Heales

HEALTHY LIFE EXTENSION SOCIETY

Scientific News
6th of January 2024
Sven Bulterijs

Business/Conferences/ General news

Heales
HEALTHY LIFE EXTENSION SOCIETY

Heales
HEALTHY LIFE EXTENSION SOCIETY

120 wordt het nieuwe 80: “Als het werkt bij de muis, misschien dan ook bij de mens?”

© Shutterstock

“Een goede gezondheid.” Geen nieuwjaarswens zonder die drie woorden. Want dat wil iedereen: gezond blijven, zo lang mogelijk. Maar is ouderdom onvermijdelijk, of een ziekte die je kunt genezen? Het is een vraag die ook wetenschappers bezighoudt. Muizen en wormen helpen hen. En ervaringsdeskundigen helpen ons.

120 wordt het nieuwe 80

"Misschien word ik wel duizend jaar." De uitspraak leverde de Vlaamse dokter Herman Le Compte naast eeuwige roem ook een stevige schorsing op door wat hij de "Horde van Geneesheren" noemde. Dat Le Compte in 2008 op 78-jarige leeftijd overleed aan een hartafwijking, was een tegenvaller. De man was ervan overtuigd dat we "de mens tot in het oneindige gezond kunnen houden" dankzij stamcellen "die ieder orgaan kunnen herstellen".

Velen dachten dat Le Compte een fantast was. Het hielp ook niet dat de dokter vaak met zijn imitator Chris Van den Durpel in talkshows en spelletjes ging zitten. Maar dat cel-en gentherapie ons kunnen helpen om langer gezond te leven, was geen fabeltje. Meer nog: vijftien jaar na de dood van Le Compte, is *longevity*-Engels voor levensduur – een tak van de wetenschap waar spectaculaire resultaten worden verwacht. Dat is nodig, want onze gezonde levensjaren stijgen niet even snel als onze levensjaren. In 2050 zal een derde van onze bevolking ouder zijn dan 65. Als we mensen langer gezond kunnen laten leven, is dat goed voor de economie én voor de gezondheidszorg.

150 jaar

Een van die wetenschappers die ons langer gezond willen houden, is verouderingsfysioloog Sven Bulterijs. Hij maakt deel uit van GRAY (Ghent University Research for Aging Young), een groep knappe koppen die werken aan "het boosten van gezond verouderen".

Bulterijs kan een lach niet onderdrukken wanneer we hem vragen of het klopt dat er nu al baby's geboren zijn die 150 zullen worden. "Het is alsof je aan een architect vraagt wanneer het eerste gebouw van een kilometer hoog gebouwd zal worden (*het hoogste gebouw is voorlopig de Burj Khalifa in Dubai, met 828 meter, red.*). Die vraag hangt af van het feit of wereld de visie, het doorzettingsvermogen en het geld zal hebben om zo'n wolkenkrabber te bouwen. Om dezelfde reden is het volgens mij mogelijk om onze levensduur ver boven de huidige levensduur te krijgen, afhankelijk van veel factoren, zoals geld voor onderzoek."

De kruistocht tegen veroudering is zo heilig geworden dat er prijzengeld wordt uitgereikt aan onderzoekers die stenen verleggen in de poel van de levensduur. Zo is de ietwat excentrieke maar briljante Britse biochemicus Aubrey de Grey de man achter de Methuselah Muis Prijs, genoemd naar de grootvader van Noah, die volgens de Bijbel 969 kaarsjes mocht uitblazen. De prijs is miljoenen dollars waard en wordt sinds 2003 uitgereikt aan onderzoekers die het leven van een muis zo lang mogelijk verlengen en de meest succesvolle strategie om te verjongen ontwikkelen.

"Van de worm kunnen we de levensduur vertienvoudigen. Misschien werkt zo'n interventie dan ook bij de mens"

SVEN BULTERIJS
VEROUDERINGSFYSIOLOOG

De eerste om de prijs te winnen, was de Amerikaan Andrzej Bartke, die een dwergmuis genetisch zo manipuleerde dat het dier pas na vier jaar, elf maanden en drie weken het loodje legde. Dat is bijna dubbel zo lang als gemiddeld. Volgens verouderingsfysioloog Bulterijs mogen we die prestatie niet onderschatten. "De muis is niet het enige dier waarvan we de levensduur aanzienlijk kunnen verlengen. Ik werk zelf op de worm, en daar kunnen we de levensduur vertienvoudigen. We zien dat onze interventies (*ingrepen van de mens, red.*) bij meer dan één soort proefdier de levensduur verlengen. Misschien werkt zo'n interventie dan ook bij de mens."

Genetisch identiek

Het voordeel van wormen is dat ze genetisch identiek zijn. je zou ze kunnen vergelijken met klonen, omdat ze zichzelf bevruchten en dus geen moeder en vader hebben. "Zet die wormen in dezelfde omgeving met dezelfde temperatuur en dezelfde voeding, en je stelt vast dat de ene worm langer leeft dan de andere, ook al is hijzu identiek. Wetenschap-

"Een goede gezondheid." Geen nieuwjaarswens zonder die drie woorden. Want dat wil iedereen: gezond blijven, zo lang mogelijk. Maar: **is ouderdom onvermijdelijk, of een ziekte die je kunt genezen?** Het is een vraag die ook wetenschappers bezighoudt. Muizen en wormen helpen hen. En ervaringsdeskundigen helpen ons.

TEKST: TOM DE CEUR

Jeanne wil nog minstens 105 worden. "Tenzij ik begin te sukkelen."

Jeanne blaast 101 kaarsjes uit: "Ik heb de hartslag van Eddy Merckx"

Vandaag, 6 januari, wordt Jeanne Van de Velde uit Kermt 101. Haar huis mogen ze niet versieren, "want dat trekt inbrekers aan".

Je leest het goed: deze 101-jarige woont nog thuis. In haar eentje, al komt de buurvrouw elke dag langs en hoeft ze niet meer te koken. Jeanne – Jeanneke voor de vrienden – heeft het niet voor woonzorgcentra. "Ik heb er een paar weken gezeten. Ik was gestruikeld over een stuk speelgoed van het kindje van de buren. Pols gebroken. Ziekenhuis in en dan naar dat rusthuis. Ik kon er niet rap genoeg weg zijn."

Was het dankzij geluk dat Jeanne de honderd haalde? Genen zullen wel meegespeeld hebben. Eén zus werd 96, de andere leeft nog en schurkt tegen de 90 aan. Wat met haar levensstijl? We kunnen niet zeggen dat Jeanne zich heeft kapot gewerkt: haar man Frans was rijkswachter. "Als vrouw van een rijkswachter mocht ik niet werken. zelfs niet poetsen." Gerookt heeft ze nooit, veel alcohol heeft ze nooit gedronken. Voor dit gesprek schenkt Jeanne zichzelf wel een glaasje advocaat in met de woorden: "antier, aantje, aantaater; ik drink liever bier dan water."

Slapen doet Jeanne niet voor twee uur 's nachts, opstaan niet voor elf uur. Ze geeft toe dat ze veel tv kijkt. Af en toe een seksfilm, zegt ze. Of dat niet wat te veel gevraagd is van haar hart? "Nee. Ik heb in rust een heel lage hartslag. Zoals Eddy Merckx."

Hoe ze het dan zo lang volhoudt? Het valt wel op dat Jeanne vaak lacht. En ze komt nog altijd onder de mensen. Ze gooit haar armen in de lucht en begint heen en weer te zwaaien: "Ik ben veel op gank. Ik ga dansen in zaal Mimosa in Zonhoven. En elke week komen er mensen bij mij thuis kaarten."

Jeanne wil nog minstens 105 worden. "Tenzij ik begin te sukkelen. Dan hoeft het voor mij niet meer."

Onze geldexpert Pascal Paepen geeft tips om een pensioenschok te vermijden. © Getty Images / Sofie Silbermann

Belgen blijven afhankelijk van wettelijk pensioen. Onze expert waarschuwt: “Denk niet dat de overheid je een goede oude dag bezorgt”

Interview with Dr Mehmood Khan

Victor Björk
Business Development Professional | Longevity Biotech

24 articles ✓ Following

December 6, 2023

Heales
HEALTHY LIFE EXTENSION SOCIETY

DIY Intervention Testing in Daphnia

CA Cora Anderson RJ Rachael A Jonas-Closs BM Benyamin Matei-Dediu ED Edouard Debonneuil
LP Leon Peshkin

Last updated date: Dec 28, 2023 DOI: 10.21769/p2542 Views: 533 Forks: 0

Abstract. *This guide is for amateur science enthusiasts who are looking to conduct safe and easy animal experiments at home. This can be done with the aim of educating yourself and others about ecology, aquaculture, and pharmaco-biology. Additionally, by using a safe and accessible organism, you could contribute effort and data to the community science movement. We provide accessible ways for obtaining Daphnia, keeping daphnids at home, conducting experiments, troubleshooting, recording parameters of health and lifespan, and reporting the results. You will be able to begin immediately and build up gradually. A typical experiment might take 4-8 hours a week and last 1-2 months. The basic setup cost is around $50, depending on how food and equipment are sourced. We strongly encourage the reader to contact us with any suggestions and feedback to help further improve and develop this guide.*

Heales
HEALTHY LIFE EXTENSION SOCIETY

Diagnostic Accuracy of a Large Language Model in Pediatric Case Studies

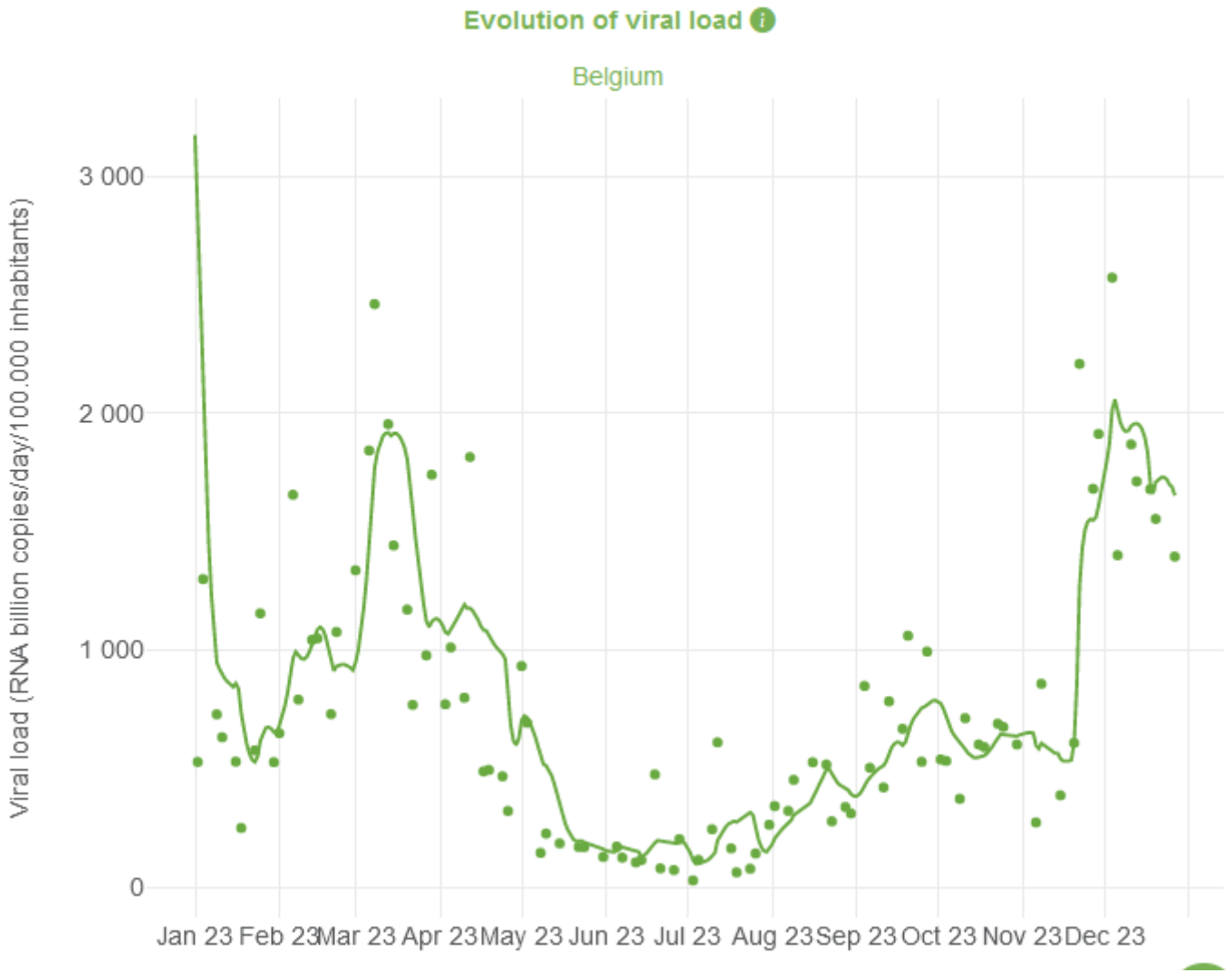
Joseph Barile, BA[1]; Alex Margolis[1]; Grace Cason[1]; et al

The capacity of large language models (LLMs) to process information and provide users with insights from vast amounts of data makes the technology well suited for algorithmic problem-solving. A recent study[1] investigated the diagnostic accuracy of ChatGPT version 4 and found that the artificial intelligence (AI) chatbot rendered a correct diagnosis in 39% of *New England Journal of Medicine* (*NEJM*) case challenges. This suggests LLM-based chatbots could be used as a supplementary tool for clinicians in diagnosing and developing a differential list for complex cases. To our knowledge, no research has explored the accuracy of LLM-based chatbots in solely pediatric scenarios, which require the consideration of the patient's age alongside symptoms. We assessed this accuracy across *JAMA Pediatrics* and *NEJM* pediatric case challenges.

ChatGPT version 3.5 gave a correct diagnosis in only 17% of cases (plus 11% were clinically related but too broad to be considered a correct diagnosis).

Heales
HEALTHY LIFE EXTENSION SOCIETY

Corona in Belgium



Aging research articles

HALD, a human aging and longevity knowledge graph for precision gerontology and geroscience analyses

Zexu Wu, Cong Feng, Yanshi Hu, Yincong Zhou, Sida Li, Shilong Zhang, Yueming Hu, Yuhao Chen, Haoyu Chao, Qingyang Ni & Ming Chen

Human aging is a natural and inevitable biological process that leads to an increased risk of aging-related diseases. Developing anti-aging therapies for aging-related diseases requires a comprehensive understanding of the mechanisms and effects of aging and longevity from a multi-modal and multi-faceted perspective. However, most of the relevant knowledge is scattered in the biomedical literature, the volume of which reached 36 million in PubMed. Here, we presented HALD, a text mining-based human aging and longevity dataset of the biomedical knowledge graph from all published literature related to human aging and longevity in PubMed. HALD integrated multiple state-of-the-art natural language processing (NLP) techniques to improve the accuracy and coverage of the knowledge graph for precision gerontology and geroscience analyses. Up to September 2023, HALD had contained 12,227 entities in 10 types (gene, RNA, protein, carbohydrate, lipid, peptide, pharmaceutical preparations, toxin, mutation, and disease), 115,522 relations, 1,855 aging biomarkers, and 525 longevity biomarkers from 339,918 biomedical articles in PubMed. HALD is available at https://bis.zju.edu.cn/hald.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Longitudinal machine learning uncouples healthy aging factors from chronic disease risks

Netta Mendelson Cohen, Aviezer Lifshitz, Rami Jaschek, Ehud Rinott, Ran Balicer, Liran I. Shlush, Gabriel I. Barbash & Amos Tanay

To understand human longevity, inherent aging processes must be distinguished from known etiologies leading to age-related chronic diseases. Such deconvolution is difficult to achieve because it requires tracking patients throughout their entire lives. Here, we used machine learning to infer health trajectories over the entire adulthood age range using extrapolation from electronic medical records with partial longitudinal coverage. Using this approach, our model tracked the state of patients who were healthy and free from known chronic disease risk and distinguished individuals with higher or lower longevity potential using a multivariate score. We showed that the model and the markers it uses performed consistently on data from Israeli, British and US populations. For example, mildly low neutrophil counts and alkaline phosphatase levels serve as early indicators of healthy aging that are independent of risk for major chronic diseases. We characterize the heritability and genetic associations of our longevity score and demonstrate at least 1 year of extended lifespan for parents of high-scoring patients compared to matched controls. Longitudinal modeling of healthy individuals is thereby established as a tool for understanding healthy aging and longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Astaxanthin and meclizine extend lifespan in UM-HET3 male mice; fisetin, SG1002 (hydrogen sulfide donor), dimethyl fumarate, mycophenolic acid, and 4-phenylbutyrate do not significantly affect lifespan in either sex at the doses and schedules used

In genetically heterogeneous (UM-HET3) mice produced by the CByB6F1 × C3D2F1 cross, the Nrf2 activator astaxanthin (Asta) extended the median male lifespan by 12% ($p = 0.003$, log-rank test), while meclizine (Mec), an mTORC1 inhibitor, extended the male lifespan by 8% ($p = 0.03$). Asta was fed at 1840 ± 520 (9) ppm and Mec at 544 ± 48 (9) ppm, stated as mean ± SE (n) of independent diet preparations. Both were started at 12 months of age. The 90th percentile lifespan for both treatments was extended in absolute value by 6% in males, but neither was significant by the Wang–Allison test. Five other new agents were also tested as follows: fisetin, SG1002 (hydrogen sulfide donor), dimethyl fumarate, mycophenolic acid, and 4-phenylbutyrate. None of these increased lifespan significantly at the dose and method of administration tested in either sex. Amounts of dimethyl fumarate in the diet averaged 35% of the target dose, which may explain the absence of lifespan effects. Body weight was not significantly affected in males by any of the test agents. Late life weights were lower in females fed Asta and Mec, but lifespan was not significantly affected in these females. The male-specific lifespan benefits from Asta and Mec may provide insights into sex-specific aspects of aging.

Sustained Vision Recovery by OSK Gene Therapy in a Mouse Model of Glaucoma

Glaucoma, a chronic neurodegenerative disease, is a leading cause of age-related blindness worldwide and characterized by the progressive loss of retinal ganglion cells (RGCs) and their axons. Previously, we developed a novel epigenetic rejuvenation therapy, based on the expression of the three transcription factors *Oct4*, *Sox2*, and *Klf4* (OSK), which safely rejuvenates RGCs without altering cell identity in glaucomatous and old mice after 1 month of treatment. In the current year-long study, mice with continuous or cyclic OSK expression induced after glaucoma-induced vision damage had occurred were tracked for efficacy, duration, and safety. Surprisingly, only 2 months of OSK fully restored impaired vision, with a restoration of vision for 11 months with prolonged expression. In RGCs, transcription from the doxycycline (DOX)-inducible Tet-On AAV system, returned to baseline 4 weeks after DOX withdrawal. Significant vision improvements remained for 1 month post switching off OSK, after which the vision benefit gradually diminished but remained better than baseline. Notably, no adverse effects on retinal structure or body weight were observed in glaucomatous mice with OSK continuously expressed for 21 months providing compelling evidence of efficacy and safety. This work highlights the tremendous therapeutic potential of rejuvenating gene therapies using OSK, not only for glaucoma but also for other ocular and systemic injuries and age-related diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Transcriptomic reprogramming screen identifies SRSF1 as rejuvenation factor

Alexandru M. Plesa, Sascha Jung, Helen H. Wang, Fawad Omar, Michael Shadpour, David Choy Buentello, Maria C. Perez-Matos, Naftali Horwitz, George Cai, Zhen-Kai Ngian, Carol V. de Magalhaes, Amy J. Wagers, William B. Mair, Antonio del Sol, George M. Church

Aging is a complex process that manifests through the time-dependent functional decline of a biological system. Age-related changes in epigenetic and transcriptomic profiles have been successfully used to measure the aging process[1,2]. Moreover, modulating gene regulatory networks through interventions such as the induction of the Yamanaka factors has been shown to reverse aging signatures and improve cell function[3,4]. However, this intervention has safety and efficacy limitations for *in vivo* rejuvenation[5,6], underscoring the need for identifying novel age reversal factors. Here, we discovered SRSF1 as a new rejuvenation factor that can improve cellular function *in vitro* and *in vivo*. Using a cDNA overexpression screen with a transcriptomic readout we identified that SRSF1 induction reprograms the cell transcriptome towards a younger state. Furthermore, we observed beneficial changes in senescence, proteasome function, collagen production, and ROS stress upon SRSF1 overexpression. Lastly, we showed that SRSF1 can improve wound healing *in vitro* and *in vivo* and is linked to organismal longevity. Our study provides a proof of concept for using transcriptomic reprogramming screens in the discovery of age reversal interventions and identifies SRSF1 as a promising target for cellular rejuvenation.

HDAC1/2 inhibitor therapy improves multiple organ systems in aged mice

Alessandra Tammaro [1 12], Eileen G. Daniels [2 3 12], Iman M. Hu [2 3 12], Kelly C. 't Hart [2 3 4 5], Kim Reid [6], Rio P. Juni [4 5], Loes M. Butter [1], Goutham Vasam [6], Rashmi Kamble [2], Aldo Jongejan [7], Richard I. Aviv [8 9], Joris J.T.H. Roelofs [1 10], Eleonora Aronica [11], Reinier A. Boon [4 5], Keir J. Menzies [6], Riekelt H. Houtkooper [2 3 5], Georges E. Janssens [2 3 13]

Aging increases the risk of age-related diseases, imposing substantial healthcare and personal costs. Targeting fundamental aging mechanisms pharmacologically can promote healthy aging and reduce this disease susceptibility. In this work, we employed transcriptome-based drug screening to identify compounds emulating transcriptional signatures of long-lived genetic interventions. We discovered compound 60 (Cmpd60), a selective histone deacetylase 1 and 2 (HDAC1/2) inhibitor, mimicking diverse longevity interventions. In extensive molecular, phenotypic, and bioinformatic assessments using various cell and aged mouse models, we found Cmpd60 treatment to improve age-related phenotypes in multiple organs. Cmpd60 reduces renal epithelial-mesenchymal transition and fibrosis in kidney, diminishes dementia-related gene expression in brain, and enhances cardiac contractility and relaxation for the heart. In sum, our two-week HDAC1/2 inhibitor treatment in aged mice establishes a multi-tissue, healthy aging intervention in mammals, holding promise for therapeutic translation to promote healthy aging in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Recapitulation of anti-aging phenotypes by global overexpression of PTEN in mice

ORIGINAL ARTICLE | Open access | Published: 19 December 2023

(2023) Cite this article

The PTEN gene negatively regulates the oncogenic PI3K-AKT pathway by encoding a lipid and protein phosphatase that dephosphorylates lipid phosphatidylinositol-3,4,5-triphosphate (PIP_3) resulting in the inhibition of PI3K and downstream inhibition of AKT. Overexpression of PTEN in mice leads to a longer lifespan compared to control littermates, although the mechanism is unknown. Here, we provide evidence that young adult PTENOE mice exhibit many characteristics shared by other slow-aging mouse models, including those with mutations that affect GH/IGF1 pathways, calorie-restricted mice, and mice treated with anti-aging drugs. PTENOE white adipose tissue (WAT) has increased UCP1, a protein linked to increased thermogenesis. WAT of PTENOE mice also shows a change in polarization of fat-associated macrophages, with elevated levels of arginase 1 (Arg1, characteristic of M2 macrophages) and decreased production of inducible nitric oxide synthase (iNOS, characteristic of M1 macrophages). Muscle and hippocampus showed increased expression of the myokine FNDC5, and higher levels of its cleavage product irisin in plasma, which has been linked to increased conversion of WAT to more thermogenic beige/brown adipose tissue. PTENOE mice also have an increase, in plasma and liver, of GPLD1, which is known to improve cognition in mice. Hippocampus of the PTENOE mice has elevation of both BDNF and DCX, indices of brain resilience and neurogenesis. These changes in fat, macrophages, liver, muscle, hippocampus, and plasma may be considered "aging rate indicators" in that they seem to be consistently changed across many of the long-lived mouse models and may help to extend lifespan by delaying many forms of late-life illness. Our new findings show that PTENOE mice can be added to the group of long-lived mice that share this multi-tissue suite of biochemical characteristics.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Sis2 regulates yeast replicative lifespan in a dose-dependent manner

Tolga T. Ölmez, David F. Moreno, Ping Liu, Zane M. Johnson, Madeline M. McGinnis, Benjamin P. Tu, Mark Hochstrasser & Murat Acar

Application of microfluidic platforms facilitated high-precision measurements of yeast replicative lifespan (RLS); however, comparative quantification of lifespan across strain libraries has been missing. Here we microfluidically measure the RLS of 307 yeast strains, each deleted for a single gene. Despite previous reports of extended lifespan in these strains, we found that 56% of them did not actually live longer than the wild-type; while the remaining 44% showed extended lifespans, the degree of extension was often different from what was previously reported. Deletion of *SIS2* gene led to the largest RLS increase observed. Sis2 regulated yeast lifespan in a dose-dependent manner, implying a role for the coenzyme A biosynthesis pathway in lifespan regulation. Introduction of the human PPCDC gene in the *sis2Δ* background neutralized the lifespan extension. RNA-seq experiments revealed transcriptional increases in cell-cycle machinery components in *sis2Δ* background. High-precision lifespan measurement will be essential to elucidate the gene network governing lifespan.

Enhancing autophagy or increasing longevity by administration of urolithins

US20230390238A1

United States

Download PDF | Find Prior Art | Similar

Inventor: Christopher L. Rinsch, William Blanco-Bose, Bernard Schneider, Laurent Mouchiround, Dongryeol Ryu, Penelope Andreux, Johan Auwerx

Current Assignee : Amazentis SA

Abstract

Disclosed are methods, compounds, and compositions useful for increasing autophagy and promoting longevity. The methods, compounds, and compositions relate to urolithins and urolithin precursors and use thereof. Certain urolithins are represented by Formula I, while certain urolithin precursors are represented by Formula IV. The urolithin may be urolithin A, urolithin B, urolithin C, or urolithin D. The urolithin precursor may be ellagic acid or an ellagitannin. The methods include in vivo, ex vivo, and in vitro uses of the compounds and compositions.

Downregulation of mitochondrial metabolism is a driver for fast skeletal muscle loss during mouse aging

Raquel Fernando, Anastasia V. Shindyapina, Mario Ost, Didac Santesmasses, Yan Hu, Alexander Tyshkovskiy, Sun Hee Yim, Jürgen Weiss, Vadim N. Gladyshev, Tilman Grune ✉ & José Pedro Castro

Skeletal muscle aging is characterized by the loss of muscle mass, strength and function, mainly attributed to the atrophy of glycolytic fibers. Underlying mechanisms driving the skeletal muscle functional impairment are yet to be elucidated. To unbiasedly uncover its molecular mechanisms, we recurred to gene expression and metabolite profiling in a glycolytic muscle, *Extensor digitorum longus* (EDL), from young and aged C57BL/6JRj mice. Employing multi-omics approaches we found that the main age-related changes are connected to mitochondria, exhibiting a downregulation in mitochondrial processes. Consistent is the altered mitochondrial morphology. We further compared our mouse EDL aging signature with human data from the GTEx database, reinforcing the idea that our model may recapitulate muscle loss in humans. We are able to show that age-related mitochondrial downregulation is likely to be detrimental, as gene expression signatures from commonly used lifespan extending interventions displayed the opposite direction compared to our EDL aging signature.

Skeletal muscle TFEB signaling promotes central nervous system function and reduces neuroinflammation during aging and neurodegenerative disease

Skeletal muscle has recently arisen as a regulator of central nervous system (CNS) function and aging, secreting bioactive molecules known as myokines with metabolism-modifying functions in targeted tissues, including the CNS. Here, we report the generation of a transgenic mouse with enhanced skeletal muscle lysosomal and mitochondrial function via targeted overexpression of transcription factor E-B (TFEB). We discovered that the resulting geroprotective effects in skeletal muscle reduce neuroinflammation and the accumulation of tau-associated pathological hallmarks in a mouse model of tauopathy. Muscle-specific TFEB overexpression significantly ameliorates proteotoxicity, reduces neuroinflammation, and promotes transcriptional remodeling of the aged CNS, preserving cognition and memory in aged mice. Our results implicate the maintenance of skeletal muscle function throughout aging in direct regulation of CNS health and disease and suggest that skeletal muscle originating factors may act as therapeutic targets against age-associated neurodegenerative disorders.

Gut inflammation associated with age and Alzheimer's disease pathology: a human cohort study

Age-related disease may be mediated by low levels of chronic inflammation ("inflammaging"). Recent work suggests that gut microbes can contribute to inflammation via degradation of the intestinal barrier. While aging and age-related diseases including Alzheimer's disease (AD) are linked to altered microbiome composition and higher levels of gut microbial components in systemic circulation, the role of intestinal inflammation remains unclear. To investigate whether greater gut inflammation is associated with advanced age and AD pathology, we assessed fecal samples from older adults to measure calprotectin, an established marker of intestinal inflammation which is elevated in diseases of gut barrier integrity. Multiple regression with maximum likelihood estimation and Satorra–Bentler corrections were used to test relationships between fecal calprotectin and clinical diagnosis, participant age, cerebrospinal fluid biomarkers of AD pathology, amyloid burden measured using ^{11}C-Pittsburgh compound B positron emission tomography (PiB PET) imaging, and performance on cognitive tests measuring executive function and verbal learning and recall. Calprotectin levels were elevated in advanced age and were higher in participants diagnosed with amyloid-confirmed AD dementia. Additionally, among individuals with AD dementia, higher calprotectin was associated with greater amyloid burden as measured with PiB PET. Exploratory analyses indicated that calprotectin levels were also associated with cerebrospinal fluid markers of AD, and with lower verbal memory function even among cognitively unimpaired participants. Taken together, these findings suggest that intestinal inflammation is linked with brain pathology even in the earliest disease stages. Moreover, intestinal inflammation may exacerbate the progression toward AD.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Follow this

Biolearn, an open-source library for biomarkers of aging

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

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

The CEPH aging cohort and biobank: a valuable collection of biological samples from exceptionally long-lived French individuals and their offspring for longevity studies

Alexandre How-Kit [1 2], Mourad Sahbatou [3], Lise M Hardy [3 4], Nicolas P Tessier [3 4], Valérie Schiavon [5], Hélène Le Buanec [5], Jean-Marc Sebaoun [6], Hélène Blanché [4 6], Jean-François Zagury [7], Jean-François Deleuze [8 9 10 11]

The increasing aging of the human population is currently and for the coming decades a major public health issue in many countries, requiring the implementation of global public health policies promoting healthy and successful aging. Individuals are not equal in the face of aging and some can present exceptional healthspan and/or lifespan, which are notably influenced by both genetic and environmental factors. Research and studies on human aging, healthy aging and longevity should rely in particular on cohorts of long-lived individuals, also including biological samples allowing studies on the biology of aging and longevity. In this manuscript, we provide for the first time a complete description of the CEPH (Centre d'Etude du Polymophisme Humain) Aging cohort, an exceptional cohort recruited during the 90s to 2000s, including more than 1700 French long-lived individuals (≥ 90 years old) born between 1875 and 1916 as well as for some of them their siblings and offspring. Among the participants, 1265 were centenarians, including 255 semi-supercentenarians ([105-110] years old) and 25 supercentenarians (≥ 110 years old). The available anthropometric, epidemiologic and clinical data for the cohort participants are described and especially the collection of blood-derived biological samples associated with the cohort which includes DNA, cryopreserved cells and cell lines, plasma, and serum. This biological collection from the first cohort of centenarians in the world is an inestimable resource for ongoing and future molecular, cellular, and functional studies aimed at deciphering the mechanisms of human (successful) aging and longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Genetic associations with longevity are on average stronger in females than in males

It is long observed that females tend to live longer than males in nearly every country. However, the underlying mechanism remains elusive. In this study, we discovered that genetic associations with longevity are on average stronger in females than in males through bio-demographic analyses of genome-wide association studies (GWAS) dataset of 2178 centenarians and 2299 middle-age controls of Chinese Longitudinal Healthy Longevity Study (CLHLS). This discovery is replicated across North and South regions of China, and is further confirmed by North-South discovery/replication analyses of different and independent datasets of Chinese healthy aging candidate genes with CLHLS participants who are not in CLHLS GWAS, including 2972 centenarians and 1992 middle-age controls. Our polygenic risk score analyses of eight exclusive groups of sex-specific genes, analyses of sex-specific and not-sex-specific individual genes, and Genome-wide Complex Trait Analysis using all SNPs all reconfirm that genetic associations with longevity are on average stronger in females than in males. Our discovery/replication analyses are based on genetic datasets of in total 5150 centenarians and compatible middle-age controls, which comprises the worldwide largest sample of centenarians. The present study's findings may partially explain the well-known male-female health-survival paradox and suggest that genetic variants may be associated with different reactions between males and females to the same vaccine, drug treatment and/or nutritional intervention. Thus, our findings provide evidence to steer away from traditional view that "one-size-fits-all" for clinical interventions, and to consider sex differences for improving healthcare efficiency. We suggest future investigations focusing on effects of interactions between sex-specific genetic variants and environment on longevity as well as biological function.

Heales
HEALTHY LIFE EXTENSION SOCIETY

An accurate aging clock developed from large-scale gut microbiome and human gene expression data

Vishakh Gopu • Francine R. Camacho • Ryan Toma • Pedro J. Torres • Ying Cai • Subha Krishnan • Sathyapriya Rajagopal • Hal Tily • Momchilo Vuyisich • Guruduth Banavar [2] • Show less •

Accurate measurement of the biological markers of the aging process could provide an “aging clock” measuring predicted longevity and enable the quantification of the effects of specific lifestyle choices on healthy aging. Using machine learning techniques, we demonstrate that chronological age can be predicted accurately from (1) the expression level of human genes in capillary blood and (2) the expression level of microbial genes in stool samples. The latter uses a very large metatranscriptomic dataset, stool samples from 90,303 individuals, which arguably results in a higher quality microbiome-aging model than prior work. Our analysis suggests associations between biological age and lifestyle/health factors, e.g., people on a paleo diet or with IBS tend to have higher model-predicted ages and people on a vegetarian diet tend to have lower model-predicted ages. We delineate the key pathways of systems-level biological decline based on the age-specific features of our model.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Deciphering the role of immune cell composition in epigenetic age acceleration: Insights from cell-type deconvolution applied to human blood epigenetic clocks

Ze Zhang, Samuel R. Reynolds, Hannah G. Stolrow, Ji-Qing Chen, Brock C. Christensen, Lucas A. Salas

Aging is a significant risk factor for various human disorders, and DNA methylation clocks have emerged as powerful tools for estimating biological age and predicting health-related outcomes. Methylation data from blood DNA has been a focus of more recently developed DNA methylation clocks. However, the impact of immune cell composition on epigenetic age acceleration (EAA) remains unclear as only some clocks incorporate partial cell type composition information when analyzing EAA. We investigated associations of 12 immune cell types measured by cell-type deconvolution with EAA predicted by six widely-used DNA methylation clocks in data from >10,000 blood samples. We observed significant associations of immune cell composition with EAA for all six clocks tested. Across the clocks, nine or more of the 12 cell types tested exhibited significant associations with EAA. Higher memory lymphocyte subtype proportions were associated with increased EAA, and naïve lymphocyte subtypes were associated with decreased EAA. To demonstrate the potential confounding of EAA by immune cell composition, we applied EAA in rheumatoid arthritis. Our research maps immune cell type contributions to EAA in human blood and offers opportunities to adjust for immune cell composition in EAA studies to a significantly more granular level. Understanding associations of EAA with immune profiles has implications for the interpretation of epigenetic age and its relevance in aging and disease research. Our detailed map of immune cell type contributions serves as a resource for studies utilizing epigenetic clocks across diverse research fields, including aging-related diseases, precision medicine, and therapeutic interventions.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

Longevity interventions modulate mechanotransduction and extracellular matrix homeostasis in *C. elegans*

Alina C. Teuscher, Cyril Statzer, Anita Goyala, Seraina A. Domenig, Ingmar Schoen, Max Hess, Alexander M. Hofer, Andrea Fossati, Viola Vogel, Orcun Goksel, Ruedi Aebersold & Collin Y. Ewald

Dysfunctional extracellular matrices (ECM) contribute to aging and disease. Repairing dysfunctional ECM could potentially prevent age-related pathologies. Interventions promoting longevity also impact ECM gene expression. However, the role of ECM composition changes in healthy aging remains unclear. Here we perform proteomics and in-vivo monitoring to systematically investigate ECM composition (matreotype) during aging in *C. elegans* revealing three distinct collagen dynamics. Longevity interventions slow age-related collagen stiffening and prolong the expression of collagens that are turned over. These prolonged collagen dynamics are mediated by a mechanical feedback loop of hemidesmosome-containing structures that span from the exoskeletal ECM through the hypodermis, basement membrane ECM, to the muscles, coupling mechanical forces to adjust ECM gene expression and longevity via the transcriptional co-activator YAP-1 across tissues. Our results provide in-vivo evidence that coordinated ECM remodeling through mechanotransduction is required and sufficient to promote longevity, offering potential avenues for interventions targeting ECM dynamics.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Single-worm quantitative proteomics reveals aging heterogeneity in isogenic *Caenorhabditis elegans*

Tian-Yi Zhu, Shang-Tong Li, Dan-Dan Liu, Xiajun Zhang, Lianqi Zhou, Rong Zhou ✉, Bing Yang ✉

The heterogeneity of aging has been investigated at cellular and organic levels in the mouse model and human, but the exploration of aging heterogeneity at whole-organism level is lacking. *C. elegans* is an ideal model organism for studying this question as they are self-fertilized and cultured in the same chamber. Despite the tremendous progress made in single-cell proteomic analysis, there is few single-worm proteomics studies about aging. Here, we apply single-worm quantitative mass spectrometry to quantify the heterogenous proteomic changes during aging across individuals, a total of 3524 proteins from 157 *C. eleagns* individuals were quantified. A reconstructed *C. elegans* aging trajectory and proteomic landscape of fast-aging individuals were used to analyze the heterogeneity of *C. elegans* aging. We characterized inter-individual proteomic variation during aging and revealed contributing factors that distinguish fast-aging individuals from their siblings.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Early life changes in histone landscape protect against age-associated amyloid toxicities through HSF-1-dependent regulation of lipid metabolism

Bryndon J. Oleson, Janakraj Bhattrai, Sarah L. Zalubas, Tessa R. Kravchenko, Yuanyuan Ji, Emily L. Jiang, Christine C. Lu, Ciara R. Madden, Julia G. Coffman, Daphne Bazopoulou, Jace W. Jones & Ursula Jakob

Transient events during development can exert long-lasting effects on organismal lifespan. Here we demonstrate that exposure of *Caenorhabditis elegans* to reactive oxygen species during development protects against amyloid-induced proteotoxicity later in life. We show that this protection is initiated by the inactivation of the redox-sensitive H3K4me3-depositing COMPASS complex and conferred by a substantial increase in the heat-shock-independent activity of heat shock factor 1 (HSF-1), a longevity factor known to act predominantly during *C. elegans* development. We show that depletion of HSF-1 leads to marked rearrangements of the organismal lipid landscape and a significant decrease in mitochondrial β-oxidation and that both lipid and metabolic changes contribute to the protective effects of HSF-1 against amyloid toxicity. Together, these findings link developmental changes in the histone landscape, HSF-1 activity and lipid metabolism to protection against age-associated amyloid toxicities later in life.

Heales
HEALTHY LIFE EXTENSION SOCIETY

SKN-1/NRF2 upregulation by vitamin A is conserved from nematodes to mammals and is critical for lifespan extension in *Caenorhabditis elegans*

Chaweewan Sirakawin, Dongfa Lin, Ziyue Zhou, Xiaoxin Wang, Rhianne Kelleher, Shangyuan Huang, Weimiao Long, Andre Pires-daSilva, Yu Liu, Jingjing Wang, Ilya A. Vinnikov

Vitamin A (VA) is a micronutrient essential for the physiology of many organisms, but its role in longevity and age-related diseases remains unclear. In this work, we used *Caenorhabditis elegans* to study the impact of various bioactive compounds on lifespan. We demonstrate that VA extends lifespan and reduces lipofuscin and fat accumulation while increasing resistance to heat and oxidative stress. This resistance can be attributed to high levels of detoxifying enzymes called glutathione S-transferases, induced by the transcription factor skinhead-1 (SKN-1). Notably, VA upregulated the transcript levels of *skn-1* or its mammalian ortholog *NRF2* in both *C. elegans*, human cells, and liver tissues of mice. Moreover, the loss-of-function genetic models demonstrated a critical involvement of the SKN-1 pathway in longevity extension by VA. Our study thus provides novel insights into the molecular mechanism of anti-aging and anti-oxidative effects of VA, suggesting that this micronutrient could be used for the prevention and/or treatment of age-related disorders.

Icariin Improves Stress Resistance and Extends Lifespan in *Caenorhabditis elegans* through *hsf-1* and *daf-2*-Driven Hormesis

by Monika N. Todorova [1], Martina S. Savova [1,2], Liliya V. Mihaylova [1,2] and Milen I. Georgiev [1,2,*]

Aging presents an increasingly significant challenge globally, driven by the growing proportion of individuals aged 60 and older. Currently, there is substantial research interest in pro-longevity interventions that target pivotal signaling pathways, aiming not only to extend lifespan but also to enhance healthspan. One particularly promising approach involves inducing a hormetic response through the utilization of natural compounds defined as hormetins. Various studies have introduced the flavonoid icariin as beneficial for age-related diseases such as cardiovascular and neurodegenerative conditions. To validate its potential pro-longevity properties, we employed *Caenorhabditis elegans* as an experimental platform. The accumulated results suggest that icariin extends the lifespan of *C. elegans* through modulation of the DAF-2, corresponding to the insulin/IGF-1 signaling pathway in humans. Additionally, we identified increased resistance to heat and oxidative stress, modulation of lipid metabolism, improved late-life healthspan, and an extended lifespan upon icariin treatment. Consequently, a model mechanism of action was provided for icariin that involves the modulation of various players within the stress-response network. Collectively, the obtained data reveal that icariin is a potential hormetic agent with geroprotective properties that merits future developments.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Technology Feature | Published: 02 January 2024

Aging research comes of age

Vivien Marx

Nature Methods (2024) | Cite this article

As money pours into aging research, the field can combine its many methods to home on what underpins aging. Approaches differ, but researchers share the desire to not overpromise quick-fix anti-aging methods.

Editorial

Leveraging AI to identify dual-purpose aging and disease targets

Geoffrey Ho Duen Leung, Chun Wai Wong, **Frank W. Pun**, Alex Aliper, Feng Ren & **Alex Zhavoronkov**

Received 18 Aug 2022, Accepted 22 Nov 2023, Published online: 01 Dec 2023

Heales
HEALTHY LIFE EXTENSION SOCIETY

ADVERTISEMENT FEATURE Advertiser retains sole responsibility for the content of this article

BioViva's CMV vector: a platform for better gene-therapy delivery

BioViva Science is a gene-therapy company focused on treating aging-related complex diseases with a new gene-therapy platform.

By BioViva Science

Heales
HEALTHY LIFE EXTENSION SOCIETY

The Information Theory of Aging

Yuancheng Ryan Lu, Xiao Tian & David A. Sinclair

Nature Aging **3**, 1486–1499 (2023) | Cite this article

Information storage and retrieval is essential for all life. In biology, information is primarily stored in two distinct ways: the genome, comprising nucleic acids, acts as a foundational blueprint and the epigenome, consisting of chemical modifications to DNA and histone proteins, regulates gene expression patterns and endows cells with specific identities and functions. Unlike the stable, digital nature of genetic information, epigenetic information is stored in a digital–analog format, susceptible to alterations induced by diverse environmental signals and cellular damage. The Information Theory of Aging (ITOA) states that the aging process is driven by the progressive loss of youthful epigenetic information, the retrieval of which via epigenetic reprogramming can improve the function of damaged and aged tissues by catalyzing age reversal.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mechanisms, pathways and strategies for rejuvenation through epigenetic reprogramming

Andrea Cipriano, Mahdi Moqri, Sun Y. Maybury-Lewis, Ryan Rogers-Hammond, Tineke Anna de Jong, Alexander Parker, Sajede Rasouli, Hans Robert Schöler, David A. Sinclair ✉ & Vittorio Sebastiano ✉

Nature Aging (2023) | Cite this article

Over the past decade, there has been a dramatic increase in efforts to ameliorate aging and the diseases it causes, with transient expression of nuclear reprogramming factors recently emerging as an intriguing approach. Expression of these factors, either systemically or in a tissue-specific manner, has been shown to combat age-related deterioration in mouse and human model systems at the cellular, tissue and organismal level. Here we discuss the current state of epigenetic rejuvenation strategies via partial reprogramming in both mouse and human models. For each classical reprogramming factor, we provide a brief description of its contribution to reprogramming and discuss additional factors or chemical strategies. We discuss what is known regarding chromatin remodeling and the molecular dynamics underlying rejuvenation, and, finally, we consider strategies to improve the practical uses of epigenetic reprogramming to treat aging and age-related diseases, focusing on the open questions and remaining challenges in this emerging field.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Epigenetic Clocks and Programmatic Aging

David Gems *, Roop Singh Virk, João Pedro de Magalhães

The last decade has seen remarkable progress in the characterization of methylation clocks that track biological age in humans and many other mammalian species. While the biological processes of aging that underlie these clocks have remained unclear, several clues have pointed to a link to developmental mechanisms. These include the presence in the vicinity of clock CpG sites of genes that specify development, including those of the Hox (homeobox) and polycomb classes. Here we discuss how recent advances in programmatic theories of aging provide a framework within which methylation clocks can be understood as part of a developmental process of aging. This includes how such clocks evolve, how developmental mechanisms cause aging, and how they give rise to late-life disease. The combination of ideas from evolutionary biology, biogerontology and developmental biology open a path to a new discipline, that of *developmental gerontology* (*devo-gero*). Drawing on the properties of methylation clocks, we offer several new hypotheses that exemplify devo-gero thinking. We suggest that polycomb controls a trade-off between earlier developmental fidelity and later developmental plasticity. We also propose the existence of an evolutionarily-conserved *developmental sequence* spanning ontogenesis, adult development and aging, that both constrains and determines the evolution of aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Chance, ignorance, and the paradoxes of cancer: Richard Peto on developing preventative strategies under uncertainty

During the early 1980s both cancer biology and epidemiological methods were being transformed. In 1984 the leading cancer epidemiologist Richard Peto – who, in 1981, had published the landmark *Causes of Cancer* with Richard Doll – wrote a short chapter on "The need for ignorance in cancer research", in which the worlds of epidemiology and speculative Darwinian biology met. His reflections on how evolutionary theory related to cancer have become known as "Peto's paradox", whilst his articulation of "black box epidemiology" provided the logic of subsequent practice in the field. We reprint this sparkling and prescient example of biologically-informed epidemiological theorising at its best in this issue of the *European Journal of Epidemiology*, together with four commentaries that focus on different aspects of its rich content. Here were provide some contextual background to the 1984 chapter, and our own speculations regarding various paradoxes in cancer epidemiology. We suggest that one reason for the relative lack of progress in indentifying novel modifiable causes of cancer over the last 40 years may reflect such exposures being ubiquitous within environments, and discuss the lessons for epidemiology that would follow from this.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

From Churchill to Elephants: The Role of Protective Genes Against Cancer

Annalisa Gazzellone and Eugenio Sangiorgi *

Richard Peto's Paradox, first described in 1975 from an epidemiological perspective, established an inverse correlation between the probability of developing cancer in multicellular organisms and the number of cells. Larger animals exhibit fewer tumors compared to smaller ones, though exceptions exist. Mice are more susceptible to cancer than humans, while elephants and whales demonstrate significantly lower cancer prevalence rates than humans. How nature and evolution have addressed the issue of cancer in the animal kingdom remains largely unexplored. In the field of medicine, much attention has been devoted to cancer predisposing genes, as they offer avenues for intervention, including blocking, downregulating, early diagnosis, and targeted treatment. Predisposing genes also tend to manifest clinically earlier and more aggressively, making them easier to identify. However, despite significant strides in modern medicine, the role of protective genes lags behind. Identifying genes with a mild predisposing effect poses a significant challenge. Consequently, comprehending the protective function conferred by genes becomes even more elusive, and their very existence is subject to questioning. While the role of variable expressivity and penetrance defects of the same variant in a family is well-documented for many hereditary cancer syndromes, attempts to delineate the function of protective/modifier alleles have been restricted to a few instances. In this review, we endeavor to elucidate the role of protective genes observed in the animal kingdom and within certain genetic syndromes that appear to act as cancer-resistant/repressor alleles. The ultimate goal is to discern why individuals, like Winston Churchill, managed to live up to 91 years of age, despite engaging in minimal physical activity, consuming large quantities of alcohol daily, and not abstaining from smoking.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging Hallmarks and Progression and Age-Related Diseases: A Landscape View of Research Advancement

Rumiana Tenchov, Janet M. Sasso, Xinmei Wang, and Qiongqiong Angela Zhou*

Aging is a dynamic, time-dependent process that is characterized by a gradual accumulation of cell damage. Continual functional decline in the intrinsic ability of living organisms to accurately regulate homeostasis leads to increased susceptibility and vulnerability to diseases. Many efforts have been put forth to understand and prevent the effects of aging. Thus, the major cellular and molecular hallmarks of aging have been identified, and their relationships to age-related diseases and malfunctions have been explored. Here, we use data from the CAS Content Collection to analyze the publication landscape of recent aging-related research. We review the advances in knowledge and delineate trends in research advancements on aging factors and attributes across time and geography. We also review the current concepts related to the major aging hallmarks on the molecular, cellular, and organismic level, age-associated diseases, with attention to brain aging and brain health, as well as the major biochemical processes associated with aging. Major age-related diseases have been outlined, and their correlations with the major aging features and attributes are explored. We hope this review will be helpful for apprehending the current knowledge in the field of aging mechanisms and progression, in an effort to further solve the remaining challenges and fulfill its potential.

Non-Genomic Hallmarks of Aging—The Review

by Drahomira Holmannova [1], Pavel Borsky [1,*], Helena Parova [2], Tereza Stverakova [2], Milan Vosmik [3], Libor Hruska [3], Zdenek Fiala [1] and Lenka Borska [1]

Aging is a natural, gradual, and inevitable process associated with a series of changes at the molecular, cellular, and tissue levels that can lead to an increased risk of many diseases, including cancer. The most significant changes at the genomic level (DNA damage, telomere shortening, epigenetic changes) and non-genomic changes are referred to as hallmarks of aging. The hallmarks of aging and cancer are intertwined. Many studies have focused on genomic hallmarks, but non-genomic hallmarks are also important and may additionally cause genomic damage and increase the expression of genomic hallmarks. Understanding the non-genomic hallmarks of aging and cancer, and how they are intertwined, may lead to the development of approaches that could influence these hallmarks and thus function not only to slow aging but also to prevent cancer. In this review, we focus on non-genomic changes. We discuss cell senescence, disruption of proteostasis, deregualation of nutrient sensing, dysregulation of immune system function, intercellular communication, mitochondrial dysfunction, stem cell exhaustion and dysbiosis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging and aging-related diseases: from molecular mechanisms to interventions and treatments

Jun Guo, Xiuqing Huang, Lin Dou, Mingjing Yan, Tao Shen, Weiqing Tang & Jian Li

Aging is a gradual and irreversible pathophysiological process. It presents with declines in tissue and cell functions and significant increases in the risks of various aging-related diseases, including neurodegenerative diseases, cardiovascular diseases, metabolic diseases, musculoskeletal diseases, and immune system diseases. Although the development of modern medicine has promoted human health and greatly extended life expectancy, with the aging of society, a variety of chronic diseases have gradually become the most important causes of disability and death in elderly individuals. Current research on aging focuses on elucidating how various endogenous and exogenous stresses (such as genomic instability, telomere dysfunction, epigenetic alterations, loss of proteostasis, compromise of autophagy, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, deregulated nutrient sensing) participate in the regulation of aging. Furthermore, thorough research on the pathogenesis of aging to identify interventions that promote health and longevity (such as caloric restriction, microbiota transplantation, and nutritional intervention) and clinical treatment methods for aging-related diseases (depletion of senescent cells, stem cell therapy, antioxidative and anti-inflammatory treatments, and hormone replacement therapy) could decrease the incidence and development of aging-related diseases and in turn promote healthy aging and longevity.

Age Is Just a Number: Progress and Obstacles in the Discovery of New Candidate Drugs for Sarcopenia

by Hyun-Jun Kim, Da-Woon Jung * and Darren Reece Williams *

Sarcopenia is a disease characterized by the progressive loss of skeletal muscle mass and function that occurs with aging. The progression of sarcopenia is correlated with the onset of physical disability, the inability to live independently, and increased mortality. Due to global increases in lifespan and demographic aging in developed countries, sarcopenia has become a major socioeconomic burden. Clinical therapies for sarcopenia are based on physical therapy and nutritional support, although these may suffer from low adherence and variable outcomes. There are currently no clinically approved drugs for sarcopenia. Consequently, there is a large amount of pre-clinical research focusing on discovering new candidate drugs and novel targets. In this review, recent progress in this research will be discussed, along with the challenges that may preclude successful translational research in the clinic. The types of drugs examined include mitochondria-targeting compounds, anti-diabetes agents, small molecules that target non-coding RNAs, protein therapeutics, natural products, and repositioning candidates. In light of the large number of drugs and targets being reported, it can be envisioned that clinically approved pharmaceuticals to prevent the progression or even mitigate sarcopenia may be within reach.

Cellular senescence in brain aging and neurodegeneration

LS Melo dos Santos [a d], M. Trombetta-Lima [b c], BJL Eggen [b], M. Demaria [a]

Cellular senescence is a state of terminal cell cycle arrest associated with various macromolecular changes and a hypersecretory phenotype. In the brain, senescent cells naturally accumulate during aging and at sites of age-related pathologies. Here, we discuss the recent advances in understanding the accumulation of senescent cells in brain aging and disorders. Here we highlight the phenotypical heterogeneity of different senescent brain cell types, highlighting the potential importance of subtype-specific features for physiology and pathology. We provide a comprehensive overview of various senescent cell types in naturally occurring aging and the most common neurodegenerative disorders. Finally, we critically discuss the potential of adapting senotherapeutics to improve brain health and reduce pathological progression, addressing limitations and future directions for application and development.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cellular senescence in skeletal disease: mechanisms and treatment

Xu He, Wei Hu, Yuanshu Zhang, Mimi Chen, Yicheng Ding, Huilin Yang, Fan He ✉, Qiaoli Gu ✉ & Qin Shi ✉

Cellular & Molecular Biology Letters **28**, Article number: 88 (2023) | Cite this article

Abstract

The musculoskeletal system supports the movement of the entire body and provides blood production while acting as an endocrine organ. With aging, the balance of bone homeostasis is disrupted, leading to bone loss and degenerative diseases, such as osteoporosis, osteoarthritis, and intervertebral disc degeneration. Skeletal diseases have a profound impact on the motor and cognitive abilities of the elderly, thus creating a major challenge for both global health and the economy. Cellular senescence is caused by various genotoxic stressors and results in permanent cell cycle arrest, which is considered to be the underlying mechanism of aging. During aging, senescent cells (SnCs) tend to aggregate in the bone and trigger chronic inflammation by releasing senescence-associated secretory phenotypic factors. Multiple signalling pathways are involved in regulating cellular senescence in bone and bone marrow microenvironments. Targeted SnCs alleviate age-related degenerative diseases. However, the association between senescence and age-related diseases remains unclear. This review summarises the fundamental role of senescence in age-related skeletal diseases, highlights the signalling pathways that mediate senescence, and discusses potential therapeutic strategies for targeting SnCs.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cellular senescence and kidney aging

Nikolai Rex [1], Anette Melk [2], Roland Schmitt [1 3]

Affiliations + expand

PMID: 38126209 PMCID: PMC10739085 DOI: 10.1042/CS20230140

Free PMC article

Abstract

Life expectancy is increasing worldwide, and by 2050 the proportion of the world's population over 65 years of age is estimated to surpass 1.5 billion. Kidney aging is associated with molecular and physiological changes that cause a loss of renal function and of regenerative potential. As the aging population grows, it is crucial to understand the mechanisms underlying these changes, as they increase the susceptibility to developing acute kidney injury (AKI) and chronic kidney disease (CKD). Various cellular processes and molecular pathways take part in the complex process of kidney aging. In this review, we will focus on the phenomenon of cellular senescence as one of the involved mechanisms at the crossroad of kidney aging, age-related disease, and CKD. We will highlight experimental and clinical findings about the role of cellular senescence in kidney aging and CKD. In addition, we will review challenges in senescence research and emerging therapeutic aspects. We will highlight the great potential of senolytic strategies for the elimination of harmful senescent cells to promote healthy kidney aging and to avoid age-related disease and CKD. This review aims to give insight into recent discoveries and future developments, providing a comprehensive overview of current knowledge on cellular senescence and anti-senescent therapies in the kidney field.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Geroprotector drugs and exercise: friends or foes on healthy longevity?

Christian J. Elliehausen, Rozalyn M. Anderson, Gary M. Diffee, Timothy W. Rhoads, Dudley W. Lamming, Troy A. Hornberger & Adam R. Konopka

Physical activity and several pharmacological approaches individually combat age-associated conditions and extend healthy longevity in model systems. It is tantalizing to extrapolate that combining geroprotector drugs with exercise could extend healthy longevity beyond any individual treatment. However, the current dogma suggests that taking leading geroprotector drugs on the same day as exercise may limit several health benefits. Here, we review leading candidate geroprotector drugs and their interactions with exercise and highlight salient gaps in knowledge that need to be addressed to identify if geroprotector drugs can have a harmonious relationship with exercise.

Clinical research on extreme longevity: The FACET experience

Domenico Azzolino [a], Gabriel Dias Rodrigues [b], Valentina Maria Manzini [c], Marco Proietti [b d], Beatrice Arosio [b], Nicola Montano [b e], Matteo Cesari [b]

People with extreme longevity represent a unique model to study the biology of aging. Unfortunately, their inclusion in research projects is challenging with the consequent lack of evidence and the need to rely on small convenience samples. Given the growing global aging population, especially in the segment of the oldest old (i.e., aged 90 and older), research in this population has become crucial. Furthermore, by studying the characteristics of extremely longeval persons, it might be possible to 1) better understand the mechanisms of aging, and 2) identify endogenous or exogenous factors contributing to a long life. The design and implementation of research activities in the oldest people need special consideration and a pragmatic approach. Possible implementable solutions and suggestions are provided from experience gained during the conduction of the FAtigue in CEnTenarians (FACET) study.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Biology of cognitive aging across species

Sho Kakizawa [1], Joong-Jean Park [2], Ayako Tonoki [3]

Affiliations + expand

PMID: 38126240 DOI: 10.1111/ggi.14782

Abstract

Aging is associated with cognitive decline, which can critically affect quality of life. Examining the biology of cognitive aging across species will lead to a better understanding of the fundamental mechanisms involved in this process, and identify potential interventions that could help to improve cognitive function in aging individuals. This minireview aimed to explore the mechanisms and processes involved in cognitive aging across a range of species, from flies to rodents, and covers topics, such as the role of reactive oxygen species and autophagy/mitophagy in cognitive aging. Overall, this literature provides a comprehensive overview of the biology of cognitive aging across species, highlighting the latest research findings and identifying potential avenues for future research. Geriatr Gerontol Int 2023; ••: ••-••.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The genetic landscape of age-related hearing loss

Yuzuru Ninoyu • Rick A. Friedman

Age-related hearing loss (ARHL) is a prevalent concern in the elderly population. Recent genome-wide and phenome-wide association studies (GWASs and PheWASs) have delved into the identification of causative variants and the understanding of pleiotropy, highlighting the polygenic intricacies of this complex condition. While recent large-scale GWASs have pinpointed significant SNPs and risk variants associated with ARHL, the detailed mechanisms, encompassing both genetic and epigenetic modifications, remain to be fully elucidated. This review presents the latest advances in association studies, integrating findings from both human studies and model organisms. By juxtaposing historical perspectives with contemporary genomics, we aim to catalyze innovative research and foster the development of novel therapeutic strategies for ARHL.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Targeting the redox system for cardiovascular regeneration in aging

Meret Sarah Allemann, Pratintip Lee, Jürg H. Beer, Seyed Soheil Saeedi Saravi

Cardiovascular aging presents a formidable challenge, as the aging process can lead to reduced cardiac function and heightened susceptibility to cardiovascular diseases. Consequently, there is an escalating, unmet medical need for innovative and effective cardiovascular regeneration strategies aimed at restoring and rejuvenating aging cardiovascular tissues. Altered redox homeostasis and the accumulation of oxidative damage play a pivotal role in detrimental changes to stem cell function and cellular senescence, hampering regenerative capacity in aged cardiovascular system. A mounting body of evidence underscores the significance of targeting redox machinery to restore stem cell self-renewal and enhance their differentiation potential into youthful cardiovascular lineages. Hence, the redox machinery holds promise as a target for optimizing cardiovascular regenerative therapies. In this context, we delve into the current understanding of redox homeostasis in regulating stem cell function and reprogramming processes that impact the regenerative potential of the cardiovascular system. Furthermore, we offer insights into the recent translational and clinical implications of redox-targeting compounds aimed at enhancing current regenerative therapies for aging cardiovascular tissues.

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Evolutionary constraint and innovation across hundreds of placental mammals

Zoonomia is the largest comparative genomics resource for mammals produced to date. By aligning genomes for 240 species, we identify bases that, when mutated, are likely to affect fitness and alter disease risk. At least 332 million bases (~10.7%) in the human genome are unusually conserved across species (evolutionarily constrained) relative to neutrally evolving repeats, and 4552 ultraconserved elements are nearly perfectly conserved. Of 101 million significantly constrained single bases, 80% are outside protein-coding exons and half have no functional annotations in the Encyclopedia of DNA Elements (ENCODE) resource. Changes in genes and regulatory elements are associated with exceptional mammalian traits, such as hibernation, that could inform therapeutic development. Earth's vast and imperiled biodiversity offers distinctive power for identifying genetic variants that affect genome function and organismal phenotypes.