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Scientific News
6th of February 2022
Sven Bulterijs

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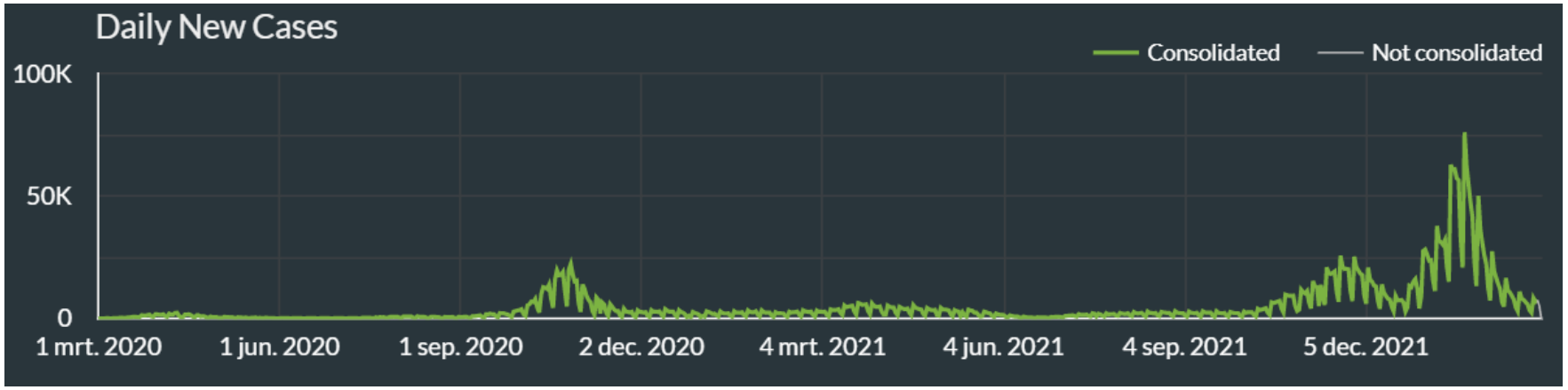
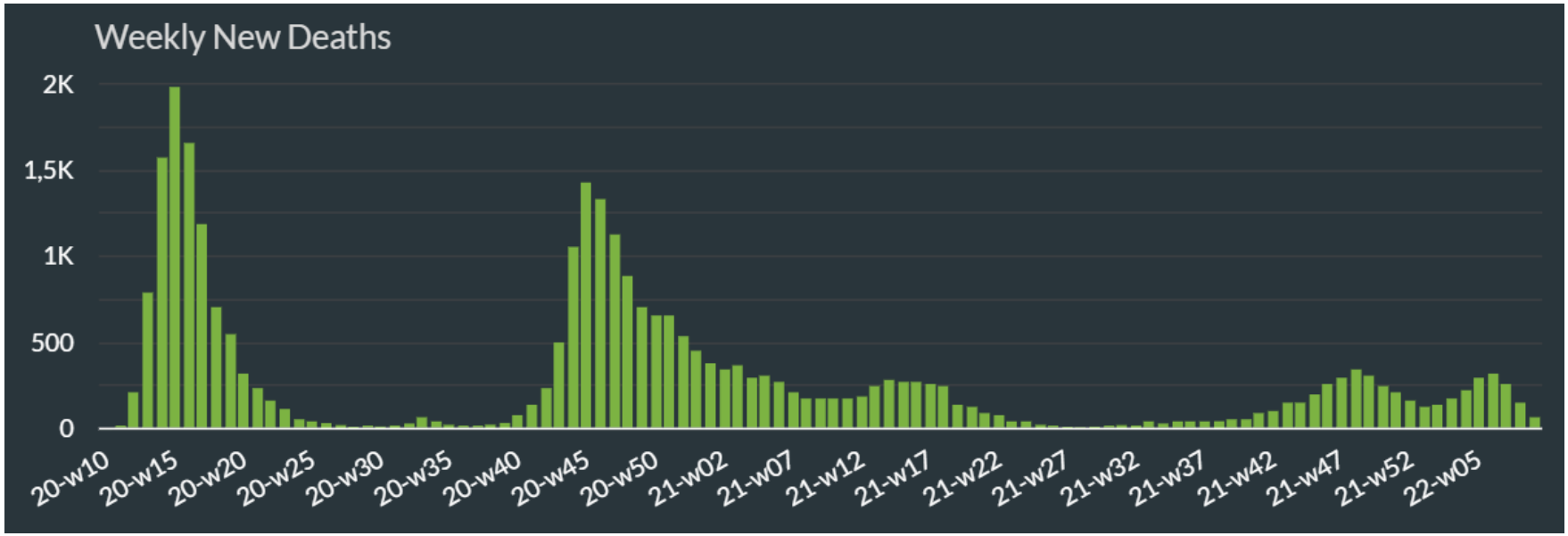
Belgium





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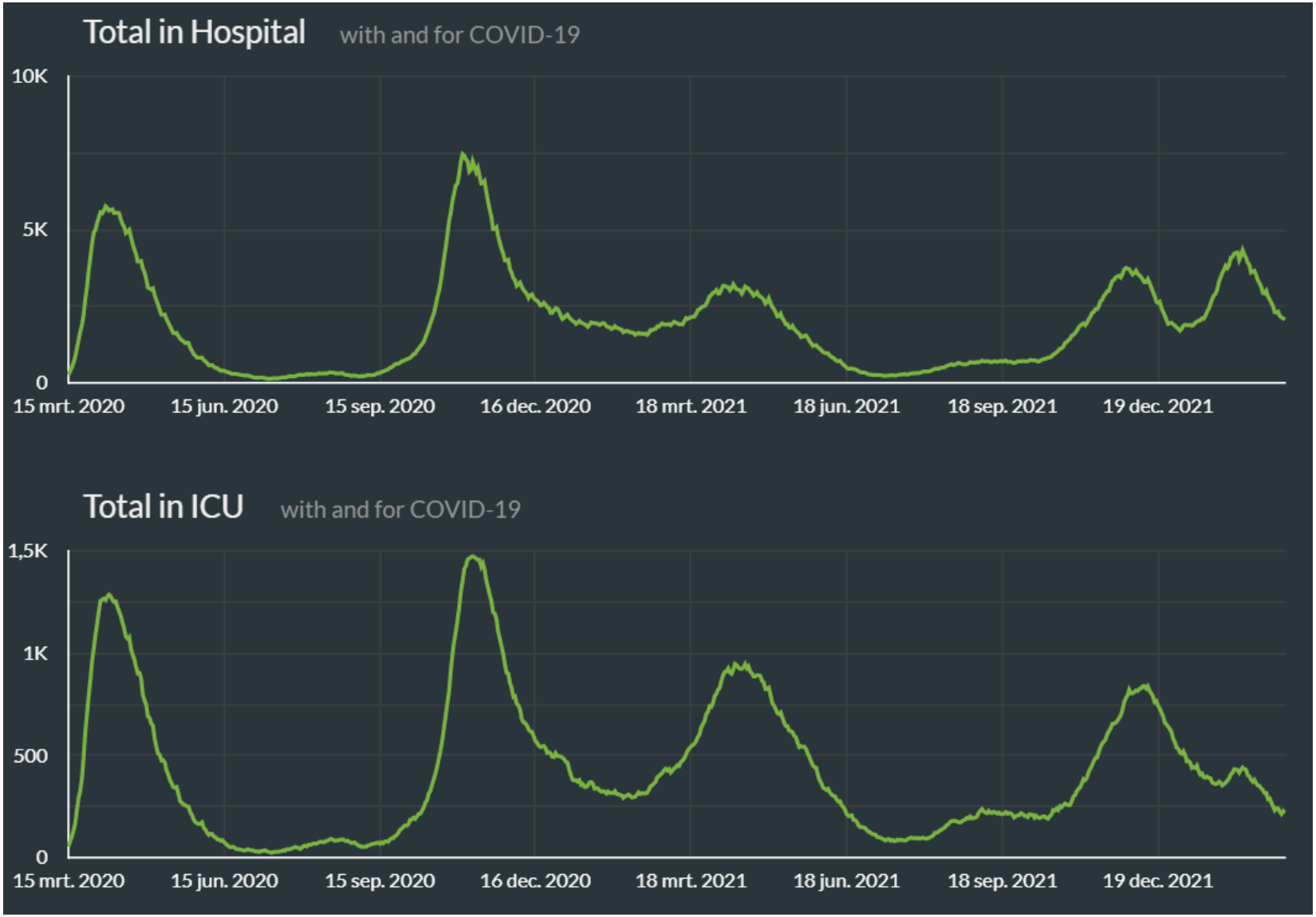

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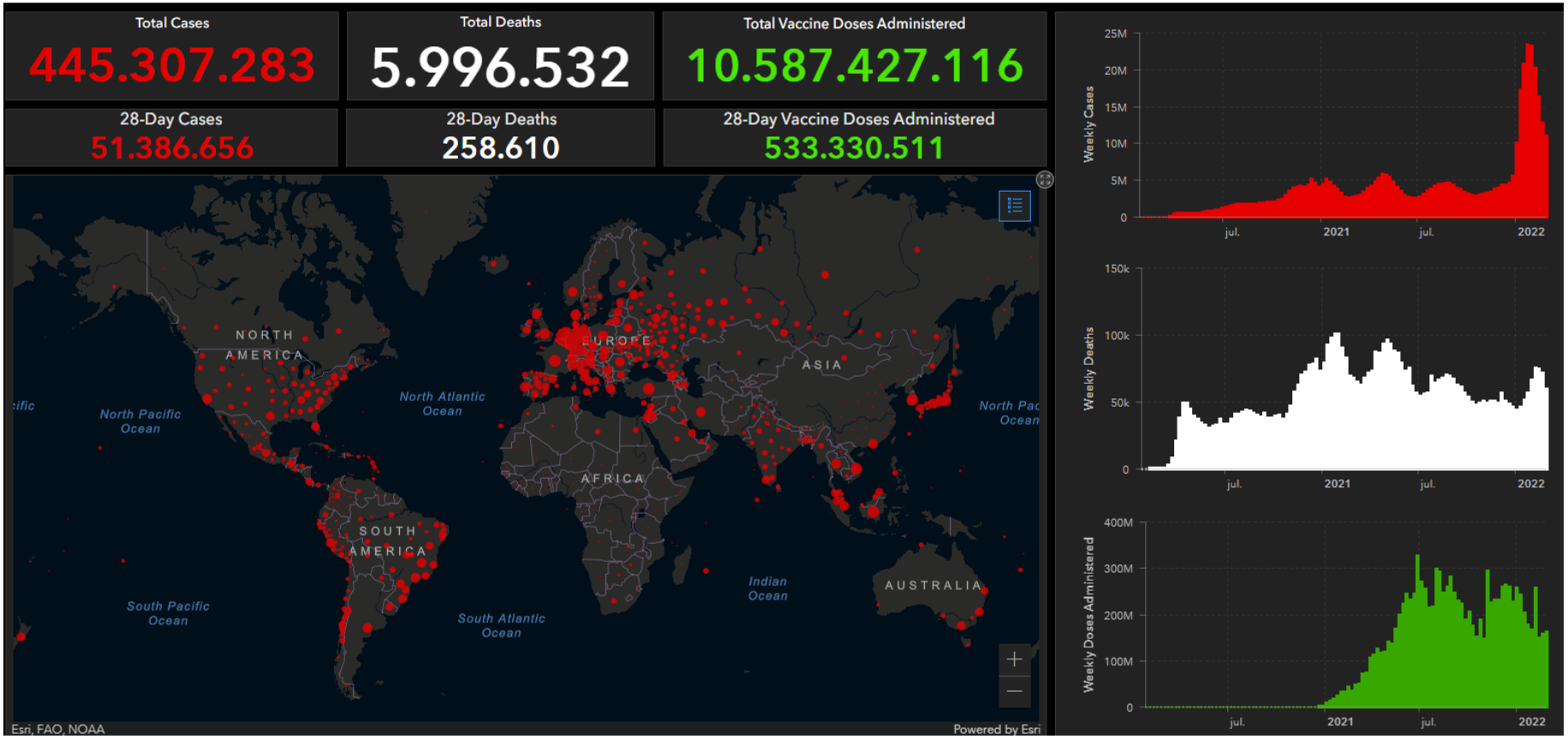

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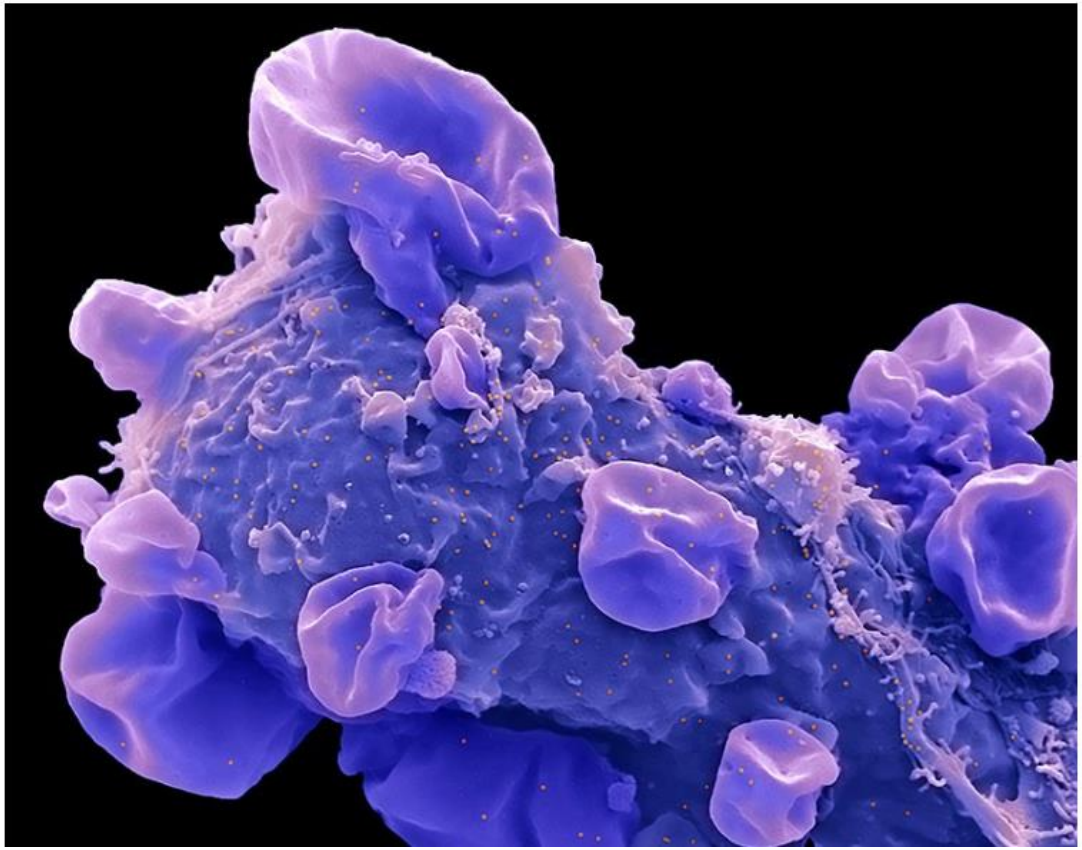
The next variant: three key questions about what's after Omicron

The emergence of a new variant is just a matter of time, scientists say.

Heidi Ledford



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Heart-disease risk soars after COVID — even with a mild case

Massive study shows a long-term, substantial rise in risk of cardiovascular disease, including heart attack and stroke, after a SARS-CoV-2 infection.

Saima May Sidik

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Neutralizing antibody responses elicited by SARS-CoV-2 mRNA vaccination wane over time and are boosted by breakthrough infection

The waning efficacy of SARS-CoV-2 vaccines, combined with the continued emergence of variants resistant to vaccine-induced immunity, has reignited debate over the need for booster vaccine doses. To address this, we examined the neutralizing antibody response against the spike protein of five major SARS-CoV-2 variants, D614G, Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Omicron (B.1.1.529), in health care workers (HCWs) vaccinated with SARS-CoV-2 mRNA vaccines. Serum samples were collected pre-vaccination, three weeks post-first vaccination, one month post-second vaccination, and six months post-second vaccination. Minimal neutralizing antibody titers were detected against Omicron pseudovirus at all four time points, including for a majority of patients who had SARS-CoV-2 breakthrough infections. Neutralizing antibody titers against all other variant spike protein-bearing pseudoviruses declined dramatically from one to six months after the second mRNA vaccine dose, although SARS-CoV-2 infection boosted vaccine responses. Additionally, mRNA-1273-vaccinated HCWs exhibited about two-fold higher neutralizing antibody titers than BNT162b2-vaccinated HCWs. Together these results demonstrate possible waning of antibody-mediated protection against SARS-CoV-2 variants that is dependent on prior infection status and the mRNA vaccine received. They also show that the Omicron variant spike protein can almost completely escape from neutralizing antibodies elicited in recipients of only two mRNA vaccine doses.

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SARS-CoV-2 Omicron-neutralizing memory B-cells are elicited by two doses of BNT162b2 mRNA vaccine

RYUTARO KOTAKI, YU ADACHI, SAYA MORIYAMA, TAISHI ONODERA, SHUETSU FUKUSHI, TAKAKI NAGAKURA, KEISUKE TONOUCHI, KAZUTAKA TERAHARA, LIN SUN, [...] YOSHIMASA TAKAHASHI +10 authors Authors Info & Affiliations

Multiple SARS-CoV-2 variants possess mutations in the spike receptor-binding domain (RBD) with potential to evade neutralizing antibody. In particular, the Beta and Omicron variants escape from antibody neutralizing activity in those who received two doses of BNT162b2 mRNA vaccine. Nonetheless, boosting with a third vaccine dose or by breakthrough infection improves the overall breadth of the neutralizing antibodies, but the mechanism remains unclear. Here, we longitudinally profiled the cellular composition of RBD-binding memory B cell subsets and their antibody binding and neutralizing activity against SARS-CoV-2 variants following the second dose of mRNA vaccine. Two doses of the mRNA vaccine elicited plasma neutralizing antibodies with a limited activity against Beta and Omicron but induced an expanded antibody breadth overtime, up to 4.9 months post vaccination. In contrast, more than one third of RBD-binding IgG^+ memory B cells with a resting phenotype initially bound the Beta and Omicron variants and steadily increased the B cell receptor (BCR) breadth overtime. As a result, a fraction of the resting memory B cell subset secreted Beta and Omicron-neutralizing antibody when stimulated in vitro. The neutralizing breadth of the resting memory B cell subset helps us understand the prominent recall of Omicron-neutralizing antibodies after an additional booster or breakthrough infection in fully vaccinated individuals.

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News Feature | Published: 31 January 2022

Fresh from the biotech pipeline: too much, too fast?

Melanie Senior

Nature Biotechnology **40**, 155–162 (2022) | Cite this article

2021 witnessed regulators' continued push to accelerate approvals and adjust to COVID-19, but has the pendulum swung too far in drug makers' favor?

Aging research articles

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Molecular hallmarks of heterochronic parabiosis at single-cell resolution

Róbert Pálovics, Andreas Keller ✉, Nicholas Schaum, Weilun Tan, Tobias Fehlmann, Michael Borja, Fabian Kern, Liana Bonanno, Kruti Calcuttawala, James Webber, Aaron McGeever, The Tabula Muris Consortium, Jian Luo, Angela Oliveira Pisco, Jim Karkanias, Norma F. Neff, Spyros Darmanis ✉, Stephen R. Quake ✉ & Tony Wyss-Coray ✉

Nature (2022) | Cite this article

4279 Accesses | **84** Altmetric | Metrics

Abstract

The ability to slow or reverse biological ageing would have major implications for mitigating disease risk and maintaining vitality[1]. Although an increasing number of interventions show promise for rejuvenation[2], their effectiveness on disparate cell types across the body and the molecular pathways susceptible to rejuvenation remain largely unexplored. Here we performed single-cell RNA sequencing on 20 organs to reveal cell-type-specific responses to young and aged blood in heterochronic parabiosis. Adipose mesenchymal stromal cells, haematopoietic stem cells and hepatocytes are among those cell types that are especially responsive. On the pathway level, young blood invokes new gene sets in addition to reversing established ageing patterns, with the global rescue of genes encoding electron transport chain subunits pinpointing a prominent role of mitochondrial function in parabiosis-mediated rejuvenation. We observed an almost universal loss of gene expression with age that is largely mimicked by parabiosis: aged blood reduces global gene expression, and young blood restores it in select cell types. Together, these data lay the groundwork for a systemic understanding of the interplay between blood-borne factors and cellular integrity.

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Old blood from heterochronic parabionts accelerates vascular aging in young mice: transcriptomic signature of pathologic smooth muscle remodeling

Vascular aging has a central role in the pathogenesis of cardiovascular diseases contributing to increased mortality of older adults. There is increasing evidence that, in addition to the documented role of cell-autonomous mechanisms of aging, cell-nonautonomous mechanisms also play a critical role in the regulation of vascular aging processes. Our recent transcriptomic studies (Kiss T. et al. Geroscience. 2020;42(2):727-748) demonstrated that circulating anti-geronic factors from young blood promote vascular rejuvenation in aged mice. The present study was designed to expand upon the results of this study by testing the hypothesis that circulating pro-geronic factors also contribute to the genesis of vascular aging phenotypes. To test this hypothesis, through heterochronic parabiosis, we determined the extent to which shifts in the vascular transcriptome (RNA-seq) are modulated by the old systemic environment. We reanalyzed existing RNA-seq data, comparing the transcriptome in the aorta arch samples isolated from isochronic parabiont aged (20-month-old) C57BL/6 mice [A-(A); parabiosis for 8 weeks] and young isochronic parabiont (6-month-old) mice [Y-(Y)] and also assessing transcriptomic changes in the aortic arch in young (6-month-old) parabiont mice [Y-(A); heterochronic parabiosis for 8 weeks] induced by the presence of old blood derived from aged (20-month-old) parabionts. We identified 528 concordant genes whose expression levels differed in the aged phenotype and were shifted towards the aged phenotype by the presence of old blood in young Y-(A) animals. Among them, the expression of 221 concordant genes was unaffected by the presence of young blood in A-(Y) mice. GO enrichment analysis suggests that old blood-regulated genes may contribute to pathologic vascular remodeling. IPA Upstream Regulator analysis (performed to identify upstream transcriptional regulators that may contribute to the observed transcriptomic changes) suggests that the mechanism of action of pro-geronic factors present in old blood may include inhibition of pathways mediated by SRF (serum response factor), insulin-like growth factor-1 (IGF-1) and VEGF-A. In conclusion, relatively short-term exposure to old blood can accelerate vascular aging processes. Our findings provide additional evidence supporting the significant plasticity of vascular aging and the existence of circulating pro-geronic factors mediating pathological remodeling of the vascular smooth muscle cells and the extracellular matrix.

Keywords: Aging; Aneurysm; Aorta; Atherosclerosis; Heterochronic parabiosis; Transcriptome; Vascular aging.

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Caloric restriction in humans reveals immunometabolic regulators of health span

O. SPADARO, Y. YOUM, I. SHCHUKINA, S. RYU, S. SIDOROV, A. RAVUSSIN, K. NGUYEN, E. ALADYEVA, A. N. PREDEUS, [...] V. D. DIXIT

The extension of life span driven by 40% caloric restriction (CR) in rodents causes trade-offs in growth, reproduction, and immune defense that make it difficult to identify therapeutically relevant CR-mimetic targets. We report that about 14% CR for 2 years in healthy humans improved thymopoiesis and was correlated with mobilization of intrathymic ectopic lipid. CR-induced transcriptional reprogramming in adipose tissue implicated pathways regulating mitochondrial bioenergetics, anti-inflammatory responses, and longevity. Expression of the gene *Pla2g7* encoding platelet activating factor acetyl hydrolase (PLA2G7) is inhibited in humans undergoing CR. Deletion of Pla2g7 in mice showed decreased thymic lipoatrophy, protection against age-related inflammation, lowered NLRP3 inflammasome activation, and improved metabolic health. Therefore, the reduction of PLA2G7 may mediate the immunometabolic effects of CR and could potentially be harnessed to lower inflammation and extend the health span.

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PREPRINT

A mass spectrometry-based atlas of extracellular matrix proteins across 25 mouse organs

Maxwell C McCabe, Anthony J Saviola, Kirk C Hansen

doi: https://doi.org/10.1101/2022.03.04.482898

Abstract

The extracellular matrix is a critical non-cellular component of multi-cellular organisms containing a variety of proteins, glycoproteins, and proteoglycans which has been implicated in a wide variety of essential biological processes, including development, wound healing, and aging. Due to low solubility, many ECM proteins have been underrepresented in previous proteomics datasets. Using an optimized 3-step decellularization and ECM extraction method involving chaotrope extraction and digestion via hydroxylamine hydrochloride, we have generated coverage of the matrisome across 25 organs. We observe that the top 100 most abundant proteins from the ECM fractions of all tissues are generally present in all tissues, indicating that tissue matrices are principally composed of a shared set of ECM proteins. However, these proteins vary up to 4,000-fold between tissues, resulting in highly unique matrix profiles even with the same primary set of proteins. A data reduction approach was used to reveal related networks of expressed ECM proteins across varying tissues, including basement membrane and collagen subtypes.

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The mouse metallomic landscape of aging and metabolism

Jean-David Morel, Lucie Sauzéat, Ludger J. E. Goeminne, Pooja Jha, Evan Williams, Riekelt H. Houtkooper, Ruedi Aebersold, Johan Auwerx & Vincent Balter

Nature Communications **13**, Article number: 607 (2022) | Cite this article

3435 Accesses | **40** Altmetric | Metrics

Abstract

Organic elements make up 99% of an organism but without the remaining inorganic bioessential elements, termed the metallome, no life could be possible. The metallome is involved in all aspects of life, including charge balance and electrolytic activity, structure and conformation, signaling, acid-base buffering, electron and chemical group transfer, redox catalysis energy storage and biomineralization. Here, we report the evolution with age of the metallome and copper and zinc isotope compositions in five mouse organs. The aging metallome shows a conserved and reproducible fingerprint. By analyzing the metallome in tandem with the phenome, metabolome and proteome, we show networks of interactions that are organ-specific, age-dependent, isotopically-typified and that are associated with a wealth of clinical and molecular traits. We report that the copper isotope composition in liver is age-dependent, extending the existence of aging isotopic clocks beyond bulk organic elements. Furthermore, iron concentration and copper isotope composition relate to predictors of metabolic health, such as body fat percentage and maximum running capacity at the physiological level, and adipogenesis and OXPHOS at the biochemical level. Our results shed light on the metallome as an overlooked omic layer and open perspectives for potentially modulating cellular processes using careful and selective metallome manipulation.

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Healthy aging and muscle function are positively associated with NAD$^+$ abundance in humans

Georges E. Janssens, Lotte Grevendonk, Ruben Zapata Perez, Bauke V. Schomakers, Johan de Vogel-van den Bosch, Jan M. W. Geurts, Michel van Weeghel, Patrick Schrauwen, Riekelt H. Houtkooper ✉ & Joris Hoeks ✉

Nature Aging (2022) | Cite this article

Abstract

Skeletal muscle is greatly affected by aging, resulting in a loss of metabolic and physical function. However, the underlying molecular processes and how (lack of) physical activity is involved in age-related metabolic decline in muscle function in humans is largely unknown. Here, we compared, in a cross-sectional study, the muscle metabolome from young to older adults, whereby the older adults were exercise trained, had normal physical activity levels or were physically impaired. Nicotinamide adenine dinucleotide (NAD$^+$) was one of the most prominent metabolites that was lower in older adults, in line with preclinical models. This lower level was even more pronounced in impaired older individuals, and conversely, exercise-trained older individuals had NAD$^+$ levels that were more similar to those found in younger individuals. NAD$^+$ abundance positively correlated with average number of steps per day and mitochondrial and muscle functioning. Our work suggests that a clear association exists between NAD$^+$ and health status in human aging.

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Post-GWAS functional analysis identifies CUX1 as a regulator of p16^{INK4a} and cellular senescence

Danli Jiang, Wei Sun, Ting Wu, Meijuan Zou, Sathish Babu Vasamsetti, Xiaoyu Zhang, Yihan Zhao, Julie A. Phillippi, Amr H. Sawalha, Sina Tavakoli, Partha Dutta, Jonathan Florentin, Stephen Y. Chan, Tammy S. Tollison, Di Wu, Jing Cui, Ian Huntress, Xinxia Peng, Toren Finkel & Gang Li

Nature Aging **2**, 140–154 (2022) | Cite this article

1088 Accesses | **6** Altmetric | Metrics

Abstract

Accumulation of senescent cells with age is an important driver of aging and age-related diseases. However, the mechanisms and signaling pathways that regulate senescence remain elusive. In this report, we performed post-genome-wide association studies (GWAS) functional studies on the *CDKN2A/B* locus, a locus known to be associated with multiple age-related diseases and overall human lifespan. We demonstrate that transcription factor CUX1 (Cut-Like Homeobox 1) specifically binds to an atherosclerosis-associated functional single-nucleotide polymorphism (fSNP) (rs1537371) within the locus and regulates the *CDKN2A/B*-encoded proteins p14^{ARF}, p15^{INK4b} and p16^{INK4a} and the antisense noncoding RNA in the CDK4 (INK4) locus (ANRIL) in endothelial cells (ECs). Endothelial CUX1 expression correlates with telomeric length and is induced by both DNA-damaging agents and oxidative stress. Moreover, induction of CUX1 expression triggers both replicative and stress-induced senescence via activation of *p16^{INK4a}* expression. Thus, our studies identify CUX1 as a regulator of p16^{INK4a}-dependent endothelial senescence and a potential therapeutic target for atherosclerosis and other age-related diseases.

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PREPRINT

Rapamycin treatment during development extends lifespan and healthspan

Anastasia V. Shindyapina, Yongmin Cho, Alaattin Kaya, Alexander Tyshkovskiy, José P. Castro, Juozas Gordevicius, Jesse R. Poganik, Steve Horvath, Leonid Peshkin, Vadim N. Gladyshev

doi: https://doi.org/10.1101/2022.02.18.481092

Abstract

The possibility that pace of development is tightly connected to aging is supported by the fact that the onset of reproduction is associated with lifespan and that many longevity interventions target growth and development. However, it has been unknown whether targeting development with pharmacological intervention can lead to a longer lifespan. To test this possibility, we subjected genetically diverse UMHET3 mice to the mTOR inhibitor rapamycin for the first 45 days of life and followed them up until death. Treated mice grew slower, with most of the deceleration occurring in the first week, and remained smaller for their entire lives. Their reproductive age was delayed but without affecting offspring numbers. The treatment was sufficient to extend the median lifespan by 10%, with the most effect in males, and to preserve better health as measured by frailty index, gait speed, and glucose and insulin tolerance tests. Mechanistically, the liver transcriptome of treated mice was younger at the completion of treatment and stayed younger into the old ages in males. Rapamycin initially reduced DNA methylation age of livers, however, that effect was lost with aging. Analogous to mice, rapamycin exposure only during development robustly extended the lifespan of *Daphnia magna* as well as reduced their body size, suggesting evolutionary conserved mechanisms of this early life effect. Overall, the results demonstrate that short-term rapamycin treatment during early life is a novel longevity intervention that establishes causality between pace of development and longevity in evolutionary distant organisms.

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PREPRINT

Lifespan can be extended during a specific time window early in life

G. Aiello, C. Sabino, D. Pernici, M. Audano, F. Antonica, M. Gianesello, A. Quattrone, N. Mitro, A. Romanel, A. Soldano, L. Tiberi

doi: https://doi.org/10.1101/2022.02.18.480980

Abstract

Lifespan is determined by complex and tangled mechanisms that are largely unknown. The early postnatal stage has been proposed to play a role in lifespan, but its contribution is still controversial. Here, we found that a short rapamycin treatment during early life can prolong lifespan in *Mus musculus* and *Drosophila melanogaster*. Notably, the same treatment at later time points has no evident effect on lifespan, suggesting that we found a crucial time-window involved in lifespan modulation. We discovered that sulfotransferases are upregulated during early rapamycin treatment both in newborn mice and *Drosophila* larvae. Furthermore, overexpression of the sulfotransferase *dST1* triggers an increment in the lifespan of *Drosophila melanogaster*. Our findings unveil a novel link between early-life treatments and long-term effects on lifespan.

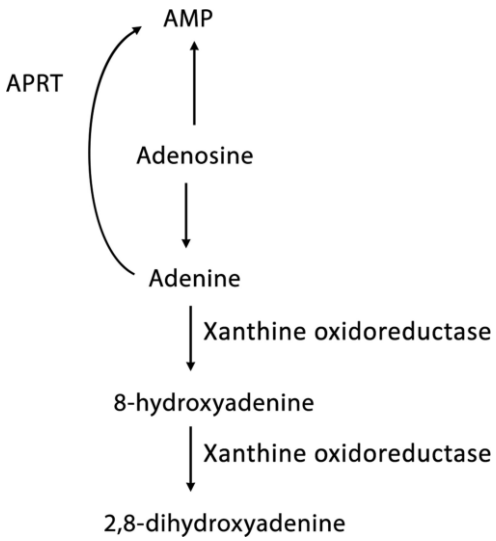
One Sentence Summary Early life events increase lifespan.

PREPRINT

Sex-specific regulation of metabolic health and vertebrate lifespan by AMP biosynthesis

Gwendoline Astre, Tehila Atlan, Uri Goshtchevsky, Kobi Shapira, Adi Oron-Gottesman, Tomer Levy, Ariel Velan, Margarita Smirnov, Joris Deelen, Erez Y Levanon, Itamar Harel

doi: https://doi.org/10.1101/2022.01.10.475524



Abstract

Energy homeostasis is disrupted with age, which then fuels multiple age-related pathologies. The AMP-activated protein kinase (AMPK) is the primary sensor of cellular energy in eukaryotes. However, the genetic regulation of vertebrate aging by AMPK remains poorly understood. Here, we manipulate energy levels in the turquoise killifish by mutating *APRT*, a key enzyme in AMP biosynthesis. These manipulations produced a male-specific lifespan extension and restored metabolic plasticity. Exploring the observed sex differences using an integrated omics approach implicated the mitochondria as an important player. Mechanistically, APRT regulated mitochondrial functions and AMPK activity, mimicking energy starvation in heterozygous cells. A fasting-like state was also detected, particularly in heterozygous males, accompanied by resistance to high-fat diet and an increase in mitochondrial copy numbers. Finally, life-long intermittent fasting eliminated the longevity benefits mediated by the *APRT* mutation. These observations identify the AMP/AMPK axis as a sex-specific regulator of vertebrate longevity and metabolic health.

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Transfer of the longevity-associated variant of BPIFB4 gene rejuvenates immune system and vasculature by a reduction of CD38^{+} macrophages and NAD^{+} decline

As we age, our body experiences chronic, systemic inflammation contributing to the morbidity and mortality of the elderly. The senescent immune system has been described to have a causal role in driving systemic aging and therefore may represent a key therapeutic target to prevent pathological consequences associated with aging and extend a healthy lifespan. Previous studies from our group associated a polymorphic haplotype variant in the BPIFB4 gene (LAV-BPIFB4) with exceptional longevity. Transfer of the LAV-BPIFB4 in preclinical models halted the progression of cardiovascular diseases (CVDs) and frailty by counterbalancing chronic inflammation. In the present study, we aimed to delineate the action of systemic adeno-associated viral vector-mediated LAV-BPIFB4 gene transfer (AAV-LAV-BPIFB4) on the deleterious age-related changes of the immune system and thereby the senescence-associated events occurring in C57BL/6J mice aged 26 months. Our in vivo data showed that 26-months-old mice had a higher frequency of CD45^{+}SA-beta Gal^{+} immune cells in peripheral blood than young (4-months-old) C57BL/6J mice. Notably, AAV-LAV-BPIFB4 gene transfer in aged mice reduced the pool of peripheral immunosenescent cells that were shown to be enriched in the spleen. In addition, the proper tuning of the immune secretory phenotype (IL1β^{low}, IL6^{low}, IL10^{high}) associated with a significant reduction in SA-beta Gal-positive area of aorta from AAV-LAV treated mice. At the functional level, the reduction of senescence-associated inflammation ensured sustained NAD^{+} levels in the plasma of AAV-LAV-BPIFB4 old mice by preventing the NADase CD38 increase in F4/80+ tissue-resident macrophages and Ly6C^{high} pro-inflammatory monocytes of the spleen and bone marrow. Finally, to validate the clinical implication of our findings, we showed that Long-living-individuals (LLIs, >95 years), which delay CVDs onset, especially if LAV-carriers, were characterized by high NAD^{+} levels. In conclusion, the new senotherapeutic action of LAV-BPIFB4 may offer a valuable therapeutic tool to control aging and reduce the burden of its pathophysiological disorders, such as CVDs.

Tick tock, tick tock: Mouse culture and tissue aging captured by an epigenetic clock

Christopher Minteer, Marco Morselli, Margarita Meer, Jian Cao, Albert Higgins-Chen, Sabine M. Lang, Matteo Pellegrini, Qin Yan, Morgan E. Levine

First published: 01 February 2022 | https://doi.org/10.1111/acel.13553

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Abstract

Aging is associated with dramatic changes to DNA methylation (DNAm), although the causes and consequences of such alterations are unknown. Our ability to experimentally uncover mechanisms of epigenetic aging will be greatly enhanced by our ability to study and manipulate these changes using in vitro models. However, it remains unclear whether the changes elicited by cells in culture can serve as a model of what is observed in aging tissues in vivo. To test this, we serially passaged mouse embryonic fibroblasts (MEFs) and assessed changes in DNAm at each time point via reduced representation bisulfite sequencing. By developing a measure that tracked cellular aging in vitro, we tested whether it tracked physiological aging in various mouse tissues and whether anti-aging interventions modulate this measure. Our measure, termed CultureAGE, was shown to strongly increase with age when examined in multiple tissues (liver, lung, kidney, blood, and adipose). As a control, we confirmed that the measure was not a marker of cellular senescence, suggesting that it reflects a distinct yet progressive cellular aging phenomena that can be induced in vitro. Furthermore, we demonstrated slower epigenetic aging in animals undergoing caloric restriction and a resetting of our measure in lung and kidney fibroblasts when re-programmed to iPSCs. Enrichment and clustering analysis implicated EED and Polycomb group (PcG) factors as potentially important chromatin regulators in translational culture aging phenotypes. Overall, this study supports the concept that physiologically relevant aging changes can be induced in vitro and used to uncover mechanistic insights into epigenetic aging.

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PREPRINT

Novel feature selection methods for construction of accurate epigenetic clocks

Adam Li, Alice E Kane, Amber Mueller, Brad English, Anthony Arena, Daniel Vera, David A Sinclair

Epigenetic clocks allow the accurate prediction of age based on the methylation status of specific CpG sites in a variety of tissues. These predictive models can be used to distinguish the biological age of an organism from its chronological age, and are a powerful tool to measure the effectiveness of aging interventions. There is a growing need for methods to efficiently construct epigenetic clocks. The most common approach is to create clocks using elastic net regression modelling of all measured CpG sites, without first identifying specific features or CpGs of interest. The addition of feature selection approaches provides the opportunity to reduce the cost and time of clock development by decreasing the number of CpG sites included in clocks. Here, we apply both classic feature selection methods and novel combinatorial methods to the development of epigenetic clocks. We perform feature selection on the human whole blood methylation dataset of ~470,000 CpG features published by Hannum and colleagues (2015). We develop clocks to predict age, using a variety of feature selection approaches, and all clocks have R2 correlation scores of greater than 0.73. The most predictive clock uses 35 CpG sites for a R2 correlation score of 0.87. The five most frequent sites across all clocks are also modelled to build a clock with a R2 correlation score of 0.83. These two clocks are validated on two external datasets where they maintain excellent predictive accuracy and outperform Hannum et al's model in accuracy of age prediction despite using significantly less CpGs. We also identify the associated gene regulatory regions of these CpG sites, which may be possible targets for future aging studies. These novel feature selection algorithms will lower the number of sites needed to be sequenced to build clocks and allow conventionally expensive aging epigenetic studies to cost a fraction of what it would normally.

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PREPRINT

Tissue-specific landscape of protein aggregation and quality control in an aging vertebrate

Yiwen R. Chen, Itamar Harel, Param Priya Singh, Inbal Ziv, Eitan Moses, Uri Goshtchevsky, Ben E. Machado, Anne Brunet, Daniel F. Jarosz

doi: https://doi.org/10.1101/2022.02.26.482120

SUMMARY

Protein aggregation is a hallmark of age-related neurodegeneration. Yet, aggregation during normal aging and in tissues other than the brain is poorly understood. Here we leverage the African turquoise killifish to systematically profile protein aggregates in seven tissues of an aging vertebrate. Age-dependent aggregation is strikingly tissue-specific, and not simply driven by protein expression differences. Experimental interrogation, combined with machine learning, indicates that this specificity is linked to both protein-autonomous biophysical features and tissue-selective alterations in protein quality control. Co-aggregation of protein quality control machinery during aging may further reduce proteostasis capacity, exacerbating aggregate burden. A segmental progeria model with accelerated aging in specific tissues exhibits selectively increased aggregation in these same tissues. Intriguingly, many age-related protein aggregates arise in wild-type proteins that, when mutated, drive human diseases. Our data chart a comprehensive landscape of protein aggregation during aging and reveal strong, tissue-specific associations with dysfunction and disease.

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PTEPRINT

Functional, transcriptional, and microbial shifts associated with healthy pulmonary aging: insights from rhesus macaques

Nicholas S. Rhoades, Michael Davies, Sloan A. Lewis, Isaac R. Cinco, Steven G. Kohama, Luiz E. Bermudez, Kevin L. Winthrop, Cristina Fuss, Julie A. Mattison, Eliot R. Spindel, Ilhem Messaoudi

Older individuals are at increased risk of developing severe respiratory infections due to age-related changes in the immunological, microbial, and functional landscape of the lung. However, our understanding of the impact of age on the respiratory tract remains limited as samples from healthy humans are challenging to obtain and confounding variables such as smoking and environmental pollutant exposure make it difficult to assess the true impact of aging. On the other hand, studies in rodent models are biased by their specific pathogen free status. In this study, we utilize a rhesus macaque model of healthy aging to examine the functional, immunological, and microbial consequences of aging in the lung. Pulmonary function testing in this large (n=34 adult, n=49 aged) cross-sectional study established age and sex differences similar to humans supporting the translational accuracy of this model. Additionally, an increased abundance of myeloid cells (alveolar and infiltrating macrophages) and a concomitant decrease in T-cells were also observed in aged animals. Single cell RNA sequencing indicated a transcriptional shift in the pulmonary CD8+ T-cell population from *GRZMB* expressing cells to *IFN* expressing cells, while frequency of *IL-1B* expressing alveolar macrophages was significantly reduced. Interestingly, the lung microbiome of many animals was dominated by a single microbe, *Tropheryma* spp., the prevalence of which decreased with age. These data provide a comprehensive picture of the functional, microbial and immunological changes of the lung in healthy macaque aging and provide insight into the increased prevalence and severity of respiratory disease in the elderly.

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PREPRINT

Proteostasis is differentially modulated by inhibition of translation initiation or elongation

Khalyd J. Clay, Yongzhi Yang, Michael Petrascheck

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Abstract

Recent work has revealed an increasingly important role for mRNA translation in maintaining proteostasis. Inhibiting translation protects from various proteostatic insults, including heat, expression of aggregation-prone proteins, or aging. However, multiple studies have come to differing conclusions about the mechanisms underlying the protective effects of translation inhibition. Here, we systematically lower translation either by pharmacologically inhibiting translation initiation or elongation and show that each step activates distinct protective responses in *Caenorhabditis elegans*. Targeting initiation triggers an HSF-1 dependent mechanism that protects from heat and age-associated protein misfolding but not from proteotoxicity caused by proteasome dysfunction. Conversely, targeting elongation triggers an HSF-1 independent mechanism that protects from heat and proteasome dysfunction but not from age-associated protein aggregation. Furthermore, while inhibiting translation initiation increases lifespan in wild-type worms, inhibiting translation elongation only extends lifespan when the animals exhibit preexisting proteotoxic stress—either as a result of aggregation-prone protein expression or *hsf-1* deficiency. Together our findings suggest that organisms evolved complementary mechanisms that the mRNA translation machinery can trigger to restore proteostasis.

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PREPRINT

DJ-1 glyoxalase activity makes a modest contribution to cellular defense against methylglyoxal damage in neurons

Melissa Conti Mazza, Sarah Shuck, Jiusheng Lin, Michael A. Moxley, John Termini, Mark R. Cookson, Mark A. Wilson

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

Abstract

Human DJ-1 is a cytoprotective protein whose absence causes Parkinson's disease and is also associated with other diseases. DJ-1 has an established role as a redox-regulated protein that defends against oxidative stress and mitochondrial dysfunction. Multiple studies have suggested that DJ-1 is also a protein/nucleic acid deglycase that plays a key role in the repair of glycation damage caused by methylglyoxal (MG), a reactive α-keto aldehyde formed by central metabolism. Contradictory reports suggest that DJ-1 is a glyoxalase but not a deglycase and does not play a major role in glycation defense. Resolving this issue is important for understanding how DJ-1 protects cells against insults that can cause disease. We find that DJ-1 reduces levels of reversible adducts of MG with guanine and cysteine in vitro. The steady-state kinetics of DJ-1 acting on reversible hemithioacetal substrates are fitted adequately with a computational kinetic model that requires only a DJ-1 glyoxalase activity, supporting the conclusion that deglycation is an apparent rather than a true activity of DJ-1. Sensitive and quantitative isotope-dilution mass spectrometry shows that DJ-1 modestly reduces the levels of some irreversible guanine and lysine glycation products in primary and cultured neuronal cell lines and whole mouse brain, consistent with a small but measurable effect on total neuronal glycation burden. However, DJ-1 does not improve cultured cell viability in exogenous MG. In total, our results suggest that DJ-1 is not a deglycase and has only a minor role in protecting neurons against methylglyoxal toxicity.

C. elegans aging research

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Metformin induces S-adenosylmethionine restriction to extend the Caenorhabditis elegans healthspan through H3K4me3 modifiers

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Free article

Abstract

Metformin, a widely prescribed first-line drug for the treatment of type II diabetes mellitus, has been shown to extend lifespan and delay the onset of age-related diseases. The precisely mechanisms by which these effects are realized remain elusive. We find that metformin exposure is restricted to adults, which is sufficient to extend lifespan. However, limiting metformin exposure to the larvae has no significant effect on Caenorhabditis elegans longevity. Here, we show that after metformin treatment, the level of S-adenosylmethionine (SAM) is reduced in adults but not in the larvae. Potential mechanisms by which reduced SAM might increase lifespan include altering the histone methylation. However, the molecular connections between metformin, SAM limitation, methyltransferases, and healthspan-associated phenotypes are unclear. Through genetic screening of C. elegans, we find that metformin promotes the healthspan through an H3K4 methyltransferase/demethylase complex to downregulate the targets, including mTOR and S6 kinase. Thus, our studies provide molecular links between meformin, SAM limitation, histone methylation, and healthspan and elucidate the mode action of metformin-regulated healthspan extension will boost its therapeutic application in the treatment of human aging and age-related diseases.

Keywords: Caenorhabditis elegans; Metformin; histone methylation; lifespan; mTOR signaling.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

What is an aging-related disease? An epidemiological perspective

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David G Le Couteur, PhD FRACP ✉, Janani Thillainadesan, PhD FRACP

The Journals of Gerontology: Series A, glac039, https://doi.org/10.1093/gerona/glac039
Published: 15 February 2022 **Article history** ▾

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Abstract

There are no established or standardized definitions of aging-related disease. Data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 were used to model the relationship between age and incidence of diseases. Clustering analysis identified four groups of non-communicable diseases: Group A diseases with an exponential increase in incidence with age; Group B diseases with an exponential increase in incidence that usually peaked in latelife which then declined or plateaued at the oldest ages; and Group C and D diseases with an onset in earlier life and where incidence was stable or decreased in old age. From an epidemiological perspective, Group A diseases are 'aging-related diseases' because there is an exponential association between age and incidence, and the slope of the incidence curves remains positive throughout old age. These included the major non-communicable diseases dementia, stroke and ischemic heart disease. Whether any of the other diseases are aging-related is uncertain because their incidence either does not change or more often decreases in old age. Only biological studies can determine how the aging process contributes to any of these diseases and this may lead to a reclassification of disease on the basis of whether they are directly caused by, or are in continuity with the biological changes of aging. In the absence of this mechanistic data, we propose the term 'aging-related disease' should be used with precision based on epidemiological evidence.

Perspective | Published: 02 February 2022

An open science study of ageing in companion dogs

Kate E. Creevy, Joshua M. Akey, Matt Kaeberlein, Daniel E. L. Promislow ✉ & The Dog Aging Project Consortium

Nature **602**, 51–57 (2022) | Cite this article

Abstract

The Dog Aging Project is a long-term longitudinal study of ageing in tens of thousands of companion dogs. The domestic dog is among the most variable mammal species in terms of morphology, behaviour, risk of age-related disease and life expectancy. Given that dogs share the human environment and have a sophisticated healthcare system but are much shorter-lived than people, they offer a unique opportunity to identify the genetic, environmental and lifestyle factors associated with healthy lifespan. To take advantage of this opportunity, the Dog Aging Project will collect extensive survey data, environmental information, electronic veterinary medical records, genome-wide sequence information, clinicopathology and molecular phenotypes derived from blood cells, plasma and faecal samples. Here, we describe the specific goals and design of the Dog Aging Project and discuss the potential for this open-data, community science study to greatly enhance understanding of ageing in a genetically variable, socially relevant species living in a complex environment.

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Targeting aging mechanisms: pharmacological perspectives

Alexey Moskalev [1], Zulfiya Guvatova [2], Ines De Almeida Lopes [3], Charles W Beckett [3], Brian K Kennedy [4], Joao Pedro De Magalhaes [5], Alexander A Makarov [6]

Affiliations + expand

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Abstract

Geroprotectors slow down aging and promote healthy longevity in model animals. Although hundreds of compounds have been shown to extend the life of laboratory model organisms, clinical studies on potential geroprotectors are exceedingly rare, especially in healthy elders. This review aims to classify potential geroprotectors based on the mechanisms by which they influence aging. These pharmacological interventions can be classified into the following groups: those that prevent oxidation; proteostasis regulators; suppressors of genomic instability; epigenetic drugs; those that preserve mitochondrial function; inhibitors of aging-associated signaling pathways; hormetins; senolytics/senostatics; anti-inflammatory drugs; antifibrotic agents; neurotrophic factors; factors preventing the impairment of barrier function; immunomodulators; and prebiotics, metabiotics, and enterosorbents.

Science & Society

Cellular reprogramming and the rise of rejuvenation biotech

João Pedro de Magalhães [1, 3], Alejandro Ocampo [2]

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https://doi.org/10.1016/j.tibtech.2022.01.011

Cells can be rejuvenated and biological clocks reset using cellular reprogramming. A growing number of companies now aim to use cellular reprogramming to develop therapies for rejuvenating human beings. Can the 'young' science of rejuvenation, currently mostly based on *in vitro* studies, drive a new biotech field toward clinical applications?

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Telomere dysfunction in ageing and age-related diseases

Francesca Rossiello, Diana Jurk, João F. Passos & Fabrizio d'Adda di Fagagna

Nature Cell Biology **24**, 135–147 (2022) | Cite this article

Abstract

Ageing organisms accumulate senescent cells that are thought to contribute to body dysfunction. Telomere shortening and damage are recognized causes of cellular senescence and ageing. Several human conditions associated with normal ageing are precipitated by accelerated telomere dysfunction. Here, we systematize a large body of evidence and propose a coherent perspective to recognize the broad contribution of telomeric dysfunction to human pathologies.

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Mitochondrial and metabolic dysfunction in ageing and age-related diseases

João A. Amorim, Giuseppe Coppotelli, Anabela P. Rolo, Carlos M. Palmeira, Jaime M. Ross & David A. Sinclair

Nature Reviews Endocrinology (2022) | Cite this article

Abstract

Organismal ageing is accompanied by progressive loss of cellular function and systemic deterioration of multiple tissues, leading to impaired function and increased vulnerability to death. Mitochondria have become recognized not merely as being energy suppliers but also as having an essential role in the development of diseases associated with ageing, such as neurodegenerative and cardiovascular diseases. A growing body of evidence suggests that ageing and age-related diseases are tightly related to an energy supply and demand imbalance, which might be alleviated by a variety of interventions, including physical activity and calorie restriction, as well as naturally occurring molecules targeting conserved longevity pathways. Here, we review key historical advances and progress from the past few years in our understanding of the role of mitochondria in ageing and age-related metabolic diseases. We also highlight emerging scientific innovations using mitochondria-targeted therapeutic approaches.

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Systems approaches to investigate the role of NF-κB signaling in aging

Masatoshi Haga; Mariko Okada

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The nuclear factor-κB (NF-κB) signaling pathway is one of the most well-studied pathways related to inflammation, and its involvement in aging has attracted considerable attention. As aging is a complex phenomenon and is the result of a multi-step process, the involvement of the NF-κB pathway in aging remains unclear. To elucidate the role of NF-κB in the regulation of aging, different systems biology approaches have been employed. A multi-omics data-driven approach can be used to interpret and clarify unknown mechanisms but cannot generate mechanistic regulatory structures alone. In contrast, combining this approach with a mathematical modeling approach can identify the mechanistics of the phenomena of interest. The development of single-cell technologies has also helped clarify the heterogeneity of the NF-κB response and underlying mechanisms. Here, we review advances in the understanding of the regulation of aging by NF-κB by focusing on omics approaches, single-cell analysis, and mathematical modeling of the NF-κB network.

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Invited review: Unearthing the mechanisms of age-related neurodegenerative disease using *Caenorhabditis elegans*

Ashley N. Hayden [a, b, 1], Emily J. Leptich [a, b, 1], Rachel N. Arey [a, c]

As human life expectancy increases, neurodegenerative diseases present a growing public health threat, for which there are currently few effective treatments. There is an urgent need to understand the molecular and genetic underpinnings of these disorders so new therapeutic targets can be identified. Here we present the argument that the simple nematode worm *Caenorhabditis elegans* is a powerful tool to rapidly study neurodegenerative disorders due to their short lifespan and vast array of genetic tools, which can be combined with characterization of conserved neuronal processes and behavior orthologous to those disrupted in human disease. We review how pre-existing *C. elegans* models provide insight into human neurological disease as well as an overview of current tools available to study neurodegenerative diseases in the worm, with an emphasis on genetics and behavior. We also discuss open questions that *C. elegans* may be particularly well suited for in future studies and how worms will be a valuable preclinical model to better understand these devastating neurological disorders.

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The hyperfunction theory: An emerging paradigm for the biology of aging

David Gems [1]

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Free PMC article

Abstract

The process of senescence (aging) is predominantly determined by the action of wild-type genes. For most organisms, this does not reflect any adaptive function that senescence serves, but rather evolutionary effects of declining selection against genes with deleterious effects later in life. To understand aging requires an account of how evolutionary mechanisms give rise to pathogenic gene action and late-life disease, that integrates evolutionary (ultimate) and mechanistic (proximate) causes into a single explanation. A well-supported evolutionary explanation by G.C. Williams argues that senescence can evolve due to pleiotropic effects of alleles with antagonistic effects on fitness and late-life health (antagonistic pleiotropy, AP). What has remained unclear is how gene action gives rise to late-life disease pathophysiology. One ultimate-proximate account is T.B.L. Kirkwood's disposable soma theory. Based on the hypothesis that stochastic molecular damage causes senescence, this reasons that aging is coupled to reproductive fitness due to preferential investment of resources into reproduction, rather than somatic maintenance. An alternative and more recent ultimate-proximate theory argues that aging is largely caused by programmatic, developmental-type mechanisms. Here ideas about AP and programmatic aging are reviewed, particularly those of M.V. Blagosklonny (the hyperfunction theory) and J.P. de Magalhães (the developmental theory), and their capacity to make sense of diverse experimental findings is assessed.

Keywords: Antagonistic pleiotropy; Hyperfunction; Insulin/IGF-1 signalling; Programmatic aging; Quasi-programs; Theories of aging; mTOR.