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Scientific News
8th of January 2023
Sven Bulterijs

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Business/Conferences/ General news

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May we make large breakthroughs in our fight against aging in 2023!

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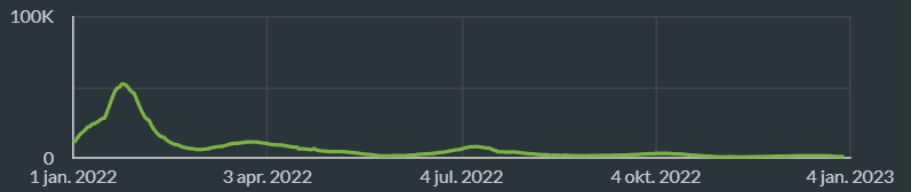
Belgium

		Daily Average	
Cases	4,7 mln.	865 * -37%	
Hospital Admissions for COVID-19	145,5K	95,9 -25%	
Deaths	33,4K	11,1 * -6%	

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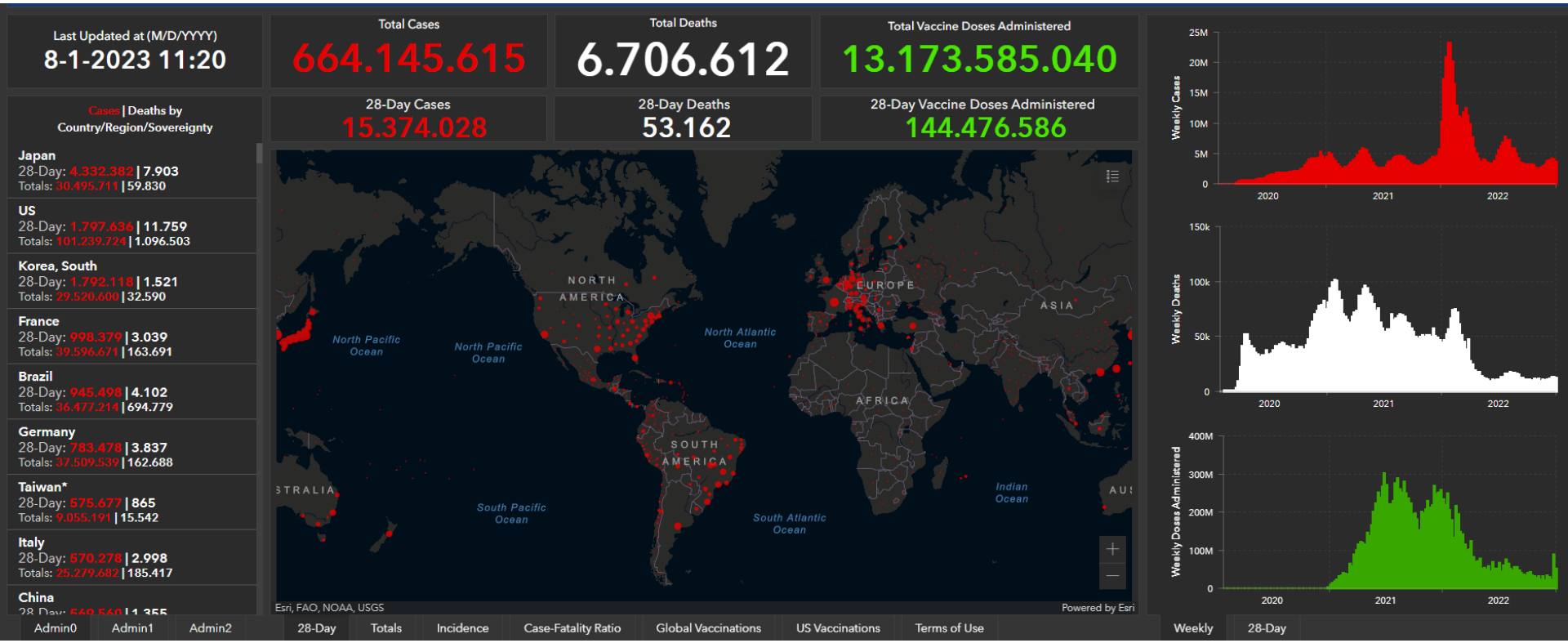
World



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Lung damage found in 11% of severe COVID survivors

By **Frank Diamond** • Dec 6, 2022 10:55am

Long COVID | American Lung Association | Radiology | respiratory diseases

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Robust Mouse Rejuvenation project details announced

Author: **Eleanor Garth** | Published on: **December 22, 2022** | Last updated: **December 22, 2022**

Editor's choice

Empowering cells
energy and recov
winning move

Study disproves b

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Six shifts for healthy aging are needed.

Investment, measurement, and innovation are among the solutions

1. Invest in the promotion of healthy aging
2. Improve measurements of health and get better data
3. Scale interventions proven to promote healthy aging
4. Accelerate innovation across the healthy aging ecosystem
5. Unleash the potential of all industries to enable healthy aging
6. Empower and motivate older adults to live to their full potential

McKinsey & Company

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Year in Review | Published: 23 December 2022

11 clinical trials that will shape medicine in 2023

Carrie Arnold & Paul Webster

Table 1 Clinical trials to watch in 2023

From: 11 clinical trials that will shape medicine in 2023

Treatment	Organization	Description	Phase	Lead indication
Exenatide	University College London	Neuroprotective effect of exenatide, used to treat type 2 diabetes, over a 2-year follow-up period	3	Parkinson's disease
Diet and exercise	European Research Council	Long-term effect of a weight-loss intervention based on a reduced-calorie Mediterranean diet, physical activity and behavioral support	3	Obesity and metabolic syndrome
Lecanemab	Eisai/Biogen	Monoclonal antibody to amyloid-β, for the treatment of mild cognitive impairment with Alzheimer's disease	3	Alzheimer's disease
mRNA-1273 and bivalent vaccine	South Africa Medical Research Council	Efficacy of vaccines against COVID-19 in people with HIV	3	COVID-19
Mirvetuximab soravtansine	Immunogen	ADC that targets tumors with high expression of folate receptor-α	3	Recurrent platinum-resistant ovarian cancer
Fexinidazole	Drugs for Neglected Diseases	Efficacy of the oral drug fexinidazole for *rhodesiense* sleeping sickness versus that of the existing drugs melarsoprol and suramine	2/3	Stage 2 *T. brucei rhodesiense* infection
CTX001	CRISPR Therapeutics and Vertex Pharmaceuticals	Autologous CRISPR–Cas9-modified $CD34^+$ human hematopoietic stem and progenitor cells	1/2/3	Sickle-cell disease
GenPHSat	Charité–Universitätsmedizin Berlin	Base editing to repair a mutation in muscle stem cells, to rebuild muscle	1/2	Muscular dystrophy
Digoxin	ETH Zurich	Dissociation of CTC clusters	1	Metastatic breast cancer
PSA, kallikrein panel, MRI, and prostate biopsy	Tampere University	A new screening approach that reduces harm from PSA screening while maintaining mortality reduction	Population-based randomized trial	Prostate cancer
HPV DNA testing and liquid-based cytology	Australian Centre for the Prevention of Cervical Cancer	HPV testing versus Pap smears to detect early-stage cervical cancer	Population-based randomized trial	Cervical cancer

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JOURNAL ARTICLE

Is Aging a Disease? The Theoretical Definition of Aging in the Light of the Philosophy of Medicine

Get access >

Cristian Saborido ✉, Pablo García-Barranquero

The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine, Volume 47, Issue 6, December 2022, Pages 770–783,
https://doi.org/10.1093/jmp/jhac030
Published: 23 December 2022

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Abstract

In the philosophical debate on aging, it is common to raise the question of the theoretical definition of aging in terms of its possible characterization as a disease. Understanding aging as a disease seems to imply its medicalization, which has important practical consequences. In this paper, we analyze the question of whether aging is a disease by appealing to the concept of disease in the philosophy of medicine. As a result of this analysis, we argue that a pragmatist approach to the conception of disease is the best alternative to highlight the relevance of the medicalization of aging. From this pragmatist perspective, it can be seen that the notion of aging is going through a conceptual change, and aging can today be understood as a not radically different process from any other condition that is usually considered a disease.

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RegenerativeMedicineDaily

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If Aging is Not a Disease, Then Neither is Cancer!

By Joe Bennett

Humans are often remarkably so very stubborn in their mindsets. As much as we would be quick to deny it, we are all guilty of being stubborn and refusing to change our minds on certain topics. Now this is not necessarily a bad thing, and you really should have a good reason for changing your mind on a subject. However, that assumes that you had a good reason for your opinion to begin with, which unfortunately is not often the case. Nothing more perfectly exemplifies this phenomenon better than the broader scientific community's reluctance to define the aging process as a disease, as opposed to 'a natural process that is part of life'. This opinion (although slowly changing) is rooted in what can best be described as cognitive dissonance, apathy, and what can only really be described as Stockholm syndrome with extra steps.

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New Journal

Aging Biology

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Our mission: *Aging Biology* is a journal run by scientists and for scientists. Our mission is to publish high quality research on the fundamental mechanisms of aging and longevity.

Our Sponsors

Aging Biology publishes highly significant research into the biology of aging and longevity that bridges from basic molecular mechanisms to *in vivo* aging biology.

Introducing Aging Biology

1 2 3 4 5 6

Aging Biology was founded by former Editors in Chief of Aging Cell.

In 2022, a **dispute** with the publisher resulted in the resignation of five editors in chief and majority of the editorial board that went on to establish *Aging Biology*. We will continue the tradition of publishing high quality science with the review process run by the leading scientists in the field of aging.

Current Announcements

December 10, 2022

We are pleased to announce the publication of the first articles in our journal. See **Papers in Press.**

- A **new study** by Luigi Fontana group shows that intermittent fasing leads to weight loss but does not reduce inflammation in humans.

Editorial

...

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Aging research articles

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PREPRINT

Gene Therapy Mediated Partial Reprogramming Extends Lifespan and Reverses Age-Related Changes in Aged Mice

Carolina Cano Macip, Rokib Hasan, Victoria Hoznek, Jihyun Kim, Louis E. Metzger IV, Saumil Sethna, Noah Davidsohn

doi: https://doi.org/10.1101/2023.01.04.522507

This article is a preprint and has not been certified by peer review [what does this mean?].

0 0 0 0 0 0 109

Abstract Full Text Info/History Metrics Preview PDF

Abstract

Aging is a complex process best characterized as the chronic dysregulation of cellular processes leading to deteriorated tissue and organ function. While aging cannot currently be prevented, its impact on lifespan and healthspan in the elderly can potentially be minimized by interventions that aim to return these cellular processes to optimal function. Recent studies have demonstrated that partial reprogramming using the Yamanaka factors (or a subset; *OCT4*, *SOX2*, and *KLF4; OSK)* can reverse age-related changes *in vitro* and *in vivo*. However, it is still unknown whether the Yamanaka factors (or a subset) are capable of extending the lifespan of aged wild type mice. Here, we show that systemically delivered AAVs, encoding an inducible OSK system, in 124-week-old mice extends the median remaining lifespan by 109% over wild-type controls and enhances several health parameters. Importantly, we observed a significant improvement in frailty scores indicating that we were able to improve the healthspan along with increasing the lifespan. Furthermore, in human keratinocytes expressing exogenous OSK, we observed significant epigenetic markers of age-reversal, suggesting a potential reregulation of genetic networks to a younger, potentially healthier state. Together, these results may have important implications for the development of partial reprogramming interventions to reverse age-associated diseases in the elderly.

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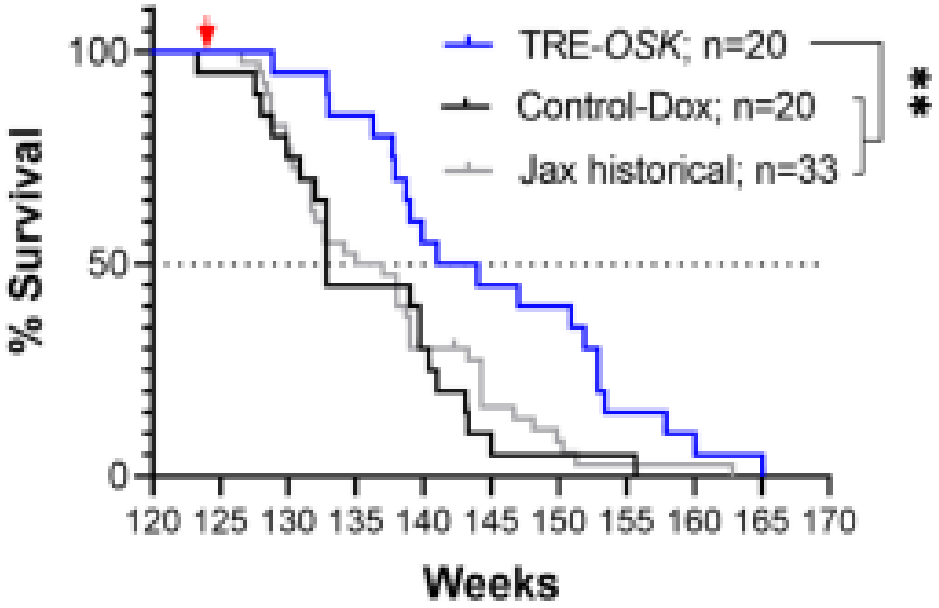
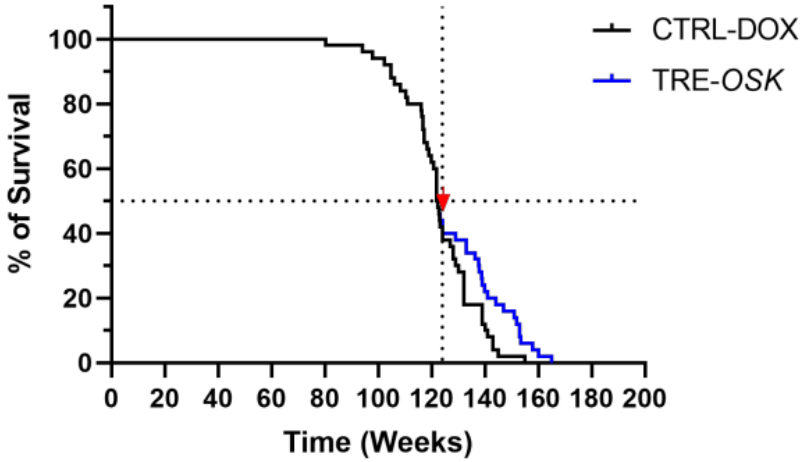
Gene Therapy Mediated Partial Reprogramming Extends Lifespan and Reverses Age-Related Changes in Aged Mice





Supplementary Fig. 1: Overall survival proportion curves for control mice and TRE-*OSK* mice over the entire lifespan.

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Transplanting rejuvenated blood stem cells extends lifespan of aged immunocompromised mice

Sara Montserrat-Vazquez, Noelle J. Ali, Francesca Matteini, Javier Lozano, Tu Zhaowei, Eva Mejia-Ramirez, Gina Marka, Angelika Vollmer, Karin Soller, Mehmet Sacma, Vadim Sakk, Loris Mularoni, Jan Philipp Mallm, Mireya Plass, Yi Zheng, Hartmut Geiger & M. Carolina Florian

npj Regenerative Medicine **7**, Article number: 78 (2022) | Cite this article

5157 Accesses | **40** Altmetric | Metrics

Abstract

One goal of regenerative medicine is to rejuvenate tissues and extend lifespan by restoring the function of endogenous aged stem cells. However, evidence that somatic stem cells can be targeted in vivo to extend lifespan is still lacking. Here, we demonstrate that after a short systemic treatment with a specific inhibitor of the small RhoGTPase Cdc42 (CASIN), transplanting aged hematopoietic stem cells (HSCs) from treated mice is sufficient to extend the healthspan and lifespan of aged immunocompromised mice without additional treatment. In detail, we show that systemic CASIN treatment improves strength and endurance of aged mice by increasing the myogenic regenerative potential of aged skeletal muscle stem cells. Further, we show that CASIN modifies niche localization and H4K16ac polarity of HSCs in vivo. Single-cell profiling reveals changes in HSC transcriptome, which underlie enhanced lymphoid and regenerative capacity in serial transplantation assays. Overall, we provide proof-of-concept evidence that a short systemic treatment to decrease Cdc42 activity improves the regenerative capacity of different endogenous aged stem cells in vivo, and that rejuvenated HSCs exert a broad systemic effect sufficient to extend murine health- and lifespan.

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Analysis | Open Access | Published: 09 December 2022

Aging is associated with a systemic length-associated transcriptome imbalance

Thomas Stoeger, Rogan A. Grant, Alexandra C. McQuattie-Pimentel, Kishore R. Anekalla, Sophia S. Liu, Heliodoro Tejedor-Navarro, Benjamin D. Singer, Hiam Abdala-Valencia, Michael Schwake, Marie-Pier Tetreault, Harris Perlman, William E. Balch, Navdeep S. Chandel, Karen M. Ridge, Jacob I. Sznajder, Richard I. Morimoto, Alexander V. Misharin, G. R. Scott Budinger & Luis A. Nunes Amaral

Nature Aging **2**, 1191–1206 (2022) | Cite this article

32k Accesses | **579** Altmetric | Metrics

Abstract

Aging is among the most important risk factors for morbidity and mortality. To contribute toward a molecular understanding of aging, we analyzed age-resolved transcriptomic data from multiple studies. Here, we show that transcript length alone explains most transcriptional changes observed with aging in mice and humans. We present three lines of evidence supporting the biological importance of the uncovered transcriptome imbalance. First, in vertebrates the length association primarily displays a lower relative abundance of long transcripts in aging. Second, eight antiaging interventions of the Interventions Testing Program of the National Institute on Aging can counter this length association. Third, we find that in humans and mice the genes with the longest transcripts enrich for genes reported to extend lifespan, whereas those with the shortest transcripts enrich for genes reported to shorten lifespan. Our study opens fundamental questions on aging and the organization of transcriptomes.

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PREPRINT

Aging-associated changes in transcriptional elongation influence metazoan longevity

Cédric Debès, Antonios Papadakis, Sebastian Grönke, Özlem Karalay, Luke Tain, Athanasia Mizi, Shuhei Nakamura, Oliver Hahn, Carina Weigelt, Natasa Josipovic, Anne Zirkel, Isabell Brusius, Konstantinos Sofiadis, Mantha Lamprousi, Yu-Xuan Lu, Wenming Huang, Reza Esmaillie, Torsten Kubacki, Martin R. Späth, Bernhard Schermer, Thomas Benzing, Roman-Ulrich Müller, Adam Antebi, Linda Partridge, Argyris Papantonis, Andreas Beyer

doi: https://doi.org/10.1101/719864

This article is a preprint and has not been certified by peer review [what does this mean?].

0 0 0 0 0 0 21

Abstract

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

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J Am Chem Soc. 2022 Dec 7;144(48):21843-21847. doi: 10.1021/jacs.2c09626. Epub 2022 Nov 21.

Pentosinane, a Post-Translational Modification of Human Proteins with Underappreciated Stability

Edward A deRamon [1], Venkata R Sabbasani [1], Matthew D Streeter [1], Yannan Liu [1], Timothy R Newhouse [1], David M McDonald [1], David A Spiegel [1]

Affiliations + expand

PMID: 36410375 DOI: 10.1021/jacs.2c09626

Abstract

Pentosinane is a structurally complex nonenzymatic post-translational modification of proteins believed to be present in all living things. It falls into the category of advanced glycation end products (AGEs) and is structurally related to the other AGEs pentosidine and glucosepane. Although pentosidine and glucosepane have been widely studied for their role in wide-ranging conditions (e.g., diabetes mellitus, Alzheimer's disease, and human aging), relatively little is known about pentosinane. Interestingly, previous reports have suggested that pentosidine may derive from pentosinane. The (patho)physiological significance of pentosinane in humans is largely unexplored. As a first step to address this knowledge gap, we report herein the first total synthesis of pentosinane. Our synthesis is high yielding (1.7% over seven steps), concise, and enantioselective, and it leverages a strategy for synthesizing 2,5-diaminoimidazoles previously developed by our lab. Access to synthetic pentosinane has allowed us to perform additional studies showing that its oxidation to pentosidine is both pH and oxygen dependent and is substantially slower under physiological conditions than previously believed. Additionally, pentosinane rapidly decomposes under harshly acidic conditions typically employed for pentosidine isolation. Taken together, these results suggest that pentosinane is likely to be more abundant *in vivo* than previously appreciated. We believe these results represent a critical step toward illuminating the role(s) of pentosinane in human biology.

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Network analyses unveil ageing-associated pathways evolutionarily conserved from fungi to animals

The genetic roots of the diverse paces and shapes of ageing and of the large variations in longevity observed across the tree of life are poorly understood. Indeed, pathways associated with ageing/longevity are incompletely known, both in terms of their constitutive genes/proteins and of their molecular interactions. Moreover, there is limited overlap between the genes constituting these pathways across mammals. Yet, dedicated comparative analyses might still unravel evolutionarily conserved, important pathways associated with longevity or ageing. Here, we used an original strategy with a double evolutionary and systemic focus to analyse protein interactions associated with ageing or longevity during the evolution of five species of Opisthokonta. We ranked these proteins and interactions based on their evolutionary conservation and centrality in past and present protein–protein interaction (PPI) networks, providing a big systemic picture of the evolution of ageing and longevity pathways that identified which pathways emerged in which Opisthokonta lineages, were conserved, and/or central. We confirmed that longevity/ageing-associated proteins (LAPs), be they pro- or anti-longevity, are highly central in extant PPI, consistently with the antagonistic pleiotropy theory of ageing, and identified key antagonistic regulators of ageing/longevity, 52 of which with homologues in humans. While some highly central LAPs were evolutionarily conserved for over a billion years, we report a clear transition in the functionally important components of ageing/longevity within bilaterians. We also predicted 487 novel evolutionarily conserved LAPs in humans, 54% of which are more central than mTOR, and 138 of which are druggable, defining new potential targets for anti-ageing treatments in humans.

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Lifespan benefits for the combination of rapamycin plus acarbose and for captopril in genetically heterogeneous mice

Randy Strong [1], Richard A Miller [2], Catherine J Cheng [3], James F Nelson [3], Jonathan Gelfond [4], Shailaja Kesaraju Allani [5], Vivian Diaz [3], Angela Olsen Dorigatti [6], Jonathan Dorigatti [6], Elizabeth Fernandez [1], Andrzej Galecki [7], Brett Ginsburg [8], Karyn L Hamilton [9], Martin A Javors [8], Kerry Kornfeld [10], Matt Kaeberlein [11], Suja Kumar [12], David B Lombard [2], Marisa Lopez-Cruzan [8], Benjamin F Miller [13], Peter Rabinovitch [11], Peter Reifsnyder [14], Nadia A Rosenthal [14], Molly A Bogue [14], Adam B Salmon [6], Yousin Suh [15], Eric Verdin [16 17], Herbert Weissbach [5], John Newman [16 17], Francesca Maccchiarini [18], David E Harrison [14]

Affiliations + expand

PMID: 36179270 PMCID: PMC9741502 DOI: 10.1111/acel.13724

Free PMC article

Abstract

Mice bred in 2017 and entered into the C2017 cohort were tested for possible lifespan benefits of (R/S)-1,3-butanediol (BD), captopril (Capt), leucine (Leu), the Nrf2-activating botanical mixture PB125, sulindac, syringaresinol, or the combination of rapamycin and acarbose started at 9 or 16 months of age (RaAc9, RaAc16). In male mice, the combination of Rapa and Aca started at 9 months and led to a longer lifespan than in either of the two prior cohorts of mice treated with Rapa only, suggesting that this drug combination was more potent than either of its components used alone. In females, lifespan in mice receiving both drugs was neither higher nor lower than that seen previously in Rapa only, perhaps reflecting the limited survival benefits seen in prior cohorts of females receiving Aca alone. Capt led to a significant, though small (4% or 5%), increase in female lifespan. Capt also showed some possible benefits in male mice, but the interpretation was complicated by the unusually low survival of controls at one of the three test sites. BD seemed to produce a small (2%) increase in females, but only if the analysis included data from the site with unusually short-lived controls. None of the other 4 tested agents led to any lifespan benefit. The C2017 ITP dataset shows that combinations of anti-aging drugs may have effects that surpass the benefits produced by either drug used alone, and that additional studies of captopril, over a wider range of doses, are likely to be rewarding.

Keywords: acarbose plus rapamycin; captopril; survival.

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Sexual identity of enterocytes regulates autophagy to determine intestinal health, lifespan and responses to rapamycin

Jennifer C. Regan, Yu-Xuan Lu, Enric Ureña, Ralf L. Meilenbrock, James H. Catterson, Disna Kißler, Jenny Fröhlich, Emilie Funk & Linda Partridge

Nature Aging **2**, 1145–1158 (2022) | Cite this article

5869 Accesses | **222** Altmetric | Metrics

Abstract

Pharmacological attenuation of mTOR presents a promising route for delay of age-related disease. Here we show that treatment of *Drosophila* with the mTOR inhibitor rapamycin extends lifespan in females, but not in males. Female-specific, age-related gut pathology is markedly slowed by rapamycin treatment, mediated by increased autophagy. Treatment increases enterocyte autophagy in females, via the H3/H4 histone-Bchs axis, whereas males show high basal levels of enterocyte autophagy that are not increased by rapamycin feeding. Enterocyte sexual identity, determined by *transformer*^{Female} expression, dictates sexually dimorphic cell size, H3/H4-*Bchs* expression, basal rates of autophagy, fecundity, intestinal homeostasis and lifespan extension in response to rapamycin. Dimorphism in autophagy is conserved in mice, where intestine, brown adipose tissue and muscle exhibit sex differences in autophagy and response to rapamycin. This study highlights tissue sex as a determining factor in the regulation of metabolic processes by mTOR and the efficacy of mTOR-targeted, anti-aging drug treatments.

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› Nat Commun. 2022 Dec 10;13(1):7652. doi: 10.1038/s41467-022-35157-w.

Causal inference in medical records and complementary systems pharmacology for metformin drug repurposing towards dementia

Marie-Laure Charpignon [# 1], Bella Vakulenko-Lagun [# 2], Bang Zheng [# 3], Colin Magdamo [4], Bowen Su [5], Kyle Evans [4 6], Steve Rodriguez [4 6], Artem Sokolov [6], Sarah Boswell [6], Yi-Han Sheu [7], Melek Somai [8], Lefkos Middleton [3 9], Bradley T Hyman [4], Rebecca A Betensky [10], Stan N Finkelstein [1 11], Roy E Welsch [1 12], Ioanna Tzoulaki [13 14 15], Deborah Blacker [16 17], Sudeshna Das [18], Mark W Albers [19 20]

Affiliations + expand

PMID: 36496454 PMCID: PMC9741618 DOI: 10.1038/s41467-022-35157-w

Free PMC article

Abstract

Metformin, a diabetes drug with anti-aging cellular responses, has complex actions that may alter dementia onset. Mixed results are emerging from prior observational studies. To address this complexity, we deploy a causal inference approach accounting for the competing risk of death in emulated clinical trials using two distinct electronic health record systems. In intention-to-treat analyses, metformin use associates with lower hazard of all-cause mortality and lower cause-specific hazard of dementia onset, after accounting for prolonged survival, relative to sulfonylureas. In parallel systems pharmacology studies, the expression of two AD-related proteins, APOE and SPP1, was suppressed by pharmacologic concentrations of metformin in differentiated human neural cells, relative to a sulfonylurea. Together, our findings suggest that metformin might reduce the risk of dementia in diabetes patients through mechanisms beyond glycemic control, and that SPP1 is a candidate biomarker for metformin's action in the brain.

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p21 induces a senescence program and skeletal muscle dysfunction

Recent work has established associations between elevated p21, the accumulation of senescent cells, and skeletal muscle dysfunction in mice and humans. Using a mouse model of p21 overexpression (p21OE), we examined if p21 mechanistically contributes to cellular senescence and pathological features in skeletal muscle. We show that p21 induces several core properties of cellular senescence in skeletal muscle, including an altered transcriptome, DNA damage, mitochondrial dysfunction, and the senescence-associated secretory phenotype (SASP). Furthermore, p21OE mice exhibit manifestations of skeletal muscle pathology, such as atrophy, fibrosis, and impaired physical function when compared to age-matched controls. These findings suggest p21 alone is sufficient to drive a cellular senescence program and reveal a novel source of skeletal muscle loss and dysfunction.

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Article | Open Access | Published: 17 November 2022

A Glb1-2A-mCherry reporter monitors systemic aging and predicts lifespan in middle-aged mice

Jie Sun, Ming Wang, Yaqi Zhong, Xuan Ma, Shimin Sun, Chenzhong Xu, Linyuan Peng, Guo Li, Liting Zhang, Zuojun Liu, Ding Ai & Baohua Liu

Nature Communications **13**, Article number: 7028 (2022) | Cite this article

2974 Accesses | **30** Altmetric | Metrics

Abstract

The progressive decline of physiological function and the increased risk of age-related diseases challenge healthy aging. Multiple anti-aging manipulations, such as senolytics, have proven beneficial for health; however, the biomarkers that label in vivo senescence at systemic levels are lacking, thus hindering anti-aging applications. In this study, we generate a *Glb1*$^{+/m}$–Glb1-2A-mCherry (GAC) reporter allele at the *Glb1* gene locus, which encodes lysosomal β-galactosidase—an enzyme elevated in tissues of old mice. A linear correlation between GAC signal and chronological age is established in a cohort of middle-aged (9 to 13 months) *Glb1*$^{+/m}$ mice. The high GAC signal is closely associated with cardiac hypertrophy and a shortened lifespan. Moreover, the GAC signal is exponentially increased in pathological senescence induced by bleomycin in the lung. Senolytic dasatinib and quercetin (D + Q) reduce GAC signal in bleomycin treated mice. Thus, the Glb1-2A-mCherry reporter mice monitors systemic aging and function decline, predicts lifespan, and may facilitate the understanding of aging mechanisms and help in the development of anti-aging interventions.

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The sex-specific metabolic signature of C57BL/6NRj mice during aging

Doruntina Bresilla, Hansjoerg Habisch, Iva Pritišanac, Kim Zarse, Warisara Parichatikanond, Michael Ristow, Tobias Madl & Corina T. Madreiter-Sokolowski

Scientific Reports **12**, Article number: 21050 (2022) | Cite this article

510 Accesses | **2** Altmetric | Metrics

Abstract

Due to intact reactive oxygen species homeostasis and glucose metabolism, C57BL/6NRj mice are especially suitable to study cellular alterations in metabolism. We applied Nuclear Magnetic resonance spectroscopy to analyze five different tissues of this mouse strain during aging and included female and male mice aged 3, 6, 12, and 24 months. Metabolite signatures allowed separation between the age groups in all tissues, and we identified the most prominently changing metabolites in female and male tissues. A refined analysis of individual metabolite levels during aging revealed an early onset of age-related changes at 6 months, sex-specific differences in the liver, and a biphasic pattern for various metabolites in the brain, heart, liver, and lung. In contrast, a linear decrease of amino acids was apparent in muscle tissues. Based on these results, we assume that age-related metabolic alterations happen at a comparably early aging state and are potentially associated with a metabolic switch. Moreover, identified differences between female and male tissues stress the importance of distinguishing between sexes when studying age-related changes and developing new treatment approaches. Besides, metabolomic features seem to be highly dependent on the genetic background of mouse strains.

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Cell-cell metabolite exchange creates a pro-survival metabolic environment that extends lifespan

Clara Correia-Melo • Stephan Kamrad • Roland Tengölics • ... Balázs Papp • Mohammad Tauqeer Alam • Markus Ralser [15] • Show all authors • Show footnotes

Metabolism is deeply intertwined with aging. Effects of metabolic interventions on aging have been explained with intracellular metabolism, growth control, and signaling. Studying chronological aging in yeast, we reveal a so far overlooked metabolic property that influences aging via the exchange of metabolites. We observed that metabolites exported by young cells are re-imported by chronologically aging cells, resulting in cross-generational metabolic interactions. Then, we used self-establishing metabolically cooperating communities (SeMeCo) as a tool to increase metabolite exchange and observed significant lifespan extensions. The longevity of the SeMeCo was attributable to metabolic reconfigurations in methionine consumer cells. These obtained a more glycolytic metabolism and increased the export of protective metabolites that in turn extended the lifespan of cells that supplied them with methionine. Our results establish metabolite exchange interactions as a determinant of cellular aging and show that metabolically cooperating cells can shape the metabolic environment to extend their lifespan.

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Morbidity and mortality in elderly dogs – a model for human aging

Patrícia Dias-Pereira [1]

Affiliations + expand

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Free PMC article

Abstract

Over the last decades, canines have experienced a marked increase in their lifespan, mirroring human populations. Several authors have pointed out the domestic dog as a suitable animal model for geropathology translational research. The aim of this study is to assess age-related morbidities and mortality in a population of 269 elderly canines (130 males and 139 females) submitted to necropsy. The organic systems exhibiting the higher number of age-related morbidities were the reproductive, cardiovascular and urinary systems and, in females, also the mammary gland. The prevalence of cardiovascular and urinary disease was significantly higher in males and mammary lesions were exclusively found in females. Urinary disease was more frequent in small breeds dogs, while peritoneum and male genital morbidities were significantly higher in larger breeds. Hyperplastic and degenerative lesions were common morbidities found in this elderly dog population. The main cause of death was neoplasia, which accounted for almost half of the deaths. Cardiovascular and urinary pathology also emerged as a frequent cause of mortality. These findings partially parallel data obtained for human species, displaying cancer and cardiovascular pathology as major causes of disease and death in elderlies. Our data reinforce the potential of the domestic dog for further translational investigations on gerontology, meeting the concept of One Health.

Keywords: Aging; Animal model; Canine; Geropathology; Morbidity; Mortality; Necropsy; One health.

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Catalase-deficient mice induce aging faster through lysosomal dysfunction

Raghbendra Kumar Dutta [1], Joon No Lee [1], Yunash Maharjan [1], Channy Park [1], Seong-Kyu Choe [2], Ye-Shih Ho [3], Hyug Moo Kwon [4], Raekil Park [5]

Background: Lysosomes are a central hub for cellular metabolism and are involved in the regulation of cell homeostasis through the degradation or recycling of unwanted or dysfunctional organelles through the autophagy pathway. Catalase, a peroxisomal enzyme, plays an important role in cellular antioxidant defense by decomposing hydrogen peroxide into water and oxygen. In accordance with pleiotropic significance, both impaired lysosomes and catalase have been linked to many age-related pathologies with a decline in lifespan. Aging is characterized by progressive accumulation of macromolecular damage and the production of high levels of reactive oxygen species. Although lysosomes degrade the most long-lived proteins and organelles via the autophagic pathway, the role of lysosomes and their effect on catalase during aging is not known. The present study investigated the role of catalase and lysosomal function in catalase-knockout (KO) mice.

Methods: We performed experiments on WT and catalase KO younger (9 weeks) and mature adult (53 weeks) male mice and Mouse embryonic fibroblasts isolated from WT and KO mice from E13.5 embryos as in vivo and in ex-vivo respectively. Mouse phenotyping studies were performed with controls, and a minimum of two independent experiments were performed with more than five mice in each group.

Results: We found that at the age of 53 weeks (mature adult), catalase-KO mice exhibited an aging phenotype faster than wild-type (WT) mice. We also found that mature adult catalase-KO mice induced leaky lysosome by progressive accumulation of lysosomal content, such as cathespin D, into the cytosol. Leaky lysosomes inhibited autophagosome formation and triggered impaired autophagy. The dysregulation of autophagy triggered mTORC1 (mechanistic target of rapamycin complex 1) activation. However, the antioxidant N-acetyl-L-cysteine and mTORC1 inhibitor rapamycin rescued leaky lysosomes and aging phenotypes in catalase-deficient mature adult mice.

Conclusions: This study unveils the new role of catalase and its role in lysosomal function during aging. Video abstract.

Keywords: Aging; Catalase; Lysosome; ROS; mTORC1.

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Gut microbiota of the young ameliorates physical fitness of the aged in mice

Background: Aging is a natural process that an organism gradually loses its physical fitness and functionality. Great efforts have been made to understand and intervene in this deteriorating process. The gut microbiota affects host physiology, and dysbiosis of the microbial community often underlies the pathogenesis of host disorders. The commensal microbiota also changes with aging; however, the interplay between the microbiota and host aging remains largely unexplored. Here, we systematically examined the ameliorating effects of the gut microbiota derived from the young on the physiology and phenotypes of the aged.

Results: As the fecal microbiota was transplanted from young mice at 5 weeks after birth into 12-month-old ones, the thickness of the muscle fiber and grip strength were increased, and the water retention ability of the skin was enhanced with thickened stratum corneum. Muscle thickness was also marginally increased in 25-month-old mice after transferring the gut microbiota from the young. Bacteria enriched in 12-month-old mice that received the young-derived microbiota significantly correlated with the improved host fitness and altered gene expression. In the dermis of these mice, transcription of Dbn1 was most upregulated and DBN1-expressing cells increased twice. Dbn1-heterozygous mice exhibited impaired skin barrier function and hydration.

Conclusions: We revealed that the young-derived gut microbiota rejuvenates the physical fitness of the aged by altering the microbial composition of the gut and gene expression in muscle and skin. Dbn1, for the first time, was found to be induced by the young microbiota and to modulate skin hydration. Our results provide solid evidence that the gut microbiota from the young improves the vitality of the aged. Video Abstract.

Keywords: C57BL/6; Ki-67; Microbiome; Programmed aging; Sarcopenia.

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Genetic sex determination, sex chromosome size and sex-specific lifespans across tetrapods

Zahida Sultanova, Philip A. Downing, Pau Carazo

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Zahida Sultanova and Philip A. Downing Joint first author.

Abstract

Sex differences in lifespan are ubiquitous across the tree of life and exhibit broad taxonomic patterns that remain a puzzle, such as males living longer than females in birds and vice versa in mammals. The prevailing unguarded X hypothesis explains sex differences in lifespan by differential expression of recessive mutations on the X or Z chromosome of the heterogametic sex, but has only received indirect support to date. An alternative hypothesis is that the accumulation of deleterious mutations and repetitive elements on the Y or W chromosome might lower the survival of the heterogametic sex ('toxic Y' hypothesis). Here, we use a new database to report lower survival of the heterogametic relative to the homogametic sex across 136 species of birds, mammals, reptiles and amphibians, as expected if sex chromosomes shape sex-specific lifespans, and consistent with previous findings. We also found that the relative sizes of both the X and the Y chromosomes in mammals (but not the Z or the W chromosomes in birds) are associated with sex differences in lifespan, as predicted by the unguarded X and the 'toxic Y'. Furthermore, we report that the relative size of the Y is negatively associated with male lifespan in mammals, so that small Y size correlates with increased male lifespan. In theory, toxic Y effects are expected to be particularly strong in mammals, and we did not find similar effects in birds. Our results confirm the role of sex chromosomes in explaining sex differences in lifespan across tetrapods and further suggest that, at least in mammals, 'toxic Y' effects may play an important part in this role.

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Molecular and spatial signatures of mouse brain aging at single-cell resolution

William E. Allen • Timothy R. Blosser • Zuri A. Sullivan • Catherine Dulac • Xiaowei Zhuang [5] • Show footnotes

The diversity and complex organization of cells in the brain have hindered systematic characterization of age-related changes in its cellular and molecular architecture, limiting our ability to understand the mechanisms underlying its functional decline during aging. Here, we generated a high-resolution cell atlas of brain aging within the frontal cortex and striatum using spatially resolved single-cell transcriptomics and quantified changes in gene expression and spatial organization of major cell types in these regions over the mouse lifespan. We observed substantially more pronounced changes in cell state, gene expression, and spatial organization of non-neuronal cells over neurons. Our data revealed molecular and spatial signatures of glial and immune cell activation during aging, particularly enriched in the subcortical white matter, and identified both similarities and notable differences in cell-activation patterns induced by aging and systemic inflammatory challenge. These results provide critical insights into age-related decline and inflammation in the brain.

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Open Genes — a new comprehensive database of human genes associated with aging and longevity

Ekaterina Rafikova, Nikolay Nemirovich-Danchenko, Anna Ogmen, and 8 more

This is a preprint; it has not been peer reviewed by a journal.

https://doi.org/10.21203/rs.3.rs-2306130/v1
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Abstract

Open Genes database is created to enhance and simplify the search for potential aging therapy targets. We collected data on 2402 genes associated with aging and developed convenient tools for searching and comparing gene features. We provided a comprehensive description for genes, such as lifespan-extending interventions, aging-related changes, longevity associations, gene evolution, associations with diseases and hallmarks of aging, and functions of gene products.

We provided detailed structured data for each experiment needed to evaluate the quality and interpret the study result. Our goal was to stay objective and precise while connecting a particular gene and human aging. We distinguished 6 types of studies and 12 criteria for adding genes to our database. Genes were classified according to the confidence level of the link between the gene and aging. All data collected in a database are provided both by API and user interface. The database is publicly available on a website https://open-genes.org/.

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C. elegans aging research

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Brief Communication | Published: 30 December 2022

Optogenetic rejuvenation of mitochondrial membrane potential extends *C. elegans* lifespan

Brandon J. Berry, Anežka Vodičková, Annika Müller-Eigner, Chen Meng, Christina Ludwig, Matt Kaeberlein, Shahaf Peleg & Andrew P. Wojtovich

Nature Aging (2022) | Cite this article

1654 Accesses | **383** Altmetric | Metrics

Abstract

Mitochondrial dysfunction plays a central role in aging but the exact biological causes are still being determined. Here, we show that optogenetically increasing mitochondrial membrane potential during adulthood using a light-activated proton pump improves age-associated phenotypes and extends lifespan in *Caenorhabditis elegans*. Our findings provide direct causal evidence that rescuing the age-related decline in mitochondrial membrane potential is sufficient to slow the rate of aging and extend healthspan and lifespan.

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Long-Term Culture and Monitoring of Isolated Caenorhabditis elegans on Solid Media in Multi-Well Devices

The nematode Caenorhabditis elegans is among the most common model systems used in aging research owing to its simple and inexpensive culture techniques, rapid reproduction cycle (~3 days), short lifespan (~3 weeks), and numerous available tools for genetic manipulation and molecular analysis. The most common approach for conducting aging studies in C. elegans, including survival analysis, involves culturing populations of tens to hundreds of animals together on solid nematode growth media (NGM) in Petri plates. While this approach gathers data on a population of animals, most protocols do not track individual animals over time. Presented here is an optimized protocol for the long-term culturing of individual animals on microfabricated polydimethylsiloxane (PDMS) devices called WorMotels. Each device allows up to 240 animals to be cultured in small wells containing NGM, with each well isolated by a copper sulfate-containing moat that prevents the animals from fleeing. Building on the original WorMotel description, this paper provides a detailed protocol for molding, preparing, and populating each device, with descriptions of common technical complications and advice for troubleshooting. Within this protocol are techniques for the consistent loading of small-volume NGM, the consistent drying of both the NGM and bacterial food, options for delivering pharmacological interventions, instructions for and practical limitations to reusing PDMS devices, and tips for minimizing desiccation, even in low-humidity environments. This technique allows the longitudinal monitoring of various physiological parameters, including stimulated activity, unstimulated activity, body size, movement geometry, healthspan, and survival, in an environment similar to the standard technique for group culture on solid media in Petri plates. This method is compatible with high-throughput data collection when used in conjunction with automated microscopy and analysis software. Finally, the limitations of this technique are discussed, as well as a comparison of this approach to a recently developed method that uses microtrays to culture isolated nematodes on solid media.

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PREPRINT

Two Muscle-Specific and Direct Transcriptional Targets of DAF-16/FOXO Activated by Reduced Insulin/IGF-1 Signaling

Shifei Wu, Yan Li, Charline Roy, Ying Wang, Ben Mulcahy, William Li, John Calarco, Wesley Hung, Mei Zhen

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This article is a preprint and has not been certified by peer review [what does this mean?].

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Abstract Full Text Info/History Metrics Preview PDF

Abstract

C. elegans insulin/insulin-like growth factor 1 signaling (IIS) affects diverse physiological processes through the DAF-16/FOXO transcription factor. Despite its presence in all somatic cells, DAF-16's physiological effects, such as modulation of dauer formation, synapse maturation, axon regeneration, and adult longevity, exhibit prevalent tissue-specificity as well as tissue crosstalk. This implies that tissue-specific DAF-16 transcriptional programs contribute to the functional diversity of IIS. To further examine this possibility, we sought to identify tissue-specific and direct transcriptional targets of DAF-16 in muscle cells. Following FACS-sorting to enrich mature muscle cells from young adult animals, we compared the muscle transcriptomes under high and low IIS states, with and without DAF-16. We further analyzed and compared the DAF-16 docking sites in muscle and intestine cells from published datasets. These analyses revealed 14 potential muscle-specific DAF-16 transcriptional targets, among which we validated two that are strongly and specifically activated by DAF-16 in muscles: a secreted protein C54F6.5 and a calcium-binding protein CEX-1/Calexcitin. Both genes exhibit DAF-16-independent non-muscle expression, explaining their low rank or absence from the current DAF-16 target lists generated by multiple independent whole-animal microarray or mRNA-sequencing analyses. These results support the notion of tissue-specific DAF-16 transcriptional programs and highlight the importance of verifying FOXO targets in a cell-type-specific manner.

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JOURNAL ARTICLE

Mitochondrial dysfunction, aging, and the mitochondrial unfolded protein response in *Caenorhabditis elegans*

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Cole M Haynes, Siegfried Hekimi

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https://doi.org/10.1093/genetics/iyac160
Published: 07 November 2022 **Article history**

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Abstract

We review the findings that establish that perturbations of various aspects of mitochondrial function, including oxidative phosphorylation, can promote lifespan extension, with different types of perturbations acting sometimes independently and additively on extending lifespan. We also review the great variety of processes and mechanisms that together form the mitochondrial unfolded protein response. We then explore the relationships between different types of mitochondrial dysfunction-dependent lifespan extension and the mitochondrial unfolded protein response. We conclude that, although several ways that induce extended lifespan through mitochondrial dysfunction require a functional mitochondrial unfolded protein response, there is no clear indication that activation of the mitochondrial unfolded protein response is sufficient to extend lifespan, despite the fact that the mitochondrial unfolded protein response impacts almost every aspect of mitochondrial function. In fact, in some contexts, mitochondrial unfolded protein response activation is deleterious. To explain this pattern, we hypothesize that, although triggered by mitochondrial dysfunction, the lifespan extension observed might not be the result of a change in mitochondrial function.

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Stimulation of RAS-dependent ROS signaling extends longevity by modulating a developmental program of global gene expression

ROBYN BRANICKY, YING WANG, ARMAN KHAKI, JU-LING LIU, MAXIMILIAN KRAMER-DRAUBERG, AND SIEGFRIED HEKIMI Authors Info & Affiliation

We show that elevation of mitochondrial superoxide generation increases *Caenorhabditis elegans* life span by enhancing a RAS-dependent ROS (reactive oxygen species) signaling pathway (RDRS) that controls the expression of half of the genome as well as animal composition and physiology. RDRS stimulation mimics a program of change in gene expression that is normally observed at the end of postembryonic development. We further show that RDRS is regulated by negative feedback from the superoxide dismutase 1 (SOD-1)-dependent conversion of superoxide into cytoplasmic hydrogen peroxide, which, in turn, acts on a redox-sensitive cysteine (C118) of RAS. Preventing C118 oxidation by replacement with serine, or mimicking oxidation by replacement with aspartic acid, leads to opposite changes in the expression of the same large set of genes that is affected when RDRS is stimulated by mitochondrial superoxide. The identities of these genes suggest that stimulation of the pathway extends life span by boosting turnover and repair while moderating damage from metabolic activity.

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Genetic basis of enhanced stress resistance in long-lived mutants highlights key role of innate immunity in determining longevity

Sonja K. Soo, Annika Traa, Zenith D. Rudich, Alibek Moldakozhayev, Meeta Mistry, Jeremy M. Van Raamsdonk

Mutations that extend lifespan are associated with enhanced resistance to stress. To better understand the molecular mechanisms underlying this relationship, we directly compared lifespan extension, resistance to external stressors, and gene expression in a panel of nine long-lived *Caenorhabditis elegans* mutants from different pathways of lifespan extension. All of the examined long-lived mutants exhibited increased resistance to one or more types of stress. Resistance to each of the examined types of stress had a significant, positive correlation with lifespan, with bacterial pathogen resistance showing the strongest relationship. Analysis of transcriptional changes indicated that all of the examined long-lived mutants showed a significant upregulation of multiple stress response pathways. Interestingly, there was a very significant overlap between genes highly correlated with stress resistance and genes highly correlated with longevity, suggesting that the same genetic pathways drive both phenotypes. This was especially true for genes correlated with bacterial pathogen resistance, which showed an 84% overlap with genes correlated with lifespan. To further explore the relationship between innate immunity and longevity, we disrupted the p38-mediated innate immune signaling pathway in each of the long-lived mutants and found that this pathway is required for lifespan extension in eight of nine mutants. Overall, our results demonstrate a strong correlation between stress resistance and longevity that results from the high degree of overlap in genes contributing to each phenotype. Moreover, these findings demonstrate the importance of the innate immune system in lifespan determination and indicate that the same underlying genes drive both immunity and longevity.

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REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Hallmarks of aging: An expanding universe

Carlos López-Otín • Maria A. Blasco • Linda Partridge • Manuel Serrano • Guido Kroemer

Aging is driven by hallmarks fulfilling the following three premises: (1) their age-associated manifestation, (2) the acceleration of aging by experimentally accentuating them, and (3) the opportunity to decelerate, stop, or reverse aging by therapeutic interventions on them. We propose the following twelve hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. These hallmarks are interconnected among each other, as well as to the recently proposed hallmarks of health, which include organizational features of spatial compartmentalization, maintenance of homeostasis, and adequate responses to stress.

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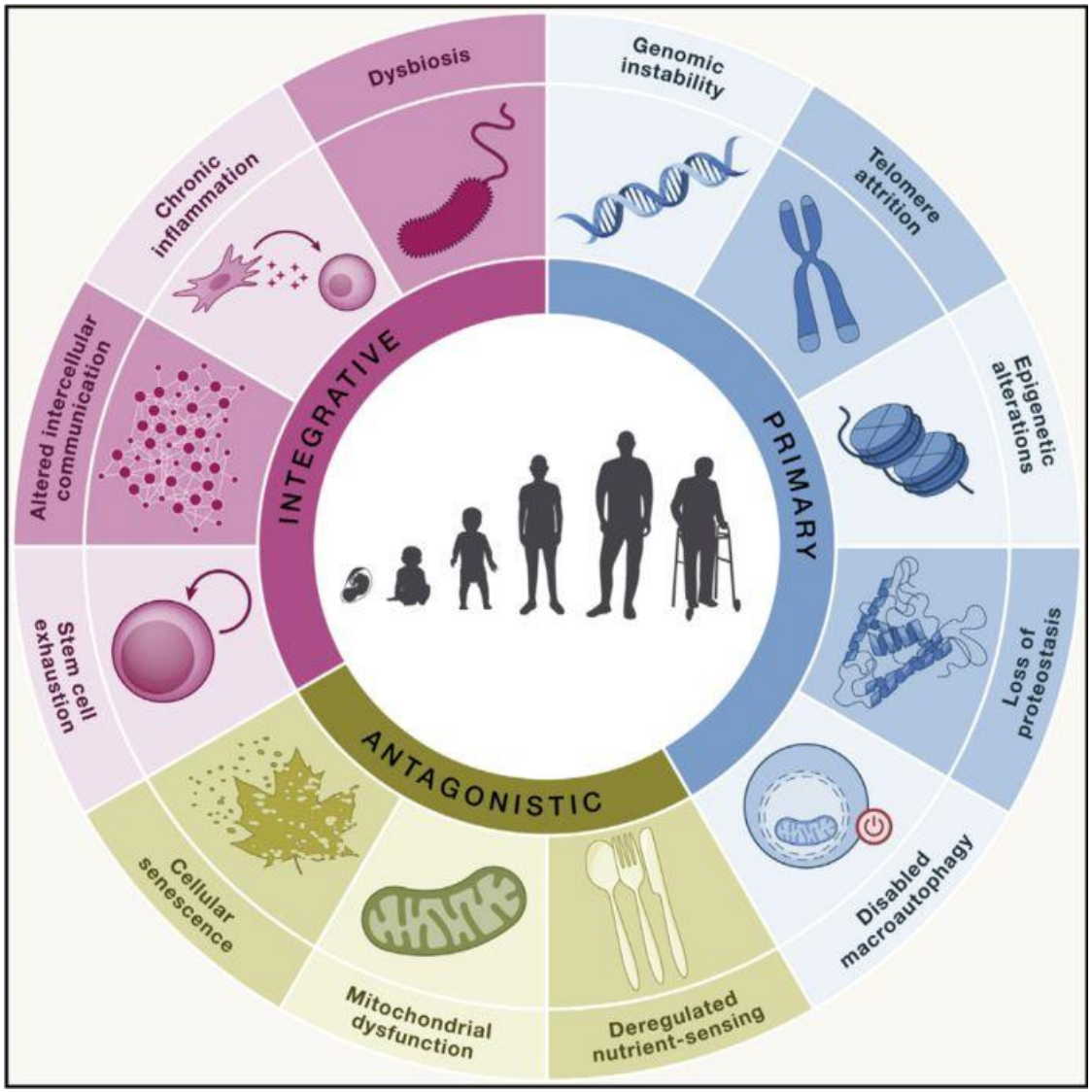
Hallmarks of aging: An expanding universe

Carlos López-Otín • Maria A. Blasco • Linda Partridge • Manuel Serrano • Guido Kroemer



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Meta-hallmarks of aging and cancer

Carlos López-Otín • Federico Pietrocola • David Roiz-Valle • Lorenzo Galluzzi • Guido Kroemer

Both aging and cancer are characterized by a series of partially overlapping “hallmarks” that we subject here to a meta-analysis. Several hallmarks of aging (i.e., genomic instability, epigenetic alterations, chronic inflammation, and dysbiosis) are very similar to specific cancer hallmarks and hence constitute common “meta-hallmarks,” while other features of aging (i.e., telomere attrition and stem cell exhaustion) act likely to suppress oncogenesis and hence can be viewed as preponderantly “antagonistic hallmarks.” Disabled macroautophagy and cellular senescence are two hallmarks of aging that exert context-dependent oncosuppressive and pro-tumorigenic effects. Similarly, the equivalence or antagonism between aging-associated deregulated nutrient-sensing and cancer-relevant alterations of cellular metabolism is complex. The agonistic and antagonistic relationship between the processes that drive aging and cancer has bearings for the age-related increase and oldest age-related decrease of cancer morbidity and mortality, as well as for the therapeutic management of malignant disease in the elderly.

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Aging and aging-related diseases: from molecular mechanisms to interventions and treatments

Jun Guo, Xiuqing Huang, Lin Dou, Mingjing Yan, Tao Shen, Weiqing Tang & Jian Li

Signal Transduction and Targeted Therapy **7**, Article number: 391 (2022) | Cite this article

6004 Accesses | **123** Altmetric | Metrics

Abstract

Aging is a gradual and irreversible pathophysiological process. It presents with declines in tissue and cell functions and significant increases in the risks of various aging-related diseases, including neurodegenerative diseases, cardiovascular diseases, metabolic diseases, musculoskeletal diseases, and immune system diseases. Although the development of modern medicine has promoted human health and greatly extended life expectancy, with the aging of society, a variety of chronic diseases have gradually become the most important causes of disability and death in elderly individuals. Current research on aging focuses on elucidating how various endogenous and exogenous stresses (such as genomic instability, telomere dysfunction, epigenetic alterations, loss of proteostasis, compromise of autophagy, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, deregulated nutrient sensing) participate in the regulation of aging. Furthermore, thorough research on the pathogenesis of aging to identify interventions that promote health and longevity (such as caloric restriction, microbiota transplantation, and nutritional intervention) and clinical treatment methods for aging-related diseases (depletion of senescent cells, stem cell therapy, antioxidative and anti-inflammatory treatments, and hormone replacement therapy) could decrease the incidence and development of aging-related diseases and in turn promote healthy aging and longevity.

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Three Tiers to biological escape velocity: The quest to outwit aging

Raymond D. Palmer

As longevity companies emerge with new products and the fields of anti-aging research develop new cutting-edge therapies, three distinct classes of longevity methodologies emerge. This discussion finds that there are three clear classes (Tiers) of longevity systems that are currently under development, and all three will be paramount to achieve biological escape velocity (where tissues can be repaired faster than aging can damage them). These classes are referred to as Tier 1, Tier 2, and Tier 3 treatments and are described in detail below. These three Tiers are required for easy identification for pharmaceutical companies and research companies to determine the type of therapy they may choose to deliver being noninvasive, invasive, time consuming, or simple end user products. Specific targets and goals need to be defined clearly from an early perspective in the development of these technologies for future precision medicines. This allows consumers of future anti-aging technologies to consider which Tier a particular therapy may be, delivering a more informed choice.

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Epigenetic clocks, aging, and cancer

Global methylation changes in aging cells affect cancer risk and tissue homeostasis

SARAH E. JOHNSTONE, VADIM N. GLADYSHEV, MARTIN J. ARYEE, AND BRADLEY E. BERNSTEIN Authors Info & Affiliations

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20.972

Cancer and aging are accompanied by stereotyped changes to the epigenetic landscape, including progressive loss of DNA methylation over gene-poor genomic regions (*1*, *2*). Global hypomethylation arises in cells that have undergone many divisions, likely owing to imperfect maintenance. Evidence suggests that global hypomethylation represents a "mitotic clock" that counts divisions in somatic cells and functions to restrain aging cells and limit malignant progression. Therapies that modulate the pace of methylation loss or eliminate hypomethylated cells could alleviate agingassociated diseases or cancers.

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Randomization, design and analysis for interdependency in aging research: no person or mouse is an island

Investigators traditionally use randomized designs and corresponding analysis procedures to make causal inferences about the effects of interventions, assuming independence between an individual's outcome and treatment assignment and the outcomes of other individuals in the study. Often, such independence may not hold. We provide examples of interdependency in model organism studies and human trials and group effects in aging research and then discuss methodologic issues and solutions. We group methodologic issues as they pertain to (1) single-stage individually randomized trials; (2) cluster-randomized controlled trials; (3) pseudo-cluster-randomized trials; (4) individually randomized group treatment; and (5) two-stage randomized designs. Although we present possible strategies for design and analysis to improve the rigor, accuracy and reproducibility of the science, we also acknowledge real-world constraints. Consequences of nonadherence, differential attrition or missing data, unintended exposure to multiple treatments and other practical realities can be reduced with careful planning, proper study designs and best practices.

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Role of autophagy in aging: The good, the bad, and the ugly

Siamak Tabibzadeh

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Abstract

Autophagy (self-eating) is a conserved catabolic homeostatic process required for cellular metabolic demands by removal of the damaged molecules and organelles and for alleviation of stress initiated by pathology and infection. By such actions, autophagy is essential for the prevention of aging, disease, and cancer. Genetic defects of autophagy genes lead to a host of developmental, metabolic, and pathological aberrations. Similarly, the age-induced decline in autophagy leads to the loss of cellular homeostatic control. Paradoxically, such a valuable mechanism is hijacked by diseases, during tumor progression and by senescence, presumably due to high levels of metabolic demand. Here, we review both the role of autophagy in preventing cellular decline in aging by fulfillment of cellular bioenergetic demands and its contribution to the maintenance of the senescent state and SASP by acting on energy and nutritional sensors and diverse signaling pathways.

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Extracellular Matrix Dynamics as an Emerging yet Understudied Hallmark of Aging and Longevity

Cyril Statzer, Ji Young Cecilia Park, Collin Y. Ewald*

The biomechanical properties of extracellular matrices (ECM) and their consequences for cellular homeostasis have recently emerged as a driver of aging. Here we review the age-dependent deterioration of ECM in the context of our current understanding of the aging processes. We discuss the reciprocal interactions of longevity interventions with ECM remodeling. And the relevance of ECM dynamics captured by the matrisome and the matreotypes associated with health, disease, and longevity. Furthermore, we highlight that many established longevity compounds promote ECM homeostasis. A large body of evidence for the ECM to qualify as a hallmark of aging is emerging, and the data in invertebrates is promising. However, direct experimental proof that activating ECM homeostasis is sufficient to slow aging in mammals is lacking. We conclude that further research is required and anticipate that a conceptual framework for ECM biomechanics and homeostasis will provide new strategies to promote health during aging.

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Antibodies in action: the role of humoral immunity in the fight against atherosclerosis

Joshua A Taylor [1] [2], Mark A Hutchinson [1], Patricia J Gearhart [1], Robert W Maul [3]

Affiliations + expand

PMID: 36461105 PMCID: PMC9717479 DOI: 10.1186/s12979-022-00316-6

Free PMC article

Abstract

The sequestering of oxidation-modified low-density lipoprotein by macrophages results in the accumulation of fatty deposits within the walls of arteries. Necrosis of these cells causes a release of intercellular epitopes and the activation of the adaptive immune system, which we predict leads to robust autoantibody production. T cells produce cytokines that act in the plaque environment and further stimulate B cell antibody production. B cells in atherosclerosis meanwhile have a mixed role based on subclass. The current model is that B-1 cells produce protective IgM antibodies in response to oxidation-specific epitopes that work to control plaque formation, while follicular B-2 cells produce class-switched antibodies (IgG, IgA, and IgE) which exacerbate the disease. Over the course of this review, we discuss further the validation of these protective antibodies while evaluating the current dogma regarding class-switched antibodies in atherosclerosis. There are several contradictory findings regarding the involvement of class-switched antibodies in the disease. We hypothesize that this is due to antigen-specificity, and not simply isotype, being important, and that a closer evaluation of these antibodies' targets should be conducted. We propose that specific antibodies may have therapeutical potential in preventing and controlling plaque development within a clinical setting.

Keywords: AID; Antibodies; Atherosclerosis; B cells.

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OTHER RESEARCH & REVIEWS

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Inheritance of paternal DNA damage by histone-mediated repair restriction

Siyao Wang [1 2], David H Meyer [3 4], Björn Schumacher [5 6]

Affiliations + expand

PMID: 36544019 DOI: 10.1038/s41586-022-05544-w

Abstract

How paternal exposure to ionizing radiation affects genetic inheritance and disease risk in the offspring has been a long-standing question in radiation biology. In humans, nearly 80% of transmitted mutations arise in the paternal germline[1], but the transgenerational effects of ionizing radiation exposure has remained controversial and the mechanisms are unknown. Here we show that in sex-separated Caenorhabditis elegans strains, paternal, but not maternal, exposure to ionizing radiation leads to transgenerational embryonic lethality. The offspring of irradiated males displayed various genome instability phenotypes, including DNA fragmentation, chromosomal rearrangement and aneuploidy. Paternal DNA double strand breaks were repaired by maternally provided error-prone polymerase theta-mediated end joining. Mechanistically, we show that depletion of an orthologue of human histone H1.0, HIS-24, or the heterochromatin protein HPL-1, could significantly reverse the transgenerational embryonic lethality. Removal of HIS-24 or HPL-1 reduced histone 3 lysine 9 dimethylation and enabled error-free homologous recombination repair in the germline of the F_1 generation from ionizing radiation-treated P_0 males, consequently improving the viability of the F_2 generation. This work establishes the mechanistic underpinnings of the heritable consequences of paternal radiation exposure on the health of offspring, which may lead to congenital disorders and cancer in humans.

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Papers and patents are becoming less disruptive over time

Michael Park, Erin Leahey & Russell J. Funk

Nature **613**, 138–144 (2023) | Cite this article

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Abstract

Theories of scientific and technological change view discovery and invention as endogenous processes[1,2], wherein previous accumulated knowledge enables future progress by allowing researchers to, in Newton's words, 'stand on the shoulders of giants'[3,4,5,6,7]. Recent decades have witnessed exponential growth in the volume of new scientific and technological knowledge, thereby creating conditions that should be ripe for major advances[8,9]. Yet contrary to this view, studies suggest that progress is slowing in several major fields[10,11]. Here, we analyse these claims at scale across six decades, using data on 45 million papers and 3.9 million patents from six large-scale datasets, together with a new quantitative metric—the CD index[12]—that characterizes how papers and patents change networks of citations in science and technology. We find that papers and patents are increasingly less likely to break with the past in ways that push science and technology in new directions. This pattern holds universally across fields and is robust across multiple different citation- and text-based metrics[1,13,14,15,16,17]. Subsequently, we link this decline in disruptiveness to a narrowing in the use of previous knowledge, allowing us to reconcile the patterns we observe with the 'shoulders of giants' view. We find that the observed declines are unlikely to be driven by changes in the quality of published science, citation practices or field-specific factors. Overall, our results suggest that slowing rates of disruption may reflect a fundamental shift in the nature of science and technology.

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