Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
7th of July 2024
Sven Bulterijs

Business/Conferences/ General news

Heales
HEALTHY LIFE EXTENSION SOCIETY

Leonard Hayflick, PhD

Author: Eleanor Garth | Published on: August 7, 2024 | Last updated: August 7, 2024

Longevity world mourns a pioneer of aging research whose 'Hayflick Limit' revolutionized our understanding of cell biology.

Clinical trial with rapamycin for muscle function in New-Zealand

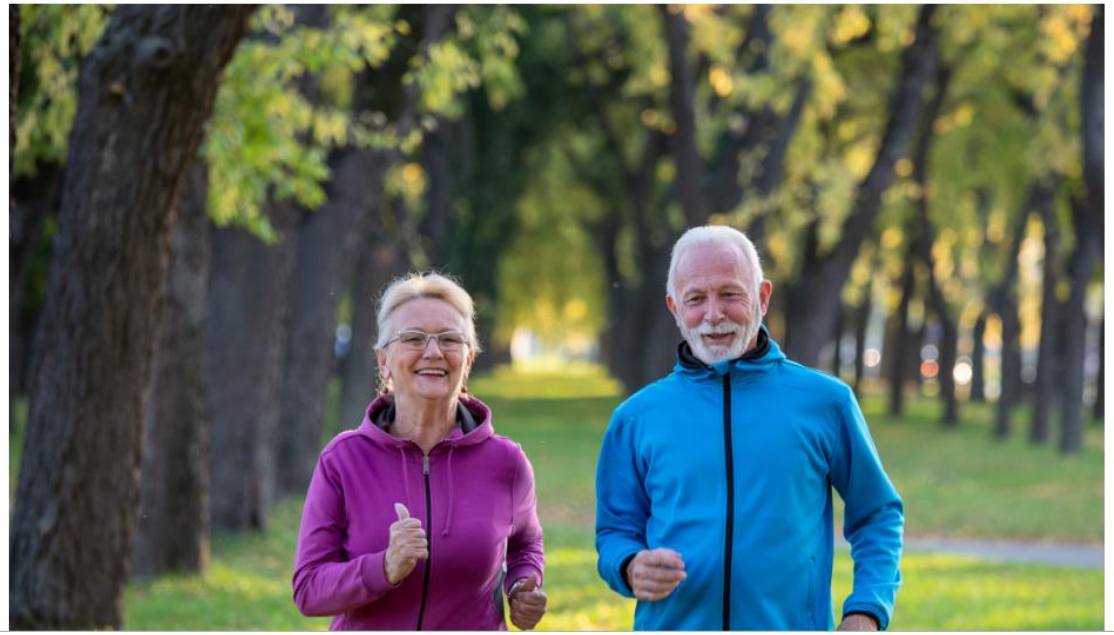
Aotearoa Clinical Trials

Recruiting Trials

Enrolling RealTime Studies

Sponsors | Investigators | Participants | Trial Sites | About Us

Research Studies » Exercise and medication trial



Application for Current Clinical Research Study

Research Study

Exercise and medication trial

Please enter your Full Legal Name

*First Name

Aging research articles

Heales
HEALTHY LIFE EXTENSION SOCIETY

Inhibition of IL-11 signalling extends mammalian healthspan and lifespan

For healthspan and lifespan, ERK, AMPK and mTORC1 represent critical pathways and inflammation is a centrally important hallmark[1,2,3,4,5,6,7]. Here we examined whether IL-11, a pro-inflammatory cytokine of the IL-6 family, has a negative effect on age-associated disease and lifespan. As mice age, IL-11 is upregulated across cell types and tissues to regulate an ERK–AMPK–mTORC1 axis to modulate cellular, tissue- and organismal-level ageing pathologies. Deletion of *Il11* or *Il11ra1* protects against metabolic decline, multi-morbidity and frailty in old age. Administration of anti-IL-11 to 75-week-old mice for 25 weeks improves metabolism and muscle function, and reduces ageing biomarkers and frailty across sexes. In lifespan studies, genetic deletion of *Il11* extended the lives of mice of both sexes, by 24.9% on average. Treatment with anti-IL-11 from 75 weeks of age until death extends the median lifespan of male mice by 22.5% and of female mice by 25%. Together, these results demonstrate a role for the pro-inflammatory factor IL-11 in mammalian healthspan and lifespan. We suggest that anti-IL-11 therapy, which is currently in early-stage clinical trials for fibrotic lung disease, may provide a translational opportunity to determine the effects of IL-11 inhibition on ageing pathologies in older people.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Neuron-specific partial reprogramming in the dentate gyrus impacts mouse behavior and ameliorates age-related decline in memory and learning

Alba Vílchez-Acosta, María del Carmen Maza, Alberto Parras, Alejandra Planells, Sara Picó, Gabriela Desdín-Micó, Calida Mrabti, Clémence Branchina, Céline Yacoub Maroun, Yuri Deigin, Alejandro Ocampo

Age-associated neurodegenerative disorders represent significant challenges due to progressive neuronal decline and limited treatments. In aged mice, partial reprogramming, characterized by pulsed expression of reprogramming factors, has shown promise in improving function in various tissues, but its impact on the aging brain remains poorly understood. Here we investigated the impact of *in vivo* partial reprogramming on mature neurons in the dentate gyrus of young and aged mice. Using two different approaches – a neuron-specific transgenic reprogrammable mouse model and neuron-specific targeted lentiviral delivery of OSKM reprogramming factors – we demonstrated that *in vivo* partial reprogramming of mature neurons in the dentate gyrus, a neurogenic niche in the adult mouse brain, can influence animal behavior, and ameliorate age-related decline in memory and learning. These findings underscore the potential of *in vivo* partial reprogramming as an important therapeutic intervention to rejuvenate the neurogenic niche and ameliorate cognitive decline associated with aging or neurodegeneration.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cognitive rejuvenation in old rats by hippocampal OSKM gene therapy

Several studies have indicated that interrupted epigenetic reprogramming using Yamanaka transcription factors (OSKM) can rejuvenate cells from old laboratory animals and humans. However, the potential of OSKM-induced rejuvenation in brain tissue has been less explored. Here, we aimed to restore cognitive performance in 25.3-month-old female Sprague–Dawley rats using OSKM gene therapy for 39 days. Their progress was then compared with the cognitive performance of untreated 3.5-month-old rats as well as old control rats treated with a placebo adenovector. The Barnes maze test, used to assess cognitive performance, demonstrated enhanced cognitive abilities in old rats treated with OSKM compared to old control animals. In the treated old rats, there was a noticeable trend towards improved spatial memory relative to the old controls. Further, OSKM gene expression did not lead to any pathological alterations within the 39 days. Analysis of DNA methylation following OSKM treatment yielded three insights. First, epigenetic clocks for rats suggested a marginally significant epigenetic rejuvenation. Second, chromatin state analysis revealed that OSKM treatment rejuvenated the methylome of the hippocampus. Third, an epigenome-wide association analysis indicated that OSKM expression in the hippocampus of old rats partially reversed the age-related increase in methylation. In summary, the administration of Yamanaka genes via viral vectors rejuvenates the functional capabilities and the epigenetic landscape of the rat hippocampus.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Aging limits stemness and tumorigenesis in the lung by reprogramming iron homeostasis

Aging is associated with a decline in the number and fitness of adult stem cells [1-4] . Aging-associated loss of stemness is posited to suppress tumorigenesis [5,6] , but this hypothesis has not been tested *in vivo* . Here, using physiologically aged autochthonous genetically engineered mouse models and primary cells [7,8] , we demonstrate aging suppresses lung cancer initiation and progression by degrading stemness of the alveolar cell of origin. This phenotype is underpinned by aging-associated induction of the transcription factor NUPR1 and its downstream target lipocalin-2 in the cell of origin in mice and humans, leading to a functional iron insufficiency in the aged cells. Genetic inactivation of the NUPR1-lipocalin-2 axis or iron supplementation rescue stemness and promote tumorigenic potential of aged alveolar cells. Conversely, targeting the NUPR1- lipocalin-2 axis is detrimental to young alveolar cells via induction of ferroptosis. We find that aging-associated DNA hypomethylation at specific enhancer sites associates with elevated NUPR1 expression, which is recapitulated in young alveolar cells by inhibition of DNA methylation. We uncover that aging drives a functional iron insufficiency, which leads to loss of stemness and tumorigenesis, but promotes resistance to ferroptosis. These findings have significant implications for the therapeutic modulation of cellular iron homeostasis in regenerative medicine and in cancer prevention. Furthermore, our findings are consistent with a model whereby most human cancers initiate in young individuals, revealing a critical window for such cancer prevention efforts.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Titration of RAS alters senescent state and influences tumour initiation

Oncogenic RAS-induced senescence (OIS) is an autonomous tumour suppressor mechanism associated with premalignancy[1,2]. Achieving this phenotype typically requires a high level of oncogenic stress, yet the phenotype provoked by lower oncogenic dosage remains unclear. Here we develop oncogenic RAS dose-escalation models in vitro and in vivo, revealing a RAS dose-driven non-linear continuum of downstream phenotypes. In a hepatocyte OIS model in vivo, ectopic expression of NRAS(G12V) does not induce tumours, in part owing to OIS-driven immune clearance[3]. Single-cell RNA sequencing analyses reveal distinct hepatocyte clusters with typical OIS or progenitor-like features, corresponding to high and intermediate levels of NRAS(G12V), respectively. When titred down, NRAS(G12V)-expressing hepatocytes become immune resistant and develop tumours. Time-series monitoring at single-cell resolution identifies two distinct tumour types: early-onset aggressive undifferentiated and late-onset differentiated hepatocellular carcinoma. The molecular signature of each mouse tumour type is associated with different progenitor features and enriched in distinct human hepatocellular carcinoma subclasses. Our results define the oncogenic dosage-driven OIS spectrum, reconciling the senescence and tumour initiation phenotypes in early tumorigenesis.

Intermittent clearance of *p21*-highly-expressing cells extends lifespan and confers sustained benefits to health and physical function

A key challenge in aging research is extending lifespan in tandem with slowing down functional decline so that life with good health (healthspan) can be extended. Here, we show that monthly clearance, starting from 20 months, of a small number of cells that highly express $p21^{Cip1}$ ($p21^{high}$) improves cardiac and metabolic function and extends both median and maximum lifespans in mice. Importantly, by assessing the health and physical function of these mice monthly until death, we show that clearance of $p21^{high}$ cells improves physical function at all remaining stages of life, suggesting healthspan extension. Mechanistically, $p21^{high}$ cells encompass several cell types with a relatively conserved proinflammatory signature. Clearance of $p21^{high}$ cells reduces inflammation and alleviates age-related transcriptomic signatures of various tissues. These findings demonstrate the feasibility of healthspan extension in mice and indicate $p21^{high}$ cells as a therapeutic target for healthy aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Discovery and Repurposing of Multi-Target Senolytics through Structure-Based Virtual Screening

Cellular Senescence is a state of irreversible cell cycle arrest in response to various stressors that can damage the cell. Senescent Cells (SCs) exhibit multiple alterations at the morphological and molecular levels, one of the most significant being the development and activation of Senescent Cell Anti-Apoptotic Pathways (SCAPs). Due to this characteristic, SCs accumulate in organs and tissues during aging. The accumulation of these cells has been associated with the onset and progression of various chronic degenerative diseases, and their selective elimination allows for the slowing down, halting, and reversing of many age-associated ailments. Small molecules called senolytics, which inhibit SCAPs, have been proposed to selectively eliminate SCs. Herein, we identified new senolytics through computational and rational drug design approaches. Among the identified molecules are the FDA-approved drug tolvaptan, the experimental Phase II drug sotrastaurin, and the experimental drugs cryptotanshinone and bicuculline. The effectiveness of these molecules in targeting senescent cells was confirmed through experiments using two different models of cellular senescence in human lung fibroblasts. Our results suggest that some molecules work by selectively inducing apoptosis through a multi-target mechanism, inhibiting several SCAPs, including PIK3CD, SERPINE1, EFNB1, and PDGFB. These newly identified FDA-approved and experimental drugs have the potential to be repurposed as new senolytic agents.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Senescent cell heterogeneity and responses to senolytic treatment are related to cell cycle status during cell growth arrest

Cellular senescence has been strongly linked to aging and age-related diseases. It is well established that the phenotype of senescent cells is highly heterogeneous and influenced by their cell type and senescence-inducing stimulus. Recent single-cell RNA-sequencing studies identified heterogeneity within senescent cell populations. However, proof of functional differences between such subpopulations is lacking. To identify functionally distinct senescent cell subpopulations, we employed high-content image analysis to measure senescence marker expression in primary human endothelial cells and fibroblasts. We found that G2-arrested senescent cells feature higher senescence marker expression than G1-arrested senescent cells. To investigate functional differences, we compared IL-6 secretion and response to ABT263 senolytic treatment in G1 and G2 senescent cells. We determined that G2-arrested senescent cells secrete more IL-6 and are more sensitive to ABT263 than G1-arrested cells. We hypothesize that cell cycle dependent DNA content is a key contributor to the heterogeneity within senescent cell populations. This study demonstrates the existence of functionally distinct senescent subpopulations even in culture. This data provides the first evidence of selective cell response to senolytic treatment among senescent cell subpopulations. Overall, this study emphasizes the importance of considering the senescent cell heterogeneity in the development of future senolytic therapies.

Heales
HEALTHY LIFE EXTENSION SOCIETY

p16-dependent increase of PD-L1 stability regulates immunosurveillance of senescent cells

The accumulation of senescent cells promotes ageing and age-related diseases, but molecular mechanisms that senescent cells use to evade immune clearance and accumulate in tissues remain to be elucidated. Here we report that p16-positive senescent cells upregulate the immune checkpoint protein programmed death-ligand 1 (PD-L1) to accumulate in ageing and chronic inflammation. We show that p16-mediated inhibition of cell cycle kinases CDK4/6 induces PD-L1 stability in senescent cells via downregulation of its ubiquitin-dependent degradation. p16-expressing senescent alveolar macrophages elevate PD-L1 to promote an immunosuppressive environment that can contribute to an increased burden of senescent cells. Treatment with activating anti-PD-L1 antibodies engaging Fcγ receptors on effector cells leads to the elimination of PD-L1 and p16-positive cells. Our study uncovers a molecular mechanism of p16-dependent regulation of PD-L1 protein stability in senescent cells and reveals the potential of targeting PD-L1 to improve immunosurveillance of senescent cells and ameliorate senescence-associated inflammation.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Six drivers of aging identified among genes differentially expressed with age

Ariella Coler-Reilly, Zachary Pincus, Erica L. Scheller, Roberto Civitelli

Many studies have compared gene expression in young and old samples to gain insights on aging, the primary risk factor for most major chronic diseases. However, these studies only describe associations, failing to distinguish drivers of aging from compensatory geroprotective responses and incidental downstream effects. Here, we introduce a workflow to characterize the causal effects of differentially expressed genes on lifespan. First, we performed a meta-analysis of 25 gene expression datasets comprising samples of various tissues from healthy, untreated adult mammals (humans, dogs, and rodents) at two distinct ages. We ranked each gene according to the number of distinct datasets in which the gene was differentially expressed with age in a consistent direction. The top age-upregulated genes were TMEM176A, EFEMP1, CP, and HLA-A; the top age-downregulated genes were CA4, SIAH, SPARC, and UQCR10. Second, the effects of the top ranked genes on lifespan were measured by applying post-developmental RNA interference of the corresponding ortholog in the nematode C. elegans (two trials, with roughly 100 animals per genotype per trial). Out of 10 age-upregulated and 9 age-downregulated genes that were tested, two age-upregulated genes (*csp-3*/CASP1 and *spch-2*/RSRC1) and four age-downregulated genes (*C42C1.8*/DIRC2, *ost-1*/SPARC, *fzy-1*/CDC20, and *cah-3*/CA4) produced significant and reproducible lifespan extension. Notably, the data do not suggest that the direction of differential expression with age is predictive of the effect on lifespan. Our study provides novel insight into the relationship between differential gene expression and aging phenotypes, pilots an unbiased workflow that can be easily repeated and expanded, and pinpoints six genes with evolutionarily conserved, causal roles in the aging process for further study.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The circadian rhythm: A key variable in aging?

Patrick R. Winterhalter ✉, Adrian-Iustin Georgevici, Nitin J. Gharpure, Gábor Szabó, Andreas Simm

The determination of age-related transcriptional changes may contribute to the understanding of health and life expectancy. The broad application of results from age cohorts may have limitations. Altering sample sizes per time point or sex, using a single mouse strain or tissue, a limited number of replicates, or omitting the middle of life can bias the surveys. To achieve higher general validity and to identify less distinctive players, bulk RNA sequencing of a mouse cohort, including seven organs of two strains from both sexes of 5 ages, was performed. Machine learning by bootstrapped variable importance and selection methodology (Boruta) was used to identify common aging features where the circadian rhythms (CiR) transcripts appear as promising age markers in an unsupervised analysis. Pathways of 11 numerically analyzed local network clusters were affected and classified into four major gene expression profiles, whereby CiR and proteostasis candidates were particularly conspicuous with partially opposing changes. In a data-based interaction association network, the CiR-proteostasis axis occupies an exposed central position, highlighting its relevance. The computation of 11,830 individual transcript associations provides potential superordinate contributors, such as hormones, to age-related changes, as in CiR. In hormone-sensitive LNCaP cells, short-term supraphysiologic levels of the sex hormones dihydrotestosterone or estradiol increase the expression of the CiR transcript Bhlhe40 and the associated senescence regulator Cdkn2b (p15). According to these findings, the bilateral dysregulation of CiR appears as a fundamental protagonist of aging, whose transcripts could serve as a biological marker and its restoration as a therapeutic opportunity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The genetic architecture of biological age in nine human organ systems

Junhao Wen ✉, Ye Ella Tian, Ioanna Skampardoni, Zhijian Yang, Yuhan Cui, Filippos Anagnostakis, Elizabeth Mamourian, Bingxin Zhao, Arthur W. Toga, Andrew Zalesky & Christos Davatzikos

Investigating the genetic underpinnings of human aging is essential for unraveling the etiology of and developing actionable therapies for chronic diseases. Here, we characterize the genetic architecture of the biological age gap (BAG; the difference between machine learning-predicted age and chronological age) across nine human organ systems in 377,028 participants of European ancestry from the UK Biobank. The BAGs were computed using cross-validated support vector machines, incorporating imaging, physical traits and physiological measures. We identify 393 genomic loci–BAG pairs ($P < 5 \times 10^{-8}$) linked to the brain, eye, cardiovascular, hepatic, immune, metabolic, musculoskeletal, pulmonary and renal systems. Genetic variants associated with the nine BAGs are predominantly specific to the respective organ system (organ specificity) while exerting pleiotropic links with other organ systems (interorgan cross-talk). We find that genetic correlation between the nine BAGs mirrors their phenotypic correlation. Further, a multiorgan causal network established from two-sample Mendelian randomization and latent causal variance models revealed potential causality between chronic diseases (for example, Alzheimer's disease and diabetes), modifiable lifestyle factors (for example, sleep duration and body weight) and multiple BAGs. Our results illustrate the potential for improving human organ health via a multiorgan network, including lifestyle interventions and drug repurposing strategies.

Retro-age: A unique epigenetic biomarker of aging captured by DNA methylation states of retroelements

Reactivation of retroelements in the human genome has been linked to aging. However, whether the epigenetic state of specific retroelements can predict chronological age remains unknown. We provide evidence that locus-specific retroelement DNA methylation can be used to create retroelement-based epigenetic clocks that accurately measure chronological age in the immune system, across human tissues, and pan-mammalian species. We also developed a highly accurate retroelement epigenetic clock compatible with EPICv.2.0 data that was constructed from CpGs that did not overlap with existing first- and second-generation epigenetic clocks, suggesting a unique signal for epigenetic clocks not previously captured. We found retroelement-based epigenetic clocks were reversed during transient epigenetic reprogramming, accelerated in people living with HIV-1, and responsive to antiretroviral therapy. Our findings highlight the utility of retroelement-based biomarkers of aging and support a renewed emphasis on the role of retroelements in geroscience.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Biological aging of different blood cell types

Biological age (BA) captures detrimental age-related changes. The best-known and most-used BA indicators include DNA methylation–based epigenetic clocks and telomere length (TL). The most common biological sample material for epidemiological aging studies, whole blood, is composed of different cell types. We aimed to compare differences in BAs between blood cell types and assessed the BA indicators' cell type-specific associations with chronological age (CA). An analysis of DNA methylation–based BA indicators, including TL, methylation level at cg16867657 in *ELOVL2*, as well as the Hannum, Horvath, DNAmPhenoAge, and DunedinPACE epigenetic clocks, was performed on 428 biological samples of 12 blood cell types. BA values were different in the majority of the pairwise comparisons between cell types, as well as in comparison to whole blood ($p < 0.05$). DNAmPhenoAge showed the largest cell type differences, up to 44.5 years and DNA methylation-based TL showed the lowest differences. T cells generally had the "youngest" BA values, with differences across subsets, whereas monocytes had the "oldest" values. All BA indicators, except DunedinPACE, strongly correlated with CA within a cell type. Some differences such as DNAmPhenoAge-difference between naïve CD4 + T cells and monocytes were constant regardless of the blood donor's CA (range 20–80 years), while for DunedinPACE they were not. In conclusion, DNA methylation–based indicators of BA exhibit cell type–specific characteristics. Our results have implications for understanding the molecular mechanisms underlying epigenetic clocks and underscore the importance of considering cell composition when utilizing them as indicators for the success of aging interventions.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Cell-type specific epigenetic clocks to quantify biological age at cell-type resolution

The ability to accurately quantify biological age could help monitor and control healthy aging. Epigenetic clocks have emerged as promising tools for estimating biological age, yet so far, most of these clocks have been developed from heterogeneous bulk tissues, and are thus composites of two aging processes, one reflecting the change of cell-type composition with age and another reflecting the aging of individual cell-types. There is thus a need to dissect and quantify these two components of epigenetic clocks, and to develop epigenetic clocks that can yield biological age estimates at cell-type resolution. Here we demonstrate that in blood and brain, approximately 35% of an epigenetic clocks accuracy is driven by underlying shifts in lymphocyte and neuronal subsets, respectively. Using brain and liver tissue as prototypes, we build and validate neuron and hepatocyte specific DNA methylation clocks, and demonstrate that these cell-type specific clocks yield improved estimates of chronological age in the corresponding cell and tissue-types. We find that neuron and glia specific clocks display biological age acceleration in Alzheimer Disease with the effect being strongest for glia in the temporal lobe. The hepatocyte clock is found accelerated in liver under various pathological conditions. In contrast, non-cell-type specific clocks do not display biological age-acceleration, or only do so more marginally. In summary, this work highlights the importance of dissecting epigenetic clocks and quantifying biological age at cell-type resolution.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The molecular impact of cigarette smoking resembles aging across tissues

Jose Miguel Ramirez, Rogério Ribeiro, Oleksandra Soldatkina, Athos Moraes, Raquel García-Pérez, Pedro G. Ferreira, Marta Melé

Tobacco smoke is the main cause of preventable mortality worldwide. Smoking increases the risk of developing many diseases and has been proposed as an aging accelerator. Yet, the molecular mechanisms driving smoking-related health decline and aging acceleration in most tissues remain unexplored. Here, we characterize gene expression, alternative splicing, DNA methylation and histological alterations induced by cigarette smoking across human tissues. We show that smoking impacts tissue architecture and triggers systemic inflammation. We find that in many tissues, the effects of smoking significantly overlap those of aging in the same direction. Specifically, both age and smoking upregulate inflammatory genes and drive hypomethylation at enhancers. In addition, we observe widespread smoking-driven hypermethylation at target regions of the Polycomb repressive complex, which is a well-known aging effect. Smoking-induced epigenetic changes overlap causal aging CpGs, suggesting that these methylation changes may directly mediate aging acceleration observed in smokers. Finally, we find that smoking effects that are shared with aging are more persistent over time. Overall, our multi-tissue and multi-omic analysis of the effects of cigarette smoking provides an extensive characterization of the impact of tobacco smoke across tissues and unravels the molecular mechanisms driving smoking-induced tissue homeostasis decline and aging acceleration.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A combination of the geroprotectors trametinib and rapamycin is more effective than either drug alone

Lisonia Gkioni, Tobias Nespital, Carolina Monzó, Jitin Bali, Taim Nassr, Anna Lena Cremer, Andreas Beyer, Heiko Backes, Sebastian Grönke, Linda Partridge

Genetic suppression of activity of the insulin/IGF/mTORC1/Ras network can ameliorate the effects of ageing in animals. The network provides multiple drug targets because of its role in metabolic disease and cancer, and these are candidates for repurposing for geroprotection. For instance, inhibition of the activity of the mTORC1 complex by rapamycin can extend lifespan in multiple organisms including mice, with early indications of efficacy in humans. Trametinib inhibits MEKs in the Ras pathway and can extend lifespan in *Drosophila*. However, it is not yet known if trametinib alone or in combination with rapamycin can extend mouse lifespan or improve health at older ages. We assessed survival and health indices of female and male mice treated with trametinib or rapamycin alone, or with the two in combination at the same doses. Trametinib treatment extended lifespan in both sexes, while its combination with rapamycin caused further, additive prolongation. Combination treatment reduced liver tumours in both sexes and spleen tumours in males, and ameliorated the age-related increase in brain glucose uptake. There was a striking reduction in inflammation in the brain, kidney, spleen and muscle with combination treatment, accompanied by reduced circulating levels of pro-inflammatory cytokines. Trametinib alone is therefore geroprotective in mice, but combined trametinib and rapamycin treatment is more geroprotective than treatment with either drug alone, suggesting immediate translational potential for humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Rapalink-1 reveals novel mTOR-dependent genes and the role of agmatinases in cellular growth and chronological lifespan

Juhi Kumar, Charalampos Rallis

mTOR is a conserved pro-ageing pathway with characterised inhibitors such as rapamycin, rapalogues and torins. A third-generation inhibitor, rapalink-1, has been developed, however, its effects on organismal gene expression and lifespan have not been evaluated. Here, we demonstrate that rapalink-1 affects fission yeast spatial and temporal growth and prolongs chronological lifespan. Endosome and vesicle-mediated transport and homeostasis processes related to autophagy and Pik3, the orthologue of human PI3K, render cells resistant to rapalink-1. Our study reveals mTOR-regulated genes with unknown roles in ageing including all fission yeast agmatinases, the enzymes responsible for processing agmatine to putrescine and urea. We identify sensitive and resistant mutants to agmatine and putrescine and show that all fission yeast agmatinase enzymes are required for normal lifespan. Genetic interactome assays for the agmatinase *agm1* and further cell and molecular analyses, demonstrate that impairing the agmatinergic branch of arginine catabolism results in mTOR activity levels that are beneficial for growth but detrimental for chronological ageing. Our study reveals metabolic feedback circuits with possible implications to other systems, including human cells.

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.

Markers of Mitochondrial Function and DNA Repair Associated with Physical Function in Centenarians

Mitochondrial dysfunction and genomic instability are key hallmarks of aging. The aim of this study was to evaluate whether maintenance of physical capacities at very old age is associated with key hallmarks of aging. To investigate this, we measured mitochondrial bioenergetics, mitochondrial DNA (mtDNA) copy number and DNA repair capacity in peripheral blood mononuclear cells from centenarians. In addition, circulating levels of NAD+/NADH, brain-derived neurotrophic factor (BDNF) and carbonylated proteins were measured in plasma and these parameters were correlated to physical capacities. Centenarians without physical disabilities had lower mitochondrial respiration values including ATP production, reserve capacity, maximal respiration and non-mitochondrial oxygen-consumption rate and had higher mtDNA copy number than centenarians with moderate and severe disabilities ($p < 0.05$). In centenarian females, grip strength had a positive association with mtDNA copy number ($p < 0.05$), and a borderline positive trend for activity of the central DNA repair enzyme, APE 1 ($p = 0.075$), while a negative trend was found with circulating protein carbonylation ($p = 0.07$) in the entire cohort. Lastly, a trend was observed for a negative association between BDNF and activity of daily living disability score ($p = 0.06$). Our results suggest that mechanisms involved in maintaining mitochondrial function and genomic stability may be associated with maintenance of physical function in centenarians.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Mitochondrial respiration atlas reveals differential changes in mitochondrial function across sex and age

Dylan C. Sarver, Muzna Saqib, Fangluo Chen, G. William Wong

Organ function declines with age, and large-scale transcriptomic analyses have highlighted differential aging trajectories across tissues. The mechanism underlying shared and organ-selective functional changes across the lifespan, however, still remains poorly understood. Given the central role of mitochondria in powering cellular processes needed to maintain tissue health, we therefore undertook a systematic assessment of respiratory activity across 33 different tissues in young (2.5 months) and old (20 months) mice of both sexes. Our high-resolution mitochondrial respiration atlas reveals: 1) within any group of mice, mitochondrial activity varies widely across tissues, with the highest values consistently seen in heart, brown fat, and kidney; 2) biological sex is a significant but minor contributor to mitochondrial respiration, and its contributions are tissue-specific, with major differences seen in the pancreas, stomach, and white adipose tissue; 3) age is a dominant factor affecting mitochondrial activity, especially across most brain regions, different fat depots, skeletal muscle groups, eyes, and different regions of the gastrointestinal tract; 4) age-effects can be sex- and tissue-specific, with some of the largest effects seen in pancreas, heart, adipose tissue, and skeletal muscle; and 5) while aging alters the functional trajectories of mitochondria in a majority of tissues, some are remarkably resilient to age-induced changes. Altogether, our data provide the most comprehensive compendium of mitochondrial respiration and illuminate functional signatures of aging across diverse tissues and organ systems.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

AGEing of Collagen: The Effects of Glycation on Collagen's Stability, Mechanics and Assembly

Advanced Glycation End Products (AGEs) are the end result of the irreversible, non-enzymatic glycation of proteins by reducing sugars. These chemical modifications accumulate with age and have been associated with various age-related and diabetic complications. AGEs predominantly accumulate on proteins with slow turnover rates, of which collagen is a prime example. Glycation has been associated with tissue stiffening and reduced collagen fibril remodelling. In this study, we investigate the effects of glycation on the stability of type I collagen, its molecular-level mechanics and its ability to perform its physiological role of self-assembly. Collagen AGEing is induced *in vitro* by incubation with ribose. We confirm and assess glycation using fluorescence measurements and changes in collagen's electrophoretic mobility. Susceptibility to trypsin digestion and circular dichroism (CD) spectroscopy are used to probe changes in collagen's triple helical stability, revealing decreased stability due to glycation. Atomic Force Microscopy (AFM) imaging is used to quantify how AGEing affects collagen flexibility, where we find molecular-scale stiffening. Finally we use microscopy to show that glycated collagen molecules are unable to self-assemble into fibrils. These findings shed light on the molecular mechanisms underlying AGE-induced tissue changes, offering insight into how glycation modifies protein structure and stability.

Don’t die like me: Which proteins are responsible for the selective neuronal vulnerability within the *substantia nigra*?

A hallmark of Parkinson’s disease is the specific degeneration of dopaminergic neurons in the *substantia nigra pars compacta*. Interestingly, not all of these neurons are affected to the same extent. Studies revealed that neurons located more ventrally within the *substantia nigra pars compacta* have a higher prevalence to degenerate than those located in the dorsal tier. The underlying reasons for this selective neuronal vulnerability are still unknown. The aim of the present study was to gain a better understanding of molecular differences between these two neuronal subpopulations that may explain the selective neuronal vulnerability within the human *substantia nigra*. For this purpose, the neurons from the ventral as well as dorsal tier of the *substantia nigra* were specifically isolated out of neuropathologically unremarkable human *substantia nigra* sections with laser microdissection. Following, their proteome was analyzed by data independent acquisition mass spectrometry. The samples were analysed donor-specifically and not pooled for this purpose. A total of 5,391 proteins were identified in the *substantia nigra*. Of these, 2,453 proteins could be quantified in 100% of the dorsal tier samples. 1,629 could be quantified in 100% of the ventral tier samples. Nine proteins were differentially regulated with a log2 value ≥0.5 and a Qvalue ≤0.05. Of these 7 were higher abundant in the dorsal tier and 2 higher in the ventral tier. These proteins are associated with the cytoskeleton, neuronal plasticity, or calcium homeostasis. With these findings a deeper understanding can be gained of the selective neuronal vulnerability within the *substantia nigra* and of protective mechanisms against neurodegeneration in specific neuronal subpopulations.

Unexpected Low Rate of Amyloid-β Pathology in Multiple Sclerosis Patients

The life expectancy of people with multiple sclerosis (MS) has increased, yet we have noted that development of a typical Alzheimer disease dementia syndrome is uncommon. We hypothesized that Alzheimer disease pathology is uncommon in MS patients. In 100 MS patients, the rate of amyloid-β plasma biomarker positivity was approximately half the rate in 300 non-MS controls matched on age, sex, apolipoprotein E proteotype, and cognitive status. Interestingly, most MS patients who did have amyloid-β pathology had features atypical for MS at diagnosis. These results support that MS is associated with reduced Alzheimer disease risk, and suggest new avenues of research. ANN NEUROL 2024

Brain responses to intermittent fasting and the healthy living diet in older adults

Diet may promote brain health in metabolically impaired older individuals. In an 8-week randomized clinical trial involving 40 cognitively intact older adults with insulin resistance, we examined the effects of 5:2 intermittent fasting and the healthy living diet on brain health. Although intermittent fasting induced greater weight loss, the two diets had comparable effects in improving insulin signaling biomarkers in neuron-derived extracellular vesicles, decreasing the brain-age-gap estimate (reflecting the pace of biological aging of the brain) on magnetic resonance imaging, reducing brain glucose on magnetic resonance spectroscopy, and improving blood biomarkers of carbohydrate and lipid metabolism, with minimal changes in cerebrospinal fluid biomarkers for Alzheimer's disease. Intermittent fasting and healthy living improved executive function and memory, with intermittent fasting benefiting more certain cognitive measures. In exploratory analyses, sex, body mass index, and apolipoprotein E and *SLC16A7* genotypes modulated diet effects. The study provides a blueprint for assessing brain effects of dietary interventions and motivates further research on intermittent fasting and continuous diets for brain health optimization. For further information, please see ClinicalTrials.gov ↗ registration: NCT02460783.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The maintenance of oocytes in the mammalian ovary involves extreme protein longevity

Women are born with all of their oocytes. The oocyte proteome must be maintained with minimal damage throughout the woman's reproductive life, and hence for decades. Here we report that oocyte and ovarian proteostasis involves extreme protein longevity. Mouse ovaries had more extremely long-lived proteins than other tissues, including brain. These long-lived proteins had diverse functions, including in mitochondria, the cytoskeleton, chromatin and proteostasis. The stable proteins resided not only in oocytes but also in long-lived ovarian somatic cells. Our data suggest that mammals increase protein longevity and enhance proteostasis by chaperones and cellular antioxidants to maintain the female germline for long periods. Indeed, protein aggregation in oocytes did not increase with age and proteasome activity did not decay. However, increasing protein longevity cannot fully block female germline senescence. Large-scale proteome profiling of ~8,890 proteins revealed a decline in many long-lived proteins of the proteostasis network in the aging ovary, accompanied by massive proteome remodeling, which eventually leads to female fertility decline.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Integrative deep immune profiling of the elderly reveals systems-level signatures of aging, sex, smoking, and clinical traits

Elderly individuals have higher disease susceptibility and lower vaccine responsiveness, highlighting the need to better comprehend the aging immune system and its clinical associations. Here we conducted a deep immune profiling study of 550 elderly individuals (61–94 years) and 100 young adults (22–38 years). Utilizing high-dimensional spectral flow cytometry to identify 97 immune cell populations and 48-plex cytokine profiling, we detailed intricate age-and sex-related changes in the elderly immune system at an unprecedented depth. Synthesizing information from clinical, laboratory, and immunological data through an integrative multi-block analysis, we reveal overarching systems-level signatures of aging, such as increased concentrations of specific cytokines and frequencies of defined innate and adaptive immune cell subpopulations. Extending this approach, we identified unique immune signatures of smoking, obesity, and several diseases including osteoporosis, heart failure and gout. Our systems biology approach enables to uncover new relationships between clinical characteristics and immunological traits.

PREPRINT

The Emergent Aging Model: Aging as an Emergent Property of Biological Systems

Hong Qin

Based on the study of cellular aging using the single-cell model organism of budding yeast and corroborated by other studies, we propose the Emergent Aging Model (EAM). EAM hypothesizes that aging is an emergent property of complex biological systems, exemplified by biological networks such as gene networks. An emergent property refers to traits that a system has at the system level but which its low-level components do not. EAM is based on a quantitative definition of aging using the mortality rate. A biological entity with a constant mortality rate is considered non-aging which is equivalent to a first-order chemical reaction. Aging can be quantitatively defined as an increasing mortality rate over time, corresponding to an organism's increasing chance of dying over time. EAM posits that biological aging can arise at the system level of an organism, even if the system is composed of only non-aging components. EAM is consistent with the observation that aging is largely stochastic, influenced by numerous genes and epigenetic factors, with no single gene or factor known as the bona fide cause of aging. A parsimonious version of EAM can predict the Gompertz model of biological aging, the Strehler-Mildvan correlation, and the trade-off between initial reproductive fitness (asexual reproductive fitness) and late-life survival. EAM has been applied to experimental results of the replicative lifespan of the budding yeast and can potentially offer new insights into the aging process of other biological species.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Comparative lifespan and healthspan of nonhuman primate species common to biomedical research

There is a critical need to generate age- and sex-specific survival curves to characterize chronological aging consistently across nonhuman primates (NHP) used in biomedical research. Accurate measures of chronological aging are essential for inferences into genetic, demographic, and physiological variables driving differences in NHP lifespan within and between species. Understanding NHP lifespans is relevant to public health because unraveling the demographic, molecular, and clinical bases of health across the life course in translationally relevant NHP species is fundamentally important to the study of human aging. Data from more than 110,000 captive individual NHP were contributed by 15 major research institutions to generate sex-specific Kaplan-Meier survival curves using uniform methods in 12 translational aging models: *Callithrix jacchus* (common marmoset), *Chlorocebus aethiops sabaeus* (vervet/African green), *Macaca fascicularis* (cynomolgus macaque), *M. fuscata* (Japanese macaque), *M. mulatta* (rhesus macaque), *M. nemestrina* (pigtail macaque), *M. radiata* (bonnet macaque), *Pan troglodytes* spp. (chimpanzee), *Papio hamadryas* spp. (baboon), *Plecturocebus cupreus* (coppery titi monkey), *Saguinus oedipus* (cotton-top tamarin), and *Saimiri* spp. (squirrel monkey). After employing strict inclusion criteria, primary analysis results are based on 12,269 NHP that survived to adulthood and died of natural/health-related causes. A secondary analysis was completed for 32,616 NHP that died of any cause. For the primary analyses, we report ages of 25th, 50th, 75th, and 85th percentiles of survival, maximum observed ages, rates of survivorship, and sex-based differences captured by quantile regression models and Kolmogorov-Smirnov tests. Our findings show a pattern of reduced male survival among catarrhines (African and Asian primates), especially macaques, but not platyrrhines (Central and South American primates). For many species, median lifespans were lower than previously reported. An important consideration is that these analyses may offer a better reflection of healthspan than lifespan. Captive NHP used in research are typically euthanized for humane welfare reasons before their natural end of life, often after diagnosis of their first major disease requiring long-term treatment with reduced quality of life (e.g., endometriosis, cancer, osteoarthritis).

Supporting the idea that these data are capturing healthspan, for several species typical age at onset of chronic disease is similar to the median lifespan estimates. This data resource represents the most comprehensive characterization of sex-specific lifespan and age-at-death distributions for 12 biomedically relevant species, to date. The results clarify the relationships among NHP ages and will provide a valuable resource for the aging research community, improving human-NHP age equivalencies, informing investigators of the expected survival rates of NHP assigned to studies, providing a metric for comparisons in future studies, and contributing to our understanding of the factors that drive lifespan differences within and among species.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

ER-phagy drives age-onset remodeling of endoplasmic reticulum structure-function and lifespan

The endoplasmic reticulum (ER) comprises an array of structurally distinct subdomains, each with characteristic functions. While altered ER-associated processes are linked to age-onset pathogenesis, whether shifts in ER morphology underlie these functional changes is unclear. We report that ER remodeling is a conserved feature of the aging process in models ranging from yeast to C. elegans and mammals. Focusing on C. elegans as an exemplar of metazoan aging, we find that as animals age, ER mass declines in virtually all tissues and ER morphology shifts from rough sheets to tubular ER. The accompanying large-scale shifts in proteomic composition correspond to the ER turning from protein synthesis to lipid metabolism. To drive this substantial remodeling, ER-phagy is activated early in adulthood, promoting turnover of rough ER in response to rises in luminal protein-folding burden and reduced global protein synthesis. Surprisingly, ER remodeling is a pro-active and protective response during aging, as ER-phagy impairment limits lifespan in yeast and diverse lifespan-extending paradigms promote profound remodeling of ER morphology even in young animals. Altogether our results reveal ER-phagy and ER morphological dynamics as pronounced, underappreciated mechanisms of both normal aging and enhanced longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A mechanistic analysis of metformin's biphasic effects on lifespan and healthspan in *C. elegans*: Elixir in youth, poison in elder

Aging, a complex biological process influenced by genetic, environmental, and pharmacological factors, presents a significant challenge in understanding its underlying mechanisms. In this study, we explored the divergent impacts of metformin treatment on the lifespan and healthspan of young and old C. elegans, demonstrating a intriguing "elixir in youth, poison in elder" phenomenon. By scrutinizing the gene expression changes in response to metformin in young (day 1 of adulthood) and old (days 8) groups, we identified *nhr-57* and *C46G7.1* as potential modulators of age-specific responses. Notably, *nhr-57* and *C46G7.1* exhibit contrasting regulation patterns, being up-regulated in young worms but down-regulated in old counterparts following metformin treatment. Functional studies employing knockdown approaches targeting *nhr-57*, a gene under the control of *hif-1* with a documented protective function against pore-forming toxins in C. elegans, and *C46G7.1*, unveiled their critical roles in modulating lifespan and healthspan, as well as in mediating the biphasic effects of metformin. Furthermore, deletion of *hif-1* retarded the influence of metformin, implicating the involvement of *hif-1*/*nhr-57* in age-specific drug responses. These findings underscored the necessity of deciphering the mechanisms governing age-related susceptibility to pharmacological agents to tailor interventions for promoting successful aging.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

ChatGPT's Role in Gerontology Research

Background: ChatGPT and other ChatBots have emerged as tools for interacting with information in manners resembling natural human speech. Consequently, the technology is used across various disciplines, including business, education, and even in biomedical sciences. There is a need to better understand how ChatGPT can be used to advance gerontology research. Therefore, we evaluated ChatGPT responses to questions on specific topics in gerontology research, and brainstormed recommendations for its use in the field.

Methods: We conducted semi-structured brainstorming sessions to identify uses of ChatGPT in gerontology research. We divided a team of multidisciplinary researchers into four topical groups: a) gero-clinical science, b) basic geroscience, c) informatics as it relates to electronic health records (EHR), and d) gero-technology. Each group prompted ChatGPT on a theory-, methods-, and interpretation-based question and rated responses for accuracy and completeness based on standardized scales.

Results: ChatGPT responses were rated by all groups as generally accurate. However, the completeness of responses was rated lower, except by members of the informatics group, who rated responses as highly comprehensive.

Conclusions: ChatGPT accurately depicts some major concepts in gerontological research. However, researchers have an important role in critically appraising the completeness of its responses. Having a single generalized resource like ChatGPT may help summarize the preponderance of evidence in the field to identify gaps in knowledge and promote cross-disciplinary collaboration.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A Unified Framework for Systematic Curation and Evaluation of Aging Biomarkers

Aging biomarkers are essential for understanding and quantifying the aging process and developing targeted longevity interventions. However, validation of these tools has been hindered by the lack of standardized approaches for cross-population validation, disparate biomarker designs, and inconsistencies in dataset structures. To address these challenges, we developed Biolearn, an open-source library that provides a unified framework for the curation, harmonization, and systematic evaluation of aging biomarkers. Leveraging Biolearn, we conducted a comprehensive evaluation of various aging biomarkers across multiple datasets. Our systematic approach involved three key steps: (1) harmonizing existing and novel aging biomarkers in standardized formats; (2) unifying public datasets to ensure coherent structuring and formatting; and (3) applying computational methodologies to assess the harmonized biomarkers against the unified datasets. This evaluation yielded valuable insights into the performance, robustness, and generalizability of aging biomarkers across different populations and datasets. The Biolearn python library, which forms the foundation of this systematic evaluation, is freely available at https://Bio-Learn.github.io. Our work establishes a unified framework for the curation and evaluation of aging biomarkers, paving the way for more efficient and effective clinical validation and application in the field of longevity research.

International consensus on fasting terminology

Although fasting is increasingly applied for disease prevention and treatment, consensus on terminology is lacking. Using Delphi methodology, an international, multidisciplinary panel of researchers and clinicians standardized definitions of various fasting approaches in humans. Five online surveys and a live online conference were conducted with 38 experts, 25 of whom completed all 5 surveys. Consensus was achieved for the following terms: “fasting” (voluntary abstinence from some or all foods or foods and beverages), “modified fasting” (restriction of energy intake to max. 25% of energy needs), “fluid-only fasting,” “alternate-day fasting,” “short-term fasting” (lasting 2–3 days), “prolonged fasting” (≥4 consecutive days), and “religious fasting.” “Intermittent fasting” (repetitive fasting periods lasting ≤48 h), “time-restricted eating,” and “fasting-mimicking diet” were discussed most. This study provides expert recommendations on fasting terminology for future research and clinical applications, facilitating communication and cross-referencing in the field.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Resolving the current controversy of use and reuse of housekeeping proteins in ageing research: Focus on saving people's tax dollars

The use of housekeeping genes and proteins to normalize mRNA and protein levels in biomedical research has faced growing scrutiny. Researchers encounter challenges in determining the optimal frequency for running housekeeping proteins such as β-actin, Tubulin, and GAPDH for nuclear-encoded proteins, and Porin, HSP60, and TOM20 for mitochondrial proteins alongside experimental proteins. The regulation of these proteins varies with age, gender, disease progression, epitope nature, gel running conditions, and their reported sizes can differ among antibody suppliers. Additionally, anonymous readers have raised concerns about peer-reviewed and published articles, creating confusion and concern within the research and academic institutions. To clarify these matters, this minireview discusses the role of reference housekeeping proteins in Western blot analysis and outlines key considerations for their use as normalization controls. Instead of Western blotting of housekeeping proteins, staining of total proteins, using Amido Black and Coomassie Blue can be visualized the total protein content on a membrane. The reducing repeated Western blotting analysis of housekeeping proteins, will save resources, time and efforts and in turn increase the number of competitive grants from NIH and funding agencies. We also discussed the use of dot blots over traditional Western blots, when protein levels are low in rare tissues/specimens and cell lines. We sincerely hope that the facts, figures, and discussions presented in this article will clarify the current controversy regarding housekeeping protein(s) use, reuse, and functional aspects of housekeeping proteins. The contents presented in our article will be useful to students, scholars and researchers of all levels in cell biology, protein chemistry and mitochondrial research.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Strategies for modeling aging and age-related diseases

D. Jothi & Linda Anna Michelle Kulka

The ability to reprogram patient-derived-somatic cells to IPSCs (Induced Pluripotent Stem Cells) has led to a better understanding of aging and age-related diseases like Parkinson's, and Alzheimer's. The established patient-derived disease models mimic disease pathology and can be used to design drugs for aging and age-related diseases. However, the age and genetic mutations of the donor cells, the employed reprogramming, and the differentiation protocol might often pose challenges in establishing an appropriate disease model. In this review, we will focus on the various strategies for the successful reprogramming and differentiation of patient-derived cells to disease models for aging and age-related diseases, emphasizing the accuracy in the recapitulation of disease pathology and ways to overcome the limitations of its potential application in cell replacement therapy and drug development.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The bottlenose dolphin (*Tursiops truncatus*): A novel model for studying healthy arterial aging

Endothelial function declines with aging and independently predicts future cardiovascular disease (CVD) events. Diving also impairs endothelial function in humans. Yet, dolphins, being long-lived mammals adapted to diving, undergo repetitive cycles of tissue hypoxia-reoxygenation and disturbed shear stress without manifesting any apparent detrimental effects, as CVD is essentially nonexistent in these animals. Thus, dolphins may be a unique model of healthy arterial aging and may provide insights into strategies for clinical medicine. Emerging evidence shows that the circulating milieu (bioactive factors in the blood) is at least partially responsible for transducing reductions in age-related endothelial function. To assess if dolphins have preserved endothelial function with aging due to a protected circulating milieu, we tested if the serum (pool of the circulating milieu) of bottlenose dolphins (*Tursiops truncatus*) induces the same arterial aging phenotype as the serum of age-equivalent humans. We incubated conduit arteries from young and old mice with dolphin and human serum and measured endothelial function *ex vivo* via endothelium-dependent dilation to acetylcholine. While young arteries incubated with serum from mid-life/older adult human serum had lower endothelial function, those incubated with dolphin serum consistently maintained high endothelial function regardless the age of the donor. Thus, studying the arterial health of dolphins could lead to potential novel therapeutic strategies to improve age-related endothelial dysfunction in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Neural ageing and synaptic plasticity: prioritizing brain health in healthy longevity

Ageing is characterized by a gradual decline in the efficiency of physiological functions and increased vulnerability to diseases. Ageing affects the entire body, including physical, mental, and social well-being, but its impact on the brain and cognition can have a particularly significant effect on an individual's overall quality of life. Therefore, enhancing lifespan and physical health in longevity studies will be incomplete if cognitive ageing is over looked. Promoting successful cognitive ageing encompasses the objectives of mitigating cognitive decline, as well as simultaneously enhancing brain function and cognitive reserve. Studies in both humans and animal models indicate that cognitive decline related to normal ageing and age-associated brain disorders are more likely linked to changes in synaptic connections that form the basis of learning and memory. This activity-dependent synaptic plasticity reorganises the structure and function of neurons not only to adapt to new environments, but also to remain robust and stable over time. Therefore, understanding the neural mechanisms that are responsible for age-related cognitive decline becomes increasingly important. In this review, we explore the multifaceted aspects of healthy brain ageing with emphasis on synaptic plasticity, its adaptive mechanisms and the various factors affecting the decline in cognitive functions during ageing. We will also explore the dynamic brain and neuroplasticity, and the role of lifestyle in shaping neuronal plasticity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A multiomic atlas of the aging hippocampus reveals molecular changes in response to environmental enrichment

Aging involves the deterioration of organismal function, leading to the emergence of multiple pathologies. Environmental stimuli, including lifestyle, can influence the trajectory of this process and may be used as tools in the pursuit of healthy aging. To evaluate the role of epigenetic mechanisms in this context, we have generated bulk tissue and single cell multi-omic maps of the male mouse dorsal hippocampus in young and old animals exposed to environmental stimulation in the form of enriched environments. We present a molecular atlas of the aging process, highlighting two distinct axes, related to inflammation and to the dysregulation of mRNA metabolism, at the functional RNA and protein level. Additionally, we report the alteration of heterochromatin domains, including the loss of bivalent chromatin and the uncovering of a heterochromatin-switch phenomenon whereby constitutive heterochromatin loss is partially mitigated through gains in facultative heterochromatin. Notably, we observed the multi-omic reversal of a great number of aging-associated alterations in the context of environmental enrichment, which was particularly linked to glial and oligodendrocyte pathways. In conclusion, our work describes the epigenomic landscape of environmental stimulation in the context of aging and reveals how lifestyle intervention can lead to the multi-layered reversal of aging-associated decline.

Unraveling the complexity of human brain: Structure, function in healthy and disease states

The human brain stands as an intricate organ, embodying a nexus of structure, function, development, and diversity. This review delves into the multifaceted landscape of the brain, spanning its anatomical intricacies, diverse functional capacities, dynamic developmental trajectories, and inherent variability across individuals. The dynamic process of brain development, from early embryonic stages to adulthood, highlights the nuanced changes that occur throughout the lifespan. The brain, a remarkably complex organ, is composed of various anatomical regions, each contributing uniquely to its overall functionality. Through an exploration of neuroanatomy, neurophysiology, and electrophysiology, this review elucidates how different brain structures interact to support a wide array of cognitive processes, sensory perception, motor control, and emotional regulation. Moreover, it addresses the impact of age, sex, and ethnic background on brain structure and function, and gender differences profoundly influence the onset, progression, and manifestation of brain disorders shaped by genetic, hormonal, environmental, and social factors. Delving into the complexities of the human brain, it investigates how variations in anatomical configuration correspond to diverse functional capacities across individuals. Furthermore, it examines the impact of neurodegenerative diseases on the structural and functional integrity of the brain. Specifically, our article explores the pathological processes underlying neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases, shedding light on the structural alterations and functional impairments that accompany these conditions. We will also explore the current research trends in neurodegenerative diseases and identify the existing gaps in the literature. Overall, this article deepens our understanding of the fundamental principles governing brain structure and function and paves the way for a deeper understanding of individual differences and tailored approaches in neuroscience and clinical practice—additionally, a comprehensive understanding of structural and functional changes that manifest in neurodegenerative diseases.

Toward Systemic Lipofuscin Removal

Author: Michael Renteln | AUTHORS INFO & AFFILIATIONS

Lipofuscin is indigestible garbage that accumulates in the autophagic vesicles and cytosol of postmitotic cells with age. Drs. Brunk and Terman postulated that lipofuscin accumulation is the main or at least a major driving factor in aging. They even posited that the evolution of memory is the reason why we get lipofuscin at all, as stable synaptic connections must be maintained over time, meaning that the somas of neurons must also remain in the same locale. In other words, they cannot dilute out their garbage over time through cell division. Mechanistically, their position certainly makes sense given that rendering a large percentage of a postmitotic cell's lysosomes useless must almost certainly negatively affect that cell and the surrounding microenvironment. It may be the case that lipofuscin accumulation is the main issue with regard to current age-related disease. Degradation *in situ* may be an insurmountable task currently. However, a method of systemic lipofuscin removal is discussed herein.

Map of epigenetic age acceleration: A worldwide analysis

Igor Yusipov [a b 1], Alena Kalyakulina [a b], Arseniy Trukhanov [c], Claudio Franceschi [b], Mikhail Ivanchenko [a b]

We present a systematic analysis of epigenetic age acceleration based on by far the largest collection of publicly available DNA methylation data for healthy samples (93 datasets, 23 K samples), focusing on the geographic (25 countries) and ethnic (31 ethnicities) aspects around the world. We employed the most popular epigenetic tools for assessing age acceleration and examined their quality metrics and ability to extrapolate to epigenetic data from different tissue types and age ranges different from the training data of these models. In most cases, the models proved to be inconsistent with each other and showed different signs of age acceleration, with the PhenoAge model tending to systematically underestimate and different versions of the GrimAge model tending to systematically overestimate the age prediction of healthy subjects. Referring to data availability and consistency, most countries and populations are still not represented in GEO, moreover, different datasets use different criteria for determining healthy controls. Because of this, it is difficult to fully isolate the contribution of "geography/environment", "ethnicity" and "healthiness" to epigenetic age acceleration. Among the explored metrics, only the DunedinPACE, which measures aging rate, appears to adequately reflect the standard of living and socioeconomic indicators in countries, although it has a limited application to blood methylation data only. Invariably, by epigenetic age acceleration, males age faster than females in most of the studied countries and populations.

Towards Healthy Longevity: Comprehensive Insights from Molecular Targets and Biomarkers to Biological Clocks

by Khalishah Yusri [1,2,†], Sanjay Kumar [1,2,†], Sheng Fong [3,4], Jan Gruber [1,2,5] and Vincenzo Sorrentino [1,2,6,*]

Aging is a complex and time-dependent decline in physiological function that affects most organisms, leading to increased risk of age-related diseases. Investigating the molecular underpinnings of aging is crucial to identify geroprotectors, precisely quantify biological age, and propose healthy longevity approaches. This review explores pathways that are currently being investigated as intervention targets and aging biomarkers spanning molecular, cellular, and systemic dimensions. Interventions that target these hallmarks may ameliorate the aging process, with some progressing to clinical trials. Biomarkers of these hallmarks are used to estimate biological aging and risk of aging-associated disease. Utilizing aging biomarkers, biological aging clocks can be constructed that predict a state of abnormal aging, age-related diseases, and increased mortality. Biological age estimation can therefore provide the basis for a fine-grained risk stratification by predicting all-cause mortality well ahead of the onset of specific diseases, thus offering a window for intervention. Yet, despite technological advancements, challenges persist due to individual variability and the dynamic nature of these biomarkers. Addressing this requires longitudinal studies for robust biomarker identification. Overall, utilizing the hallmarks of aging to discover new drug targets and develop new biomarkers opens new frontiers in medicine. Prospects involve multi-omics integration, machine learning, and personalized approaches for targeted interventions, promising a healthier aging population.

Heales
HEALTHY LIFE EXTENSION SOCIETY

From Genesis to Old Age: Exploring the Immune System One Cell at a Time with Flow Cytometry

by **Anis Larbi** [1,2]

The immune system is a highly complex and tightly regulated system that plays a crucial role in protecting the body against external threats, such as pathogens, and internal abnormalities, like cancer cells. It undergoes development during fetal stages and continuously learns from each encounter with pathogens, allowing it to develop immunological memory and provide a wide range of immune protection. Over time, after numerous encounters and years of functioning, the immune system can begin to show signs of erosion, which is commonly named immunosenescence. In this review, we aim to explore how the immune system responds to initial encounters with antigens and how it handles persistent stimulations throughout a person's lifetime. Our understanding of the immune system has greatly benefited from advanced technologies like flow cytometry. In this context, we will discuss the valuable contribution of flow cytometry in enhancing our knowledge of the immune system behavior in aging, with a specific focus on T-cells. Moreover, we will expand our discussion to the flow cytometry-based assessment of extracellular vesicles, a recently discovered communication channel in biology, and their implications for immune system functioning.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging of the eye: Lessons from cataracts and age-related macular degeneration

Ales Cvekl, Jan Vijg

Aging is the greatest risk factor for chronic human diseases, including many eye diseases. Geroscience aims to understand the effects of the aging process on these diseases, including the genetic, molecular, and cellular mechanisms that underlie the increased risk of disease over the lifetime. Understanding of the aging eye increases general knowledge of the cellular physiology impacted by aging processes at various biological extremes. Two major diseases, age-related cataract and age-related macular degeneration (AMD) are caused by dysfunction of the lens and retina, respectively. Lens transparency and light refraction are mediated by lens fiber cells lacking nuclei and other organelles, which provides a unique opportunity to study a single aging hallmark, i.e., loss of proteostasis, within an environment of limited metabolism. In AMD, local dysfunction of the photoreceptors/retinal pigmented epithelium/Bruch's membrane/choriocapillaris complex in the macula leads to the loss of photoreceptors and eventually loss of central vision, and is driven by nearly all the hallmarks of aging and shares features with Alzheimer's disease, Parkinson's disease, cardiovascular disease, and diabetes. The aging eye can function as a model for studying basic mechanisms of aging and, vice versa, well-defined hallmarks of aging can be used as tools to understand age-related eye disease.

Age-Associated Calcification: Insights from Murine Models

by Sonia Nasi [1,*], Mario Romani [2] and Nathalie Busso [1]

Calcification refers to the deposition of calcium-containing crystals either intracellularly or within the extracellular matrix. Physiologic calcification is a normal process occurring during bone and tooth development and growth. In contrast, pathologic calcification occurs in soft tissues that typically do not undergo mineralization, such as blood vessels, cartilage, tendons, and skin. Pathological calcification is significantly associated with tissue impairment and the development of secondary diseases, such as atherosclerosis, osteoarthritis, tendinopathy, and skin ulcers. Aging, a natural process linked to numerous pathologic conditions, is one of the most recognized risk factors for pathological calcification. In this manuscript, we review the current state of knowledge regarding the role of aging in calcification across different tissues. We focus on the mechanisms activated during normal aging, including cellular senescence, decreased pyrophosphate levels, increased secretion of extracellular vesicles, elevated oxidative stress, and higher levels of pro-mineralizing cytokines, all of which can contribute to pathological calcification. Finally, we discuss the available animal models used to study the impact of aging on calcification.

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

A petavoxel fragment of human cerebral cortex reconstructed at nanoscale resolution

To fully understand how the human brain works, knowledge of its structure at high resolution is needed. Presented here is a computationally intensive reconstruction of the ultrastructure of a cubic millimeter of human temporal cortex that was surgically removed to gain access to an underlying epileptic focus. It contains about 57,000 cells, about 230 millimeters of blood vessels, and about 150 million synapses and comprises 1.4 petabytes. Our analysis showed that glia outnumber neurons 2:1, oligodendrocytes were the most common cell, deep layer excitatory neurons could be classified on the basis of dendritic orientation, and among thousands of weak connections to each neuron, there exist rare powerful axonal inputs of up to 50 synapses. Further studies using this resource may bring valuable insights into the mysteries of the human brain.