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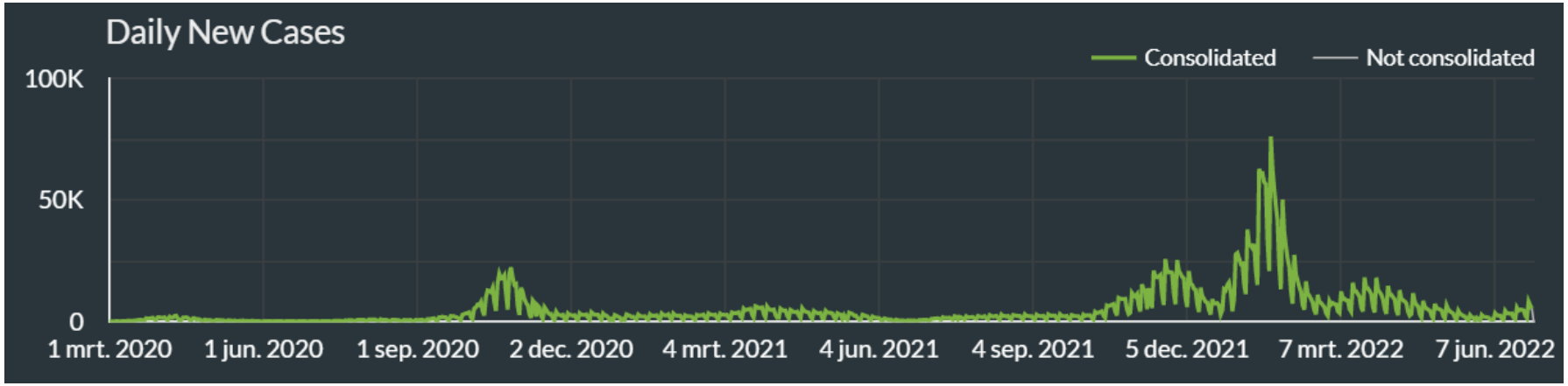
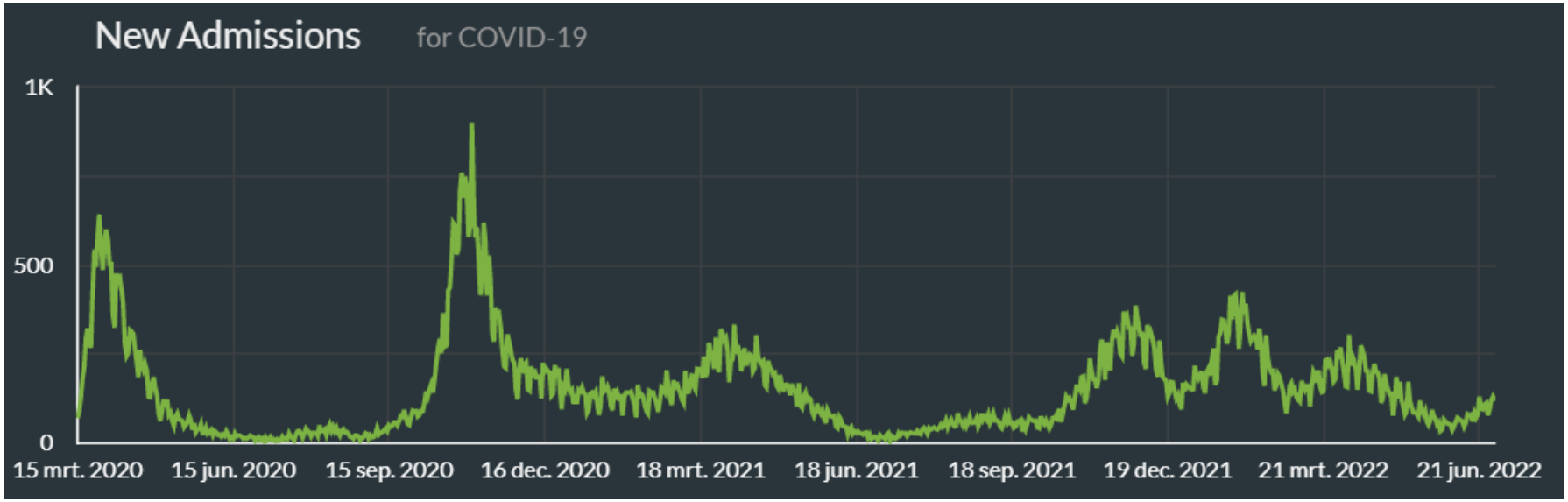
Scientific News
June & July 2022
Sven Bulterijs

Business/Conferences/ General news

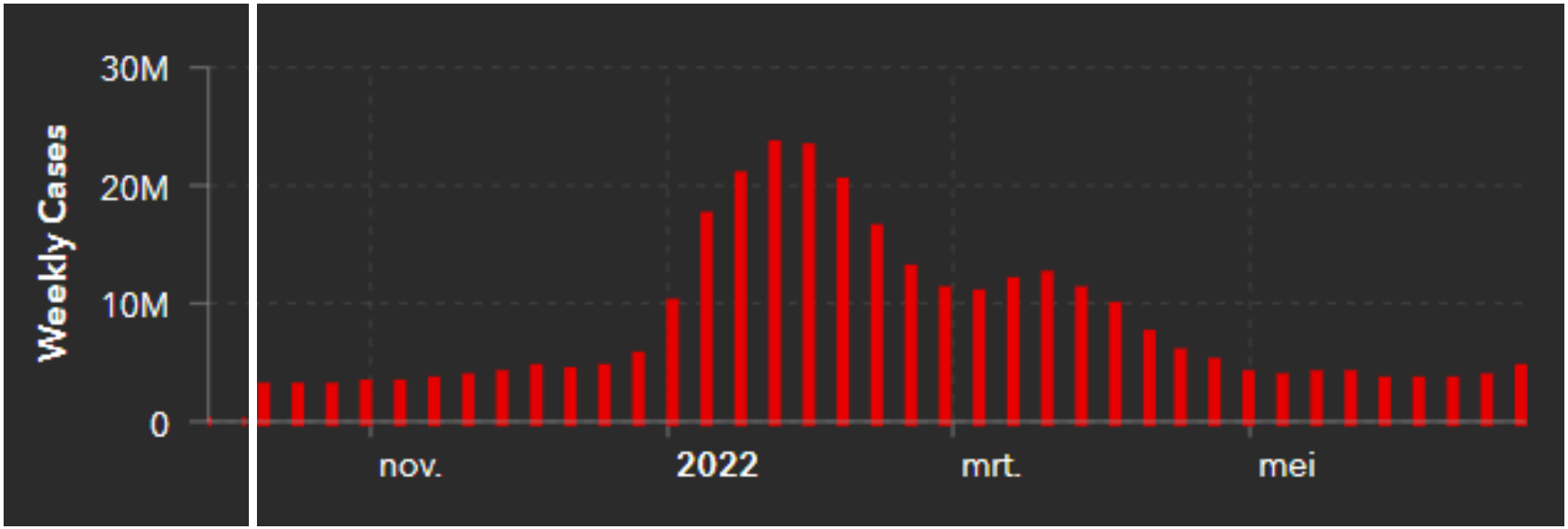
Belgium





World

Total Cases	Total Deaths	Total Vaccine Doses Administered
548.868.777	6.338.655	11.751.994.185
28-Day Cases	**28-Day Deaths**	**28-Day Vaccine Doses Administered**
17.029.897	40.741	205.464.480



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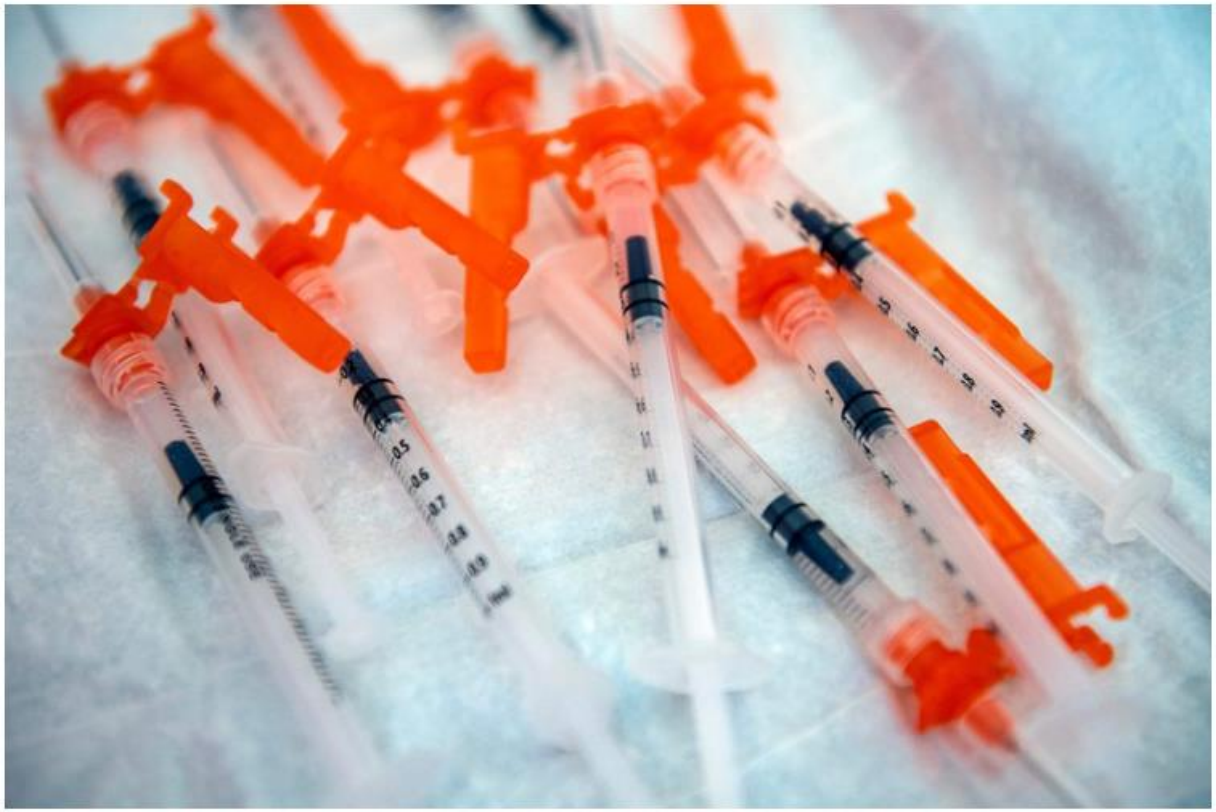
Fast-evolving COVID variants complicate vaccine updates

COVID-19 vaccines are due for an upgrade, scientists say, but emerging variants and fickle immune reactions mean it's not clear what new jabs should look like.

Ewen Callaway



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Limited cross-variant immunity from SARS-CoV-2 Omicron without vaccination

SARS-CoV-2 Delta and Omicron are globally relevant variants of concern. Although individuals infected with Delta are at risk of developing severe lung disease, infection with Omicron often causes milder symptoms, especially in vaccinated individuals[1,2]. The question arises of whether widespread Omicron infections could lead to future cross-variant protection, accelerating the end of the pandemic. Here we show that without vaccination, infection with Omicron induces a limited humoral immune response in mice and humans. Sera from mice overexpressing the human ACE2 receptor and infected with Omicron neutralize only Omicron, but not other variants of concern, whereas broader cross-variant neutralization was observed after WA1 and Delta infections. Unlike WA1 and Delta, Omicron replicates to low levels in the lungs and brains of infected animals, leading to mild disease with reduced expression of pro-inflammatory cytokines and diminished activation of lung-resident T cells. Sera from individuals who were unvaccinated and infected with Omicron show the same limited neutralization of only Omicron itself. By contrast, Omicron breakthrough infections induce overall higher neutralization titres against all variants of concern. Our results demonstrate that Omicron infection enhances pre-existing immunity elicited by vaccines but, on its own, may not confer broad protection against non-Omicron variants in unvaccinated individuals.

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LENTO BIO, AN ICHOR LIFE SCIENCES PORTFOLIO COMPANY, LAUNCHES WITH AIMS TO DEVELOP ANTI-GLYCATION DRUGS FOR PRESBYOPIA AND DISEASES OF AGING

Potsdam, N.Y. –. Lento Bio, Inc., a preclinical pharmaceutical company focused on developing small-molecule therapeutics to target molecular damage driving age-related disease, announced its launch today. The company will initially focus on developing pharmaceutical eyedrops to treat a common vision disorder, presbyopia, or age-related farsightedness. Lento Bio will be supported and incubated by Ichor Life Sciences, a pre-clinical contract research organization, at Clarkson University's Peyton Hall Biotechnology Incubator. Lento Bio is the first start-up company to join Ichor in establishing a North Country biotechnology cluster.

Presbyopia is caused by stiffening of the eye lens, which stems from molecular crosslinks including advanced glycation end products (AGE) that cause tissue rigidity. The small molecule drugs being developed by Lento Bio will target underlying molecular damage accumulation with the goal of reversing the process of tissue-stiffening in the ocular lens. Upon successful completion of its first project, Lento Bio plans to apply its anti-glycation products more widely to include systemic diseases of aging.

Lento Bio was founded and will be led by Dr. Kris Barnes as CEO. Dr. Barnes received a Ph.D. from Weill Cornell Graduate School of Medical Sciences and subsequently worked as a consultant for pharmaceutical and biotech companies developing novel disease treatments. He brings experience in ophthalmology basic science research as well as disease-indication specific industry knowledge.

"Lento Bio is starting from a solid foundation of established research into molecular aging damage and will focus development efforts towards the most accessible and relevant disease indications. Through bringing the problem to the science we aim to accelerate the creation of clinical assets and validate our disease hypothesis," says Dr. Barnes. "We look forward towards collaborating with the scientific teams at Ichor and Clarkson University to pursue research and development of small molecule drugs."

Feature | Published: 01 June 2022

The Worldview national ranking of health biotech sectors

John Hodgson & Deanna Schreiber-Gregory

Nature Biotechnology **40**, 821–828 (2022) | Cite this article

A survey of national R&D-driven health biotech sectors ranks Switzerland, Sweden and the United States as leading centers for R&D-driven biotech. John Hodgson and Deanna Schreiber-Gregory report.

The relative competitiveness of national biotech sectors across the globe remains a matter of conjecture. Although some governments report data on their own sectors, they often use inconsistent definitions of what constitutes biotech, rendering comparisons difficult. Self-reported national data may be biased, subjectively positioning a local sector in a favorable light. Even within a country, data on biotech companies originating from a region, state or city may not be internally consistent. What's more, in many cases, data on a national sector may not be updated on a regular basis, depending on the shifting priorities of policymakers as administrations come and go. With such inconsistent reporting and inconsistencies in the data, a comprehensive approach to gauging the relative strengths and weaknesses of national biotech sectors remains elusive.

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How long would you like to live? A 25-year prospective observation of the association between desired longevity and mortality

Yuta Yokokawa [1], Toshimasa Sone [1], Sanae Matsuyama [1], Yukai Lu [1], Yumi Sugawara [1], Akira Fukao [2], Ichiro Tsuji [1]

Background: Desired longevity represents how strongly people esteem possible extensions of their own lifetime. The association between desired longevity and mortality risk has been reported in only one prospective study, which examined a small sample of older participants. We aimed to examine the hypothesis that desired longevity at middle-age predicted long-term survival.

Methods: In the prospective cohort study, residents aged 40-64 years were asked how long they would like to live and asked to choose one from three options: longer than, as long as, or shorter than the life expectancy. We used Cox proportional hazards model to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality according to the three groups for desired longevity, treating the "longer than" group as the reference. We conducted mediation analysis to investigate the mechanism for the association between desired longevity and mortality.

Results: 39,902 residents were recruited to the study. Risk of all-cause mortality was significantly higher in the "shorter than" group (HR 1.12; 95% CI, 1.04-1.21). The association was independent of sex, age, marital status, education, medical history and health status. Regarding cause of death, mortality risk of cancer (HR 1.14; 95% CI, 1.00-1.29) and suicide (HR 2.15; 95% CI, 1.37-3.38) were also higher in the "shorter than" group. The unhealthy lifestyle mediated this association with all-cause mortality by 30.4%.

Conclusions: Shorter desired longevity was significantly associated with an increased risk of all-cause mortality, and mortality from cancer and suicide. Lifestyle behaviors particularly mediated this association.

Keywords: desired longevity; lifestyle behaviors; mediation analysis.

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Another knock back for amyloid: Roche's approach to presymptomatic Alzheimer's ends in failure

By **Nick Paul Taylor** • Jun 16, 2022 11:04am

Roche | Genentech | AC Immune | Alzheimer's disease

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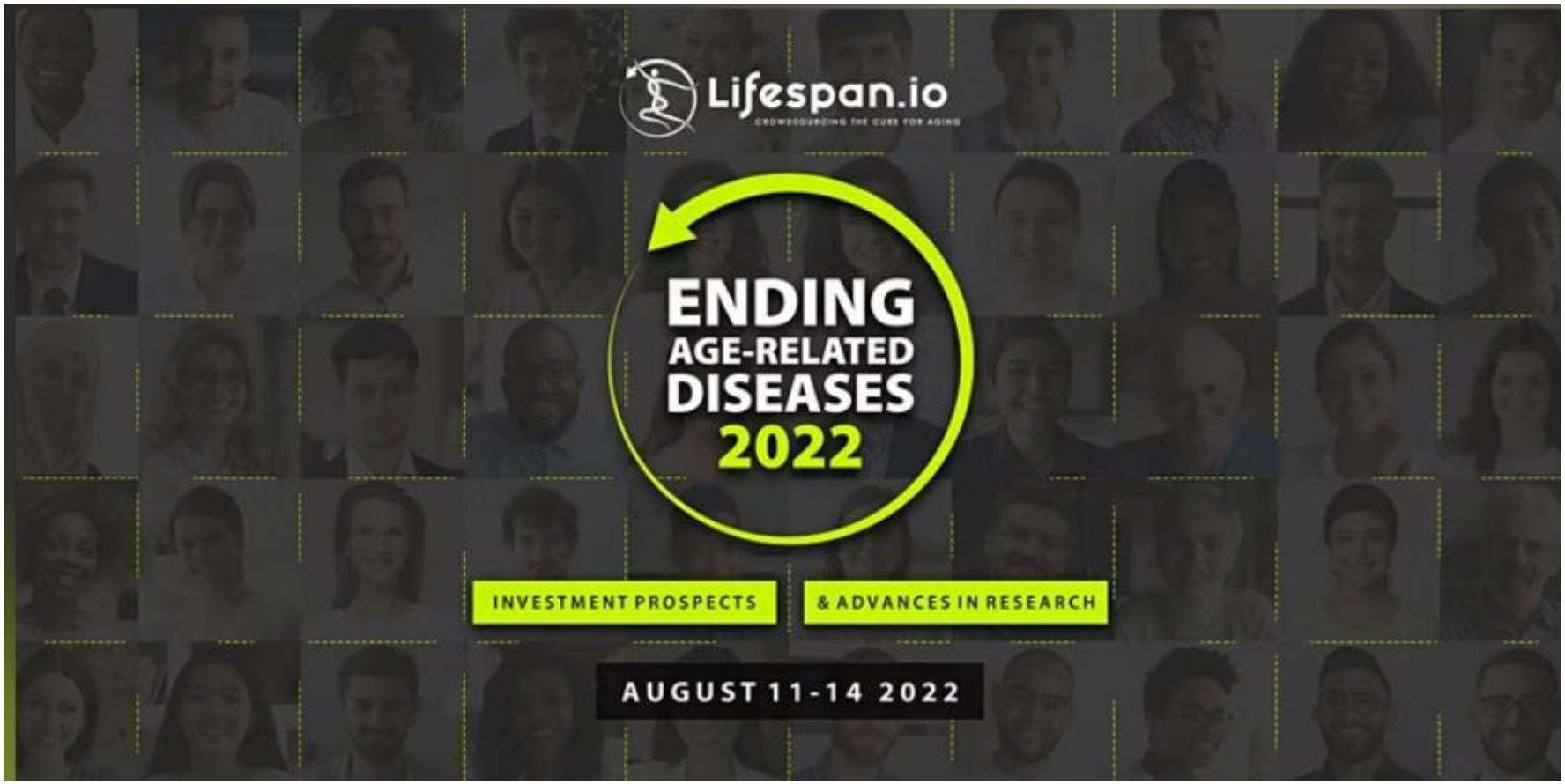

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29 AUGUST — 2 SEPTEMBER

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Aging research articles

New intranasal and injectable gene therapy for healthy life extension

Dabbu Kumar Jaijyan, Anca Selariu, Ruth Cruz-Cosme, Mingming Tong, Shaomin Yang, Alketa Stefa, David Kekich, Junichi Sadoshima, Utz Herbig, Qiyi Tang, George Church, Elizabeth L. Parrish, and Hua Zhu -9

As the global elderly population grows, it is socioeconomically and medically critical to provide diverse and effective means of mitigating the impact of aging on human health. Previous studies showed that the adeno-associated virus (AAV) vector induced overexpression of certain proteins, which can suppress or reverse the effects of aging in animal models. In our study, we sought to determine whether the high-capacity cytomegalovirus vector (CMV) can be an effective and safe gene delivery method for two such protective factors: telomerase reverse transcriptase (TERT) and follistatin (FST). We found that the mouse cytomegalovirus (MCMV) carrying exogenous TERT or FST ($MCMV_{TERT}$ or $MCMV_{FST}$) extended median lifespan by 41.4% and 32.5%, respectively. We report CMV being used successfully as both an intranasal and injectable gene therapy system to extend longevity. Specifically, this treatment significantly improved glucose tolerance, physical performance, as well as preventing body mass loss and alopecia. Further, telomere shortening associated with aging was ameliorated by TERT and mitochondrial structure deterioration was halted in both treatments. Intranasal and injectable preparations performed equally well in safely and efficiently delivering gene therapy to multiple organs, with long-lasting benefits and without carcinogenicity or unwanted side effects. Translating this research to humans could have significant benefits associated with quality of life and an increased health span.

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Diverse partial reprogramming strategies restore youthful gene expression and transiently suppress cell identity

Antoine E. Roux [1], Chunlian Zhang [1], Jonathan Paw [1], José Zavala-Solorio [1], Evangelia Malahias [1], Twaritha Vijay [1], Ganesh Kolumam [1], Cynthia Kenyon [1], Jacob C. Kimmel [1, 2, 3]

Partial pluripotent reprogramming can reverse features of aging in mammalian cells, but the impact on somatic identity and the necessity of individual reprogramming factors remain unknown. Here, we used single-cell genomics to map the identity trajectory induced by partial reprogramming in multiple murine cell types and dissected the influence of each factor by screening all Yamanaka Factor subsets with pooled single-cell screens. We found that partial reprogramming restored youthful expression in adipogenic and mesenchymal stem cells but also temporarily suppressed somatic identity programs. Our pooled screens revealed that many subsets of the Yamanaka Factors both restore youthful expression and suppress somatic identity, but these effects were not tightly entangled. We also found that a multipotent reprogramming strategy inspired by amphibian regeneration restored youthful expression in myogenic cells. Our results suggest that various sets of reprogramming factors can restore youthful expression with varying degrees of somatic identity suppression. A record of this paper's Transparent Peer Review process is included in the supplemental information.

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The relationship between epigenetic age and the hallmarks of ageing in human cells

Sylwia Kabacik, Donna Lowe, Leonie Fransen, Martin Leonard, Siew-Lan Ang, Christopher Whiteman, Sarah Corsi, Howard Cohen, Sarah Felton, Radhika Bali, Steve Horvath & Ken Raj

Epigenetic clocks are mathematically derived age estimators that are based on combinations of methylation values that change with age at specific CpGs in the genome. These clocks are widely used to measure the age of tissues and cells[1,2]. The discrepancy between epigenetic age (EpiAge), as estimated by these clocks, and chronological age is referred to as EpiAge acceleration. Epidemiological studies have linked EpiAge acceleration to a wide variety of pathologies, health states, lifestyle, mental state and environmental factors[2], indicating that epigenetic clocks tap into critical biological processes that are involved in aging. Despite the importance of this inference, the mechanisms underpinning these clocks remained largely uncharacterized and unelucidated. Here, using primary human cells, we set out to investigate whether epigenetic aging is the manifestation of one or more of the aging hallmarks previously identified[3]. We show that although epigenetic aging is distinct from cellular senescence, telomere attrition and genomic instability, it is associated with nutrient sensing, mitochondrial activity and stem cell composition.

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eClock: An ensemble-based method to accurately predict ages with a biased distribution from DNA methylation data

Yu Liu

Published: May 6, 2022 • https://doi.org/10.1371/journal.pone.0267349

Abstract

DNA methylation is closely related to senescence, so it has been used to develop statistical models, called clock models, to predict chronological ages accurately. However, because the training data always have a biased age distribution, the model performance becomes weak for the samples with a small age distribution density. To solve this problem, we developed the R package *eClock*, which uses a bagging-SMOTE method to adjust the biased distribution and predict age with an ensemble model. Moreover, it also provides a bootstrapped model based on bagging only and a traditional clock model. The performance on three datasets showed that the bagging-SMOTE model significantly improved rare sample age prediction. In addition to model construction, the package also provides other functions such as data visualization and methylation feature conversion to facilitate the research in relevant areas.

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Large-scale chromatin reorganization reactivates placenta-specific genes that drive cellular aging

Nuclear deformation, a hallmark frequently observed in senescent cells, is presumed to be associated with the erosion of chromatin organization at the nuclear periphery. However, how such gradual changes in higher-order genome organization impinge on local epigenetic modifications to drive cellular mechanisms of aging has remained enigmatic. Here, through large-scale epigenomic analyses of isogenic young, senescent, and progeroid human mesenchymal progenitor cells (hMPCs), we delineate a hierarchy of integrated structural state changes that manifest as heterochromatin loss in repressive compartments, euchromatin weakening in active compartments, switching in interfacing topological compartments, and increasing epigenetic entropy. We found that the epigenetic de-repression unlocks the expression of pregnancy-specific beta-1 glycoprotein (*PSG*) genes that exacerbate hMPC aging and serve as potential aging biomarkers. Our analyses provide a rich resource for uncovering the principles of epigenomic landscape organization and its changes in cellular aging and for identifying aging drivers and intervention targets with a genome-topology-based mechanism.

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Evidence that conserved essential genes are enriched for pro-longevity factors

Naci Oz, Elena M. Vayndorf, Mitsuhiro Tsuchiya, Samantha McLean, Lesly Turcios-Hernandez, Jason N. Pitt, Benjamin W. Blue, Michael Muir, Michael G. Kiflezghi, Alexander Tyshkovskiy, Alexander Mendenhall, Matt Kaeberlein ✉ & Alaattin Kaya ✉

GeroScience (2022) | Cite this article

Abstract

At the cellular level, many aspects of aging are conserved across species. This has been demonstrated by numerous studies in simple model organisms like *Saccharomyces cerevisiae*, *Caenorhabdits elegans*, and *Drosophila melanogaster*. Because most genetic screens examine loss of function mutations or decreased expression of genes through reverse genetics, essential genes have often been overlooked as potential modulators of the aging process. By taking the approach of increasing the expression level of a subset of conserved essential genes, we found that 21% of these genes resulted in increased replicative lifespan in *S. cerevisiae*. This is greater than the ~ 3.5% of genes found to affect lifespan upon deletion, suggesting that activation of essential genes may have a relatively disproportionate effect on increasing lifespan. The results of our experiments demonstrate that essential gene overexpression is a rich, relatively unexplored means of increasing eukaryotic lifespan.

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PREPRINT

Tissue-specific impacts of aging and genetics on gene expression patterns in humans

Ryo Yamamoto, Ryan Chung, Juan Manuel Vazquez, Huanjie Sheng, Philippa Steinberg, Nilah M Ioannidis, Peter H Sudmant

Age is the primary risk factor for many common human diseases including heart disease, Alzheimer's dementias, cancers, and diabetes. Determining how and why tissues age differently is key to understanding the onset and progression of such pathologies. Here, we set out to quantify the relative contributions of genetics and aging to gene expression patterns from data collected across 27 tissues from 948 humans. We show that age impacts the predictive power of expression quantitative trait loci across several tissues. Jointly modelling the contributions of age and genetics to transcript level variation we find that the heritability (h^2) of gene expression is largely consistent among tissues. In contrast, the average contribution of aging to gene expression variance varied by more than 20-fold among tissues with Embedded Image in 5 tissues. We find that the coordinated decline of mitochondrial and translation factors is a widespread signature of aging across tissues. Finally, we show that while in general the force of purifying selection is stronger on genes expressed early in life compared to late in life as predicted by Medawar's hypothesis, a handful of highly proliferative tissues exhibit the opposite pattern. These *non-Medawarian* tissues exhibit high rates of cancer and age-of-expression associated somatic mutations in cancer. In contrast, gene expression variation that is under genetic control is strongly enriched for genes under relaxed constraint. Together we present a novel framework for predicting gene expression phenotypes from genetics and age and provide insights into the tissue-specific relative contributions of genes and the environment to phenotypes of aging.

Intermediate alleles of HTT: A new pathway in longevity

Assunta Ingannato [a], Silvia Bagnoli [a], Valentina Bessi [a], Camilla Ferrari [a], Salvatore Mazzeo [a, b], Sandro Sorbi [a, b], Benedetta Nacmias [a, b]

Centenarians are the best example of successful aging, reaching extreme longevity escaping age-related diseases. Genome sequencing studies provided evidence for genetic factors linked to heathy long life, including genes related to age-dependent diseases. HTT (Huntingtin) gene is linked to Huntington's Disease, but also associated to longevity in capuchins and mice. HTT Intermediate alleles (IAs) are defined as CAG repeat expansion between 27 and 35. According to recent data IAs might increase Alzheimer's Disease risk, but also might have a neuroprotective effect and can confer an advantage in brain development. Here, we investigated, for the first time, the possible implication of HTT IAs in extreme longevity and their possible association in cognitive decline. We analysed the distribution of IAs in Italian Centenarians ($n = 143$) and compared with pathological controls with cognitive decline ($n = 232$, including 80 Alzheimer's Disease, 78 Frontotemporal Dementia and 74 Subjective Cognitive Decline patients) and healthy controls ($n = 104$). Our data show a statistically significant higher frequency of IAs in Centenarians with respect to pathological controls with cognitive decline ($\mathbf{p = .031}$; OR = 2.3097 95% CI 1.0591 to 5.0371), with a percentage of 11.2 respect to 5.4 respectively. The highest presence of IAs in Centenarians confirms and extends in humans a possible implication of HTT gene in exceptional lifespan and in brain development with a neuroprotective effect.

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Artificially stimulating retrotransposon activity increases mortality and accelerates a subset of aging phenotypes in *Drosophila*

Joyce Rigal, Ane Martin Anduaga, Elena Bitman, Emma Rivellese, Sebastian Kadener, Michael T. Marr II

Transposable elements (TE) are mobile sequences of DNA that can become transcriptionally active as an animal ages. Whether TE activity is simply a byproduct of heterochromatin breakdown or can contribute towards the aging process is not known. Here we place the TE *gypsy* under the control of the UAS GAL4 system to model TE activation during aging. We find that increased TE activity shortens the lifespan of male *D. melanogaster*. The effect is only apparent in middle aged animals. The increase in mortality is not seen in young animals. An intact reverse transcriptase is necessary for the decrease in lifespan implicating a DNA mediated process in the effect. The decline in lifespan in the active *gypsy* flies is accompanied by the acceleration of a subset of aging phenotypes. TE activity increases sensitivity to oxidative stress and promotes a decline in circadian rhythmicity. The overexpression of the Forkhead-box O family (FOXO) stress response transcription factor can partially rescue the detrimental effects of increased TE activity on lifespan. Our results provide evidence that active TEs can behave as effectors in the aging process and suggest a potential novel role for dFOXO in its promotion of longevity in *D. melanogaster*.

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Clonal dynamics of haematopoiesis across the human lifespan

Emily Mitchell, Michael Spencer Chapman, ... Peter J. Campbell ✉ + Show authors

Age-related change in human haematopoiesis causes reduced regenerative capacity[1], cytopenias[2], immune dysfunction[3] and increased risk of blood cancer[4,5,6], but the reason for such abrupt functional decline after 70 years of age remains unclear. Here we sequenced 3,579 genomes from single cell-derived colonies of haematopoietic cells across 10 human subjects from 0 to 81 years of age. Haematopoietic stem cells or multipotent progenitors (HSC/MPPs) accumulated a mean of 17 mutations per year after birth and lost 30 base pairs per year of telomere length. Haematopoiesis in adults less than 65 years of age was massively polyclonal, with high clonal diversity and a stable population of 20,000–200,000 HSC/MPPs contributing evenly to blood production. By contrast, haematopoiesis in individuals aged over 75 showed profoundly decreased clonal diversity. In each of the older subjects, 30–60% of haematopoiesis was accounted for by 12–18 independent clones, each contributing 1–34% of blood production. Most clones had begun their expansion before the subject was 40 years old, but only 22% had known driver mutations. Genome-wide selection analysis estimated that between 1 in 34 and 1 in 12 non-synonymous mutations were drivers, accruing at constant rates throughout life, affecting more genes than identified in blood cancers. Loss of the Y chromosome conferred selective benefits in males. Simulations of haematopoiesis, with constant stem cell population size and constant acquisition of driver mutations conferring moderate fitness benefits, entirely explained the abrupt change in clonal structure in the elderly. Rapidly decreasing clonal diversity is a universal feature of haematopoiesis in aged humans, underpinned by pervasive positive selection acting on many more genes than currently identified.

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SGLT2 inhibition attenuates arterial dysfunction and decreases vascular F-actin content and expression of proteins associated with oxidative stress in aged mice

Aging of the vasculature is characterized by endothelial dysfunction and arterial stiffening, two key events in the pathogenesis of cardiovascular disease (CVD). Treatment with sodium glucose transporter 2 (SGLT2) inhibitors is now known to decrease cardiovascular morbidity and mortality in type 2 diabetes. However, whether SGLT2 inhibition attenuates vascular aging is unknown. We first confirmed in a cohort of adult subjects that aging is associated with impaired endothelial function and increased arterial stiffness and that these two variables are inversely correlated. Next, we investigated whether SGLT2 inhibition with empagliflozin (Empa) ameliorates endothelial dysfunction and reduces arterial stiffness in aged mice with confirmed vascular dysfunction. Specifically, we assessed mesenteric artery endothelial function and stiffness (via flow-mediated dilation and pressure myography mechanical responses, respectively) and aortic stiffness (in vivo via pulse wave velocity and ex vivo via atomic force microscopy) in Empa-treated (14 mg/kg/day for 6 weeks) and control 80-week-old C57BL/6 J male mice. We report that Empa-treated mice exhibited improved mesenteric endothelial function compared with control, in parallel with reduced mesenteric artery and aortic stiffness. Additionally, Empa-treated mice had greater vascular endothelial nitric oxide synthase activation, lower phosphorylated cofilin, and filamentous actin content, with downregulation of pathways involved in production of reactive oxygen species. Our findings demonstrate that Empa improves endothelial function and reduces arterial stiffness in a preclinical model of aging, making SGLT2 inhibition a potential therapeutic alternative to reduce the progression of CVD in older individuals.

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Methods Mol Biol. 2022;2399:193-218. doi: 10.1007/978-1-0716-1831-8_9.

Unraveling Pathways of Health and Lifespan with Integrated Multiomics Approaches

Miguel A Aon [# 1 2], Michel Bernier [# 1], Rafael de Cabo [3]

Affiliations + expand

PMID: 35604558 DOI: 10.1007/978-1-0716-1831-8_9

Abstract

Distinct and shared pathways of health and lifespan can be untangled following a concerted approach led by experimental design and a rigorous analytical strategy where the confounding effects of diet and feeding regimens can be dissected. In this chapter, we use integrated analysis of multiomics (transcriptomics-metabolomics) data in liver from mice to gain insight into pathways associated with improved health and survival. We identify a unique metabolic hub involving glycine-serine-threonine metabolism at the core of lifespan, and a pattern of shared pathways related to improved health.

Keywords: Computational systems biology; Diet; Gene and functional ontologies; Healthy aging; Integrated pathway analysis; Time-restricted feeding; Topology-based pathway network analysis.

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Genetic trade-offs between complex diseases and longevity

Dingxue Hu, Yan Li, Detao Zhang, Jiahong Ding, Zijun Song, Junxia Min, Yi Zeng, Chao Nie

First published: 26 June 2022 | https://doi.org/10.1111/acel.13654

Dingxue Hu and Yan Li are contributed equally to this work.

Abstract

Longevity was influenced by many complex diseases and traits. However, the relationships between human longevity and genetic risks of complex diseases were not broadly studied. Here, we constructed polygenic risk scores (PRSs) for 225 complex diseases/traits and evaluated their relationships with human longevity in a cohort with 2178 centenarians and 2299 middle-aged individuals. Lower genetic risks of stroke and hypotension were observed in centenarians, while higher genetic risks of schizophrenia (SCZ) and type 2 diabetes (T2D) were detected in long-lived individuals. We further stratified PRSs into cell-type groups and significance-level groups. The results showed that the immune component of SCZ genetic risk was positively linked to longevity, and the renal component of T2D genetic risk was the most deleterious. Additionally, SNPs with very small *p*-values ($p \leq 1x10^{-5}$) for SCZ and T2D were negatively correlated with longevity. While for the less significant SNPs ($1x10^{-5} < p \leq 0.05$), their effects on disease and longevity were positively correlated. Overall, we identified genetically informed positive and negative factors for human longevity, gained more insights on the accumulation of disease risk alleles during evolution, and provided evidence for the theory of genetic trade-offs between complex diseases and longevity.

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Heterochronic parabiosis induces stem cell revitalization and systemic rejuvenation across aged tissues

The young circulatory milieu capable of delaying aging in individual tissues is of interest as rejuvenation strategies, but how it achieves cellular- and systemic-level effects has remained unclear. Here, we constructed a single-cell transcriptomic atlas across aged tissues/organs and their rejuvenation in heterochronic parabiosis (HP), a classical model to study systemic aging. In general, HP rejuvenated adult stem cells and their niches across tissues. In particular, we identified hematopoietic stem and progenitor cells (HSPCs) as one of the most responsive cell types to young blood exposure, from which a continuum of cell state changes across the hematopoietic and immune system emanated, through the restoration of a youthful transcriptional regulatory program and cytokine-mediated cell-cell communications in HSPCs. Moreover, the reintroduction of the identified rejuvenating factors alleviated age-associated lymphopoiesis decline. Overall, we provide comprehensive frameworks to explore aging and rejuvenating trajectories at single-cell resolution and revealed cellular and molecular programs that instruct systemic revitalization by blood-borne factors.

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Young CSF restores oligodendrogenesis and memory in aged mice via Fgf17

Tal Iram ✉, Fabian Kern, Achint Kaur, Saket Myneni, Allison R. Morningstar, Heather Shin, Miguel A. Garcia, Lakshmi Yerra, Robert Palovics, Andrew C. Yang, Oliver Hahn, Nannan Lu, Steven R. Shuken, Michael S. Haney, Benoit Lehallier, Manasi Iyer, Jian Luo, Henrik Zetterberg, Andreas Keller, J. Bradley Zuchero & Tony Wyss-Coray ✉

Recent understanding of how the systemic environment shapes the brain throughout life has led to numerous intervention strategies to slow brain ageing[1,2,3]. Cerebrospinal fluid (CSF) makes up the immediate environment of brain cells, providing them with nourishing compounds[4,5]. We discovered that infusing young CSF directly into aged brains improves memory function. Unbiased transcriptome analysis of the hippocampus identified oligodendrocytes to be most responsive to this rejuvenated CSF environment. We further showed that young CSF boosts oligodendrocyte progenitor cell (OPC) proliferation and differentiation in the aged hippocampus and in primary OPC cultures. Using SLAMseq to metabolically label nascent mRNA, we identified serum response factor (SRF), a transcription factor that drives actin cytoskeleton rearrangement, as a mediator of OPC proliferation following exposure to young CSF. With age, SRF expression decreases in hippocampal OPCs, and the pathway is induced by acute injection with young CSF. We screened for potential SRF activators in CSF and found that fibroblast growth factor 17 (Fgf17) infusion is sufficient to induce OPC proliferation and long-term memory consolidation in aged mice while Fgf17 blockade impairs cognition in young mice. These findings demonstrate the rejuvenating power of young CSF and identify Fgf17 as a key target to restore oligodendrocyte function in the ageing brain.

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Transcriptomic Signatures of Telomerase-Dependent and -Independent Ageing, in the Zebrafish gut and Brain

Raquel R. Martins, Michael Rera, Catarina M. Henriques

Telomerase is best known for its role in the maintenance of telomere length and its implications for ageing and cancer. The mechanisms, kinetics and tissue-specificity underlying the protective or deleterious mechanisms of telomerase, however, remain largely unknown. Here, we sought to determine the telomerase-dependent and -independent transcriptomic changes with ageing, in the gut and brain, as examples of high and low proliferative tissues, respectively. We hypothesised this could shed light on common telomerase-dependent and -independent therapeutic targets aimed at preventing or ameliorating age-associated dysfunction in both tissues. For this, we used the zebrafish model which, similarly to humans, depends on telomerase for health- and lifespan. We performed whole tissue RNA sequencing of gut and brain, in naturally aged zebrafish alongside prematurely aged telomerase null mutants (tert-/-), throughout their lifespan. Our study highlights stem cell exhaustion as the first main hallmark of ageing to be de-regulated in WT zebrafish gut and brain. Towards the end of life, altered intercellular communication becomes the main hallmark of ageing de-regulated in both gut and brain, and this is accelerated in both tissues, in the absence of telomerase. Finally, we identify 7 key gene changes common between the gut and brain at the early stages of ageing, highlighting potential early intervention therapeutic targets for preventing age-associated dysfunction in both tissues.

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Telomeric 8-oxo-guanine drives rapid premature senescence in the absence of telomere shortening

Ryan P. Barnes, Mariarosaria de Rosa, Sanjana A. Thosar, Ariana C. Detwiler, Vera Roginskaya, Bennett Van Houten, Marcel P. Bruchez, Jacob Stewart-Ornstein & Patricia L. Opresko

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Abstract

Oxidative stress is a primary cause of cellular senescence and contributes to the etiology of numerous human diseases. Oxidative damage to telomeric DNA has been proposed to cause premature senescence by accelerating telomere shortening. Here, we tested this model directly using a precision chemoptogenetic tool to produce the common lesion 8-oxo-guanine (8oxoG) exclusively at telomeres in human fibroblasts and epithelial cells. A single induction of telomeric 8oxoG is sufficient to trigger multiple hallmarks of p53-dependent senescence. Telomeric 8oxoG activates ATM and ATR signaling, and enriches for markers of telomere dysfunction in replicating, but not quiescent cells. Acute 8oxoG production fails to shorten telomeres, but rather generates fragile sites and mitotic DNA synthesis at telomeres, indicative of impaired replication. Based on our results, we propose that oxidative stress promotes rapid senescence by producing oxidative base lesions that drive replication-dependent telomere fragility and dysfunction in the absence of shortening and shelterin loss.

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Small-molecule activation of OGG1 increases oxidative DNA damage repair by gaining a new function

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Oxidative DNA damage is recognized by 8-oxoguanine (8-oxoG) DNA glycosylase 1 (OGG1), which excises 8-oxoG, leaving a substrate for apurinic endonuclease 1 (APE1) and initiating repair. Here, we describe a small molecule (TH10785) that interacts with the phenylalanine-319 and glycine-42 amino acids of OGG1, increases the enzyme activity 10-fold, and generates a previously undescribed β,δ-lyase enzymatic function. TH10785 controls the catalytic activity mediated by a nitrogen base within its molecular structure. In cells, TH10785 increases OGG1 recruitment to and repair of oxidative DNA damage. This alters the repair process, which no longer requires APE1 but instead is dependent on polynucleotide kinase phosphatase (PNKP1) activity. The increased repair of oxidative DNA lesions with a small molecule may have therapeutic applications in various diseases and aging.

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Inference of age-associated transcription factor regulatory activity changes in single cells

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Abstract

Transcription factors (TFs) control cell identity and function. How their activity is altered during healthy aging is critical for an improved understanding of aging and disease risk, yet relatively little is known about such changes at cell-type resolution. Here we present and validate a TF activity estimation method for single cells from the hematopoietic system that is based on TF regulons, and apply it to a mouse single-cell RNA-sequencing atlas, to infer age-associated differentiation activity changes in the immune cells of different organs. This revealed an age-associated signature of macrophage dedifferentiation, which is shared across tissue types, and aggravated in tumor-associated macrophages. By extending the analysis to all major cell types, we reveal cell-type and tissue-type-independent age-associated alterations to regulatory factors controlling antigen processing, inflammation, collagen processing and circadian rhythm, that are implicated in age-related diseases. Finally, our study highlights the limitations of using TF expression to infer age-associated changes, underscoring the need to use regulatory activity inference methods.

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Molecular mechanisms of exceptional lifespan increase of *Drosophila melanogaster* with different genotypes after combinations of pro-longevity interventions

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Abstract

Aging is one of the global challenges of our time. The search for new anti-aging interventions is also an issue of great actuality. We report on the success of *Drosophila melanogaster* lifespan extension under the combined influence of dietary restriction, co-administration of berberine, fucoxanthin, and rapamycin, photodeprivation, and low-temperature conditions up to 185 days in w^{1118} strain and up to 213 days in long-lived *E(z)/w* mutants. The trade-off was found between longevity and locomotion. The transcriptome analysis showed an impact of epigenetic alterations, lipid metabolism, cellular respiration, nutrient sensing, immune response, and autophagy in the registered effect.

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Dietary restriction and the transcription factor clock delay eye aging to extend lifespan in Drosophila Melanogaster

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Free PMC article

Abstract

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 Drosophila melanogaster by promoting circadian homeostatic processes that protect the visual system from age- and light-associated damage. Altering the positive limb core molecular clock transcription factor, CLOCK, or CLOCK-output genes, accelerates visual senescence, induces a systemic immune response, and shortens lifespan. Flies subjected to dietary restriction are protected from the lifespan-shortening effects of photoreceptor activation. Inversely, photoreceptor inactivation, achieved via mutating rhodopsin or housing flies in constant darkness, primarily extends the lifespan of flies reared on a high-nutrient diet. Our findings establish the eye as a diet-sensitive modulator of lifespan and indicates that vision is an antagonistically pleiotropic process that contributes to organismal aging.

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Comparative transcriptomics reveals circadian and pluripotency networks as two pillars of longevity regulation

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Mammals differ more than 100-fold in maximum lifespan. Here, we conducted comparative transcriptomics on 26 species with diverse lifespans. We identified thousands of genes with expression levels negatively or positively correlated with a species' maximum lifespan (Neg- or Pos-MLS genes). Neg-MLS genes are primarily involved in energy metabolism and inflammation. Pos-MLS genes show enrichment in DNA repair, microtubule organization, and RNA transport. Expression of Neg- and Pos-MLS genes is modulated by interventions, including mTOR and PI3K inhibition. Regulatory networks analysis showed that Neg-MLS genes are under circadian regulation possibly to avoid persistent high expression, whereas Pos-MLS genes are targets of master pluripotency regulators OCT4 and NANOG and are upregulated during somatic cell reprogramming. Pos-MLS genes are highly expressed during embryogenesis but significantly downregulated after birth. This work provides targets for anti-aging interventions by defining pathways correlating with longevity across mammals and uncovering circadian and pluripotency networks as central regulators of longevity.

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Lipid metabolism dysfunction induced by age-dependent DNA methylation accelerates aging

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Signal Transduction and Targeted Therapy **7**, Article number: 162 (2022) | Cite this article

Abstract

Epigenetic alterations and metabolic dysfunction are two hallmarks of aging. However, the mechanism of how their interaction regulates aging, particularly in mammals, remains largely unknown. Here we show ELOVL fatty acid elongase 2 (Elovl2), a gene whose epigenetic alterations are most highly correlated with age prediction, contributes to aging by regulating lipid metabolism. We applied artificial intelligence to predict the protein structure of ELOVL2 and the interaction with its substrate. Impaired Elovl2 function disturbs lipid synthesis with increased endoplasmic reticulum stress and mitochondrial dysfunction, leading to key aging phenotypes at both cellular and physiological level. Furthermore, restoration of mitochondrial activity can rescue age-related macular degeneration (AMD) phenotypes induced by Elovl2 deficiency in human retinal pigmental epithelial (RPE) cells; this indicates a conservative mechanism in both human and mouse. Taken together, we revealed an epigenetic-metabolism axis contributing to aging and illustrate the power of an AI-based approach in structure-function studies.

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PREPRINT

Insulin signaling and extended longevity in ants

In most organisms, the cost of reproduction is a shorter lifespan. However, the reproductive caste in eusocial insect species (queen) exhibits an extraordinarily longer lifespan than non-reproductive castes (workers) despite having a similar genome, thus contradicting the aging dogma. In the absence of the queen, *Harpegnathos saltator* ants can undergo a caste switch from workers to reproductive pseudo-queens (gamergates). Gamergates exhibit a dramatically prolonged lifespan. When placed in the presence of a reproductive, they revert to worker status and their lifespan is then shortened accordingly.

To understand this unique relationship between reproduction and longevity, we analyzed tissue-specific gene expression between castes. Insulin is upregulated in the gamergate brain that leads to oogenesis, but surprisingly correlates with extended longevity. This correlates with increased lipid synthesis and elevated production of vitellogenin in the fat body, which are both transported to the egg. We show that the production of vitellogenin in the fat body is due to the systemic activation of the MAPK branch of the insulin/IGF signaling (IIS)-pathway. In contrast, reduced expression of insulin receptors in the fat body of gamergates and the production in their developing ovary of an anti-insulin (Imp-L2) lead to the downregulation of the AKT/FOXO branch of the IIS-signaling pathway in the fat body, and to the dramatically extended longevity. This reveals a dual-pathway mechanism that reconciles increased longevity in the context of active reproduction in eusocial insects.

One Sentence Summary Insulin-dependent reproduction in ants correlates with extended longevity through insulin inhibition by anti-insulin Imp-L2.

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PREPRINT

The use of non-model *Drosophila* species to study natural variation in TOR pathway signaling

Nutrition and growth are strongly linked, but not much is known about how nutrition leads to growth. To understand the connection between nutrition through the diet, growth, and proliferation, we need to study the phenotypes resulting from the activation and inhibition of central metabolic pathways. One of the most highly conserved metabolic pathways across eukaryotes is the Target of Rapamycin (TOR) pathway, whose primary role is to detect the availability of nutrients and to either induce or halt cellular growth. Here we used the model organism Drosophila melanogaster (D. mel .) and three non-model Drosophila species with different dietary needs, Drosophila guttifera (D. gut .), Drosophila deflecta (D. def .), and Drosophila tripunctata (D. tri .), to study the effects of dietary amino acid availability on fecundity and longevity. In addition, we inhibited the Target of Rapamycin (TOR) pathway, using rapamycin, to test how the inhibition interplays with the nutritional stimuli in these four fruit fly species. We hypothesized that the inhibition of the TOR pathway would reverse the phenotypes observed under conditions of overfeeding. Our results show that female fecundity increased with higher yeast availability in all four species but decreased in response to TOR inhibition. The longevity data were more varied: most species experienced an increase in median lifespan in both genders with an increase in yeast availability, while the lifespan of D. mel. females decreased. When exposed to the TOR inhibitor rapamycin, the life spans of most species decreased, except for D. tri, while we observed a major reduction in fecundity across all species. The obtained data can benefit future studies on the evolution of metabolism by showing the potential of using non-model species to track changes in metabolism. Particularly, our data show the possibility to use relatively closely related Drosophila species to gain insight on the evolution of TOR signaling.

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PREPRINT

Aging causes changes in transcriptional noise across a diverse set of cell types

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Abstract

Aging and its associated diseases result from complex changes in cell state which can be examined with single-cell transcriptomic approaches. We analyzed gene expression noise, a measure of cellular heterogeneity, across age and many cell types and tissues using the single cell atlas *Tabula Muris Senis*, and characterized the noise properties of most coding genes. We developed a quantitative, well-calibrated statistical model of single-cell RNAseq measurement from which we sensitively detected changes in gene expression noise. We found thousands of genes with significantly changing gene expression noise with age. Not all genes had increasing noise with age—many showed a robust decreases of noise. There were clear biological correlation between subsets of genes, with a systemic decrease of noise in oxidative phosphorylation pathways while immune pathways involved in antigen presentation saw an increase. These effects were seen robustly across cell types and tissues, impacting many organs of healthy, aging mice.

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Skin Aging in Long-Lived Naked Mole-Rats is Accompanied by Increased Expression of Longevity-Associated and Tumor Suppressor Genes

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Naked mole rats (NMRs, *Heterocephalus glaber*) are long-lived mammals that possess a natural resistance to cancer and other age-related pathologies, maintaining a healthy life span for >30 years. Here, using immunohistochemical and RNAseq analyses, we compare skin morphology, cellular composition and global transcriptome signatures between young and aged (3-4 versus 19-23-year-old) NMRs. We demonstrate that similar to human skin, aging in NMRs is accompanied by a decrease of epidermal thickness, keratinocyte proliferation, and a decline in the number of Merkel cells, T-cells, antigen-presenting cells and melanocytes. Similar to human skin aging, expression levels of dermal collagens are decreased, while Mmp-9 and Mmp-11 levels increased in aged versus young NMR skin. RNAseq analyses reveal that in contrast to human or mouse skin aging, the transcript levels of several longevity-associated (*Igfbp3, Igf2bp3, Ing2*) and tumor-suppressor genes (*Btg2, Cdkn1a, Cdkn2c, Dnmt3a, Hic1, Socs3, Sfrp1, Sfrp5, Thbs1, Tsc1, Zfp36*) are increased in aged NMR skin. Overall, these data suggest that specific features in the NMR skin aging transcriptome might contribute to the resistance of NMRs to spontaneous skin carcinogenesis and provide a platform for further investigations of NMRs as a model organism for studying the biology and disease resistance of human skin.

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PREPRINT

Dysregulation of ADAM10 shedding activity as a mechanism of cancer resistance in the naked mole-rat

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Abstract

The naked mole-rat (NMR, Heterocephalus glaber) is of significant interest to biogerontological research, rarely developing age-associated diseases, such as cancer. The transmembrane glycoprotein CD44 is upregulated in certain cancers and CD44 cleavage by a disintegrin and metalloproteinase 10 (ADAM10) regulates cellular migration. Here we provide evidence that altered CD44 signalling may be involved in NMR cancer resistance. Although mature ADAM10 is expressed in primary NMR skin fibroblasts, and ionomycin increases cell surface ADAM10 localization, we observed an absence of endogenous CD44 shedding, as well as of exogenous and overexpressed betacellulin, whereas ionomycin induced ADAM10-dependent cleavage of CD44 and betacellulin in mouse primary skin fibroblasts. Overexpressing a hyperactive form of the Ca2+-dependent phospholipid scramblase ANO6 in NMR primary skin fibroblasts increased phosphatidylserine externalization, rescuing the ADAM10 sheddase activity and promoting wound closure. These findings suggest that dysregulation of ADAM10 shedding activity may contribute to the NMR's cancer resistance.

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Comparative Study of Protein Aggregation Propensity and Mutation Tolerance Between Naked Mole-Rat and Mouse

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The molecular mechanisms of aging and life expectancy have been studied in model organisms with short lifespans. However, long-lived species may provide insights into successful strategies for healthy aging, potentially opening the door for novel therapeutic interventions in age-related diseases. Notably, naked mole-rats, the longest-lived rodent, present attenuated aging phenotypes compared with mice. Their resistance toward oxidative stress has been proposed as one hallmark of their healthy aging, suggesting their ability to maintain cell homeostasis, specifically their protein homeostasis. To identify the general principles behind their protein homeostasis robustness, we compared the aggregation propensity and mutation tolerance of naked mole-rat and mouse orthologous proteins. Our analysis showed no proteome-wide differential effects in aggregation propensity and mutation tolerance between these species, but several subsets of proteins with a significant difference in aggregation propensity. We found an enrichment of proteins with higher aggregation propensity in naked mole-rat, and these are functionally involved in the inflammasome complex and nucleic acid binding. On the other hand, proteins with lower aggregation propensity in naked mole-rat have a significantly higher mutation tolerance compared with the rest of the proteins. Among them, we identified proteins known to be associated with neurodegenerative and age-related diseases. These findings highlight the intriguing hypothesis about the capacity of the naked mole-rat proteome to delay aging through its proteomic intrinsic architecture.

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Human organ rejuvenation by VEGF-A: Lessons from the skin

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Transplanting aged human skin onto young SCID/beige mice morphologically rejuvenates the xenotransplants. This is accompanied by angiogenesis, epidermal repigmentation, and substantial improvements in key aging-associated biomarkers, including ß-galactosidase, $p16^{ink4a}$, SIRT1, PGC1α, collagen 17A, and MMP1. Angiogenesis- and hypoxia-related pathways, namely, vascular endothelial growth factor A (VEGF-A) and HIF1A, are most up-regulated in rejuvenated human skin. This rejuvenation cascade, which can be prevented by VEGF-A–neutralizing antibodies, appears to be initiated by murine VEGF-A, which then up-regulates VEGF-A expression/secretion within aged human skin. While intradermally injected VEGF-loaded nanoparticles suffice to induce a molecular rejuvenation signature in aged human skin on old mice, VEGF-A treatment improves key aging parameters also in isolated, organ-cultured aged human skin, i.e., in the absence of functional skin vasculature, neural, or murine host inputs. This identifies VEGF-A as the first pharmacologically pliable master pathway for human organ rejuvenation in vivo and demonstrates the potential of our humanized mouse model for clinically relevant aging research.

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Slow and negligible senescence among testudines challenges evolutionary theories of senescence

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Is senescence inevitable and universal for all living organisms, as evolutionary theories predict? Although evidence generally supports this hypothesis, it has been proposed that certain species, such as turtles and tortoises, may exhibit slow or even negligible senescence—i.e., avoiding the increasing risk of death from gradual deterioration with age. In an extensive comparative study of turtles and tortoises living in zoos and aquariums, we show that ~75% of 52 species exhibit slow or negligible senescence. For ~80% of species, aging rates are lower than those in modern humans. We find that body weight positively relates to adult life expectancy in both sexes, and sexual size dimorphism explains sex differences in longevity. Unlike humans and other species, we show that turtles and tortoises may reduce senescence in response to improvements in environmental conditions.

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Diverse aging rates in ectothermic tetrapods provide insights for the evolution of aging and longevity

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Comparative studies of mortality in the wild are necessary to understand the evolution of aging; yet, ectothermic tetrapods are underrepresented in this comparative landscape, despite their suitability for testing evolutionary hypotheses. We present a study of aging rates and longevity across wild tetrapod ectotherms, using data from 107 populations (77 species) of nonavian reptiles and amphibians. We test hypotheses of how thermoregulatory mode, environmental temperature, protective phenotypes, and pace of life history contribute to demographic aging. Controlling for phylogeny and body size, ectotherms display a higher diversity of aging rates compared with endotherms and include phylogenetically widespread evidence of negligible aging. Protective phenotypes and life-history strategies further explain macroevolutionary patterns of aging. Analyzing ectothermic tetrapods in a comparative context enhances our understanding of the evolution of aging.

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PREPRINT

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

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

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PREPRINT

Time-resolved transcriptomic profiling of senescence-associated secretory phenotype (SASP) in multiple senescent cell subtypes

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ABSTRACT

Cellular senescence, irreversible cell cycle arrest, is induced by various triggers including telomere shortening, oncogene activation, and DNA damage. Senescent cells exhibit the senescence-associated secretory phenotype (SASP), a pathological feature that contributes to organismal aging. We previously showed that transient plasma membrane damage (PMD) induces a novel subtype of cellular senescence (PMDS) accompanied by SASP, but the overall expression profiles of SASP during PMDS induction was unknown. Here, using mRNA-seq, qPCR, and bioinformatics, we revealed the time-resolved SASP transcriptomic profile in PMDS in comparison with calcium influx-induced senescence, DNA damage response-induced senescence, and replicative senescence. Although the expression of SASP factors was postulated to increase steadily during senescence, we counterintuitively found that the variety of SASP peaks in early PMDS. The pathway comparison analyses and Ingenuity Pathway Analysis suggest that, in early PMDS, wound-healing SASP factors, namely *Il-6*, *Mmp1*, and *Mmp3*, inhibit the GPVI collagen signaling pathway, which in turn further upregulates the same SASP factors, forming a feedback loop. At late senescence, common SASP factors including *Il-6* and *Ccl2* are upregulated in all senescent cell subtypes. Thus, SASP is diverse at early senescence and becomes relatively uniform at late senescence. Diverse SASP may contribute to senescent cell subtype-specific paracrine/autocrine functions in vivo.

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Senescence-induced endothelial phenotypes underpin immune-mediated senescence surveillance

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Abstract

Senescence is a stress-responsive tumor suppressor mechanism associated with expression of the senescence-associated secretory phenotype (SASP). Through the SASP, senescent cells trigger their own immune-mediated elimination, which if evaded leads to tumorigenesis. Senescent parenchymal cells are separated from circulating immunocytes by the endothelium, which is targeted by microenvironmental signaling. Here we show that SASP induces endothelial cell NF-κB activity and that SASP-induced endothelial expression of the canonical NF-κB component *Rela* underpins senescence surveillance. Using human liver sinusoidal endothelial cells (LSECs), we show that SASP-induced endothelial NF-κB activity regulates a conserved transcriptional program supporting immunocyte recruitment. Furthermore, oncogenic hepatocyte senescence drives murine LSEC NF-κB activity in vivo. Critically, we show two distinct endothelial pathways in senescence surveillance. First, endothelial-specific loss of *Rela* prevents development of Stat1-expressing $CD4^+$ T lymphocytes. Second, the SASP up-regulates ICOSLG on LSECs, with the ICOS-ICOSLG axis contributing to senescence cell clearance. Our results show that the endothelium is a nonautonomous SASP target and an organizing center for immune-mediated senescence surveillance.

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PREPRINT

Human skeletal muscle ageing atlas

Skeletal muscle ageing increases the incidence of age-associated frailty and sarcopenia in the elderly worldwide, leading to increased morbidity and mortality. However, our understanding of the cellular and molecular mechanisms of muscle ageing is still far from complete. Here, we generate a single-cell and single-nucleus transcriptomic atlas of skeletal muscle ageing from 15 donors across the adult human lifespan, accompanied by myofiber typing using imaging. Our atlas reveals ageing mechanisms acting across different compartments of the muscle, including muscle stem cells (MuSCs), myofibers and the muscle microenvironment. Firstly, we uncover two mechanisms driving MuSC ageing, namely a decrease in ribosome biogenesis and an increase in inflammation. Secondly, we identify a set of nuclei populations explaining the preferential degeneration of the fast-twitch myofibers and suggest two mechanisms acting to compensate for their loss. Importantly, we identify a neuromuscular junction accessory population, which helps myofiber to compensate for aged-related denervation. Thirdly, we reveal multiple microenvironment cell types contributing to the inflammatory milieu of ageing muscle by producing cytokines and chemokines to attract immune cells. Finally, we provide a comparable mouse muscle ageing atlas and further investigate conserved and specific ageing hallmarks across species. In summary, we present a comprehensive human skeletal muscle ageing resource by combining different data modalities, which significantly expands our understanding of muscle biology and ageing.

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HEALTHY LIFE EXTENSION SOCIETY

Differential effects of calorie restriction and rapamycin on age-related molecular and functional changes in skeletal muscle

Aging is a multifactorial process associated with progressive degradation of physiological integrity and function. One of the greatest factors contributing to the deleterious effects of aging is the decline of functional ability due to loss of muscle mass, strength, and function, a condition termed sarcopenia. Calorie restriction (CR) has consistently been shown to extend lifespan and delay the onset and progression of various age-related diseases, including sarcopenia. Additional anti-aging interventions that are receiving scientific attention are CR mimetics. Of these pharmacological compounds, rapamycin has shown similar CR-related longevity benefits without the need for diet restrictions. To investigate the potential role of rapamycin as an anti-sarcopenic alternative to CR, we conducted a study in male and female C57BL/6 J mice to assess the effects of rapamycin on age-related gene expression changes in skeletal muscle associated with loss of muscle mass, strength, and function, relative to control. We hypothesize that the effects of rapamycin will closely align with CR with respect to physical function and molecular indices associated with muscle quality. Our results indicate CR and rapamycin provide partial protection against age-related decline in muscle, while engaging uniquely different molecular pathways in skeletal muscle. Our preclinical findings of the therapeutic potential of rapamycin or a CR regimen on geroprotective benefits in muscle should be extended to translational studies towards the development of effective strategies for the prevention and management of sarcopenia.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults

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Targeting mitophagy to activate the recycling of faulty mitochondria during aging is a strategy to mitigate muscle decline. We present results from a randomized, placebo-controlled trial in middle-aged adults where we administer a postbiotic compound Urolithin A (Mitopure), a known mitophagy activator, at two doses for 4 months (NCT03464500). The data show significant improvements in muscle strength (~12%) with intake of Urolithin A. We observe clinically meaningful improvements with Urolithin A on aerobic endurance (peak oxygen oxygen consumption [VO_2]) and physical performance (6 min walk test) but do not notice a significant improvement on peak power output (primary endpoint). Levels of plasma acylcarnitines and C-reactive proteins are significantly lower with Urolithin A, indicating higher mitochondrial efficiency and reduced inflammation. We also examine expression of proteins linked to mitophagy and mitochondrial metabolism in skeletal muscle and find a significant increase with Urolithin A administration. This study highlights the benefit of Urolithin A to improve muscle performance.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Mitochondrial interactome remodeling in aging mouse skeletal muscle associated with functional decline

Anna A. Bakhtina, Gavin Pharaoh, Andrew D. Keller, Rudy Stuppard, David J. Marcinek, James E. Bruce

Genomic, transcriptomic, and proteomic approaches have been employed to gain insight into molecular underpinnings of aging in laboratory animals and in humans. However, protein function in biological systems is under complex regulation and includes factors in addition to abundance levels, such as modifications, localization, conformation, and protein-protein interactions. We have applied new robust quantitative chemical cross-linking technologies to uncover changes muscle mitochondrial interactome contributing to functional decline in aging. Statistically significant age-related changes in protein cross-link levels relating to assembly of electron transport system complexes I and IV, activity of glutamate dehydrogenase, and coenzyme-A binding in fatty acid beta-oxidation and TCA enzymes were observed. These changes showed remarkable correlation with measured CI based respiration differences within the same young-old animal pairs, indicating these cross-link levels offer new molecular insight on commonly observed age-related phenotypic differences. Overall, these system-wide quantitative mitochondrial interactome data provide the first molecular-level insight on ETS complex and substrate utilization enzyme remodeling that occur during age-related mitochondrial dysfunction. Each observed cross-link can serve as a protein conformational or protein-protein interaction probe in future studies making this dataset a unique resource for many additional in-depth molecular studies that are needed to better understand complex molecular changes that occur with aging.

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Astrocytic urea cycle detoxifies Aβ-derived ammonia while impairing memory in Alzheimer's disease

Yeon Ha Ju • Mridula Bhalla • Seung Jae Hyeon • ... Hyunbeom Lee • Hoon Ryu • C. Justin Lee [9] • Show all authors • Show footnotes

Alzheimer's disease (AD) is one of the foremost neurodegenerative diseases, characterized by beta-amyloid (Aβ) plaques and significant progressive memory loss. In AD, astrocytes are proposed to take up and clear Aβ plaques. However, how Aβ induces pathogenesis and memory impairment in AD remains elusive. We report that normal astrocytes show non-cyclic urea metabolism, whereas Aβ-treated astrocytes show switched-on urea cycle with upregulated enzymes and accumulated entering-metabolite aspartate, starting-substrate ammonia, end-product urea, and side-product putrescine. Gene silencing of astrocytic ornithine decarboxylase-1 (ODC1), facilitating ornithine-to-putrescine conversion, boosts urea cycle and eliminates aberrant putrescine and its toxic byproducts ammonia and H_2O_2 and its end product GABA to recover from reactive astrogliosis and memory impairment in AD. Our findings implicate that astrocytic urea cycle exerts opposing roles of beneficial Aβ detoxification and detrimental memory impairment in AD. We propose ODC1 inhibition as a promising therapeutic strategy for AD to facilitate removal of toxic molecules and prevent memory loss.

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PREPRINT

Biological Constraint as a Cause of Aging

David Gems * and Carina Kern

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Abstract

Aging rate differs greatly between species, indicating that the process of senescence is largely genetically determined. Senescence evolves in part due to antagonistic pleiotropy (AP), where selection favors gene variants that increase fitness earlier in life but promote pathology later. Identifying the biological mechanisms by which AP causes senescence is key to understanding the endogenous causes of aging and its attendant diseases. Here we argue that the frequent occurrence of AP as a property of genes reflects the presence of constraint in the biological systems that they specify. This arises particularly because the functionally interconnected nature of biological systems constrains the simultaneous optimization of coupled traits (interconnection constraints), or because individual traits cannot evolve (impossibility constraints). We present an account of aging that integrates AP and biological constraint with recent programmatic aging concepts, including costly programs, quasi-programs, hyperfunction and hypofunction. We argue that AP mechanisms of costly programs and triggered quasi-programs are consequences of constraint, in which costs resulting from hyperfunction or hypofunction cause senescent pathology. Impossibility constraint can also cause hypofunction independently of AP. We also describe how AP corresponds to Stephen Jay Gould's constraint-based concept of evolutionary spandrels, and argue that pathologies arising from AP are bad spandrels. Biological constraint is a missing link between ultimate and proximate causes of senescence, including diseases of aging. That this was not realized previously may reflect a combination of hyperadaptationism among evolutionary biologists, and the erroneous assumption by biogerontologists that molecular damage accumulation is the principal primary cause of aging.

C. elegans aging research

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Identification of healthspan-promoting genes in Caenorhabditis elegans based on a human GWAS study

Nadine Saul [# 1], Ineke Dhondt [# 2], Mikko Kuokkanen [3 4], Markus Perola [3], Clara Verschuuren [2], Brecht Wouters [5], Henrik von Chrzanowski [6 7], Winnok H De Vos [8], Liesbet Temmerman [5], Walter Luyten [5], Aleksandra Zečić [2], Tim Loier [2], Christian Schmitz-Linneweber [6], Bart P Braeckman [2]

Affiliations + expand

PMID: 35748965 DOI: 10.1007/s10522-022-09969-8

Abstract

To find drivers of healthy ageing, a genome-wide association study (GWAS) was performed in healthy and unhealthy older individuals. Healthy individuals were defined as free from cardiovascular disease, stroke, heart failure, major adverse cardiovascular event, diabetes, dementia, cancer, chronic obstructive pulmonary disease (COPD), asthma, rheumatism, Crohn's disease, malabsorption or kidney disease. Six single nucleotide polymorphisms (SNPs) with unknown function associated with ten human genes were identified as candidate healthspan markers. Thirteen homologous or closely related genes were selected in the model organism C. elegans for evaluating healthspan after targeted RNAi-mediated knockdown using pathogen resistance, muscle integrity, chemotaxis index and the activity of known longevity and stress response pathways as healthspan reporters. In addition, lifespan was monitored in the RNAi-treated nematodes. RNAi knockdown of yap-1, wwp-1, paxt-1 and several acdh genes resulted in heterogeneous phenotypes regarding muscle integrity, pathogen resistance, chemotactic behaviour, and lifespan. Based on these observations, we hypothesize that their human homologues WWC2, CDKN2AIP and ACADS may play a role in health maintenance in the elderly.

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Ingestion of single guide RNAs induces gene overexpression and extends lifespan in *Caenorhabditis elegans via* CRISPR activation

Fabian Fischer [1] ‡ ✉, Christoph Benner [1, 2, ‡], Anita Goyala [3], Giovanna Grigolon [1], Davide Vitiello [1], JiaYee Wu [1], Kim Zarse [1, 4], Collin Y. Ewald [3], Michael Ristow [1, 4] ✉

Inhibition of gene expression in *Caenorhabditis elegans*, a versatile model organism for studying the genetics of development and aging, is achievable by feeding nematodes with bacteria expressing specific dsRNAs. Overexpression of hypoxia-inducible factor 1 (*hif-1*) or heat-shock factor 1 (*hsf-1*) by conventional transgenesis has previously been shown to promote nematodal longevity. However, it is unclear whether other methods of gene overexpression are feasible, particularly with the advent of CRISPR-based techniques. Here, we show that feeding *C. elegans* engineered to stably express a Cas9-derived synthetic transcription factor with bacteria expressing promoter-specific single guide RNAs (sgRNAs) also allows activation of gene expression. We demonstrate that CRISPR activation *via* ingested sgRNAs specific for the respective promoter regions of *hif-1* or *hsf-1* increases gene expression and extends lifespan of *C. elegans*. Furthermore, and as an *in silico* resource for future studies aiming to use CRISPR activation in *C. elegans*, we provide predicted promoter-specific sgRNA target sequences for >13,000 *C. elegans* genes with experimentally defined transcription start sites. We anticipate that the approach and components described herein will help to facilitate genome-wide gene overexpression studies, for example, to identify modulators of aging or other phenotypes of interest, by enabling induction of transcription by feeding of sgRNA-expressing bacteria to nematodes.

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PREPRINT

UNC-45 has a crucial role in maintaining muscle sarcomeres during aging in *Caenorhabditis elegans*

Courtney J. Matheny, Hiroshi Qadota, Marion Kimelman, Aaron O. Bailey, Andres F. Oberhauser, Guy M. Benian

As people live longer, age-related diseases, like sarcopenia, will become a greater public health concern. We use the model organism C. elegans to better understand the molecular mechanisms behind muscle maintenance. Muscle function is dependent on having properly organized and functioning thick filaments, which are primarily composed of myosin. The myosin head requires the chaperone UNC-45 to initially fold it after translation and is likely used to re-fold back to functionality after thermal or chemical stress induced unfolding. We observe an early onset of sarcopeania when UNC-45 is perturbed during adulthood. We observe that during adult aging, there is a sequential decline of HSP-90, UNC-45, and then myosin. Myosin and UNC-45 protein decline are independent of steady state mRNA levels. Loss of UNC-45 is correlated with an increase in phosphorylation of the protein. By mass spectrometry, S111 was identified as being phosphorylated and this modification may affect binding to HSP-90. A longevity mutant with delayed onset of sarcopenia also shows a delay in the loss of HSP-90, UNC-45, and myosin. We also see a decrease in UNC-45 protein, but not transcript, in an hsp-90 loss of function mutant, suggesting a role for HSP-90 in stabilizing UNC-45. This leads us to propose the model that during aging, a loss of HSP-90 leads to UNC-45 being post translationally modified, such as phosphorylation, and degraded, which then leads to a loss of myosin, and thus muscle mass and function. A better understanding of how myosin and its chaperone proteins are regulated and affected by aging will lead to better preventative care and treatment of sarcopenia and, possibly, the age-related decline of heart muscle function.

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PREPRINT

A lysosomal surveillance response (LySR) that reduces proteotoxicity and extends healthspan

Terytty Yang Li, Arwen W. Gao, Xiaoxu Li, Yasmine J. Liu, Rachel N. Arey, Kimberly Morales, Amélia Lalou, Qi Wang, Tanes Lima, Johan Auwerx

doi: https://doi.org/10.1101/2022.06.13.495962

Abstract

Lysosomes are cytoplasmic organelles central for the degradation of macromolecules to maintain cellular homeostasis and health. Here, we discovered an adaptive lysosomal transcriptional response that we termed the Lysosomal Surveillance Response (LySR). Typified by the induction of a large group of transcripts involved in lysosomal function and proteolysis, the LySR can be triggered by silencing of specific vacuolar H+-ATPase subunits in Caenorhabditis elegans. Notably, LySR activation enhances the clearance of protein aggregates in worm models of Alzheimer's and Huntington's disease and amyotrophic lateral sclerosis, thereby boosting fitness and extending lifespan. The GATA transcription factor, ELT-2, regulates the LySR program as well as its associated beneficial effects. In mammalian cells, overexpression of GATA4/GATA6, the mammalian orthologs of ELT-2, is sufficient to induce the expression of multiple lysosome-specific proteases and alleviate proteotoxicity. Activating the LySR pathway may therefore represent an attractive mechanism to reduce proteotoxicity and, as such, potentially extend healthspan.

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Riboflavin Depletion Promotes Longevity and Metabolic Hormesis in Caenorhabditis elegans

Armen Yerevanian, Luke Murphy, Sinclair Emans, Yifei Zhou, Fasih Ahsan, Daniel Baker, Sainan Li, Adebanjo Adedoja, Lucydalila Cedillo, Einstein Gnanatheepam, Khoi Dao, Mohit Jain, Irene Georgakoudi, Alexander A. Soukas

doi: https://doi.org/10.1101/2022.06.30.498343

Abstract

Riboflavin is an essential cofactor in many enzymatic processes and in the production of flavin adenine dinucleotide (FAD). Here we report that the partial depletion of riboflavin through knockdown of the C. elegans riboflavin transporter 1 (rft-1) promotes metabolic health by reducing intracellular flavin concentrations. Knockdown of rft-1 significantly increases lifespan in a manner dependent on FOXO/daf-16, AMP-activated protein kinase (AMPK)/aak-2, the mitochondrial unfolded protein response, and mTOR complex 2 (mTORC2). Riboflavin depletion promotes altered energetic and redox states and increases adiposity, independent of lifespan genetic dependencies. Riboflavin depleted animals also exhibit activation of caloric restriction reporters without a reduction in caloric intake. Our findings indicate that riboflavin depletion activates an integrated, hormetic response that promotes lifespan and healthspan in C. elegans.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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How ubiquitous is aging in vertebrates?

Two new studies find little evidence of aging in some turtle species

STEVEN N. AUSTAD AND CALEB E. FINCH

SCIENCE · 23 Jun 2022 · Vol 376, Issue 6600 · pp. 1384-1385 · DOI: 10.1126/science.adc9442

Abstract

The exceptional longevity of chelonians (turtles) has long been appreciated, with reliable although anecdotal reports of individuals surviving for more than 150 years, which raises the question of whether they age at all. On pages 1466 and 1459 of this issue, da Silva *et al.* (*1*) and Reinke *et al.* (*2*), respectively, evaluate survival data from various chelonians and other ectothermic (coldblooded) tetrapods, including amphibians, snakes, crocodilians, and the tuatara. They find scant evidence of demographic senescence (increased mortality with age) in a number of turtles and several other species in either zoo or wild populations.

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Semelparous Death as one Element of Iteroparous Aging Gone Large

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The aging process in semelparous and iteroparous species is different, but how different? Death in semelparous organisms (e.g., Pacific salmon) results from suicidal reproductive effort (reproductive death). Aging (senescence) in iteroparous organisms such as humans is often viewed as a quite different process. Recent findings suggest that the nematode *Caenorhabditis elegans*, widely used to study aging, undergoes reproductive death. In post-reproductive *C. elegans* hermaphrodites, intestinal biomass is repurposed to produce yolk which when vented serves as a milk to support larval growth. This apparent benefit of lactation comes at the cost of intestinal atrophy in the mother. Germline removal and inhibition of insulin/IGF-1 signaling (IIS) suppress *C. elegans* reproductive pathology and greatly increase lifespan. Blocking sexual maturity, e.g., by gonadectomy, suppresses reproductive death thereby strongly increasing lifespan in semelparous organisms, but typically has little effect on lifespan in iteroparous ones. Similarly, reduced IIS causes relatively modest increases in lifespan in iteroparous organisms. We argue that the more regulated and plastic mechanisms of senescence in semelparous organisms, involving costly resource reallocation under endocrine control, exist as one extreme of an etiological continuum with mechanisms operative in iteroparous organisms. We suggest that reproductive death evolved by exaggeration of mechanisms operative in iteroparous species, where other mechanisms also promote senescence. Thus, knowledge of *C. elegans* senescence can guide understanding of mechanisms contributing to human aging.

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Measuring biological age using omics data

Jarod Rutledge [# 1 2 3], Hamilton Oh [# 2 3 4], Tony Wyss-Coray [5 6 7]

Affiliations + expand

PMID: 35715611 DOI: 10.1038/s41576-022-00511-7

Abstract

Age is the key risk factor for diseases and disabilities of the elderly. Efforts to tackle age-related diseases and increase healthspan have suggested targeting the ageing process itself to 'rejuvenate' physiological functioning. However, achieving this aim requires measures of biological age and rates of ageing at the molecular level. Spurred by recent advances in high-throughput omics technologies, a new generation of tools to measure biological ageing now enables the quantitative characterization of ageing at molecular resolution. Epigenomic, transcriptomic, proteomic and metabolomic data can be harnessed with machine learning to build 'ageing clocks' with demonstrated capacity to identify new biomarkers of biological ageing.

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Guidelines for measuring reactive oxygen species and oxidative damage in cells and in vivo

Michael P. Murphy ✉, Hülya Bayir, Vsevolod Belousov, Christopher J. Chang, Kelvin J. A. Davies, Michael J. Davies, Tobias P. Dick, Toren Finkel, Henry J. Forman, Yvonne Janssen-Heininger, David Gems, Valerian E. Kagan, Balaraman Kalyanaraman, Nils-Göran Larsson, Ginger L. Milne, Thomas Nyström, Henrik E. Poulsen, Rafael Radi, Holly Van Remmen, Paul T. Schumacker, Paul J. Thornalley, Shinya Toyokuni, Christine C. Winterbourn, Huiyong Yin & Barry Halliwell ✉

Nature Metabolism **4**, 651–662 (2022) | Cite this article

18k Accesses | **286** Altmetric | Metrics

Abstract

Multiple roles of reactive oxygen species (ROS) and their consequences for health and disease are emerging throughout biological sciences. This development has led researchers unfamiliar with the complexities of ROS and their reactions to employ commercial kits and probes to measure ROS and oxidative damage inappropriately, treating ROS (a generic abbreviation) as if it were a discrete molecular entity. Unfortunately, the application and interpretation of these measurements are fraught with challenges and limitations. This can lead to misleading claims entering the literature and impeding progress, despite a well-established body of knowledge on how best to assess individual ROS, their reactions, role as signalling molecules and the oxidative damage that they can cause. In this consensus statement we illuminate problems that can arise with many commonly used approaches for measurement of ROS and oxidative damage, and propose guidelines for best practice. We hope that these strategies will be useful to those who find their research requiring assessment of ROS, oxidative damage and redox signalling in cells and in vivo.

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Targeting cellular senescence to combat cancer and ageing

Chen Wang, Xue Hao, Rugang Zhang

First published: 08 June 2022 | https://doi.org/10.1002/1878-0261.13266

Abstract

Senescence is a complex cellular process that is implicated in various physiological and pathological processes. It is characterized by a stable state of cell growth arrest and by a secretome of diverse pro-inflammatory factors, chemokines and growth factors. In this review, we summarize the context-dependent role of cellular senescence in ageing and in age-related diseases, such as cancer. We discuss current approaches to targeting senescence to develop therapeutic strategies to combat cancer and to promote healthy ageing, and we outline our vision for future research directions for senescence-based interventions in these fields.

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Regulation and roles of RNA modifications in aging-related diseases

Zeyidan Jiapaer, Dingwen Su, Lingyang Hua, Helge Immo Lehmann, Priyanka Gokulnath, Gururaja Vulugundam, Shannan Song, Lingying Zhang, Ye Gong, Guoping Li

First published: 19 June 2022 | https://doi.org/10.1111/acel.13657

Zeyidan Jiapaer, Dingwen Su and Lingyang Hua authors contribute equally to this work.

Abstract

With the aging of the global population, accumulating interest is focused on manipulating the fundamental aging-related signaling pathways to delay the physiological aging process and eventually slow or prevent the appearance or severity of multiple aging-related diseases. Recently, emerging evidence has shown that RNA modifications, which were historically considered infrastructural features of cellular RNAs, are dynamically regulated across most of the RNA species in cells and thereby critically involved in major biological processes, including cellular senescence and aging. In this review, we summarize the current knowledge about RNA modifications and provide a catalog of RNA modifications on different RNA species, including mRNAs, miRNAs, lncRNA, tRNAs, and rRNAs. Most importantly, we focus on the regulation and roles of these RNA modifications in aging-related diseases, including neurodegenerative diseases, cardiovascular diseases, cataracts, osteoporosis, and fertility decline. This would be an important step toward a better understanding of fundamental aging mechanisms and thereby facilitating the development of novel diagnostics and therapeutics for aging-related diseases.

OTHER RESEARCH & REVIEWS

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The metastatic spread of breast cancer accelerates during sleep

Zoi Diamantopoulou, Francesc Castro-Giner, Fabienne Dominique Schwab, Christiane Foerster, Massimo Saini, Selina Budinjas, Karin Strittmatter, Ilona Krol, Bettina Seifert, Viola Heinzelmann-Schwarz, Christian Kurzeder, Christoph Rochlitz, Marcus Vetter, Walter Paul Weber & Nicola Aceto

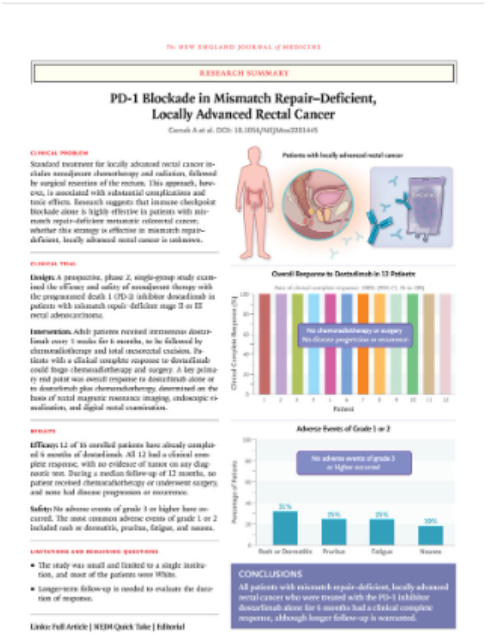
Nature (2022) | Cite this article

Abstract

The metastatic spread of cancer is achieved by the haematogenous dissemination of circulating tumour cells (CTCs). Generally, however, the temporal dynamics that dictate the generation of metastasis-competent CTCs are largely uncharacterized, and it is often assumed that CTCs are constantly shed from growing tumours or are shed as a consequence of mechanical insults[1]. Here we observe a striking and unexpected pattern of CTC generation dynamics in both patients with breast cancer and mouse models, highlighting that most spontaneous CTC intravasation events occur during sleep. Further, we demonstrate that rest-phase CTCs are highly prone to metastasize, whereas CTCs generated during the active phase are devoid of metastatic ability. Mechanistically, single-cell RNA sequencing analysis of CTCs reveals a marked upregulation of mitotic genes exclusively during the rest phase in both patients and mouse models, enabling metastasis proficiency. Systemically, we find that key circadian rhythm hormones such as melatonin, testosterone and glucocorticoids dictate CTC generation dynamics, and as a consequence, that insulin directly promotes tumour cell proliferation in vivo, yet in a time-dependent manner. Thus, the spontaneous generation of CTCs with a high proclivity to metastasize does not occur continuously, but it is concentrated within the rest phase of the affected individual, providing a new rationale for time-controlled interrogation and treatment of metastasis-prone cancers.

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

METHODS We initiated a prospective phase 2 study in which single-agent dostarlimab, an anti–PD-1 monoclonal antibody, was administered every 3 weeks for 6 months in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma. This treatment was to be followed by standard chemoradiotherapy and surgery. Patients who had a clinical complete response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery. The primary end points are sustained clinical complete response 12 months after completion of dostarlimab therapy or pathological complete response after completion of dostarlimab therapy with or without chemoradiotherapy and overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.



RESULTS A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on magnetic resonance imaging, ^{18}F-fluorodeoxyglucose–positron-emission tomography, endoscopic evaluation, digital rectal examination, or biopsy. At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.

CONCLUSIONS Mismatch repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade. Longer follow-up is needed to assess the duration of response. (Funded by the Simon and Eve Colin Foundation and others; ClinicalTrials.gov number, NCT04165772.)

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Structure of cytoplasmic ring of nuclear pore complex by integrative cryo-EM and AlphaFold

PIETRO FONTANA, YING DONG, XIONG PI, ALEXANDER B. TONG, COREY W. HECKSEL, LONGFEI WANG, TIAN-MIN FU, CARLOS BUSTAMANTE, AND HAO WU Authors Info & Affiliations

SCIENCE · 10 Jun 2022 · Vol 376, Issue 6598 · DOI: 10.1126/science.abm9326

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RELATED PERSPECTIVE

Solving the nuclear pore puzzle

Structured Abstract

INTRODUCTION

The nuclear pore complex (NPC) is the molecular conduit in the nuclear membrane of eukaryotic cells that regulates import and export of biomolecules between the nucleus and the cytosol, with vertebrate NPCs ~110 to 125 MDa in molecular mass and ~120 nm in diameter. NPCs are organized into four main rings: the cytoplasmic ring (CR) at the cytosolic side, the inner ring and the luminal ring on the plane of the nuclear membrane, and the nuclear ring facing the nucleus. Each ring possesses an approximate eightfold symmetry and is composed of multiple copies of different nucleoporins. NPCs have been implicated in numerous biological processes, and their dysfunctions are associated with a growing number of serious human diseases. However, despite pioneering studies from many groups over the past two decades, we still lack a full understanding of NPCs' organization, dynamics, and complexity.

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Functional and multiscale 3D structural investigation of brain tissue through correlative in vivo physiology, synchrotron microtomography and volume electron microscopy

Understanding the function of biological tissues requires a coordinated study of physiology and structure, exploring volumes that contain complete functional units at a detail that resolves the relevant features. Here, we introduce an approach to address this challenge: Mouse brain tissue sections containing a region where function was recorded using in vivo 2-photon calcium imaging were stained, dehydrated, resin-embedded and imaged with synchrotron X-ray computed tomography with propagation-based phase contrast (SXRT). SXRT provided context at subcellular detail, and could be followed by targeted acquisition of multiple volumes using serial block-face electron microscopy (SBEM). In the olfactory bulb, combining SXRT and SBEM enabled disambiguation of in vivo-assigned regions of interest. In the hippocampus, we found that superficial pyramidal neurons in CA1a displayed a larger density of spine apparati than deeper ones. Altogether, this approach can enable a functional and structural investigation of subcellular features in the context of cells and tissues.