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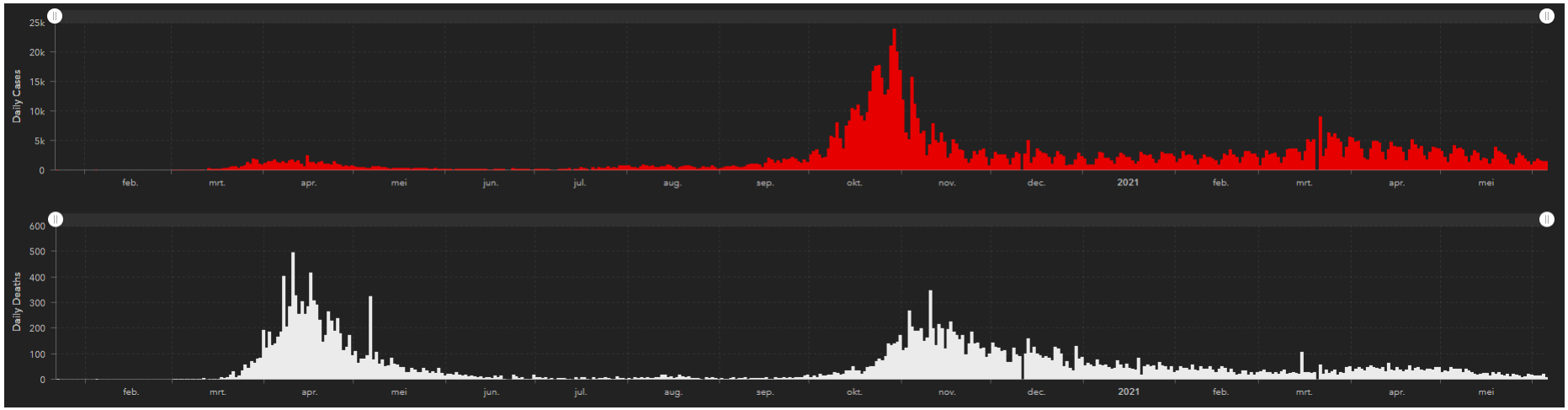
Scientific News
6th of June 2021
Sven Bulterijs

Business/Conferences/ General news

Belgium



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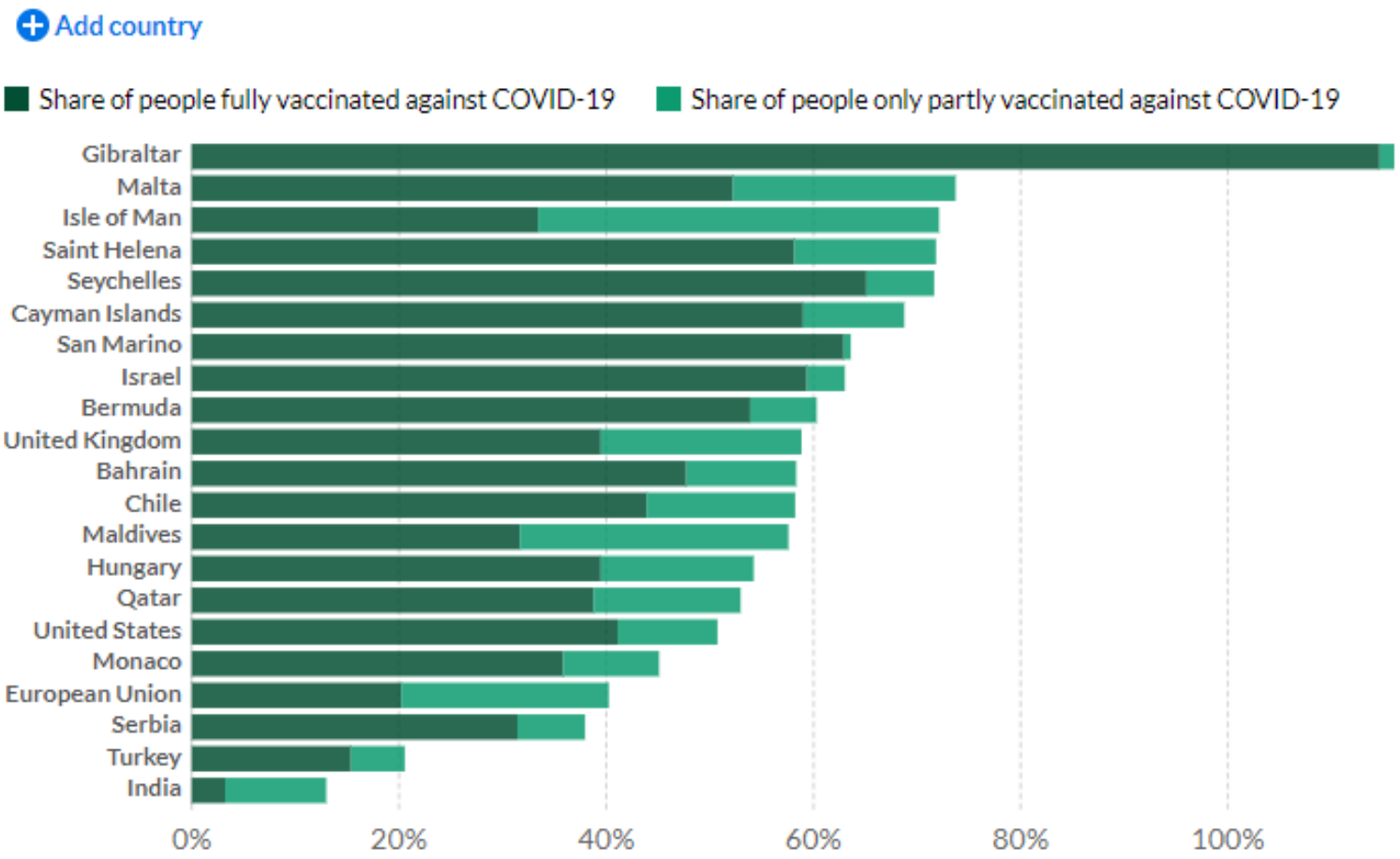
Share of people vaccinated against COVID-19, Jun 4, 2021

This data is only available for countries which report the breakdown of doses administered by first and second doses.

Our World in Data



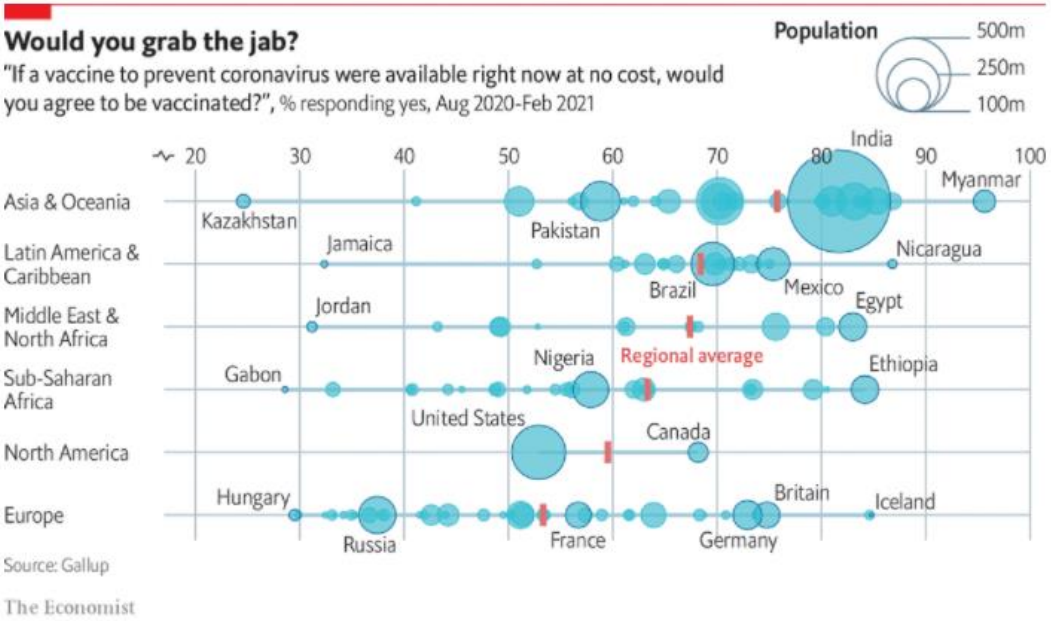
Gallup poll

Over 1 Billion Worldwide Unwilling to Take COVID-19 Vaccine

BY **JULIE RAY**

Global herd immunity is still out of reach

Vaccine hesitancy threatens the pandemic response



MORE THAN 5m Americans who have received a first dose of the covid-19 vaccine are skipping appointments for their second, according to the Centres for Disease Control and Prevention. Some mistakenly think they are sufficiently protected with a single shot; others fear side effects. Such hesitation is common around the world, according to a new poll by Gallup. In a survey of 300,000 people across 117 countries, the pollster found that only 68% of adults would agree to be vaccinated if a free jab were available to them; 29% said they would refuse.

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Ruim drie op tien Vlaamse jongeren willen zich niet laten vaccineren

Hoewel de vaccinatiebereidheid groot is in Vlaanderen, wacht straks nog de lastige opdracht om voldoende jongeren te bereiken. 'Zich niet laten vaccineren is een uiting van wantrouwen in politiek beleid.'

Jan-Frederik Abbeloos
Donderdag 20 mei 2021 om 3.25 uur

© Fred Debrock

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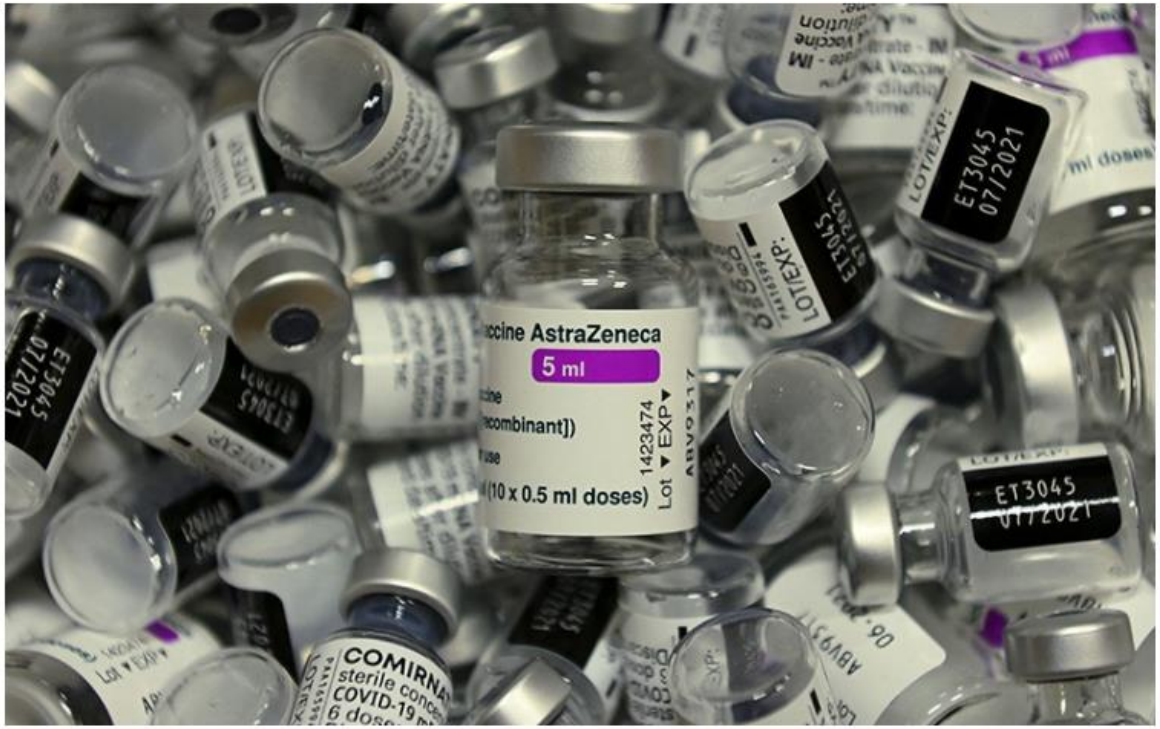
Mix-and-match COVID vaccines trigger potent immune response

Preliminary results from a trial of more than 600 people are the first to show the benefits of combining different vaccines.

Ewen Callaway



Countries with fluctuating supplies of COVID-19 vaccines could benefit from using different vaccines for the first and second dose. Credit: Christof Stache/AFP/Getty

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MEGAN MOLTENI BACKCHANNEL 05.13.2021 06:00 AM

The 60-Year-Old Scientific Screwup That Helped Covid Kill

All pandemic long, scientists brawled over how the virus spreads. *Droplets! No, aerosols!* At the heart of the fight was a teensy error with huge consequences.

EARLY ONE MORNING, Linsey Marr tiptoed to her dining room table, slipped on a headset, and fired up Zoom. On her computer screen, dozens of familiar faces began to appear. She also saw a few people she didn't know, including Maria Van Kerkhove, the World Health Organization's technical lead for Covid-19, and other expert advisers to the WHO. It was just past 1 pm Geneva time on April 3, 2020, but in Blacksburg, Virginia, where Marr lives with her husband and two children, dawn was just beginning to break.

Marr is an aerosol scientist at Virginia Tech and one of the few in the world who also studies infectious diseases. To her, the new coronavirus looked as if it could hang in the air, infecting anyone who breathed in enough of it. For people indoors, that posed a considerable risk. But the WHO didn't seem to have caught on. Just days before, the organization had tweeted "FACT: #COVID19 is NOT airborne." That's why Marr was skipping her usual morning workout to join 35 other aerosol scientists. They were trying to warn the WHO it was making a big mistake.

Over Zoom, they laid out the case. They ticked through a growing list of superspreading events in restaurants, call centers, cruise ships, and a choir rehearsal, instances where people got sick even when they were across the room from a contagious person. The incidents contradicted the WHO's main safety guidelines of keeping 3 to 6 feet of distance

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"In a Phase 3 clinical trial, sotrovimab reduced the risk of hospitalization or death in high-risk adults by 85% compared with a placebo."

Vir and GSK monoclonal antibody authorized for emergency use in COVID-19

Sotrovimab may protect against virus variants, although sales potential is uncertain

by **Ryan Cross**

June 3, 2021 | A version of this story appeared in Volume 99, Issue 21

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PREPRINT

The complete sequence of a human genome

In 2001, Celera Genomics and the International Human Genome Sequencing Consortium published their initial drafts of the human genome, which revolutionized the field of genomics. While these drafts and the updates that followed effectively covered the euchromatic fraction of the genome, the heterochromatin and many other complex regions were left unfinished or erroneous. Addressing this remaining 8% of the genome, the Telomere-to-Telomere (T2T) Consortium has finished the first truly complete 3.055 billion base pair (bp) sequence of a human genome, representing the largest improvement to the human reference genome since its initial release. The new T2T-CHM13 reference includes gapless assemblies for all 22 autosomes plus Chromosome X, corrects numerous errors, and introduces nearly 200 million bp of novel sequence containing 2,226 paralogous gene copies, 115 of which are predicted to be protein coding. The newly completed regions include all centromeric satellite arrays and the short arms of all five acrocentric chromosomes, unlocking these complex regions of the genome to variational and functional studies for the first time.

Elisabeth Bik is an independent consultant who specializes in detecting manipulated scientific images.
SGERBIC/CC 4.0

Scientists rally around misconduct consultant facing legal threat after challenging COVID-19 drug researcher

By Cathleen O'Grady | May. 27, 2021 , 5:05 PM

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May 17th, 2021

Vitalik Buterin Donates More than $2 Million to the Methuselah Foundation

Permalink Read 15 Comments Add a Comment Posted by Reason

The blockchain and cryptocurrency space is known to produce events that require more than a little explanation for an outsider to even begin to understand what exactly has taken place. I will not attempt to do that here. In the midst of one of those events, involving dog themed joke currencies that are nonetheless somehow magically worth real money, albeit to some highly variable degree depending on who has control of them, and what everyone else thinks that controller will do with them, well known entrepreneur Vitalik Buterin, founder of Ethereum, donated 1,000 Ether to the Methuselah Foundation. That amounts to more that $2 million at the present time, a sizable fraction of the yearly budget of that organization.

Buterin has made substantial philanthropic donations to advance the state of longevity in the past, such as to the SENS Research Foundation, and has spoken on the desirability of producing therapies to treat aging as a medical condition. The Methuselah Foundation is the parent organization of the SENS Research Foundation, and organized some of the first research programs to work on mechanisms of aging that were insufficiently supported by the broader research community. Since then, the Methuselah Foundation has undertaken a range of projects, many of which aim to advance the state of the art in tissue engineering, and launched the Methuselah Fund to invest in early stage startups in the longevity industry.

Vitalik Buterin donates more than $60M to charity after selling meme tokens including Shiba Inu

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BioWorld™

The news source of record covering the development of innovative human therapies for 25+ years

Clarivate Cortellis™

May 7, 2021
Volume 32, No. 88
Special Reprint

Kizoo to invest $362M in 'rejuvenation biotech'

By Cormac Sheridan

DUBLIN – Michael Greve, one of Germany's most successful internet entrepreneurs and investors, is personally committing €300 million (US$362 million) to building a portfolio of biotechnology firms focused on different aspects of aging.

His investment vehicle, Kizoo Technology Capital GmbH, of Karlsruhe, has already provided seed funding to more than a dozen early stage firms. Greve is now ready to invest in follow-on rounds, particularly in four core companies he described as "category openers" in rejuvenation biotech. "We are really super focused, because there are so many things we could do," he told *BioWorld*.

Michael Greve, owner, Kizoo Technology Capital, and founder, The Forever Healthy Foundation

Combating the aging process is not just an organizing principle for the fund. Greve is a believer in the idea that healthy lifespans can be dramatically extended, both by synthesizing and applying current knowledge more systematically and by uncovering new biological insights into the root causes of aging, which will lead to

Those and the fund's other biotech investments are all early stage ventures – Kizoo has so far invested about $15 million in its biotechnology portfolio. As its gears up to commit larger amounts of capital to its most promising investees, it will seek out partners to co-invest, Greve said. Other portfolio firms are also seeking additional investment.

In the context of mainstream biotech – and mainstream biotech investing – Kizoo's interests are distinctly leftfield. "It totally sounds like science fiction," Greve agreed. "In the end, we have to deliver proof." Portfolio firms, moreover, will not get a free ride. "They have to deliver like any other company," he said. "That's why we're so open to syndication, because that gives us a reality check."

Greve is by no means the first German entrepreneur to train his attention on and allocate his resources to biotech. Dietmar Hopp, a co-founder of the enterprise software firm SAP SE, has been a substantial investor in German biotech. Hopp's investment in mRNA vaccine developer Curevac AG has been spectacularly successful. The Walldorf-based investment vehicle Dievini Hopp Biotech holding GmbH & Co. KG holds just over 42% of its equity, a stake currently worth $7.9 billion. The Strüngmann

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Amyl raises $22M to target common element of protein aggregates

by Nick Paul Taylor | Jun 3, 2021 7:50am

Amyl plans to develop drugs that clear aggregates, prevent accumulation and block cell-to-cell spread of misfolded proteins. (Marquardt_Photography)

Amyl Therapeutics has raised €18.3 million ($22.3 million) to advance therapies against diseases driven by the buildup of amyloid. The cash equips Amyl to take drugs that target misfolded proteins linked to progressive peripheral and neurodegenerative rare diseases to preclinical proof of concept.

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4 JUN AT 09:00 UTC+02 – 7 JUN AT 08:59 UTC+02

Victor Run 2021 Virtual Race - Run to Support Longevity Research

Free · Online event

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TUE, Jun 15, 7 PM (GMT+2)

Longevity Panel - The scientists working on reversing aging

From WELLNESS CLUB

w/ Laura Minquini, Robert Ziman, Avi Roy, Bill Andrews, Nathan Cheng, Liz Parrish, Alexandra Stolzing, Jean Hebert, João Pedro Magalhães, David Gobel, Aubrey de Grey, Jeremiah Owyang — A panel discussion with the scientist making longevity a reality. How are they approaching the science? Are we any closer to achieving it? In the next decade what technologies will enable longevity?

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ARDD 2021

THE 8th AGING RESEARCH & DRUG DISCOVERY MEETING

31 AUGUST — 3 SEPTEMBER

30 AUGUST — LONGEVITY MEDICINE WORKSHOP

According to the United Nations, the proportion of people aged over 65 now outnumber children younger than 5. The enormous growth in the elderly population is posing a socioeconomic challenge to societies worldwide, and necessitates new sweeping interventions for age-associated diseases. This year we have an incredibly exciting program with global thought-leaders sharing their latest insights into aging and how we target aging process ensuring everyone lives a healthier and longer life. Welcome to the 8th Aging Research and Drug Discovery Meeting.

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CONFERENCE. BIG DATA, A.I. AND HEALTHY LONGEVITY. HOW TO PROGRESS FASTER AND BETTER FOR ALL SCIENTISTS? THURSDAY SEPTEMBER 9, 2021

MAI 28, 2021 DIDIERCOEURNELLE

Joint Heales and International Longevity Alliance (online) conference on Thursday, September 9 from 5-10pm CET (Brussels), 8 am-1pm PDT (San Francisco), titled:

Big Data, A.I. and Healthy Longevity.

Aging research articles

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PREPRINT

Partial reprogramming restores youthful gene expression through transient suppression of cell identity

Antoine Roux, Chunlian Zhang, Jonathan Paw, José Zavala-Solorio, Twaritha Vijay, Ganesh Kolumam, Cynthia Kenyon, Jacob C. Kimmel

Transient induction of pluripotent reprogramming factors has been reported to reverse some features of aging in mammalian cells and tissues. However, the impact of transient reprogramming on somatic cell identity programs and the necessity of individual pluripotency factors remain unknown. Here, we mapped trajectories of transient reprogramming in young and aged cells from multiple murine cell types using single cell transcriptomics to address these questions. We found that transient reprogramming restored youthful gene expression in adipogenic cells and mesenchymal stem cells but also temporarily suppressed somatic cell identity programs. We further screened Yamanaka Factor subsets and found that many combinations had an impact on aging gene expression and suppressed somatic identity, but that these effects were not tightly entangled. We also found that a transient reprogramming approach inspired by amphibian regeneration restored youthful gene expression in aged myogenic cells. Our results suggest that transient pluripotent reprogramming poses a neoplastic risk, but that restoration of youthful gene expression can be achieved with alternative strategies.

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PREPRINT

A single short reprogramming early in life improves fitness and increases lifespan in old age

Quentin Alle, Enora Le Borgne, Paul Bensadoun, Camille Lemey, Nelly Béchir, Mélissa Gabanou, Fanny Estermann, Christelle Bertrand-Gaday, Laurence Pessemesse, Karine Toupet, Jérôme Vialaret, Christophe Hirtz, Danièle Noël, Christian Jorgensen, François Casas, Ollivier Milhavet, Jean-Marc Lemaitre

Forced and maintained expression of four transcription factors OCT4, SOX2, KLF4 and c-MYC (OSKM), can reprogram somatic cells into induced Pluripotent Stem Cells (iPSCs) and a limited OSKM induction is able to rejuvenate the cell physiology without changing the cell identity. We therefore sought to determine if a burst of OSKM might improve tissue fitness and delay age-related pathologies in a whole animal. For this, we used a sensitive model of heterozygous premature aging mice carrying just one mutated Lamin A allele producing progerin. We briefly treated two months-young heterozygotes mice with OSKM and monitored their natural age-related deterioration by various health parameters. Surprisingly, a single two and a half weeks reprogramming was sufficient to improve body composition and functional capacities, over the entire lifespan. Mice treated early in life had improved tissue structures in bone, lung, spleen, kidney and skin, with an increased lifespan of 15%, associated to a differential DNA methylation signature. Altogether, our results indicate that a single short reprogramming early in life might initiate and propagate an epigenetically related rejuvenated cell physiology, to promote a healthy lifespan.

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PREPRINT

Longevity interventions temporally scale healthspan in *Caenorhabditis elegans*

Cyril Statzer, Peter Reichert, Jürg Dual, Collin Y. Ewald

Longer lived individuals, such as centenarians or longevity mutants of model organisms, have later onsets and lower incidence rates of late-life morbidities or disabilities than the average population. However, whether increased lifespan is caused by a compression of the portion of life spent in a state of morbidity, i.e., "sickspan," is highly debated. It is unclear which health matrices are representative for measuring healthspan (time spent in good health); however, muscular performance is generally a good indicator for the health status in humans and a predictor for their mortality, regardless of the underlying cause. Here, we developed a novel microfluidic device that employs acoustophoretic force fields to quantify the maximum muscle strength and dynamic power in aging *C. elegans* populations. We found that longevity mutants have a delayed onset and lower declining rates in maximum muscle strength compared to wild type. Reconciling previous conflicting reports, we confirmed that certain longevity mutants exhibited a mild increase in relative sickspan measured by voluntary movement matrices, which is not the case when using our acoustophoretic force measurements, swim endurance, or other approaches. Using six different biomarkers for healthspan, we observed a time-dependent onset of morbidity, starting with a loss of stress resilience, a decline in dynamic power, and a decline in structural integrity, culminating finally in inactivity (lethargy) and a loss of mobility. We observed that a subset of aging biomarkers correlate with each other and maybe functionally interconnected. Surprisingly, we did not observe a compression of sickspan in longevity mutants but instead observed a temporal scaling of healthspan with diminishing returns for extreme lifespan extensions. Given the conservation of these longevity interventions, this raises the question of whether the healthspan of mammalian longevity interventions is temporally scaled as well.

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PREPRINT

Modulation of fracture healing by the transient accumulation of senescent cells

Dominik Saul, David G. Monroe, Jennifer L. Rowsey, Robyn L. Kosinsky, Stephanie J. Vos, Madison L. Doolittle, Joshua N. Farr, Sundeep Khosla

Senescent cells have detrimental effects across tissues with aging but may have beneficial effects on tissue repair, specifically on skin wound healing. However, the potential role of senescent cells in fracture healing has not been defined. Here, we performed an *in silico* analysis of public mRNAseq data and found that senescence and senescence-associated secretory phenotype (SASP) markers increased during fracture healing. We next directly established that the expression of senescence biomarkers increased markedly during murine fracture healing. We also identified a subset of cells in the fracture callus that displayed hallmarks of senescence, including distension of satellite heterochromatin and telomeric DNA damage. Then, using a genetic mouse model ($p16^{LUC}$) containing a $p16^{Ink4a}$-dnven luciferase reporter, we demonstrated transient *in vivo* senescent cell accumulation during callus formation. Finally, we intermittently treated young adult mice following fracture with drugs that selectively eliminate senescent cells ("senolytics", Dasatinib plus Quercetin), and showed that this regimen both decreased senescence and SASP markers in the fracture callus and significantly accelerated the time course of fracture healing. Our findings thus demonstrate that senescent cells accumulate transiently in the murine fracture callus and, in contrast to the skin, their clearance does not impair but rather may improve fracture healing.

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Senescence-associated β-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans

Ricardo I. Martínez-Zamudio, Hannah K. Dewald, Themistoklis Vasilopoulos, Lisa Gittens-Williams, Patricia Fitzgerald-Bocarsly, Utz Herbig

Aging leads to a progressive functional decline of the immune system, rendering the elderly increasingly susceptible to disease and infection. The degree to which immune cell senescence contributes to this decline remains unclear, however, since markers that label immune cells with classical features of cellular senescence accurately and comprehensively have not been identified. Using a second-generation fluorogenic substrate for β-galactosidase and multi-parameter flow cytometry, we demonstrate here that peripheral blood mononuclear cells (PBMCs) isolated from healthy humans increasingly display cells with high senescence-associated β-galactosidase (SA-βGal) activity with advancing donor age. The greatest age-associated increases were observed in CD8+ T-cell populations, in which the fraction of cells with high SA-βGal activity reached average levels of 64% in donors in their 60s. CD8+ T cells with high SA-βGal activity, but not those with low SA-βGal activity, were found to exhibit features of telomere dysfunction-induced senescence and p16-mediated senescence, were impaired in their ability to proliferate, developed in various T-cell differentiation states, and had a gene expression signature consistent with the senescence state previously observed in human fibroblasts. Based on these results, we propose that senescent CD8+ T cells with classical features of cellular senescence accumulate to levels that are significantly higher than previously reported and additionally provide a simple yet robust method for the isolation and characterization of senescent CD8+ T cells with predictive potential for biological age.

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Invariant natural killer T cells coordinate removal of senescent cells

Shivani Arora [5] • Peter J. Thompson [5, 6] • Yao Wang • Aritra Bhattacharyya • Hara Apostolopoulou • Rachel Hatano • Ram P. Naikawadi • Ajit Shah • Paul J. Wolters • Suneil Koliwad • Mallar Bhattacharya Anil Bhushan [7] • Show less • Show footnotes

Background

The failure of immune surveillance to remove senescent cells drives age-related diseases. Here, we target an endogenous immune surveillance mechanism that can promote elimination of senescent cells and reverse disease progression.

Methods

We identify a class of lipid-activated T cells,invariant natural killer T cells (iNKTs), that are involved in the removal of pathologic senescent cells. We use two disease models in which senescent cells accumulate to test whether activation of iNKT cells was sufficient to eliminate senescent cells *in vivo*.

Findings

Senescent preadipocytes accumulate in white adipose tissue of chronic high-fat diet (HFD)-fed mice, and activation of iNKT cells with the prototypical glycolipid antigen alpha-galactosylceramide (αGalCer) led to a reduction of these cells with improved glucose control. Similarly, senescent cells accumulate within the lungs of mice injured by inhalational bleomycin, and αGalCer-induced activation of iNKT cells greatly limited this accumulation, decreased the lung fibrosis, and improved survival. Furthermore, co-culture experiments showed that the preferential cytotoxic activity of iNKT cells to senescent cells is conserved in human cells.

Conclusions

These results uncover a senolytic capacity of tissue-resident iNKT cells and pave the way for anti-senescence therapies that target these cells and their mechanism of activation.

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An aged immune system drives senescence and ageing of solid organs

Matthew J. Yousefzadeh, Rafael R. Flores, [...]Laura J. Niedernhofer

Nature **594**, 100–105 (2021) | Cite this article

16k Accesses | **322** Altmetric | Metrics

Abstract

Ageing of the immune system, or immunosenescence, contributes to the morbidity and mortality of the elderly[1,2]. To define the contribution of immune system ageing to organism ageing, here we selectively deleted *Ercc1*, which encodes a crucial DNA repair protein[3,4], in mouse haematopoietic cells to increase the burden of endogenous DNA damage and thereby senescence[5,6,7] in the immune system only. We show that *Vav-iCre*$^{+/-}$;*Ercc1*$^{-/fl}$ mice were healthy into adulthood, then displayed premature onset of immunosenescence characterized by attrition and senescence of specific immune cell populations and impaired immune function, similar to changes that occur during ageing in wild-type mice[8,9,10]. Notably, non-lymphoid organs also showed increased senescence and damage, which suggests that senescent, aged immune cells can promote systemic ageing. The transplantation of splenocytes from *Vav-iCre*$^{+/-}$;*Ercc1*$^{-/fl}$ or aged wild-type mice into young mice induced senescence *in trans*, whereas the transplantation of young immune cells attenuated senescence. The treatment of *Vav-iCre*$^{+/-}$;*Ercc1*$^{-/fl}$ mice with rapamycin reduced markers of senescence in immune cells and improved immune function[11,12]. These data demonstrate that an aged, senescent immune system has a causal role in driving systemic ageing and therefore represents a key therapeutic target to extend healthy ageing.

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PREPRINT

Single-cell profiling of skeletal muscle reveals a novel senolytic target: CRYAB

Chandani Limbad, Ryosuke Doi, Julia McGirr, Serban Ciotlos, Kevin Perez, Radha Daya, Judith Campisi, Simon Melov

DOI: 10.21203/rs.3.rs-456991/v1 Download PDF

Abstract

Skeletal muscle mass and function can decline with aging, resulting in a syndrome known as sarcopenia. This decline is linked to functional alterations in critical cell types within mature muscle, including fibro-adipogenic progenitors (FAPs) and satellite cells (SCs), driven in part by cellular senescence. We utilized single-cell RNA sequencing and isolated FAPs and SCs to identify novel targets responsible for senescent cell killing - senolysis. We identified the small alpha-crystalline heat shock protein CRYAB as a novel senolytic target. Using chemical inhibitor screening of CRYAB, we identified 25-hydroxycholesterol (25HC), an endogenous metabolite of cholesterol biosynthesis, as a potent senolytic capable of killing senescent cells. We validated 25HC as a senolytic in mouse and human cells in culture and in vivo in mouse skeletal muscle. Thus, 25HC represents a potential new class of senolytics, which may be useful in combating diseases or physiologies in which cellular senescence is a key driver.

Late-Life Treatment with the Senolytic ABT-263 Reverses Aortic Stiffening and Improves Endothelial Function with Aging

Sophia Mahoney, David Hutton, Matthew Rossman, Vienna Brunt, Nicholas VanDongen, Abigail Casso, Nathan Greenberg, Brian Ziemba, Simon Melov, Judith Campisi, Douglas Seals, Zachary Clayton

Methods

Old (27 mo) male C57BL6/N mice were treated with vehicle ([V]; 10% EtOH, 30% PEG400 and 60% Phosal 50 PG; n = 7) or ABT (50 mg/kg/day in [V]; n = 6) by oral gavage using a 1 week on – 2 weeks off – 1 week on dosing paradigm. A cohort of young adult mice (6 mo; n = 5) served as a young control (YC) reference group. Aortic pulse wave velocity (PWV), an *in vivo* measure of aortic stiffness, was measured pre- and post-treatment. Aortic elastic modulus was assessed by performing stress-strain testing in excised aortic rings. Endothelial function was assessed via *ex vivo* carotid artery endothelial-dependent dilation (EDD) with increasing concentrations of acetylcholine (ACh). NO bioavailability (ACh in the presence of the NO-synthase inhibitor, L-NAME) and the role of excessive ROS in regulating EDD (ACh with the addition of the ROS scavenger, TEMPOL) were assessed as potential mechanisms.

Results

Aortic stiffness. ABT reversed aortic PWV in old mice (pre: 456 ± 7 vs post: 375 ± 11 cm/sec, $P = 0.0003$), to levels of YC (348 ± 13 cm/sec; $P = 0.14$ vs. ABT), whereas no effect was observed in the [V]-treated group. Reduced aortic PWV with ABT was accompanied by lower aortic EM (V: 2738 ± 152 kPa, ABT: 2228 ± 155 kPa, YC: 2120 ± 362 kPa; $P = 0.03$). ***Endothelial function.*** ABT-treated mice had greater peak EDD relative to [V]-treated animals and comparable to YC (ABT: 94 ± 3% vs. V: 78 ± 5%, $P = 0.01$; YC: 91 ±2). Group differences in peak EDD were abolished in the presence of L-NAME, suggesting that ABT rescued EDD by restoring NO bioavailability. TEMPOL restored peak EDD in [V]-treated old mice to YC levels (92 ±5%, $P = 0.003$ vs. ACh alone), while having no effect in ABT or YC animals, suggesting that ABT selectively ameliorated the tonic ROS-related suppression of EDD with aging.

Conclusion

Cellular senescence is mechanistically implicated in age-related arterial dysfunction, and treatment with the senolytic compound ABT-263 may be a therapeutic strategy for improving arterial function, with the potential for reducing CVD risk with aging.

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Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit

Timothy V. Pyrkov, Konstantin Avchaciov, Andrei E. Tarkhov, Leonid I. Menshikov, Andrei V. Gudkov & Peter O. Fedichev

Nature Communications **12**, Article number: 2765 (2021) | Cite this article

41k Accesses | **998** Altmetric | Metrics

Abstract

We investigated the dynamic properties of the organism state fluctuations along individual aging trajectories in a large longitudinal database of CBC measurements from a consumer diagnostics laboratory. To simplify the analysis, we used a log-linear mortality estimate from the CBC variables as a single quantitative measure of the aging process, henceforth referred to as dynamic organism state indicator (DOSI). We observed, that the age-dependent population DOSI distribution broadening could be explained by a progressive loss of physiological resilience measured by the DOSI auto-correlation time. Extrapolation of this trend suggested that DOSI recovery time and variance would simultaneously diverge at a critical point of 120 − 150 years of age corresponding to a complete loss of resilience. The observation was immediately confirmed by the independent analysis of correlation properties of intraday physical activity levels fluctuations collected by wearable devices. We conclude that the criticality resulting in the end of life is an intrinsic biological property of an organism that is independent of stress factors and signifies a fundamental or absolute limit of human lifespan.

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Multi-species and multi-tissue methylation clocks for age estimation in toothed whales and dolphins

Todd R. Robeck, Zhe Fei, Ake T. Lu, Amin Haghani, Eve Jourdain, Joseph A. Zoller, Caesar Z. Li, Karen J. Steinman, Stacy DiRocco, Todd Schmitt, Steve Osborn, Bill Van Bonn, Etsuko Katsumata, June Mergl, Javier Almunia, Magdalena Rodriguez, Martin Haulena, Christopher Dold & Steve Horvath

Communications Biology **4**, Article number: 642 (2021) | Cite this article

584 Accesses | **30** Altmetric | Metrics

Abstract

The development of a precise blood or skin tissue DNA Epigenetic Aging Clock for Odontocete (OEAC) would solve current age estimation inaccuracies for wild odontocetes. Therefore, we determined genome-wide DNA methylation profiles using a custom array (HorvathMammalMethyl40) across skin and blood samples (n = 446) from known age animals representing nine odontocete species within 4 phylogenetic families to identify age associated CG dinucleotides (CpGs). The top CpGs were used to create a cross-validated OEAC clock which was highly correlated for individuals (r = 0.94) and for unique species (median r = 0.93). Finally, we applied the OEAC for estimating the age and sex of 22 wild Norwegian killer whales. DNA methylation patterns of age associated CpGs are highly conserved across odontocetes. These similarities allowed us to develop an odontocete epigenetic aging clock (OEAC) which can be used for species conservation efforts by provide a mechanism for estimating the age of free ranging odontocetes from either blood or skin samples.

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Modeling transcriptomic age using knowledge-primed artificial neural networks

Nicholas Holzscheck, Cassandra Falckenhayn, Jörn Söhle, Boris Kristof, Ralf Siegner, André Werner, Janka Schössow, Clemens Jürgens, Henry Völzke, Horst Wenck, Marc Winnefeld, Elke Grönniger & Lars Kaderali

npj Aging and Mechanisms of Disease **7**, Article number: 15 (2021) | Cite this article

Abstract

The development of 'age clocks', machine learning models predicting age from biological data, has been a major milestone in the search for reliable markers of biological age and has since become an invaluable tool in aging research. However, beyond their unquestionable utility, current clocks offer little insight into the molecular biological processes driving aging, and their inner workings often remain non-transparent. Here we propose a new type of age clock, one that couples predictivity with interpretability of the underlying biology, achieved through the incorporation of prior knowledge into the model design. The clock, an artificial neural network constructed according to well-described biological pathways, allows the prediction of age from gene expression data of skin tissue with high accuracy, while at the same time capturing and revealing aging states of the pathways driving the prediction. The model recapitulates known associations of aging gene knockdowns in simulation experiments and demonstrates its utility in deciphering the main pathways by which accelerated aging conditions such as Hutchinson–Gilford progeria syndrome, as well as pro-longevity interventions like caloric restriction, exert their effects.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Genetic associations for two biological age measures point to distinct aging phenotypes

Chia-Ling Kuo, Luke C. Pilling, Zuyun Liu, Janice L. Atkins, Morgan E. Levine

Biological age measures outperform chronological age in predicting various aging outcomes, yet little is known regarding genetic predisposition. We performed genome-wide association scans of two age-adjusted biological age measures (PhenoAgeAcceleration and BioAgeAcceleration), estimated from clinical biochemistry markers (Levine et al., 2018; Levine, 2013) in European-descent participants from UK Biobank. The strongest signals were found in the *APOE* gene, tagged by the two major protein-coding SNPs, PhenoAgeAccel—rs429358 (*APOE* e4 determinant) ($p = 1.50 \times 10^{-72}$); BioAgeAccel—rs7412 (*APOE* e2 determinant) ($p = 3.16 \times 10^{-60}$). Interestingly, we observed inverse *APOE* e2 and e4 associations and unique pathway enrichments when comparing the two biological age measures. Genes associated with BioAgeAccel were enriched in lipid related pathways, while genes associated with PhenoAgeAccel showed enrichment for immune system, cell function, and carbohydrate homeostasis pathways, suggesting the two measures capture different aging domains. Our study reaffirms that aging patterns are heterogeneous across individuals, and the manner in which a person ages may be partly attributed to genetic predisposition.

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A Compendium of Age-Related PheWAS and GWAS Traits for Human Genetic Association Studies, Their Networks and Genetic Correlations

Seung-Soo Kim[1], Adam D. Hudgins[1,2], Brenda Gonzalez[2], Sofiya Milman[3], Nir Barzilai[3], Jan Vijg[2], Zhidong Tu[4] and Yousin Suh[1,5*]

The rich data from the genome-wide association studies (GWAS) and phenome-wide association studies (PheWAS) offer an unprecedented opportunity to identify the biological underpinnings of age-related disease (ARD) risk and multimorbidity. Surprisingly, however, a comprehensive list of ARDs remains unavailable due to the lack of a clear definition and selection criteria. We developed a method to identify ARDs and to provide a compendium of ARDs for genetic association studies. Querying 1,358 electronic medical record-derived traits, we first defined ARDs and age-related traits (ARTs) based on their prevalence profiles, requiring a unimodal distribution that shows an increasing prevalence after the age of 40 years, and which reaches a maximum peak at 60 years of age or later. As a result, we identified a list of 463 ARDs and ARTs in the GWAS and PheWAS catalogs. We next translated the ARDs and ARTs to their respective 276 Medical Subject Headings diseases and 45 anatomy terms. The most abundant disease categories are neoplasms (48 terms), cardiovascular diseases (44 terms), and nervous system diseases (27 terms). Employing data from a human symptoms-disease network, we found 6 symptom-shared disease groups, representing cancers, heart diseases, brain diseases, joint diseases, eye diseases, and mixed diseases. Lastly, by overlaying our ARD and ART list with genetic correlation data from the UK Biobank, we found 54 phenotypes in 2 clusters with high genetic correlations. Our compendium of ARD and ART is a highly useful resource, with broad applicability for studies of the genetics of aging, ARD, and multimorbidity.

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Cyclodextrin dimers: a versatile approach to optimizing encapsulation and their application to therapeutic extraction of toxic oxysterols

Amelia M. Anderson [a, b], Tamari Kirtadze [a], Milo Malanga [c], Darren Dinh [a], Carolyn Barnes [b], Angielyn Campo [b], Daniel M. Clemens [a], Rebeca Garcia-Fandiño [a, e, d], Ángel Piñeiro [a, e, d], Matthew S. O'Connor [a, b]

We have developed a novel class of specifically engineered, dimerized cyclodextrin nanostructures for the encapsulation of toxic biomolecules such as 7-ketocholesterol (7KC). 7KC accumulates over time and causes dysfunction in many cell types, linking it to several age-related diseases including atherosclerosis and age-related macular degeneration (AMD). Presently, treatments for these diseases are invasive, expensive, and show limited benefits. Cyclodextrins (CDs) are cyclic glucose oligomers utilized to capture small, hydrophobic molecules. Here, a combination of *in silico*, *in vitro*, and *ex vivo* methods is used to implement a synergistic rational drug design strategy for developing CDs to remove atherogenic 7KC from cells and tissues. Mechanisms by which CDs encapsulate sterols are discussed, and we conclude that covalently linked head-to-head dimers of βCDs have substantially improved affinity for 7KC compared to monomers. We find that inclusion complexes can be stabilized or destabilized in ways that allow the design of CD dimers with increased 7KC selectivity while maintaining an excellent safety profile. These CD dimers are being developed as therapeutics to treat atherosclerosis and other debilitating diseases of aging.

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PREPRINT

Transcriptomic changes highly similar to Alzheimer's disease are observed in a subpopulation of individuals during normal brain aging

Shouneng Peng, Lu Zeng, Jean-vianney Haure-mirande, Minghui Wang, Derek M. Huffman, Vahram Haroutunian, Michelle Erlich, Bin Zhang, Zhidong Tu

Aging is a major risk factor for late-onset Alzheimer's disease (LOAD). How aging contributes to the development of LOAD remains elusive. In this study, we examine multiple large-scale human brain transcriptomic data from both normal aging and LOAD to understand the molecular interconnection between aging and LOAD. We find that shared gene expression changes between aging and LOAD are mostly seen in the hippocampus and several cortical regions. In the hippocampus, phosphoprotein, alternative splicing and cytoskeleton are the commonly dysregulated biological pathways in both aging and AD, while synapse, ion transport, and synaptic vesicle genes are commonly down-regulated. Aging-specific changes are associated with acetylation and methylation, while LOAD-specific changes are related to glycoprotein (both up- and down-regulations), inflammatory response (up-regulation), myelin sheath and lipoprotein (down-regulation). We also find that normal aging brains from relatively young donors (45-70 years old) cluster into subgroups and some subgroups show gene expression changes highly similar to those seen in LOAD brains. Using brain transcriptome data from older individuals (>70 years), we find that samples from cognitive normal older individuals cluster with the "healthy aging" subgroup while AD samples mainly cluster with the AD similar subgroups. This implies that individuals in the healthy aging subgroup will likely remain cognitive normal when they become older and vice versa. In summary, our results suggest that on the transcriptome level, aging and LOAD have strong interconnections in some brain regions in a subpopulation of cognitive normal aging individuals. This supports the theory that the initiation of LOAD occurs decades earlier than the manifestation of clinical phenotype and it may be essential to closely study the "normal brain aging" in a subgroup of individuals in their 40s-60s to identify the very early events in LOAD development.

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Online ahead of print.

Microvascular degeneration occurs before plaque onset and progresses with age in 3xTg AD mice

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Affiliations + expand

PMID: 34062487 DOI: 10.1016/j.neurobiolaging.2021.04.019

Abstract

Heart disease and vascular disease positively correlate with the incidence of Alzheimer's disease (AD). Although there is ostensible involvement of dysfunctional cerebrovasculature in AD pathophysiology, the characterization of the specific changes and development of vascular injury during AD remains unclear. In the present study, we established a time-course for the structural changes and degeneration of the angioarchitecture in AD. We used cerebrovascular corrosion cast and μCT imaging to evaluate the geometry, topology, and complexity of the angioarchitecture in the brain of wild type and 3xTg AD mice. We hypothesized that changes to the microvasculature occur early during the disease, and these early identifiable aberrations would be more prominent in the brain subregions implicated in the cognitive decline of AD. Whole-brain analysis of the angioarchitecture indicated early morphological abnormalities and degeneration of microvascular networks in 3xTg AD mice. Our analysis of the hippocampus and cortical subregions revealed microvascular degeneration with onset and progression that was subregion dependent.

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Neurovascular coupling and oxygenation are decreased in hippocampus compared to neocortex because of microvascular differences

K. Shaw, L. Bell, K. Boyd, D. M. Grijseels, D. Clarke, O. Bonnar, H. S. Crombag & C. N. Hall

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Abstract

The hippocampus is essential for spatial and episodic memory but is damaged early in Alzheimer's disease and is very sensitive to hypoxia. Understanding how it regulates its oxygen supply is therefore key for designing interventions to preserve its function. However, studies of neurovascular function in the hippocampus in vivo have been limited by its relative inaccessibility. Here we compared hippocampal and visual cortical neurovascular function in awake mice, using two photon imaging of individual neurons and vessels and measures of regional blood flow and haemoglobin oxygenation. We show that blood flow, blood oxygenation and neurovascular coupling were decreased in the hippocampus compared to neocortex, because of differences in both the vascular network and pericyte and endothelial cell function. Modelling oxygen diffusion indicates that these features of the hippocampal vasculature may restrict oxygen availability and could explain its sensitivity to damage during neurological conditions, including Alzheimer's disease, where the brain's energy supply is decreased.

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HEALTHY LIFE EXTENSION SOCIETY

Cis P-tau underlies vascular contribution to cognitive impairment and dementia and can be effectively targeted by immunotherapy in mice

Compelling evidence supports vascular contributions to cognitive impairment and dementia (VCID) including Alzheimer's disease (AD), but the underlying pathogenic mechanisms and treatments are not fully understood. Cis P-tau is an early driver of neurodegeneration resulting from traumatic brain injury, but its role in VCID remains unclear. Here, we found robust cis P-tau despite no tau tangles in patients with VCID and in mice modeling key aspects of clinical VCID, likely because of the inhibition of its isomerase Pin1 by DAPK1. Elimination of cis P-tau in VCID mice using cis-targeted immunotherapy, brain-specific Pin1 overexpression, or DAPK1 knockout effectively rescues VCID-like neurodegeneration and cognitive impairment in executive function. Cis mAb also prevents and ameliorates progression of AD-like neurodegeneration and memory loss in mice. Furthermore, single-cell RNA sequencing revealed that young VCID mice display diverse cortical cell type–specific transcriptomic changes resembling old patients with AD, and the vast majority of these global changes were recovered by cis-targeted immunotherapy. Moreover, purified soluble cis P-tau was sufficient to induce progressive neurodegeneration and brain dysfunction by causing axonopathy and conserved transcriptomic signature found in VCID mice and patients with AD with early pathology. Thus, cis P-tau might play a major role in mediating VCID and AD, and antibody targeting it may be useful for early diagnosis, prevention, and treatment of cognitive impairment and dementia after neurovascular insults and in AD.

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HEALTHY LIFE EXTENSION SOCIETY

How epigallocatechin gallate binds and assembles oligomeric forms of human alpha-synuclein

Camilla B. Andersen † • Yuichi Yoshimura ‡ • Janni Nielsen • Daniel E. Otzen •

The intrinsically disordered human protein α-synuclein (αSN) can self-associate into oligomers and amyloid fibrils. Several lines of evidence suggest that oligomeric αSN is cytotoxic, making it important to devise strategies to either prevent oligomer formation and/or inhibit the ensuing toxicity. (–)-epigallocatechin gallate (EGCG) has emerged as a molecular modulator of αSN self-assembly, as it reduces the flexibility of the C-terminal region of αSN in the oligomer and inhibits the oligomer's ability to perturb phospholipid membranes and induce cell death. However, a detailed structural and kinetic characterization of this interaction is still lacking. Here, we use liquid-state NMR spectroscopy to investigate how EGCG interacts with monomeric and oligomeric forms of αSN. We find that EGCG can bind to all parts of monomeric αSN but exhibits highest affinity for the N-terminal region. Monomeric αSN binds ~54 molecules of EGCG in total during oligomerization. Furthermore, kinetic data suggests that EGCG dimerization is coupled with the αSN association reaction. In contrast, preformed oligomers only bind ~ 7 EGCG molecules per protomer, in agreement with the more compact nature of the oligomer compared to the natively unfolded monomer. In previously conducted cell assays as little as 0.36 EGCG per αSN reduce oligomer toxicity by 50%. Our study thus demonstrates that αSN cytotoxicity can be inhibited by small molecules at concentrations at least an order of magnitude below full binding capacity. We speculate this is due to cooperative binding of protein stabilized EGCG dimers, which in turn implies synergy between protein association and EGCG dimerization.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Restoration of energy homeostasis by SIRT6 extends healthy lifespan

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1916 Accesses | **180** Altmetric | Metrics

Abstract

Aging leads to a gradual decline in physical activity and disrupted energy homeostasis. The NAD^+-dependent SIRT6 deacylase regulates aging and metabolism through mechanisms that largely remain unknown. Here, we show that SIRT6 overexpression leads to a reduction in frailty and lifespan extension in both male and female B6 mice. A combination of physiological assays, in vivo multi-omics analyses and ^{13}C lactate tracing identified an age-dependent decline in glucose homeostasis and hepatic glucose output in wild type mice. In contrast, aged SIRT6-transgenic mice preserve hepatic glucose output and glucose homeostasis through an improvement in the utilization of two major gluconeogenic precursors, lactate and glycerol. To mediate these changes, mechanistically, SIRT6 increases hepatic gluconeogenic gene expression, de novo NAD^+ synthesis, and systemically enhances glycerol release from adipose tissue. These findings show that SIRT6 optimizes energy homeostasis in old age to delay frailty and preserve healthy aging.

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HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Distinct and additive effects of calorie restriction and rapamycin in aging skeletal muscle

Daniel J. Ham, Anastasiya Börsch, Kathrin Chojnowska, Shuo Lin, Aurel B. Leuchtmann, Alexander S. Ham, Marco Thürkauf, Julien Delezie, Regula Furrer, Dominik Burri, Michael Sinnreich, Christoph Handschin, Lionel A. Tintignac, Mihaela Zavolan, Nitish Mittal, Markus A. Rüegg

As global life expectancy continues to climb, maintaining skeletal muscle function is increasingly essential to ensure a good life quality for aging populations. Calorie restriction (CR) is the most potent and reproducible intervention to extend health and lifespan, but is largely unachievable in humans. Therefore, identification of "CR mimetics" has received much attention. CR targets nutrient-sensing pathways centering on mTORC1. The mTORC1 inhibitor, rapamycin, has been proposed as a potential CR mimetic and is proven to counteract age-related muscle loss. Therefore, we tested whether rapamycin acts via similar mechanisms as CR to slow muscle aging. Contrary to our expectation, long-term CR and rapamycin-treated geriatric mice display distinct skeletal muscle gene expression profiles despite both conferring benefits to aging skeletal muscle. Furthermore, CR improved muscle integrity in a mouse with nutrient-insensitive sustained muscle mTORC1 activity and rapamycin provided additive benefits to CR in aging mouse muscles. Therefore, RM and CR exert distinct, compounding effects in aging skeletal muscle, opening the possibility of parallel interventions to counteract muscle aging.

Heales
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PREPRINT

Dietary restriction and *clock* delay eye aging to extend lifespan in *D. melanogaster*

Brian A. Hodge, Geoffrey T. Meyerhof, Subhash D. Katewa, Ting Lian, Charles Lau, Sudipta Bar, Nicole Leung, Menglin Li, David Li-Kroeger, Simon Melov, Birgit Schilling, Craig Montell, Pankaj Kapahi

Many vital processes in the eye are under circadian regulation, and circadian dysfunction has emerged as a potential driver of eye aging. Dietary restriction is one of the most robust lifespan-extending therapies and amplifies circadian rhythms with age. Herein, we demonstrate that dietary restriction extends lifespan in *D. melanogaster* by promoting circadian homoeostatic processes that protect the visual system from age- and light- associated damage. Disrupting circadian rhythms in the eye by inhibiting the transcription factor, Clock (CLK), or CLK-output genes, accelerated visual senescence, induced a systemic immune response, and shortened lifespan. Flies subjected to dietary restriction were protected from the lifespan-shortening effects of photoreceptor activation. Inversely, photoreceptor inactivation, achieved via mutating rhodopsin or housing flies in constant darkness, primarily extended lifespan in flies reared on a high-nutrient diet. Our findings establish the eye as a diet-sensitive modulator of lifespan and indicate that vision is an antagonistically pleiotropic process that contributes to organismal aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Age-related telomere attrition causes aberrant gene expression in sub-telomeric regions

Xiao Dong ✉, Shixiang Sun, Lei Zhang, Seungsoo Kim, Zhidong Tu, Cristina Montagna, Alexander Y. Maslov, Yousin Suh, Tao Wang, Judith Campisi, Jan Vijg ✉

Telomere attrition has been proposed as a biomarker and causal factor in aging. In addition to causing cellular senescence and apoptosis, telomere shortening has been found to affect gene expression in subtelomeric regions. Here, we analyzed the distribution of age-related differentially expressed genes from the GTEx RNA sequencing database of 54 tissue types from 979 human subjects and found significantly more upregulated than downregulated genes in subtelomeric regions as compared to the genome-wide average. Our data demonstrate spatial relationships between telomeres and gene expression in aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Long-lived termite kings and queens activate telomerase in somatic organs

Justina Koubová†, Marie Pangrácová†, Marek Jankásek, Ondřej Lukšan, Tomáš Jehlík, Jana Brabcová, Pavel Jedlička, Jan Křivánek, Radmila Čapková Frydrychová ✉ and Robert Hanus ✉

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Review history

Abstract

Kings and queens of termites, like queens of other advanced eusocial insects, are endowed with admirable longevity, which dramatically exceeds the life expectancies of their non-reproducing nest-mates and related solitary insects. In the quest to find the mechanisms underlying the longevity of termite reproductives, we focused on somatic maintenance mediated by telomerase. This ribonucleoprotein is well established for pro-longevity functions in vertebrates, thanks primarily to its ability of telomere extension. However, its participation in lifespan regulation of insects, including the eusocial taxa, remains understudied. Here, we report a conspicuous increase of telomerase abundance and catalytic activity in the somatic organs of primary and secondary reproductives of the termite *Prorhinotermes simplex* and confirm a similar pattern in two other termite species. These observations stand in contrast with the telomerase downregulation characteristic for most adult somatic tissues in vertebrates and also in solitary insects and non-reproducing castes of termites. At the same time, we did not observe caste-specific differences in telomere lengths that might explain the differential longevity of termite castes. We conclude that although the telomerase activation in termite reproductives is in line with the broadly assumed association between telomerase and longevity, its direct phenotypic impact remains to be elucidated.

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HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Extreme longevity of highly fecund termite queens achieved by mitochondrial and insulin upregulation without harmful lipid signatures or accumulation

Sarah Séité, Mark C. Harrison, David Sillam-Dussès, Roland Lupoli, Tom J. M. Van Dooren, Alain Robert, Laure-Anne Poissonnier, Arnaud Lemainque, David Renault, Sébastien Acket, Muriel Andrieu, José Viscarra, Hei Sook Sul, Z. Wilhelm de Beer, Erich Bornberg-Bauer, Mireille Vasseur-Cognet

Eusocial termite queens achieve nearly maximal fertility throughout their extremely long life without apparent signs of aging. Termites represent, therefore, an ideal model for aging research. To investigate the molecular mechanisms underlying their long reproductive life, we carried out transcriptomic, lipidomic and metabolomic analyses on fat bodies of sterile short-lived workers, long-lived kings and five stages spanning twenty years of adult queen maturation. In mature reproductives, genes supporting a robust mitochondrial functioning or associated with genome stability were upregulated. In most organisms, insulin signaling increases fertility but decreases lifespan, often accompanied by harmful lipid signatures. Our findings suggest that an upregulation of insulin-like peptide (Ilp9) in the fat body of termite queens is accompanied by a specific lipid metabolism, limiting fat storage, thus sustaining both high fertility and maintaining extreme lifespan. Our results highlight potential molecular targets for research into aging-related metabolic diseases linked to the accumulation of excess fat.

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HEALTHY LIFE EXTENSION SOCIETY

Aging as a consequence of selection to reduce the environmental risk of dying

Stig W. Omholt and Thomas B. L. Kirkwood

Each animal in the Darwinian theater is exposed to a number of abiotic and biotic risk factors causing mortality. Several of these risk factors are intimately associated with the act of energy acquisition as such and with the amount of reserve the organism has available from this acquisition for overcoming temporary distress. Because a considerable fraction of an individual's lifetime energy acquisition is spent on somatic maintenance, there is a close link between energy expenditure on somatic maintenance and mortality risk. Here, we show, by simple life-history theory reasoning backed up by empirical cohort survivorship data, how reduction of mortality risk might be achieved by restraining allocation to somatic maintenance, which enhances lifetime fitness but results in aging. Our results predict the ubiquitous presence of senescent individuals in a highly diverse group of natural animal populations, which may display constant, increasing, or decreasing mortality with age. This suggests that allocation to somatic maintenance is primarily tuned to expected life span by stabilizing selection and is not necessarily traded against reproductive effort or other traits. Due to this ubiquitous strategy of modulating the somatic maintenance budget so as to increase fitness under natural conditions, it follows that individuals kept in protected environments with very low environmental mortality risk will have their expected life span primarily defined by somatic damage accumulation mechanisms laid down by natural selection in the wild.

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Article | Open Access | Published: 11 May 2021

Molecular evolution and the decline of purifying selection with age

Changde Cheng & Mark Kirkpatrick

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Abstract

Life history theory predicts that the intensity of selection declines with age, and this trend should impact how genes expressed at different ages evolve. Here we find consistent relationships between a gene's age of expression and patterns of molecular evolution in two mammals (the human *Homo sapiens* and the mouse *Mus musculus*) and two insects (the malaria mosquito *Anopheles gambiae* and the fruit fly *Drosophila melanogaster*). When expressed later in life, genes fix nonsynonymous mutations more frequently, are more polymorphic for nonsynonymous mutations, and have shorter evolutionary lifespans, relative to those expressed early. The latter pattern is explained by a simple evolutionary model. Further, early-expressed genes tend to be enriched in similar gene ontology terms across species, while late-expressed genes show no such consistency. In humans, late-expressed genes are more likely to be linked to cancer and to segregate for dominant disease-causing mutations. Last, the effective strength of selection ($N_e s$) decreases and the fraction of beneficial mutations increases with a gene's age of expression. These results are consistent with the diminishing efficacy of purifying selection with age, as proposed by Medawar's classic hypothesis for the evolution of senescence, and provide links between life history theory and molecular evolution.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Quantitative analysis of population-scale family trees with millions of relatives

Abstract

Family trees have vast applications in fields as diverse as genetics, anthropology, and economics. However, the collection of extended family trees is tedious and usually relies on resources with limited geographical scope and complex data usage restrictions. We collected 86 million profiles from publicly available online data shared by genealogy enthusiasts. After extensive cleaning and validation, we obtained population-scale family trees, including a single pedigree of 13 million individuals. We leveraged the data to partition the genetic architecture of human longevity and to provide insights into the geographical dispersion of families. We also report a simple digital procedure to overlay other data sets with our resource.

Whole-genome sequencing analysis of semi-supercentenarians

Extreme longevity is the paradigm of healthy aging as individuals who reached the extreme decades of human life avoided or largely postponed all major age-related diseases. In this study, we sequenced at high coverage (90X) the whole genome of 81 semi-supercentenarians and supercentenarians [105+/110+] (mean age: 106.6 ± 1.6) and of 36 healthy unrelated geographically matched controls (mean age 68.0 ± 5.9) recruited in Italy. The results showed that 105+/110+ are characterized by a peculiar genetic background associated with efficient DNA repair mechanisms, as evidenced by both germline data (common and rare variants) and somatic mutations patterns (lower mutation load if compared to younger healthy controls). Results were replicated in a second independent cohort of 333 Italian centenarians and 358 geographically matched controls. The genetics of 105+/110+ identified DNA repair and clonal haematopoiesis as crucial players for healthy aging and for the protection from cardiovascular events.

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HEALTHY LIFE EXTENSION SOCIETY

Analysis of aging-related protein interactome and cross-network module comparisons across tissues provide new insights into aging

Vinay Randhawa [a] ✉, Manoj Kumar [a, b] ✉

Delaying the human aging process and thus eliminating the risk factors for age-related diseases is one of the prime objectives. While various aging-associated genes and proteins have been characterized, which provide a significant understanding of the human aging process, a significant success in regulating aging is not achieved yet. Understanding how aging proteins interact with each other and also with other proteins could provide important insights into the underlying mechanisms governing the aging process. Therefore, in this work, information of gene expression was included to the static aging-related protein interactome to understand the network-based relationships among aging-related essential (AE) proteins, aging-related non-essential (ANE) proteins, and housekeeping-proteins that could regulate or influence aging. Comprehensive analyses provided various systems-level insights into the regulatory characteristics of aging; for example, (i) network-based correlation analysis predicted functional relationships among AE proteins and ANE proteins; (ii) network variability analysis predicted aging to affect different tissues in strikingly different ways by differentially regulating various regulatory interactions; (iii) cross-network comparisons identified two aging-related modules to be significantly conserved across most of the tissues. Overall, the findings obtained during this study could be helpful for researchers to delay, prevent, or even reverse various aspects of the aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Biological mechanisms of aging predict age-related disease multimorbidities in patients

Helen C Fraser, Valerie Kuan, Ronja Johnen, Magdalena Zwierzyna, Aroon D Hingorani, Andreas Beyer, Linda Partridge

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Abstract

Genetic, environmental and pharmacological interventions into the aging process can confer resistance to a multiple age-related diseases in laboratory animals, including rhesus monkeys. These findings imply that mechanisms of aging might contribute to patterns of multimorbidity in humans, and hence could be targeted to prevent multiple conditions simultaneously. To address this question, we text mined 917,645 literature abstracts followed by manual curation, and found strong, non-random associations between age-related diseases and aging mechanisms, confirmed by gene set enrichment analysis of GWAS data. Integration of these associations with clinical data from 3.01 million patients showed that age-related diseases associated with each of five aging mechanisms were more likely than chance to be present together in patients. Genetic evidence revealed that innate and adaptive immunity, the intrinsic apoptotic signalling pathway and activity of the ERK1/2 pathway played a significant role across multiple aging mechanisms and multiple, diverse age-related diseases. Mechanisms of aging therefore contribute to multiple age-related diseases and to patterns of human age-related multimorbidity, and could potentially be targeted to prevent more than one age-related condition in the same patient.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging-associated lncRNAs are evolutionarily conserved and participate in NFκB signaling

Donghong Cai & Jing-Dong J. Han

Nature Aging **1**, 438–453 (2021) | Cite this article

Abstract

The transcriptome undergoes global changes during aging, including both protein-coding and noncoding RNAs. Using comparative genomics, we identify aging-associated long noncoding RNAs (lncRNAs) that are under evolutionary constraint and are more conserved than lncRNAs that do not change with age. Aging-associated lncRNAs are enriched for functional elements, including binding sites for RNA-binding proteins and transcription factors, in particular nuclear factor kappa B (NFκB). Using CRISPR screening, we discovered that 13 of the aging-associated lncRNAs were regulators of the NFκB pathway, and we named this family 'NFκB modulating aging-related lncRNAs (NFKBMARLs)'. Further characterization of NFκBMARL-1 reveals it can be traced to 29 Ma before humans and is induced by NFκB during aging, inflammation and senescence. Reciprocally, NFκBMARL-1 directly regulates transcription of the NFκB inhibitor NFKBIZ in *cis* within the same topologically associated domain by binding to the NFKBIZ enhancer and recruiting RELA to the NFKBIZ promoter. These findings reveal many aging-associated lncRNAs are evolutionarily conserved components of the NFκB pathway.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

End-of-life targeted auxin-mediated degradation of DAF-2 Insulin/IGF-1 receptor promotes longevity free from growth-related pathologies

Richard Venz, Tina Pekec, Iskra Katic, Rafal Ciosk, Collin Y. Ewald

Preferably, lifespan-extending therapies should work when applied late in life without causing undesired pathologies. However, identifying lifespan-extending interventions that are effective late in life and which avoid undesired secondary pathologies remains elusive. Reducing Insulin/IGF-1 signaling (IIS) increases lifespan across species, but the effects of reduced IIS interventions in extreme geriatric ages remains unknown. Using the nematode *C. elegans*, we engineered the conditional depletion of the DAF-2/insulin/IGF-1 transmembrane receptor using an auxin-inducible degradation (AID) system that allows for the temporal and spatial reduction in DAF-2 protein levels at time points after which interventions such as RNAi may lose efficacy. Using this system, we found that AID-mediated depletion of DAF-2 protein efficiently extends animal lifespan. Depletion of DAF-2 during early adulthood resulted in multiple adverse phenotypes, including growth retardation, germline shrinkage, egg-retention, and reducing offspring. By contrast, however, AID-mediated depletion of DAF-2 specifically in the intestine resulted in an extension of lifespan without these deleterious effects. Importantly, AID-mediated depletion of DAF-2 protein in animals past their median lifespan allowed for an extension of lifespan without affecting growth or behavioral capacity. Thus, both late-in-life targeting and tissue-specific targeting of IIS minimize the deleterious effects typically seen with interventions that reduced IIS, suggesting potential therapeutic methods by which longevity and healthspan can be increased in even geriatric populations.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A small-molecule Psora-4 acts as a caloric restriction mimetic to promote longevity in *C. elegans*

Tesfahun Dessale Admasu, Diogo Barardo, Li Fang Ng, Krishna Chaithanya Batchu, Amaury Cazenave-Gassiot, Markus R. Wenk & Jan Gruber

GeroScience (2021) | Cite this article

168 Accesses | **10** Altmetric | Metrics

Abstract

In populations around the world, the fraction of humans aged 65 and above is increasing at an unprecedented rate. Aging is the main risk factor for the most important degenerative diseases and this demographic shift poses significant social, economic, and medical challenges. Pharmacological interventions directly targeting mechanisms of aging are an emerging strategy to delay or prevent age-dependent diseases. Successful application of this approach has the potential to yield dramatic health, social, and economic benefits. Psora-4 is an inhibitor of the voltage-gated potassium channel, Kv1.3, that has previously been shown to increase longevity and health span in the nematode *Caenorhabditis elegans* (*C. elegans*). Our recent discovery that Psora-4 lifespan benefits in *C. elegans* are synergistic with those of several other lifespan-extending drugs has motivated us to investigate further the mechanism by which Psora-4 extends lifespan. Here, we report that Psora-4 increases the production of free radicals and modulates genes related to stress response and that its effect intersects closely with the target set of caloric restriction (CR) genes, suggesting that it, in part, acts as CR mimetic. This effect may be related to the role of potassium channels in energy metabolism. Our discovery of a potassium channel blocker as a CR mimetic suggests a novel avenue for mimicking CR and extending a healthy lifespan.

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The symbiotic relationship between *Caenorhabditis elegans* and members of its microbiome contributes to worm fitness and lifespan extension

Results

A total of 16 members of *C. elegans* microbiome were screened under chemically-induced toxicity. Worms grown with *Chryseobacterium* sp. CHNTR56 MYb120 or *Comamonas* sp. 12022 MYb131, were most resistant to oxidative chemical stress (SiO_2 nanoparticles and juglone), as measured by progeny output. Further investigation showed that *Chryseobacterium* sp. CHNTR56 positively influenced the worm's lifespan, whereas the combination of both isolates had a synergistic effect. RNAseq analysis of young adult worms, grown with either isolate, revealed the enrichment of cellular detoxification mechanisms (glutathione metabolism, drug metabolism and metabolism of xenobiotics) and signaling pathways (TGF-beta and Wnt signaling pathways). Upregulation of cysteine synthases (*cysl* genes) in the worms, associated with glutathione metabolism, was also observed. Nanopore sequencing uncovered that the genomes of the two isolates have evolved to favor the specific route of the de novo synthesis pathway of vitamin B6 (cofactor of cysl enzymes) through *serC* or *pdxA2* homologs. Finally, co-culture with vitamin B6 extended worm lifespan.

Conclusions

In summary, our study indicates that certain colonizing members of *C. elegans* have genomic diversity in vitamin B6 synthesis and promote host fitness and lifespan extension. The regulation of host cellular detoxification genes (i.e. *gst*) along with *cysl* genes at the transcriptome level and the bacterium-specific vitamin B6 synthesis mechanism at the genome level are in an agreement with enhanced host glutathione-based cellular detoxification due to this interspecies relationship. *C. elegans* is therefore a promising alternative model to study host-microbiome interactions in host fitness and lifespan.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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PREPRINT

The Hoverfly and the Wasp: A Critique of the Hallmarks of Aging as a Paradigm

David Gems * and João Pedro de Magalhães

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Abstract

With the goal of representing common denominators of aging in different organisms López-Otín et al. in 2013 described nine hallmarks of aging. Since then, this representation has become a major reference point for the biogerontology field. The template for the hallmarks of aging account originated from landmark papers by Hanahan and Weinberg (2000, 2011) defining first six and later ten hallmarks of cancer. Here we assess the strengths and weaknesses of the hallmarks of aging account. As a checklist of diverse major foci of current aging research, it has provided a useful shared overview for biogerontology during a time of transition in the field. It also seems useful in applied biogerontology, to identify interventions (e.g. drugs) that impact multiple symptomatic features of aging. However, while the hallmarks of cancer provide a paradigmatic account of the causes of cancer with profound explanatory power, the hallmarks of aging do not. A worry is that as a non-paradigm the hallmarks of aging have obscured the urgent need to define a genuine paradigm, one that can provide a useful basis for understanding the mechanistic causes of the diverse aging pathologies. We argue that biogerontology must look and move beyond the hallmarks to understand the process of aging.

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Hallmarks of T cell aging

Maria Mittelbrunn & Guido Kroemer

Nature Immunology **22**, 687–698 (2021) | Cite this article

2452 Accesses | **10** Altmetric | Metrics

Abstract

The aged adaptive immune system is characterized by progressive dysfunction as well as increased autoimmunity. This decline is responsible for elevated susceptibility to infection and cancer, as well as decreased vaccination efficacy. Recent evidence indicates that $CD4^+$ T cell–intrinsic alteratins contribute to chronic inflammation and are sufficient to accelerate an organism-wide aging phenotype, supporting the idea that T cell aging plays a major role in body-wide deterioration. In this Review, we propose ten molecular hallmarks to represent common denominators of T cell aging. These hallmarks are grouped into four primary hallmarks (thymic involution, mitochondrial dysfunction, genetic and epigenetic alterations, and loss of proteostasis) and four secondary hallmarks (reduction of the TCR repertoire, naive–memory imbalance, T cell senescence, and lack of effector plasticity), and together they explain the manifestation of the two integrative hallmarks (immunodeficiency and inflammaging). A major challenge now is weighing the relative impact of these hallmarks on T cell aging and understanding their interconnections, with the final goal of defining molecular targets for interventions in the aging process.

Alternative Animal Models of Aging Research

Susanne Holtze[1*], Ekaterina Gorshkova[2,3], Stan Braude[4], Alessandro Cellerino[5,6], Philip Dammann[7,8], Thomas B. Hildebrandt[1,9], Andreas Hoeflich[10], Steve Hoffmann[11], Philipp Koch[12], Eva Terzibasi Tozzini[13], Maxim Skulachev[14], Vladimir P. Skulachev[14] and Arne Sahm[11*]

Most research on mechanisms of aging is being conducted in a very limited number of classical model species, i.e., laboratory mouse (*Mus musculus*), rat (*Rattus norvegicus domestica*), the common fruit fly (*Drosophila melanogaster*) and roundworm (*Caenorhabditis elegans*). The obvious advantages of using these models are access to resources such as strains with known genetic properties, high-quality genomic and transcriptomic sequencing data, versatile experimental manipulation capabilities including well-established genome editing tools, as well as extensive experience in husbandry. However, this approach may introduce interpretation biases due to the specific characteristics of the investigated species, which may lead to inappropriate, or even false, generalization. For example, it is still unclear to what extent knowledge of aging mechanisms gained in short-lived model organisms is transferable to long-lived species such as humans. In addition, other specific adaptations favoring a long and healthy life from the immense evolutionary toolbox may be entirely missed. In this review, we summarize the specific characteristics of emerging animal models that have attracted the attention of gerontologists, we provide an overview of the available data and resources related to these models, and we summarize important insights gained from them in recent years. The models presented include short-lived ones such as killifish (*Nothobranchius furzeri*), long-lived ones such as primates (*Callithrix jacchus, Cebus imitator, Macaca mulatta*), bathyergid mole-rats (*Heterocephalus glaber, Fukomys spp.*), bats (*Myotis spp.*), birds, olms (*Proteus anguinus*), turtles, greenland sharks, bivalves (*Arctica islandica*), and potentially non-aging ones such as *Hydra* and *Planaria*.

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Review Article | Open Access | Published: 26 May 2021

Roles of tRNA metabolism in aging and lifespan

Zheng Zhou, Bao Sun, Dongsheng Yu & Meng Bian

Cell Death & Disease **12**, Article number: 548 (2021) | Cite this article

322 Accesses | **2** Altmetric | Metrics

Abstract

Transfer RNAs (tRNAs) mainly function as adapter molecules that decode messenger RNAs (mRNAs) during protein translation by delivering amino acids to the ribosome. Traditionally, tRNAs are considered as housekeepers without additional functions. Nevertheless, it has become apparent from biological research that tRNAs are involved in various physiological and pathological processes. Aging is a form of gradual decline in physiological function that ultimately leads to increased vulnerability to multiple chronic diseases and death. Interestingly, tRNA metabolism is closely associated with aging and lifespan. In this review, we summarize the emerging roles of tRNA-associated metabolism, such as tRNA transcription, tRNA molecules, tRNA modifications, tRNA aminoacylation, and tRNA derivatives, in aging and lifespan, aiming to provide new ideas for developing therapeutics and ultimately extending lifespan in humans.

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Emerging functions of circular RNA in aging

Eunah Kim • Yoon Ki Kim • Seung-Jae V. Lee

Circular RNA (circRNA) is a closed, single-stranded transcript widely detected in eukaryotes. Recent studies indicate that the levels of circRNAs change with age in various tissues in multiple species, ranging from nematodes to mammals. Here we discuss the functional roles of circRNAs in animal aging and longevity. We review studies regarding the differential expression of circRNAs that contributes to cellular senescence and the pathogenesis of aging-associated diseases. We explore the features of aging-associated circRNAs by discussing their potential as biomarkers of aging, tissue specificity, physiological roles, action mechanisms, and evolutionarily conserved characteristics. Our review provides insights into current progress in circRNA research and their significant functions in the aging process.

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Impact of the Natural Compound Urolithin A on Health, Disease, and Aging

Davide D'Amico [1], Pénélope A. Andreux [1], Pamela Valdés [1], Anurag Singh [1], Chris Rinsch [1], Johan Auwerx [2]

Urolithin A (UA) is a natural compound produced by gut bacteria from ingested ellagitannins (ETs) and ellagic acid (EA), complex polyphenols abundant in foods such as pomegranate, berries, and nuts. UA was discovered 40 years ago, but only recently has its impact on aging and disease been explored. UA enhances cellular health by increasing mitophagy and mitochondrial function and reducing detrimental inflammation. Several preclinical studies show how UA protects against aging and age-related conditions affecting muscle, brain, joints, and other organs. In humans, benefits of UA supplementation in the muscle are supported by recent clinical trials in elderly people. Here, we review the state of the art of UA's biology and its translational potential as a nutritional intervention in humans.

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Brain Somatic Mutation in Aging and Alzheimer's Disease

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Affiliations + expand

PMID: 33979534 DOI: 10.1146/annurev-genom-121520-081242

Abstract

Somatic mutations arise postzygotically, producing genetic differences between cells in an organism. Well established as a driver of cancer, somatic mutations also exist in nonneoplastic cells, including in the brain. Technological advances in nucleic acid sequencing have enabled recent breakthroughs that illuminate the roles of somatic mutations in aging and degenerative diseases of the brain. Somatic mutations accumulate during aging in human neurons, a process termed genosenium. A number of recent studies have examined somatic mutations in Alzheimer's disease (AD), primarily from the perspective of genes causing familial AD. We have also gained new information on genome-wide mutations, providing insights into the cellular events driving somatic mutation and cellular dysfunction. This review highlights recent concepts, methods, and findings in the progress to understand the role of brain somatic mutation in aging and AD. Expected final online publication date for the *Annual Review of Genomics and Human Genetics*, Volume 22 is August 2021. Please see http://www.annualreviews.org/page/journal/pubdates for revised estimates.

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DNA Repair Repertoire of the Enigmatic Hydra

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Since its discovery by Abraham Trembley in 1744, hydra has been a popular research organism. Features like spectacular regeneration capacity, peculiar tissue dynamics, continuous pattern formation, unique evolutionary position, and an apparent lack of organismal senescence make hydra an intriguing animal to study. While a large body of work has taken place, particularly in the domain of evolutionary developmental biology of hydra, in recent years, the focus has shifted to molecular mechanisms underlying various phenomena. DNA repair is a fundamental cellular process that helps to maintain integrity of the genome through multiple repair pathways found across taxa, from archaea to higher animals. DNA repair capacity and senescence are known to be closely associated, with mutations in several repair pathways leading to premature ageing phenotypes. Analysis of DNA repair in an animal like hydra could offer clues into several aspects including hydra's purported lack of organismal ageing, evolution of DNA repair systems in metazoa, and alternative functions of repair proteins. We review here the different DNA repair mechanisms known so far in hydra. Hydra genes from various DNA repair pathways show very high similarity with their vertebrate orthologues, indicating conservation at the level of sequence, structure, and function. Notably, most hydra repair genes are more similar to deuterostome counterparts than to common model invertebrates, hinting at ancient evolutionary origins of repair pathways and further highlighting the relevance of organisms like hydra as model systems. It appears that hydra has the full repertoire of DNA repair pathways, which are employed in stress as well as normal physiological conditions and may have a link with its observed lack of senescence. The close correspondence of hydra repair genes with higher vertebrates further demonstrates the need for deeper studies of various repair components, their interconnections, and functions in this early metazoan.

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The regulation of healthspan and lifespan by dietary amino acids

Reji Babygirija [a, b, c] ✉, Dudley W. Lamming [a, b, c] ✉

As a key macronutrient and source of essential macromolecules, dietary protein plays a significant role in health. For many years, protein-rich diets have been recommended as healthy due to the satiety-inducing and muscle-building effects of protein, as well as the ability of protein calories to displace allegedly unhealthy calories from fats and carbohydrates. However, clinical studies find that consumption of dietary protein is associated with an increased risk of multiple diseases, especially diabetes, while studies in rodents have demonstrated that protein restriction can promote metabolic health and even lifespan. Emerging evidence suggests that the effects of dietary protein on health and longevity are not mediated simply by protein quantity but are instead mediated by protein quality – the specific amino acid composition of the diet. Here, we discuss how dietary protein and specific amino acids including methionine, the branched chain amino acids (leucine, isoleucine, and valine), tryptophan and glycine regulate metabolic health, healthspan, and aging, with attention to the specific molecular mechanisms that may participate in these effects. Finally, we discuss the potential applicability of these findings to promoting healthy aging in humans.

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Aging of the Retina: Molecular and Metabolic Turbulences and Potential Interventions

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Abstract

Multifaceted and divergent manifestations across tissues and cell types have curtailed advances in deciphering the cellular events that accompany advanced age and contribute to morbidities and mortalities. Increase in human lifespan during the past century has heightened awareness of the need to prevent age-associated frailty of neuronal and sensory systems to allow a healthy and productive life. In this review, we discuss molecular and physiological attributes of aging of the retina, with a goal of understanding age-related impairment of visual function. We highlight the epigenome–metabolism nexus and proteostasis as key contributors to retinal aging and discuss lifestyle changes as potential modulators of retinal function. Finally, we deliberate promising intervention strategies for promoting healthy aging of the retina for improved vision.

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Pathogenic mechanisms contributing to the vulnerability of aging human photoreceptor cells

Tapas C. Nag

Eye (2021) | Cite this article

11 Accesses | **2** Altmetric | Metrics

Abstract

In human retina, photoreceptor cell death (PCD) is a slow but conspicuous event, which continues with aging. Rods die earlier than cones, the latter continue to alter in a subtle manner until advanced aging. This review summarizes the existing information on age-related changes in photoreceptor cells, especially cones and analyses the possible associated factors. Oxidative and nitrosative stress are involved in photoreceptor alterations, which may stem from light and iron toxicity and other sources. Lipid peroxidation in macular photoreceptor outer segments and mitochondrial aberrations are prominent in aging. It is important to understand how those changes ultimately trigger PCD. The redistribution of calbindin D-28K and long/middle-wavelength-sensitive opsin in the parafoveal and perifoveal cones, anomalies in their somata and axons are strong predictors of their increasing vulnerability with aging. Signs of reduced autophagy, with autophagosomes containing organelle remnants are seen in aging photoreceptor cells. Currently, mechanisms that lead to human PCD are unknown; some observations favour apoptosis as a pathway. Since cones appear to change slowly, there is an opportunity to reverse those changes before they die. Therefore, a full understanding of how cones alter and the molecular pathways they utilize for survival must be the future research goal. Recent approaches to prevent PCD in aging and diseases are highlighted.

OTHER RESEARCH & REVIEWS

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Transient inhibition of mTOR in human pluripotent stem cells enables robust formation of mouse-human chimeric embryos

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Science Advances 13 May 2020:
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Abstract

It has not been possible to generate naïve human pluripotent stem cells (hPSCs) that substantially contribute to mouse embryos. We found that a brief inhibition of mTOR with Torin1 converted hPSCs from primed to naïve pluripotency. The naïve hPSCs were maintained in the same condition as mouse embryonic stem cells and exhibited high clonogenicity, rapid proliferation, mitochondrial respiration, X chromosome reactivation, DNA hypomethylation, and transcriptomes sharing similarities to those of human blastocysts. When transferred to mouse blastocysts, naïve hPSCs generated 0.1 to 4% human cells, of all three germ layers, including large amounts of enucleated red blood cells, suggesting a marked acceleration of hPSC development in mouse embryos. Torin1 induced nuclear translocation of TFE3; TFE3 with mutated nuclear localization signal blocked the primed-to-naïve conversion. The generation of chimera-competent naïve hPSCs unifies some common features of naïve pluripotency in mammals and may enable applications such as human organ generation in animals.