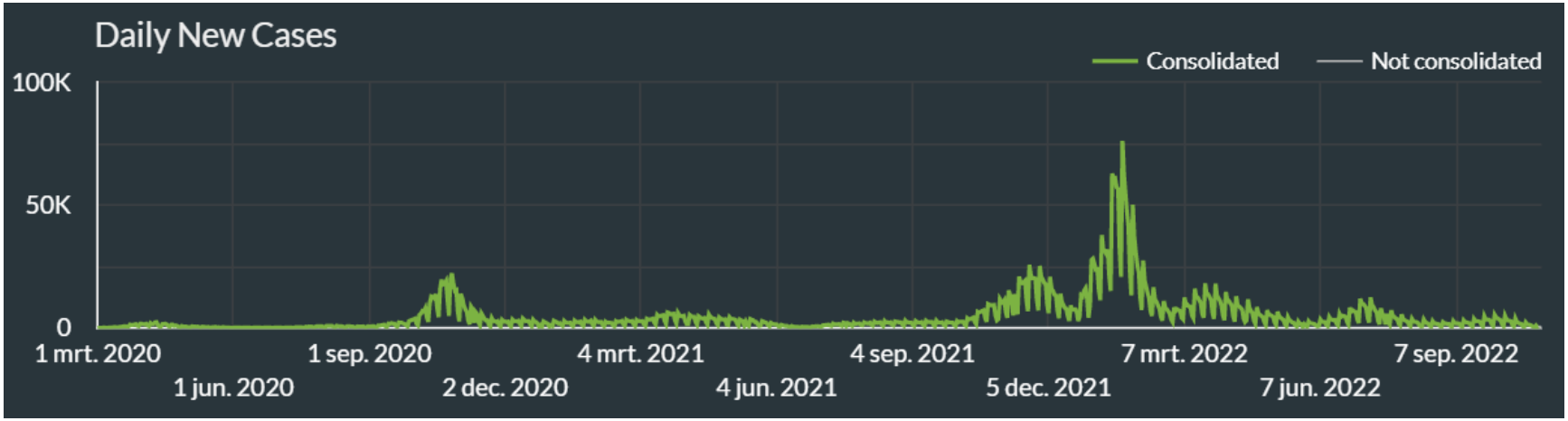
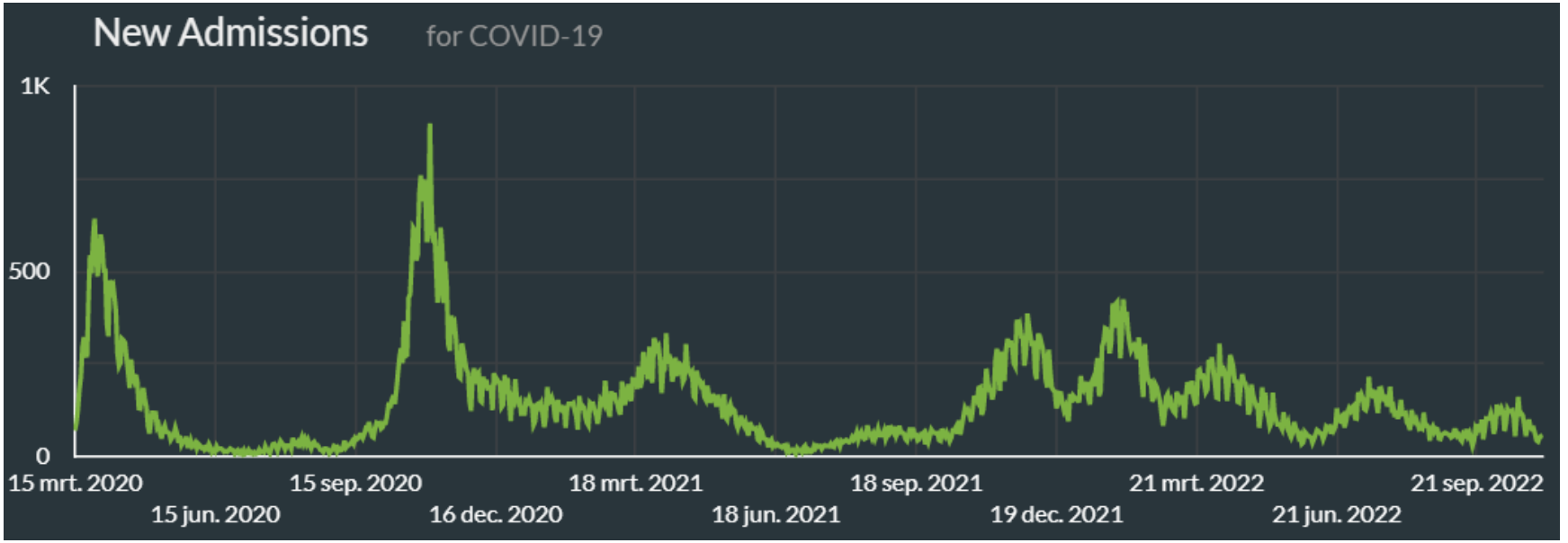
Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
6th of November 2022
Sven Bulterijs

Business/Conferences/ General news

Belgium





World

Fout databron	Total Deaths	Total Vaccine Doses Administered
⚠	6.600.338	12.849.295.684
28-Day Cases	**28-Day Deaths**	**28-Day Vaccine Doses Administered**
11.212.196	42.120	1.164.159.617

Cases | Deaths by Country/Region/Sovereignty

Germany
28-Day: 1.875.139 | 4.000
Totals: 35.823.771 | 154.535

France
28-Day: 1.156.633 | 1.855
Totals: 37.140.238 | 158.317

Japan
28-Day: 1.091.228 | 1.554
Totals: 22.702.372 | 47.133

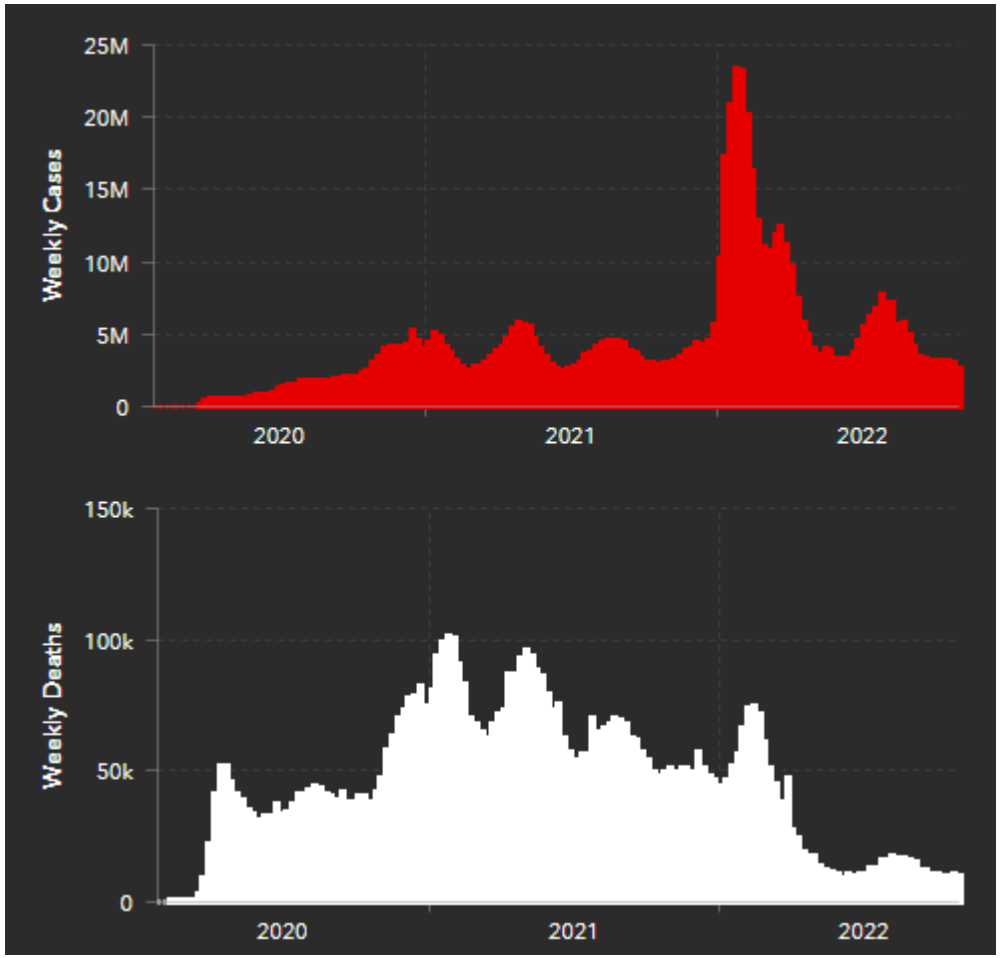
US
28-Day: 1.046.663 | 9.861
Totals: 97.734.261 | 1.072.582

Taiwan*
28-Day: 1.036.204 | 1.686
Totals: 7.887.538 | 13.198

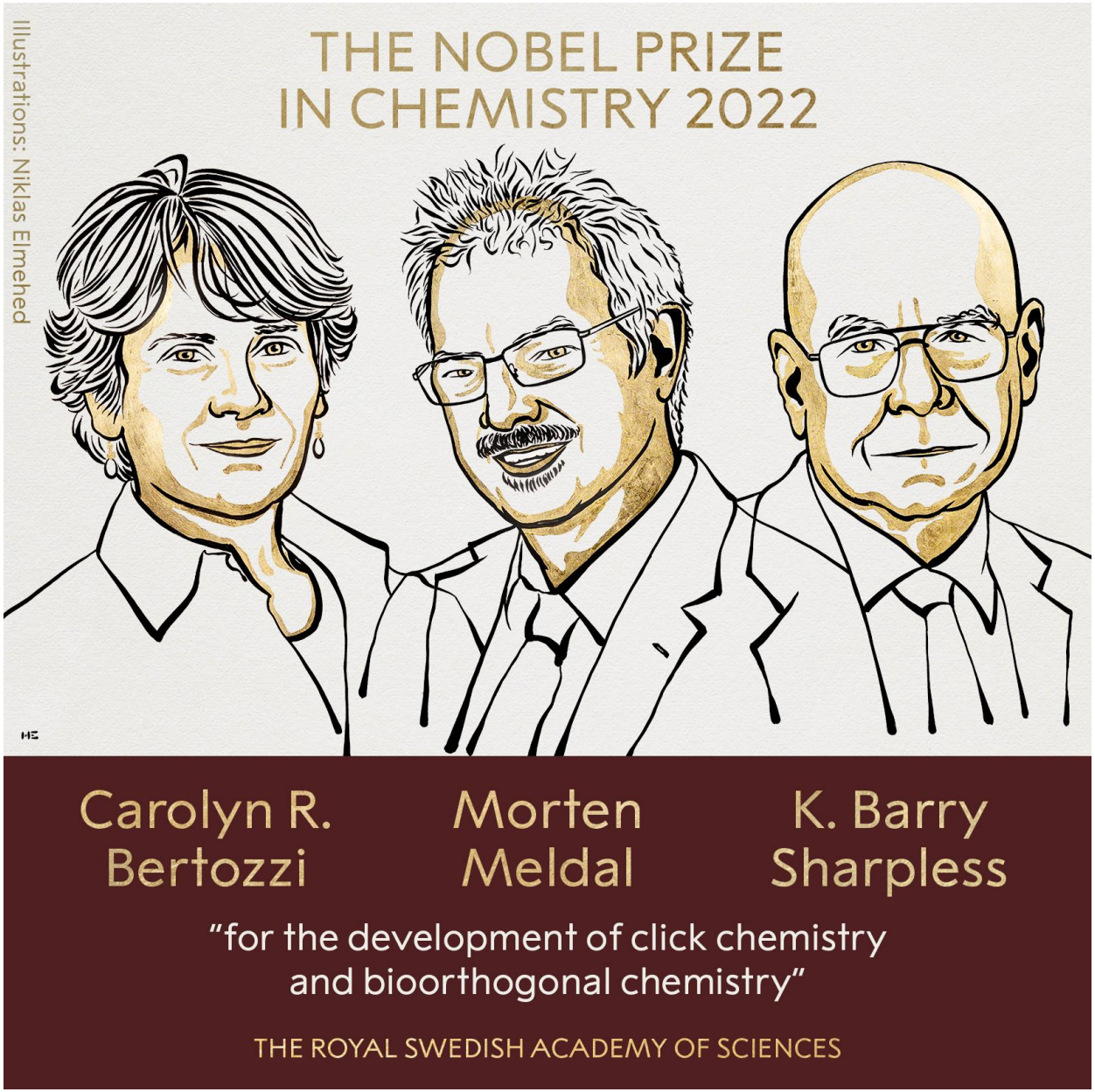
Korea, South
28-Day: 867.450 | 697
Totals: 25.838.239 | 29.372

Italy
28-Day: 860.718 | 1.958
Totals: 23.642.011 | 179.436

Russia
28-Day: 272.212 | 2.389
Totals: 21.158.672 | 382.705



Heales
HEALTHY LIFE EXTENSION SOCIETY



Heales
HEALTHY LIFE EXTENSION SOCIETY

LECANEMAB CONFIRMATORY PHASE 3 CLARITY AD STUDY MET PRIMARY ENDPOINT, SHOWING HIGHLY STATISTICALLY SIGNIFICANT REDUCTION OF CLINICAL DECLINE IN LARGE GLOBAL CLINICAL STUDY OF 1,795 PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE

SEPTEMBER 27, 2022 • INVESTOR RELATIONS

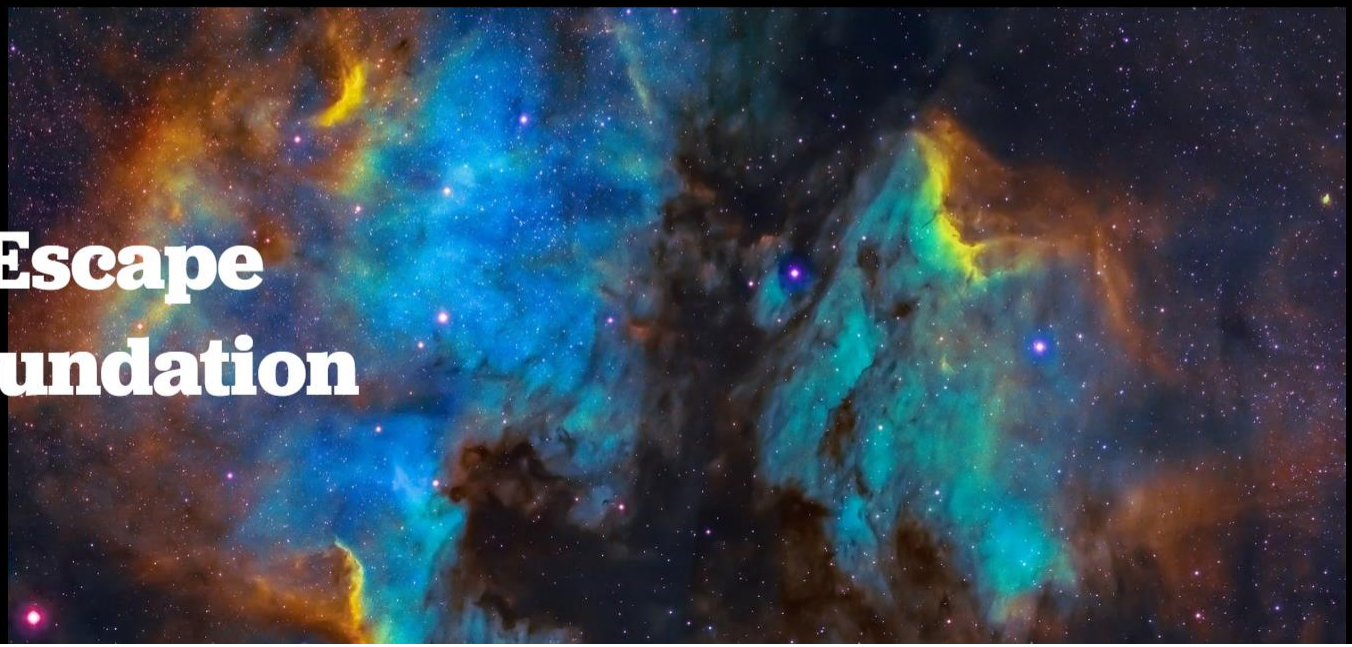
- *ALL KEY SECONDARY ENDPOINTS ALSO MET, DEMONSTRATING HIGHLY STATISTICALLY SIGNIFICANT RESULTS*
- *PROFILE OF AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA) INCIDENCE WAS WITHIN EXPECTATIONS*
- *EISAI AIMS TO FILE FOR TRADITIONAL APPROVAL IN THE U.S., AND TO SUBMIT MARKETING AUTHORIZATION APPLICATIONS IN JAPAN AND EUROPE BY THE END OF EISAI FY2022, WHICH ENDS ON MARCH 31, 2023*

Heales
HEALTHY LIFE EXTENSION SOCIETY

LEV Foundation

Projects Team Donate Contact

Longevity Escape Velocity Foundation



Heales
HEALTHY LIFE EXTENSION SOCIETY

The bird is fine, the bird is fine, the bird is fine, it's dead.

The pursuit of immortality is getting older. So are we.

By Jonathan Weiner

October 20, 2022

Heales
HEALTHY LIFE EXTENSION SOCIETY

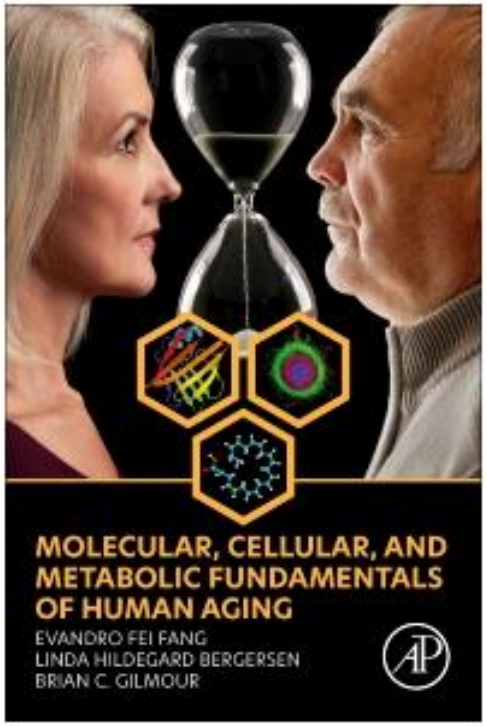
INTERVIEW BART VAN CRAEYNEST EN WILLEM SAS

‘Op lange termijn staan we er slechter voor dan Italië’

De cijfers kleuren donkerrood, de uitdaging zilvergrijs, de toekomst alles behalve rozig. De economen Bart Van Craeynest en Willem Sas maken de stand van het land op. ‘Als inertie een kwaliteit is, scoort België goed.’

Door **Stijn Decock, Ruben Mooijman**
Foto **Fred Debrock**
Zaterdag 5 november 2022 om 3.25 uur

New book



Molecular, Cellular, and Metabolic Fundamentals of Human Aging

1st Edition - October 23, 2022

☆☆☆☆☆ Write a review

Authors: Evandro Fei Fang, Linda Hildegard Bergersen, Brian C. Gilmour

eBook ISBN: 9780323916189

Heales
HEALTHY LIFE EXTENSION SOCIETY

Symposium

24 November 2022
Vrije Universiteit Brussel
Health Campus
Aud. Vanden Driessche

LifeMe
Lifestyle as medicine

Heales
HEALTHY LIFE EXTENSION SOCIETY

nov. 24

Elk jaar jonger? De wetenschap van veroudering én verjonging.

Het 3e LifeMe symposium focust op de nieuwste wetenschappelijke ontwikkelingen om langer gezond te blijven door veroudering aan te pakken!

Aging research articles

Heales
HEALTHY LIFE EXTENSION SOCIETY

Rapamycin treatment during development extends life span and health span of male mice and *Daphnia magna*

ANASTASIA V. SHINDYAPINA, YONGMIN CHO, ALAATTIN KAYA, ALEXANDER TYSHKOVSKIY, JOSÉ P. CASTRO, AMY DEIK, JUOZAS GORDEVICIUS, JESSE R. POGANIK, CLARY B. CLISH, [...] VADIM N. GLADYSHEV +3 authors Authors Info & Affiliations

SCIENCE ADVANCES • 16 Sep 2022 • Vol 8, Issue 37 • DOI: 10.1126/sciadv.abo5482

5.589

Abstract

Development is tightly connected to aging, but whether pharmacologically targeting development can extend life remains unknown. Here, we subjected genetically diverse UMHET3 mice to rapamycin for the first 45 days of life. The mice grew slower and remained smaller than controls for their entire lives. Their reproductive age was delayed without affecting offspring numbers. The treatment was sufficient to extend the median life span by 10%, with the strongest effect in males, and helped to preserve health as measured by frailty index scores, gait speed, and glucose and insulin tolerance tests. Mechanistically, the liver transcriptome and epigenome of treated mice were younger at the completion of treatment. Analogous to mice, rapamycin exposure during development robustly extended the life span of *Daphnia magna* and reduced its body size. Overall, the results demonstrate that short-term rapamycin treatment during development is a novel longevity intervention that acts by slowing down development and aging, suggesting that aging may be targeted already early in life.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Drug prediction for reversing AD/PD transcriptional profiles using an aging of systems-centric approach

Gabriela Bunu, Dmitri Toren, Eugen Ursu, Simona Ghenea, Vadim E. Fraifeld, Robi Tacutu

doi: https://doi.org/10.1101/2022.11.01.514657

Abstract

Age-related pathologies are so widely presented in old age that in most cases they are hardly distinguishable at the molecular level from the so-called ‘‘normal’’ aging. Both aging and age-related diseases are characterized by a wide range of transcriptional and epigenetic changes that underlie the physiological or pathological phenotype, with plenty of overlap in their signatures, but also with differences. In most pathological conditions it is rather the dysregulation of a complex network of genes than a problem with a single gene dysregulation that causes its emergence or progression, and aging differently gives a “predisposition” towards an age-related pathology or another, or in a favorable situation towards none. The important question is how similar are the transcriptional changes during “healthy” aging with those that occur in age-related diseases. In this study, we explore gene expression data to answer this question and aim to predict which drugs and compounds could have a reversing effect on their common drift.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Extreme Gradient Boosting algorithm classification for predicting lifespan-extending chemical compounds

Mariia Yarmolenko, Brendan Howlin

This is a preprint; it has not been peer reviewed by a journal.

https://doi.org/10.21203/rs.3.rs-2199002/v1

Abstract

Human ageing has a great impact on global economy and society's health with the risk factors for many chronic diseases. Discovery of the pharmaceutical interventions with the potential of promoting longevity and delaying the onset of age-associated diseases is one of the most challenging tasks in anti-ageing research today. The aim of this study was to build a new machine learning model based on the data of the DrugAge database to predict whether a chemical compound will extend the lifespan of the worm species Caenorhabditis elegans. The predictive models were built using the optimized Extreme Gradient Boosting algorithm with molecular fingerprints and molecular descriptors as features. The ranking of the models' features was done with the built-in Extreme Gradient Boosting feature importance function and interpreted with confidence using Shapley values. The top 15 most important features included 2D molecular descriptors related to the subdivided surface areas, atom and bond counts, and electrostatic properties. The best performing model was applied to predict the class of compounds in the external database, DrugBank, consisting of approved small-molecules. The chemical compounds of the external database with a predictive probability of for increasing the lifespan of Caenorhabditis elegans were broadly separated into (i) flavonoids and isoflavonoids, (ii) fatty acids and conjugates, and (iii) other classes of compounds.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cellular senescence is immunogenic and promotes anti-tumor immunity

Ines Marin ; Olga Boix ; Andrea Garcia-Garijo ; Isabelle Sirois ; Adria Caballe ; Eduardo Zarzuela ; Irene Ruano ; Camille Stephan-Otto Attolini ; Neus Prats ; Jose Alberto Lopez-Dominguez ; Marta Kovatcheva ; Elena Garralda ; Javier Munoz ; Etienne Caron ; Maria Abad ; Alena Gros ; Federico Pietrocola ; Manuel Serrano

+ Author & Article Information

Cancer Discov CD-22-0523.

https://doi.org/10.1158/2159-8290.CD-22-0523 Article history

Abstract

Cellular senescence is a stress response that activates innate immune cells, but little is known about its interplay with the adaptive immune system. Here, we show that senescent cells combine several features that render them highly efficient in activating dendritic cells (DCs) and antigen-specific CD8 T cells. This includes the release of alarmins, activation of interferon signaling, enhanced MHC class I machinery, and presentation of senescence-specific self-peptides that can activate CD8 T cells. In the context of cancer, immunization with senescent cancer cells elicits strong anti-tumor protection mediated by DCs and CD8 T cells. Interestingly, this protection is superior to immunization with cancer cells undergoing immunogenic cell death. Finally, the induction of senescence in human primary cancer cells also augments their ability to activate autologous antigen-specific tumor-infiltrating CD8 lymphocytes. Our study indicates that senescent cancer cells can be exploited to develop efficient and protective CD8-dependent anti-tumor immune responses.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Senescence rewires microenvironment sensing to facilitate anti-tumor immunity

Hsuan-An Chen ; Yu-Jui Ho ; Riccardo Mezzadra ; Jose M. Adrover ; Ryan Smolkin ; Changyu Zhu ; Katharina Woess ; Nicholas Bernstein ; Georgia Schmitt ; Linda Fong ; Wei Luan ; Alexandra Wuest ; Sha Tian ; Xiang Li ; Caroline Broderick ; Ronald C. Hendrickson ; Mikala Egeblad ; Zhenghao Chen ; Direna Alonso-Curbelo ; Scott W. Lowe

Check for updates

+ Author & Article Information

Cancer Discov CD-22-0528.

https://doi.org/10.1158/2159-8290.CD-22-0528 Article history

Split-Screen Views PDF Share Tools Versions

Abstract

Cellular senescence involves a stable cell cycle arrest coupled to a secretory program that, in some instances, stimulates the immune clearance of senescent cells. Using an immune competent liver cancer model in which senescence triggers CD8 T cell-mediated tumor rejection, we show that senescence also remodels the cell surface proteome to alter how tumor cells sense environmental factors, as exemplified by Type II interferon (IFN-γ). Compared to proliferating cells, senescent cells upregulate the IFN-γ receptor, become hypersensitized to microenvironmental IFN-γ, and more robustly induce the antigen presenting machinery—-effects also recapitulated in human tumor cells undergoing therapy-induced senescence. Disruption of IFN-γ sensing in senescent cells blunts their immune-mediated clearance without disabling the senescence state or its characteristic secretory program. Our results demonstrate that senescent cells have an enhanced ability to both send and receive environmental signals, and imply that each process is required for their effective immune surveillance.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

The efficacy of chemotherapy is limited by intratumoural senescent cells that persist through the upregulation of PD-L2

Selim Chaib, José Alberto López-Domínguez, Marta Lalinde, Neus Prats, Inés Marín, Kathleen Meyer, María Isabel Muñoz, Mònica Aguilera, Lidia Mateo, Camille Stephan-Otto Attolini, Susana Llanos, Marta Escorihuela, Sandra Pérez-Ramos, Fatima Al-Shahrour, Timothy P Cash, Tamara Tchkonia, James L Kirkland, Joaquín Arribas, Manuel Serrano

doi: https://doi.org/10.1101/2022.11.04.501681

Abstract

Anti-cancer therapies often result in a subset of surviving cancer cells that undergo therapy-induced senescence (TIS). Senescent cancer cells strongly modify the intratumoural microenvironment favoring immunosuppression and, thereby, tumour growth. An emerging strategy to optimise current therapies is to combine them with treatments that eliminate senescent cells. To this end, we undertook an unbiased proteomics approach to identify surface markers contributing to senescent cells immune evasion. Through this approach, we discovered that the immune checkpoint inhibitor PD-L2, but not PD-L1, is upregulated across multiple senescent human and murine cells. Importantly, blockade of PD-L2 strongly synergises with genotoxic chemotherapy, causing remission of solid tumours in mice. We show that PD-L2 inhibition prevents the persistence of chemotherapy-induced senescent cells, which exert cell-extrinsic immunomodulatory actions. In particular, upon chemotherapy, tumours deficient in PD-L2 fail to produce cytokines of the CXCL family, do not recruit myeloid-derived suppressor cells (MDSCs) and are eliminated in a CD8 T cell-dependent manner. We conclude that blockade of PD-L2 improves chemotherapy efficacy by reducing the intratumoural burden of senescent cells and their associated recruitment of immunosuppressive cells. These findings provide a novel strategy to exploit vulnerabilities arising in tumour cells as a result of therapy-induced damage and cellular senescence.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Blocking PD-L1–PD-1 improves senescence surveillance and ageing phenotypes

Teh-Wei Wang, Yoshikazu Johmura ✉, Narumi Suzuki, Satotaka Omori, Toshiro Migita, Kiyoshi Yamaguchi, Seira Hatakeyama, Satoshi Yamazaki, Eigo Shimizu, Seiya Imoto, Yoichi Furukawa, Akihiko Yoshimura & Makoto Nakanishi ✉

The accumulation of senescent cells is a major cause of age-related inflammation and predisposes to a variety of age-related diseases[1]. However, little is known about the molecular basis underlying this accumulation and its potential as a target to ameliorate the ageing process. Here we show that senescent cells heterogeneously express the immune checkpoint protein programmed death-ligand 1 (PD-L1) and that PD-L1$^+$ senescent cells accumulate with age in vivo. PD-L1$^-$ cells are sensitive to T cell surveillance, whereas PD-L1$^+$ cells are resistant, even in the presence of senescence-associated secretory phenotypes (SASP). Single-cell analysis of p16$^+$ cells in vivo revealed that PD-L1 expression correlated with higher levels of SASP. Consistent with this, administration of programmed cell death protein 1 (PD-1) antibody to naturally ageing mice or a mouse model with normal livers or induced nonalcoholic steatohepatitis reduces the total number of p16$^+$ cells in vivo as well as the PD-L1$^+$ population in an activated CD8$^+$ T cell-dependent manner, ameliorating various ageing-related phenotypes. These results suggest that the heterogeneous expression of PD-L1 has an important role in the accumulation of senescent cells and inflammation associated with ageing, and the elimination of PD-L1$^+$ senescent cells by immune checkpoint blockade may be a promising strategy for anti-ageing therapy.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A generalizable epigenetic clock captures aging in two nonhuman primates

Elisabeth A. Goldman, Kenneth L. Chiou, Marina M. Watowich, Arianne Mercer, Sierra N. Sams, Julie E. Horvath, Jordan A. Anderson, Cayo Biobank Research Unit, Jenny Tung, James P. Higham, Lauren J.N. Brent, Melween I. Martínez, Michael J. Montague, Michael L. Platt, Kirstin N. Sterner, Noah Snyder-Mackler

doi: https://doi.org/10.1101/2022.11.01.514719

ABSTRACT

Epigenetic clocks generated from DNA methylation array data provide important insights into biological aging, disease susceptibility, and mortality risk. However, these clocks cannot be applied to high-throughput, sequence-based datasets more commonly used to study nonhuman animals. Here, we built a generalizable epigenetic clock using genome-wide DNA methylation data from 493 free-ranging rhesus macaques. Using a sliding-window approach that maximizes generalizability across datasets and species, this model predicted age with high accuracy (± 1.42 years) in held-out test samples, as well as in two independent test sets: rhesus macaques from a captive population (n=43) and wild baboons in Kenya (n=271). Our model can also be used to generate insight into the factors hypothesized to alter epigenetic aging, including social status and exposure to traumatic events. Our results thus provide a flexible tool for predicting age in other populations and species and illustrate how connecting behavioral data with the epigenetic clock can uncover social influences on biological age.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Transcription, structure, and organoids translate time across the lifespan of humans and great apes

Christine J. Charvet, Kwadwo Ofori, Carmen Falcone, Brier A. Rigby-Dames

doi: https://doi.org/10.1101/2022.10.28.513899

Abstract

How the neural structures supporting human cognition develop and arose in evolution is an enduring question of interest. Yet, we still lack appropriate procedures to align ages across primates, and this lacuna has hindered progress in understanding the evolution of biological programs. We generated a dataset of unprecedented size consisting of 573 time points from abrupt and gradual changes in behavior, anatomy, and transcription across human and 8 non-human primate species. We included time points from diverse human populations to capture within-species variation in the generation of cross-species age alignments. We also extracted corresponding ages from organoids. The identification of corresponding ages across the lifespan of 8 primate species, including apes (e.g., orangutans, gorillas) and monkeys (i.e., marmosets, macaques) reveal that some biological pathways are extended in humans compared with some non-human primates. Particularly, the human lifespan is unusually extended relative to studied nonhuman primates demonstrating that very old age is a phase of life in humans that does not map to other studied primate species. More generally, our work prompts a reevaluation in the choice of a model system to understand aging given very old age in humans is a period of life with a clear counterpart in great apes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Aging impairs astrocytes in the human cerebral cortex

Alexander Popov, Nadezda Brazhe, Kseniia Morozova, Konstantin Yashin, Maxim Bychkov, Olga Nosova, Oksana Sutyagina, Alexey Brazhe, Evgenia Parshina, Li Li, Igor Medyanik, Dmitry E Korzhevskii, Zakhar Shenkarev, Ekaterina Lyukmanova, Alexei Verkhratsky, Alexey Semyanov

doi: https://doi.org/10.1101/2022.10.31.514523

Abstract

How aging affects cellular components of the human brain active milieu remains largely unknown. We analyzed astrocytes and neurons in the neocortical access tissue of younger (22 - 50 years) and older (51 - 72 years) adult patients who underwent glioma resection. Aging decreased the amount of reduced mitochondrial cytochromes in astrocytes but not neurons. The total amount of protein was decreased in astrocytes and increased in neurons. Aged astrocytes showed morphological dystrophy quantified by the decreased length of branches, decreased volume fraction of leaflets, and shrinkage of the anatomical domain. Dystrophy correlated with the loss of gap junction coupling between astrocytes and increased input resistance. Aging was accompanied by the upregulation of glial fibrillary acidic protein (GFAP) and downregulation of membrane-cytoskeleton linker Ezrin associated with leaflets. No significant changes in neuronal excitability or spontaneous inhibitory postsynaptic signaling were observed. Thus, brain aging is associated with the impaired morphological presence and mitochondrial malfunction of astrocytes, but not neurons.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Rejuvenation of the aged brain immune cell landscape in mice through p16-positive senescent cell clearance

Xu Zhang, Vesselina M. Pearsall, Chase M. Carver, Elizabeth J. Atkinson, Benjamin D. S. Clarkson, Ethan M. Grund, Michelle Baez-Faria, Kevin D. Pavelko, Jennifer M. Kachergus, Thomas A. White, Renee K. Johnson, Courtney S. Malo, Alan M. Gonzalez-Suarez, Katayoun Ayasoufi, Kurt O. Johnson, Zachariah P. Tritz, Cori E. Fain, Roman H. Khadka, Mikolaj Ogrodnik, Diana Jurk, Yi Zhu, Tamara Tchkonia, Alexander Revzin, James L. Kirkland, ... Marissa J. Schafer + Show authors

Nature Communications **13**, Article number: 5671 (2022) | Cite this article

6852 Accesses | **96** Altmetric | Metrics

Abstract

Cellular senescence is a plausible mediator of inflammation-related tissue dysfunction. In the aged brain, senescent cell identities and the mechanisms by which they exert adverse influence are unclear. Here we used high-dimensional molecular profiling, coupled with mechanistic experiments, to study the properties of senescent cells in the aged mouse brain. We show that senescence and inflammatory expression profiles increase with age and are brain region- and sex-specific. *p16*-positive myeloid cells exhibiting senescent and disease-associated activation signatures, including upregulation of chemoattractant factors, accumulate in the aged mouse brain. Senescent brain myeloid cells promote peripheral immune cell chemotaxis in vitro. Activated resident and infiltrating immune cells increase in the aged brain and are partially restored to youthful levels through p16-positive senescent cell clearance in female *p16-InkAttac* mice, which is associated with preservation of cognitive function. Our study reveals dynamic remodeling of the brain immune cell landscape in aging and suggests senescent cell targeting as a strategy to counter inflammatory changes and cognitive decline.

Integrity of neuronal size in the entorhinal cortex is a biologic substrate of exceptional cognitive aging

Caren Nassif, Allegra Kawles, Ivan Ayala, Grace Minogue, Nathan P. Gill, Robert A. Shepard, Antonia Zouridakis, Rachel Keszycki, Hui Zhang, Qinwen Mao [MD, PhD], Margaret E. Flanagan [MD], Eileen H. Bigio [MD], M.-Marsel Mesulam [MD], Emily Rogalski [PhD], Changiz Geula [PhD], and Tamar Gefen [PhD]

Average aging is associated with a gradual decline of memory capacity. SuperAgers are humans over age 80 who show exceptional episodic memory at least as good as individuals 20-30 years their junior. This study investigated whether neuronal integrity in entorhinal cortex (ERC), an area critical for memory and selectively vulnerable to neurofibrillary degeneration, differentiated SuperAgers from cognitively-healthy younger individuals, cognitively-average peers ("Normal Elderly"), and individuals with amnestic Mild Cognitive Impairment (aMCI). Postmortem sections of the ERC were stained with cresyl violet to visualize neurons, and immunostained with PHF-1 to visualize neurofibrillary tangles. The cross-sectional area (i.e., size) of layer II and layer III/V ERC neurons were quantified. Two-thirds of total participants were female. Unbiased stereology was employed to quantitate tangles in a subgroup of SuperAgers and Normal Elderly. Linear mixed-effect models were used to determine differences across groups. Quantitative measurements found the soma size of layer II ERC neurons in post-mortem brain specimens were significantly larger in SuperAgers compared to all groups ($p<0.05$)—including younger individuals 20-30 their junior ($p<0.005$). SuperAgers had significantly *fewer* stereologically quantified AD-related neurofibrillary tangles in layer II ERC than Normal Elderly ($p<0.05$). This difference in tangle burden in layer II between SuperAgers and Normal Elderly suggest that tangle-bearing neurons may be prone to shrinkage during aging. The finding that SuperAgers show ERC layer II neurons that are substantially larger even compared to individuals 20-30 years younger is remarkable, suggesting that layer II ERC integrity is a biologic substrate of exceptional memory in old age.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Centenarians consistently present a younger epigenetic age than their chronological age with four epigenetic clocks based on a small number of CpG sites

Antoine Daunay[1] , Lise M. Hardy[1,2] , Yosra Bouyacoub[1,2] , Mourad Sahbatou[1] , Mathilde Touvier[3] , Hélène Blanché[2,4] , Jean-François Deleuze[1,2,4,5] , Alexandre How-Kit[1]

Aging is a progressive time-dependent biological process affecting differentially individuals, who can sometimes present exceptional longevity. Epigenetic alterations are one of the hallmarks of aging, which comprise the epigenetic drift and clock at DNA methylation level. In the present study, we estimated the DNA methylation-based age (DNAmage) using four epigenetic clocks based on a small number of CpGs in French centenarians and semi-supercentenarians (CSSC, n=214) as well as nonagenarians' and centenarians' offspring (NCO, n=143) compared to individuals from the French general population (CG, n=149). DNA methylation analysis of the nine CpGs included in the epigenetic clocks showed high correlation with chronological age (-0.66>R>0.54) and also the presence of an epigenetic drift for four CpGs that was only visible in CSSC. DNAmage analysis showed that CSSC and to a lesser extend NCO present a younger DNAmage than their chronological age (15-28.5 years for CSSC, 4.4-11.5 years for NCO and 4.2-8.2 years for CG), which were strongly significant in CSSC compared to CG (p-values<2.2e-16). These differences suggest that epigenetic aging and potentially biological aging are slowed in exceptionally long-lived individuals and that epigenetic clocks based on a small number of CpGs are sufficient to reveal alterations of the global epigenetic clock.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A rare human centenarian variant of SIRT6 enhances genome stability and interaction with Lamin A

Matthew Simon, Jiping Yang, Jonathan Gigas, Eric J Earley, Eric Hillpot, Lei Zhang, Maria Zagorulya, Greg Tombline, Michael Gilbert, Samantha L Yuen, Alexis Pope, Michael Van Meter, Stephan Emmrich, Denis Firsanov, Advait Athreya, Seyed Ali Biashad, Jeehae Han, Seungjin Ryu, Archana Tare, Yizhou Zhu, Adam Hudgins, Gil Atzmon, Nir Barzilai, Aaron Wolfe, Kelsey Moody, Benjamin A Garcia, [...] Vera Gorbunova

Author Information

The EMBO Journal (2022) 41: e110393 | https://doi.org/10.15252/embj.2021110393

Abstract

Sirtuin 6 (SIRT6) is a deacylase and mono-ADP ribosyl transferase (mADPr) enzyme involved in multiple cellular pathways implicated in aging and metabolism regulation. Targeted sequencing of SIRT6 locus in a population of 450 Ashkenazi Jewish (AJ) centenarians and 550 AJ individuals without a family history of exceptional longevity identified enrichment of a SIRT6 allele containing two linked substitutions (N308K/A313S) in centenarians compared with AJ control individuals. Characterization of this SIRT6 allele (centSIRT6) demonstrated it to be a stronger suppressor of LINE1 retrotransposons, confer enhanced stimulation of DNA double-strand break repair, and more robustly kill cancer cells compared with wild-type SIRT6. Surprisingly, centSIRT6 displayed weaker deacetylase activity, but stronger mADPr activity, over a range of NAD^+ concentrations and substrates. Additionally, centSIRT6 displayed a stronger interaction with Lamin A/C (LMNA), which was correlated with enhanced ribosylation of LMNA. Our results suggest that enhanced SIRT6 function contributes to human longevity by improving genome maintenance via increased mADPr activity and enhanced interaction with LMNA.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Tissue-specific impacts of aging and genetics on gene expression patterns in humans

Ryo Yamamoto, Ryan Chung, Juan Manuel Vazquez, Huanjie Sheng, Philippa L. Steinberg, Nilah M. Ioannidis & Peter H. Sudmant

Nature Communications **13**, Article number: 5803 (2022) | Cite this article

Abstract

Age is the primary risk factor for many common human diseases. Here, we quantify the relative contributions of genetics and aging to gene expression patterns across 27 tissues from 948 humans. We show that the predictive power of expression quantitative trait loci is impacted by age in many tissues. Jointly modelling the contributions of age and genetics to transcript level variation we find expression heritability (h^2) is consistent among tissues while the contribution of aging varies by >20-fold with $R^2_{\text{age}} > h^2$ in 5 tissues. We find that while the force of purifying selection is stronger on genes expressed early versus late in life (Medawar's hypothesis), several highly proliferative tissues exhibit the opposite pattern. These non-Medawarian tissues exhibit high rates of cancer and age-of-expression-associated somatic mutations. In contrast, genes under genetic control are under relaxed constraint. Together, we demonstrate the distinct roles of aging and genetics on expression phenotypes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Aging clocks, entropy, and the limits of age-reversal

Andrei E. Tarkhov, Kirill A. Denisov, Peter O. Fedichev

doi: https://doi.org/10.1101/2022.02.06.479300

Abstract

We analyze aging signatures of DNA methylation and longitudinal electronic medical records from the UK Biobank datasets and observe that aging is driven by a large number of independent and infrequent transitions between metastable states in a vast configuration space. The compound effect of configuration changes can be captured by a single stochastic variable, thermodynamic biological age (tBA), tracking entropy produced, and hence information lost during aging. We show that tBA increases with age, causes the linear and irreversible drift of physiological state variables, reduces resilience, and drives the exponential acceleration of chronic disease incidence and death risks. The entropic character of aging drift sets severe constraints on the possibilities of age reversal. However, we highlight the universal features of configuration transitions, suggest practical ways of suppressing the rate of aging in humans, and speculate on the possibility of achieving negligible senescence.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Unsupervised learning of aging principles from longitudinal data

Konstantin Avchaciov, Marina P. Antoch, Ekaterina L. Andrianova, Andrei E. Tarkhov, Leonid I. Menshikov, Olga Burmistrova, Andrei V. Gudkov & Peter O. Fedichev

Nature Communications **13**, Article number: 6529 (2022) | Cite this article

Abstract

Age is the leading risk factor for prevalent diseases and death. However, the relation between age-related physiological changes and lifespan is poorly understood. We combined analytical and machine learning tools to describe the aging process in large sets of longitudinal measurements. Assuming that aging results from a dynamic instability of the organism state, we designed a deep artificial neural network, including auto-encoder and auto-regression (AR) components. The AR model tied the dynamics of physiological state with the stochastic evolution of a single variable, the "dynamic frailty indicator" (dFI). In a subset of blood tests from the Mouse Phenome Database, dFI increased exponentially and predicted the remaining lifespan. The observation of the limiting dFI was consistent with the late-life mortality deceleration. dFI changed along with hallmarks of aging, including frailty index, molecular markers of inflammation, senescent cell accumulation, and responded to life-shortening (high-fat diet) and life-extending (rapamycin) treatments.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A single short reprogramming early in life initiates and propagates an epigenetically related mechanism improving fitness and promoting an increased healthy lifespan

Quentin Alle, Enora Le Borgne, Paul Bensadoun, Camille Lemey, Nelly Béchir, Mélissa Gabanou, Fanny Estermann, Christelle Bertrand-Gaday, Laurence Pessemesse ... See all authors

First published: 17 October 2022 | https://doi.org/10.1111/acel.13714

Quentin Alle and Enora Le Borgne contributed equally to this work as first authors.
Paul Bensadoun and Camille Lemey contributed equally to this work as second authors.

Abstract

Recent advances in cell reprogramming showed that OSKM induction is able to improve cell physiology in vitro and in vivo. Here, we show that a single short reprogramming induction is sufficient to prevent musculoskeletal functions deterioration of mice, when applied in early life. In addition, in old age, treated mice have improved tissue structures in kidney, spleen, skin, and lung, with an increased lifespan of 15% associated with organ-specific differential age-related DNA methylation signatures rejuvenated by the treatment. Altogether, our results indicate that a single short reprogramming early in life might initiate and propagate an epigenetically related mechanism to promote a healthy lifespan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mechanism of Thymus Rejuvenation in Elderly Macaques

Yan-Ying Wang, Le Chang, Gao-Hong Zhu, Gong-Hua Li, Qing-Peng Kong, Long-Bao Lv, Qiang Wang, Chuan Tian, Ye Li, Xiang-Qing Zhu, and Xing-Hua Pan

Published Online: 13 Oct 2022 | https://doi.org/10.1089/rej.2022.0013

View article Permissions & Citations Share

Abstract

Senile thymus atrophy is an important factor leading to decreased immune function. Repairing the atrophic thymus tissue structure, rebuilding immune function, and replenishing the number of exogenous stem cells may be ideal methods. In this study, bone marrow mesenchymal stem cells were intravenously infused into elderly macaques. We found that thymus volume was substantially increased, some thymus tissue regeneration was observed, the degree of thymus tissue fibrosis decreased, collagen fiber deposition decreased, cortical and medulla structures emerged gradually, the number of apoptotic cells decreased significantly, and the expression of apoptosis-related proteins decreased. For the effects of stem cell therapy on aging-related genes, we performed transcriptomic analysis of thymus tissue. The results show the expression pattern of the tissue transcriptome tended to be similar to the thymus expression pattern in young macaques compared with the elderly group, reverse aging-related proteins. Based on the results, it is suggested that stem cell therapy is an ideal method to prevent or reverse the aging of the thymus.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Causal analysis identifies small HDL particles and physical activity as key determinants of longevity of older adults

Background: The hard endpoint of death is one of the most significant outcomes in both clinical practice and research settings. Our goal was to discover direct causes of longevity from medically accessible data.

Methods: Using a framework that combines local causal discovery algorithms with discovery of maximally predictive and compact feature sets (the "Markov boundaries" of the response) and equivalence classes, we examined 186 variables and their relationships with survival over 27 years in 1507 participants, aged ≥71 years, of the longitudinal, community-based D-EPESE study.

Findings: As few as 8-15 variables predicted longevity at 2-, 5- and 10-years with predictive performance (area under receiver operator characteristic curve) of 0·76 (95% CIs 0·69, 0·83), 0·76 (0·72, 0·81) and 0·66 (0·61, 0·71), respectively. Numbers of small high-density lipoprotein particles, younger age, and fewer pack years of cigarette smoking were the strongest determinants of longevity at 2-, 5- and 10-years, respectively. Physical function was a prominent predictor of longevity at all time horizons. Age and cognitive function contributed to predictions at 5 and 10 years. Age was not among the local 2-year prediction variables (although significant in univariable analysis), thus establishing that age is not a direct cause of 2-year longevity in the context of measured factors in our data that determine longevity.

Interpretation: The discoveries in this study proceed from causal data science analyses of deep clinical and molecular phenotyping data in a community-based cohort of older adults with known lifespan.

Funding: NIH/NIA R01AG054840, R01AG12765, and P30-AG028716, NIH/NIA Contract N01-AG-12102 and NCRR 1UL1TR002494-01.

Keywords: Aging; Causal analysis; High-density lipoprotein; Inflammation; Longevity; Markov boundary; Physical activity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

AgingBank: a manually curated knowledgebase and high-throughput analysis platform that provides experimentally supported multi-omics data relevant to aging in multiple species

Get access >

Yue Gao, Shipeng Shang, Shuang Guo, Xinyue Wang, Hanxiao Zhou, Yue Sun, Jing Gan, Yakun Zhang, Xia Li ✉, Shangwei Ning ... Show more

Abstract

Discovering the biological basis of aging is one of the greatest remaining challenges for biomedical field. Work on the biology of aging has discovered a range of interventions and pathways that control aging rate. Thus, we developed AgingBank (http://bio-bigdata.hrbmu.edu.cn/AgingBank) which was a manually curated comprehensive database and high-throughput analysis platform that provided experimentally supported multi-omics data relevant to aging in multiple species. AgingBank contained 3771 experimentally verified aging-related multi-omics entries from studies across more than 50 model organisms, including human, mice, worms, flies and yeast. The records included genome (single nucleotide polymorphism, copy number variation and somatic mutation), transcriptome [mRNA, long non-coding RNA (lncRNA), microRNA (miRNA) and circular RNA (circRNA)], epigenome (DNA methylation and histone modification), other modification and regulation elements (transcription factor, enhancer, promoter, gene silence, alternative splicing and RNA editing). In addition, AgingBank was also an online computational analysis platform containing five useful tools (Aging Landscape, Differential Expression Analyzer, Data Heat Mapper, Co-Expression Network and Functional Annotation Analyzer), nearly 112 high-throughput experiments of genes, miRNAs, lncRNAs, circRNAs and methylation sites related with aging. Cancer & Aging module was developed to explore the relationships between aging and cancer. Submit & Analysis module allows users upload and analyze their experiments data. AginBank is a valuable resource for elucidating aging-related biomarkers and relationships with other diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

AgeAnno: a knowledgebase of single-cell annotation of aging in human

Kexin Huang, Hoaran Gong, Jingjing Guan, Lingxiao Zhang, Changbao Hu, Weiling Zhao, Liyu Huang, Wei Zhang, Pora Kim ✉, Xiaobo Zhou ✉

Abstract

Aging is a complex process that accompanied by molecular and cellular alterations. The identification of tissue-/cell type-specific biomarkers of aging and elucidation of the detailed biological mechanisms of aging-related genes at the single-cell level can help to understand the heterogeneous aging process and design targeted anti-aging therapeutics. Here, we built AgeAnno (https://relab.xidian.edu.cn/AgeAnno/#/), a knowledgebase of single cell annotation of aging in human, aiming to provide comprehensive characterizations for aging-related genes across diverse tissue-cell types in human by using single-cell RNA and ATAC sequencing data (scRNA and scATAC). The current version of AgeAnno houses 1 678 610 cells from 28 healthy tissue samples with ages ranging from 0 to 110 years. We collected 5580 aging-related genes from previous resources and performed dynamic functional annotations of the cellular context. For the scRNA data, we performed analyses include differential gene expression, gene variation coefficient, cell communication network, transcription factor (TF) regulatory network, and immune cell proportionc. AgeAnno also provides differential chromatin accessibility analysis, motif/TF enrichment and footprint analysis, and co-accessibility peak analysis for scATAC data. AgeAnno will be a unique resource to systematically characterize aging-related genes across diverse tissue-cell types in human, and it could facilitate antiaging and aging-related disease research.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

Intestine-specific removal of DAF-2 nearly doubles lifespan in Caenorhabditis elegans with little fitness cost

Yan-Ping Zhang [# 1 2], Wen-Hong Zhang [# 1 2], Pan Zhang [1], Qi Li [3], Yue Sun [1], Jia-Wen Wang [1], Shaobing O Zhang [3], Tao Cai [1], Cheng Zhan [1], Meng-Qiu Dong [4 5]

Affiliations + expand

PMID: 36284093 PMCID: PMC9596710 DOI: 10.1038/s41467-022-33850-4

Free PMC article

Abstract

Twenty-nine years following the breakthrough discovery that a single-gene mutation of daf-2 doubles Caenorhabditis elegans lifespan, it remains unclear where this insulin/IGF-1 receptor gene is expressed and where it acts to regulate ageing. Using knock-in fluorescent reporters, we determined that daf-2 and its downstream transcription factor daf-16 are expressed ubiquitously. Using tissue-specific targeted protein degradation, we determined that intracellular DAF-2-to-DAF-16 signaling in the intestine plays a major role in lifespan regulation, while that in the hypodermis, neurons, and germline plays a minor role. Notably, intestine-specific loss of DAF-2 activates DAF-16 in and outside the intestine, causes almost no adverse effects on development and reproduction, and extends lifespan by 94% in a way that partly requires non-intestinal DAF-16. Consistent with intestine supplying nutrients to the entire body, evidence from this and other studies suggests that altered metabolism, particularly down-regulation of protein and RNA synthesis, mediates longevity by reduction of insulin/IGF-1 signaling.

Heales
HEALTHY LIFE EXTENSION SOCIETY

H3K9me1/2 methylation limits the lifespan of *daf-2* mutants in *C. elegans*

Meng Huang [# 1], Minjie Hong [# 1], Xinhao Hou [1], Chengming Zhu [1], Di Chen [2], Xiangyang Chen [1], Shouhong Guang [1 3], Xuezhu Feng [1]

Affiliations + expand

PMID: 36125117 PMCID: PMC9514849 DOI: 10.7554/eLife.74812

Free PMC article

Abstract

Histone methylation plays crucial roles in the development, gene regulation, and maintenance of stem cell pluripotency in mammals. Recent work shows that histone methylation is associated with aging, yet the underlying mechanism remains unclear. In this work, we identified a class of putative histone 3 lysine 9 mono/dimethyltransferase genes (*met-2, set-6, set-19, set-20, set-21, set-32,* and *set-33*), mutations in which induce synergistic lifespan extension in the long-lived DAF-2 (insulin growth factor 1 [IGF-1] receptor) mutant in *Caenorhabditis elegans*. These putative histone methyltransferase plus *daf-2* double mutants not only exhibited an average lifespan nearly three times that of wild-type animals and a maximal lifespan of approximately 100 days, but also significantly increased resistance to oxidative and heat stress. Synergistic lifespan extension depends on the transcription factor DAF-16 (FOXO). mRNA-seq experiments revealed that the mRNA levels of DAF-16 Class I genes, which are activated by DAF-16, were further elevated in the *daf-2;set* double mutants. Among these genes, *tts-1, F35E8.7, ins-35, nhr-62, sod-3, asm-2,* and *Y39G8B.7* are required for the lifespan extension of the *daf-2;set-21* double mutant. In addition, treating *daf-2* animals with the H3K9me1/2 methyltransferase G9a inhibitor also extends lifespan and increases stress resistance. Therefore, investigation of DAF-2 and H3K9me1/2 deficiency-mediated synergistic longevity will contribute to a better understanding of the molecular mechanisms of aging and therapeutic applications.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The unfolded protein response reverses the effects of glucose on lifespan in chemically-sterilized *C. elegans*

Caroline Beaudoin-Chabot, Lei Wang, Cenk Celik, Aishah Tul-Firdaus Abdul Khalid, Subhash Thalappilly, Shiyi Xu, Jhee Hong Koh, Venus Wen Xuan Lim, Ann Don Low & Guillaume Thibault

Nature Communications **13**, Article number: 5889 (2022) | Cite this article

Abstract

Metabolic diseases often share common traits, including accumulation of unfolded proteins in the endoplasmic reticulum (ER). Upon ER stress, the unfolded protein response (UPR) is activated to limit cellular damage which weakens with age. Here, we show that *Caenorhabditis elegans* fed a bacterial diet supplemented high glucose at day 5 of adulthood (HGD-5) extends their lifespan, whereas exposed at day 1 (HGD-1) experience shortened longevity. We observed a metabolic shift only in HGD-1, while glucose and infertility synergistically prolonged the lifespan of HGD-5, independently of DAF-16. Notably, we identified that UPR stress sensors ATF-6 and PEK-1 contributed to the longevity of HGD-5 worms, while *ire-1* ablation drastically increased HGD-1 lifespan. Together, we postulate that HGD activates the otherwise quiescent UPR in aged worms to overcome ageing-related stress and restore ER homeostasis. In contrast, young animals subjected to HGD provokes unresolved ER stress, conversely leading to a detrimental stress response.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Riboflavin depletion promotes longevity and metabolic hormesis in *Caenorhabditis elegans*

Armen Yerevanian, Luke M. Murphy, Sinclair Emans, Yifei Zhou, Fasih M. Ahsan, Daniel Baker, Sainan Li, Adebanjo Adedoja, Lucydalila Cedillo, Nicole L. Stuhr, Einstein Gnanatheepam ... See all authors

First published: 30 September 2022 | https://doi.org/10.1111/acel.13718

SECTIONS PDF TOOLS SHARE

Abstract

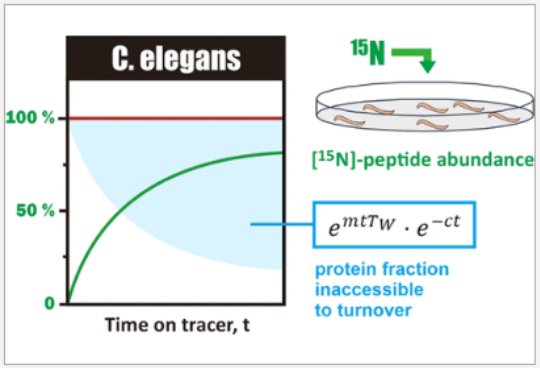
Riboflavin is an essential cofactor in many enzymatic processes and in the production of flavin adenine dinucleotide (FAD). Here, we report that the partial depletion of riboflavin through knockdown of the *C. elegans* riboflavin transporter 1 (*rft-1*) promotes metabolic health by reducing intracellular flavin concentrations. Knockdown of *rft-1* significantly increases lifespan in a manner dependent upon AMP-activated protein kinase (AMPK)/*aak-2*, the mitochondrial unfolded protein response, and FOXO/*daf-16*. Riboflavin depletion promotes altered energetic and redox states and increases adiposity, independent of lifespan genetic dependencies. Riboflavin-depleted animals also exhibit the activation of caloric restriction reporters without any reduction in caloric intake. Our findings indicate that riboflavin depletion activates an integrated hormetic response that promotes lifespan and healthspan in *C. elegans*.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Efficiency of Protein Renewal Is Limited by Feed Intake and Not by Protein Lifetime in Aging *Caenorhabditis elegans*

Jasmeet Kaur Khanijou, Zhuangli Yee, Manfred Raida, Jin Meng Lee, Evan Zhi En Tay, Jan Gruber, and Thomas Walczyk*

Protein turnover maintains the proteome's functional integrity. Here, protein turnover efficiency over time in wild-type *Caenorhabditis elegans* was assessed using inverse [^{15}N]-pulse labeling up to 7 days after the egg-laying phase at 20 °C. Isotopic analysis of some abundant proteins was executed favoring data quality over quantity for mathematical modeling. Surprisingly, isotopic enrichment over time reached an upper limit showing an apparent cessation of protein renewal well before death, with protein fractions inaccessible to turnover ranging from 14 to 83%. For life span modulation, worms were raised at different temperatures after egg laying. Mathematical modeling of isotopic enrichment points either to a slowdown of protein turnover or to an increasing protein fraction resistant to turnover with time. Most notably, the estimated time points of protein turnover cessation from our mathematical model were highly correlated with the observed median life span. Thrashing and pumping rates over time were linearly correlated with isotopic enrichment, therefore linking protein/tracer intake to protein turnover rate and protein life span. If confirmed, life span extension is possible by optimizing protein turnover rate through modulating protein intake in *C. elegans* and possibly other organisms. While proteome maintenance benefits from a high protein turnover rate, protein turnover is fundamentally energy-intensive, where oxidative stress contributes to damage that it is supposed to repair.



Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Intermittent hypoxia therapy engages multiple longevity pathways to double lifespan in *C.elegans*

Jason N. Pitt, Eduardo Chavez, Kathryn M. Provencher, Michelle Chen, Christina Tran, Jennifer Tran, Karen Huang, Anuj Vaid, Marian L Abadir, Naheed Arang, Scott F. Leiser, Mark B. Roth, Matt Kaeberlein

doi: https://doi.org/10.1101/2022.10.13.512140

Abstract

Genetic activation of the hypoxia response robustly extends lifespan in *C. elegans*, while environmental hypoxia shows more limited benefit. Here we describe an intermittent hypoxia therapy (IHT) able to double the lifespan of wildtype worms. The lifespan extension observed in IHT does not require HIF-1 but is partially blocked by loss of DAF-16/FOXO. RNAseq analysis shows that IHT triggers a transcriptional state distinct from continuous hypoxia and affects down-stream genes of multiple longevity pathways. We performed a temperature sensitive forward genetic screen to isolate mutants with delayed nuclear localization of DAF-16 in response to IHT and suppression of IHT longevity. One of these mutations mapped to the enzyme Inositol Polyphosphate MultiKinase (IPMK-1). *ipmk-1* mutants, like *daf-16* mutants, partially suppress the benefits of IHT, while other effectors of phosphatidyl inositol signaling pathways (PLCβ4, IPPK, Go/iα) more robustly suppress IHT longevity.

One-Sentence Summary Intermittent hypoxia therapy is frequency dependent, HIF independent, and requires FOXO, PLCβ, Go/iα, IPMK, and IPPK.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Perspective | Published: 14 October 2022

Why Gilgamesh failed: the mechanistic basis of the limits to human lifespan

Brandon Milholland & Jan Vijg

Nature Aging **2**, 878–884 (2022) | Cite this article

Abstract

The purpose of this Perspective is to clarify for an interdisciplinary audience the fundamental concepts of human longevity and provide evidence for a limit to human lifespan. This observed limit is placed into a broader framework by showing how it has arisen through the process of evolution and by enumerating the molecular mechanisms that may enforce it. Finally, we look toward potential future developments and the prospects for possibly circumventing the current limit.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metformin has heterogeneous effects on model organism lifespans and is beneficial when started at an early age in Caenorhabditis elegans: A systematic review and meta-analysis

Austin J Parish [1 2], William R Swindell [3]

Affiliations + expand

PMID: 36281624 DOI: 10.1111/acel.13733

Free article

Abstract

There is growing interest in the use of metformin to extend lifespan and prevent the onset of age-related disorders in non-diabetic individuals. The impact of metformin on lifespan and aging has been studied in several model organisms, with varying effects. We conducted a systematic review of studies that performed laboratory experiments investigating the effect of metformin on overall lifespan in healthy Mus musculus mice and in Caenorhabditis elegans nematodes. Lifespan results for mice and nematodes were analyzed in separate meta-analyses, and there was a significant amount of heterogeneity across experiments within each species. We found that metformin was not significantly associated with an overall lifespan-prolonging effect in either mice or nematodes. For nematodes, however, there was a lifespan-prolonging effect in experiments using live OP50 Escherichia coli as a food source, an effect that was larger when metformin was started earlier in life. Our work highlights the importance of testing compounds in a diversity of model organisms. Moreover, in all species, including humans, it may be necessary to study the effect of metformin on aging in both younger and older cohorts.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Rapamycin not Dietary Restriction improves resilience against pathogens: a meta-analysis

Eleanor J Phillips, Mirre J P Simons

doi: https://doi.org/10.1101/2022.10.06.511121

Abstract

Dietary Restriction (DR) and rapamycin both increase lifespan across a number of taxa. Despite this positive effect on lifespan and other aspects of health, reductions in some physiological functions have been reported for DR and rapamycin has been used as an immunosuppressant. Perhaps surprisingly, both interventions have been suggested to improve immune function and delay immunosenescence. The immune system is complex and consists of many components. Therefore, arguably, the most holistic measurement of immune function is survival from an acute pathogenic infection. We reanalysed published post-infection short-term survival data of mice (n=1223 from 23 studies comprising 46 effect sizes involving DR (n=17) and rapamycin treatment (n=29) and analysed these results using meta-analysis. Rapamycin treatment significantly increased post infection survival rate (lnHR=-0.72; CI=-1.17, -0.28; p=0.0015). In contrast, DR reduced post-infection survival (lnHR=0.80; CI=0.08, 1.52; p=0.03). Importantly, the overall effect size of rapamycin treatment was significantly lower (P<0.001) than the estimate from DR studies, suggesting opposite effects on immune function. Our results show that immunomodulation caused by rapamycin treatment is beneficial to the survival from acute infection. For DR our results are based on a smaller number of studies, but do warrant caution as they indicate possible immune costs of DR. Our quantitative synthesis suggests that the geroprotective effects of rapamycin extend to the immune system and warrants further clinical trials of rapamycin to boost immunity in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

COVID-19 and cellular senescence

Clemens A Schmitt [1 2 3 4 5], Tamar Tchkonia [6], Laura J Niedernhofer [7], Paul D Robbins [7], James L Kirkland [6], Soyoung Lee [8 9 10]

Affiliations + expand

PMID: 36198912 PMCID: PMC9533263 DOI: 10.1038/s41577-022-00785-2

Free PMC article

Abstract

The clinical severity of coronavirus disease 2019 (COVID-19) is largely determined by host factors. Recent advances point to cellular senescence, an ageing-related switch in cellular state, as a critical regulator of SARS-CoV-2-evoked hyperinflammation. SARS-CoV-2, like other viruses, can induce senescence and exacerbates the senescence-associated secretory phenotype (SASP), which is comprised largely of pro-inflammatory, extracellular matrix-degrading, complement-activating and pro-coagulatory factors secreted by senescent cells. These effects are enhanced in elderly individuals who have an increased proportion of pre-existing senescent cells in their tissues. SASP factors can contribute to a 'cytokine storm', tissue-destructive immune cell infiltration, endothelialitis (endotheliitis), fibrosis and microthrombosis. SASP-driven spreading of cellular senescence uncouples tissue injury from direct SARS-CoV-2-inflicted cellular damage in a paracrine fashion and can further amplify the SASP by increasing the burden of senescent cells. Preclinical and early clinical studies indicate that targeted elimination of senescent cells may offer a novel therapeutic opportunity to attenuate clinical deterioration in COVID-19 and improve resilience following infection with SARS-CoV-2 or other pathogens.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The Naked Mole-Rat as a Model for Healthy Aging

Annual Review of Animal Biosciences
Vol. 11:- (Volume publication date February 2023)
Review in Advance first posted online on November 1, 2022. (Changes may still occur before final publication.)
https://doi.org/10.1146/annurev-animal-050322-074744

Kaori Oka,[1] Masanori Yamakawa,[2] Yoshimi Kawamura,[1] Nobuyuki Kutsukake,[2,3] and Kyoko Miura[1,4]

Abstract

Naked mole-rats (NMRs, *Heterocephalus glaber*) are the longest-lived rodents with a maximum life span exceeding 37 years. They exhibit a delayed aging phenotype and resistance to age-related functional decline/diseases. Specifically, they do not display increased mortality with age, maintain several physiological functions until nearly the end of their lifetime, and rarely develop cancer and Alzheimer's disease. NMRs live in a hypoxic environment in underground colonies in East Africa and are highly tolerant of hypoxia. These unique characteristics of NMRs have attracted considerable interest from zoological and biomedical researchers. This review summarizes previous studies of the ecology, hypoxia tolerance, longevity/delayed aging, and cancer resistance of NMRs and discusses possible mechanisms contributing to their healthy aging. In addition, we discuss current issues and future perspectives to fully elucidate the mechanisms underlying delayed aging and resistance to age-related diseases in NMRs.

Heales
HEALTHY LIFE EXTENSION SOCIETY

FOXO transcription factors as therapeutic targets in human diseases

Alba Orea-Soufi [1], Jihye Paik [2], José Bragança [3], Timothy A Donlon [4], Bradley J Willcox [5], Wolfgang Link [6]

Affiliations + expand

PMID: 36280450 DOI: 10.1016/j.tips.2022.09.010

Abstract

Forkhead box (FOX)O proteins are transcription factors (TFs) with four members in mammals designated FOXO1, FOXO3, FOXO4, and FOXO6. FOXO TFs play a pivotal role in the cellular adaptation to diverse stress conditions. FOXO proteins act as context-dependent tumor suppressors and their dysregulation has been implicated in several age-related diseases. FOXO3 has been established as a major gene for human longevity. Accordingly, FOXO proteins have emerged as potential targets for the therapeutic development of drugs and geroprotectors. In this review, we provide an overview of the most recent advances in our understanding of FOXO regulation and function in various pathological conditions. We discuss strategies targeting FOXOs directly or by the modulation of upstream regulators, shedding light on the most promising intervention points. We also reveal the most relevant clinical indications and discuss the potential, trends, and challenges of modulating FOXO activity for therapeutic purposes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Molecular inhibition of RAS signalling to target ageing and age-related health

In collection: The RAS Pathway

Mihails Laskovs, Linda Partridge, Cathy Slack

+ Author and article information

Dis Model Mech (2022) 15 (10): dmm049627.

https://doi.org/10.1242/dmm.049627

Split-screen Views PDF Versions Share Tools

ABSTRACT

The RAS/MAPK pathway is a highly conserved signalling pathway with a well-established role in cancer. Mutations that hyperactivate this pathway are associated with unregulated cell proliferation. Evidence from a range of model organisms also links RAS/MAPK signalling to ageing. Genetic approaches that reduce RAS/MAPK signalling activity extend lifespan and also improve healthspan, delaying the onset and/or progression of age-related functional decline. Given its role in cancer, therapeutic interventions that target and inhibit this pathway's key components are under intense investigation. The consequent availability of small molecule inhibitors raises the possibility of repurposing these compounds to ameliorate the deleterious effects of ageing. Here, we review evidence that RAS/MAPK signalling inhibitors already in clinical use, such as trametinib, acarbose, statins, metformin and dihydromyricetin, lead to lifespan extension and to improved healthspan in a range of model systems. These findings suggest that the repurposing of small molecule inhibitors of RAS/MAPK signalling might offer opportunities to improve health during ageing, and to delay or prevent the development of age-related disease. However, challenges to this approach, including poor tolerance to treatment in older adults or development of drug resistance, first need to be resolved before successful clinical implementation.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Role of Nrf2 in aging, Alzheimer's and other neurodegenerative diseases

Mathew George [1], Matthan Tharakan [2], John Culberson [3], Arubala P Reddy [4], P Hemachandra Reddy [5]

Affiliations + expand

PMID: 36243357 DOI: 10.1016/j.arr.2022.101756

Abstract

Nuclear Factor-Erythroid Factor 2 (Nrf2) is an important transcription factor that regulates the expression of large number of genes in healthy and disease states. Nrf2 is made up of 605 amino acids and contains 7 conserved regions known as Nrf2-ECH homology domains. Nrf2 regulates the expression of several key components of oxidative stress, mitochondrial biogenesis, mitophagy, autophagy and mitochondrial function in all organs of the human body, in the peripheral and central nervous systems. Mounting evidence also suggests that altered expression of Nrf2 is largely involved in aging, neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's diseases, Amyotrophic lateral sclerosis, Stroke, Multiple sclerosis and others. The purpose of this article is to detail the essential role of Nrf2 in oxidative stress, antioxidative defense, detoxification, inflammatory responses, transcription factors, proteasomal and autophagic/mitophagic degradation, and metabolism in aging and neurodegenerative diseases. This article also highlights the Nrf2 structural and functional activities in healthy and disease states, and also discusses the current status of Nrf2 research and therapeutic strategies to treat aging and neurodegenerative diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Therapeutic Antiaging Strategies

by Shailendra Kumar Mishra [1], Vyshnavy Balendra [2], Josephine Esposto [3], Ahmad A. Obaid [4], Ricardo B. Maccioni [5], Niraj Kumar Jha [6,7,8], George Perry [9], Mahmoud Moustafa [10,11], Mohammed Al-Shehri [10], Mahendra P. Singh [12], Anmar Anwar Khan [13], Emanuel Vamanu [14,*] and Sandeep Kumar Singh [1,*]

Aging constitutes progressive physiological changes in an organism. These changes alter the normal biological functions, such as the ability to manage metabolic stress, and eventually lead to cellular senescence. The process itself is characterized by nine hallmarks: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. These hallmarks are risk factors for pathologies, such as cardiovascular diseases, neurodegenerative diseases, and cancer. Emerging evidence has been focused on examining the genetic pathways and biological processes in organisms surrounding these nine hallmarks. From here, the therapeutic approaches can be addressed in hopes of slowing the progression of aging. In this review, data have been collected on the hallmarks and their relative contributions to aging and supplemented with in vitro and in vivo antiaging research experiments. It is the intention of this article to highlight the most important antiaging strategies that researchers have proposed, including preventive measures, systemic therapeutic agents, and invasive procedures, that will promote healthy aging and increase human life expectancy with decreased side effects. View Full-Text

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Evolutionary-scale prediction of atomic level protein structure with a language model

Zeming Lin, Halil Akin, Roshan Rao, Brian Hie, Zhongkai Zhu, Wenting Lu, Nikita Smetanin, Robert Verkuil, Ori Kabeli, Yaniv Shmueli, Allan dos Santos Costa, Maryam Fazel-Zarandi, Tom Sercu, Salvatore Candido, Alexander Rives

doi: https://doi.org/10.1101/2022.07.20.500902

Abstract

Artificial intelligence has the potential to open insight into the structure of proteins at the scale of evolution. It has only recently been possible to extend protein structure prediction to two hundred million cataloged proteins. Characterizing the structures of the exponentially growing billions of protein sequences revealed by large scale gene sequencing experiments would necessitate a breakthrough in the speed of folding. Here we show that direct inference of structure from primary sequence using a large language model enables an order of magnitude speed-up in high resolution structure prediction. Leveraging the insight that language models learn evolutionary patterns across millions of sequences, we train models up to 15B parameters, the largest language model of proteins to date. As the language models are scaled they learn information that enables prediction of the three-dimensional structure of a protein at the resolution of individual atoms. This results in prediction that is up to 60x faster than state-of-the-art while maintaining resolution and accuracy. Building on this, we present the ESM Metagenomic Atlas. This is the first large-scale structural characterization of metagenomic proteins, with more than 617 million structures. The atlas reveals more than 225 million high confidence predictions, including millions whose structures are novel in comparison with experimentally determined structures, giving an unprecedented view into the vast breadth and diversity of the structures of some of the least understood proteins on earth.