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Sven Bulterijs

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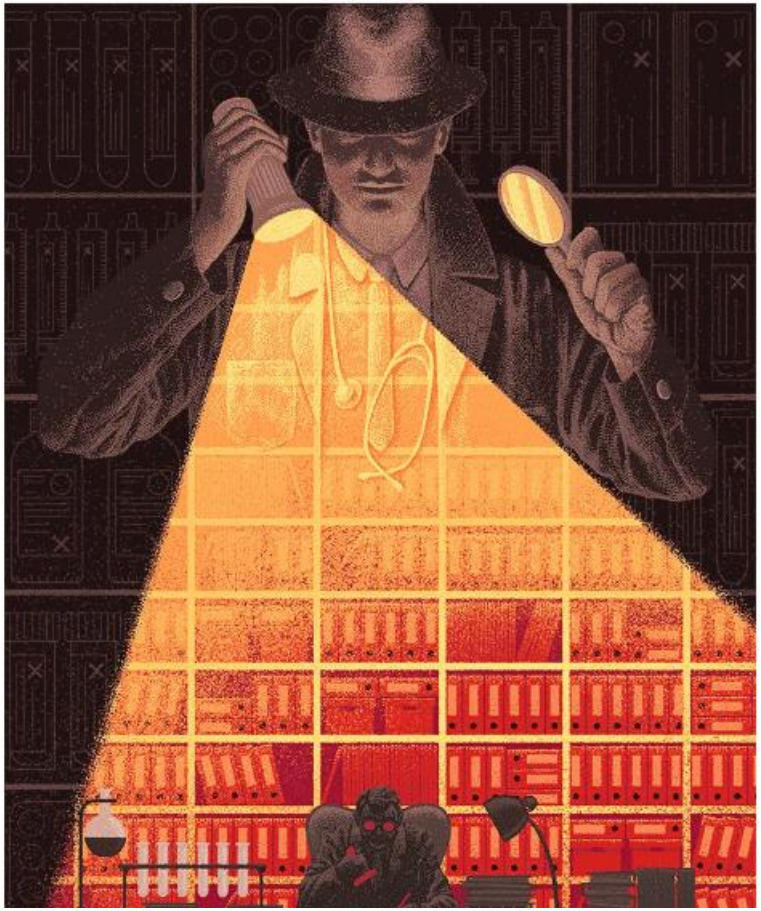
Medicine is plagued by untrustworthy clinical trials. How many studies are faked or flawed?

Investigations suggest that, in some fields, at least one-quarter of clinical trials might be problematic or even entirely made up, warn some researchers. They urge stronger scrutiny.

Richard Van Noorden



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The Obesity Drug Revolution Just Got Real

Wegovy reduces risk of heart attack, stroke in study, paving way for greater insurance coverage

By David Wainer Follow

Aug. 8, 2023 10:24 am ET

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Longitudinal positron emission tomography and postmortem analysis reveals widespread neuroinflammation in SARS-CoV-2 infected rhesus macaques

Background: Coronavirus disease 2019 (COVID-19) patients initially develop respiratory symptoms, but they may also suffer from neurological symptoms. People with long-lasting effects after acute infections with severe respiratory syndrome coronavirus 2 (SARS-CoV-2), i.e., post-COVID syndrome or long COVID, may experience a variety of neurological manifestations. Although we do not fully understand how SARS-CoV-2 affects the brain, neuroinflammation likely plays a role.

Methods: To investigate neuroinflammatory processes longitudinally after SARS-CoV-2 infection, four experimentally SARS-CoV-2 infected rhesus macaques were monitored for 7 weeks with 18-kDa translocator protein (TSPO) positron emission tomography (PET) using [^{18}F]DPA714, together with computed tomography (CT). The baseline scan was compared to weekly PET-CTs obtained post-infection (pi). Brain tissue was collected following euthanasia (50 days pi) to correlate the PET signal with TSPO expression, and glial and endothelial cell markers. Expression of these markers was compared to brain tissue from uninfected animals of comparable age, allowing the examination of the contribution of these cells to the neuroinflammatory response following SARS-CoV-2 infection.

Results: TSPO PET revealed an increased tracer uptake throughout the brain of all infected animals already from the first scan obtained post-infection (day 2), which increased to approximately twofold until day 30 pi. Postmortem immunohistochemical analysis of the hippocampus and pons showed TSPO expression in cells expressing ionized calcium-binding adaptor molecule 1 (IBA1), glial fibrillary acidic protein (GFAP), and collagen IV. In the hippocampus of SARS-CoV-2 infected animals the TSPO$^+$ area and number of TSPO$^+$ cells were significantly increased compared to control animals. This increase was not cell type specific, since both the number of IBA1$^+$TSPO$^+$ and GFAP$^+$TSPO$^+$ cells was increased, as well as the TSPO$^+$ area within collagen IV$^+$ blood vessels.

Conclusions: This study manifests [^{18}F]DPA714 as a powerful radiotracer to visualize SARS-CoV-2 induced neuroinflammation. The increased uptake of [^{18}F]DPA714 over time implies an active neuroinflammatory response following SARS-CoV-2 infection. This inflammatory signal coincides with an increased number of TSPO expressing cells, including glial and endothelial cells, suggesting neuroinflammation and vascular dysregulation. These results demonstrate the long-term neuroinflammatory response following a mild SARS-CoV-2 infection, which potentially precedes long-lasting neurological symptoms.

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How Old Can Humans Get?

An expert on aging thinks humans could live to be 1,000 years old—with a few tweaks to our genetic "software"

By Bill Gifford on July 31, 2023

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Multi-omic rejuvenation and life span extension on exposure to youthful circulation

Bohan Zhang, David E. Lee, Alexandre Trapp, Alexander Tyshkovskiy, Ake T. Lu, Akshay Bareja, Csaba Kerepesi, Lauren K. McKay, Anastasia V. Shindyapina, Sergey E. Dmitriev, Gurpreet S. Baht, Steve Horvath, Vadim N. Gladyshev ✉ & James P. White ✉

Heterochronic parabiosis (HPB) is known for its functional rejuvenation effects across several mouse tissues. However, its impact on biological age and long-term health is unknown. Here we performed extended (3-month) HPB, followed by a 2-month detachment period of anastomosed pairs. Old detached mice exhibited improved physiological parameters and lived longer than control isochronic mice. HPB drastically reduced the epigenetic age of blood and liver based on several clock models using two independent platforms. Remarkably, this rejuvenation effect persisted even after 2 months of detachment. Transcriptomic and epigenomic profiles of anastomosed mice showed an intermediate phenotype between old and young, suggesting a global multi-omic rejuvenation effect. In addition, old HPB mice showed gene expression changes opposite to aging but akin to several life span-extending interventions. Altogether, we reveal that long-term HPB results in lasting epigenetic and transcriptome remodeling, culminating in the extension of life span and health span.

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PREPRINT

Reversal of Biological Age in Multiple Rat Organs by Young Porcine Plasma Fraction

Steve Horvath, Kavita Singh, Ken Raj, Shraddha Khairnar, Akshay Sanghavi, Agnivesh Shrivastava, Joseph A. Zoller, Caesar Z. Li, Claudia B. Herenu, Martina Canatelli-Mallat, Marianne Lehmann, Siniša Habazin, Mislav Novokmet, Frano Vučković, Leah C. Solberg Woods, Angel Garcia Martinez, Tengfei Wang, Priscila Chiavellini, Andrew J. Levine, Hao Chen, Robert T Brooke, Juozas Gordevicius, Gordan Lauc, Rodolfo G. Goya, Harold L. Katcher

Young blood plasma is known to confer beneficial effects on various organs in mice and rats. However, it was not known whether plasma from young pigs rejuvenates old rat tissues at the epigenetic level; whether it alters the epigenetic clock, which is a highly accurate molecular biomarker of aging. To address this question, we developed and validated six different epigenetic clocks for rat tissues that are based on DNA methylation values derived from n=613 tissue samples. As indicated by their respective names, the rat pan-tissue clock can be applied to DNA methylation profiles from all rat tissues, while the rat brain-, liver-, and blood clocks apply to the corresponding tissue types. We also developed two epigenetic clocks that apply to both human and rat tissues by adding n=1366 human tissue samples to the training data. We employed these six rat clocks to investigate the rejuvenation effects of a porcine plasma fraction treatment in different rat tissues. The treatment more than halved the epigenetic ages of blood, heart, and liver tissue. A less pronounced, but statistically significant, rejuvenation effect could be observed in the hypothalamus. The treatment was accompanied by progressive improvement in the function of these organs as ascertained through numerous biochemical/physiological biomarkers and behavioral responses to assess cognitive functions. An immunoglobulin G (IgG) N-glycosylation pattern shift from pro-to anti-inflammatory also indicated reversal of glycan aging. Overall, this study demonstrates that a young porcine plasma-derived treatment markedly reverses aging in rats according to epigenetic clocks, IgG glycans, and other biomarkers of aging.

Rejuvenating effects of young extracellular vesicles in aged rats and in cellular models of human senescence

Lilian Grigorian Shamagian ✉, Russell G. Rogers, Kristin Luther, David Angert, Antonio Echavez, Weixin Liu, Ryan Middleton, Travis Antes, Jackelyn Valle, Mario Fourier, Liz Sanchez, Eva Jaghatspanyan, Javier Mariscal, Rui Zhang & Eduardo Marbán

Rejuvenation of an old organism was achieved in heterochronic parabiosis experiments, implicating different soluble factors in this effect. Extracellular vesicles (EVs) are the secretory effectors of many cells, including cardiosphere-derived cells (CDCs) with demonstrated anti-senescent effect. 1. To determine the role of EVs (versus other blood fractions) on the rejuvenating effect of the young blood. 2. To evaluate the anti-aging properties of therapeutically administered EVs secreted by young-CDCs in an old organism. Neonatal blood fractioned in 4 components (whole blood, serum, EV-depleted serum and purified EVs) was used to treat old human cardiac stromal cells (CSPCs). CDCs were generated from neonatal rat hearts and the secreted CDC-EVs were purified. CDC-EVs were then tested in naturally-aged rats, using monthly injections over 4-months period. For validation in human samples, pediatric CDC-EVs were tested in aged human CSPCs and progeric fibroblasts. While the purified EVs reproduced the rejuvenating effects of the whole blood, CSPCs treated with EV-depleted serum exhibited the highest degree of senescence. Treatment with young CDC-EVs induce structural and functional improvements in the heart, lungs, skeletal muscle, and kidneys of old rats, while favorably modulating glucose metabolism and anti-senescence pathways. Lifespan was prolonged. EVs secreted by young CDCs exert broad-ranging anti-aging effects in aged rodents and in cellular models of human senescence. Our work not only identifies CDC-EVs as possible therapeutic candidates for a wide range of age-related pathologies, but also raises the question of whether EVs function as endogenous modulators of senescence.

A short dasatinib and quercetin treatment is sufficient to reinstate potent adult neuroregenesis in the aged killifish

Jolien Van houcke, Valerie Mariën, Caroline Zandecki, Rajagopal Ayana, Elise Pepermans, Kurt Boonen, Eve Seuntjens, Geert Baggerman & Lutgarde Arckens

The young African turquoise killifish has a high regenerative capacity, but loses it with advancing age, adopting several aspects of the limited form of mammalian regeneration. We deployed a proteomic strategy to identify pathways that underpin the loss of regenerative power caused by aging. Cellular senescence stood out as a potential brake on successful neurorepair. We applied the senolytic cocktail Dasatinib and Quercetin (D + Q) to test clearance of chronic senescent cells from the aged killifish central nervous system (CNS) as well as rebooting the neurogenic output. Our results show that the entire aged killifish telencephalon holds a very high senescent cell burden, including the parenchyma and the neurogenic niches, which could be diminished by a short-term, late-onset D + Q treatment. Reactive proliferation of non-glial progenitors increased substantially and lead to restorative neurogenesis after traumatic brain injury. Our results provide a cellular mechanism for age-related regeneration resilience and a proof-of-concept of a potential therapy to revive the neurogenic potential in an already aged or diseased CNS.

cGAS–STING drives ageing-related inflammation and neurodegeneration

Muhammet F Gulen [# 1], Natasha Samson [# 1], Alexander Keller [1], Marius Schwabenland [2], Chong Liu [1], Selene Glück [1], Vivek V Thacker [1], Lucie Favre [3], Bastien Mangeat [4], Lona J Kroese [5], Paul Krimpenfort [5], Marco Prinz [2 6 7], Andrea Ablasser [8 9]

Low-grade inflammation is a hallmark of old age and a central driver of ageing-associated impairment and disease[1]. Multiple factors can contribute to ageing-associated inflammation[2]; however, the molecular pathways that transduce aberrant inflammatory signalling and their impact in natural ageing remain unclear. Here we show that the cGAS-STING signalling pathway, which mediates immune sensing of DNA[3], is a critical driver of chronic inflammation and functional decline during ageing. Blockade of STING suppresses the inflammatory phenotypes of senescent human cells and tissues, attenuates ageing-related inflammation in multiple peripheral organs and the brain in mice, and leads to an improvement in tissue function. Focusing on the ageing brain, we reveal that activation of STING triggers reactive microglial transcriptional states, neurodegeneration and cognitive decline. Cytosolic DNA released from perturbed mitochondria elicits cGAS activity in old microglia, defining a mechanism by which cGAS-STING signalling is engaged in the ageing brain. Single-nucleus RNA-sequencing analysis of microglia and hippocampi of a cGAS gain-of-function mouse model demonstrates that engagement of cGAS in microglia is sufficient to direct ageing-associated transcriptional microglial states leading to bystander cell inflammation, neurotoxicity and impaired memory capacity. Our findings establish the cGAS-STING pathway as a driver of ageing-related inflammation in peripheral organs and the brain, and reveal blockade of cGAS-STING signalling as a potential strategy to halt neurodegenerative processes during old age.

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Overnight olfactory enrichment using an odorant diffuser improves memory and modifies the uncinate fasciculus in older adults

Objective: Cognitive loss in older adults is a growing issue in our society, and there is a need to develop inexpensive, simple, effective in-home treatments. This study was conducted to explore the use of olfactory enrichment at night to improve cognitive ability in healthy older adults.

Methods: Male and female older adults ($N = 43$), age 60–85, were enrolled in the study and randomly assigned to an Olfactory Enriched or Control group. Individuals in the enriched group were exposed to 7 different odorants a week, one per night, for 2 h, using an odorant diffuser. Individuals in the control group had the same experience with *de minimis* amounts of odorant. Neuropsychological assessments and fMRI scans were administered at the beginning of the study and after 6 months.

Results: A statistically significant 226% improvement was observed in the enriched group compared to the control group on the Rey Auditory Verbal Learning Test and improved functioning was observed in the left uncinate fasciculus, as assessed by mean diffusivity.

Conclusion: Minimal olfactory enrichment administered at night produces improvements in both cognitive and neural functioning. Thus, olfactory enrichment may provide an effective and low-effort pathway to improved brain health.

Retirement and cognitive aging in a racially diverse sample of older Americans

Ross Andel PhD, Britney M. Veal BA, Virginia J. Howard PhD, Leslie A. MacDonald ScD, Suzanne E. Judd PhD, Michael Crowe PhD

Methods

Longitudinal examination of up to 10 years (mean = 7.1 ± 2.2 years) using data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study–a national, longitudinal study of Black and White adults ≥45 years of age. Data were from 2226 members of the REGARDS study who retired around the time when an occupational ancillary survey was administered. Cognitive function was an average of *z*-scores for tests of verbal fluency, memory, and global function.

Results

Cognitive functioning was stable before retirement (Estimate = 0.05, $p = 0.322$), followed by a significant decline after retirement (Estimate = −0.15, $p < 0.001$). The decline was particularly pronounced in White (Estimate = −0.19, $p < 0.001$) compared with Black (Estimate = −0.07, $p = 0.077$) participants, twice as large in men (Estimate = −0.20, $p < 0.001$) compared with women (Estimate = −0.11, $p < 0.001$), highest among White men (Estimate = −0.22, $p < 0.001$) and lowest in Black women (Estimate = −0.04, $p = 0.457$). Greater post-retirement cognitive decline was also observed among participants who attended college (Estimate = −0.14, $p = 0.016$). While greater work complexity (Estimate = 0.92, $p < 0.05$) and higher income (Estimate = 1.03, $p < 0.05$) were related to better cognitive function at retirement, neither was significantly related to cognitive change after retirement.

Conclusion

Cognitive functioning may decline at an accelerated rate immediately post-retirement, more so in White adults and men than Black adults and women. Lifelong structural inequalities including occupational segregation and other social determinants of cognitive health may obscure the role of retirement in cognitive aging.

Transcriptomes of human primary skin fibroblasts of healthy individuals reveal age-associated mRNAs and long noncoding RNAs

Dimitrios Tsitsipatis, Jennifer L. Martindale, Krystyna Mazan-Mamczarz, Allison B. Herman, Yulan Piao, Nirad Banskota, Jen-Hao Yang, Linna Cui, Carlos Anerillas, Ming-Wen Chang ... See all authors

Changes in the transcriptomes of human tissues with advancing age are poorly cataloged. Here, we sought to identify the coding and long noncoding RNAs present in cultured primary skin fibroblasts collected from 82 healthy individuals across a wide age spectrum (22–89 years old) who participated in the GESTALT (Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing) study of the National Institute on Aging, NIH. Using high-throughput RNA sequencing and a linear regression model, we identified 1437 coding RNAs (mRNAs) and 1177 linear and circular long noncoding (lncRNAs) that were differentially abundant as a function of age. Gene set enrichment analysis (GSEA) revealed select transcription factors implicated in coordinating the transcription of subsets of differentially abundant mRNAs, while long noncoding RNA enrichment analysis (LncSEA) identified RNA-binding proteins predicted to participate in the age-associated lncRNA profiles. In summary, we report age-associated changes in the global transcriptome, coding and noncoding, from healthy human skin fibroblasts and propose that these transcripts may serve as biomarkers and therapeutic targets in aging skin.

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PREPRINT

Transposable element expression with variation in gonosome number supports a toxic Y effect on human longevity

Jordan Teoli, Marie Fablet, Claire Bardel, Anamaria Necsulea, Audrey Labalme, Hervé Lejeune, Jean-François Lemaitre, François Gueyffier, Damien Sanlaville, Cristina Vieira, Gabriel AB Marais, Ingrid Plotton

Lifespan differences between sexes is a puzzling question in human and evolutionary biology. Sex chromosomes have been proposed as playing a central role, and the Y male chromosome has been suspected of having a toxic genomic impact in this trait. As Y chromosomes are typically enriched in transposable elements (TE), this hypothesis suggests that in aged individuals, in which TE are less repressed, an increase of somatic mutations and acceleration of the aging process will be observed. Using an unprecedent expression dataset from humans with atypical karyotypes we show an increased TE expression, related to the Y chromosome. These findings fit with previous reports that the 47,XYY human population displays a shorter lifespan, and support the existence of a toxic Y effect on men lifespan.

Lifespan-extending interventions induce consistent patterns of fatty acid oxidation in mouse livers

Aging manifests as progressive deteriorations in homeostasis, requiring systems-level perspectives to investigate the gradual molecular dysregulation of underlying biological processes. Here, we report systemic changes in the molecular regulation of biological processes under multiple lifespan-extending interventions. Differential Rank Conservation (DIRAC) analyses of mouse liver proteomics and transcriptomics data show that mechanistically distinct lifespan-extending interventions (acarbose, 17α-estradiol, rapamycin, and calorie restriction) generally tighten the regulation of biological modules. These tightening patterns are similar across the interventions, particularly in processes such as fatty acid oxidation, immune response, and stress response. Differences in DIRAC patterns between proteins and transcripts highlight specific modules which may be tightened via augmented cap-independent translation. Moreover, the systemic shifts in fatty acid metabolism are supported through integrated analysis of liver transcriptomics data with a mouse genome-scale metabolic model. Our findings highlight the power of systems-level approaches for identifying and characterizing the biological processes involved in aging and longevity.

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PREPRINT

Five years later, with double the demographic data, naked mole-rat mortality rates continue to defy Gompertzian laws by not increasing with age

J. Graham Ruby, Megan Smith, Rochelle Buffenstein

The naked mole-rat (*Heterocephalus glaber*) is a mouse-sized rodent species, notable for its eusociality and long lifespan. Previously, we reported that demographic aging, i.e., the exponential increase of mortality hazard that accompanies advancing age in mammals and other organisms, does not occur in naked mole-rats (**Ruby et al, 2018**). The demographic data supporting that conclusion had taken over three decades to accumulate, starting with the original rearing of *H.glaber* in captivity. In the five years following that study, we ~doubled our quantity of demographic data. Here, we re-evaluated our prior conclusions in light of these new data and found them to be supported and indeed strengthened. We additionally provided insight into the social dynamics of captive *H.glaber* with data and analyses of body weight and colony size versus mortality. Finally, we provide a phylogenetically-proximal comparator in the form of lifespan data from our Damaraland mole-rat (*Fukomys damarensis*) colony and demographic meta-analysis of those data along with published data from Ansell's mole-rat (*Fukomys anselli*). We found *Fukomys* mortality hazard to increase gradually with age, an observation with implications on the evolution of exceptional lifespan among mole-rats and the ecological factors that may have accompanied that evolution.

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Universal DNA methylation age across mammalian tissues

Aging, often considered a result of random cellular damage, can be accurately estimated using DNA methylation profiles, the foundation of pan-tissue epigenetic clocks. Here, we demonstrate the development of universal pan-mammalian clocks, using 11,754 methylation arrays from our Mammalian Methylation Consortium, which encompass 59 tissue types across 185 mammalian species. These predictive models estimate mammalian tissue age with high accuracy ($r > 0.96$). Age deviations correlate with human mortality risk, mouse somatotropic axis mutations and caloric restriction. We identified specific cytosines with methylation levels that change with age across numerous species. These sites, highly enriched in polycomb repressive complex 2-binding locations, are near genes implicated in mammalian development, cancer, obesity and longevity. Our findings offer new evidence suggesting that aging is evolutionarily conserved and intertwined with developmental processes across all mammals.

A combination of metformin and galantamine exhibits synergistic benefits in the treatment of sarcopenia

Age-associated sarcopenia, characterized by a progressive loss in muscle mass and strength, is the largest cause of frailty and disability in the elderly worldwide. Current treatments involve nonpharmacological guidelines that few subjects can abide by, highlighting the need for effective drugs. Preclinical models were employed to test the benefits of RJx-01, a combination drug composed of metformin and galantamine, on sarcopenia. In worms, RJx-01 treatment improved lifespan, locomotion, pharyngeal pumping, and muscle fiber organization. The synergistic effects of RJx-01 were recapitulated in a transgenic mouse model that displays an exacerbated aging phenotype (*Opa1*$^{-/-}$). In these mice, RJx-01 ameliorated physical performance, muscle mass and force, neuromuscular junction stability, and systemic inflammation. RJx-01 also improved physical performance and muscle strength in 22-month-old WT mice and also improved skeletal muscle ultrastructure, mitochondrial morphology, autophagy, lysosomal function, and satellite cell content. Denervation and myofiber damage were decreased in RJx-01–treated animals compared with controls. RJx-01 improved muscle quality rather than quantity, indicating that the improvement in quality underlies the beneficial effects of the combination drug. The studies herein indicate synergistic beneficial effects of RJx-01 in the treatment of sarcopenia and support the pursuit of RJx-01 in a human clinical trial as a therapeutic intervention for sarcopenia.

The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis

Methods and results

We systematically searched relevant electronic databases from inception until 12 June 2022. The main endpoints were all-cause mortality and CV mortality. An inverse-variance weighted random-effects model was used to calculate the number of steps/day and mortality. Seventeen cohort studies with a total of 226 889 participants (generally healthy or patients at CV risk) with a median follow-up 7.1 years were included in the meta-analysis. A 1000-step increment was associated with a 15% decreased risk of all-cause mortality [hazard ratio (HR) 0.85; 95% confidence interval (CI) 0.81–0.91; $P < 0.001$], while a 500-step increment was associated with a 7% decrease in CV mortality (HR 0.93; 95% CI 0.91–0.95; $P < 0.001$). Compared with the reference quartile with median steps/day 3967 (2500–6675), the Quartile 1 (Q1, median steps: 5537), Quartile 2 (Q2, median steps 7370), and Quartile 3 (Q3, median steps 11 529) were associated with lower risk for all-cause mortality (48, 55, and 67%, respectively; $P < 0.05$, for all). Similarly, compared with the lowest quartile of steps/day used as reference [median steps 2337, interquartile range 1596–4000), higher quartiles of steps/day (Q1 = 3982, Q2 = 6661, and Q3 = 10 413) were linearly associated with a reduced risk of CV mortality (16, 49, and 77%; $P < 0.05$, for all). Using a restricted cubic splines model, we observed a nonlinear dose–response association between step count and all-cause and CV mortality ($P_{\text{nonlineraly}} < 0.001$, for both) with a progressively lower risk of mortality with an increased step count.

Conclusion

This meta-analysis demonstrates a significant inverse association between daily step count and all-cause mortality and CV mortality with more the better over the cut-off point of 3967 steps/day for all-cause mortality and only 2337 steps for CV mortality.

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Multivariate genome-wide analysis of aging-related traits identifies novel loci and new drug targets for healthy aging

The concept of aging is complex, including many related phenotypes such as healthspan, lifespan, extreme longevity, frailty and epigenetic aging, suggesting shared biological underpinnings; however, aging-related endpoints have been primarily assessed individually. Using data from these traits and multivariate genome-wide association study methods, we modeled their underlying genetic factor ('mvAge'). mvAge (effective n = ~1.9 million participants of European ancestry) identified 52 independent variants in 38 genomic loci. Twenty variants were novel (not reported in input genome-wide association studies). Transcriptomic imputation identified age-relevant genes, including *VEGFA* and *PHB1*. Drug-target Mendelian randomization with metformin target genes showed a beneficial impact on mvAge (P value = 8.41×10^{-5}). Similarly, genetically proxied thiazolidinediones (P value = 3.50×10^{-10}), proprotein convertase subtilisin/kexin 9 inhibition (P value = 1.62×10^{-6}), angiopoietin-like protein 4, beta blockers and calcium channel blockers also had beneficial Mendelian randomization estimates. Extending the drug-target Mendelian randomization framework to 3,947 protein-coding genes prioritized 122 targets. Together, these findings will inform future studies aimed at improving healthy aging.

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No time to die: Evolution of a post-reproductive life stage

P. Monaghan ✉, E. R. Ivimey-Cook

In some species, permanent curtailment of reproduction part-way through the lifespan of adult females is a feature of their evolved life history. The existence of such a post-reproductive life stage is apparently rare; reasonably robust evidence for this is confined to only six species (humans, Asian elephants and four whales). That it occurs at all appears to contradict our view of natural selection operating to maximize fitness and special circumstances must exist to explain its occurrence. We evaluate the main hypotheses posited to explain the evolution of this life stage, why it occurs in a restricted group of animals, and why only in females. We bring together literature from multiple biological disciplines and levels of enquiry, ranging through evolutionary ecology, developmental biology, physiology, neuroscience, molecular biology, and human medicine. We conclude that while time-limited fertility is not in itself adaptive, the duration of subsequent survival is likely to be linked to inclusive fitness benefits. We present a new hypothesis which posits that the duration of female fertility in certain long-lived, highly encephalised species, with no post-natal oogenesis, is limited by the need for intense screening of oocyte mitochondria. This is required to support endothermy coupled with the very high energy requirement for the development and maintenance of the exceptionally large brain size required for complex social living. This limits the number and shelf-life of oocytes, creating an antagonistically pleotropic effect that is beneficial to the production of high performing offspring but carries the later life cost of time-limited female fertility. But the end of the fertile period is no time to die. Inclusive fitness benefits arising from protracted parental care of offspring, overlapping generations, and kin group structures means that continued survival of post-reproductive females is favoured by selection. We suggest further lines of research to test these ideas.

C. elegans aging research

C. elegans ageing is accelerated by a self-destructive reproductive programme

Carina C Kern [1], Shivangi Srivastava [1], Marina Ezcurra [1 2], Kuei Ching Hsiung [1], Nancy Hui [1], StJohn Townsend [1 3], Dominik Maczik [1], Bruce Zhang [1], Victoria Tse [1], Viktoras Konstantellos [1], Jürg Bähler [1], David Gems [4]

In post-reproductive C. elegans, destructive somatic biomass repurposing supports production of yolk which, it was recently shown, is vented and can serve as a foodstuff for larval progeny. This is reminiscent of the suicidal reproductive effort (reproductive death) typical of semelparous organisms such as Pacific salmon. To explore the possibility that C. elegans exhibits reproductive death, we have compared sibling species pairs of the genera Caenorhabditis and Pristionchus with hermaphrodites and females. We report that yolk venting and constitutive, early pathology involving major anatomical changes occur only in hermaphrodites, which are also shorter lived. Moreover, only in hermaphrodites does germline removal suppress senescent pathology and markedly increase lifespan. This is consistent with the hypothesis that C. elegans exhibit reproductive death that is suppressed by germline ablation. If correct, this would imply a major difference in the ageing process between C. elegans and most higher organisms, and potentially explain the exceptional plasticity in C. elegans ageing.

Individual cell types in *C.elegans* age differently and activate distinct cell-protective responses

Antoine Emile Roux [1 2], Han Yuan [1 2], Katie Podshivalova [1], David Hendrickson [1], Rex Kerr [1], Cynthia Kenyon [1], David Kelley [1 3]

Aging is characterized by a global decline in physiological function. However, by constructing a complete single-cell gene expression atlas, we find that *Caenorhabditis elegans* aging is not random in nature but instead is characterized by coordinated changes in functionally related metabolic, proteostasis, and stress-response genes in a cell-type-specific fashion, with downregulation of energy metabolism being the only nearly universal change. Similarly, the rates at which cells age differ significantly between cell types. In some cell types, aging is characterized by an increase in cell-to-cell variance, whereas in others, variance actually decreases. Remarkably, multiple resilience-enhancing transcription factors known to extend lifespan are activated across many cell types with age; we discovered new longevity candidates, such as GEI-3, among these. Together, our findings suggest that cells do not age passively but instead react strongly, and individualistically, to events that occur during aging. This atlas can be queried through a public interface.

Olfactory chemosensation extends lifespan through TGF-β signaling and UPR activation

Evandro A. De-Souza, Maximillian A. Thompson & Rebecca C. Taylor

Animals rely on chemosensory cues to survive in pathogen-rich environments. In *Caenorhabditis elegans*, pathogenic bacteria trigger aversive behaviors through neuronal perception and activate molecular defenses throughout the animal. This suggests that neurons can coordinate the activation of organism-wide defensive responses upon pathogen perception. In this study, we found that exposure to volatile pathogen-associated compounds induces activation of the endoplasmic reticulum unfolded protein response (UPR^{ER}) in peripheral tissues after *xbp-1* splicing in neurons. This odorant-induced UPR^{ER} activation is dependent upon DAF-7/transforming growth factor beta (TGF-β) signaling and leads to extended lifespan and enhanced clearance of toxic proteins. Notably, rescue of the DAF-1 TGF-β receptor in RIM/RIC interneurons is sufficient to significantly recover UPR^{ER} activation upon 1-undecene exposure. Our data suggest that the cell non-autonomous UPR^{ER} rewires organismal proteostasis in response to pathogen detection, pre-empting proteotoxic stress. Thus, chemosensation of particular odors may be a route to manipulation of stress responses and longevity.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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PREPRINT

Somatic mutations in human ageing: New insights from DNA sequencing and inherited mutations

Kasit Chatsirisupachai, João Pedro de Magalhães

The accumulation of somatic mutations is a driver of cancer and has long been associated with ageing. Due to limitations in quantifying mutation burden with age in non-cancerous tissues, the impact of somatic mutations in other ageing phenotypes is unclear. Recent advances in DNA sequencing technologies have allowed the large-scale quantification of somatic mutations in ageing. These studies have revealed a gradual accumulation of mutations in most normal tissues with age as well as a substantial clonal expansion driven mostly by cancer-related mutations. Nevertheless, because of the relatively modest burden of age-related somatic mutations identified so far and their stochastic nature, it is difficult to envision how somatic mutation accumulation alone can explain most ageing phenotypes that develop gradually. Studies across species have also found that longer-lived species have lower somatic mutation rates, though these could be explained by selective pressures to reduce or postpone cancer as longevity increases. Overall, with a few exceptions like cancer, results from recent DNA sequencing studies do not add weight to the idea that somatic mutations with age drive ageing phenotypes and the phenotypic role, if any, of somatic mutations in ageing remains unclear. Recent studies in patients with somatic mutation burden and no signs of accelerated ageing further question the role of somatic mutations in ageing.

A "Best Choice Medicine" (BCM) Route to Drug Development to Solve the Aging-Associated Non-Communicable Disease Burden

Elizabeth L. Parrish[1*] and William H. Andrews [2]

Objective: The Objective of this paper is to propose a new modality called Best Choice Medicine (BCM) to provide possible life-saving experimental treatments to patients suffering from Aging-Associated Non-Communicable Diseases (AA-NCDs) who would otherwise not survive without treatment. Likewise, BCM would expedite the drug approval process in the U.S. by generating immediate data from these patients. BCM resembles Medical Tourism in many ways except that it would be done within the U.S. To better appreciate Medical Tourism as a field patients were queried for their feedback on their own experiences with Medical Tourism.

Method: Thirteen people who spent significant time and money participating in Medical Tourism were queried in a non-randomized non-controlled survey to understand their perceptions of the Medical Tourism field.

Results: The thirteen people chose to participate in Medical Tourism mostly due to lack of treatments available through the regulatory system in their own countries. They also believed that they should be able to choose therapies for themselves. And all participants said that they would consider participating in medical tourism again.

Conclusions: Although this is a small study the researchers believe that this research shows the need for a new and more assessable regulatory route, such as BCM, in the United States. This preliminary study is a launchpad for doing more in-depth studies to develop and evaluate the concept of BCM further.

Wearable sweat analysis to determine biological age

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Abstract

A real-time, noninvasive, and clinically applicable aging test in humans has yet to be established. Herein we propose a sweat- and wearable-based test to determine biological age. This test would empower users to monitor their aging process and take an active role in managing their lifestyle and health.

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Towards disease-oriented dosing of rapamycin for longevity: does aging exist or only age-related diseases?

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Abstract

Both individuals taking rapamycin, an anti-aging drug, and those not taking it will ultimately succumb to age-related diseases. However, the former, if administered disease-oriented dosages for a long time, may experience a delayed onset of such diseases and live longer. The goal is to delay a particular disease that is expected to be life-limiting in a particular person. Age-related diseases, quasi-programmed during development, progress at varying rates in different individuals. Rapamycin is a prophylactic anti-aging drug that decelerates early development of age-related diseases. I further discuss hyperfunction theory of quasi-programmed diseases, which challenges the need for the traditional concept of aging itself.

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Mechanotransduction through hemidesmosomes during aging and longevity

In collection: Adhesion , Mechanobiology

Collin Y. Ewald , Alexander Nyström

Hemidesmosomes are structural protein complexes localized at the interface of tissues with high mechanical demand and shear forces. Beyond tissue anchoring, hemidesmosomes have emerged as force-modulating structures important for translating mechanical cues into biochemical and transcriptional adaptation (i.e. mechanotransduction) across tissues. Here, we discuss the recent insights into the roles of hemidesmosomes in age-related tissue regeneration and aging in *C. elegans*, mice and humans. We highlight the emerging concept of preserved dynamic mechanoregulation of hemidesmosomes in tissue maintenance and healthy aging.

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Environment, Epigenetics, and the Pace of Human Aging

Annual Review of Anthropology

The trajectory of human aging varies widely from one individual to the next due to complex interactions between the genome and the environment that influence the aging process. Such differences in age-specific mortality and disease risk among same-aged individuals reflect variation in the pace of biological aging. Certain mechanisms involved in the progression of biological aging originate in the epigenome, where chemical modifications to the genome are able to alter gene expression without modifying the underlying DNA sequence. The epigenome serves as an interface for environmental signals, which are able to “get under the skin” to influence health and aging. A number of the molecular mechanisms involved in the aging process have been identified, although few aging phenotypes have been definitively traced to their underlying molecular causes thus far. In this review, we discuss variation in human biological aging and the epigenome's role in promoting heterogeneity in human longevity and healthspan.

Scientific evidence of foods that improve the lifespan and healthspan of different organisms

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Age is a risk factor for numerous diseases. Although the development of modern medicine has greatly extended the human lifespan, the duration of relatively healthy old age, or 'healthspan', has not increased. Targeting the detrimental processes that can occur before the onset of age-related diseases can greatly improve health and lifespan. Healthspan is significantly affected by what, when and how much one eats. Dietary restriction, including calorie restriction, fasting or fasting-mimicking diets, to extend both lifespan and healthspan has recently attracted much attention. However, direct scientific evidence that consuming specific foods extends the lifespan and healthspan seems lacking. Here, we synthesized the results of recent studies on the lifespan and healthspan extension properties of foods and their phytochemicals in various organisms to confirm how far the scientific research on the effect of food on the lifespan has reached.

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