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Scientific News
3rd of Januari 2021
Sven Bulterijs

Business/Conferences/ General news

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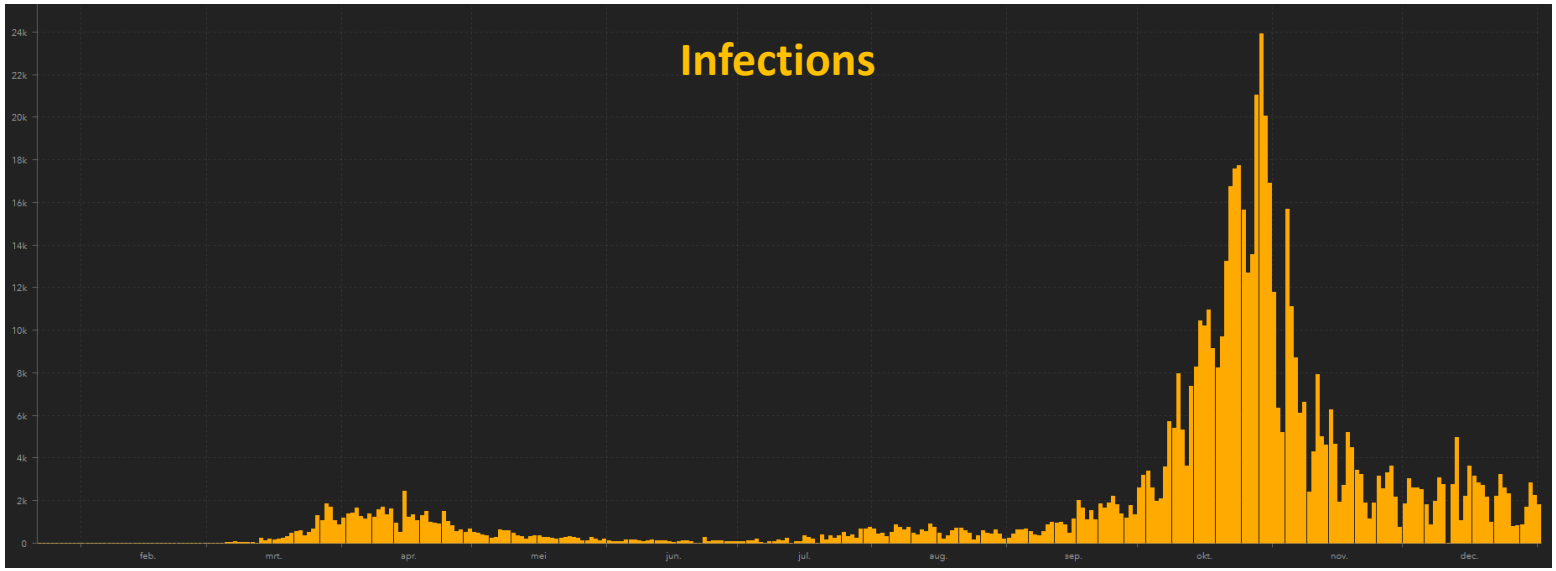
#UnlockLongevity

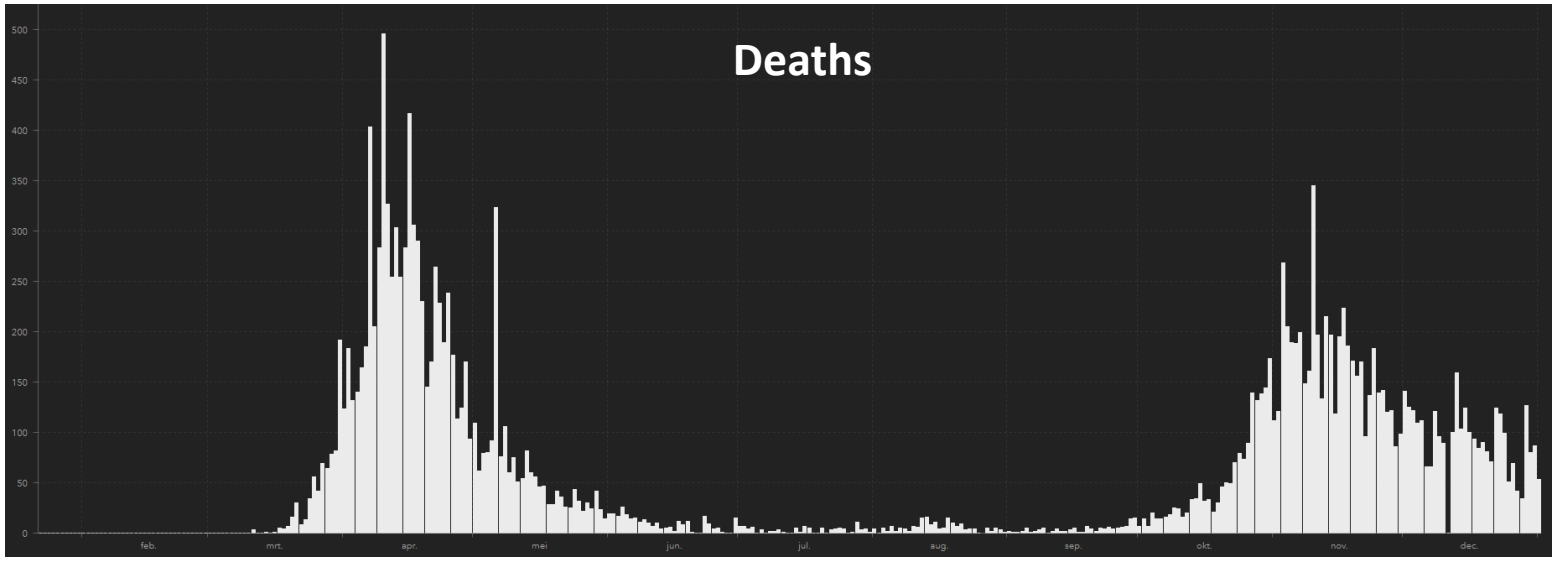
Thanks to a generous matching challenge by Oculus co-founder Michael Antonov, up to $600,000 donated before the end of 2020 will be **doubled**!

"I've followed and supported SENS research over the last few years and am excited to up my commitment this year because their organized, practical approach to combating aspects of aging, such as breaking down of crosslinks, rejuvenating the mitochondria and clearance of senescent cells has potential to help human lives and achieve age reversal in the near future."

– Michael Antonov

Belgium





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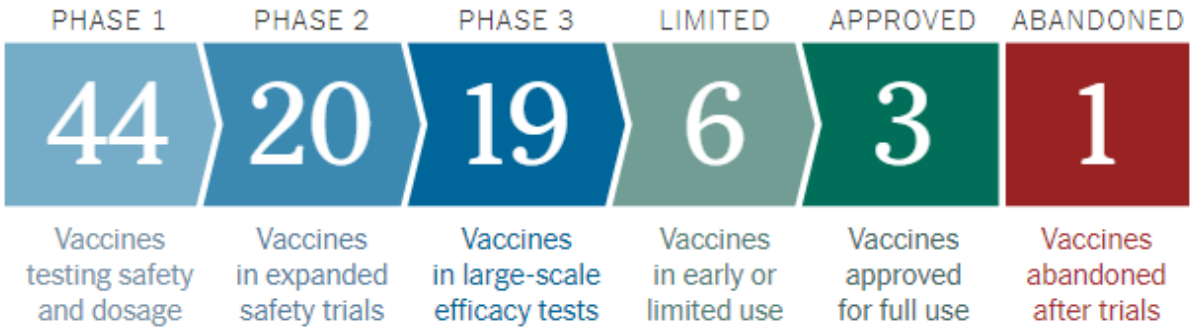
NY Times

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Jan. 2, 2021



New additions and recent updates

Dec. 31 The W.H.O. gives emergency validation to the **Pfizer-BioNTech** vaccine.

Dec. 30 China approves the **Sinopharm** vaccine.

Dec. 30 Britain authorizes the **Oxford-AstraZeneca** vaccine for emergency use.

Dec. 30 **Sinopharm** announces an efficacy rate of 79 percent.

Dec. 28 **Novavax** begins a Phase 3 trial in the United States.

Dec. 27 **Kazakhstan** moves to Phase 3.

Dec. 24 **Iran** enters Phase 1.

Dec. 23 Canada approves the **Moderna** vaccine.

Dec. 22 Maryland-based **Altimmune** enters Phase 1.

Dec. 21 The European Union authorizes the **Pfizer-BioNTech** vaccine.

Dec. 19 **Kazakhstan** moves to Phase 2.

Dec. 18 The F.D.A. authorizes **Moderna**'s vaccine for emergency use.

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Covid-19 vaccine: First person receives Pfizer jab in UK

8 December 2020

Covid-19: First vaccine given in US as roll-out begins

14 December 2020

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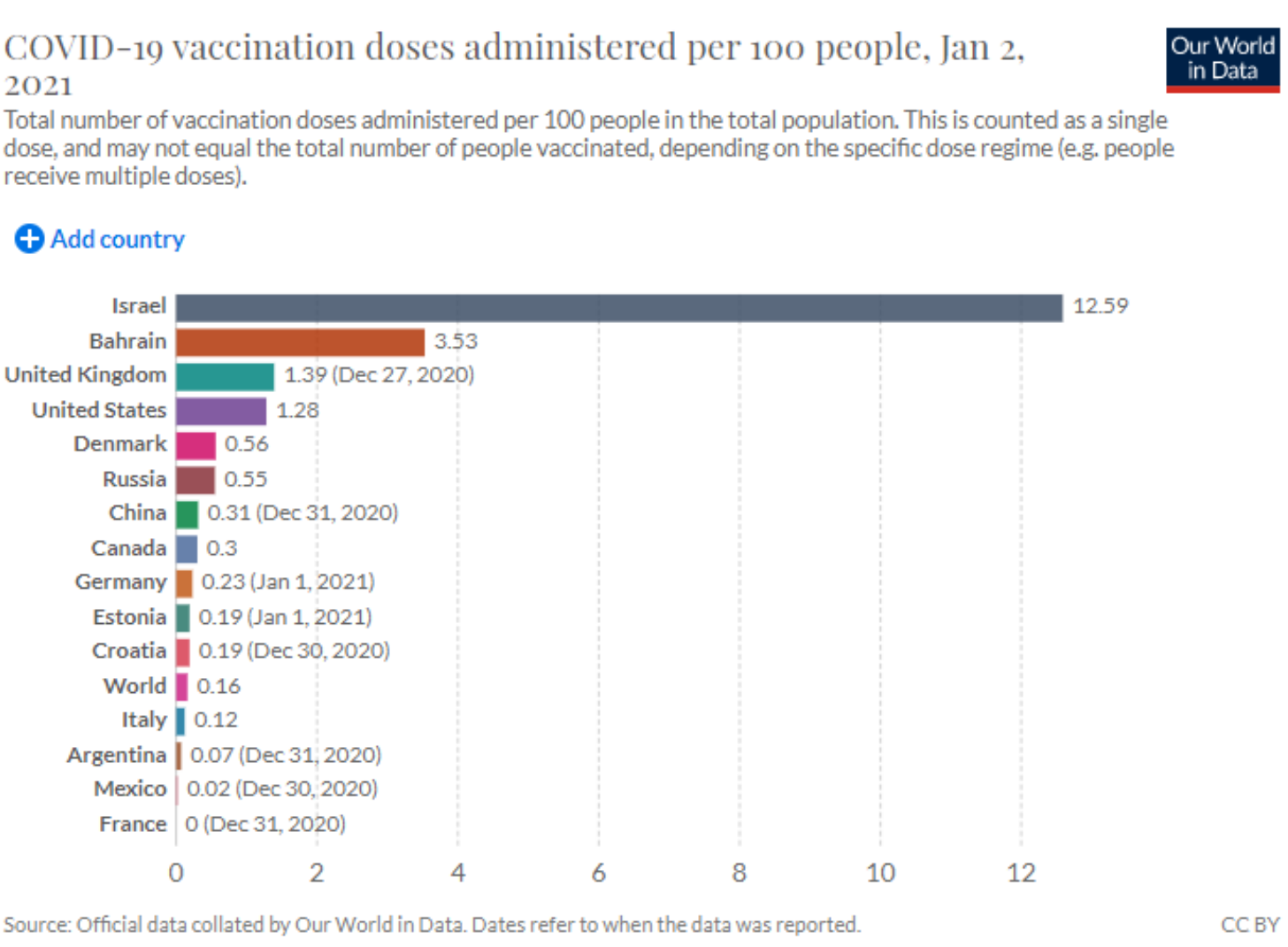

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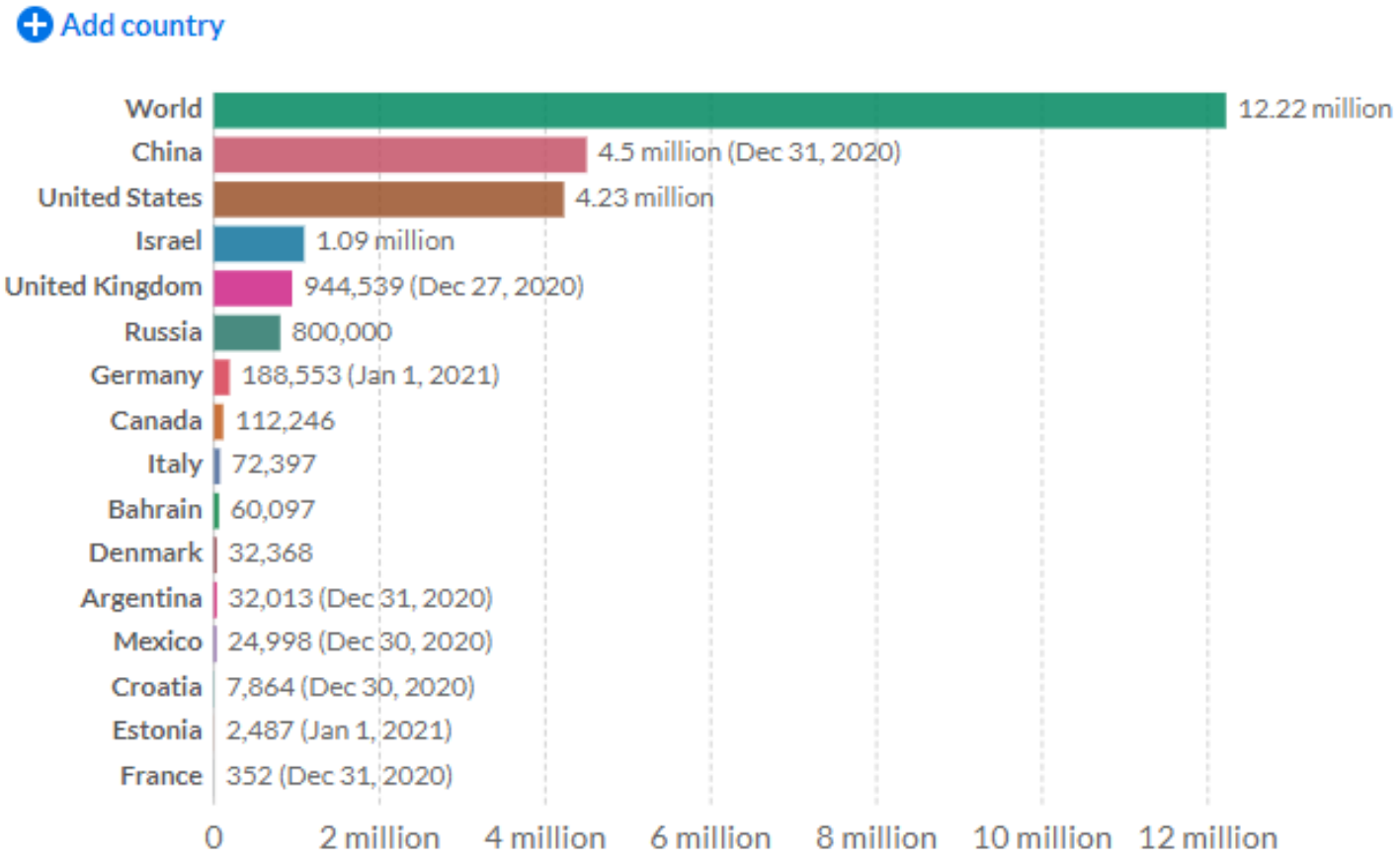
COVID-19 vaccination doses administered, Jan 2, 2021

Our World in Data

Total number of vaccination doses administered. This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).



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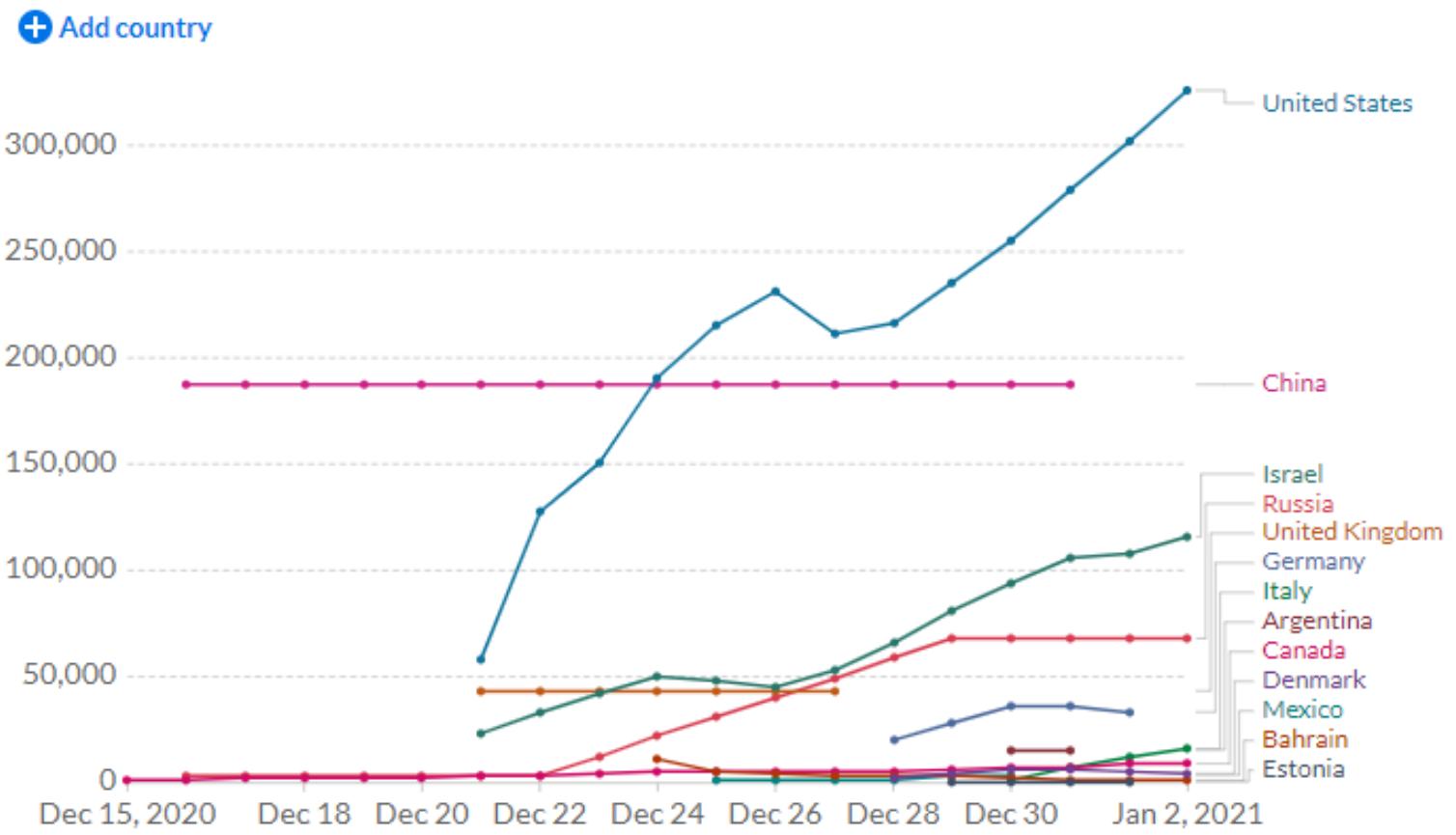
Daily COVID-19 vaccination doses administered

Shown is the rolling 7-day average. This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).

Our World in Data



Source: Official data collated by Our World in Data. Dates refer to when the data was reported.

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COVID-19: A Challenge to Physiology of Aging

Aleksei G Golubev [1]

The death toll of the current COVID-19 pandemic is strongly biased toward the elderly. COVID-19 case fatality rate (CFR) increases with age exponentially, its doubling time being about 7 years, irrespective of countries and epidemic stages. The same age-dependent mortality pattern known as the Gompertz law is featured by the total mortality and its main constituents attributed to cardiovascular, metabolic, neurological, and oncological diseases. Among patients dying of COVID-19, most have at least one of these conditions, whereas none is found in most of those who pass it successfully. Thus, gerontology is indispensable in dealing with the pandemic, which becomes a benchmark for validating the gerontological concepts and advances. The two basic alternative gerontological concepts imply that either aging results from the accumulation of stochastic damage, or is programmed. Based on these different grounds, several putative anti-aging drugs have been proposed as adjuvant means for COVID-19 prevention and/or treatment. These proposals are reviewed in the context of attributing the molecular targets of these drugs to the signaling pathways between the sensors of resource availability and the molecular mechanisms that allocate resources to storage, growth and reproduction or to self-maintenance and repair. Each of the drugs appears to reproduce only a part of the physiological responses to reduced resource availability caused by either dietary calories restriction or physical activity promotion, which are the most robust means of mitigating the adverse manifestations of aging. In the pathophysiological terms, the conditions of the endothelium, which worsen as age increases and may be significantly improved by the physical activity, is a common limiting factor for the abilities to withstand both physical stresses and challenges imposed by COVID-19. However, the current anti-epidemic measures promote sedentary indoor lifestyles, at odds with the most efficient behavioral interventions known to decrease the vulnerability to both the severe forms of COVID-19 and the prevalent aging-associated diseases. To achieve a proper balance in public health approaches to COVID-19, gerontologists should be involved in crosstalk between virologists, therapists, epidemiologists, and policy makers. The present publication suggests a conceptual background for that.

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Pandemic research for older people: doing it better next time FREE

Miles D Witham ✉, Adam L Gordon, Emily J Henderson, Rowan H Harwood

- Older people have not been adequately served by the COVID-19 research response.
- Lack of academic capacity, infrastructure and research preparedness are barriers.
- Preparing platforms and study designs, networks and identifying key questions before the next pandemic are essential steps.

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WHO reveals leading causes of death and disability worldwide: 2000-2019

9 December 2020 | News release | Geneva, Switzerland | Reading time: 5 min (1236 words)

Noncommunicable diseases now make up 7 of the world's top 10 causes of death, according to WHO's 2019 Global Health Estimates, published today. This is an increase from 4 of the 10 leading causes in 2000. The new data cover the period from 2000 to 2019 inclusive.

Heart disease remains the number 1 killer; diabetes and dementia enter the top 10

Heart disease has remained the leading cause of death at the global level for the last 20 years. However, it is now killing more people than ever before. The number of deaths from heart disease increased by more than 2 million since 2000, to nearly 9 million in 2019. Heart disease now represents 16% of total deaths from all causes. More than half of the 2 million additional deaths were in the WHO Western Pacific region. Conversely, the European region has seen a relative decline in heart disease, with deaths falling by 15% [1].

Alzheimer's disease and other forms of dementia are now among the top 10 causes of death worldwide, ranking 3rd in both the Americas and Europe in 2019. Women are disproportionally affected: globally, 65% of deaths from Alzheimer's and other forms of dementia are women.

Deaths from diabetes increased by 70% globally between 2000 and 2019, with an 80% rise in deaths among males. In the Eastern Mediterranean, deaths from diabetes have more than doubled and represent the greatest percentage increase of all WHO regions.

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WHO (2)

People are living longer – but with more disability

The estimates further confirm the growing trend for longevity: in 2019, people were living more than 6 years longer than in 2000, with a global average of more than 73 years in 2019 compared to nearly 67 in 2000. But on average, only 5 of those additional years were lived in good health.

Indeed, disability is on the rise. To a large extent, the diseases and health conditions that are causing the most deaths are those that are responsible for the greatest number of healthy life-years lost. Heart disease, diabetes, stroke, lung cancer and chronic obstructive pulmonary disease were collectively responsible for nearly 100 million additional healthy life-years lost in 2019 compared to 2000.

Injuries are another major cause of disability and death: there has been a significant rise in road traffic injuries in the African region since 2000, with an almost 50% increase in both death and healthy life-years lost. Similar but slightly smaller increases (at around 40%) were also observed for the Eastern Mediterranean region. Globally, deaths from road traffic injuries are 75% male.

In the Americas, drug use has emerged as a significant contributor to both disability and death. There was a nearly threefold increase in deaths from drug use disorders in the Americas between 2000 and 2019. This region is also the only one for which drug use disorder is a top 10 contributor to healthy life-years lost due to premature deaths and disability, while in all other regions, drug use does not make the top 25.

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Aging research articles

Pharmacological blockade of TNFα prevents sarcopenia and prolongs survival in aging mice

Sarcopenia is a hallmark of aging. Inflammation due to increased generation of cytokines such as TNFα, IL-1β and IL-6 has been implicated in the pathogenesis of sarcopenia. In skeletal muscle of C57BL/6 mice from 12 until 28 months of age, we observed a progressive reduction of myofiber cross sectional area, loss of type II fibers and infiltration by inflammatory cells. Muscle strength decreased in parallel. Pharmacological TNFα blockade by weekly subcutaneous injection of Etanercept from 16 to 28 months of age prevented atrophy and loss of type II fibers, with significant improvements in muscle function and mice lifespan. The effects on leukocyte recruitment were limited. These results provide a proof of principle that endogenous TNFα is sufficient to cause sarcopenia and to reduce animal survival, and open a novel perspective on novel potential pharmacological treatment strategies based on TNFα blockade to prevent the noxious events associated with aging.

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DeepMAge: A Methylation Aging Clock Developed with Deep Learning

Fedor Galkin[1,2], Polina Mamoshina[1], Kirill Kochetov[1], Denis Sidorenko[3], Alex Zhavoronkov[1,3,4,*]

DNA methylation aging clocks have become an invaluable tool in biogerontology research since their inception in 2013. Today, a variety of machine learning approaches have been tested for the purpose of predicting human age based on molecular-level features. Among these, deep learning, or neural networks, is an especially promising approach that has been used to construct accurate clocks using blood biochemistry, transcriptomics, and microbiomics data—feats unachieved by other algorithms. In this article, we explore how deep learning performs in a DNA methylation setting and compare it to the current industry standard—the 353 CpG clock published in 2013. The aging clock we are presenting (DeepMAge) is a neural network regressor trained on 4,930 blood DNA methylation profiles from 17 studies. Its absolute median error was 2.77 years in an independent verification set of 1,293 samples from 15 studies. DeepMAge shows biological relevance by assigning a higher predicted age to people with various health-related conditions, such as ovarian cancer, irritable bowel diseases, and multiple sclerosis.

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Cellular proteostasis decline in human senescence

Niv Sabath, Flonia Levy-Adam, Amal Younis, Kinneret Rozales, Anatoly Meller, Shani Hadar, Sharon Soueid-Baumgarten, and Reut Shalgi

Proteostasis collapse, the diminished ability to maintain protein homeostasis, has been established as a hallmark of nematode aging. However, whether proteostasis collapse occurs in humans has remained unclear. Here, we demonstrate that proteostasis decline is intrinsic to human senescence. Using transcriptome-wide characterization of gene expression, splicing, and translation, we found a significant deterioration in the transcriptional activation of the heat shock response in stressed senescent cells. Furthermore, phosphorylated HSF1 nuclear localization and distribution were impaired in senescence. Interestingly, alternative splicing regulation was also dampened. Surprisingly, we found a decoupling between different unfolded protein response (UPR) branches in stressed senescent cells. While young cells initiated UPR-related translational and transcriptional regulatory responses, senescent cells showed enhanced translational regulation and endoplasmic reticulum (ER) stress sensing; however, they were unable to trigger UPR-related transcriptional responses. This was accompanied by diminished ATF6 nuclear localization in stressed senescent cells. Finally, we found that proteasome function was impaired following heat stress in senescent cells, and did not recover upon return to normal temperature. Together, our data unraveled a deterioration in the ability to mount dynamic stress transcriptional programs upon human senescence with broad implications on proteostasis control and connected proteostasis decline to human aging.

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Prevalent intron retention fine-tunes gene expression and contributes to cellular senescence

Jun Yao, Dong Ding, Xueping Li, Ting Shen, Haihui Fu, Hua Zhong, Gang Wei ✉, Ting Ni ✉

Intron retention (IR) is the least well-understood alternative splicing type in animals, and its prevalence and function in physiological and pathological processes have long been underestimated. Cellular senescence contributes to individual aging and age-related diseases and can also serve as an important cancer prevention mechanism. Dynamic IR events have been observed in senescence models and aged tissues; however, whether and how IR impacts senescence remain unclear. Through analyzing polyA$^+$ RNA-seq data from human replicative senescence models, we found IR was prevalent and dynamically regulated during senescence and IR changes negatively correlated with expression alteration of corresponding genes. We discovered that knocking down (KD) splicing factor U2AF1, which showed higher binding density to retained introns and decreased expression during senescence, led to senescence-associated phenotypes and global IR changes. Intriguingly, *U2AF1*-KD-induced IR changes also negatively correlated with gene expression. Furthermore, we demonstrated that U2AF1-mediated IR of specific gene (*CPNE1* as an example) contributed to cellular senescence. Decreased expression of *U2AF1*, higher IR of *CPNE1*, and reduced expression of *CPNE1* were also discovered in dermal fibroblasts with age. We discovered prevalent IR could fine-tune gene expression and contribute to senescence-associated phenotypes, largely extending the biological significance of IR.

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Evaluating the neuroprotective impact of senolytic drugs on human vision

Nevin W. El-Nimri, Spencer M. Moore, Linda M. Zangwill, James A. Proudfoot, Robert N. Weinreb, Dorota Skowronska-Krawczyk & Sally L. Baxter

Glaucoma, a chronic neurodegenerative disease of retinal ganglion cells (RGCs), is a leading cause of irreversible blindness worldwide. Its management currently focuses on lowering intraocular pressure to slow disease progression. However, disease-modifying, neuroprotective treatments for glaucoma remain a major unmet need. Recently, senescent cells have been observed in glaucomatous eyes, exposing a potential pathway for alternative glaucoma therapies. Prior studies demonstrated that targeting senescent RGCs for removal (i.e., a senolytic approach) protected healthy RGCs and preserved visual function in a mouse ocular hypertension model. However, the effects of senolytic drugs on vision in human patients are unknown. Here, we used existing clinical data to conduct a retrospective cohort study in 28 human glaucoma patients who had been exposed to senolytics. Senolytic exposure was not associated with decreased visual acuity, elevated intraocular pressure, or documentation of senolytic-related adverse ocular effects by treating ophthalmologists. Additionally, patients exposed to senolytics (n = 9) did not exhibit faster progression of glaucomatous visual field damage compared to matched glaucoma patients (n = 26) without senolytic exposure. These results suggest that senolytic drugs do not carry significant ocular toxicity and provide further support for additional evaluation of the potential neuroprotective effects of senolytics on glaucoma and other neurodegenerative diseases.

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Inhibition of 3-phosphoinositide–dependent protein kinase 1 (PDK1) can revert cellular senescence in human dermal fibroblasts

Sugyun An, Si-Young Cho, Junsoo Kang, Soobeom Lee, Hyung-Su Kim, Dae-Jin Min, EuiDong Son, and Kwang-Hyun Cho

Cellular senescence is defined as a stable, persistent arrest of cell proliferation. Here, we examine whether senescent cells can lose senescence hallmarks and reenter a reversible state of cell-cycle arrest (quiescence). We constructed a molecular regulatory network of cellular senescence based on previous experimental evidence. To infer the regulatory logic of the network, we performed phosphoprotein array experiments with normal human dermal fibroblasts and used the data to optimize the regulatory relationships between molecules with an evolutionary algorithm. From ensemble analysis of network models, we identified 3-phosphoinositide–dependent protein kinase 1 (PDK1) as a promising target for inhibitors to convert the senescent state to the quiescent state. We showed that inhibition of PDK1 in senescent human dermal fibroblasts eradicates senescence hallmarks and restores entry into the cell cycle by suppressing both nuclear factor κB and mTOR signaling, resulting in restored skin regeneration capacity. Our findings provide insight into a potential therapeutic strategy to treat age-related diseases associated with the accumulation of senescent cells.

Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength

Treatments are lacking for sarcopenia, a debilitating age-related skeletal muscle wasting syndrome. Here we identify elevated 15-PGDH, the Prostaglandin E2 (PGE2)-degrading enzyme, as a hallmark of aged tissues, including skeletal muscle. The resulting reduction in PGE2 signaling is a major contributor to muscle atrophy in aged mice and results from 15-PGDH-expressing myofibers and interstitial cells within muscle. Inhibition of 15-PGDH, by targeted genetic knockdown or a small molecule inhibitor, increases aged muscle mass, strength, and exercise performance. These physiological benefits arise from rejuvenated PGE2 levels which augment mitochondrial function and autophagy and decrease TGF-beta and ubiquitin-proteasome pathways. Our studies demonstrate a previously unrecognized role for PGE2 signaling in countering muscle atrophy and identify 15-PGDH as a promising therapeutic target to counter sarcopenia.

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PREPRINT

15-PGDH as a Negative Regulator of Age-Related Organ Fitness

Emerging evidence implicates the eicosanoid molecule prostaglandin E2 (PGE2) in conferring a regenerative phenotype to multiple organ systems following tissue injury. As aging is in part characterized by loss of tissue stem cell regenerative capacity, we tested the hypothesis that the prostaglandin-degrading enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) contributes to the diminished organ fitness of aged mice. Here we demonstrate that genetic loss of 15-PGDH (*Hpgd*) confers a protective effect on aging of murine hematopoietic and gastrointestinal (GI) tissues. Aged mice lacking 15-PGDH display increased hematopoietic output as assessed by peripheral blood cell counts, bone marrow and splenic stem cell compartments, and accelerated post-transplantation recovery compared to their WT counterparts. Loss of *Hpgd* expression also resulted in enhanced GI fitness and reduced local inflammation in response to colitis. Together these results suggest that 15-PGDH negatively regulates aged tissue regeneration, and that 15-PGDH inhibition may be a viable therapeutic strategy to ameliorate age-associated loss of organ fitness.

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Heart and neural crest derivative 2-induced preservation of sympathetic neurons attenuates sarcopenia with aging

Methods

We examined age-dependent expression of the *heart and neural crest derivative 2* (Hand2), a critical transcription factor for SN maintenance, and we tested the possibility that inducing its expression exclusively in sympathetic neurons (SN) will prevent (i) motor denervation, (ii) impaired neuromuscular junction (NMJ) transmission, and (iii) loss of muscle mass and function in old mice. To test this hypothesis, we delivered a viral vector carrying Hand2 expression or an empty vector exclusively in SNs by vein injection in 16-month-old C57BL/6 mice that were sacrificed 6 months later. Techniques include RNA-sequencing, real-time PCR, genomic DNA methylation, viral vector construct, tissue immunohistochemistry, immunoblot, confocal microscopy, electrophysiology, and *in vivo* mouse physical performance.

Results

Hand2 expression declines throughout life, but inducing its expression increased (i) the number and size of SNs, (ii) muscle sympathetic innervation, (iii) muscle weight and force and whole-body strength, (iv) myofiber size but not muscle fibre-type composition, (v) NMJ transmission and nerve-evoked muscle force, and (vi) motor innervation in old mice. Additionally, the SN controls a set of genes to reduce inflammation and to promote transcription factor activity, cell signalling, and synapse in the skeletal muscle. Hand2 DNA methylation may contribute, at least partially, to gene silencing.

Conclusions

Selective expression of Hand2 in the mouse SNs from middle age through old age increases muscle mass and force by (i) regulating skeletal muscle sympathetic and motor innervation; (ii) improving acetylcholine receptor stability and NMJ transmission; (iii) preventing inflammation and myofibrillar protein degradation; (iv) increasing autophagy; and (v) probably enhancing protein synthesis.

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Conference abstract

Differences in Longitudinal Fasting Blood Glucose and Mortality Risk Across the Lifespan Between Mice and Humans

Dushani Palliyaguru, Eric Shiroma, John Nam, Luigi Ferrucci, Rafael de Cabo, and SLAM Investigators

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Abstract

Aging profoundly affects metabolism where trajectories of metabolic indices serve as strong predictors of health, disease and mortality. Mice and non-human primates are widely used to model all aspects of human biology, including metabolism. However, there is limited knowledge on how different species metabolically age during their life course. Here, we compare longitudinal predictors of health and mortality of three major metabolic indices among mice, non-human primates and humans. Longitudinal fasting blood glucose, body weight and body composition over the lifespan were compared across species in mice (Study of Longitudinal Aging in Mice), Rhesus monkeys (NIA and Wisconsin colonies) and humans (Baltimore Longitudinal Study on Aging). Survival analysis was conducted to calculate the risk of death for subjects with highest and lowest quartiles of fasting blood glucose. We will present data highlighting species-specific mechanisms of glucose homeostasis over the lifespan and its association with mortality.

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Conference abstract

Time-Restricted Feeding and Caloric Restriction Impact on Spontaneous Neoplasms in Female Mice

Annamaria Rudderow, Eleonora Duregon, Michel Bernier, and Rafael de Cabo

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Abstract

In older humans, multiple chronic diseases and increased life expectancy impose a disproportionate socioeconomic burden. Dietary interventions are valuable strategies for promoting healthy aging. Caloric restriction (CR) without malnutrition is a robust intervention able to delay disease onset and increase survival in model organisms. However, the impracticability of chronic CR outweighs the potential long-term benefits in humans. Time-restricted feeding (TRF), i.e. the limitation in the timing of food intake without necessarily reducing caloric intake, can protect against metabolic disorders through the synchronization of the circadian rhythm. This study compares whether limiting access to ad libitum (AL) food for a few hours per day mimics the beneficial effects of a CR diet. A large cohort of C57BL/6J female mice (n=250) was distributed into five feeding paradigms at midlife: AL, TRF for 8 hours, TRF for 4 hours, 20% CR and 20% CR fed twice a day (CRx2). Pathological analyses at death reveal a shift in fatal neoplasms toward an older age in TRF8 mice. AL mice had the highest prevalence of tumors (93%) and TRF4 had the lowest (77%). The highest tumor burden was observed in AL mice while CRx2 animals had the lowest number of neoplasms. Histiocytic sarcoma and lymphoma were the most represented malignancies, with CR mice exhibiting the highest rate of histiocytic sarcoma (75%) and the lowest rate of lymphoma (10%). These results indicate that time- and calorie-restricted feeding regimens can slow down malignant neoplasm progression and extend health span in female mice, even when started in adulthood.

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Conference abstract

4:10 Cycles of Very Low Calories Protect Against Tumor Xenografts, but Not Metastases in the Absence of Chemotherapy

Laura Corrales-Diaz Pomatto, Oye Bosompra, Sarah Wong, Monica Bodogai, Jonathan Kato, Melissa Carpenter, Arya Biragyn, and Rafael de Cabo

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Abstract

Cancer is a leading cause of mortality, with its incidence only expected to rise with an increasingly aging population. Dietary interventions, primarily caloric restriction (CR), lower cellular energy metabolism and have long been utilized to slow the aging process and protect against age-related diseases, including cancer. However, due to the stringency of CR, dietary alternatives that offer the same beneficial outcomes in cancer prevention and longevity have become increasingly attractive. Periodic cycles (4 days twice a month) of low caloric intake followed by a standard ad libitum (AL) diet was previously shown to promote health-span in mice and humans and protect against primary tumorigenesis and enhanced the effects of chemotherapy. The aim of our study was to compare the tumorigenic potential of 4T1 cells, a murine model of stage IV breast cancer, in young and aged female BALB/c mice fed either periodic cycles of low caloric diets versus chronic 20% CR. Compared to AL controls, we found a significant delay in primary tumor growth in mice regardless of diet composition by the 4:10 cycles of very low caloric intake. However, unlike in CR, CR-alternative diets were not protective against lung metastases in the absence of chemotherapy. Our study sheds light into the underlying differences of calorie-based interventions in the absence of chemotherapy.

Conference abstract

Amyloid beta-42 Levels in Companion Dog Brains Correlate with Age and Cognitive Function

Silvan Urfer,[1] Martin Darvas,[1] Dirk Keene,[1] Kálman Czeibert,[2] Enikő Kubinyi,[2] Sára Sándor,[2] Franco Guscetti,[3] and Matt Kaeberlein[1]

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Abstract

The privately owned companion dog is an increasingly important model in aging research because it shares the human environment, is exposed to similar environmental risk factors, receives comparable medical care, and develops many of the same age-related pathologies. One such pathology is Canine Cognitive Dysfunction (CCD), which shares many of the clinical features of human Alzheimer's Disease (AD), including progressive loss of cognitive function, loss of normal sleep patterns, increased anxiety, and aimless wandering. Amyloid-beta 42 (Aβ42) plaques similar to these found in humans with AD are known to naturally occur in the brains of aged dogs, making them an intriguing potential model for AD in humans. As part of the Dog Aging Project (www.dogagingproject.org), we studied frozen samples taken from the frontal cortex, medial temporal cortex, entorhinal cortex, and hippocampus of n=24 companion dogs of various ages that were euthanized for unrelated health reasons and donated by their owners. Brains were removed and frozen within 4 hours post mortem. Using a novel quantitative Luminex assay, we found a significant correlation between age and Aβ42 levels in all of these brain regions, as well as a significant correlation between Aβ42 levels and cognitive function scores as measured by the Canine Cognitive Dysfunction Scale. We will now investigate histopathology in the same dogs and brain regions, and investigate whether we can also measure Tau and pTau in these samples using Luminex and mass spectrometry.

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Conference abstract

A Panel of DNA Methylation and Proteomic Biomarkers for Specific Aging Pathways

Albert Higgins-Chen,[1] Luigi Ferrucci,[2] and Morgan Levine[3]

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Abstract

Most aging biomarkers such as DNA methylation and proteomic clocks have focused on measuring overall "biological age," a single number that predicts age-related morbidity and mortality better than absolute chronological age. While intuitive and interpretable, this single biological age number does not account for the possibility that different individuals may preferentially experience aging in different molecular and cellular pathways, and therefore does not suggest personalized aging interventions. We reasoned that a panel of biomarkers each capturing specific aging pathways, such as mitochondrial dysfunction or cellular senescence, may capture the heterogeneity of aging better than existing composite measures. To address this, we employed weighted gene co-expression network analysis to cluster tissue-specific transcriptomes and the serum proteome into specific modules with distinct biological functions and characterized how these modules change with age. We trained DNA methylation proxies of these functional modules that we then applied to independent validation data to identify associations with age-related morbidity and mortality. Clustering analysis using the DNA methylation biomarkers showed that different individuals show distinct patterns of aging. These pathway-specific biomarkers will elucidate how different aging mechanisms interact with each other to produce the larger phenomenon of aging, and for evaluating novel therapeutics targeting specific hallmarks of aging.

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Brain Lesions in Aging Zoo-Housed Naked Mole-Rats (*Heterocephalus glaber*)

Jerrold M. Ward, Andrew N. Cartoceti, Martha A. Delaney

First Published November 18, 2020 | Brief Report | Check for updates
https://doi.org/10.1177/0300985820969982

Article information

Altmetric 2

Abstract

Naked mole-rats (NMRs) are common in the managed care of zoos and valuable models for aging research. Limited information on NMR neuropathology is available despite many studies regarding their aging physiology. Histologic sections of brain from 27 adult (5–27 years old) NMRs from 2 zoos were reviewed to determine presence or absence of lesions associated with advanced age in humans and other mammals. A majority (23/27; 85%) of NMR brains had cerebral cortical neuronal changes with rounded or angular neurons, cytoplasmic vacuoles containing pale yellow pigment, periodic acid–Schiff (PAS)-positive granules and green autofluorescence, compatible with lipofuscinosis. Less severe lesions were present in cerebellar Purkinje cells, medulla, and hippocampal neurons. The hypothalamic neuropil of all NMRs had scattered variably sized PAS-positive granules and 10 (37%) had larger round bodies consistent with corpora amylacea. The youngest NMRs, 5 to 7 years old, generally had minimal or no cerebrocortical lesions. Further studies will help understand brain aging in this long-lived species.

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Mitochondrial DNA in extracellular vesicles declines with age

Stephanie Lazo, Nicole Noren Hooten, Jamal Green, Erez Eitan, Nicolle A. Mode, Qing-Rong Liu, Alan B. Zonderman, Ngozi Ezike, Mark P. Mattson, Paritosh Ghosh, Michele K. Evans

The mitochondrial free radical theory of aging suggests that accumulating oxidative damage to mitochondria and mitochondrial DNA (mtDNA) plays a central role in aging. Circulating cell-free mtDNA (ccf-mtDNA) isolated from blood may be a biomarker of disease. Extracellular vesicles (EVs) are small (30–400 nm), lipid-bound vesicles capable of shuttling proteins, nucleic acids, and lipids as part of intercellular communication systems. Here, we report that a portion of ccf-mtDNA in plasma is encapsulated in EVs. To address whether EV mtDNA levels change with human age, we analyzed mtDNA in EVs from individuals aged 30–64 years cross-sectionally and longitudinally. EV mtDNA levels decreased with age. Furthermore, the maximal mitochondrial respiration of cultured cells was differentially affected by EVs from old and young donors. Our results suggest that plasma mtDNA is present in EVs, that the level of EV-derived mtDNA is associated with age, and that EVs affect mitochondrial energetics in an EV age-dependent manner.

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PREPRINT

The function of SIRT3 explored through the substrate interaction network

Jarmila Nahálková

SIRT3 is the mitochondrial protein lysine deacetylase with a prominent role in the maintenance of mitochondrial integrity vulnerable in the range of diseases. The present study examines the SIRT3 substrate interaction network for the identification of its biological functions in the cellular anti-aging mechanisms. The pathway enrichment, the protein function prediction, and the protein node prioritization analysis were performed based on 407 SIRT3 substrates, which were collected by the data mining. The substrates are interlinked by 1230 direct protein-protein interactions included in the GeneMania database. The analysis of the SIRT3 substrate interaction network highlighted Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and non-alcoholic fatty liver disease (NAFLD) as the most associated with SIRT3 lysine deacetylase activity. The most important biological functions of SIRT3 substrates are within the respiratory electron transport chain, tricarboxylic acid cycle and fatty acid, triacylglycerol, and ketone body metabolism. In brown adipose tissue, SIRT3 activity contributes to the adaptive thermogenesis by the increase of energy production of the organisms. SIRT3 exhibits several modes of neuroprotective actions in the brain and liver including prevention of the mitochondrial damages due to the respiratory electron transfer chain failure, the quenching of ROS, the inhibition of the mitochondrial membrane potential loss, and the regulation of mitophagy. Related to its role in Alzheimer's disease, SIRT3 activation performs as a repressor of BACE1 through SIRT3-LKB1-AMPK-CREB-PGC-1α-PPARG-BACE1 (SIRT3-BACE1) pathway, which was created based on the literature mining and by employing Wikipathways application. The pathway enrichment analysis of the extended interaction network of the SIRT3-BACE1 pathway nodes displayed the functional relation to the circadian clock, which also deteriorates during the progress of AD and it is the causative of AD, PD, and HD. The use of SIRT3 activators in combination with the stimulating effect of regular exercise is further discussed as an attractive option for the improvement of cognitive decline during aging and the progressive stages of neurodegeneration.

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Modeling the human aging transcriptome across tissues, health status, and sex

Maxim N. Shokhirev ✉, Adiv A. Johnson

Aging in humans is an incredibly complex biological process that leads to increased susceptibility to various diseases. Understanding which genes are associated with healthy aging can provide valuable insights into aging mechanisms and possible avenues for therapeutics to prolong healthy life. However, modeling this complex biological process requires an enormous collection of high-quality data along with cutting-edge computational methods. Here, we have compiled a large meta-analysis of gene expression data from RNA-Seq experiments available from the Sequence Read Archive. We began by reprocessing more than 6000 raw samples—including mapping, filtering, normalization, and batch correction—to generate 3060 high-quality samples spanning a large age range and multiple different tissues. We then used standard differential expression analyses and machine learning approaches to model and predict aging across the dataset, achieving an R^2 value of 0.96 and a root-mean-square error of 3.22 years. These models allow us to explore aging across health status, sex, and tissue and provide novel insights into possible aging processes. We also explore how preprocessing parameters affect predictions and highlight the reproducibility limits of these machine learning models. Finally, we develop an online tool for predicting the ages of human transcriptomic samples given raw gene expression counts. Together, this study provides valuable resources and insights into the transcriptomics of human aging.

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Tissue-specific Gene Expression Changes Are Associated with Aging in Mice

Aging is a complex process that can be characterized by functional and cognitive decline in an individual. Aging can be assessed based on the functional capacity of vital organs and their intricate interactions with one another. Thus, the nature of aging can be described by focusing on a specific organ and an individual itself. However, to fully understand the complexity of aging, one must investigate not only a single tissue or biological process but also its complex interplay and interdependencies with other biological processes. Here, using RNA-seq, we monitored changes in the transcriptome during aging in four tissues (including brain, blood, skin and liver) in mice at 9 months, 15 months, and 24 months, with a final evaluation at the very old age of 30 months. We identified several genes and processes that were differentially regulated during aging in both tissue-dependent and tissue-independent manners. Most importantly, we found that the electron transport chain (ETC) of mitochondria was similarly affected at the transcriptome level in the four tissues during the aging process. We also identified the liver as the tissue showing the largest variety of differentially expressed genes (DEGs) over time. Lcn2 (Lipocalin-2) was found to be similarly regulated among all tissues, and its effect on longevity and survival was validated using its orthologue in *Caenorhabditis elegans*. Our study demonstrated that the molecular processes of aging are relatively subtle in their progress, and the aging process of every tissue depends on the tissue's specialized function and environment. Hence, individual gene or process alone cannot be described as the key of aging in the whole organism.

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Evidence for the 'rate-of-living' hypothesis between mammals and lizards, but not in birds, with field metabolic rate

Longevity, an important life-history trait, is determined by extrinsic and/or intrinsic causing mortality. Here, we used body mass (BM), field metabolic rate (FMR), longevity, and female maturity data reported from 300 amniote species to test whether 1) longevity was related to BM, FMR and female maturity, and 2) FMR, female maturity, or both, had a direct effect on longevity and whether an indirect effect of FMR on female maturity improved model fit. The results showed that BM was positively correlated with longevity and FMR, but negatively correlated with mass-specific FMR (*m*FMR) in amniotes. Phylogenetic confirmatory path analysis showed that, in the best model, longevity had a direct negative correlation with *m*FMR in lizards, and an indirect negative correlation with *m*FMR through female maturity in mammals. However, longevity had a direct positive correlation with *m*FMR in birds. Furthermore, longevity was positively correlated with female maturity in endotherms (birds and mammals) but weakly correlated with female maturity in ectotherms (lizards). Thus, our results are consistent with the life-history theory and the "rate-of-living" hypothesis in lizards and mammals but not support them in birds.

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Long-term intake of the illegal diet pill DNP reduces lifespan in a captive bird model

Antoine Stier [1], Pierre Bize [2], Sylvie Massemin [3], François Criscuolo [3]

2,4-Dinitrophenol (DNP), a molecule uncoupling mitochondrial oxidative phosphorylation from oxygen consumption, is illegally used by humans as a diet pill, but is nonetheless investigated as a potential human medicine against 'metabesity'. Due to its proven acute toxicity and the scarceness of long-term studies on DNP administration in vertebrates, we determined the impact of a long-term DNP treatment (~4 $mg.kg^{-1}.day^{-1}$, i.e. within the range taken illegally by humans) on body mass, metabolism, ageing and lifespan in a captive bird model, the zebra finch. The chronic absorption of DNP over life (>4 years) led to a mild increase in energy expenditure (ca. +11% compared to control group), without significantly altering the normal slight increase in body mass with age. DNP did not significantly influence the alteration of physical performance, the rise in oxidative damage, or the progressive shortening of telomeres with age. However, DNP-treated individuals had a significantly shorter lifespan (ca. -21% in median lifespan compared to control group), thereby raising potential concerns about DNP use as a diet pill or medicine.

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PREPRINT

The evolutionary landscape of primate longevity

Is it possible to slow the rate of aging, or do biological constraints limit its plasticity? We test this 'invariant rate of aging' hypothesis with an unprecedented collection of 39 human and nonhuman primate datasets across seven genera. We first recapitulate, in nonhuman primates, the highly regular relationship between life expectancy and lifespan equality seen in humans. We next demonstrate that variation in the rate of aging within genera is orders of magnitude smaller than variation in pre-adult and age-independent mortality. Finally, we demonstrate that changes in the rate of aging, but not other mortality parameters, produce striking, species-atypical changes in mortality patterns. Our results support the invariant rate of aging hypothesis, implying biological constraints on how much the human rate of aging can be slowed.

C. elegans aging research

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Distinct temporal actions of different types of unfolded protein responses during aging

Yi Sheng [1], Guang Yang [1], Zachary Markovich [1], Sung Min Han [1], Rui Xiao [1 2 3]

Proteotoxic stress is a common challenge for all organisms. Among various mechanisms involved in defending such stress, the evolutionarily conserved unfolded protein responses (UPRs) play a key role across species. Interestingly, UPRs can occur in different subcellular compartments including the endoplasmic reticulum (UPR^{ER}), mitochondria (UPR^{MITO}), and cytoplasm (UPR^{CYTO}) through distinct mechanisms. While previous studies have shown that the UPRs are intuitively linked to organismal aging, a systematic assay on the temporal regulation of different type of UPRs during aging is still lacking. Here, using Caenorhabditis elegans (C. elegans) as the model system, we found that the endogenous UPRs (UPR^{ER}, UPR^{MITO}, and UPR^{CYTO}) elevate with age, but their inducibility exhibits an age-dependent decline. Moreover, we revealed that the temporal requirements to induce different types of UPRs are distinct. Namely, while the UPR^{MITO} can only be induced during the larval stage, the UPR^{ER} can be induced until early adulthood and the inducibility of UPR^{CYTO} is well maintained until mid-late stage of life. Furthermore, we showed that different tissues may exhibit distinct temporal profiles of UPR inducibility during aging. Collectively, our findings demonstrate that UPRs of different subcellular compartments may have distinct temporal mechanisms during aging.

Dietary and environmental factors have opposite AhR-dependent effects on *C. elegans* healthspan

Genetic, dietary, and environmental factors concurrently shape the aging process. The aryl hydrocarbon receptor (AhR) was discovered as a dioxin-binding transcription factor involved in the metabolism of different environmental toxicants in vertebrates. Since then, the variety of pathophysiological processes regulated by the AhR has grown, ranging from immune response, metabolic pathways, and aging. Many modulators of AhR activity may impact on aging and age-associated pathologies, but, whether their effects are AhR-dependent has never been explored. Here, using *Caenorhabditis elegans*, as an elective model organism for aging studies, we show for the first time that lack of *Ce*AHR-1 can have opposite effects on health and lifespan in a context-dependent manner. Using known mammalian AhR modulators we found that, *ahr-1* protects against environmental insults (benzo(a)pyrene and UVB light) and identified a new role for AhR-bacterial diet interaction in animal lifespan, stress resistance, and age-associated pathologies. We narrowed down the dietary factor to a bacterially extruded metabolite likely involved in tryptophan metabolism. This is the first study clearly establishing *C. elegans* as a good model organism to investigate evolutionarily conserved functions of AhR-modulators and -regulated processes, indicating it can be exploited to contribute to the discovery of novel information about AhR in mammals.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Review

Hallmarks of Health

Carlos López-Otín [1, 2, 3], Guido Kroemer [4, 5, 6, 7, 8]

Health is usually defined as the absence of pathology. Here, we endeavor to define health as a compendium of organizational and dynamic features that maintain physiology. The biological causes or hallmarks of health include features of spatial compartmentalization (integrity of barriers and containment of local perturbations), maintenance of homeostasis over time (recycling and turnover, integration of circuitries, and rhythmic oscillations), and an array of adequate responses to stress (homeostatic resilience, hormetic regulation, and repair and regeneration). Disruption of any of these interlocked features is broadly pathogenic, causing an acute or progressive derailment of the system coupled to the loss of numerous stigmata of health.

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Decline in biological resilience as key manifestation of aging: Potential mechanisms and role in health and longevity

Decline in biological resilience (ability to recover) is a key manifestation of aging that contributes to increase in vulnerability to death with age eventually limiting longevity even in people without major chronic diseases. Understanding the mechanisms of this decline is essential for developing efficient anti-aging and pro-longevity interventions. In this paper we discuss: a) mechanisms of the decline in resilience with age, and aging components that contribute to this decline, including depletion of body reserves, imperfect repair mechanisms, and slowdown of physiological processes and responses with age; b) anti-aging interventions that may improve resilience or attenuate its decline; c) biomarkers of resilience available in human and experimental studies; and d) genetic factors that could influence resilience. There are open questions about optimal anti-aging interventions that would oppose the decline in resilience along with extending longevity limits. However, the area develops quickly, and prospects are exciting.

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A Geroscience approach for Parkinson's Disease: conceptual framework and design of PROPAG-AGEING project

Advanced age is the major risk factor for idiopathic Parkinson's disease (PD), but to date the biological relationship between PD and ageing remains elusive. Here we describe the rationale and the design of the H2020 funded project "PROPAG-AGEING", whose aim is to characterize the contribution of the ageing process to PD development. We summarize current evidences that support the existence of a continuum between ageing and PD and justify the use of a Geroscience approach to study PD. We focus in particular on the role of inflammaging, the chronic, low-grade inflammation characteristic of elderly physiology, which can propagate and transmit both locally and systemically. We then describe PROPAG-AGEING design, which is based on the multi-omic characterization of peripheral samples from clinically characterized drug-naïve and advanced PD, PD discordant twins, healthy controls and "super-controls", i.e. centenarians, who never showed clinical signs of motor disability, and their offspring. Omic results are then validated in a large number of samples, including *in vitro* models of dopaminergic neurons and healthy siblings of PD patients, who are at higher risk of developing PD, with the final aim of identifying the molecular perturbations that can deviate the trajectories of healthy ageing towards PD development.

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Senescent cells as promising targets to tackle age-related diseases

Eva Prašnikar [a, b], Jure Borišek [a], Andrej Perdih [a]

As the world's population progressively ages, the burden on the socio-economic and health systems is escalating, demanding sustainable and lasting solutions. Cellular senescence, one of the hallmarks of ageing, is a state of irreversible cell cycle arrest that occurs in response to various genotoxic stressors and is considered an important factor in the development of many age-related diseases and therefore a potential therapeutic target. Here, the role of senescent cells in age-related diseases is discussed, focusing on their formation and main characteristics. The mechanisms leading to senescent cells are presented, including replicative and premature senescence as well as senescence that occurs in various physiological processes, such as wound healing. The second part comprises a comprehensive description of various biomarkers currently used for the detection of senescent cells along with the investigated therapeutic approaches, namely senolytics, senomorphics and the clearance of senescent cells by the immune system. Potential delivery systems suitable for such therapies and model organisms to study senescence are also briefly examined. This in-depth overview of cellular senescence contributes to a deeper understanding of a rapidly evolving area aimed to tackle the age-related diseases in a more mechanistic way, as well as highlights future research opportunities.

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Cellular Senescence and the Senescence-Associated Secretory Phenotype as Drivers of Skin Photoaging

Eleni Fitsiou [1, 4], Tanya Pulido [2, 4], Judith Campisi [2, 3], Fatouma Alimirah [2], Marco Demaria [1]

Chronic exposure to UVR is known to disrupt tissue homeostasis, accelerate the onset of age-related phenotypes, and increase the risk for skin cancer—a phenomenon defined as photoaging.

In this paper, we review the current knowledge on how UV exposure causes cells to prematurely enter cellular senescence. We describe the mechanisms contributing to the accumulation of senescent cells in the skin and how the persistence of cellular senescence can promote impaired regenerative capacity, chronic inflammation, and tumorigenesis associated with photoaging. We conclude by highlighting the potential of senolytic drugs in delaying the onset and progression of age-associated phenotypes in the skin.

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Similarities and interplay between senescent cells and macrophages

Jacques Behmoaras [1], Jesús Gil [2 3]

Affiliations + expand

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Abstract

Senescence is a cellular program that prevents the replication of old, damaged, or cancerous cells. Senescent cells become growth arrested and undergo changes in their morphology, chromatin organization, and metabolism, and produce a bioactive secretome. This secretome, the senescence-associated secretory phenotype (SASP), mediates many of the pathophysiological effects associated with senescent cells, for example, recruiting and activating immune cells such as macrophages. The relation between senescent cells and macrophages is intriguing: senescent cells recruit macrophages, can induce them to undergo senescence, or can influence their polarization. Senescent cells and macrophages share multiple phenotypic characteristics; both have a high secretory status, increased lysosome numbers, or the ability to activate the inflammasome. Senescent cells accumulate during aging and disease, and killing them results in widespread benefits. Here we discuss similarities between senescent cells and macrophages and interpret the latest developments in macrophage biology to understand the molecular mechanisms of cellular senescence. We describe evidence and effects of senescence in macrophages and speculate on the ontogeny of the senescent-like state in macrophages. Finally, we examine the macrophage-senescent cell interplay and its impact on macrophage effector functions during inflammatory conditions and in the tumor microenvironment.

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Senescence in RASopathies, a possible novel contributor to a complex pathophenoype

Senescence is a biological process that induces a permanent cell cycle arrest and a specific gene expression program in response to various stressors. Following studies over the last few decades, the concept of senescence has evolved from an antiproliferative mechanism in cancer (oncogene-induced senescence) to a critical component of physiological processes associated with embryonic development, tissue regeneration, ageing and its associated diseases. In somatic cells, oncogenic mutations in RAS-MAPK pathway genes are associated with oncogene-induced senescence and cancer, while germline mutations in the same pathway are linked to a group of monogenic developmental disorders generally termed RASopathies. Here, we consider that in these disorders, senescence induction may result in opposing outcomes, a tumour protective effect and a possible contributor to a premature ageing phenotype identified in Costello syndrome, which belongs to the RASopathy group. In this review, we will highlight the role of senescence in organismal homeostasis and we will describe the current knowledge about senescence in RASopathies. Additionally, we provide a perspective on examples of experimentally characterised RASopathy mutations that, alone or in combination with various stressors, may also trigger an age-dependent chronic senescence, possibly contributing to the age-dependent worsening of RASopathy pathophenotype and the reduction of lifespan.

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Is exercise a senolytic medicine? A systematic review

Cellular senescence, a state of irreversible growth arrest triggered by various stressors, engages in a category of pathological processes, whereby senescent cells accumulate in mitotic tissues. Senolytics as novel medicine against aging and various diseases through the elimination of senescent cells has emerged rapidly in recent years. Exercise is a potent anti-aging and anti-chronic disease medicine, which has shown the capacity to lower the markers of cellular senescence over the past decade. However, whether exercise is a senolytic medicine for aging and various diseases remains unclear. Here, we have conducted a systematic review of the published literature studying the senolytic effects of exercise or physical activity on senescent cells under various states in both human and animal models. Exercise can reduce the markers of senescent cells in healthy humans, while it lowered the markers of senescent cells in obese but not healthy animals. The discrepancy between human and animal studies may be due to the relatively small volume of research and the variations in markers of senescent cells, types of cells/tissues, and health conditions. These findings suggest that exercise has senolytic properties under certain conditions, which warrant further investigations.

Mitochondrial unfolded protein response: An emerging pathway in human diseases

Mitochondrial unfolded protein response (UPR^{mt}) is a mitochondria stress response, which the transcriptional activation programs of mitochondrial chaperone proteins and proteases are initiated to maintain proteostasis in mitochondria. Additionally, the activation of UPR^{mt} delays aging and extends lifespan by maintaining mitochondrial proteostasis. Growing evidences suggests that UPR^{mt} plays an important role in diverse human diseases, especially ageing-related diseases. Therefore, this review focuses on the role of UPR^{mt} in ageing and ageing-related neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease. The activation of UPR^{mt} and the high expression of UPR^{mt} components contribute to longevity extension. The activation of UPR^{mt} may ameliorate Alzheimer's disease, Parkinson's disease and Huntington's disease. Besides, UPR^{mt} is also involved in the occurrence and development of cancers and heart diseases. UPR^{mt} contributes to the growth, invasive and metastasis of cancers. UPR^{mt} has paradoxical roles in heart diseases. UPR^{mt} not only protects against heart damage, but may sometimes aggravates the development of heart diseases. Considering the pleiotropic actions of UPR^{mt} system, targeting UPR^{mt} pathway may be a potent therapeutic avenue for neurodegenerative diseases, cancers and heart diseases.

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Advances in transcriptome analysis of human brain aging

Seokjin Ham & Seung-Jae V. Lee

Aging is associated with gradual deterioration of physiological and biochemical functions, including cognitive decline. Transcriptome profiling of brain samples from individuals of varying ages has identified the whole-transcriptome changes that underlie age-associated cognitive declines. In this review, we discuss transcriptome-based research on human brain aging performed by using microarray and RNA sequencing analyses. Overall, decreased synaptic function and increased immune function are prevalent in most regions of the aged brain. Age-associated gene expression changes are also cell dependent and region dependent and are affected by genotype. In addition, the transcriptome changes that occur during brain aging include different splicing events, intersample heterogeneity, and altered levels of various types of noncoding RNAs. Establishing transcriptome-based hallmarks of human brain aging will improve the understanding of cognitive aging and neurodegenerative diseases and eventually lead to interventions that delay or prevent brain aging.

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Glycogen Synthase Kinase 3β: A New Gold Rush in Anti-Alzheimer's Disease Multitarget Drug Discovery?

Miniperspective

Angela De Simone, Vincenzo Tumiatti, Vincenza Andrisano, and Andrea Milelli*

Alzheimer's disease (AD), like other multifactorial diseases, is the result of a systemic breakdown of different physiological networks. As result, several lines of evidence suggest that it could be more efficiently tackled by molecules directed toward different dysregulated biochemical targets or pathways. In this context, the selection of targets to which the new molecules will be directed is crucial. For years, the design of such multitarget-directed ligands (MTDLs) has been based on the selection of main targets involved in the "cholinergic" and the "β-amyloid" hypothesis. Recently, there have been some reports on MTDLs targeting the glycogen synthase kinase 3β (GSK-3β) enzyme, due to its appealing properties. Indeed, this enzyme is involved in tau hyperphosphorylation, controls a multitude of CNS-specific signaling pathways, and establishes strict connections with several factors implicated in AD pathogenesis. In the present Miniperspective, we will discuss the reasons behind the development of GSK-3β-directed MTDLs and highlight some of the recent efforts to obtain these new classes of MTDLs as potential disease-modifying agents.

Vascular dysfunction as a potential culprit of sarcopenia

Yun Kyung Jeon [1], Myung Jun Shin [2], Sunil Kumar Saini [3], Carlo Custodero [4], Monica Aggarwal [5], Stephen D Anton [3], Christiaan Leeuwenburgh [3], Robert T Mankowski [6]

Aging-related changes to biological structures such as cardiovascular and musculoskeletal systems contribute to the development of comorbid conditions including cardiovascular disease and frailty, and ultimately lead to premature death. Although, frail older adults often demonstrate both cardiovascular and musculoskeletal comorbidities, the etiology of sarcopenia, and especially the contribution of cardiovascular aging is unclear. Aging-related vascular calcification is prevalent in older adults and is a known risk factor for cardiovascular disease and death. The effect vascular calcification has on function during aging is not well understood. Emerging findings suggest vascular calcification can impact skeletal muscle perfusion, negatively affecting nutrient and oxygen delivery to skeletal muscle, ultimately accelerating muscle loss and functional decline. The present review summarizes existing evidence on the biological mechanisms linking vascular calcification with sarcopenia during aging.

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Caloric restriction: implications for sarcopenia and potential mechanisms

Sarcopenia is a potential risk factor for weakness, disability and death in elderly individuals. Therefore, seeking effective methods to delay and treat sarcopenia and to improve the quality of life of elderly individuals is a trending topic in geriatrics. Caloric restriction (CR) is currently recognized as an effective means to extend the lifespan and delay the decline in organ function caused by aging. In this review, we describe the effects of CR on improving muscle protein synthesis, delaying muscle atrophy, regulating muscle mitochondrial function, maintaining muscle strength, promoting muscle stem cell (MuSC) regeneration and differentiation, and thus protecting against sarcopenia. We also summarize the possible cellular mechanisms by which CR delays sarcopenia. CR can delay sarcopenia by reducing the generation of oxygen free radicals, reducing oxidative stress damage, enhancing mitochondrial function, improving protein homeostasis, reducing iron overload, increasing autophagy and apoptosis, and reducing inflammation. However, the relationships between CR and genetics, sex, animal strain, regimen duration and energy intake level are complex. Therefore, further study of the proper timing and application method of CR to prevent sarcopenia is highly important for the aging population.

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Reactive Oxygen Species (ROS)-Responsive Prodrugs, Probes, and Theranostic Prodrugs: Applications in the ROS-Related Diseases

Elevated levels of reactive oxygen species (ROS) have commonly been implicated in a variety of diseases, including cancer, inflammation, and neurodegenerative diseases. In light of significant differences in ROS levels between the nonpathogenic and pathological tissues, an increasing number of ROS-responsive prodrugs, probes, and theranostic prodrugs have been developed for the targeted treatment and precise diagnosis of ROS-related diseases. This review will summarize and provide insight into recent advances in ROS-responsive prodrugs, fluorescent probes, and theranostic prodrugs, with applications to different ROS-related diseases and various subcellular organelle-targetable and disease-targetable features. The ROS-responsive moieties, the self-immolative linkers, and the typical activation mechanism for the ROS-responsive release are also summarized and discussed.

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Cell non-autonomous regulation of health and longevity

As the demographics of the modern world skew older, understanding and mitigating the effects of aging is increasingly important within biomedical research. Recent studies in model organisms demonstrate that the aging process is frequently modified by an organism's ability to perceive and respond to changes in its environment. Many well-studied pathways that influence aging involve sensory cells, frequently neurons, that signal to peripheral tissues and promote survival during the presence of stress. Importantly, this activation of stress response pathways is often sufficient to improve health and longevity even in the absence of stress. Here, we review the current landscape of research highlighting the importance of cell non-autonomous signaling in modulating aging from *C. elegans* to mammals. We also discuss emerging concepts including retrograde signaling, approaches to mapping these networks, and development of potential therapeutics.

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The untwining of immunosenescence and aging

Weili Xu, Glenn Wong, You Yi Hwang & Anis Larbi

From a holistic point of view, aging results from the cumulative erosion of the various systems. Among these, the immune system is interconnected to the rest as immune cells are present in all organs and recirculate through bloodstream. Immunosenescence is the term used to define the remodelling of immune changes during aging. Because immune cells—and particularly lymphocytes—can further differentiate after their maturation in response to pathogen recognition, it is therefore unclear when senescence is induced in these cells. Additionally, it is also unclear which signals triggers senescence in immune cells (i) aging per se, (ii) specific response to pathogens, (iii) underlying conditions, or (iv) inflammaging. In this review, we will cover the current knowledge and concepts linked to immunosenescence and we focus this review on lymphocytes and T cells, which represent the typical model for replicative senescence. With the evidence presented, we propose to disentangle the senescence of

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Clinical perspectives and concerns of metformin as an anti-aging drug

Chuyao Wang, Bangwei Chen, Qian Feng, Chao Nie ✉, Tao Li ✉

As percentages of elderly people rise in many societies, age-related diseases have become more prevalent than ever. Research interests have been shifting to delaying age-related diseases by delaying or reversing aging itself. We use metformin as an entry point to talk about the important molecular and genetic longevity-regulating mechanisms that have been extensively studied with it. Then we review a number of observational studies, animal studies, and clinical trials to reflect the clinical potentials of the mechanisms in lifespan extension, cardiovascular diseases, tumors, and neurodegeneration. Finally, we highlight remaining concerns that are related to metformin and future anti-aging research.

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NAD^+ metabolism and its roles in cellular processes during ageing

Anthony J. Covarrubias, Rosalba Perrone, Alessia Grozio & Eric Verdin

Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme for redox reactions, making it central to energy metabolism. NAD^+ is also an essential cofactor for non-redox NAD^+-dependent enzymes, including sirtuins, CD38 and poly(ADP-ribose) polymerases. NAD^+ can directly and indirectly influence many key cellular functions, including metabolic pathways, DNA repair, chromatin remodelling, cellular senescence and immune cell function. These cellular processes and functions are critical for maintaining tissue and metabolic homeostasis and for healthy ageing. Remarkably, ageing is accompanied by a gradual decline in tissue and cellular NAD^+ levels in multiple model organisms, including rodents and humans. This decline in NAD^+ levels is linked causally to numerous ageing-associated diseases, including cognitive decline, cancer, metabolic disease, sarcopenia and frailty. Many of these ageing-associated diseases can be slowed down and even reversed by restoring NAD^+ levels. Therefore, targeting NAD^+ metabolism has emerged as a potential therapeutic approach to ameliorate ageing-related disease, and extend the human healthspan and lifespan. However, much remains to be learnt about how NAD^+ influences human health and ageing biology. This includes a deeper understanding of the molecular mechanisms that regulate NAD^+ levels, how to effectively restore NAD^+ levels during ageing, whether doing so is safe and whether NAD^+ repletion will have beneficial effects in ageing humans.

OTHER RESEARCH & REVIEWS

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A chimeric hemagglutinin-based universal influenza virus vaccine approach induces broad and long-lasting immunity in a randomized, placebo-controlled phase I trial

Seasonal influenza viruses constantly change through antigenic drift and the emergence of pandemic influenza viruses through antigenic shift is unpredictable. Conventional influenza virus vaccines induce strain-specific neutralizing antibodies against the variable immunodominant globular head domain of the viral hemagglutinin protein. This necessitates frequent re-formulation of vaccines and handicaps pandemic preparedness. In this completed, observer-blind, randomized, placebo-controlled phase I trial (NCT03300050), safety and immunogenicity of chimeric hemagglutinin-based vaccines were tested in healthy, 18–39-year-old US adults. The study aimed to test the safety and ability of the vaccines to elicit broadly cross-reactive antibodies against the hemagglutinin stalk domain. Participants were enrolled into five groups to receive vaccinations with live-attenuated followed by AS03-adjuvanted inactivated vaccine ($n = 20$), live-attenuated followed by inactivated vaccine ($n = 15$), twice AS03-adjuvanted inactivated vaccine ($n = 16$) or placebo ($n = 5$, intranasal followed by intramuscular; $n = 10$, twice intramuscular) 3 months apart. Vaccination was found to be safe and induced a broad, strong, durable and functional immune response targeting the conserved, immunosubdominant stalk of the hemagglutinin. The results suggest that chimeric hemagglutinins have the potential to be developed as universal vaccines that protect broadly against influenza viruses.

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Neuroprotective effects and mechanisms of action of nicotinamide mononucleotide (NMN) in a photoreceptor degenerative model of retinal detachment

Currently, no pharmacotherapy has been proven effective in treating photoreceptor degeneration in patients. Discovering readily available and safe neuroprotectants is therefore highly sought after. Here, we investigated nicotinamide mononucleotide (NMN), a precursor of nicotinamide adenine dinucleotide (NAD^+), in a retinal detachment (RD) induced photoreceptor degeneration. NMN administration after RD resulted in a significant reduction of $TUNEL^+$ photoreceptors, $CD11b^+$ macrophages, and GFAP labeled glial activation; a normalization of protein carbonyl content (PCC), and a preservation of the outer nuclear layer (ONL) thickness. NMN administration significantly increased NAD^+ levels, SIRT1 protein expression, and heme oxygenase-1 (HO-1) expression. Delayed NMN administration still exerted protective effects after RD. Mechanistic *in vitro* studies using 661W cells revealed a SIRT1/HO-1 signaling as a downstream effector of NMN-mediated protection under oxidative stress and LPS stimulation. In conclusion, NMN administration exerts neuroprotective effects on photoreceptors after RD and oxidative injury, suggesting a therapeutic avenue to treating photoreceptor degeneration.