Scientific News
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Sven Bulterijs

Business/Conferences/ General news

COVID-19 in Belgium

Global trends in incidence, death, burden and risk factors of early-onset cancer from 1990 to 2019 ⓐ
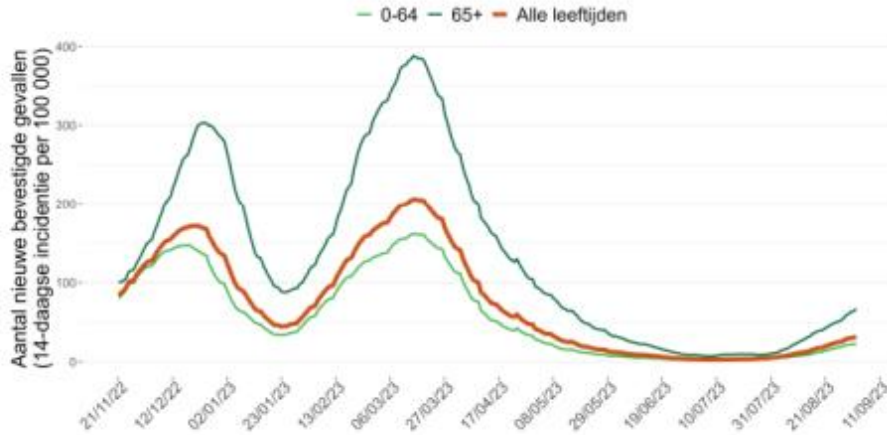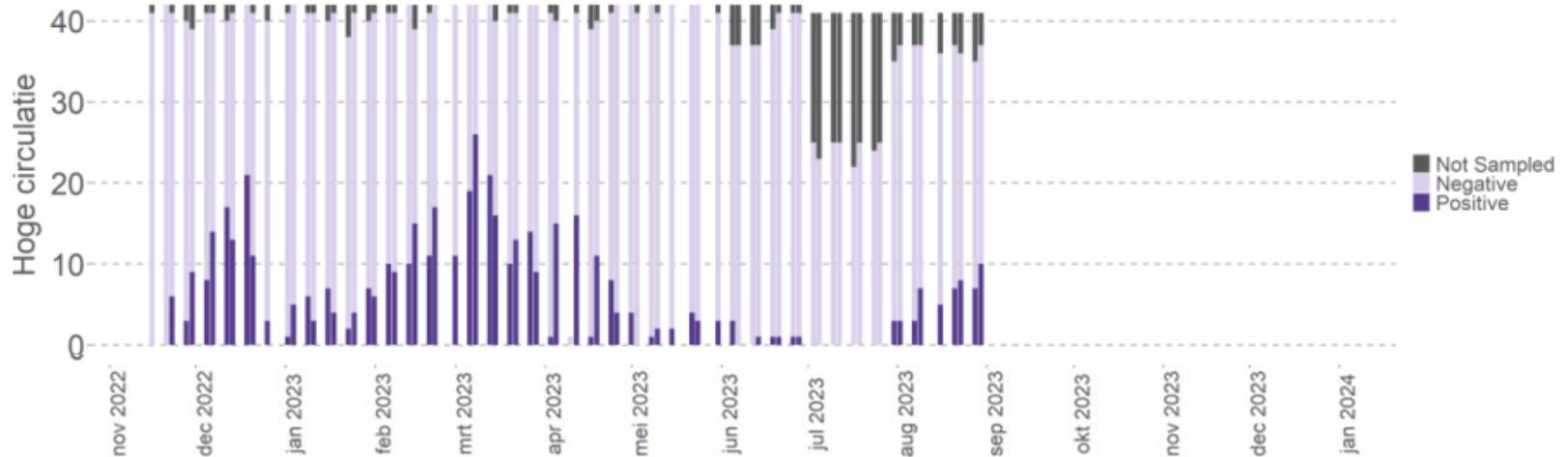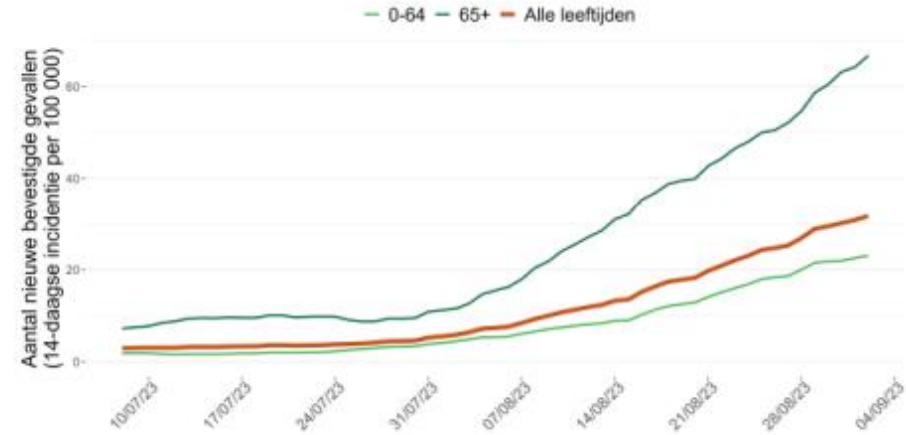
Objective This study aimed to explore the global burden of early-onset cancer based on the Global Burden of Disease (GBD) 2019 study for 29 cancers worldwid.

Methods and analysis Incidence, deaths, disability-adjusted life years (DALYs) and risk factors for 29 early-onset cancer groups were obtained from GBD.

Results Global incidence of early-onset cancer increased by 79.1% and the number of early-onset cancer deaths increased by 27.7% between 1990 and 2019. Early-onset breast, tracheal, bronchus and lung, stomach and colorectal cancers showed the highest mortality and DALYs in 2019. Globally, the incidence rates of early-onset nasopharyngeal and prostate cancer showed the fastest increasing trend, whereas early-onset liver cancer showed the sharpest decrease. Early-onset colorectal cancers had high DALYs within the top five ranking for both men and women. High-middle and middle Sociodemographic Index (SDI) regions had the highest burden of early-onset cancer. The morbidity of early-onset cancer increased with the SDI, and the mortality rate decreased considerably when SDI increased from 0.7 to 1. The projections indicated that the global number of incidence and deaths of early-onset cancer would increase by 31% and 21% in 2030, respectively. Dietary risk factors (diet high in red meat, low in fruits, high in sodium and low in milk, etc), alcohol consumption and tobacco use are the main risk factors underlying early-onset cancers.

Conclusion Early-onset cancer morbidity continues to increase worldwide with notable variances in mortality and DALYs between areas, countries, sex and cancer types. Encouraging a healthy lifestyle could reduce early-onset cancer disease burden.

Belgische wetenschappers sturen 3D-geprint miniatuurhart uit menselijke cellen naar de ruimte om veroudering te bestuderen

In Gent is een kunstmatig miniatuurhart uit menselijke cellen voorgesteld dat over twee jaar zal meereizen met het internationaal ruimtestation ISS. Het hart is met een speciale 3D-printer gemaakt, met bio-inkt van stamcellen. Het wordt geprint op een chip van amper een halve vierkante millimeter groot en zit vol met sensoren. Die kunnen van op aarde gemonitord worden en moeten inzicht geven in het verouderingsproces. In de ruimte verloopt dat immers veel sneller dan op aarde. "Door deze innovatie kunnen we gezondheidsproblemen echt patiënt per patiënt voorspellen en behandelingen uittesten", klinkt het.

Scientists hone tools to measure aging and rejuvenation interventions

Aging is malleable, at least in animal models. But to prove the efficacy of interventions aimed at extending healthspan and to test life-extending approaches in humans, longevity researchers first need to agree on the best measuring tools. With the power of 'omics, AI and large biobanks, improved biomarkers may be forthcoming. Companies and academic researchers are rallying forces, but how far have they gotten?

Lisa Melton ✉

6

You Are Likely To Live Longer Than You Think: Day Two Of The 10th ARDD Meeting

Alex Zhavoronkov, PhD Contributor ⓘ

Expert in AI for healthcare and longevity biotechnology

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Aug 30, 2023, 08:10pm EDT

Aging research articles

Health Consequences of Thymus Removal in Adults

Kameron A. Kooshesh, M.D., Brody H. Foy, D.Phil., David B. Sykes, M.D., Ph.D., Karin Gustafsson, Ph.D., and David T. Scadden, M.D.

METHODS   We evaluated the risk of death, cancer, and autoimmune disease among adult patients who had undergone thymectomy as compared with demographically matched controls who had undergone similar cardiothoracic surgery without thymectomy. T-cell production and plasma cytokine levels were also compared in a subgroup of patients.

RESULTS   After exclusions, 1420 patients who had undergone thymectomy and 6021 controls were included in the study; 1146 of the patients who had undergone thymectomy had a matched control and were included in the primary cohort. At 5 years after surgery, all-cause mortality was higher in the thymectomy group than in the control group (8.1% vs. 2.8%; relative risk, 2.9; 95% confidence interval [CI], 1.7 to 4.8), as was the risk of cancer (7.4% vs. 3.7%; relative risk, 2.0; 95% CI, 1.3 to 3.2). Although the risk of autoimmune disease did not differ substantially between the groups in the overall primary cohort (relative risk, 1.1; 95% CI, 0.8 to 1.4), a difference was found when patients with preoperative infection, cancer, or autoimmune disease were excluded from the analysis (12.3% vs. 7.9%; relative risk, 1.5; 95% CI, 1.02 to 2.2). In an analysis involving all patients with more than 5 years of follow-up (with or without a matched control), all-cause mortality was higher in the thymectomy group than in the general U.S. population (9.0% vs. 5.2%), as was mortality due to cancer (2.3% vs. 1.5%). In the subgroup of patients in whom T-cell production and plasma cytokine levels were measured (22 in the thymectomy group and 19 in the control group; mean follow-up, 14.2 postoperative years), those who had undergone thymectomy had less new production of CD4+ and CD8+ lymphocytes than controls (mean CD4+ signal joint T-cell receptor excision circle [sjTREC] count, 1451 vs. 526 per microgram of DNA [P=0.009]; mean CD8+ sjTREC count, 1466 vs. 447 per microgram of DNA [P<0.001]) and higher levels of proinflammatory cytokines in the blood.

Increased hyaluronan by naked mole-rat Has2 improves healthspan in mice

Zhihui Zhang [1], Xiao Tian [1], J Yuyang Lu [1], Kathryn Boit [1], Julia Ablaeva [1], Frances Tolibzoda Zakusilo [1], Stephan Emmrich [1], Denis Firsanov [1], Elena Rydkina [1], Seyed Ali Biashad [1], Quan Lu [1], Alexander Tyshkovskiy [2] [3], Vadim N Gladyshev [2], Steve Horvath [4] [5], Andrei Seluanov [6] [7], Vera Gorbunova [8] [9]

Affiliations + expand

Abstract

Abundant high-molecular-mass hyaluronic acid (HMM-HA) contributes to cancer resistance and possibly to the longevity of the longest-lived rodent-the naked mole-rat[1,2]. To study whether the benefits of HMM-HA could be transferred to other animal species, we generated a transgenic mouse overexpressing naked mole-rat hyaluronic acid synthase 2 gene (nmrHas2). nmrHas2 mice showed an increase in hyaluronan levels in several tissues, and a lower incidence of spontaneous and induced cancer, extended lifespan and improved healthspan. The transcriptome signature of nmrHas2 mice shifted towards that of longer-lived species. The most notable change observed in nmrHas2 mice was attenuated inflammation across multiple tissues. HMM-HA reduced inflammation through several pathways, including a direct immunoregulatory effect on immune cells, protection from oxidative stress and improved gut barrier function during ageing. These beneficial effects were conferred by HMM-HA and were not specific to the nmrHas2 gene. These findings demonstrate that the longevity mechanism that evolved in the naked mole-rat can be exported to other species, and open new paths for using HMM-HA to improve lifespan and healthspan.

DONG YANG (iD), BIN SUN (iD), SHIRONG LI, WENWEN WEI, XIUYUN LIU, XIAOYUE CUI (iD), XIANNING ZHANG, NAN LIU, LANZHEN YAN (iD), [...], AND XUDONG ZHAO (iD)

Abstract

Cellular senescence, characterized by stable cell cycle arrest, plays an important role in aging and age-associated pathologies. Eliminating senescent cells rejuvenates aged tissues and ameliorates age-associated diseases. Here, we identified that natural killer group 2 member D ligands (NKG2DLs) are up-regulated in senescent cells in vitro, regardless of stimuli that induced cellular senescence, and in various tissues of aged mice and nonhuman primates in vivo. Accordingly, we developed and demonstrated that chimeric antigen receptor (CAR) T cells targeting human NKG2DLs selectively and effectively diminish human cells undergoing senescence induced by oncogenic stress, replicative stress, DNA damage, or P16^{INK4a} overexpression in vitro. Targeting senescent cells with mouse NKG2D-CAR T cells alleviated multiple aging-associated pathologies and improved physical performance in both irradiated and aged mice. Autologous T cells armed with the human NKG2D CAR effectively delete naturally occurring senescent cells in aged nonhuman primates without any observed adverse effects. Our findings establish that NKG2D-CAR T cells could serve as potent and selective senolytic agents for aging and age-associated diseases driven by senescence.

AAV-Mediated nuclear localized PGC1α4 delivery in muscle ameliorates sarcopenia and aging-associated metabolic dysfunctions

Sarcopenia is characterized of muscle mass loss and functional decline in elder individuals which severely affects human physical activity, metabolic homeostasis, and life quality. Physical exercise is considered effective in combating muscle atrophy and sarcopenia, yet it is not feasible to elders with limited mobility. PGC-1α4, a short isoform of PGC-1α, is strongly induced in muscle under resistance training, and promotes muscle hypertrophy. In the present study, we showed that the transcriptional levels and nuclear localization of PGC1α4 was reduced during aging, accompanied with muscle dystrophic morphology, and gene programs. We thus designed NLS-PGC1α4 and ectopically express it in myotubes to enhance PGC1α4 levels and maintain its location in nucleus. Indeed, NLS-PGC1α4 overexpression increased muscle sizes in myotubes. In addition, by utilizing AAV-NLS-PGC1α4 delivery into gastrocnemius muscle, we found that it could improve sarcopenia with grip strength, muscle weights, fiber size and molecular phenotypes, and alleviate age-associated adiposity, insulin resistance and hepatic steatosis, accompanied with altered gene signatures. Mechanistically, we demonstrated that NLS-PGC-1α4 improved insulin signaling and enhanced glucose uptake in skeletal muscle. Besides, via RNA-seq analysis, we identified myokines IGF1 and METRNL as potential targets of NLS-PGC-1α4 that possibly mediate the improvement of muscle and adipose tissue functionality and systemic energy metabolism in aged mice. Moreover, we found a negative correlation between PGC1α4 and age in human skeletal muscle. Together, our results revealed that NLS-PGC1α4 overexpression improves muscle physiology and systematic energy homeostasis during aging and suggested it as a potent therapeutic strategy against sarcopenia and aging-associated metabolic diseases.

Mass spectrometry-based multi-omics identifies metabolic signatures of sarcopenia in rhesus monkey skeletal muscle

Melissa R Pergande, Katie J Osterbauer, Kevin M Buck, David S Roberts, Nina N Wood, Priya Balasubramanian, Morgan W Mann, Kalina Rossler, Gary M Diffee, Ricki J Colman, Rozalyn M Anderson, Ying Ge

Abstract

Sarcopenia is a progressive disorder characterized by age-related loss of skeletal muscle mass and function. Although significant progress has been made over the years to identify the molecular determinants of sarcopenia, the precise mechanisms underlying the age-related loss of contractile function remains unclear. Advances in omics technologies, including mass spectrometry-based proteomic and metabolomic analyses, offer great opportunities to better understand sarcopenia. Herein, we performed mass spectrometry-based analyses of the vastus lateralis from young, middle-aged, and older rhesus monkeys to identify molecular signatures of sarcopenia. In our proteomic analysis, we identified numerous proteins that change with age, including those involved in adenosine triphosphate and adenosine monophosphate metabolism as well as fatty acid beta oxidation. In our untargeted metabolomic analysis, we identified multiple metabolites that changed with age largely related to energy metabolism including fatty acid beta oxidation. Pathway analysis of age-responsive proteins and metabolites revealed changes in muscle structure and contraction as well as lipid, carbohydrate, and purine metabolism. Together, this study discovers new metabolic signatures and offer new insights into the molecular mechanism underlying sarcopenia for the evaluation and monitoring of therapeutic treatment of sarcopenia.

13

Aging impairs the neurovascular interface in the heart

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Abstract

Aging is a major risk factor for impaired cardiovascular health. Because the aging myocardium is characterized by microcirculatory dysfunction, and because nerves align with vessels, we assessed the impact of aging on the cardiac neurovascular interface. We report that aging reduces nerve density in the ventricle and dysregulates vascular-derived neuroregulatory genes. Aging down-regulates microRNA 145 (miR-145) and derepresses the neurorepulsive factor semaphorin-3A. miR-145 deletion, which increased *Sema3a* expression or endothelial *Sema3a* overexpression, reduced axon density, mimicking the aged-heart phenotype. Removal of senescent cells, which accumulated with chronological age in parallel to the decline in nerve density, rescued age-induced denervation, reversed *Sema3a* expression, preserved heart rate patterns, and reduced electrical instability. These data suggest that senescence-mediated regulation of nerve density contributes to age-associated cardiac dysfunction.

Platelet factors attenuate inflammation and rescue cognition in ageing

Adam B Schroer [# 1], Patrick B Ventura [# 2], Juliana Sucharov [2 3], Rhea Misra [2 3], M K Kirsten Chui [2], Gregor Bieri [2], Alana M Horowitz [2 3], Lucas K Smith [2 3], Katriel Encabo [4], Imelda Tenggara [4], Julien Couthouis [5], Joshua D Gross [6], June M Chan [4 7], Anthony Luke [8], Saul A Villeda [9 10 11 12]

Affiliations + expand

Abstract

Identifying therapeutics to delay, and potentially reverse, age-related cognitive decline is critical in light of the increased incidence of dementia-related disorders forecasted in the growing older population[1]. Here we show that platelet factors transfer the benefits of young blood to the ageing brain. Systemic exposure of aged male mice to a fraction of blood plasma from young mice containing platelets decreased neuroinflammation in the hippocampus at the transcriptional and cellular level and ameliorated hippocampal-dependent cognitive impairments. Circulating levels of the platelet-derived chemokine platelet factor 4 (PF4) (also known as CXCL4) were elevated in blood plasma preparations of young mice and humans relative to older individuals. Systemic administration of exogenous PF4 attenuated age-related hippocampal neuroinflammation, elicited synaptic-plasticity-related molecular changes and improved cognition in aged mice. We implicate decreased levels of circulating pro-ageing immune factors and restoration of the ageing peripheral immune system in the beneficial effects of systemic PF4 on the aged brain. Mechanistically, we identified CXCR3 as a chemokine receptor that, in part, mediates the cellular, molecular and cognitive benefits of systemic PF4 on the aged brain. Together, our data identify platelet-derived factors as potential therapeutic targets to abate inflammation and rescue cognition in old age.

The impact of the cardiovascular component and somatic mutations on ageing

Daniel Garger, Martin Meinel, Tamina Dietl, Christina Hillig, Natalie Garzorz-Stark, Kilian Eyerich, Martin Hrabě de Angelis, Stefanie Eyerich, Michael P. Menden ✉

Mechanistic insight into ageing may empower prolonging the lifespan of humans; however, a complete understanding of this process is still lacking despite a plethora of ageing theories. In order to address this, we investigated the association of lifespan with eight phenotypic traits, that is, litter size, body mass, female and male sexual maturity, somatic mutation, heart, respiratory, and metabolic rate. In support of the somatic mutation theory, we analysed 15 mammalian species and their whole-genome sequencing deriving somatic mutation rate, which displayed the strongest negative correlation with lifespan. All remaining phenotypic traits showed almost equivalent strong associations across this mammalian cohort, however, resting heart rate explained additional variance in lifespan. Integrating somatic mutation and resting heart rate boosted the prediction of lifespan, thus highlighting that resting heart rate may either directly influence lifespan, or represents an epiphenomenon for additional lower-level mechanisms, for example, metabolic rate, that are associated with lifespan.

Nuclear genetic control of mtDNA copy number and heteroplasmy in humans

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Mitochondrial DNA (mtDNA) is a maternally inherited, high-copy-number genome required for oxidative phosphorylation[1]. Heteroplasmy refers to the presence of a mixture of mtDNA alleles in an individual and has been associated with disease and ageing. Mechanisms underlying common variation in human heteroplasmy, and the influence of the nuclear genome on this variation, remain insufficiently explored. Here we quantify mtDNA copy number (mtCN) and heteroplasmy using blood-derived whole-genome sequences from 274,832 individuals and perform genome-wide association studies to identify associated nuclear loci. Following blood cell composition correction, we find that mtCN declines linearly with age and is associated with variants at 92 nuclear loci. We observe that nearly everyone harbours heteroplasmic mtDNA variants obeying two principles: (1) heteroplasmic single nucleotide variants tend to arise somatically and accumulate sharply after the age of 70 years, whereas (2) heteroplasmic indels are maternally inherited as mixtures with relative levels associated with 42 nuclear loci involved in mtDNA replication, maintenance and novel pathways. These loci may act by conferring a replicative advantage to certain mtDNA alleles. As an illustrative example, we identify a length variant carried by more than 50% of humans at position chrM:302 within a G-quadruplex previously proposed to mediate mtDNA transcription/replication switching[2,3]. We find that this variant exerts *cis*-acting genetic control over mtDNA abundance and is itself associated in-*trans* with nuclear loci encoding machinery for this regulatory switch. Our study suggests that common variation in the nuclear genome can shape variation in mtCN and heteroplasmy dynamics across the human population.

Bloom syndrome patients and mice display accelerated epigenetic aging

Jamie Lee, Joshua Zhang, Maeve Flanagan, Julian A. Martinez, Christopher Cunniff, Nicole Kucine, Ake T. Lu, Amin Haghani, Juozas Gordevičius, Steve Horvath, Vivian Y. Chang ✉

Bloom syndrome (BSyn) is an autosomal recessive disorder caused by variants in the *BLM* gene, which is involved in genome stability. Patients with BSyn present with poor growth, sun sensitivity, mild immunodeficiency, diabetes, and increased risk of cancer, most commonly leukemias. Interestingly, patients with BSyn do not have other signs of premature aging such as early, progressive hair loss and cataracts. We set out to determine epigenetic age in BSyn, which can be a better predictor of health and disease over chronological age. Our results show for the first time that patients with BSyn have evidence of accelerated epigenetic aging across several measures in blood lymphocytes, as compared to carriers. Additionally, homozygous *Blm* mice exhibit accelerated methylation age in multiple tissues, including brain, blood, kidney, heart, and skin, according to the brain methylation clock. Overall, we find that Bloom syndrome is associated with accelerated epigenetic aging effects in multiple tissues and more generally a strong effect on CpG methylation levels.

Universal DNA methylation age across mammalian tissues

A. T. Lu, Z. Fei, A. Haghani, T. R. Robeck, J. A. Zoller, C. Z. Li, R. Lowe, Q. Yan, J. Zhang, H. Vu, J. Ablaeva, V. A. Acosta-Rodriguez, D. M. Adams, J. Almunia, A. Aloysius, R. Ardehali, A. Arneson, C. S. Baker, G. Banks, K. Belov, N. C. Bennett, P. Black, D. T. Blumstein, E. K. Bors, … S. Horvath ✉   + Show authors

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.

Short-term fasting of a single amino acid extends lifespan

Tahlia L. Fulton, Mia R. Wansbrough, Christen K. Mirth, Matthew D.W. Piper

Diet and health are strongly linked, though the strict changes in diet required to improve health outcomes are usually difficult to sustain. We sought to understand whether short term bouts of amino acid-specific modifications to the diet of *Drosophila melanogaster* could mimic the lifespan and stress resistance benefits of dietary restriction, without the requirement for drastic reductions in food intake. We found that flies fed diets lacking the essential amino acid isoleucine, but otherwise nutritionally complete, exhibited enhanced nicotine tolerance, indicating elevated detoxification capacity. The protection from isoleucine deprivation increased with the duration of exposure, up to a maximum at 7-day isoleucine deprivation for flies 2, 3, or 4 weeks of age, and a 5-day deprivation when flies were 5 weeks of age. Because of these beneficial effects on toxin resistance, we intermittently deprived flies of isoleucine during the first 6 weeks of adulthood and monitored the effect on lifespan. Lifespan was significantly extended when flies experienced short term isoleucine deprivation at 3 and 5 weeks of age, regardless of whether they were also deprived at 1 week. These results indicate that short-term bouts of isoleucine deprivation can extend lifespan and highlight its cumulative and time-dependent benefits. Interestingly, we found that isoleucine-deprived flies lost their protection against nicotine within three days of returning to fully fed conditions. Therefore, the mechanisms underlying lifespan extension may involve transient damage clearance during the bouts of isoleucine deprivation rather than sustained enhanced detoxification capacity. These data highlight a new time-restricted, nutritionally precise method to extend life in *Drosophila melanogaster* and point to a more manageable dietary method to combat ageing.

Atlas of the aging mouse brain reveals white matter as vulnerable foci

Oliver Hahn • Aulden G. Foltz • Micaiah Atkins [11] • Blen Kedir [11] • Patricia Moran-Losada • Ian H. Guldner • Christy Munson • Fabian Kern • Róbert Pálovics • Nannan Lu • Hui Zhang • Achint Kaur • Jacob Hull • John R. Huguenard • Sebastian Grönke • Benoit Lehallier • Linda Partridge • Andreas Keller • Tony Wyss-Coray [12] • Show less • Show footnotes

Aging is the key risk factor for cognitive decline, yet the molecular changes underlying brain aging remain poorly understood. Here, we conducted spatiotemporal RNA sequencing of the mouse brain, profiling 1,076 samples from 15 regions across 7 ages and 2 rejuvenation interventions. Our analysis identified a brain-wide gene signature of aging in glial cells, which exhibited spatially defined changes in magnitude. By integrating spatial and single-nucleus transcriptomics, we found that glial aging was particularly accelerated in white matter compared with cortical regions, whereas specialized neuronal populations showed region-specific expression changes. Rejuvenation interventions, including young plasma injection and dietary restriction, exhibited distinct effects on gene expression in specific brain regions. Furthermore, we discovered differential gene expression patterns associated with three human neurodegenerative diseases, highlighting the importance of regional aging as a potential modulator of disease. Our findings identify molecular foci of brain aging, providing a foundation to target age-related cognitive decline.

Open Genes—a new comprehensive database of human genes associated with aging and longevity

Ekaterina Rafikova ✉, Nikolay Nemirovich-Danchenko, Anna Ogmen,
Anna Parfenenkova, Anastasiia Velikanova, Stanislav Tikhonov, Leonid Peshkin,
Konstantin Rafikov, Olga Spiridonova, Yulia Belova ... Show more

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Abstract

The Open Genes database was created to enhance and simplify the search for potential aging therapy targets. We collected data on 2402 genes associated with aging and developed convenient tools for searching and comparing gene features. A comprehensive description of genes has been provided, including lifespan-extending interventions, age-related changes, longevity associations, gene evolution, associations with diseases and hallmarks of aging, and functions of gene products. For each experiment, we presented the necessary structured data for evaluating the experiment's quality and interpreting the study's findings. Our goal was to stay objective and precise while connecting a particular gene to human aging. We distinguished six types of studies and 12 criteria for adding genes to our database. Genes were classified according to the confidence level of the link between the gene and aging. All the data collected in a database are provided both by an API and a user interface. The database is publicly available on a website at https://open-genes.org/.

Human Ageing Genomic Resources: updates on key databases in ageing research

🆔 João Pedro de Magalhães, Zoya Abidi, Gabriel Arantes dos Santos, Roberto A. Avelar, Diogo Barardo, Kasit Chatsirisupachai, Peter Clark, 🆔 Evandro A. De-Souza, Emily J. Johnson, Inês Lopes, Guy Novoa, Ludovic Senez, Angelo Talay, Daniel Thornton, Paul Ka Po To

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

Abstract   Full Text   Info/History   Metrics   🗋 Preview PDF

Abstract

Ageing is a complex and multifactorial process. For two decades, the Human Ageing Genomic Resources (HAGR) have aided researchers in the study of various aspects of ageing and its manipulation. Here we present the key features and recent enhancements of these resources, focusing on its six main databases. One database, GenAge, focuses on genes related to ageing, featuring 307 genes linked to human ageing and 2205 genes associated with longevity and ageing in model organisms. AnAge focuses on ageing, longevity, and life-history across animal species, containing data on 4645 species. DrugAge includes information about 1097 longevity drugs and compounds in model organisms such as mice, rats, flies, worms, and yeast. GenDR provides a list of 214 genes associated with the life-extending benefits of dietary restriction in model organisms. CellAge contains a catalogue of 866 genes associated with cellular senescence. The LongevityMap serves as a repository for genetic variants associated with human longevity, encompassing 3144 variants pertaining to 884 genes. Additionally, HAGR provides various tools as well as gene expression signatures of ageing, dietary restriction, and replicative senescence based on meta-analyses. Our databases are integrated, regularly updated, and manually curated by experts. HAGR is freely available online (https://genomics.senescence.info/).

C. elegans aging research

In-vivo screening implicates endoribonuclease *Regnase-1* in modulating senescence-associated lysosomal changes

Accumulation of senescent cells accelerates aging and age-related diseases, whereas preventing this accumulation extends the lifespan in mice. A characteristic of senescent cells is increased staining with β-galactosidase (β-gal) ex vivo. Here, we describe a progressive accumulation of β-gal staining in the model organism *C. elegans* during aging. We show that distinct pharmacological and genetic interventions targeting the mitochondria and the mTORC1 to the nuclear core complex axis, the non-canonical apoptotic, and lysosomal-autophagy pathways slow the age-dependent accumulation of β-gal. We identify a novel gene, *rege-1/Regnase-1/ZC3H12A/MCPIP1*, modulating β-gal staining via the transcription factor *ets-4/SPDEF*. We demonstrate that knocking down *Regnase-1* in human cell culture prevents senescence-associated β-gal accumulation. Our data provide a screening pipeline to identify genes and drugs modulating senescence-associated lysosomal phenotypes.

ATFS-1 counteracts mitochondrial DNA damage by promoting repair over transcription

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Affiliations + expand

Abstract

The ability to balance conflicting functional demands is critical for ensuring organismal survival. The transcription and repair of the mitochondrial genome (mtDNA) requires separate enzymatic activities that can sterically compete[1], suggesting a life-long trade-off between these two processes. Here in Caenorhabditis elegans, we find that the bZIP transcription factor ATFS-1/Atf5 (refs. [2,3]) regulates this balance in favour of mtDNA repair by localizing to mitochondria and interfering with the assembly of the mitochondrial pre-initiation transcription complex between HMG-5/TFAM and RPOM-1/mtRNAP. ATFS-1-mediated transcriptional inhibition decreases age-dependent mtDNA molecular damage through the DNA glycosylase NTH-1/NTH1, as well as the helicase TWNK-1/TWNK, resulting in an enhancement in the functional longevity of cells and protection against decline in animal behaviour caused by targeted and severe mtDNA damage. Together, our findings reveal that ATFS-1 acts as a molecular focal point for the control of balance between genome expression and maintenance in the mitochondria.

26

Partial inhibition of class III PI3K VPS-34 ameliorates motor aging and prolongs health span

Zhongliang Hu co, Yamei Luo co, Yuting Liu co, Yaru Luo, Liangce Wang, Shengsong Gou, Yuling Peng, Rui Wei, Da Jia, Yuan Wang, Shangbang Gao ✉, Yan Zhang ✉

Global increase of life expectancy is rarely accompanied by increased health span, calling for a greater understanding of age-associated behavioral decline. Motor independence is strongly associated with the quality of life of elderly people, yet the regulators for motor aging have not been systematically explored. Here, we designed a fast and efficient genome-wide screening assay in Caenorhabditis elegans and identified 34 consistent genes as potential regulators of motor aging. Among the top hits, we found VPS-34, the class III phosphatidylinositol 3-kinase that phosphorylates phosphatidylinositol (PI) to phosphatidylinositol 3-phosphate (PI(3)P), regulates motor function in aged but not young worms. It primarily functions in aged motor neurons by inhibiting PI(3)P-PI-PI(4)P conversion to reduce neurotransmission at the neuromuscular junction (NMJ). Genetic and pharmacological inhibition of VPS-34 improve neurotransmission and muscle integrity, ameliorating motor aging in both worms and mice. Thus, our genome-wide screening revealed an evolutionarily conserved, actionable target to delay motor aging and prolong health span.

27

Tubular lysosome induction couples animal starvation to healthy aging

Tatiana V. Villalobos, Bhaswati Ghosh, Kathryn R. DeLeo, Sanaa Alam, Cristian Ricaurte-Perez, Andrew Wang, Brennan M. Mercola, Tyler J. Butsch, Cara D. Ramos, Suman Das, Eric D. Eymard, K. Adam Bohnert ✉ & Alyssa E. Johnson ✉

Dietary restriction promotes longevity in several species via autophagy activation. However, changes to lysosomes underlying this effect remain unclear. Here using the nematode *Caenorhabditis elegans*, we show that the induction of autophagic tubular lysosomes (TLs), which occurs upon dietary restriction or mechanistic target of rapamycin inhibition, is a critical event linking reduced food intake to lifespan extension. We find that starvation induces TLs not only in affected individuals but also in well-fed descendants, and the presence of gut TLs in well-fed progeny is predictive of enhanced lifespan. Furthermore, we demonstrate that expression of *Drosophila* small VCP-interacting protein, a TL activator in flies, artificially induces TLs in well-fed worms and improves *C. elegans* health in old age. These findings identify TLs as a new class of lysosomes that couples starvation to healthy aging.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Biomarkers of aging for the identification and evaluation of longevity interventions

With the rapid expansion of aging biology research, the identification and evaluation of longevity interventions in humans have become key goals of this field. Biomarkers of aging are critically important tools in achieving these objectives over realistic time frames. However, the current lack of standards and consensus on the properties of a reliable aging biomarker hinders their further development and validation for clinical applications. Here, we advance a framework for the terminology and characterization of biomarkers of aging, including classification and potential clinical use cases. We discuss validation steps and highlight ongoing challenges as potential areas in need of future research. This framework sets the stage for the development of valid biomarkers of aging and their ultimate utilization in <u>clinical trials</u> and practice.

Challenges in developing Geroscience trials

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Collaborators, Affiliations + expand

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Abstract

Geroscience is becoming a major hope for preventing age-related diseases and loss of function by targeting biological mechanisms of aging. This unprecedented paradigm shift requires optimizing the design of future clinical studies related to aging in humans. Researchers will face a number of challenges, including ideal populations to study, which lifestyle and Gerotherapeutic interventions to test initially, selecting key primary and secondary outcomes of such clinical trials, and which age-related biomarkers are most valuable for both selecting interventions and predicting or monitoring clinical responses ("Gerodiagnostics"). This article reports the main results of a Task Force of experts in Geroscience.

31

Optimising preclinical models of aging for translation to clinical trials

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Affiliations + expand
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Abstract

Preclinical models have been the backbone of translational research for more than a century. Rats and mice are critical models in the preliminary stages of drug testing, both for determining efficacy and ruling out potential human-relevant toxicities. Historically, most preclinical pharmacological studies have used young, relatively healthy, inbred male models in highly-controlled environments. In the field of geriatric pharmacology, there is a growing focus on the importance of using more appropriate preclinical models both in the testing of therapeutics commonly used in older populations, and in the evaluation of potential geroprotective drug candidates. Here we provide a commentary on optimising preclinical models of ageing for translation to clinical trials. We will discuss approaches to modeling clinically-relevant contexts such as age, sex, genetic diversity, exposures and environment, as well as measures of clinically-relevant outcomes such as frailty and healthspan. We will identify the strengths and limitations of these approaches and areas for improvement. We will also briefly cover new preclinical models that move beyond rodents. We hope this commentary will be a springboard for larger discussions on optimising preclinical aging models for testing therapeutics.

Amyloid-β: A potential mediator of aging-related vascular pathologies

Fazlullah Khan [1], Hongyu Qiu [2]

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Abstract

Aging is one of the most promising risk factors for vascular diseases, however, the precise mechanisms mediating aging-related pathologies are not fully understood. Amyloid beta (Aβ), a peptide produced by the proteolytic processing of amyloid precursor protein (APP), is known as a key mediator of brain damage involved in the pathogenesis of Alzheimer's disease (AD). Recently, it was found that the accumulation of Aβ in the vascular wall is linked to a range of aging-related vascular pathologies, indicating a potential role of Aβ in the pathogenesis of aging-associated vascular diseases. In the present review, we have updated the molecular regulation of Aβ in vascular cells and tissues, summarized the relevance of the Aβ deposition with vascular aging and diseases, and the role of Aβ dysregulation in aging-associated vascular pathologies, including the impaired vascular response, endothelial dysfunction, oxidative stress, and inflammation. This review will provide advanced information in understanding aging-related vascular pathologies and a new avenue to explore therapeutic targets.

Peto's paradox: Nature has used multiple strategies to keep cancer at bay while evolving long lifespans and large body masses. A systematic mini-review

Comparative oncology is an understudied field of science. We are far from understanding the key mechanisms behind Peto's paradox, i.e. understanding how long-lived and large animals are not subject to a higher cancer burden despite the longer exposure time to mutations and the larger number of cells exposed.

In this work we investigated the scientific evidence on such mechanisms through a systematic mini-review of the literature about the relation of longevity and/or large body mass with physiological, genetic or environmental traits among mammalian species. More than forty thousand articles were retrieved from three repositories and 383 of them were screened using an active-learning-based tool. Of those, 36 articles on longevity and 37 on body mass were selected for the review. Such articles were examined focusing on: number and type of species considered, statistical methods used, traits investigated, and observed relationship with longevity and/or body mass. Where applicable, the traits investigated were matched with one or more hallmarks of cancer.

We obtained a list of potential candidate traits to explain the Peto's paradox, related to replicative immortality, cells senescence, genome instability and mutations, proliferative signaling, growth suppression evasion and cells resistance to death.

Our investigation suggests that different strategies have been followed to prevent cancer in large and long-lived species. The large number of papers retrieved emphasizes that more studies can be launched in the future, using more efficient analytical approaches, to comprehensively evaluate the convergent biological mechanisms essential for acquiring longevity and large body mass without increasing cancer risk.

Application of the Yamanaka Transcription Factors *Oct4*, *Sox2*, *Klf4*, and *c-Myc* from the Laboratory to the Clinic

by Marisol Aguirre [1,2], Manuela Escobar [3], Sebastián Forero Amézquita [3], David Cubillos [3], Camilo Rincón [3], Paula Vanegas [3], María Paula Tarazona [3], Sofía Atuesta Escobar [3], Juan Camilo Blanco [3] and Luis Gustavo Celis [3,*]

The transcription factors *Oct4*, *Sox2*, *Klf4*, and *c-Myc* enable the reprogramming of somatic cells into induced pluripotent cells. Reprogramming generates newly differentiated cells for potential therapies in cancer, neurodegenerative diseases, and rejuvenation processes. In cancer therapies, these transcription factors lead to a reduction in the size and aggressiveness of certain tumors, such as sarcomas, and in neurodegenerative diseases, they enable the production of dopaminergic cells in Parkinson's disease, the replacement of affected neuronal cells in olivopontocerebellar atrophy, and the regeneration of the optic nerve. However, there are limitations, such as an increased risk of cancer dev[...] when using *Klf4* and *c-Myc* and the occurrence of abnormal dyskinesias in the medium term, possibly generated by the uncontrolled growth of differentiated dopaminergic cells and the impairment of the survival of the new cells. Therefore, the Yamanaka transcription factors have shown therapeutic potential through cell reprogramming for some carcinomas, neurodegenerative diseases, and rejuvenation. However, the limitations found in the studies require further investigation before the use of these transcription factors in humans.

Mitochondria-associated programmed cell death as a therapeutic target for age-related disease

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Mitochondria, ubiquitous double-membrane-bound organelles, regulate energy production, support cellular activities, harbor metabolic pathways, and, paradoxically, mediate cell fate. Evidence has shown mitochondria as points of convergence for diverse cell death-inducing pathways that trigger the various mechanisms underlying apoptotic and nonapoptotic programmed cell death. Thus, dysfunctional cellular pathways eventually lead or contribute to various age-related diseases, such as neurodegenerative, cardiovascular and metabolic diseases. Thus, mitochondrion-associated programmed cell death-based treatments show great therapeutic potential, providing novel insights in clinical trials. This review discusses mitochondrial quality control networks with activity triggered by stimuli and that maintain cellular homeostasis via mitohormesis, the mitochondrial unfolded protein response, and mitophagy. The review also presents details on various forms of mitochondria-associated programmed cell death, including apoptosis, necroptosis, ferroptosis, pyroptosis, parthanatos, and paraptosis, and highlights their involvement in age-related disease pathogenesis, collectively suggesting therapeutic directions for further research.

The Reduction in the Mitochondrial Membrane Potential in Aging: The Role of the Mitochondrial Permeability Transition Pore

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Affiliations   + expand

Abstract

It is widely reported that the mitochondrial membrane potential, $\Delta\Psi m$, is reduced in aging animals. It was recently suggested that the lower $\Delta\Psi m$ in aged animals modulates mitochondrial bioenergetics and that this effect is a major cause of aging since artificially increased $\Delta\Psi m$ in *C. elegans* increased lifespan. Here, I critically review studies that reported reduction in $\Delta\Psi m$ in aged animals, including worms, and conclude that many of these observations are best interpreted as evidence that the fraction of depolarized mitochondria is increased in aged cells because of the enhanced activation of the mitochondrial permeability transition pore, mPTP. Activation of the voltage-gated mPTP depolarizes the mitochondria, inhibits oxidative phosphorylation, releases large amounts of calcium and mROS, and depletes cellular NAD^+, thus accelerating degenerative diseases and aging. Since the inhibition of mPTP was shown to restore $\Delta\Psi m$ and to retard aging, the reported lifespan extension by artificially generated $\Delta\Psi m$ in *C. elegans* is best explained by inhibition of the voltage-gated mPTP. Similarly, the reported activation of the mitochondrial unfolded protein response by reduction in $\Delta\Psi m$ and the reported preservation of $\Delta\Psi m$ in dietary restriction treatment in *C. elegans* are best explained as resulting from activation or inhibition of the voltage-gated mPTP, respectively.

Unravelling the nexus: Towards a unified model of development, ageing, and cancer

Alessandro Fontana 👤 ✉

This work presents a comprehensive model that aims to unify our understanding of embryogenesis, ageing, and cancer. While there have been previous attempts to construct models separately for two of these phenomena (such as embryogenesis and cancer, ageing and cancer), models encompassing all three are relatively scarce, if not entirely absent. The model's most notable feature is the presence of driver cells throughout the body, which may correspond to Spemann's organisers. These driver cells play a vital role in propelling development as they dynamically emerge from non-driver cells and inhabit specialised niches. Remarkably, this continuous process persists throughout an organism's entire lifespan, signifying that development unfolds from conception to the end of life. Driver cells orchestrate change events through the induction of distinctive epigenetic patterns of gene activation. Events occurring at young age drive development, are subject to high evolutionary pressure and hence carefully optimised. Events occurring after reproduction age are subject to decreasing evolutionary pressure: for this reason, such events are "pseudorandom" –deterministic but erratic. Some of these events lead to age-related benign conditions, such as gray hair. Some lead to serious age-related diseases, such as diabetes and Alzheimer's disease. Furthermore, some of these events might perturb epigenetically key pathways involved in driver activation and formation, leading to cancer. In our model, this driver cell-based mechanism represents the backbone of multicellular biology: understanding and correcting its functioning may give the chance to solve a wide range of conditions at once.

38

OTHER RESEARCH & REVIEWS

The relationship between diet, plasma glucose, and cancer prevalence across vertebrates

Stefania E Kapsetaki, Anthony J Basile, Zachary T Compton, Shawn M Rupp, Elizabeth G Duke, Amy M Boddy, Tara M Harrison, Karen L Sweazea, Carlo C Maley

Abstract

Could diet and mean plasma glucose concentration (MPGluC) explain the variation in cancer prevalence across species? We collected diet, MPGluC, and neoplasia data for 160 vertebrate species from existing databases. We found that MPGluC negatively correlates with cancer and neoplasia prevalence, mostly of gastrointestinal organs. Trophic level positively correlates with cancer and neoplasia prevalence even after controlling for species MPGluC. Most species with high MPGluC (50/78 species = 64.1%) were birds. Most species in high trophic levels (42/53 species = 79.2%) were reptiles and mammals. Our results may be explained by the evolution of insulin resistance in birds which selected for loss or downregulation of genes related to insulin-mediated glucose import in cells. This led to higher MPGluC, intracellular caloric restriction, production of fewer reactive oxygen species and inflammatory cytokines, and longer telomeres contributing to longer longevity and lower neoplasia prevalence in extant birds relative to other vertebrates.

The complete sequence of a human Y chromosome

The human Y chromosome has been notoriously difficult to sequence and assemble because of its complex repeat structure that includes long palindromes, tandem repeats and segmental duplications[1,2,3]. As a result, more than half of the Y chromosome is missing from the GRCh38 reference sequence and it remains the last human chromosome to be finished[4,5]. Here, the Telomere-to-Telomere (T2T) consortium presents the complete 62,460,029-base-pair sequence of a human Y chromosome from the HG002 genome (T2T-Y) that corrects multiple errors in GRCh38-Y and adds over 30 million base pairs of sequence to the reference, showing the complete ampliconic structures of gene families *TSPY*, *DAZ* and *RBMY*; 41 additional protein-coding genes, mostly from the *TSPY* family; and an alternating pattern of human satellite 1 and 3 blocks in the heterochromatic Yq12 region. We have combined T2T-Y with a previous assembly of the CHM13 genome[4] and mapped available population variation, clinical variants and functional genomics data to produce a complete and comprehensive reference sequence for all 24 human chromosomes.