metformin-induced longevity downstream of *skn-1*/Nrf and AMP-activated protein kinase



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Transcriptional changes of the aging lung

Minxue Jia, Paula A. Agudelo Garcia, Jose A. Ovando-Ricardez, Tracy Tabib, Humberto T. Bittar, Robert A. Lafyatis, Ana L. Mora ✉, Panayiotis V. Benos ✉, Mauricio Rojas ✉

Aging is a natural process associated with declined organ function and higher susceptibility to developing chronic diseases. A systemic single-cell type-based study provides a unique opportunity to understand the mechanisms behind age-related pathologies. Here, we use single-cell gene expression analysis comparing healthy young and aged human lungs from nonsmoker donors to investigate age-related transcriptional changes. Our data suggest that aging has a heterogenous effect on lung cells, as some populations are more transcriptionally dynamic while others remain stable in aged individuals. We found that monocytes and alveolar macrophages were the most transcriptionally affected populations. These changes were related to inflammation and regulation of the immune response. Additionally, we calculated the LungAge score, which reveals the diversity of lung cell types during aging. Changes in DNA damage repair, fatty acid metabolism, and inflammation are essential for age prediction. Finally, we quantified the senescence score in aged lungs and found that the more biased cells toward senescence are immune and progenitor cells. Our study provides a comprehensive and systemic analysis of the molecular signatures of lung aging. Our LungAge signature can be used to predict molecular signatures of physiological aging and to detect common signatures of age-related lung diseases.

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Induction of mitochondrial recycling reverts age-associated decline of the hematopoietic and immune systems

Mukul Girotra, Yi-Hsuan Chiang, Melanie Charmoy, Pierpaolo Ginefra, Helen Carrasco Hope, Charles Bataclan, Yi-Ru Yu, Frederica Schyrr, Fabien Franco, Hartmut Geiger, Stephane Cherix, Ping-Chih Ho, Olaia Naveiras, Johan Auwerx, Werner Held & Nicola Vannini

Aging compromises hematopoietic and immune system functions, making older adults especially susceptible to hematopoietic failure, infections and tumor development, and thus representing an important medical target for a broad range of diseases. During aging, hematopoietic stem cells (HSCs) lose their blood reconstitution capability and commit preferentially toward the myeloid lineage (myeloid bias)[1,2]. These processes are accompanied by an aberrant accumulation of mitochondria in HSCs[3]. The administration of the mitochondrial modulator urolithin A corrects mitochondrial function in HSCs and completely restores the blood reconstitution capability of 'old' HSCs. Moreover, urolithin A-supplemented food restores lymphoid compartments, boosts HSC function and improves the immune response against viral infection in old mice. Altogether our results demonstrate that boosting mitochondrial recycling reverts the aging phenotype in the hematopoietic and immune systems.

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PREPRINT

Molecular and phenotypic blueprint of the hematopoietic compartment reveals proliferation stress as a driver of age-associated human stem cell dysfunctions

Hematopoietic stem/progenitor cell (HSPC) aging studies have been associated with myeloid skewing, reduced clonal output, and impaired regenerative capacity, but quantitative immunophenotypic and functional analysis across human aging is lacking. Here, we provide a comprehensive phenotypic, transcriptional, and functional dissection of human hematopoiesis across the lifespan. Although primitive HSPC numbers were stable during aging, overall cellularity was reduced, especially for erythroid and lymphoid lineages. Notably, HSPC from aged individuals had superior repopulating frequency than younger counterparts in xenografts; yet aged HSPC displayed epigenetic dysregulation of cell cycle, inflammatory signatures, and a reduced capacity to counteract activation-induced proliferative stress with concomitant accumulation of DNA damage and senescence-like features upon xenotransplantation. This phenotype was recapitulated by enforcing proliferative stress *in vivo* on cord blood (CB) HSPC. Overall, our work sheds light on dysregulated responses to activation-induced proliferation underlying HSPC aging and establishes CB xenotransplantation-based models as suitable for studying age-associated hematopoietic defects.

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PREPRINT

The hydrogen sulfide donor sodium thiosulfate limits inflammation but aggravate smooth muscle cells apoptosis and aneurysm progression in a mouse model of abdominal aortic aneurysm

Intro The prevalence of abdominal aortic aneurysm (AAA) is constantly progressing with the aging of the global population. AAA rupture has a devastating 80% mortality rate and there is no treatment to slow-down AAA progression. Hydrogen sulfide (H_2S) is a ubiquitous redox-modifying gasotransmitter produced in the cardiovascular system via the reverse trans-sulfuration pathway by cystathionine γ-lyase (CSE). H_2S has protective properties on the cardiovascular system, including anti-inflammatory and antioxidant effects. Here, we hypothesized that sodium thiosulfate (STS), a clinically relevant source of H_2S, would limit AAA growth.

Methods 8-12 weeks old male WT or $Cse^{-/-}$ mice on a C57BL/6J genetic background were submitted to a model of AAA by topical elastase application on the abdominal aorta and β-aminopropionitrile fumarate treatment in the drinking water for 2 weeks post-op. Sodium thiosulfate (STS) was given via the drinking water post-op until aorta collection. *In vitro* experiments were conducted to assess the effect of STS and pro-inflammatory cytokines interleukin-1 β and 6 and tumor necrosis factor α on primary human vascular smooth muscle cell (VSMC).

Results Surprisingly, STS increased elastin degradation, AAA size and rupture, despite reducing infiltration of macrophages, antigen-presenting cells and lymphocytes in WT mice. Conversely, $Cse^{-/-}$ mice with impaired H_2S production developed smaller AAA than WT mice despite increased infiltration of immune cells. STS reduced VSMC coverage, possibly lowered VSMC proliferation, and promoted VSMC loss and extracellular matrix (ECM) breakdown. In vitro, STS aggravated pro-inflammatory cytokine-induced VSMCs apoptosis.

Nat Commun. 2023 Sep 16;14(1):5744. doi: 10.1038/s41467-023-41515-z.

Plasma metabolomic profiles associated with mortality and longevity in a prospective analysis of 13,512 individuals

Experimental studies reported biochemical actions underpinning aging processes and mortality, but the relevant metabolic alterations in humans are not well understood. Here we examine the associations of 243 plasma metabolites with mortality and longevity (attaining age 85 years) in 11,634 US (median follow-up of 22.6 years, with 4288 deaths) and 1878 Spanish participants (median follow-up of 14.5 years, with 525 deaths). We find that, higher levels of N2,N2-dimethylguanosine, pseudouridine, N4-acetylcytidine, 4-acetamidobutanoic acid, N1-acetylspermidine, and lipids with fewer double bonds are associated with increased risk of all-cause mortality and reduced odds of longevity; whereas L-serine and lipids with more double bonds are associated with lower mortality risk and a higher likelihood of longevity. We further develop a multi-metabolite profile score that is associated with higher mortality risk. Our findings suggest that differences in levels of nucleosides, amino acids, and several lipid subclasses can predict mortality. The underlying mechanisms remain to be determined.

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Physical Resilience as a Predictor of Lifespan and Late-Life Health in Genetically Heterogeneous Mice

Ashley K Brown [1], Daniel L Mazula [1], Lori Roberts [2], Carolyn Roos [1 3], Bin Zhang [1 3], Vesselina M Pearsall [1], Marissa J Schafer [1 4], Thomas A White [1], Runqing Huang [1], Navasuja Kumar [5], Jordan D Miller [1 3 4], Richard A Miller [2], Nathan K LeBrasseur [1 6 4 7]

Dynamic measures of resilience-the ability to resist and recover from a challenge-may be informative of the rate of aging before overt manifestations such as chronic disease, disability, and frailty. From this perspective mid-life resilience may predict longevity and late-life health. To test this hypothesis, we developed simple, reproducible, clinically relevant challenges and outcome measures of physical resilience that revealed differences between and within age groups of genetically heterogeneous mice, and then examined associations between mid-life resilience and both lifespan and late-life measures of physiological function. We demonstrate that time to recovery from isoflurane anesthesia and weight change following a regimen of chemotherapy significantly differed between young, middle-aged, and older mice, and were more variable in older mice. Females that recovered faster than the median time from anesthesia (more resilient) at 12 months of age lived 8% longer than their counterparts, while more resilient males in mid-life exhibited better cardiac (fractional shortening and left ventricular volumes) and metabolic (glucose tolerance) function at 24 months of age. Moreover, female mice with less than the median weight loss at day 3 of the cisplatin challenge lived 8% longer than those that lost more weight. In contrast, females that had more weight loss between days 15-20 were relatively protected against early death. These data suggest that measures of physical resilience in mid-life may provide information about individual differences in aging, lifespan, and key parameters of late-life health.

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MEG3 activates necroptosis in human neuron xenografts modeling Alzheimer's disease

SRIRAM BALUSU, KATRIEN HORRÉ, NICOLA THRUPP, KATLEEN CRAESSAERTS, AN SNELLINX, LUTGARDE SERNEELS, DRIES T'SYEN, IORDANA CHRYSIDOU, AMAIA M. ARRANZ, [...], AND BART DE STROOPER

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Authors Info & Affiliations

Neuronal cell loss is a defining feature of Alzheimer's disease (AD), but the underlying mechanisms remain unclear. We xenografted human or mouse neurons into the brain of a mouse model of AD. Only human neurons displayed tangles, Gallyas silver staining, granulovacuolar neurodegeneration (GVD), phosphorylated tau blood biomarkers, and considerable neuronal cell loss. The long noncoding RNA *MEG3* was strongly up-regulated in human neurons. This neuron-specific long noncoding RNA is also up-regulated in AD patients. *MEG3* expression alone was sufficient to induce necroptosis in human neurons in vitro. Down-regulation of *MEG3* and inhibition of necroptosis using pharmacological or genetic manipulation of receptor-interacting protein kinase 1 (RIPK1), RIPK3, or mixed lineage kinase domain-like protein (MLKL) rescued neuronal cell loss in xenografted human neurons. This model suggests potential therapeutic approaches for AD and reveals a human-specific vulnerability to AD.

Functional characterization of Alzheimer's disease genetic variants in microglia

Candidate cis-regulatory elements (cCREs) in microglia demonstrate the most substantial enrichment for Alzheimer's disease (AD) heritability compared to other brain cell types. However, whether and how these genome-wide association studies (GWAS) variants contribute to AD remain elusive. Here we prioritize 308 previously unreported AD risk variants at 181 cCREs by integrating genetic information with microglia-specific 3D epigenome annotation. We further establish the link between functional variants and target genes by single-cell CRISPRi screening in microglia. In addition, we show that AD variants exhibit allelic imbalance on target gene expression. In particular, rs7922621 is the effective variant in controlling TSPAN14 expression among other nominated variants in the same cCRE and exerts multiple physiological effects including reduced cell surface ADAM10 and altered soluble TREM2 (sTREM2) shedding. Our work represents a systematic approach to prioritize and characterize AD-associated variants and provides a roadmap for advancing genetic association to experimentally validated cell-type-specific phenotypes and mechanisms.

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Alzheimer's Disease and Aging Association: Identification and Validation of Related Genes

T. Liu, K. Hou, J. Li, T. Han, S. Liu & Jianshe Wei

Methods

Datasets GSE36980 and GSE5281 were selected to screen differentially expressed genes (DEGs), and the immune cell correlation analysis and GSEA analysis of DEGs were performed. The intersection with senescence genes was taken as differentially expressed senescence-related genes (DESRGs), and the GSE44770 dataset was used for further validation. The potential biological functions and signaling pathways were determined by GO and KEGG, and the hub genes were identified by 12 algorithms in Cytohubba. The expression of 10 hub genes in different brain regions was determined and single-cell sequencing analysis was performed, and diagnostic genes were further screened by gene expression and receiver operating characteristic (ROC) curve. Finally, a miRNA-gene network of diagnostic genes was constructed and targeted drug prediction was performed.

Results

A total of 2137 DEGs were screened from the GSE36980 and GSE5281 datasets, and 278 SRGs were identified from the CellAge database. The overlapping DEGs and SRGs constituted 29 DESRGs, including 14 senescence suppressor genes and 15 senescence inducible genes. The top 10 hub genes, including MDH1, CKB, PSMD14, SMARCA4, PEBP1, DDB2, ITPKB, ATF7IP, YAP1, and EWSR1 were screened. Furthermore, four diagnostic genes were identified: PMSD14, PEBP1, ITPKB, and ATF7IP. The ROC analysis showed that the respective area under the curves (AUCs) of PMSD14, PEBP1, ITPKB, and ATF7IP were 0.732, 0.701, 0.747, and 0.703 in the GSE36980 dataset and 0.870, 0.817, 0.902, and 0.834 in the GSE5281 dataset. In the GSE44770 dataset, PMSD14 (AUC, 0.838) and ITPKB (AUC, 0.952) had very high diagnostic values in the early stage of AD. Finally, based on these diagnostic genes, we found that the drug Abemaciclib is a targeted drug for the treatment of age-related AD. Flutamide can aggravate aging-related AD.

CD44 correlates with longevity and enhances basal ATF6 activity and ER stress resistance

The naked mole rat (NMR) is the longest-lived rodent, resistant to multiple age-related diseases including neurodegeneration. However, the mechanisms underlying the NMR's resistance to neurodegenerative diseases remain elusive. Here, we isolated oligodendrocyte progenitor cells (OPCs) from NMRs and compared their transcriptome with that of other mammals. Extracellular matrix (ECM) genes best distinguish OPCs of long- and short-lived species. Notably, expression levels of CD44, an ECM-binding protein that has been suggested to contribute to NMR longevity by mediating the effect of hyaluronan (HA), are not only high in OPCs of long-lived species but also positively correlate with longevity in multiple cell types/tissues. We found that CD44 localizes to the endoplasmic reticulum (ER) and enhances basal ATF6 activity. CD44 modifies proteome and membrane properties of the ER and enhances ER stress resistance in a manner dependent on unfolded protein response regulators without the requirement of HA. HA-independent role of CD44 in proteostasis regulation may contribute to mammalian longevity.

C. elegans aging research

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PeerJ. 2023 Aug 30;11:e15845. doi: 10.7717/peerj.15845. eCollection 2023.

Intestinal GPDH-1 regulates high glucose diet induced lifespan extension in aged worms

Jihao Mo [# 1], Zhenzhen Zhang [# 2], Xiaowei Wang [3], Miaomiao Wang [4], Ning Sun [5], Lei Wang [3], Meimei Wang [3]

Affiliations + expand

PMID: 37663291 PMCID: PMC10474827 DOI: 10.7717/peerj.15845

Free PMC article

Abstract

A high glucose diet (HGD) is associated with many metabolic diseases including type 2 diabetes, and cardiovascular diseases. Additionally, a HGD increases the oxidative stress resistance of young animals but shortens their lifespan. To investigate the role of HGD feeding on the aging of aged animals, we tested for oxidative stress resistance and changes in lifespan using *C. elegans*. We showed that a HGD extends the lifespan of aged worms that are dependent on oxidative stress resistance. Furthermore, we measured the lifespan of oxidative stress responding genes of HGD-fed worms. We found that *gpdh-1* and *col-92* are highly expressed in HGD and paraquat (PQ) treated worms. Further experiments indicated that intestinal *gpdh-1* is essential for the HGD induced lifespan extension of aged worms. Our studies provide new insights into understanding the correlation between glucose metabolism, oxidative stress resistance, and aging.

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Downregulation of transposable elements extends lifespan in *Caenorhabditis elegans*

Ádám Sturm, Éva Saskői, Bernadette Hotzi, Anna Tarnóci, János Barna, Ferenc Bodnár, Himani Sharma, Tibor Kovács, Eszter Ari, Nóra Weinhardt, Csaba Kerepesi, András Perczel, Zoltán Ivics & Tibor Vellai

Nature Communications **14**, Article number: 5278 (2023) | Cite this article

Abstract

Mobility of transposable elements (TEs) frequently leads to insertional mutations in functional DNA regions. In the potentially immortal germline, TEs are effectively suppressed by the Piwi-piRNA pathway. However, in the genomes of ageing somatic cells lacking the effects of the pathway, TEs become increasingly mobile during the adult lifespan, and their activity is associated with genomic instability. Whether the progressively increasing mobilization of TEs is a cause or a consequence of ageing remains a fundamental problem in biology. Here we show that in the nematode *Caenorhabditis elegans*, the downregulation of active TE families extends lifespan. Ectopic activation of Piwi proteins in the soma also promotes longevity. Furthermore, DNA N^6-adenine methylation at TE stretches gradually rises with age, and this epigenetic modification elevates their transcription as the animal ages. These results indicate that TEs represent a novel genetic determinant of ageing, and that N^6-adenine methylation plays a pivotal role in ageing control.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Combinatorial interventions in aging

Andrey A. Parkhitko, Elizabeth Filine & Marc Tatar

Nature Aging (2023) | Cite this article

Abstract

Insight on the underlying mechanisms of aging will advance our ability to extend healthspan, treat age-related pathology and improve quality of life. Multiple genetic and pharmacological manipulations extend longevity in different species, yet monotherapy may be relatively inefficient, and we have limited data on the effect of combined interventions. Here we summarize interactions between age-related pathways and discuss strategies to simultaneously retard these in different organisms. In some cases, combined manipulations additively increase their impact on common hallmarks of aging and lifespan, suggesting they quantitatively participate within the same pathway. In other cases, interactions affect different hallmarks, suggesting their joint manipulation may independently maximize their effects on lifespan and healthy aging. While most interaction studies have been conducted with invertebrates and show varying levels of translatability, the conservation of pro-longevity pathways offers an opportunity to identify 'druggable' targets relevant to multiple human age-associated pathologies.

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Cell senescence, the senescence-associated secretory phenotype, and cancers

Larissa G. P. Langhi Prata, Tamar Tchkonia, James L. Kirkland

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Article | Authors | Metrics | Comments | Media Coverage

Cellular senescence is a cell fate caused by multiple stresses. A 2008 article in *PLOS Biology* reported a senescence-associated secretory phenotype that can promote inflammation and cancer, eventually enabling the development of senolytic drugs.

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The AD odyssey 2023: Tales of single cell

Wenjie Luo • Wenhui Qu • Li Gan

DOI: https://doi.org/10.1016/j.cell.2023.09.001 •

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Deciphering cellular changes in Alzheimer's disease (AD) using large cohorts with defined clinical stages is essential for understanding the diverse trajectories of AD progression. In this issue of *Cell*, five studies harnessed the power of single-nuclei RNA sequencing (snRNA-seq) and single-nuclei ATAC sequencing (snATAC-seq) at unprecedented scale and revealed exciting insights into cell-type-specific mechanisms underlying the progression of AD pathogenesis.

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Alzheimer's disease as a viral disease: Revisiting the infectious hypothesis ☆

Alzheimer's disease (AD) represents the most frequent type of dementia in elderly people. Two major forms of the disease exist: *sporadic* - the causes of which have not yet been fully understood - and *familial* - inherited within families from generation to generation, with a clear autosomal dominant transmission of mutations in Presenilin 1 (*PSEN1*), 2 (*PSEN2*) or Amyloid Precursors Protein (*APP*) genes. The main hallmark of AD consists of extracellular deposits of amyloid-beta (Aβ) peptide and intracellular deposits of the hyperphosphorylated form of the tau protein. An ever-growing body of research supports the viral infectious hypothesis of sporadic forms of AD. In particular, it has been shown that several herpes viruses (i.e., HHV-1, HHV-2, HHV-3 or varicella zoster virus, HHV-4 or Epstein Barr virus, HHV-5 or cytomegalovirus, HHV-6A and B, HHV-7), flaviviruses (i.e., Zika virus, Dengue fever virus, Japanese encephalitis virus) as well as Human Immunodeficiency Virus (HIV), hepatitis viruses (HAV, HBV, HCV, HDV, HEV), SARS-CoV2, Ljungan virus (LV), Influenza A virus and Borna disease virus, could increase the risk of AD. Here, we summarized and discussed these results. Based on these findings, significant issues for future studies are also put forward.

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Anti-amyloid antibody treatments for Alzheimer's disease

Robert Perneczky [1 2 3 4 5], Geert Dom [6 7 8], Andrew Chan [9], Peter Falkai [1 8 10], Claudio Bassetti [9 11]

Affiliations + expand

PMID: 37697714 DOI: 10.1111/ene.16049

Free article

Abstract

Our aim is to review the most recent evidence on novel antibody therapies for Alzheimer's disease directed against amyloid-β. This is a joint statement of the European Association of Neurology and the European Psychiatric Association. After numerous unsuccessful endeavors to create a disease-modifying therapy for Alzheimer's disease, substantial and consistent evidence supporting the clinical effectiveness of monoclonal antibodies aimed at amyloid-β is finally emerging. The latest trials not only achieved their primary objective of slowing the progression of the disease over several months but also demonstrated positive secondary clinical outcomes and a decrease in amyloid-β levels as observed through positron emission tomography scans. Taken as a whole, these findings mark a significant breakthrough by substantiating that reducing amyloid-β yields tangible clinical benefits, beyond mere changes in biomarkers. Concurrently, the regular utilization of the new generation of drugs will determine whether statistical efficacy translates into clinically meaningful improvements. This may well signify the dawning of a new era in the development of drugs for Alzheimer's disease.

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Protein aggregation: A detrimental symptom or an adaptation mechanism?

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Affiliations + expand

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Abstract

Protein quality control mechanisms oversee numerous aspects of protein lifetime. From the point of protein synthesis, protein homeostasis machineries take part in folding, solubilization, and/or degradation of impaired proteins. Some proteins follow an alternative path upon loss of their solubility, thus are secluded from the cytosol and form protein aggregates. Protein aggregates differ in their function and composition, rendering protein aggregation a complex phenomenon that continues to receive plenty of attention in the scientific and medical communities. Traditionally, protein aggregates have been associated with aging and a large spectrum of protein folding diseases, such as neurodegenerative diseases, type 2 diabetes, or cataract. However, a body of evidence suggests that they may act as an adaptive mechanism to overcome transient stressful conditions, serving as a sink for the removal of misfolded proteins from the cytosol or storage compartments for machineries required upon stress release. In this review, we present examples and evidence elaborating different possible roles of protein aggregation and discuss their potential roles in stress survival, aging, and disease, as well as possible anti-aggregation interventions.

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A physicochemical perspective on cellular ageing

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Affiliations + expand

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Abstract

Cellular ageing described at the molecular level is a multifactorial process that leads to a spectrum of ageing trajectories. There has been recent discussion about whether a decline in physicochemical homeostasis causes aberrant phase transitions, which are a driver of ageing. Indeed, the function of all biological macromolecules, regardless of their participation in biomolecular condensates, depends on parameters such as pH, crowding, and redox state. We expand on the physicochemical homeostasis hypothesis and summarise recent evidence that the intracellular milieu influences molecular processes involved in ageing.

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Aging Rate Indicators: Speedometers for Aging Research in Mice

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Affiliations + expand

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Free PMC article

Abstract

A "biomarker of aging" is conceptualized as an index of how far an individual has moved along the path from youth to old age. In contrast, an aging rate indicator (ARI) represents a measure of speed, rather than distance, that is, a measure of how rapidly the individual is moving toward the phenotypic changes typical of old age. This essay presents and reviews recent data suggesting common characteristics of slow-aging mice, whether the slowed aging is caused by a mutant allele, the calorie restriction diet, or drugs that slow aging and extend mean and maximal lifespan. Some of the candidate ARIs, shared by nine varieties of slow-aging mice, are physiological changes seen in fat, fat-associated macrophages, muscle, liver, brain, and plasma. Others are molecular measurements, reflecting activity of mTORC1, selective mRNA translation, or each of six MAP kinases in two distinct MAPK cascades in liver, muscle, or kidney. Changes in ARIs are notable in young adult mice after 8 months of drug or diet exposure, are detectable in mutant mice at least as early as 4-6 months of age, and persist until at least 18-22 months. Many of the candidate ARIs are thought to play an influential role in cognition, inflammation, exercise responses, and control of metabolic rate, and are thus plausible as modulators of age-related physiological and neurological illnesses. In principle, screening for drugs that induce alterations in ARIs in normal young adult mice might facilitate the search for preventive medicines that can retard aging and late-life illnesses in mice or in human populations.

Signaling Circuits and the Apical Extracellular Matrix In Aging: Connections Identified in the Nematode *Caenorhabditis elegans*

Hannah Reich [1], Cathy Savage-Dunn [2]

Numerous conserved signaling pathways play critical roles in aging, including insulin, TGF-β, Wnt, and autophagy pathways. Some of these pathways also play prominent roles in the formation and maintenance of the extracellular matrix. The nematode *Caenorhabditis elegans* has been an enduringly productive system for the identification of conserved mechanisms of biological aging. Recent studies in *C. elegans* highlight the regulatory circuits between conserved signaling pathways and the extracellular matrix, revealing a bidirectional relationship between these factors and providing a platform to address how regulation of and by the extracellular matrix can impact lifespan and organismal health during aging. These discoveries provide new opportunities for clinical advances and novel therapeutic strategies.

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Nuclear hormone receptor NHR-49 is an essential regulator of stress resilience and healthy aging in *Caenorhabditis elegans*

Kelsie R S Doering [1 2 3 4], Glafira Ermakova [1 2 3 4], Stefan Taubert [1 2 3 4]

The genome of *Caenorhabditis elegans* encodes 284 nuclear hormone receptor, which perform diverse functions in development and physiology. One of the best characterized of these is NHR-49, related in sequence and function to mammalian hepatocyte nuclear factor 4α and peroxisome proliferator-activated receptor α. Initially identified as regulator of lipid metabolism, including fatty acid catabolism and desaturation, additional important roles for NHR-49 have since emerged. It is an essential contributor to longevity in several genetic and environmental contexts, and also plays vital roles in the resistance to several stresses and innate immune response to infection with various bacterial pathogens. Here, we review how NHR-49 is integrated into pertinent signaling circuits and how it achieves its diverse functions. We also highlight areas for future investigation including identification of regulatory inputs that drive NHR-49 activity and identification of tissue-specific gene regulatory outputs. We anticipate that future work on this protein will provide information that could be useful for developing strategies to age-associated declines in health and age-related human diseases.

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Chaotic aging: intrinsically disordered proteins in aging-related processes

The development of aging is associated with the disruption of key cellular processes manifested as well-established hallmarks of aging. Intrinsically disordered proteins (IDPs) and intrinsically disordered regions (IDRs) have no stable tertiary structure that provide them a power to be configurable hubs in signaling cascades and regulate many processes, potentially including those related to aging. There is a need to clarify the roles of IDPs/IDRs in aging. The dataset of 1702 aging-related proteins was collected from established aging databases and experimental studies. There is a noticeable presence of IDPs/IDRs, accounting for about 36% of the aging-related dataset, which is however less than the disorder content of the whole human proteome (about 40%). A Gene Ontology analysis of the used here aging proteome reveals an abundance of IDPs/IDRs in one-third of aging-associated processes, especially in genome regulation. Signaling pathways associated with aging also contain IDPs/IDRs on different hierarchical levels, revealing the importance of "structure-function continuum" in aging. Protein–protein interaction network analysis showed that IDPs present in different clusters associated with different aging hallmarks. Protein cluster with IDPs enrichment has simultaneously high liquid–liquid phase separation (LLPS) probability, “nuclear” localization and DNA-associated functions, related to aging hallmarks: genomic instability, telomere attrition, epigenetic alterations, and stem cells exhaustion. Intrinsic disorder, LLPS, and aggregation propensity should be considered as features that could be markers of pathogenic proteins. Overall, our analyses indicate that IDPs/IDRs play significant roles in aging-associated processes, particularly in the regulation of DNA functioning. IDP aggregation, which can lead to loss of function and toxicity, could be critically harmful to the cell. A structure-based analysis of aging and the identification of proteins that are particularly susceptible to disturbances can enhance our understanding of the molecular mechanisms of aging and open up new avenues for slowing it down.

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The evolution of aging and lifespan

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Affiliations + expand

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Free article

Abstract

Aging is a nearly inescapable trait among organisms yet lifespan varies tremendously across different species and spans several orders of magnitude in vertebrates alone. This vast phenotypic diversity is driven by distinct evolutionary trajectories and tradeoffs that are reflected in patterns of diversification and constraint in organismal genomes. Age-specific impacts of selection also shape allele frequencies in populations, thus impacting disease susceptibility and environment-specific mortality risk. Further, the mutational processes that spawn this genetic diversity in both germline and somatic cells are strongly influenced by age and life history. We discuss recent advances in our understanding of the evolution of aging and lifespan at organismal, population, and cellular scales, and highlight outstanding questions that remain unanswered.

OTHER RESEARCH & REVIEWS

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Is Target-Based Drug Discovery Efficient? Discovery and "Off-Target" Mechanisms of All Drugs

Arash Sadri*

Target-based drug discovery is the dominant paradigm of drug discovery; however, a comprehensive evaluation of its real-world efficiency is lacking. Here, a manual systematic review of about 32000 articles and patents dating back to 150 years ago demonstrates its apparent inefficiency. Analyzing the origins of all approved drugs reveals that, despite several decades of dominance, only 9.4% of small-molecule drugs have been discovered through "target-based" assays. Moreover, the therapeutic effects of even this minimal share cannot be solely attributed and reduced to their purported targets, as they depend on numerous off-target mechanisms unconsciously incorporated by phenotypic observations. The data suggest that reductionist target-based drug discovery may be a cause of the productivity crisis in drug discovery. An evidence-based approach to enhance efficiency seems to be prioritizing, in selecting and optimizing molecules, higher-level phenotypic observations that are closer to the sought-after therapeutic effects using tools like artificial intelligence and machine learning.