Heales
HEALTHY LIFE EXTENSION SOCIETY

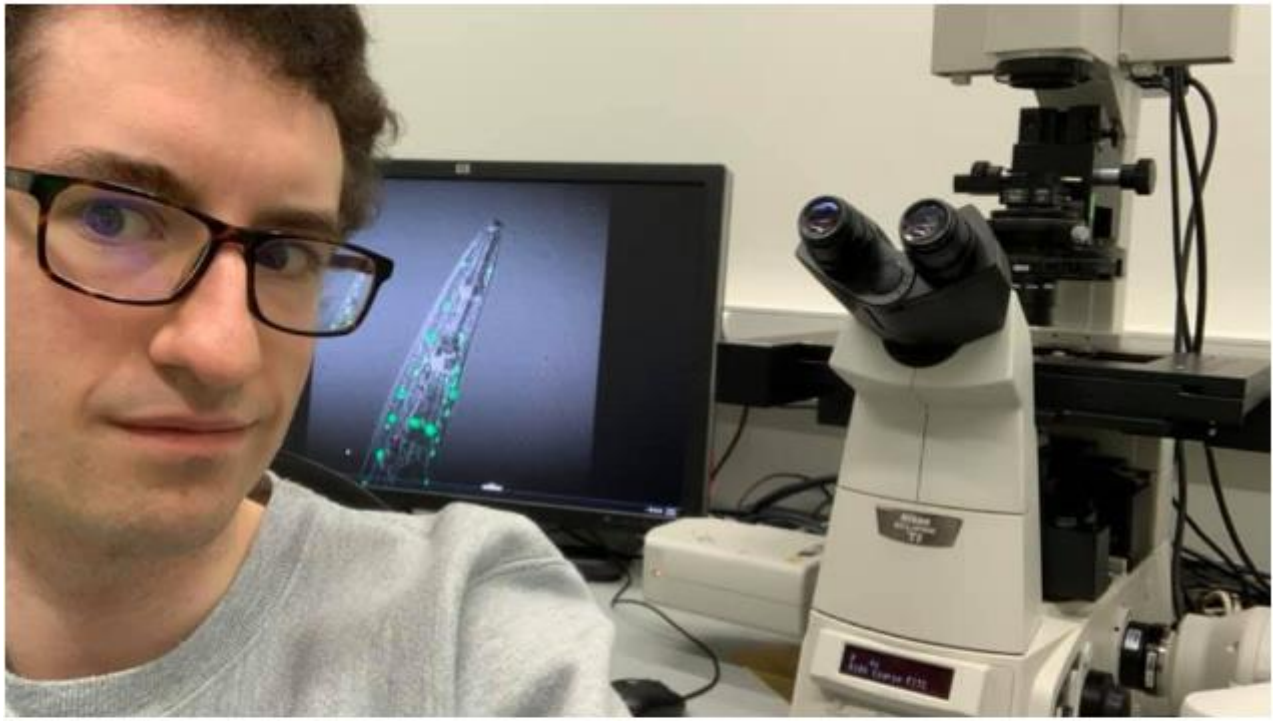
Scientific News
4th of January 2025
Sven Bulterijs

Business/Conferences/ General news

Heales
HEALTHY LIFE EXTENSION SOCIETY

Happy New Year everyone! I hope 2025 becomes an amazing year! Wishing you all the best of health and lots of happiness!

First edition of my newsletter!

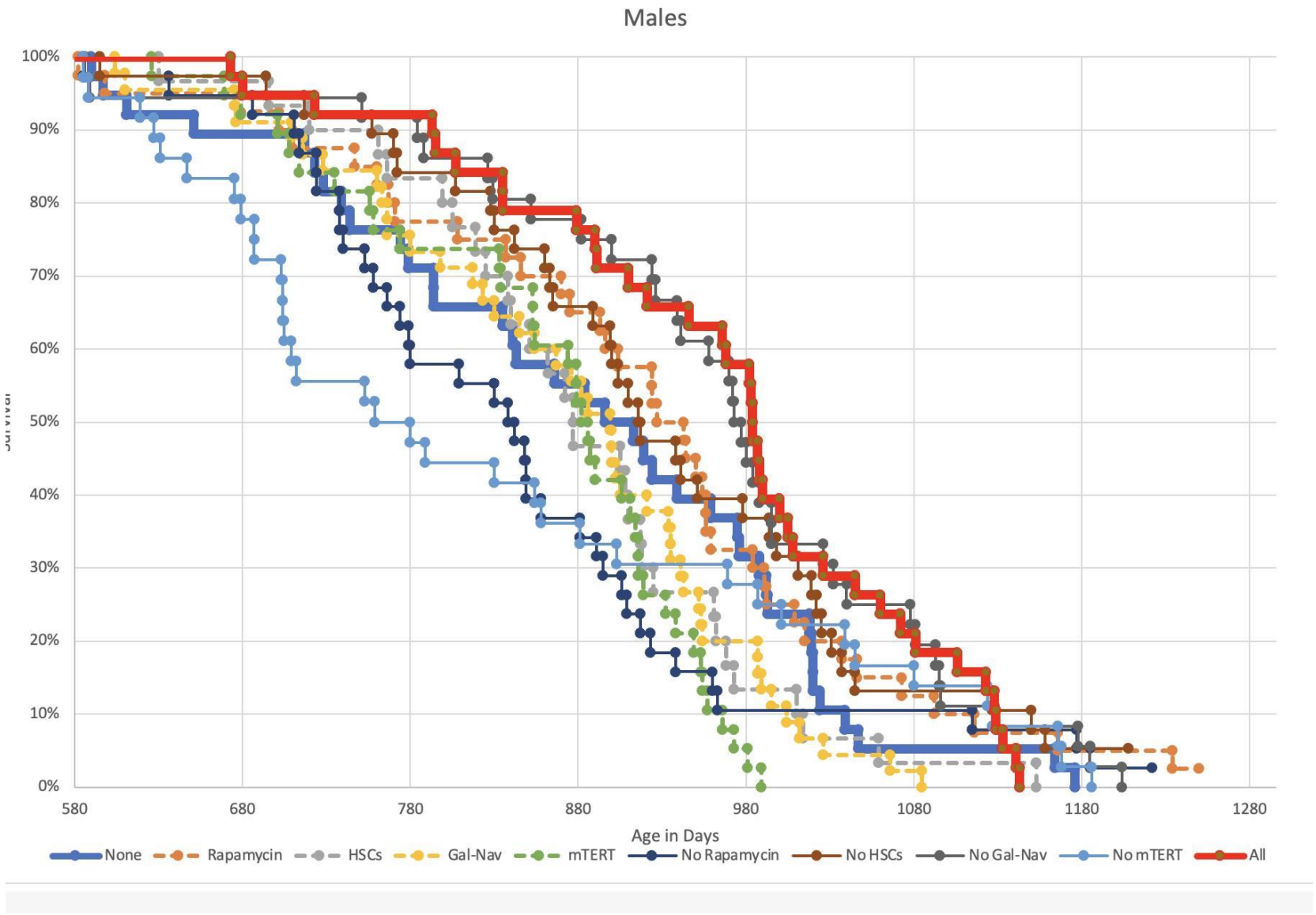


Longevity Trends: January 2025

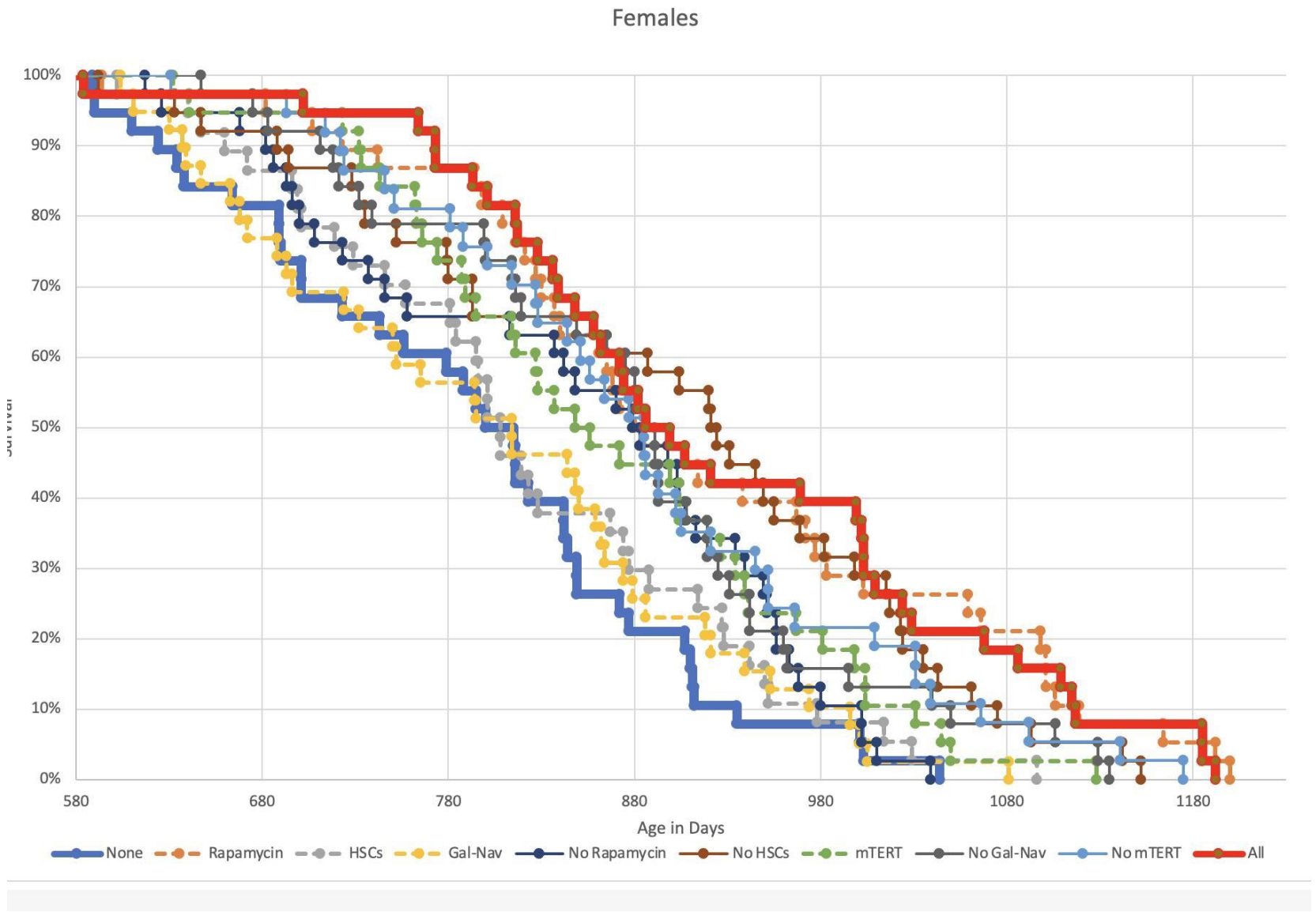
Sven Bulterijs
PhD student in Biology of Aging

January 2, 2025

Preliminary results from the RMR1 trial



Preliminary results from the RMR1 trial



Heales
HEALTHY LIFE EXTENSION SOCIETY

Tomiko Itooka, the world's oldest person, dies at 116

Plasma Proteins Reveal Organ-specific Aging and Healthspan

23 January 2025
17:00 – 18:00 CET

Upcoming conferences

Aging research articles

Heales
HEALTHY LIFE EXTENSION SOCIETY

Global Healthspan-Lifespan Gaps Among 183 World Health Organization Member States

Armin Garmany, BS[1]; Andre Terzic, MD, PhD[2]

Importance Health-adjusted life expectancy, a measure of healthy longevity, lags longevity gains, resulting in a healthspan-lifespan gap.

Objective To quantify the healthspan-lifespan gap across the globe, investigate for sex disparities, and analyze morbidity and mortality associations.

Design, Setting, and Participants This retrospective cross-sectional study used the World Health Organization (WHO) Global Health Observatory as the global data source and acquired national-level data covering all continents. The 183 WHO member states were investigated. Statistical analysis was conducted from January to May 2024.

Exposures Data represent 2 decades of longitudinal follow-up.

Main Outcomes and Measures Changes in life expectancy and health-adjusted life expectancy, as well as the healthspan-lifespan gap were quantified for all participating member states. Gap assessment was stratified by sex. Correlations of the gap with morbidity and mortality were examined.

Results The healthspan-lifespan gap has widened globally over the last 2 decades among 183 WHO member states, extending to 9.6 years. A sex difference was observed with women presenting a mean (SD) healthspan-lifespan gap of 2.4 (0.5) years wider than men ($P < .001$). Healthspan-lifespan gaps were positively associated with the burden of noncommunicable diseases and total morbidity, and negatively with mortality. The US presented the largest healthspan-lifespan gap, amounting to 12.4 years, underpinned by a rise in noncommunicable diseases.

Conclusions and Relevance This study identifies growing healthspan-lifespan gaps around the globe, threatening healthy longevity across worldwide populations. Women globally exhibited a larger healthspan-lifespan gap than men.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Dynamical modelling of the frailty index indicates that health reaches a tipping point near age 75

Glen Pridham[1,*], **Kenneth Rockwood**[2], **and Andrew Rutenberg**[1,†]

The frailty index (FI) serves as a useful quantitative summary of age-related health. We quantitatively modelled FI trajectories with age. We fit directly to longitudinal transitions in health attributes from normal to deficit and vice-versa. We used data from two large longitudinal studies: the Health and Retirement Study and the English Longitudinal Study of Ageing. The studies included 47592 individuals with 254357 total visits. Using damage (deficit emergence) and repair (deficit recovery) transitions we estimated changes to robustness and resilience, respectively. We find that both robustness and resilience decrease continuously with both increasing age and FI. Remarkably, these declines caused a tipping point in health near age 75, when damage and repair rates are equal. Beyond this tipping point, the ongoing loss of both robustness and resilience leads to a sharp increase in the FI and a commensurate increase in risk of mortality. This tipping point was observed in both sexes, noting that males showed higher initial robustness and resilience, and commensurately steeper decline, consistent with the sex-frailty paradox. We infer that robustness and resilience mitigate environmental stressors only up to an age of 75, beyond which health deficits will increasingly accumulate leading to death.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Computational and digital analyses in the INSPIRE mouse cohort to define sex-specific functional determinants of biological aging

YOHAN SANTIN, MATTIA CHIESA, AMÉLIE ALFONSO, YOSRA DOGHRI, RYEONSHI KANG, FRAHA HAIDAR, PILAR OREJA-FUENTES, OCCIANE FOUSSET, RANA ZAHREDDINE, [...], AND ANGELO PARINI +11 authors Authors Info & Affiliations

Biological age, which reflects the physiological state of an individual, offers a better predictive value than chronological age for age-related diseases and mortality. Nonetheless, determining accurate functional features of biological age remains challenging due to the multifactorial nature of aging. Here, we established a unique mouse cohort comprising 1576 male and female outbred SWISS mice subjected or not to high-fat, high-sucrose diet to investigate multiorgan/system biological aging throughout adulthood. Comprehensive functional and biological phenotyping at ages of 6, 12, 18, and 24 months revealed notable sex-specific disparities in longitudinal locomotion patterns and multifunctional aging parameters. Topological data analysis enabled the identification of functionally similar mouse clusters irrespective of chronological age. Moreover, our study pinpointed critical functional markers of biological aging such as muscle function, anxiety characteristics, urinary patterns, reticulocyte maturation, cardiac remodeling and function, and metabolic alterations, underscoring muscle function as an early indicator of biological age in male mice.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Histone mark age of human tissues and cell types

Lucas Paulo de Lima Camillo[1,2*], Muhammad Haider Asif[3], Steve Horvath[4], Erica Larschan[5,6], Ritambhara Singh[3,5*]

Aging is a complex and multifaceted process involving many epigenetic alterations. One key area of interest in aging research is the role of histone modifications, which can dynamically regulate gene expression. Here, we conducted a pan-tissue analysis of the dynamics of seven key histone modifications during human aging. Our histone-specific age prediction models showed surprisingly accurate performance, proving resilient to experimental and artificial noise. Simulation experiments for comparison with DNA methylation age predictors revealed competitive performance. Moreover, gene set enrichment analysis uncovered several critical developmental pathways for age prediction. Different from DNA methylation age predictors, genes known to be involved in aging biology are among the most important ones for the models. Last, we developed a pan-tissue pan-histone age predictor, suggesting that age-related epigenetic information is degenerated across the epigenome. This research highlights the power of histone marks as input for creating robust age predictors and opens avenues for understanding the role of epigenetic changes during aging.

Predicting lung aging using scRNA-Seq data

Qi Song, Alex Singh, John E. McDonough, Taylor S. Adams, Robin Vos, Ruben De Man, Greg Myers, Laurens J. Ceulemans, Bart M. Vanaudenaerde, Wim A. Wuyts, Xiting Yan, Jonas Schuppe, James S. Hagood, Naftali Kaminski, Ziv Bar-Joseph

Age prediction based on single cell RNA-Sequencing data (scRNA-Seq) can provide information for patients' susceptibility to various diseases and conditions. In addition, such analysis can be used to identify aging related genes and pathways. To enable age prediction based on scRNA-Seq data, we developed PolyEN, a new regression model which learns continuous representation for expression over time. These representations are then used by PolyEN to integrate genes to predict an age. Existing and new lung aging data we profiled demonstrated PolyEN's improved performance over existing methods for age prediction. Our results identified lung epithelial cells as the most significant predictors for non-smokers while lung endothelial cells led to the best chronological age prediction results for smokers.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metabolomic age (MileAge) predicts health and life span: A comparison of multiple machine learning algorithms

JULIAN MUTZ, RAQUEL INIESTA, AND CATHRYN M. LEWIS Authors Info & Affiliations

Biological aging clocks produce age estimates that can track with age-related health outcomes. This study aimed to benchmark machine learning algorithms, including regularized regression, kernel-based methods, and ensembles, for developing metabolomic aging clocks from nuclear magnetic resonance spectroscopy data. The UK Biobank data, including 168 plasma metabolites from up to $N = 225,212$ middle-aged and older adults (mean age, 56.97 years), were used to train and internally validate 17 algorithms. Metabolomic age (MileAge) delta, the difference between metabolite-predicted and chronological age, from a Cubist rule–based regression model showed the strongest associations with health and aging markers. Individuals with an older MileAge were frailer, had shorter telomeres, were more likely to suffer from chronic illness, rated their health worse, and had a higher all-cause mortality hazard (HR = 1.51; 95% CI, 1.43 to 1.59; $P < 0.001$). This metabolomic aging clock (MileAge) can be applied in research and may find use in health assessments, risk stratification, and proactive health tracking.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Subcellular NAD^+ pools are interconnected and buffered by mitochondrial NAD^+

The coenzyme NAD^+ is consumed by signalling enzymes, including poly-ADP-ribosyltransferases (PARPs) and sirtuins. Ageing is associated with a decrease in cellular NAD^+ levels, but how cells cope with persistently decreased NAD^+ concentrations is unclear. Here, we show that subcellular NAD^+ pools are interconnected, with mitochondria acting as a rheostat to maintain NAD^+ levels upon excessive consumption. To evoke chronic, compartment-specific overconsumption of NAD^+, we engineered cell lines stably expressing PARP activity in mitochondria, the cytosol, endoplasmic reticulum or peroxisomes, resulting in a decline of cellular NAD^+ concentrations by up to 50%. Isotope-tracer flux measurements and mathematical modelling show that the lowered NAD^+ concentration kinetically restricts NAD^+ consumption to maintain a balance with the NAD^+ biosynthesis rate, which remains unchanged. Chronic NAD^+ deficiency is well tolerated unless mitochondria are directly targeted. Mitochondria maintain NAD^+ by import through SLC25A51 and reversibly cleave NAD^+ to nicotinamide mononucleotide and ATP when NMNAT3 is present. Thus, these organelles can maintain an additional, virtual NAD^+ pool. Our results are consistent with a well-tolerated ageing-related NAD^+ decline as long as the vulnerable mitochondrial pool is not directly affected.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Downregulation of the NF-κB protein p65 is a shared phenotype among most anti-aging interventions

Many aspects of inflammation increase with aging in mice and humans. Transcriptomic analysis revealed that many murine anti-aging interventions produce lower levels of pro-inflammatory proteins. Here, we explore the hypothesis that different longevity interventions diminish NF-κB levels, potentially mediating some of the anti-inflammatory benefits of lifespan-extending interventions. We found that the NF-κB protein p65 is significantly downregulated in the liver of several kinds of slow-aging mice. These included both sexes of GHRKO and Snell Dwarf mutant mice, and in females only of PAPPA KO mice. P65 is also lower in both sexes of mice treated with rapamycin, canagliflozin, meclizine, or acarbose, and in mice undergoing caloric restriction. Two drugs that extend lifespan of male mice, i.e. 17α-estradiol and astaxanthin, however, did not produce lower levels of p65. We also measured other canonical NF-κB signaling regulators, including the activators IKKα and IKKβ and the inhibitor IκB-α. We found that those regulators do not consistently change in a direction that would lead to of NF-κB inhibition. In contrast, we found that NCoR1, an HDAC3 cofactor and a transcription co-repressor that regulates p65 activity, was also downregulated in many of these mouse models. Finally, we report downregulation of three p65 target proteins that regulate the metabolic and inflammatory states of the liver (HNF4α, IL-1β, and CRP) in multiple slow-aging mouse models. Together, these data suggest that NF-κB signaling, might be inhibited in liver of multiple varieties of slow aging mice. This establishes p65 as a potential target for novel longevity interventions.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Extreme longevity may be the rule not the exception in Balaenid whales

GREG A. BREED , ELS VERMEULEN , AND PETER CORKERON Authors Info & Affiliations

We fit ongoing 40+-year mark-recapture databases from the thriving southern right whale (SRW), *Eubalaena australis*, and highly endangered North Atlantic right whale (NARW), *Eubalaena glacialis*, to candidate survival models to estimate their life spans. Median life span for SRW was 73.4 years, with 10% of individuals surviving past 131.8 years. NARW life spans were likely anthropogenically shortened, with a median life span of just 22.3 years, and 10% of individuals living past 47.2 years. In the context of extreme longevity recently documented in other whale species, we suggest that all balaenid and perhaps most great whales have an unrecognized potential for great longevity that has been masked by the demographic disruptions of industrial whaling. This unrecognized longevity has profound implication for basic biology and conservation of whales.

Lifelong Glutathione Deficiency in Mice Increased Lifespan and Delayed Age-Related Motor Declines

J Thomas Mock, Paapa Mensah-Kane, Delaney L Davis, Jessica M Wong, Philip H Vann, Michael J Forster, Nathalie Sumien

Glutathione (GSH) is a crucial redox scavenger, essential for maintaining cellular redox balance. This study explores the long-term effects of chronic GSH deficiency on lifespan, motor function, cognitive performance, redox status and inflammation. $GCLM^{-/-}$ mice, with a 70-90% reduction in GSH levels, were compared to $GCLM^{+/+}$ controls across their lifespan (5, 10 and 20 months). We assessed lifespan, motor performance using balance and coordination tests, cognitive function through anxiety and memory tests, redox markers, and inflammation markers, particularly TNF-α and IL-6. Biochemical analyses of GSH levels in peripheral tissues and brain regions were conducted to evaluate redox state changes. $GCLM^{-/-}$ mice displayed extended lifespans and improved motor function at young and adult stages, with a delayed onset of motor decline with age. Cognitive function remains largely unaffected, although there are reductions in anxiety-related behaviors and minor deficits in fear-associated memory. Age-related increases in TNF-α, an inflammatory marker, are observed in both genotypes, with $GCLM^{-/-}$ mice showing a less pronounced increase, particularly in females. There were significant GSH reductions in peripheral tissues, with sporadic changes in brain regions. This stress likely triggers compensatory antioxidant responses, modulating inflammation and redox-sensitive pathways. The data suggests that lifelong GSH deficiency provides protective effects against inflammation and motor decline in younger animals but exacerbates these issues in older mice. The study offers insights into potential therapeutic strategies that leverage mild oxidative stress to promote healthy aging, emphasizing the importance of redox state and antioxidant defenses in the aging process.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Why are telomeres the length that they are? Insight from a phylogenetic comparative analysis

Derek M. Benson, Dylan J. Padilla Perez, Dale F. DeNardo

Telomeres are short repeating nucleotide sequences at the ends of chromosomes that shorten with every cellular replication. Despite the importance of keeping telomere length within a critical homeostatic range, adult telomere length can differ by two orders of magnitude across vertebrate species. Why telomere length varies so widely remains unknown, though popular hypotheses suggest that body size, lifespan, and endothermy are key variables that have coevolved with telomere length. To test the relationship among telomere length, telomerase activity (which extends telomeres), and these variables, we modeled the evolution of telomere length across 122 vertebrate species. We failed to find an influence of body mass, lifespan, or baseline metabolism on telomere length. However, we found a significant interactive effect between baseline metabolism and body mass. The presence of telomerase activity was positively correlated with telomere length across the 58 species where data for both existed. Taken together, our findings suggest that body mass may have differentially influenced the evolution of telomere length in endotherms and ectotherms and indicate that telomerase activity and telomere length may have coevolved.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The relationship between mitochondrial health, telomerase activity and longitudinal telomere attrition, considering the role of chronic stress

Mauricio Guillen-Parra [1 2 3], Jue Lin [4], Aric A Prather [3], Owen M Wolkowitz [3], Martin Picard [5 6 7 8], Elissa S Epel [9]

Telomere attrition is a hallmark of biological aging, contributing to cellular replicative senescence. However, few studies have examined the determinants of telomere attrition in vivo in humans. Mitochondrial Health Index (MHI), a composite marker integrating mitochondrial energy-transformation capacity and content, may be one important mediator of telomere attrition, as it could impact telomerase activity, a direct regulator of telomere maintenance. In this observational longitudinal study, we examined in peripheral blood mononuclear cells (PBMCs), whether MHI predicted changes in telomerase activity over a 9-month period, thus impacting telomere maintenance over this same period of time. We secondarily examined the role of chronic stress, by comparing these relationships in mothers of children with an autism spectrum disorder (caregivers) vs. mothers of a neurotypical child (controls). Here we show that both chronic stress exposure and lower MHI independently predicted decreases in telomerase activity over the subsequent 9 months. Finally, changes in telomere length were directly related with changes in telomerase activity, and indirectly with MHI and chronic stress, as revealed by a path analysis. These results highlight the potential role of chronic stress and MHI as drivers of telomere attrition in human PBMCs, through an impairment of both energy-transformation capacity and telomerase production.

IGF1 drives Wnt-induced joint damage and is a potential therapeutic target for osteoarthritis

Ana Escribano-Núñez, Frederique M. F. Cornelis, Astrid De Roover, An Sermon, Frédéric Cailotto, Rik J. Lories & Silvia Monteagudo

Osteoarthritis is the most common joint disease and a global leading cause of pain and disability. Current treatment is limited to symptom relief, yet there is no disease-modifying therapy. Its multifactorial etiology includes excessive activation of Wnt signaling, but how Wnt causes joint destruction remains poorly understood. Here, we identify that Wnt signaling promotes the transcription of insulin-like growth factor 1 (IGF1) in articular chondrocytes and that IGF1 is a major driver of Wnt-induced joint damage. Male mice with cartilage-specific *Igf1* deficiency are protected from Wnt-triggered joint disease. Mechanistically, Wnt-induced *IGF1* transcription depends on β-catenin and binding of Wnt transcription factor TCF4 to the *IGF1* gene promoter. In a clinically relevant mouse model of post-traumatic osteoarthritis, cartilage-specific deletion of *Igf1* protects against the disease in male mice. *IGF1* silencing in chondrocytes from patients with osteoarthritis restores a healthy molecular profile. Our findings reveal that reducing Wnt-induced IGF1 is a potential therapeutic strategy for osteoarthritis.

GATD3A-deficiency-induced mitochondrial dysfunction facilitates senescence of fibroblast-like synoviocytes and osteoarthritis progression

Kai Shen [# 1], Hao Zhou [# 1], Qiang Zuo [# 1], Yue Gu [2], Jiangqi Cheng [3], Kai Yan [1], Huiwen Zhang [4], Huanghe Song [1], Wenwei Liang [1], Jinchun Zhou [1], Jiuxiang Liu [1], Feng Liu [1], Chenjun Zhai [5], Weimin Fan [6]

Accumulating evidence indicates that cellular senescence is closely associated with osteoarthritis. However, there is limited research on the mechanisms underlying fibroblast-like synoviocyte senescence and its impact on osteoarthritis progression. Here, we elucidate a positive correlation between fibroblast-like synoviocyte senescence and osteoarthritis progression and reveal that GATD3A deficiency induces fibroblast-like synoviocyte senescence. Mechanistically, GATD3A deficiency enhances the binding of Sirt3 to MDH2, leading to deacetylation and decreased activity of MDH2. Reduced MDH2 activity impairs tricarboxylic acid cycle flux, resulting in mitochondrial dysfunction and fibroblast-like synoviocyte senescence. Intra-articular injection of recombinant adeno-associated virus carrying GATD3A significantly alleviates the osteoarthritis phenotype in male mice. This study increases our current understanding of GATD3A function. In particular, we reveal a novel mechanism of fibroblast-like synoviocyte senescence, suggesting that targeting GATD3A is a potential therapeutic approach for osteoarthritis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Identifying novel aging-related diagnostic and prognostic models and aging-targeted drugs for sepsis patients

Sepsis is defined as a dysfunctional, life-threatening response to infection leading to multiorgan dysfunction and failure. During the past decade, studies have highlighted the relationship between sepsis and aging. However, the role of aging-related mechanisms in the progression and prognosis of sepsis remains unclear. In the present study, we divided sepsis patients into High- and Low-aging groups based on the gene set variation analysis (GSVA) scores of GOBP-AGING gene set. Sepsis patients in the high-aging group exhibited higher levels of infiltration of innate immune cells, lower levels of infiltration of adaptive immune cells, and a worse prognosis than those in the Low-aging group. Additionally, the MPO to MME ratio (MPO/MME) appears to be an effective biomarker for predicting the prognosis of sepsis patients. Moreover, ARG1/SEC63 and ARG1/CDKN1C appear to be effective and robust biomarkers for the early diagnosis of sepsis patients. Finally, we found that thalidomide (TAL) significantly ameliorated LPS induced inflammation and organ injury and attenuated LPS induced cellular senescence in lung and kidney. Overall, this study provides new insights into the heterogeneity of sepsis, reveals the vital role of aging-related markers in the prognosis and diagnosis of sepsis and demonstrates that TAL is a novel aging-targeted drug for sepsis patients by attenuating LPS induced cellular senescence.

Polyploid superficial uroepithelial bladder barrier cells express features of cellular senescence across the lifespan and are insensitive to senolytics

Lower urinary tract dysfunction (LUTD) increases with aging. Ensuing symptoms including incontinence greatly impact quality of life, isolation, depression, and nursing home admission. The aging bladder is hypothesized to be central to this decline, however, it remains difficult to pinpoint a singular strong driver of aging-related bladder dysfunction. Many molecular and cellular changes occur with aging, contributing to decreased resilience to internal and external stressors, affecting urinary control and exacerbating LUTD. In this study, we examined whether cellular senescence, a cell fate involved in the etiology of most aging diseases, contributes to LUTD. We found that umbrella cells (UCs), luminal barrier uroepithelial cells in the bladder, show senescence features over the mouse lifespan. These polyploid UCs exhibit high cyclin D1 staining, previously reported to mediate tetraploidy-induced senescence in vitro. These senescent UCs were not eliminated by the senolytic combination of Dasatinib and Quercetin. We also tested the effect of a high-fat diet (HFD) and senescent cell transplantation on bladder function and showed that both models induce cystometric changes similar to natural aging in mice, with no effect of senolytics on HFD-induced changes. These findings illustrate the heterogeneity of cellular senescence in varied tissues, while also providing potential insights into the origin of urothelial cancer. We conclude that senescence of bladder uroepithelial cells plays a role in normal physiology, namely in their role as barrier cells, helping promote uroepithelial integrity and impermeability and maintaining the urine-blood barrier.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Systemic Senolysis in Naturally Aged Mice Using a FAST-PLV Gene Therapy Approach

Approaches to eliminate senescent cells *in vivo* using transgenic mouse models have demonstrated significant improvements in lifespan, reduction in cancer incidence, and amelioration of age-related degeneration. These approaches require, however, that the organism be genetically engineered from the embryo and/or repeatedly dosed for the organism's lifespan, making them challenging to implement in humans using current technologies. To overcome these limitations, we developed a clinically viable senolytic gene therapy consisting of a suicide gene, inducible caspase 9 (iCasp9), under control of the early senescence and tumor suppressive p53 promoter or the late senescence $p16^{Ink4a}$ promoter. *In vitro*, this gene therapy selectively activates in senescent cells and induces caspase-9-dependent apoptosis. When formulated in the FAST-PLV platform and administered systemically to aged mice, the burden of senescent cells was significantly reduced in various tissues, leading to a 123% increase in post-treatment survival for animals given a combination of p16 and p53 targeted senolytic gene therapies. Treated mice showed significantly reduced frailty, increased physical function, and improved heart health. Gross necropsy indicated a 3-fold reduced tumor incidence. In summary, we demonstrate a novel and redosable senolytic genetic medicine approach that improves healthspan by targeting senescent cells based on their transcriptional activity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Mitochondrial metabolism and epigenetic crosstalk drive the SASP

Joao Passos [1], Helene Martini [2], Jodie Birch [3], Francisco Marques [4], Stella Victorelli [5], Anthony Lagnado [6], Nicholas Pirius [7], Ana Franco [8], Gung Lee [9], Yeaeun Han [10], Jennifer Rowsey [11], Alexandre Gaspar-Maia [12], Aaron Havas [13], Rabi Murad [14], Xue Lei [15], Rebecca Porritt [16], Oliver Maddocks [17], Diana Jurk [18], Sundeep Khosla [19], Peter Adams [20]

Senescent cells drive tissue dysfunction through the senescence-associated secretory phenotype (SASP). We uncovered a central role for mitochondria in the epigenetic regulation of the SASP, where mitochondrial-derived metabolites, specifically citrate and acetyl-CoA, fuel histone acetylation at SASP gene loci, promoting their expression. We identified the mitochondrial citrate carrier (SLC25A1) and ATP-citrate lyase (ACLY) as critical for this process. Inhibiting these pathways selectively suppresses SASP without affecting cell cycle arrest, highlighting their potential as therapeutic targets for age-related inflammation. Notably, SLC25A1 inhibition reduces systemic inflammation and extends healthspan in aged mice, establishing mitochondrial metabolism as pivotal to the epigenetic control of aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Metformin inhibits nuclear egress of chromatin fragments in senescence and aging

Takuya Kumazawa, Yanxin Xu, Tara C. O'Brien, Ji-Won Lee, Yu Wang, Murat Cetinbas, Ruslan I. Sadreyev, Nabeel Bardeesy, Chia-Wei Cheng, Bin He, Zhixun Dou

Chronic inflammation is a hallmark of aging and contributes to many age-associated diseases. Metabolic intervention is a strategy to modulate inflammation. However, the connection between inflammation and metabolism during aging remains poorly understood. A mechanism driving chronic inflammation involves cytoplasmic chromatin fragments (CCFs), which appear in senescent cells and aged tissues, activating the cGAS-STING pathway. The size of the CCFs exceeds the capacity of the nuclear pore complex, raising the question of how chromatin fragments enter the cytoplasm. Here, we report that chromatin fragments exit the nucleus via nuclear egress, a membrane trafficking process at the nuclear envelope that shuttles large complexes from the nucleus to the cytoplasm. Inactivating critical nuclear egress ESCRT-III or Torsin proteins results in accumulation of chromatin fragments at the nuclear membrane, thereby impairing the activation of cGAS-STING and senescence-associated inflammation. Notably, nuclear egress of CCFs is inhibited by glucose limitation or metformin treatment. This is due to AMPK phosphorylation and autophagic degradation of the ESCRT-III component, ALIX. Metformin treatment in naturally aged mice downregulates ALIX protein and blocks cGAS activation and chronic inflammation in the small intestine. Together, our study defines a central mechanism linking nutrient sensing and chronic inflammation, two distinct hallmarks of aging, and suggests a new approach to suppress age-associated inflammation by targeting the nuclear egress of chromatin fragments.

Broad repression of DNA repair genes in senescent cells identified by integration of transcriptomic data

Yann Frey, Majd Haj, Yael Ziv, Ran Elkon, Yosef Shiloh

Cellular senescence plays a significant role in tissue aging. Senescent cells, which resist apoptosis while remaining metabolically active, generate endogenous DNA-damaging agents, primarily reactive oxygen species. Efficient DNA repair is therefore crucial in these cells, especially when they undergo senescence escape, resuming DNA replication and cellular proliferation. To investigate whether senescent cell transcriptomes reflect adequate DNA repair capacity, we conducted a comprehensive meta-analysis of 60 transcriptomic datasets comparing senescent to proliferating cells. Our analysis revealed a striking downregulation of genes encoding essential components across DNA repair pathways in senescent cells. This includes pathways active in different cell cycle phases such as nucleotide excision repair, base excision repair, nonhomologous end joining and homologous recombination repair of double-strand breaks, mismatch repair and interstrand crosslink repair. The downregulation observed suggests a significant accumulation of DNA lesions. Experimental monitoring of DNA repair readouts in cells that underwent radiation-induced senescence supported this conclusion. This phenomenon was consistent across various senescence triggers and was also observed in primary cell lines from aging individuals. These findings highlight the potential of senescent cells as 'ticking bombs' in aging-related diseases and tumors recurring following therapy-induced senescence.

Hydra has mammal-like mutation rates facilitating fast adaptation despite its nonaging phenotype

Arne Sahm [1 2 3], Konstantin Riege [2], Marco Groth [4], Martin Bens [4], Johann Kraus [5], Martin Fischer [2], Hans Kestler [5], Christoph Englert [6 7], Ralf Schaible [2], Matthias Platzer [2], Steve Hoffmann [2]

Growing evidence suggests that somatic mutations may be a major cause of the aging process. However, it remains to be tested whether the predictions of the theory also apply to species with longer life spans than humans. *Hydra* is a genus of freshwater polyps with remarkable regeneration abilities and a potentially unlimited life span under laboratory conditions. By genome sequencing of single cells and whole animals, we found that the mutation rates in *Hydra*'s stem cells are even slightly higher than in humans or mice. A potential explanation for this deviation from the prediction of the theory may lie in the adaptability offered by a higher mutation rate, as we were able to show that the genome of the widely studied *Hydra magnipapillata* strain 105 has undergone a process of strong positive selection since the strain's cultivation 50 years ago. This most likely represents a rapid adaptation to the drastically altered environmental conditions associated with the transition from the wild to laboratory conditions. Processes under positive selection in captive animals include pathways associated with *Hydra*'s simple nervous system, its nucleic acid metabolic process, cell migration, and hydrolase activity.

Lithocholic acid phenocopies anti-ageing effects of calorie restriction

Calorie restriction (CR) is a dietary intervention used to promote health and longevity[1,2]. CR causes various metabolic changes in both the production and the circulation of metabolites[1]; however, it remains unclear which altered metabolites account for the physiological benefits of CR. Here we use metabolomics to analyse metabolites that exhibit changes in abundance during CR and perform subsequent functional validation. We show that lithocholic acid (LCA) is one of the metabolites that alone can recapitulate the effects of CR in mice. These effects include activation of AMP-activated protein kinase (AMPK), enhancement of muscle regeneration and rejuvenation of grip strength and running capacity. LCA also activates AMPK and induces life-extending and health-extending effects in Caenorhabditis elegans and Drosophila melanogaster. As C. elegans and D. melanogaster are not able to synthesize LCA, these results indicate that these animals are able to transmit the signalling effects of LCA once administered. Knockout of AMPK abrogates LCA-induced phenotypes in all the three animal models. Together, we identify that administration of the CR-mediated upregulated metabolite LCA alone can confer anti-ageing benefits to metazoans in an AMPK-dependent manner.

Lithocholic acid binds TULP3 to activate sirtuins and AMPK to slow down ageing

Lithocholic acid (LCA) is accumulated in mammals during calorie restriction and it can activate AMP-activated protein kinase (AMPK) to slow down ageing[1]. However, the molecular details of how LCA activates AMPK and induces these biological effects are unclear. Here we show that LCA enhances the activity of sirtuins to deacetylate and subsequently inhibit vacuolar H^+-ATPase (v-ATPase), which leads to AMPK activation through the lysosomal glucose-sensing pathway. Proteomics analyses of proteins that co-immunoprecipitated with sirtuin 1 (SIRT1) identified TUB-like protein 3 (TULP3), a sirtuin-interacting protein[2], as a LCA receptor. In detail, LCA-bound TULP3 allosterically activates sirtuins, which then deacetylate the V1E1 subunit of v-ATPase on residues K52, K99 and K191. Muscle-specific expression of a V1E1 mutant (3KR), which mimics the deacetylated state, strongly activates AMPK and rejuvenates muscles in aged mice. In nematodes and flies, LCA depends on the TULP3 homologues tub-1 and ktub, respectively, to activate AMPK and extend lifespan and healthspan. Our study demonstrates that activation of the TULP3-sirtuin-v-ATPase-AMPK pathway by LCA reproduces the benefits of calorie restriction.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Amyloid beta precursor protein contributes to brain aging and learning decline in short-lived turquoise killifish (*Nothobranchius furzeri*)

Amyloid beta (Aβ) accumulation is associated with inflammation, neurodegeneration, and cognitive decline in the context of neurodegenerative diseases. However, the effect of Aβ during normal – i.e., non-pathological – brain aging remains poorly understood. In this study, we investigated the natural impact of Aβ precursor protein (*app*) on the aging brain using a short-lived vertebrate model, the turquoise killifish (*Nothobranchius furzeri*). We identified amyloid precursor protein derivatives in the killifish brain across different age groups and found that pyroglutamated amyloid beta —a neurotoxic Aβ variant— accumulates intra-neuronally in an age-dependent manner, co-localizing with the apoptosis marker TUNEL. The presence of intraneuronal pE11 was recapitulated in old (non-pathological) human brains, indicating that this phenotype is shared among vertebrates. To determine whether Aβ contributes to spontaneous brain aging, we used CRISPR/Cas9 to generate an "amyloid precursor protein a" (*appa*) knock-out killifish strain. Notably, *appa* -/- mutants exhibited reduced cell death and inflammation, an overall younger proteome, as well as improved learning capacity in old age. Taken together, we found that Aβ precursor protein broadly affects vertebrate brain aging, making it a promising target for anti-aging interventions.

Association of cardiorespiratory fitness with dementia risk across different levels of genetic predisposition: a large community-based longitudinal study

Shuqi Wang [1, 2], Liyao Xu [1, 2], Wenzhe Yang [1, 2], Jiao Wang [3], Abigail Dove [4], Xiuying Qi [1, 2], Weili Xu [1, 2, 4]

Objective We aimed to investigate the association of cardiorespiratory fitness (CRF) with cognitive function and dementia risk, taking genetic predisposition for dementia into account.

Methods Within the UK Biobank, 61 214 dementia-free participants aged 39–70 years were followed for up to 12 years. CRF score was estimated using a 6 min submaximal exercise test on a stationary bike and divided into tertiles (ie, low, moderate, and high; standardised by age and sex). Global cognitive function was evaluated at baseline. Dementia was identified based on medical history and medical records. Genetic predisposition for dementia was estimated using the polygenic risk score for Alzheimer's disease (PRS_{AD}), tertiled as low, moderate, or high. Data were analysed using linear regression, Poisson regression, and Laplace regression.

Results Compared with low CRF, high CRF was related to better global cognitive function (β=0.05, 95% CI 0.04 to 0.07). Over the follow-up period, 553 individuals developed dementia. Compared with low CRF, the incidence rate ratio (IRR) of all dementia was 0.60 (95% CI 0.48 to 0.76) for high CRF, and the onset of all dementia was delayed by 1.48 (95% CI 0.58 to 2.39) years among people with high versus low CRF. Among people with a moderate/high polygenic risk score, high CRF attenuated all dementia risk by 35% (IRR 0.65, 95% CI 0.52 to 0.83).

Conclusion High CRF is associated with better cognitive performance at baseline, and lower dementia risk long-term. High CRF could mitigate the impact of genetic predisposition on the development of dementia by 35%.

The association between $PM_{2.5}$ and frailty: evidence from 122 cities in China and 7 countries in Europe

Yanchao Wen [1 2], Guiming Zhu [1 2], Kexin Cao [1 2], Jie Liang [1 2], Xiangfeng Lu [3], Tong Wang [4 5]

Background: The accelerated aging process worldwide is placing a heavy burden on countries. $PM_{2.5}$ particulate matter exposure is a significant factor affecting human health and is crucial in the aging process.

Methods: We utilized data from China Health and Retirement Longitudinal Study (CHARLS) and the Survey of Health, Aging, and Retirement in Europe (SHARE) to study the relationship between $PM_{2.5}$ exposure and the frailty index. Acquire $PM_{2.5}$ exposure data for China and Europe, match them according to geographic location within the database. Our study used frailty index to evaluate frailty, which comprises 29 items. We examined the association between $PM_{2.5}$ and frailty index using fixed-effects regression models and Mendelian randomization (MR) analysis.

Results: We first examined the association between $PM_{2.5}$ and frailty index using fixed-effects regression models, revealing a notable positive link across populations in China (coefficient = 0.0003, P = 0.0380) and Europe (Coefficient = 0.0019, P < 0.0001). This suggests that $PM_{2.5}$ exposure is a significant risk factor for frailty, leading to accelerated frailty. Moreover, our MR analysis uncovered a possible causal association (OR = 1.2933, 95%CI: 1.2045-1.3820, P < 0.0001) between $PM_{2.5}$ exposure and the frailty index.

Conclusions: Our findings indicate that long-term exposure to $PM_{2.5}$ in the environment is a risk factor for physical frailty and may have a potential causal relationship. Given the rapid global aging trend, public health measures are needed to reduce $PM_{2.5}$ concentrations and prevent frailty.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Poor sleep quality is associated with probable sarcopenia in community-dwelling older adults: Results from the longevity check-up (lookup) 8

Background: Poor sleep quality may contribute to sarcopenia, but evidence remains sparse. This retrospective cross-sectional study investigated the association between subjective sleep quality and probable sarcopenia in a cohort of community-dwelling older adults enrolled in the Longevity Check-Up 8+ study.

Methods: Participants were asked about their sleep quality over the past month, with four possible options ("very good", "quite good", "quite bad", very bad"). For the analysis, participants were grouped into good or bad sleep quality categories. Probable sarcopenia was operationalized according to handgrip strength values < 27 kg for men and < 16 kg for women. Logistic regression models were used to explore the relationship between sleep quality and probable sarcopenia.

Results: 1971 participants were included in the analysis (mean age 73.4 ± 6.2 years, 50.0 % women). Bad sleep quality was reported by 28.3 % of participants and was more prevalent among women, physically inactive individuals, and those with dyslipidemia. Probable sarcopenia was more prevalent in participants with bad sleep quality (23.8 % vs. 18.7 %, p = 0.012). Logistic regression revealed that bad sleep quality was significantly associated with increased odds of probable sarcopenia in both unadjusted (odds ratio [OR] 1.36, 95 % confidence interval [CI] 1.07-1.72, p = 0.010) and fully adjusted models (OR 1.40, 95 % CI 1.08-1.81, p = 0.011).

Conclusions: Poor sleep quality is associated with increased likelihood of probable sarcopenia in older adults. This finding highlights the importance of addressing sleep quality in interventions aimed at preventing sarcopenia and promoting healthy aging.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

Similarities and differences in the gene expression signatures of physiological age versus future lifespan

Across all taxa of life, individuals within a species exhibit variable lifespans. Differences in genotype or environment are not sufficient to explain this variance, as even isogenic *Caenorhabditis elegans* nematodes reared under uniform conditions show significant variability in lifespan. To investigate this phenomenon, we used lifespan-predictive biomarkers to isolate, at mid-adulthood, prospectively long- and short-lived individuals from an otherwise identical population. We selected two biomarkers which correlated positively with lifespan, *lin-4*p::GFP and *mir-243*p::GFP, and two which correlated negatively, *mir-240/786*p::GFP and autofluorescence. The gene-expression signature of long versus short future lifespan was strikingly similar across all four biomarkers tested. Since these biomarkers are expressed in different tissues, these results suggest a shared connection to a global health state correlated with future lifespan. To further investigate this underlying state, we compared the transcriptional signature of long versus short future lifespan to that of chronologically young versus old individuals. By comparison to a high-resolution time series of the average aging transcriptome, we determined that subpopulations predicted to be long- or short-lived by biomarker expression had significantly different transcriptional ages despite their shared chronological age. We found that this difference in apparent transcriptional age accounted for the majority of differentially expressed genes associated with future lifespan. Interestingly, we also identified several genes whose expression consistently separated samples by biomarker expression independent of apparent transcriptional age. These results suggest that the commonalities in the long-lived versus short-lived state reported across different biomarkers of aging extends beyond simply transcriptionally young versus transcriptionally old.

HSF-1 promotes longevity through ubiquilin-1-dependent mitochondrial network remodelling

Annmary Paul Erinjeri, Xunyan Wang, Rhianna Williams, Riccardo Zenezini Chiozzi, Konstantinos Thalassinos & Johnathan Labbadia

Increased activity of the heat shock factor, HSF-1, suppresses proteotoxicity and enhances longevity. However, the precise mechanisms by which HSF-1 promotes lifespan are unclear. Using an RNAi screen, we identify ubiquilin-1 *(ubql-1)* as an essential mediator of lifespan extension in worms overexpressing *hsf-1*. We find that *hsf-1* overexpression leads to transcriptional downregulation of all components of the CDC-48-UFD-1-NPL-4 complex, which is central to both endoplasmic reticulum and mitochondria associated protein degradation, and that this is complemented by UBQL-1-dependent turnover of NPL-4.1. As a consequence, mitochondrial network dynamics are altered, leading to increased lifespan. Together, our data establish that HSF-1 mediates lifespan extension through mitochondrial network adaptations that occur in response to down-tuning of components associated with organellar protein degradation pathways.

Characterization of Effects of mTOR Inhibitors on Aging in *Caenorhabditis elegans*

Aihan Zhang, PhD, Gadea Meecham-Garcia, MSci, Chiminh Nguyen Hong, MSci, Peiyun Xie, BSc, Carina C Kern, PhD, Bruce Zhang, BSc, Hannah Chapman, MSc, David Gems, PhD

Pharmacological inhibition of the mechanistic target of rapamycin (mTOR) signaling pathway with rapamycin can extend lifespan in several organisms. Although this includes the nematode *Caenorhabditis elegans*, effects in this species are relatively weak and sometimes difficult to reproduce. Here we test effects of drug dosage and timing of delivery to establish the upper limits of its capacity to extend life, and investigate drug effects on age-related pathology and causes of mortality. Liposome-mediated rapamycin treatment throughout adulthood showed a dose-dependent effect, causing a maximal 21.9% increase in mean lifespan, but shortening of lifespan at the highest dose, suggesting drug toxicity. Rapamycin treatment of larvae delayed development, weakly reduced fertility and modestly extended lifespan. By contrast, treatment initiated later in life robustly increased lifespan, even from Day 16 (or ~70 years in human terms). The rapalog temsirolimus extended lifespan similarly to rapamycin, but effects of everolimus were weaker. As in mouse, rapamycin had mixed effects on age-related pathologies, inhibiting one (uterine tumor growth) but not several others, suggesting a segmental antigeroid effect. These findings should usefully inform future experimental studies with rapamycin and rapalogs in *C. elegans*.

Dietary state and impact of DMSO on Caenorhabditis elegans aging: Insights from healthspan analysis

Yutaro Fukushima [1], Asuka Kagami [2], Hirotaka Sonoda [3], Kotomi Shimokawa [3], Mary Ann Suico [4], Hirofumi Kai [4], Tsuyoshi Shuto [5]

Caenorhabditis elegans (C. elegans) is a robust model organism in cell biology, physiology, pharmacology, and toxicology. It is widely recognized for its short lifespan (about 30 days), rapid life cycle, and genetic similarities to mammals. Known for their utility in lifespan research, compounds identified in C. elegans studies have shown lifespan-extending effects in higher organisms, making them invaluable for aging research. Recent work has highlighted the importance of food source conditions, specifically whether C. elegans is fed live or dead Escherichia coli (E. coli) OP50, and solvents like dimethyl sulfoxide (DMSO) in evaluating compound efficacy and organismal health. In this study, we employed C. elegans health lifespan auto-monitoring system (C-HAS), an automated imaging technology capable of objectively analyzing lifespan and healthspan by tracking movement patterns in real-time. Our results reveal that C. elegans fed dead bacteria, specifically heat-killed (HK) and freeze-dried (Fd) E. coli, display extended lifespan and healthspan compared to those fed live bacteria, reducing the proportion of short-lived, unhealthy nematodes. Moreover, 0.1 % DMSO treatment, a concentration previously reported as not affecting nematode longevity, notably shortens both lifespan and healthspan in C. elegans under dead bacterial conditions, with similar negative effects observed across different dead bacteria types. These findings highlight the importance of considering bacterial food state and DMSO presence when conducting lifespan and healthspan studies in C. elegans. This work provides foundational insights into how specific experimental conditions impact the health quality of C. elegans, advancing our understanding of environmental influences on organismal aging.

Nuclear lipid droplets: a novel regulator of nuclear homeostasis and ageing

Konstantinos Palikaras [1], Nektarios Tavernarakis [2 3]

Aging is a fundamental driver of numerous life-threatening diseases, significantly compromising cellular structures and functions, including the integrity of the nucleus. A consistent feature of aging across diverse species is the progressive accumulation of lipid droplets (nLDs) within the nuclear compartment, which disrupts nuclear architecture and functionality. Notably, aging is accompanied by a marked increase in nLD accumulation at the nuclear envelope. Interventions known to extend lifespan, such as caloric restriction and reduced insulin signaling, significantly reduce both the rate of accumulation and the size of nLDs. The triglyceride lipase ATGL-1, which localizes to the nuclear envelope, plays a critical role in limiting nLD buildup and maintaining nuclear lipid balance, especially in long-lived mutant worms. These findings establish excessive nuclear lipid deposition as a key hallmark of aging, with profound implications for nuclear processes such as chromatin organization, DNA repair, and gene regulation. In addition, ATGL-1 emerges as a promising therapeutic target for preserving nuclear health, extending organismal healthspan, and combating age-related disorders driven by lipid dysregulation.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A gut-microbiota-muscle axis that protects against age-related motor decline by regulating mitochondrial fission in *C. elegans*

Nathan Dennis, Mireya Vazquez-Prada, Feng Xue, Laura M. Freeman, Antonis Karamalegos, Brigita Kudzminkaite, Ian Brown, Marina Ezcurra

Across diverse taxa, the composition of the microbiota is associated with lifelong host health. A mechanistic understanding of how microbial communities influence host physiology could lead to microbiota-based interventions for lifelong health. Here, we have developed a new host-microbiota model system utilising the model organism *C. elegans* combined with a defined natural microbiota (DefNatMta) consisting of 11 bacteria isolated from wild *C. elegans*, to study host-microbiota interactions in a more natural setting. We show that DefNatMta colonises the *C. elegans* gut, forming a stable and distinct gut microbiota. Using DefNatMta, we find a gut microbiota-muscle axis by which the microbiota affects age-related motility and muscular strength and protects against age-related decline in motor function. The gut microbiota-muscle axis acts by altering metabolism and mitochondrial network dynamics in muscle, and requires dynamin-related protein 1 DRP-1, a regulator of mitochondrial fission to protect against age-related motility decline. Our study demonstrates a gut microbiota-muscle axis and microbiota-mitochondria communication affecting age-related muscle function.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

An expert consensus statement on biomarkers of ageing for use in intervention studies

Biomarkers of ageing serve as important outcome measures in longevity-promoting interventions. However, there is limited consensus on which specific biomarkers are most appropriate for human intervention studies. This work aimed to address this need by establishing an expert consensus on biomarkers of ageing for use in intervention studies via the Delphi method. A three-round Delphi study was conducted using an online platform. In Round 1, expert panel members provided suggestions for candidate biomarkers of ageing. In Rounds 2 and 3, they voted on 500 initial statements (yes/no) relating to 20 biomarkers of ageing. Panel members could abstain from voting on biomarkers outside their expertise. Consensus was reached when there was ≥70% agreement on a statement/biomarker. Of the 460 international panel members invited to participate, 116 completed Round 1, 87 completed Round 2, and 60 completed Round 3. Across the 3 rounds, 14 biomarkers met consensus that spanned physiological (e.g., insulin-like growth factor 1, growth-differentiating factor-15), inflammatory (e.g., high sensitivity c-reactive protein, interleukin-6), functional (e.g., muscle mass, muscle strength, hand grip strength, Timed-Up-and-Go, gait speed, standing balance test, frailty index, cognitive health, blood pressure), and epigenetic (e.g., DNA methylation/epigenetic clocks) domains. Expert consensus identified 14 potential biomarkers of ageing which may be used as outcome measures in intervention studies. Future ageing research should identify which combination of these biomarkers has the greatest utility.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Key considerations for combination therapy in Alzheimer's clinical trials: Perspectives from an expert advisory board convened by the Alzheimer's drug discovery foundation

There is growing consensus in the Alzheimer's community that combination therapy will be needed to maximize therapeutic benefits through the course of the disease. However, combination therapy raises complex questions and decisions for study sponsors, from preclinical research through clinical trial design to regulatory, statistical, and operational considerations. In January 2024, the Alzheimer's Drug Discovery Foundation convened an expert advisory board to discuss the key considerations in each of these areas. Experts agreed on the need to prioritize a combination therapy approach that encompasses a wide range of targets associated with aging and the underlying biology of Alzheimer's disease. Progress in combination therapy could be accelerated by leveraging preclinical research and Phase 1 and 2A trials to identify the most promising combinations for further development, exploring repurposed agents with available preclinical and clinical data, building collaborations across sectors to support operational challenges, and planning for the likely impact of anti-amyloid beta-protein monoclonal antibody therapies on future clinical trial designs.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Too old for healthy aging? Exploring age limits of longevity treatments

Prerana Shrikant Chaudhari & Maria A. Ermolaeva

It is well documented that aging elicits metabolic failures, while poor metabolism contributes to accelerated aging. Metabolism in general, and energy metabolism in particular are also effective entry points for interventions that extend lifespan and improve organ function during aging. In this review, we discuss common metabolic remedies for healthy aging from the angle of their potential age-specificity. We demonstrate that some well-known metabolic treatments are mostly effective in young and middle-aged organisms, while others maintain high efficacy independently of age. The mechanistic basis of presence or lack of the age limitations is laid out and discussed.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Perspectives on biomarkers of reproductive aging for fertility and beyond

Si Wang, Jie Ren, Ying Jing, Jing Qu & Guang-Hui Liu

Reproductive aging, spanning an age-related functional decline in the female and male reproductive systems, compromises fertility and leads to a range of health complications. In this Perspective, we first introduce a comprehensive framework for biomarkers applicable in clinical settings and discuss the existing repertoire of biomarkers used in practice. These encompass functional, imaging-based and biofluid-based biomarkers, all of which reflect the physiological characteristics of reproductive aging and help to determine the reproductive biological age. Next, we delve into the molecular alterations associated with aging in the reproductive system, highlighting the gap between these changes and their potential as biomarkers. Finally, to enhance the precision and practicality of assessing reproductive aging, we suggest adopting cutting-edge technologies for identifying new biomarkers and conducting thorough validations in population studies before clinical applications. These advancements will foster improved comprehension, prognosis and treatment of subfertility, thereby increasing chances of preserving reproductive health and resilience in populations of advanced age.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Exploring the effects of estrogen deficiency and aging on organismal homeostasis during menopause

Celine Camon, Michael Garratt & Stephanie M. Correa

Sex hormone signaling declines during aging, from early midlife through menopause, as a consequence of reduced circulating estrogens and decreased receptiveness to these hormones in target tissues. Estrogens preserve energy homeostasis and promote metabolic health via coordinated and simultaneous effects throughout the brain and body. Age-associated loss of estrogen production during menopause has been implicated in a higher risk for metabolic diseases and increased mortality. However, it remains unclear whether age-associated changes in homeostasis are dependent on reduced estrogen signaling during menopause. Although menopausal hormone therapies containing estrogens can alleviate symptoms, concerns about the risks involved have contributed to a broad decline in the use of these approaches. Non-hormonal therapies have emerged that target tissues or pathways with varying levels of selectivity, reducing risk. We summarize here the broad effects of estrogen loss on homeostasis during menopause, current and emerging therapies and opportunities for understanding homeostatic disruptions associated with menopause.

Global consensus on optimal exercise recommendations for enhancing healthy longevity in older adults (ICFSR)

This consensus provides the rationale for the integration of PA into health promotion, disease prevention, and management strategies for older adults. Guidelines are included for specific modalities and dosages of exercise with proven efficacy in randomized controlled trials. Descriptions of the beneficial physiological changes, attenuation of aging phenotypes, and role of exercise in chronic disease and disability management in older adults are provided. The use of exercise in cardiometabolic disease, cancer, musculoskeletal conditions, frailty, sarcopenia, and neuropsychological health is emphasized. Recommendations to bridge existing knowledge and implementation gaps and fully integrate PA into the mainstream of geriatric care are provided. Particular attention is paid to the need for personalized medicine as it applies to exercise and geroscience, given the inter-individual variability in adaptation to exercise demonstrated in older adult cohorts. Overall, this consensus provides a foundation for applying and extending the current knowledge base of exercise as medicine for an aging population to optimize health span and quality of life.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Quantification of Epigenetic Aging in Public Health

Cynthia D.J. Kusters[1], and Steve Horvath[2,3]
View Affiliations

Vol. 46 | **https://doi.org/10.1146/annurev-publhealth-060222-015657**

Review in Advance first posted online on December 16, 2024. (Changes may still occur before final publication.)

Info Sections Get Access Tools Share

Estimators of biological age hold promise for use in preventive medicine, for early detection of chronic conditions, and for monitoring the effectiveness of interventions aimed at improving population health. Among the promising biomarkers in this field are DNA methylation–based biomarkers, commonly referred to as epigenetic clocks. This review provides a survey of these clocks, with an emphasis on second-generation clocks that predict human morbidity and mortality. It explores the validity of epigenetic clocks when considering factors such as race, sex differences, lifestyle, and environmental influences. Furthermore, the review addresses the current challenges and limitations in this research area.

Heales
HEALTHY LIFE EXTENSION SOCIETY

NAD^+ Boosting Strategies

Jared Rice [1], Sofie Lautrup [2], Evandro F Fang [3]

Affiliations + expand

PMID: 39693020 DOI: 10.1007/978-3-031-66768-8_4

Abstract

Nicotinamide adenine dinucleotide (oxidized form, NAD^+) serves as a co-substrate and co-enzyme in cells to execute its key roles in cell signalling pathways and energetic metabolism, arbitrating cell survival and death. It was discovered in 1906 by Arthur Harden and William John Young in yeast extract which could accelerate alcohol fermentation. NAD acts as an electron acceptor and cofactor throughout the processes of glycolysis, Tricarboxylic Acid Cycle (TCA), β oxidation, and oxidative phosphorylation (OXPHOS). NAD has two forms: NAD^+ and NADH. NAD^+ is the oxidising coenzyme that is reduced when it picks up electrons. NAD^+ levels steadily decline with age, resulting in an increase in vulnerability to chronic illness and perturbed cellular metabolism. Boosting NAD^+ levels in various model organisms have resulted in improvements in healthspan and lifespan extension. These results have prompted a search for means by which NAD^+ levels in the body can be augmented by both internal and external means. The aim of this chapter is to provide an overview of NAD^+, appraise clinical evidence of its importance and success in potentially extending health- and lifespan, as well as to explore NAD^+ boosting strategies.

Telomere Dynamics in Zebrafish Aging and Disease

Miguel Godinho Ferreira

Fish telomere lengths vary significantly across the numerous species, implicating diverse life strategies and environmental adaptations. Zebrafish have telomere dynamics that are comparable to humans and are emerging as a key model in which to unravel the systemic effects of telomere shortening on aging and interorgan communication. Here, we discuss zebrafish telomere biology, focusing on the organismal impact of telomere attrition beyond cellular senescence, with particular emphasis on how telomeric shortening in specific tissues can unleash widespread organ dysfunction and disease. This highlights a novel aspect of tissue communication, whereby telomere shortening in one organ can propagate through biological networks, influencing the aging process systemically. These discoveries position zebrafish as a valuable model for studying the complex interactions between telomeres, aging, and tissue cross talk, providing important insights with direct relevance to human health and longevity.

Inter-organ communication is a critical machinery to regulate metabolism and aging

Kyohei Tokizane [1] · Shin-ichiro Imai [1,2,3]

Inter-organ communication (IOC) is a complex mechanism involved in maintaining metabolic homeostasis and healthy aging. Dysregulation of distinct forms of IOC is linked to metabolic derangements and age-related pathologies, implicating these processes as a potential target for therapeutic intervention to promote healthy aging. In this review, we delve into IOC mediated by hormonal signaling, circulating factors, organelle signaling, and neuronal networks and examine their roles in regulating metabolism and aging. Given the role of the hypothalamus as a high-order control center for aging and longevity, we particularly emphasize the importance of its communication with peripheral organs and pave the way for a better understanding of this critical machinery in metabolism and aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The dominance of old blood, and age-related increase in protein production and noise

Alexandra Sviercovich, Xiaoyue Mei, Grace Xie, Michael J. Conboy, Irina M. Conboy

This concise review provides new perspectives on systemic reduction of tissue aging by comparing different strategies, such as heterochronic parabiosis, injections of young blood plasma, neutral blood exchange (NBE) and therapeutic plasma exchange (TPE). Unlike previous literature that primarily discusses the need for young blood factors, we emphasize the potential of diluting age-elevated proteins as the way to re-calibrate systemic proteome to its younger state without donor blood. Furthermore, we introduce modulation of proteome noise, as an important part of understanding tissue aging and as a critical mechanism for tissue rejuvenation. We discuss studies on the dominance of aged systemic milieu in promoting progeric phenotypes in young cells, in vitro, and in multiple tissues of young animals, in vivo. We support our arguments with evidence showing a significant age-related increase in protein synthesis, in noise of newly synthesized proteomes, and in the rapid induction of these aging phenotypes in young muscle by exposure to aged tissue. We summarize the significance of these findings for future research on aging and longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mesenchymal Stem Cell-Derived Exosomes: A Promising Therapeutic Strategy for Age-Related Diseases

Bohua Wei [1], Mengting Wei [2], Haonan Huang [3], Ting Fan [4], Zhichang Zhang [4], Xiaoyu Song [5]

Affiliations + expand

PMID: 39704104 DOI: 10.1111/cpr.13795

Abstract

The global increase in the aging population has led to a concurrent rise in the incidence of age-related diseases, posing substantial challenges to healthcare systems and affecting the well-being of the elderly. Identifying and securing effective treatments has become an urgent priority. In this context, mesenchymal stem cell-derived exosomes (MSC-Exos) have emerged as a promising and innovative modality in the field of anti-aging medicine, offering a multifaceted therapeutic approach. MSC-Exos demonstrate significant potential due to their immunomodulatory and anti-inflammatory properties, their ability to inhibit oxidative stress, and their reparative effects on senescent tissues. These attributes make them valuable in combating a range of conditions associated with aging, such as cardiovascular diseases, neurodegeneration, skin aging, and osteoarthritis. The integration of exosomes with membrane-penetrating peptides introduces a novel strategy for the delivery of biomolecules, surmounting traditional cellular barriers and enhancing therapeutic efficacy. This review provides a comprehensive synthesis of the current understanding of MSC-Exos, underscoring their role as a novel and potent therapeutic strategy against the intricate challenges of age-related diseases.

Critical review of aging clocks and factors that may influence the pace of aging

Mildred Min [1 2 3], Caitlin Egli [1 2 4], Ajay S Dulai [1 2], Raja K Sivamani [1 2 3 5 6]

Background and objectives: Aging clocks are computational models designed to measure biological age and aging rate based on age-related markers including epigenetic, proteomic, and immunomic changes, gut and skin microbiota, among others. In this narrative review, we aim to discuss the currently available aging clocks, ranging from epigenetic aging clocks to visual skin aging clocks.

Methods: We performed a literature search on PubMed/MEDLINE databases with keywords including: "aging clock," "aging," "biological age," "chronological age," "epigenetic," "proteomic," "microbiome," "telomere," "metabolic," "inflammation," "glycomic," "lifestyle," "nutrition," "diet," "exercise," "psychosocial," and "technology."

Results: Notably, several CpG regions, plasma proteins, inflammatory and immune biomarkers, microbiome shifts, neuroimaging changes, and visual skin aging parameters demonstrated roles in aging and aging clock predictions. Further analysis on the most predictive CpGs and biomarkers is warranted. Limitations of aging clocks include technical noise which may be corrected with additional statistical techniques, and the diversity and applicability of samples utilized.

Conclusion: Aging clocks have significant therapeutic potential to better understand aging and the influence of chronic inflammation and diseases in an expanding older population.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Roles of osteoclasts in pathological conditions

Sohei Kitazawa [1], Ryuma Haraguchi [1], Riko Kitazawa [1 2]

Affiliations + expand

PMID: 39704061 DOI: 10.1111/pin.13500

Abstract

Bone is a unique organ crucial for locomotion, mineral metabolism, and hematopoiesis. It maintains homeostasis through a balance between bone formation by osteoblasts and bone resorption by osteoclasts, which is regulated by the basic multicellular unit (BMU). Abnormal bone metabolism arises from an imbalance in the BMU. Osteoclasts, derived from the monocyte-macrophage lineage, are regulated by the RANKL-RANK-OPG system, which is a key factor in osteoclast differentiation. RANKL activates osteoclasts through its receptor RANK, while OPG acts as a decoy receptor that inhibits RANKL. In trabecular bone, high turnover involves rapid bone formation and resorption, influenced by conditions such as malignancy and inflammatory cytokines that increase RANKL expression. Cortical bone remodeling, regulated by aged osteocytes expressing RANKL, is less understood, despite ongoing research into how Rett syndrome, characterized by MeCP2 abnormalities, affects RANKL expression. Balancing trabecular and cortical bone involves mechanisms that preserve cortical bone, despite overall bone mass reduction due to aging or oxidative stress. Research into genes like sFRP4, which modulates bone mass, highlights the complex regulation by BMUs. The roles of the RANKL-RANK-OPG system extend beyond bone, affecting processes such as aortic valve formation and temperature regulation, which highlight the interconnected nature of biological research.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Hormetic Effects of Phytochemicals with Anti-Ageing Properties

Calogero Caruso [1], Giulia Accardi [2], Anna Aiello [2], Giuseppina Candore [2]

Affiliations + expand

PMID: 39693026 DOI: 10.1007/978-3-031-66768-8_10

Abstract

In the fields of biology and medicine, hormesis is defined as the adaptive response of cells and organisms to moderate and usually intermittent stress. Examples include radiation, pharmaceutical agents, as well as dietary and lifestyle factors such as calorie restriction and physical exercise. However, in the present chapter, we will focus on the hormetic role of certain phytochemicals, compounds that naturally occur in plants, playing roles in plant colour, flavour, and disease resistance, with nutraceutical properties. Indeed, these compounds exhibit health-promoting, disease-preventing, or medicinal properties, mostly through a hormetic mechanism.

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Progress, Pitfalls, and Impact of AI-Driven Clinical Trials

Dominika Wilczok, Alex Zhavoronkov

First published: 25 December 2024 | https://doi.org/10.1002/cpt.3542

SECTIONS PDF TOOLS SHARE

Abstract

Since the deep learning revolution of the early 2010s, significant efforts and billions of dollars have been invested in applying artificial intelligence (AI) to drug discovery and development (AIDD). However, despite high expectations, few AI-discovered or AI-designed drugs have entered human clinical trials, and none have achieved clinical approval. In this perspective, we examine the challenges impeding progress and highlight opportunities to harness AI's potential in transforming drug discovery and development.

Early downmodulation of tumor glycolysis predicts response to fasting–mimicking diet in triple–negative breast cancer patients

In preclinical experiments, cyclic fasting-mimicking diets (FMDs) showed broad anticancer effects in combination with chemotherapy. Among different tumor types, triple-negative breast cancer (TNBC) is exquisitely sensitive to FMD. However, the antitumor activity and efficacy of cyclic FMD in TNBC patients remain unclear. Here, we show that a severely calorie-restricted, triweekly, 5-day FMD regimen results in excellent pathologic complete response (pCR) rates (primary endpoint) and long-term clinical outcomes (secondary endpoints) when combined with preoperative chemotherapy in 30 patients with early-stage TNBC enrolled in the phase 2 trial BREAKFAST. Bulk and single-cell RNA sequencing analysis revealed that highly glycolytic cancer cells, myeloid cells, and pericytes from tumors achieving pCR undergo a significant, early downmodulation of pathways related to glycolysis and pyruvate metabolism. Our findings pave the wave for conducting larger clinical trials to investigate the efficacy of cyclic FMD in early-stage TNBC patients and to validate early changes of intratumor glycolysis as a predictor of clinical benefit from nutrient restriction. This study was registered at Clinicaltrials.gov (NCT04248998).

The absence of telomerase leads to immune response and tumor regression in zebrafish melanoma

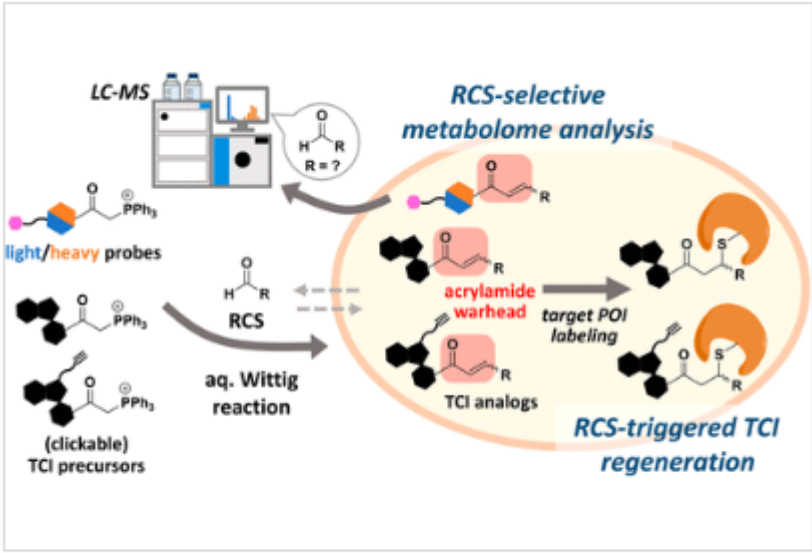
Bruno Lopes-Bastos [1,2] · Joana Nabais [2] · Tânia Ferreira [2] · … · Gianni Liti [1] · Tânia G. Carvalho [4] · Miguel Godinho Ferreira [1,2,5] … Show more

Most cancers re-activate telomerase to maintain telomere length and thus acquire immortality. Activating telomerase promoter mutations are found in many cancers, including melanoma. However, it is unclear when and if telomerase is strictly required during tumorigenesis. We combined the telomerase mutant (*tert*$^{-/-}$) with two established zebrafish melanoma models. We show that *tert*$^{-/-}$ melanomas initially develop with similar incidence and invasiveness to *tert*$^{+/+}$ tumors. However, they eventually decline in growth and regress. Late *tert*$^{-/-}$ tumors exhibit reduced cell proliferation, increased apoptosis, and melanocyte differentiation. Notably, these tumors show enhanced immune cell infiltration and can resume growth when transplanted into immunocompromised hosts. We propose that telomerase is required for melanoma in zebrafish, albeit at later stages of progression, to sustain tumor growth while avoiding immune rejection and regression. Thus, the absence of telomerase restricts melanoma through tumor-autonomous mechanisms (cell-cycle arrest, apoptosis, and melanocyte differentiation) and a non-tumor-autonomous mechanism (immune rejection).

Chemoselective Stabilized Triphenylphosphonium Probes for Capturing Reactive Carbonyl Species and Regenerating Covalent Inhibitors with Acrylamide Warheads in Cellulo

Ai-Lin Chen, Zih-Jheng Lin, Hsiao-Yu Chang, and Tsung-Shing Andrew Wang*

Reactive carbonyl species (RCS) are important biomarkers of oxidative stress-related diseases because of their highly reactive electrophilic nature. Despite their potential as triggers for prodrug activation, selective labeling approaches for RCS remain limited. Here, we utilized triphenylphosphonium groups to chemoselectively capture RCS via an aqueous Wittig reaction, forming α,β-unsaturated carbonyls that enable further functionalization. We first designed native (light) and deuterated (heavy) probes to facilitate RCS metabolomic identification through distinct MS isotope patterns. This approach allowed us to capture and relatively quantify several endogenous RCS related to advanced lipoxidation/glycation end products (ALEs/AGEs). Second, we demonstrated that various endogenous RCS can trigger the in situ generation of acrylamide warheads of targeted covalent inhibitors (TCIs) with different substituents. These structural variations influence their protein binding profiles and consequently alter their cytotoxicity, which is beneficial for the development of inhibitor cocktails.



Heales
HEALTHY LIFE EXTENSION SOCIETY

A luminescent-based protocol for NAD^+/NADH detection in C. elegans, mice, and human whole blood

He-Ling Wang [1], Jianying Zhang [2], Shu-Qin Cao [1], Maria Jose Lagartos-Donate [1], Shi-Qi Zhang [1], Sofie Lautrup [1], Zeping Hu [3], Costas A Lyssiotis [4], Riekelt H Houtkooper [5], Evandro F Fang [6]

Affiliations + expand

PMID: 39487980 PMCID: PMC11567065 DOI: 10.1016/j.xpro.2024.103428

Abstract

Here, we present a NAD^+/NADH detection assay for evaluating NAD^+, NADH, and NAD^+/NADH ratio across diverse biological models, including Caenorhabditis elegans, mouse muscle tissue, mouse whole blood, and human whole blood. We describe steps for sample collection and preparation from different models as well as detection and calculation of NAD^+ and NADH levels. This protocol is applicable for quantifying cellular/tissue NAD^+ and NADH levels across different biological models.