Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
6th of April 2024
Sven Bulterijs

Business/Conferences/ General news

Heales
HEALTHY LIFE EXTENSION SOCIETY

First pig liver transplanted into a person lasts for 10 days

Pig organs could provide temporary detox for people whose livers need time to recover or who are awaiting human donors.

By Smriti Mallapaty

Heales
HEALTHY LIFE EXTENSION SOCIETY

Global fertility in 204 countries and territories, 1950–2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021

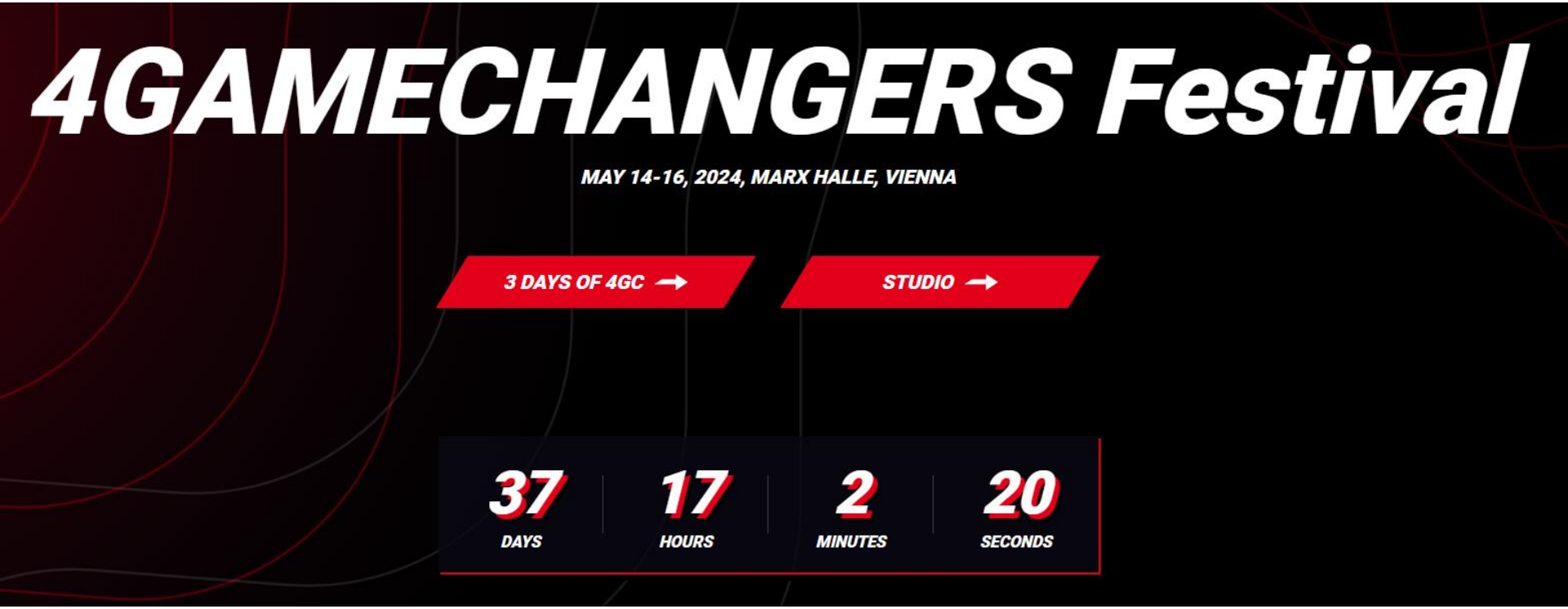
GBD 2021 Fertility and Forecasting Collaborators [†] • Show footnotes

During the period from 1950 to 2021, global TFR more than halved, from 4·84 (95% UI 4·63–5·06) to 2·23 (2·09–2·38). Global annual livebirths peaked in 2016 at 142 million (95% UI 137–147), declining to 129 million (121–138) in 2021. Fertility rates declined in all countries and territories since 1950, with TFR remaining above 2·1—canonically considered replacement-level fertility—in 94 (46·1%) countries and territories in 2021. This included 44 of 46 countries in sub-Saharan Africa, which was the super-region with the largest share of livebirths in 2021 (29·2% [28·7–29·6]). 47 countries and territories in which lowest estimated fertility between 1950 and 2021 was below replacement experienced one or more subsequent years with higher fertility; only three of these locations rebounded above replacement levels. Future fertility rates were projected to continue to decline worldwide, reaching a global TFR of 1·83 (1·59–2·08) in 2050 and 1·59 (1·25–1·96) in 2100 under the reference scenario. The number of countries and territories with fertility rates remaining above replacement was forecast to be 49 (24·0%) in 2050 and only six (2·9%) in 2100, with three of these six countries included in the 2021 World Bank-defined low-income group, all located in the GBD super-region of sub-Saharan Africa. The proportion of livebirths occurring in sub-Saharan Africa was forecast to increase to more than half of the world's livebirths in 2100, to 41·3% (39·6–43·1) in 2050 and 54·3% (47·1–59·5) in 2100. The share of livebirths was projected to decline between 2021 and 2100 in most of the six other super-regions—decreasing, for example, in south Asia from 24·8% (23·7–25·8) in 2021 to 16·7% (14·3–19·1) in 2050 and 7·1% (4·4–10·1) in 2100—but was forecast to increase modestly in the north Africa and Middle East and high-income super-regions. Forecast estimates for the alternative combined scenario suggest that meeting SDG targets for education and contraceptive met need, as well as implementing pro-natal policies, would result in global TFRs of 1·65 (1·40–1·92) in 2050 and 1·62 (1·35–1·95) in 2100. The forecasting skill metric values for the IHME model were positive across all age groups, indicating that the model is better than the constant prediction.

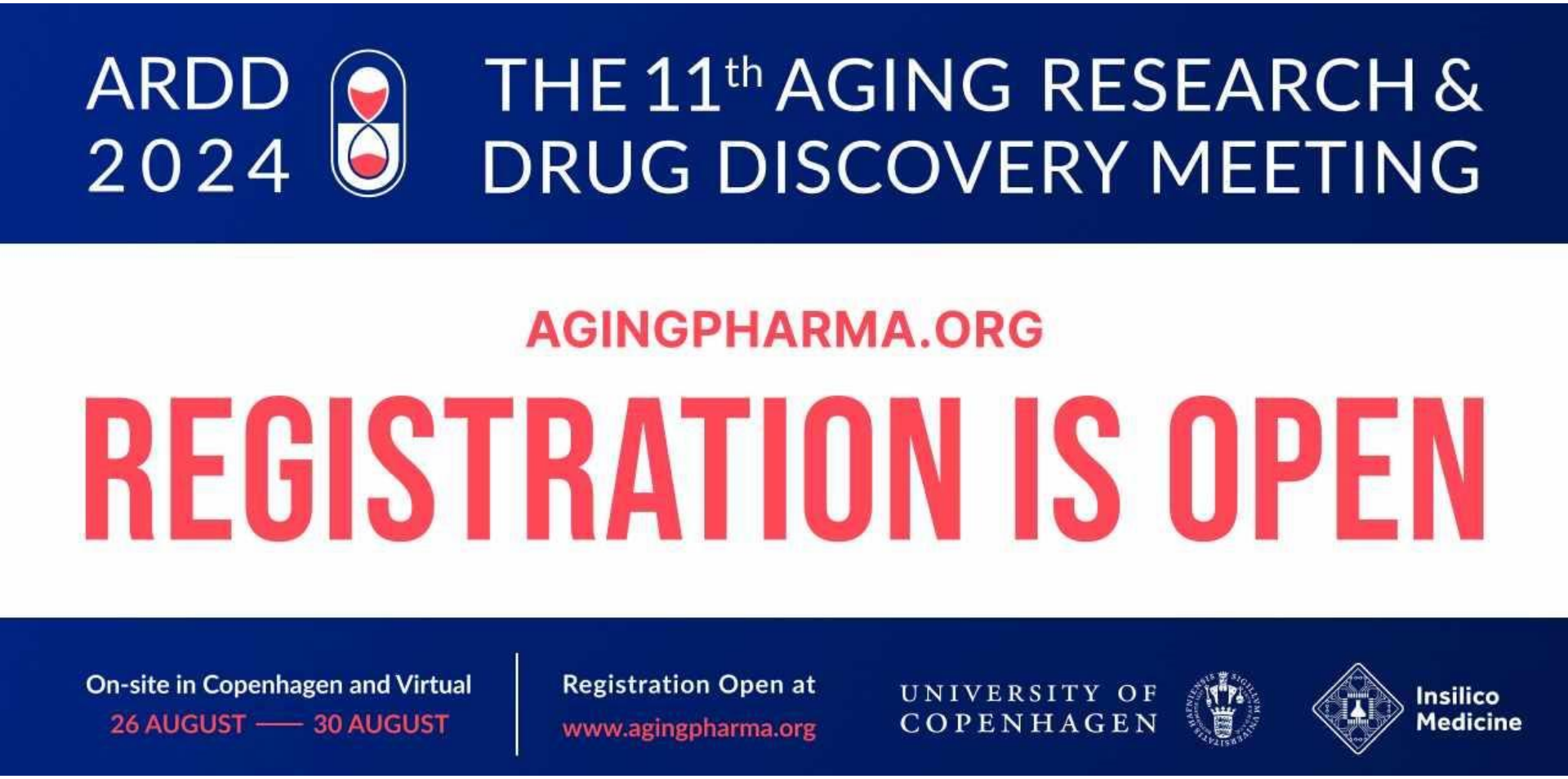
Heales
HEALTHY LIFE EXTENSION SOCIETY

Heales
HEALTHY LIFE EXTENSION SOCIETY

I will be in a panel on aging



Heales
HEALTHY LIFE EXTENSION SOCIETY



Aging research articles

Evidence of a pan-tissue decline in stemness during human aging

Gabriel Arantes dos Santos[1,2], Gustavo Daniel Vega Magdaleno[3], João Pedro de Magalhães[2]

Abstract

Despite their biological importance, the role of stem cells in human aging remains to be elucidated. In this work, we applied a machine learning methodology to GTEx transcriptome data and assigned stemness scores to 17,382 healthy samples from 30 human tissues aged between 20 and 79 years. We found that ~60% of the studied tissues exhibit a significant negative correlation between the subject's age and stemness score. The only significant exception was the uterus, where we observed an increased stemness with age. Moreover, we observed that stemness is positively correlated with cell proliferation and negatively correlated with cellular senescence. Finally, we also observed a trend that hematopoietic stem cells derived from older individuals might have higher stemness scores. In conclusion, we assigned stemness scores to human samples and show evidence of a pan-tissue loss of stemness during human aging, which adds weight to the idea that stem cell deterioration may contribute to human aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A longevity-specific bank of induced pluripotent stem cells from centenarians and their offspring

Todd W Dowrey, Samuel F Cranston, Nicholas Skvir, Yvonne Lok, Brian Gould, Bradley Petrowitz, Daniel Villar, Jidong Shan, Marianne James, Mark Dodge, Anna C Belkina, Richard M Giadone, Paola Sebastiani, Thomas T Perls, Stacy L Andersen, George James Murphy

Centenarians provide a unique lens through which to study longevity, healthy aging, and resiliency. Moreover, models of human aging and resilience to disease that allow for the testing of potential interventions are virtually non-existent. We obtained and characterized over 50 centenarian and offspring peripheral blood samples including those connected to functional independence data highlighting resistance to disability and cognitive impairment. Targeted methylation arrays were used in molecular aging clocks to compare and contrast differences between biological and chronological age in these specialized subjects. Isolated peripheral blood mononuclear cells (PBMCs) were then successfully reprogrammed into high-quality induced pluripotent stem cell (iPSC) lines which were functionally characterized for pluripotency, genomic stability, and the ability to undergo directed differentiation. The result of this work is a one-of-a-kind resource for studies of human longevity and resilience that can fuel the discovery and validation of novel therapeutics for aging-related disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Comparative analysis of mouse strains for in vivo reprogramming

Sara Pico, Alba Vilchez Acosta, Joao Agostinho de Sousa, Maria del Carmen Maza, Alberto Parras, Gabriela Desdin Mico, Calida Mrabti, Celine Yacoub Maroun, Clemence Branchina, Ferdinand von Meyenn, Alejandro Ocampo

In vivo reprogramming through the forced expression of Oct4, Sox2, Klf4, and c-Myc (OSKM) has demonstrated great potential for reversing age-associated phenotypes, as the combination of these transcription factors actively promote cell regeneration and rejuvenation in various tissues and organs. However, continuous in vivo OSKM expression raised safety concerns due to loss of cell identity, decrease in body weight, and premature death. Although cyclic short-term or targeted expression of the reprogramming factors can mitigate some of these detrimental effects in mice, systemic rejuvenation of wild type mice has remained elusive potentially due to these current technical limitations. To improve the fundamental understanding of in vivo reprogramming, we conducted a comparative analysis across multiple reprogrammable mouse strains, tissues, and expression methods, presenting a comprehensive atlas of formerly established strains. In addition, we developed novel reprogrammable mouse strains by avoiding OSKM expression in specific organs, in dividing cells, or implementing chimeric expression approaches within specific cells, thereby offering safer strategies to induce in vivo reprogramming and fully harness its potential. We hope that these new tools will become valuable resources for future research in this very exciting field of research with potential implications to human health.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Senolytic CAR T cells reverse aging-associated defects in intestinal regeneration and fitness

Onur Eskiocak, Saria Chowdhury, Vyom Shah, Emmanuella Nnuji-John, Charlie Chung, Jacob A Boyer, Alexander S Harris, Jill Habel, Michel Sadelain, Semir Beyaz, Corina Amor

PMID: 38529506 PMCID: PMC10962734 DOI: 10.1101/2024.03.19.585779

Abstract

Intestinal stem cells (ISCs) drive the rapid regeneration of the gut epithelium to maintain organismal homeostasis. Aging, however, significantly reduces intestinal regenerative capacity. While cellular senescence is a key feature of the aging process, little is known about the in vivo effects of senescent cells on intestinal fitness. Here, we identify the accumulation of senescent cells in the aging gut and, by harnessing senolytic CAR T cells to eliminate them, we uncover their detrimental impact on epithelial integrity and overall intestinal homeostasis in natural aging, injury and colitis. Ablation of intestinal senescent cells with senolytic CAR T cells in vivo or in vitro is sufficient to promote the regenerative potential of aged ISCs. This intervention improves epithelial integrity and mucosal immune function. Overall, these results highlight the ability of senolytic CAR T cells to rejuvenate the intestinal niche and demonstrate the potential of targeted cell therapies to promote tissue regeneration in aging organisms.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The impact of age and number of mutations on the size of clonal hematopoiesis

Kai Wang, Wen Zhang, Li Yi, +10, and Rui-Bao Ren Authors Info & Affiliations

Clonal hematopoiesis (CH) represents the clonal expansion of hematopoietic stem cells and their progeny driven by somatic mutations. Accurate risk assessment of CH is critical for disease prevention and clinical decision-making. The size of CH has been showed to associate with higher disease risk, yet, factors influencing the size of CH are unknown. In addition, the characteristics of CH in long-lived individuals are not well documented. Here, we report an in-depth analysis of CH in longevous (≥90 y old) and common (60~89 y old) elderly groups. Utilizing targeted deep sequencing, we found that the development of CH is closely related to age and the expression of aging biomarkers. The longevous elderly group exhibited a significantly higher incidence of CH and significantly higher frequency of *TET2* and *ASXL1* mutations, suggesting that certain CH could be beneficial to prolong life. Intriguingly, the size of CH neither correlates significantly to age, in the range of 60 to 110 y old, nor to the expression of aging biomarkers. Instead, we identified a strong correlation between large CH size and the number of mutations per individual. These findings provide a risk assessment biomarker for CH and also suggest that the evolution of the CH is influenced by factor(s) in addition to age.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Depleting myeloid-biased haematopoietic stem cells rejuvenates aged immunity

Jason B. Ross, Lara M. Myers, Joseph J. Noh, Madison M. Collins, Aaron B. Carmody, Ronald J. Messer, Erica Dhuey, Kim J. Hasenkrug ✉ & Irving L. Weissman ✉

Ageing of the immune system is characterized by decreased lymphopoiesis and adaptive immunity, and increased inflammation and myeloid pathologies[1,2]. Age-related changes in populations of self-renewing haematopoietic stem cells (HSCs) are thought to underlie these phenomena[3]. During youth, HSCs with balanced output of lymphoid and myeloid cells (bal-HSCs) predominate over HSCs with myeloid-biased output (my-HSCs), thereby promoting the lymphopoiesis required for initiating adaptive immune responses, while limiting the production of myeloid cells, which can be pro-inflammatory[4]. Ageing is associated with increased proportions of my-HSCs, resulting in decreased lymphopoiesis and increased myelopoiesis[3,5,6]. Transfer of bal-HSCs results in abundant lymphoid and myeloid cells, a stable phenotype that is retained after secondary transfer; my-HSCs also retain their patterns of production after secondary transfer[5]. The origin and potential interconversion of these two subsets is still unclear. If they are separate subsets postnatally, it might be possible to reverse the ageing phenotype by eliminating my-HSCs in aged mice. Here we demonstrate that antibody-mediated depletion of my-HSCs in aged mice restores characteristic features of a more youthful immune system, including increasing common lymphocyte progenitors, naive T cells and B cells, while decreasing age-related markers of immune decline. Depletion of my-HSCs in aged mice improves primary and secondary adaptive immune responses to viral infection. These findings may have relevance to the understanding and intervention of diseases exacerbated or caused by dominance of the haematopoietic system by my-HSCs.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

B Cells Promote T Cell Immunosenescence and Mammalian Aging Parameters

A dysregulated adaptive immune system is a key feature of aging, and is associated with age-related chronic diseases and mortality. Most notably, aging is linked to a loss in the diversity of the T cell repertoire and expansion of activated inflammatory age-related T cell subsets, though the main drivers of these processes are largely unknown. Here, we find that T cell aging is directly influenced by B cells. Using multiple models of B cell manipulation and single-cell omics, we find B cells to be a major cell type that is largely responsible for the age-related reduction of naive T cells, their associated differentiation towards pathogenic immunosenescent T cell subsets, and for the clonal restriction of their T cell receptor (TCR). Accordingly, we find that these pathogenic shifts can be therapeutically targeted via CD20 monoclonal antibody treatment. Mechanistically, we uncover a new role for insulin receptor signaling in influencing age-related B cell pathogenicity that in turn induces T cell dysfunction and a decline in healthspan parameters. These results establish B cells as a pivotal force contributing to age-associated adaptive immune dysfunction and healthspan outcomes, and suggest new modalities to manage aging and related multi-morbidity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A torpor-like state (TLS) in mice slows blood epigenetic aging and prolongs healthspan

Lorna Jayne, Aurora Lavin-Peter, Julian Roessler, Alexander Tyshkovskiy, Mateusz Antoszewski, Erika Ren, Aleksandar Markovski, Senmiao Sun, Hanqi Yao, Vijay G. Sankaran, Vadim N. Gladyshev, Robert T. Brooke, Steve Horvath, Eric C. Griffith, Sinisa Hrvatin

Torpor and hibernation are extreme physiological adaptations of homeotherms associated with pro-longevity effects. Yet the underlying mechanisms of how torpor affects aging, and whether hypothermic and hypometabolic states can be induced to slow aging and increase health span, remain unknown. We demonstrate that the activity of a spatially defined neuronal population in the avMLPA, which has previously been identified as a torpor-regulating brain region, is sufficient to induce a torpor like state (TLS) in mice. Prolonged induction of TLS slows epigenetic aging across multiple tissues and improves health span. We isolate the effects of decreased metabolic rate, long-term caloric restriction, and decreased core body temperature (T_b) on blood epigenetic aging and find that the pro-longevity effect of torpor-like states is mediated by decreased T_b. Taken together, our findings provide novel mechanistic insight into the pro-longevity effects of torpor and hibernation and support the growing body of evidence that T_b is an important mediator of aging processes.

Shared genetic architecture and causal relationship between sleep behaviors and lifespan

Yong Wu, Chu-Yi Zhang, Xiaolan Liu, Lu Wang, Ming Li, Yi Li & Xiao Xiao

Poor sleep health is associated with a wide array of increased risk for cardiovascular, metabolic and mental health problems as well as all-cause mortality in observational studies, suggesting potential links between sleep health and lifespan. However, it has yet to be determined whether sleep health is genetically or/and causally associated with lifespan. In this study, we firstly studied the genome-wide genetic association between four sleep behaviors (short sleep duration, long sleep duration, insomnia, and sleep chronotype) and lifespan using GWAS summary statistics, and both sleep duration time and insomnia were negatively correlated with lifespan. Then, two-sample Mendelian randomization (MR) and multivariable MR analyses were applied to explore the causal effects between sleep behaviors and lifespan. We found that genetically predicted short sleep duration was causally and negatively associated with lifespan in univariable and multivariable MR analyses, and this effect was partially mediated by coronary artery disease (CAD), type 2 diabetes (T2D) and depression. In contrast, we found that insomnia had no causal effects on lifespan. Our results further confirmed the negative effects of short sleep duration on lifespan and suggested that extension of sleep may benefit the physical health of individuals with sleep loss. Further attention should be given to such public health issues.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Inhibition of S6K lowers age-related inflammation and increases lifespan through the endolysosomal system

Pingze Zhang, James H. Catterson, Sebastian Grönke & Linda Partridge

Suppression of target of rapamycin complex 1 (TORC1) by rapamycin ameliorates aging in diverse species. S6 kinase (S6K) is an essential mediator, but the mechanisms involved are unclear. Here we show that activation of S6K specifically in *Drosophila* fat-body blocked extension of lifespan by rapamycin, induced accumulation of multilamellar lysosomes and blocked age-associated hyperactivation of the NF-κB-like immune deficiency (IMD) pathway, indicative of reduced inflammaging. Syntaxin 13 mediated the effects of TORC1–S6K signaling on lysosome morphology and inflammaging, suggesting they may be linked. Inflammaging depended on the IMD receptor regulatory isoform PGRP-LC, and repression of the IMD pathway from midlife extended lifespan. Age-related inflammaging was higher in females than in males and was not lowered in males by rapamycin treatment or lowered S6K. Rapamycin treatment also elevated Syntaxin 12/13 levels in mouse liver and prevented age-related increase in noncanonical NF-κB signaling, suggesting that the effect of TORC1 on inflammaging is conserved from flies to mammals.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Ergothioneine promotes longevity and healthy aging in male mice

Healthy aging has emerged as a crucial issue with the increase in the geriatric population worldwide. Food-derived sulfur-containing amino acid ergothioneine (ERGO) is a potential dietary supplement, which exhibits various beneficial effects in experimental animals although the preventive effects of ERGO on aging and/or age-related impairments such as frailty and cognitive impairment are unclear. We investigated the effects of daily oral supplementation of ERGO dissolved in drinking water on lifespan, frailty, and cognitive impairment in male mice from 7 weeks of age to the end of their lives. Ingestion of 4 ~ 5 mg/kg/day of ERGO remarkably extended the lifespan of male mice. The longevity effect of ERGO was further supported by increase in life and non-frailty spans of *Caenorhabditis elegans* in the presence of ERGO. Compared with the control group, the ERGO group showed significantly lower age-related declines in weight, fat mass, and average and maximum movement velocities at 88 weeks of age. This was compatible with dramatical suppression by ERGO of the age-related increments in plasma biomarkers (BMs) such as the chemokine ligand 9, creatinine, symmetric dimethylarginine, urea, asymmetric dimethylarginine, quinolinic acid, and kynurenine. The oral intake of ERGO also rescued age-related impairments in learning and memory ability, which might be associated with suppression of the age-related decline in hippocampal neurogenesis and TDP43 protein aggregation and promotion of microglial shift to the M2 phenotype by ERGO ingestion. Ingestion of ERGO may promote longevity and healthy aging in male mice, possibly through multiple biological mechanisms.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Metformin treatment results in distinctive skeletal muscle mitochondrial remodeling in rats with different intrinsic aerobic capacities

Matthew P Bubak, Arik Davidyan, Colleen L O'Reilly, Samim A Mondal, Jordan Kest, Stephen M Doidge, Agnieszka Katarzyna Borowik, Michael T Taylor, Evelina Voloviceva, Michael T Kinter, Steven Loyal Britton, Lauren G Koch, Michael B Stout, Tommy L Lewis Jr., Benjamin F Miller

The rationale for the use of metformin as a treatment to slow aging was largely based on data collected from metabolically unhealthy individuals. For healthspan extension metformin will also be used in periods of good health. To understand potential context specificity of metformin treatment on skeletal muscle, we used a rat model (HCR/LCR) with a divide in intrinsic aerobic capacity. Outcomes of metformin treatment differed based on baseline intrinsic mitochondrial function, oxidative capacity of the muscle (gastroc vs soleus), and the mitochondrial population (IMF vs SS). Metformin caused lower ADP-stimulated respiration in LCRs, with less of a change in HCRs. However, a washout of metformin resulted in an unexpected doubling of respiratory capacity in HCRs. These improvements in respiratory capacity were accompanied by mitochondrial remodeling that included increases in protein synthesis and changes in morphology. Our findings raise questions about whether the positive findings of metformin treatment are broadly applicable.

TP53INP2-dependent activation of muscle autophagy ameliorates sarcopenia and promotes healthy aging

David Sebastián [1 2 3], Marc Beltrà [2 3 4], Andrea Irazoki [2 3 4], David Sala [2 3 4], Pilar Aparicio [5], Cecilia Aris [6], Esmaeil Alibakhshi [7 8 9], Maria Rubio-Valera [10 11], Manuel Palacín [2 4 12], Juan Castellanos [5], Luis Lores [7], Antonio Zorzano [2 3 4]

Sarcopenia is a major contributor to disability in older adults, and thus, it is key to elucidate the mechanisms underlying its development. Increasing evidence suggests that impaired macroautophagy/autophagy contributes to the development of sarcopenia. However, the mechanisms leading to reduced autophagy during aging remain largely unexplored, and whether autophagy activation protects from sarcopenia has not been fully addressed. Here we show that the autophagy regulator TP53INP2/TRP53INP2 is decreased during aging in mouse and human skeletal muscle. Importantly, chronic activation of autophagy by muscle-specific overexpression of TRP53INP2 prevents sarcopenia and the decline of muscle function in mice. Acute re-expression of TRP53INP2 in aged mice also improves muscle atrophy, enhances mitophagy, and reduces ROS production. In humans, high levels of TP53INP2 in muscle are associated with increased muscle strength and healthy aging. Our findings highlight the relevance of an active muscle autophagy in the maintenance of muscle mass and prevention of sarcopenia.**Abbreviation**: ATG7: autophagy related 7; BMI: body mass index; EIF4EBP1: eukaryotic translation initiation factor 4E binding protein 1; MAP1LC3/LC3: microtubule associated protein 1 light chain 3; ROS: reactive oxygen species; TP53INP2: tumor protein p53 inducible nuclear protein 2; WT: wild type.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Supercentenarian and remarkable age records exhibit patterns indicative of clerical errors and pension fraud

Saul Justin Newman

The observation of individuals attaining remarkable ages, and their concentration into geographic sub-regions or 'blue zones', has generated considerable scientific interest. Proposed drivers of remarkable longevity include high vegetable intake, strong social connections, and genetic markers. Here, we reveal new predictors of remarkable longevity and 'supercentenarian' status. In the United States, supercentenarian status is predicted by the absence of vital registration. The state-specific introduction of birth certificates is associated with a 69-82% fall in the number of supercentenarian records. In Italy, England, and France, which have more uniform vital registration, remarkable longevity is instead predicted by poverty, low per capita incomes, shorter life expectancy, higher crime rates, worse health, higher deprivation, fewer 90+ year olds, and residence in remote, overseas, and colonial territories. In England and France, higher old-age poverty rates alone predict more than half of the regional variation in attaining a remarkable age. Only 18% of 'exhaustively' validated supercentenarians have a birth certificate, falling to zero percent in the USA, and supercentenarian birthdates are concentrated on days divisible by five: a pattern indicative of widespread fraud and error. Finally, the designated 'blue zones' of Sardinia, Okinawa, and Ikaria corresponded to regions with low incomes, low literacy, high crime rate and short life expectancy relative to their national average. As such, relative poverty and short lifespan constitute unexpected predictors of centenarian and supercentenarian status and support a primary role of fraud and error in generating remarkable human age records.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests

With the emergence of Alzheimer's disease (AD) disease-modifying therapies, identifying patients who could benefit from these treatments becomes critical. In this study, we evaluated whether a precise blood test could perform as well as established cerebrospinal fluid (CSF) tests in detecting amyloid-β (Aβ) plaques and tau tangles. Plasma %p-tau217 (ratio of phosporylated-tau217 to non-phosphorylated tau) was analyzed by mass spectrometry in the Swedish BioFINDER-2 cohort (n = 1,422) and the US Charles F. and Joanne Knight Alzheimer Disease Research Center (Knight ADRC) cohort (n = 337). Matched CSF samples were analyzed with clinically used and FDA-approved automated immunoassays for Aβ42/40 and p-tau181/Aβ42. The primary and secondary outcomes were detection of brain Aβ or tau pathology, respectively, using positron emission tomography (PET) imaging as the reference standard. Main analyses were focused on individuals with cognitive impairment (mild cognitive impairment and mild dementia), which is the target population for available disease-modifying treatments. Plasma %p-tau217 was clinically equivalent to FDA-approved CSF tests in classifying Aβ PET status, with an area under the curve (AUC) for both between 0.95 and 0.97. Plasma %p-tau217 was generally superior to CSF tests in classification of tau-PET with AUCs of 0.95–0.98. In cognitively impaired subcohorts (BioFINDER-2: n = 720; Knight ADRC: n = 50), plasma %p-tau217 had an accuracy, a positive predictive value and a negative predictive value of 89–90% for Aβ PET and 87–88% for tau PET status, which was clinically equivalent to CSF tests, further improving to 95% using a two-cutoffs approach. Blood plasma %p-tau217 demonstrated performance that was clinically equivalent or superior to clinically used FDA-approved CSF tests in the detection of AD pathology. Use of high-performance blood tests in clinical practice can improve access to accurate AD diagnosis and AD-specific treatments.

Rejuvenating aged microglia by $p16^{ink4a}$–siRNA–loaded nanoparticles increases amyloid–β clearance in animal models of Alzheimer's disease

Age-dependent accumulation of amyloid plaques in patients with sporadic Alzheimer's disease (AD) is associated with reduced amyloid clearance. Older microglia have a reduced ability to phagocytose amyloid, so phagocytosis of amyloid plaques by microglia could be regulated to prevent amyloid accumulation. Furthermore, considering the aging-related disruption of cell cycle machinery in old microglia, we hypothesize that regulating their cell cycle could rejuvenate them and enhance their ability to promote more efficient amyloid clearance. First, we used gene ontology analysis of microglia from young and old mice to identify differential expression of cyclin-dependent kinase inhibitor 2A ($p16^{ink4a}$), a cell cycle factor related to aging. We found that $p16^{ink4a}$ expression was increased in microglia near amyloid plaques in brain tissue from patients with AD and 5XFAD mice, a model of AD. In BV2 microglia, small interfering RNA (siRNA)-mediated p16ink4a downregulation transformed microglia with enhanced amyloid phagocytic capacity through regulated the cell cycle and increased cell proliferation. To regulate microglial phagocytosis by gene transduction, we used poly (D,L-lactic-co-glycolic acid) (PLGA) nanoparticles, which predominantly target microglia, to deliver the siRNA and to control microglial reactivity. Nanoparticle-based delivery of $p16^{ink4a}$ siRNA reduced amyloid plaque formation and the number of aged microglia surrounding the plaque and reversed learning deterioration and spatial memory deficits. We propose that downregulation of $p16^{ink4a}$ in microglia is a promising strategy for the treatment of Alzheimer's disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Biolearn, an open-source library for biomarkers of aging

Kejun Ying, Seth Paulson, Martin Perez-Guevara, Mehrnoosh Emamifar, Maximiliano Casas Martinez, Dayoon Kwon, Jesse R. Poganik, Mahdi Moqri, Vadim N. Gladyshev

Identifying and validating biomarkers of aging is pivotal for understanding the aging process and testing longevity interventions. Despite the development of numerous aging biomarkers, their clinical validation remains elusive, largely due to the lack of cross-population validation, which is hampered by disparate biomarker designs and inconsistencies in dataset structures. To bridge this gap, we introduce Biolearn, an innovative open-source library dedicated to the implementation and application of aging biomarkers. Biolearn facilitates (1) harmonization of existing aging biomarkers, while presenting a structured framework for novel biomarkers in standardized formats; (2) unification of public datasets, ensuring coherent structuring and formatting, thus simplifying cross-population validation studies; and (3) provision of computational methodologies to assess any harmonized biomarker against unified datasets. By furnishing a community-driven platform, Biolearn significantly augments the development, assessment, and validation trajectories of aging biomarkers, paving the way toward more rigorous clinical validation and, ultimately, application in clinical trials targeting healthy longevity. The Biolearn package is open-source and freely available at https://Bio-Learn.github.io/

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

The Sociodemographic and Lifestyle Correlates of Epigenetic Aging in a Nationally Representative U.S. Study of Younger Adults

Participants Data come from the National Longitudinal Study of Adolescent to Adult Health, a national cohort of adolescents in grades 7-12 in U.S. in 1994 followed for 25 years over five interview waves. Our analytic sample includes participants followed-up through Wave V in 2016-18 who provided blood samples for DNA methylation (DNAm) testing (n=4237) at Wave V.

Exposure Sociodemographic (sex, race/ethnicity, immigrant status, socioeconomic status, geographic location) and lifestyle (obesity status, exercise, tobacco, and alcohol use) characteristics.

Main Outcome Biological aging assessed from blood DNAm using 16 epigenetic clocks when the cohort was aged 33-44 in Wave V.

Results While there is considerable variation in the mean and distribution of epigenetic clock estimates and in the correlations among the clocks, we found sociodemographic and lifestyle factors are more often associated with biological aging in clocks trained to predict current or dynamic phenotypes (e.g., PhenoAge, GrimAge and DunedinPACE) as opposed to clocks trained to predict chronological age alone (e.g., Horvath). Consistent and strong associations of faster biological aging were found for those with lower levels of education and income, and those with severe obesity, no weekly exercise, and tobacco use.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A molecular index for biological age identified from the metabolome and senescence-associated secretome in humans

Shruthi Hamsanathan, Tamil Anthonymuthu, Denise Prosser, Anna Lokshin, Susan L. Greenspan, Neil M. Resnick, Subashan Perera, Satoshi Okawa, Giri Narasimhan, Aditi U. Gurkar

Unlike chronological age, biological age is a strong indicator of health of an individual. However, the molecular fingerprint associated with biological age is ill-defined. To define a high-resolution signature of biological age, we analyzed metabolome, circulating senescence-associated secretome (SASP)/inflammation markers and the interaction between them, from a cohort of healthy and rapid agers. The balance between two fatty acid oxidation mechanisms, β-oxidation and ω-oxidation, associated with the extent of functional aging. Furthermore, a panel of 25 metabolites, Healthy Aging Metabolic (HAM) index, predicted healthy agers regardless of gender and race. HAM index was also validated in an independent cohort. Causal inference with machine learning implied three metabolites, β-cryptoxanthin, prolylhydroxyproline, and eicosenoylcarnitine as putative drivers of biological aging. Multiple SASP markers were also elevated in rapid agers. Together, our findings reveal that a network of metabolic pathways underlie biological aging, and the HAM index could serve as a predictor of phenotypic aging in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Post-death Vesicles of Senescent Bone Marrow Mesenchymal Stromal Polyploids Promote Macrophage Aging and Breast Cancer

Bowen Xie, Ming Fan, Charles X Wang, Yanhong Zhang, Shanxiu Xu, Rachel Mizenko, Tzu-yin Lin, Yixin Duan, Yanyan Zhang, Jie Huang, Jonathan I Berg, Douglas Wu, Anna Li, Dake Hao, Kewa Gao, Yao-hui Sun, Clifford G Tepper, Randy P Carney, Yuanpei Li, Aijun Wang, Qizhi Gong, Magen Daly, Li-En Jao, Arta M Monjazeb, Fernando A Fierro, Jian Jian Li

Potential systemic factors contributing to aging-associated breast cancer (BC) remain elusive. Here, we reveal that the polyploid giant cells (PGCs) that contain more than two sets of genomes prevailing in aging and cancerous tissues constitute 5-10% of healthy female bone marrow mesenchymal stromal cells (fBMSCs). The PGCs can repair DNA damage and stimulate neighboring cells for clonal expansion. However, dying PGCs in advanced-senescent fBMSCs can form spikings which are then separated into membraned mtDNA-containing vesicles (Senescent PGC-Spiking Bodies; SPSBs). SPSB-phagocytosed macrophages accelerate aging with diminished clearance on BC cells and protumor M2 polarization. SPSB-carried mitochondrial OXPHOS components are enriched in BC of elder patients and associated with poor prognosis. SPSB-incorporated breast epithelial cells develop aggressive characteristics and PGCs resembling the polyploid giant cancer cells (PGCCs) in clonogenic BC cells and cancer tissues. These findings highlight an aging BMSC-induced BC risk mediated by SPSB-induced macrophage dysfunction and epithelial cell precancerous transition.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Intermittent Methionine Restriction Reduces Marrow Fat Accumulation and Preserves More Bone Mass than Continuous Methionine Restriction

Continuous methionine restriction (MR) is one of only a few dietary interventions known to dramatically extend mammalian healthspan. For example, continuously methionine-restricted rodents show less age-related pathology and are up to 45% longer-lived than controls. Intriguingly, MR is feasible for humans, andanumberofstudieshavesuggestedthatmethionine-restrictedindividualsmayreceivesimilarhealthspan benefits as rodents. However, long-term adherence to a continuously methionine-restricted diet is likely to be challenging (or even undesirable) for many individuals. To address this, we previously developed an intermittent version of MR (IMR) and demonstrated that it confers nearly identical metabolic health benefits to mice as the continuous intervention, despite having a relatively short interventional period (i.e., only three days per week). We also observed that female mice undergoing IMR show a more pronounced amelioration of diet-induced dysglycemia than continuously methionine-restricted counterparts, while male mice undergoing IMR retain more lean body mass as compared with continuously methionine-restricted controls. Prompted by such findings, we sought to determine other ways in which IMR might compare favorably with continuous MR. While it is known that continuous MR has deleterious effects on bone in mice, including loss of both trabecular and cortical bone, we considered that mice undergoing IMR might retain more bone mass. Here, we report that, as compared with continuous MR, IMR results in a preservation of both trabecular and cortical bone, as well as a dramatic reduction in the accumulation of marrow fat. Consistent with such findings, mechanical testing revealed that the bones of intermittently methionine-restricted mice are significantly stronger than those of mice subjected to the continuous intervention. Finally, static histomorphometric analyses suggest that IMR likely results in more bone mass than that produced by continuous MR, primarily by increasing the number of osteoblasts. Together, our results demonstrate that the more practicable intermittent form of MR not only confers similar metabolic health benefits to the continuous intervention but does so without markedly deleterious effects on either the amount or strength of bone. These data provide further support for the use of IMR in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Deciphering the Timing and Impact of Life-extending Drugs: A Novel Analytic Approach that Differentiates Early, Midlife, and Senescence Phase Efficacies.

Nisi Jiang, Catherine J. Cheng, Qianqian Liu, Randy Strong, Jonathan Gelfond, James F. Nelson

Evidence that life-extending interventions are not uniformly effective across the lifespan calls for an analytic tool that can estimate age-specific treatment effects on mortality hazards. Here we report such a tool, applying it to mouse data from 42 agents tested in the NIA Interventions Testing Program. This tool identified agents that either reduced (22) or increased (16) mortality hazards or did both (6), all with marked variation in the duration of efficacy and magnitude of effect size. Only 7 reduced mortality hazards after the 90% mortality, when the burden of senescence is greatest. Sex differences were apparent in all parameters. This new analytic tool complements the commonly used log-rank test. It detects more potential life-extending candidates (22 versus 10) and indicates when during the life course they are effective. It also uncovers adverse effects. Most importantly, it identifies agents that specifically reduce mortality hazards during the senescent phase of life.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Just-DNA-Seq, open-source personal genomics platform: longevity science for everyone

Kulaga Anton (1,2,3,4), Borysova Olga (4,6), Karmazin Alexey (4,7), Koval Maria (3,4), Usanov Nikolay (3,4), Fedorova Alina (3), Evfratov Sergey (3), Pushkareva Malvina (3), Ryangguk Kim (8), Tacutu Robi (2, 5) ((1) Institute for Biostatistics and Informatics in Medicine and Ageing Research (2), (3) Institute of Biochemistry of the Romanian Academy, (4) International Longevity Alliance (ILA), (5) SecvADN SRL, (6) CellFabrik SRL, (7) MitoSpace, (8) M. Glushkov Institute of Cybernetics of National Academy of Sciences of Ukraine, (8) Oak Bioinformatics LLC)

Genomic data has become increasingly accessible to the general public with the advent of companies offering whole genome sequencing at a relatively low cost. However, their reports are not verifiable due to a lack of crucial details and transparency: polygenic risk scores do not always mention all the polymorphisms involved. Simultaneously, tackling the manual investigation and interpretation of data proves challenging for individuals lacking a background in genetics. Currently, there is no open-source or commercial solution that provides comprehensive longevity reports surpassing a limited number of polymorphisms. Additionally, there are no ready-made, out-of-the-box solutions available that require minimal expertise to generate reports independently. To address these issues, we have developed the Just-DNA-Seq open-source genomic platform. Just-DNA-Seq aims to provide a user-friendly solution to genome annotation by allowing users to upload their own VCF files and receive annotations of their genetic variants and polygenic risk scores related to longevity. We also created GeneticsGenie custom GPT that can answer genetics questions based on our modules. With the Just-DNA-Seq platform, we want to provide full information regarding the genetics of long life: disease-predisposing variants, that can reduce lifespan and manifest at different age (cardiovascular, oncological, neurodegenerative diseases, etc.), pro-longevity variants and longevity drug pharmacokinetics. In this research article, we will discuss the features and capabilities of Just-DNA-Seq, and how it can benefit individuals looking to understand and improve their health. It's crucial to note that the Just-DNA-Seq platform is exclusively intended for scientific and informational purposes and is not suitable for medical applications.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Age-related dysregulation of the retinal transcriptome in African turquoise killifish

Steven Bergmans, Nicole CL Noel, Luca Masin, Ellen G Harding, Aleksandra M Krzywanska, Julie D De Schutter, Rajagopal Ayana, Chi-Kuo Hu, Lut Arckens, Philip A Ruzycki, Brian S Clark, Ryan B MacDonald, Lieve Moons

Age-related vision loss caused by neurodegenerative pathologies in the retina is becoming more prevalent in our ageing society. To understand the physiological and molecular impact of ageing on retinal homeostasis, we used the short-lived African turquoise killifish, a model known to naturally develop central nervous system (CNS) ageing hallmarks. Bulk and single-cell RNA-sequencing (scRNA-seq) of three age groups (6-, 12-, and 18-week-old) identified transcriptional ageing fingerprints in the killifish retina, unveiling pathways also identified in the aged brain, including oxidative stress, gliosis, and inflammageing. These findings were comparable to observations in ageing mouse retina. Additionally, transcriptional changes in genes related to retinal diseases, such as glaucoma and age-related macular degeneration, were observed. The cellular heterogeneity in the killifish retina was characterised, confirming the presence of all typical vertebrate retinal cell types. Data integration from age-matched samples between the bulk and scRNA-seq experiments revealed a loss of cellular specificity in gene expression upon ageing, suggesting potential disruption in transcriptional homeostasis. Differential expression analysis within the identified cell types highlighted the role of glial/immune cells as important stress regulators during ageing. Our work emphasises the value of the fast-ageing killifish in elucidating molecular signatures in age-associated retinal disease and vision decline. This study contributes to the understanding of how age-related changes in molecular pathways may impact CNS health, providing insights that may inform future therapeutic strategies for age-related pathologies.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Single-cell genomics and regulatory networks for 388 human brains

Single-cell genomics is a powerful tool for studying heterogeneous tissues such as the brain. Yet, little is understood about how genetic variants influence cell-level gene expression. Addressing this, we uniformly processed single-nuclei, multi-omics datasets into a resource comprising >2.8M nuclei from the prefrontal cortex across 388 individuals. For 28 cell types, we assessed population-level variation in expression and chromatin across gene families and drug targets. We identified >550K cell-type-specific regulatory elements and >1.4M single-cell expression-quantitative-trait loci, which we used to build cell-type regulatory and cell-to-cell communication networks. These networks manifest cellular changes in aging and neuropsychiatric disorders. We further constructed an integrative model accurately imputing single-cell expression and simulating perturbations; the model prioritized ~250 disease-risk genes and drug targets with associated cell types.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Machine learning predicts lifespan and underlying causes of death in aging *C. elegans*

Carina C. Kern, Petru Manescu, Matt Cuffaro, Catherine Au, Aihan Zhang, Hongyuan Wang, Ann F. Gilliat, Marina Ezcurra, David Gems

Senescence (aging) leads to senescent pathology that causes death, and genes control aging by determining such pathology. Here we investigate how senescent pathology mediates the effect of genotype on lifespan in *C. elegans* by means of a data-driven approach, using machine learning (ML). To achieve this we gathered extensive data on how diverse determinants of lifespan (sex, nutrition, genotype) affect patterns of age-related pathology. Our findings show that different life-extending treatments result in distinct patterns of suppression of senescent pathology. By analysing the differential effects on pathology and lifespan, our ML models were able to predict >70% of lifespan variation. Extent of pathology in the pharynx and intestine were the most important predictors of lifespan, arguing that elderly *C. elegans* die in part due to late-life disease in these organs. Notably, the mid-life pathogenetic burst characteristic of hermaphrodite senescence is absent from males.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

ELO-6 expression predicts longevity in isogenic populations of Caenorhabditis elegans

Variations of individual lifespans within genetically identical populations in homogenous environments are remarkable, with the cause largely unknown. Gene expression changes with age, and the transcriptome changes correlate with chronological aging. Here, we show that in Caenorhabditis elegans, the expression dynamic of the fatty acid elongase ELO-6 during aging predicts individual longevity in isogenic populations. The expression of elo-6 is reduced with age. From adult day 5, ELO-6 expression level exhibits variation between individuals, and the expression level is positively correlated with adult lifespan and health span. Interventions that prolong longevity enhance the expression stability of ELO-6 during aging from adult day 4 to adult day 8, indicating ELO-6 is also a populational lifespan predictor. We performed transcriptome analysis in short-lived and long-lived isogenic worms and identified differentially expressed genes, which are enriched for PQM-1 binding sites. Decreasing pqm-1 expression in young adults improved the homogeneity of ELO-6 levels between individuals and enhanced health span. Furthermore, we found reducing the expression of genes that are highly expressed in short-lived individuals, including PQM-1 target genes, enhanced ELO-6 expression stability with age and extended lifespan. Thus, our study identified ELO-6 as a predictor of individual and populational lifespan and revealed the role of pqm-1 in restricting health span and possibly causing individual lifespan variation.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

The long and winding road of reprogramming-induced rejuvenation

Ali Doğa Yücel & Vadim N. Gladyshev

Organismal aging is inherently connected to the aging of its constituent cells and systems. Reducing the biological age of the organism may be assisted by reducing the age of its cells - an approach exemplified by partial cell reprogramming through the expression of Yamanaka factors or exposure to chemical cocktails. It is crucial to protect cell type identity during partial reprogramming, as cells need to retain or rapidly regain their functions following the treatment. Another critical issue is the ability to quantify biological age as reprogrammed older cells acquire younger states. We discuss recent advances in reprogramming-induced rejuvenation and offer a critical review of this procedure and its relationship to the fundamental nature of aging. We further comparatively analyze partial reprogramming, full reprogramming and transdifferentiation approaches, assess safety concerns and emphasize the importance of distinguishing rejuvenation from dedifferentiation. Finally, we highlight translational opportunities that the reprogramming-induced rejuvenation approach offers.

Recent advances in senescence-associated secretory phenotype and osteoporosis

The worldwide elderly population is on the rise, and aging is a major osteoporosis risk factor. Senescent cells accumulation can have a detrimental effect the body as we age. The senescence-associated secretory phenotype (SASP), an essential cellular senescence hallmark, is an important mechanism connecting cellular senescence to osteoporosis. This review describes in detail the characteristics of SASPs and their regulatory agencies, and shed fresh light on how SASPs from different senescent cells contribute to osteoporosis development. Furthermore, we summarized various innovative therapy techniques that target SASPs to lower the burden of osteoporosis in the elderly and discussed the potential challenges of SASPs-based therapy for osteoporosis as a new clinical trial.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Focus on senescence: Clinical significance and practical applications

Virginia Boccardi, Miranda Ethel Orr, M. Cristina Polidori, Carmelinda Ruggiero ✉, Patrizia Mecocci

The older population is increasing worldwide, and life expectancy is continuously rising, predominantly thanks to medical and technological progress. Healthspan refers to the number of years an individual can live in good health. From a gerontological viewpoint, the mission is to extend the life spent in good health, promoting well-being and minimizing the impact of aging-related diseases to slow the aging process. Biologically, aging is a malleable process characterized by an intra- and inter-individual heterogeneous and dynamic balance between accumulating damage and repair mechanisms. Cellular senescence is a key component of this process, with senescent cells accumulating in different tissues and organs, leading to aging and age-related disease susceptibility over time. Removing senescent cells from the body or slowing down the burden rate has been proposed as an efficient way to reduce age-dependent deterioration. In animal models, senotherapeutic molecules can extend life expectancy and lifespan by either senolytic or senomorphic activity. Much research shows that dietary and physical activity-driven lifestyle interventions protect against senescence. This narrative review aims to summarize the current knowledge on targeting senescent cells to reduce the risk of age-related disease in animal models and their translational potential for humans. We focused on studies that have examined the potential role of senotherapeutics in slowing the aging process and modifying age-related disease burdens. The review concludes with a general discussion of the mechanisms underlying this unique trajectory and its implications for future research.

Heales
HEALTHY LIFE EXTENSION SOCIETY

MtDNA deletions and aging

 Charlotte Sprason Trudy Tucker  David Clancy*

Biomedical and Life Sciences, Lancaster University, Lancaster, United Kingdom

Aging is the major risk factor in most of the leading causes of mortality worldwide, yet its fundamental causes mostly remain unclear. One of the clear hallmarks of aging is mitochondrial dysfunction. Mitochondria are best known for their roles in cellular energy generation, but they are also critical biosynthetic and signaling organelles. They also undergo multiple changes with organismal age, including increased genetic errors in their independent, circular genome. A key group of studies looking at mice with increased mtDNA mutations showed that premature aging phenotypes correlated with increased deletions but not point mutations. This generated an interest in mitochondrial deletions as a potential fundamental cause of aging. However, subsequent studies in different models have yielded diverse results. This review summarizes the research on mitochondrial deletions in various organisms to understand their possible roles in causing aging while identifying the key complications in quantifying deletions across all models.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Exceptional longevity in Okinawa: Demographic trends since 1975

Michel Poulain ✉, Anne Herm

Demographers have studied the Japanese mortality pattern since Japan became the most longevous population worldwide, half a century ago. Nutrition and lifestyle were considered by epidemiologists, gerontologists and other scientists as the most important reasons explaining the Japanese superiority. In Okinawa, the mortality pattern is even more exceptional, but few demographers have pointed out this exception. Other scientists proposed different explanations – for example some genetic characteristics, less salt and more animal protein in the food, a mild climate, a higher level of activity, a better consideration of the oldest in the population and, globally speaking, a more traditional lifestyle. At the end of the 1980s, lower improvements of mortality among young adults were identified in Okinawa. In 2002, Okinawa fell from the 4th to the 26th place in the ranking of the 47 Japanese prefectures by male life expectancy. This has been considered by the population of Okinawa as a 'shock'. Our in-depth analysis of available life tables and associated mortality rates proves that the population of Okinawa is divided into two groups of generations: those born before World War II and those born after. The older generations clearly experience a highly favourable mortality pattern, whereas the younger generations show mortality levels that are definitively higher compared to mainland Japan. This contribution considers which factors may explain such a situation, including the plausible invalidation of the age of some oldest in the population. We plea for in-depth demographic age validation that will enhance all scientific findings so far and boost the exceptional longevity in Okinawa.

Geroscience and pathology: a new frontier in understanding age-related diseases

Monika Fekete [1], David Major [1], Agnes Feher [1], Vince Fazekas-Pongor [1], Andrea Lehoczki [1 2]

Geroscience, a burgeoning discipline at the intersection of aging and disease, aims to unravel the intricate relationship between the aging process and pathogenesis of age-related diseases. This paper explores the pivotal role played by geroscience in reshaping our understanding of pathology, with a particular focus on age-related diseases. These diseases, spanning cardiovascular and cerebrovascular disorders, malignancies, and neurodegenerative conditions, significantly contribute to the morbidity and mortality of older individuals. We delve into the fundamental cellular and molecular mechanisms underpinning aging, including mitochondrial dysfunction and cellular senescence, and elucidate their profound implications for the pathogenesis of various age-related diseases. Emphasis is placed on the importance of assessing key biomarkers of aging and biological age within the realm of pathology. We also scrutinize the interplay between cellular senescence and cancer biology as a central area of focus, underscoring its paramount significance in contemporary pathological research. Moreover, we shed light on the integration of anti-aging interventions that target fundamental aging processes, such as senolytics, mitochondria-targeted treatments, and interventions that influence epigenetic regulation within the domain of pathology research. In conclusion, the integration of geroscience concepts into pathological research heralds a transformative paradigm shift in our understanding of disease pathogenesis and promises breakthroughs in disease prevention and treatment.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Translation is an emerging constraint on protein homeostasis in ageing

Jack Llewellyn • Simon J. Hubbard • Joe Swift

Proteins are molecular machines that provide structure and perform vital transport, signalling and enzymatic roles. Proteins expressed by cells require tight regulation of their concentration, folding, localisation, and modifications; however, this state of protein homeostasis is continuously perturbed by tissue-level stresses. While cells in healthy tissues are able to buffer against these perturbations, for example, by expression of chaperone proteins, protein homeostasis is lost in ageing, and can lead to protein aggregation characteristic of protein folding diseases. Here, we review reports of a progressive disconnect between transcriptomic and proteomic regulation during cellular ageing. We discuss how age-associated changes to cellular responses to specific stressors in the tissue microenvironment are exacerbated by loss of ribosomal proteins, ribosomal pausing, and mistranslation.

OTHER RESEARCH & REVIEWS

A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models

Feng Ren, Alex Aliper, Jian Chen, Heng Zhao, Sujata Rao, Christoph Kuppe, Ivan V. Ozerov, Man Zhang, Klaus Witte, Chris Kruse, Vladimir Aladinskiy, Yan Ivanenkov, Daniil Polykovskiy, Yanyun Fu, Eugene Babin, Junwen Qiao, Xing Liang, Zhenzhen Mou, Hui Wang, Frank W. Pun, Pedro Torres Ayuso, Alexander Veviorskiy, Dandan Song, Sang Liu, ... Alex Zhavoronkov + Show authors

Idiopathic pulmonary fibrosis (IPF) is an aggressive interstitial lung disease with a high mortality rate. Putative drug targets in IPF have failed to translate into effective therapies at the clinical level. We identify TRAF2- and NCK-interacting kinase (TNIK) as an anti-fibrotic target using a predictive artificial intelligence (AI) approach. Using AI-driven methodology, we generated INS018_055, a small-molecule TNIK inhibitor, which exhibits desirable drug-like properties and anti-fibrotic activity across different organs in vivo through oral, inhaled or topical administration. INS018_055 possesses anti-inflammatory effects in addition to its anti-fibrotic profile, validated in multiple in vivo studies. Its safety and tolerability as well as pharmacokinetics were validated in a randomized, double-blinded, placebo-controlled phase I clinical trial (NCT05154240) involving 78 healthy participants. A separate phase I trial in China, CTR20221542, also demonstrated comparable safety and pharmacokinetic profiles. This work was completed in roughly 18 months from target discovery to preclinical candidate nomination and demonstrates the capabilities of our generative AI-driven drug-discovery pipeline.

Discovery of 3-hydroxymethyl-azetidine derivatives as potent polymerase theta inhibitors

Yazhou Wang [a], Chao Wang [a], Jinxin Liu [a], Deheng Sun [a], Fanye Meng [a], Man Zhang [a], Alex Aliper [b], Feng Ren [a], Alex Zhavoronkov [a b], Xiao Ding [a]

Inhibition of the low fidelity DNA polymerase Theta (Polθ) is emerging as an attractive, synthetic-lethal antitumor strategy in BRCA-deficient tumors. Here we report the AI-enabled development of 3-hydroxymethyl-azetidine derivatives as a novel class of Polθ inhibitors featuring central scaffolding rings. Structure-based drug design first identified **A7** as a lead compound, which was further optimized to the more potent derivative **B3** and the metabolically stable deuterated compound **C1. C1** exhibited significant antiproliferative properties in DNA repair-compromised cells and demonstrated favorable pharmacokinetics, showcasing that 3-hydroxymethyl-azetidine is an effective bio-isostere of pyrrolidin-3-ol and emphasizing the potential of AI in medicinal chemistry for precise molecular modifications.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Pan-cancer proteogenomics characterization of tumor immunity

Francesca Petralia [36] • Weiping Ma [36] • Tomer M. Yaron [36] • ... Michele Ceccarelli [38] • Pei Wang [39] • Clinical Proteomic Tumor Analysis Consortium • Show all authors • Show footnotes

Despite the successes of immunotherapy in cancer treatment over recent decades, less than <10%–20% cancer cases have demonstrated durable responses from immune checkpoint blockade. To enhance the efficacy of immunotherapies, combination therapies suppressing multiple immune evasion mechanisms are increasingly contemplated. To better understand immune cell surveillance and diverse immune evasion responses in tumor tissues, we comprehensively characterized the immune landscape of more than 1,000 tumors across ten different cancers using CPTAC pan-cancer proteogenomic data. We identified seven distinct immune subtypes based on integrative learning of cell type compositions and pathway activities. We then thoroughly categorized unique genomic, epigenetic, transcriptomic, and proteomic changes associated with each subtype. Further leveraging the deep phosphoproteomic data, we studied kinase activities in different immune subtypes, which revealed potential subtype-specific therapeutic targets. Insights from this work will facilitate the development of future immunotherapy strategies and enhance precision targeting with existing agents.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Rapid evolution of genes with anti-cancer functions during the origins of large bodies and cancer resistance in elephants

Jacob Bowman, Vincent J. Lynch

Elephants have emerged as a model system to study the evolution of body size and cancer resistance because, despite their immense size, they have a very low prevalence of cancer. Previous studies have found that duplication of tumor suppressors at least partly contributes to the evolution of anti-cancer cellular phenotypes in elephants. Still, many other mechanisms must have contributed to their augmented cancer resistance. Here, we use a suite of codon-based maximum-likelihood methods and a dataset of 13,310 protein-coding gene alignments from 261 *Eutherian* mammals to identify positively selected and rapidly evolving elephant genes. We found 496 genes (3.73% of alignments tested) with statistically significant evidence for positive selection and 660 genes (4.96% of alignments tested) that likely evolved rapidly in elephants. Positively selected and rapidly evolving genes are statistically enriched in gene ontology terms and biological pathways related to regulated cell death mechanisms, DNA damage repair, cell cycle regulation, epidermal growth factor receptor (EGFR) signaling, and immune functions, particularly neutrophil granules and degranulation. All of these biological factors are plausibly related to the evolution of cancer resistance. Thus, these positively selected and rapidly evolving genes are promising candidates for genes contributing to elephant-specific traits, including the evolution of molecular and cellular characteristics that enhance cancer resistance.