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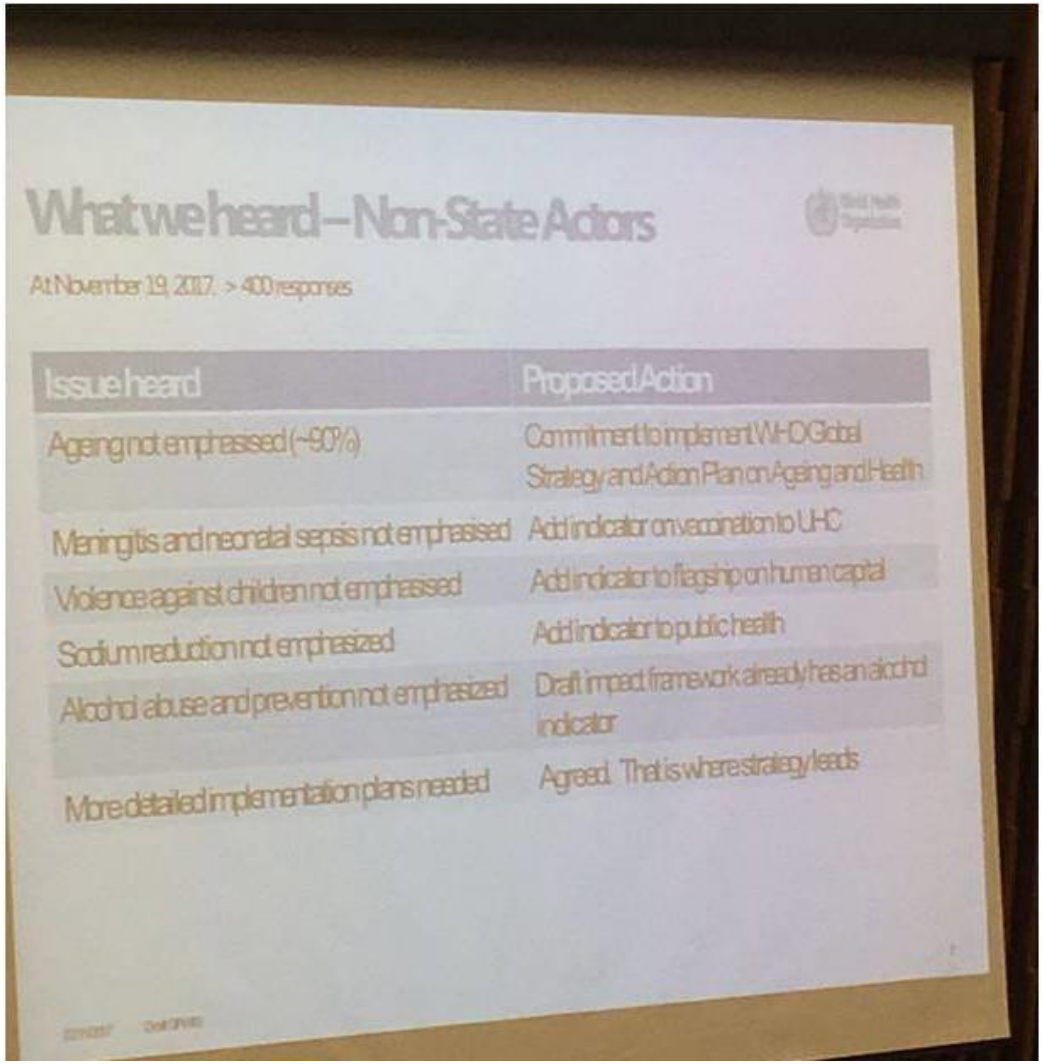
Scientific News
5th of November 2017
Sven Bulterijs

90% of survey participants commented on the lack of aging in the WHO program!



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Biogen Presents New Data from Long-Term Extension of Phase 1b Study of Investigational Alzheimer's Disease Treatment Aducanumab

- *Two-year data from Phase 1b study suggest a continued benefit on amyloid plaque reduction and the rate of clinical decline in the titration regimen group, which received a gradually increased aducanumab dose*
- *The results at two years in the titration regimen group were consistent with the dose- and time-dependent results observed in the treatment groups that received a fixed-dose of 3, 6 or 10 mg/kg aducanumab during the same time period*
- *Results from treatment groups that received a fixed-dose of 3, 6 or 10 mg/kg aducanumab for up to three years were consistent with previously reported analyses from the Phase 1b study and support the design of the ongoing Phase 3 studies of aducanumab for early Alzheimer's disease*

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Anti-aging startup ResTORbio gets $40M to fuel Phase IIb study

ResTORbio, a new company developing tech spun out of Novartis, has raised $40 million in a Series B round to speed its anti-aging program through the clinic.

The startup, which was set up earlier this year as a subsidiary of Boston-based PureTech Health, has brought in $65 million since its inception. The money will be used to advance the company's lead immunotherapy program meant to reduce respiratory tract infections in elderly subjects, which is already in Phase IIb. Results are expected next year.

Chen Schor

Leftover funds will also be used to start a study in an additional aging-related disease, although resTORbio did not share the details.

"We believe our approach may provide an opportunity to address multiple aging-related diseases beyond our initial indication for reducing the incidence of respiratory tract infections in the elderly," said president and CEO Chen Schor in a statement.

The company in-licensed its lead program, called RTB101, from the Novartis Institute of BioMedical Research back in March. RTB101 targets the rapamycin complex 1 (mTORC1) pathway. To start, resTORbio plans on developing medicines that address immunosenescence, the decline in immune function due to aging.

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Are We Reaching the Limits of *Homo sapiens*?

Adrien Marck[1,2], Juliana Antero[1], Geoffroy Berthelot[1,3,4], Guillaume Saulière[1], Jean-Marc Jancovici[5], Valérie Masson-Delmotte[6], Gilles Boeuf[7], Michael Spedding[8], Éric Le Bourg[9] and Jean-François Toussaint[1,3,10*]

Echoing scientific and industrial progress, the Twentieth century was an unprecedented period of improvement for human capabilities and performances, with a significant increase in lifespan, adult height, and maximal physiological performance. Analyses of historical data show a major slow down occurring in the most recent years. This triggered large and passionate debates in the academic scene within multiple disciplines; as such an observation could be interpreted as our upper biological limits. Such a new phase of human history may be related to structural and functional limits determined by long term evolutionary constraints, and the interaction between complex systems and their environment. In this interdisciplinary approach, we call into question the validity of subsequent forecasts and projections through innovative and related biomarkers such as sport, lifespan, and height indicators. We set a theoretical framework based on biological and environmental relevance rather than using a typical single-variable forecasting approach. As demonstrated within the article, these new views will have major social, economical, and political implications.

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CORRECTED PROOF

Breaking the Ceiling of Human Maximal Life span FREE

Moshe Shay Ben-Haim, PhD, Yariv Kanfi, PhD, Sarah J Mitchell, PhD, Noam Maoz, PhD, Kelli L Vaughan, MS, Ninette Amariglio, PhD, Batia Lerrer, PhD, Rafael de Cabo, PhD, Gideon Rechavi, MD, PhD ✉, Haim Y Cohen, PhD

The Journals of Gerontology: Series A, glx219, https://doi.org/10.1093/gerona/glx219
Published: 07 November 2017 **Article history** ▾

Abstract

While average human life expectancy has increased dramatically in the last century, the maximum life span has only modestly increased. These observations prompted the notion that human life span might have reached its maximal natural limit of ~115 years. To evaluate this hypothesis, we conducted a systematic analysis of all-cause human mortality throughout the 20th century. Our analyses revealed that, once cause of death is accounted for, there is a proportional increase in both median age of death and maximum life span. To examine whether pathway targeted aging interventions affected both *median* and *maximum* life span, we analyzed hundreds of interventions performed in multiple organisms (yeast, worms, flies, and rodents). Three criteria: median, maximum, and last survivor life spans were all significantly extended, and to a similar extent. Altogether, these findings suggest that targeting the biological/genetic causes of aging can allow breaking the currently observed ceiling of human maximal life span.

A null mutation in *SERPINE1* protects against biological aging in humans

Abstract

Plasminogen activator inhibitor–1 (PAI-1) has been shown to be a key component of the senescence-related secretome and a direct mediator of cellular senescence. In murine models of accelerated aging, genetic deficiency and targeted inhibition of PAI-1 protect against aging-like pathology and prolong life span. However, the role of PAI-1 in human longevity remains unclear. We hypothesized that a rare loss-of-function mutation in *SERPINE1* (c.699_700dupTA), which encodes PAI-1, could play a role in longevity and metabolism in humans. We studied 177 members of the Berne Amish community, which included 43 carriers of the null *SERPINE1* mutation. Heterozygosity was associated with significantly longer leukocyte telomere length, lower fasting insulin levels, and lower prevalence of diabetes mellitus. In the extended Amish kindred, carriers of the null SERPINE1 allele had a longer life span. Our study indicates a causal effect of PAI-1 on human longevity, which may be mediated by alterations in metabolism. Our findings demonstrate the utility of studying loss-of-function mutations in populations with geographic and genetic isolation and shed light on a novel therapeutic target for aging.

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NPJ Aging Mech Dis. 2017 Nov 20;3:16. doi: 10.1038/s41514-017-0018-7. eCollection 2017.

Health benefits of late-onset metformin treatment every other week in mice.

Alfaras I[1], Mitchell SJ[1], Mora H[1], Lugo DR[1], Warren A[2], Navas-Enamorado I[1], Hoffmann V[3], Hine C[4], Mitchell JR[4], Le Couteur DG[2,5], Cogger VC[2,5], Bernier M[1], de Cabo R[1].

⊕ Author information

Abstract

Chronic 1% metformin treatment is nephrotoxic in mice, but this dose may nonetheless confer health benefits if given intermittently rather than continuously. Here, we examined the effects of 1% metformin given every-other week (EOW) or two consecutive weeks per month (2WM) on survival of 2-year-old male mice fed standard chow. EOW and 2WM mice had comparable life span compared with control mice. A significant reduction in body weight within the first few weeks of metformin treatment was observed without impact on food consumption and energy expenditure. Moreover, there were differences in the action of metformin on metabolic markers between the EOW and 2WM groups, with EOW metformin conferring greater benefits. Age-associated kidney lesions became more pronounced with metformin, although without pathological consequences. In the liver, metformin treatment led to an overall reduction in steatosis and was accompanied by distinct transcriptomic and metabolomic signatures in response to EOW versus 2WM regimens. Thus, the absence of adverse outcomes associated with chronic, intermittent use of 1% metformin in old mice has clinical translatability into the biology of aging in humans.

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Ageing Res Rev. 2017 Nov;40:31-44. doi: 10.1016/j.arr.2017.08.003. Epub 2017 Aug 10.

Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis.

Campbell JM[1], Bellman SM[2], Stephenson MD[2], Lisy K[3].

Author information

Abstract

This systematic review investigated whether the insulin sensitiser metformin has a geroprotective effect in humans. Pubmed and Embase were searched along with databases of unpublished studies. Eligible research investigated the effect of metformin on all-cause mortality or diseases of ageing relative to non-diabetic populations or diabetics receiving other therapies with adjustment for disease control achieved. Overall, 260 full-texts were reviewed and 53 met the inclusion criteria. Diabetics taking metformin had significantly lower all-cause mortality than non-diabetics (hazard ratio (HR)=0.93, 95%CI 0.88-0.99), as did diabetics taking metformin compared to diabetics receiving non-metformin therapies (HR=0.72, 95%CI 0.65-0.80), insulin (HR=0.68, 95%CI 0.63-0.75) or sulphonylurea (HR=0.80, 95%CI 0.66-0.97). Metformin users also had reduced cancer compared to non-diabetics (rate ratio=0.94, 95%CI 0.92-0.97) and cardiovascular disease (CVD) compared to diabetics receiving non-metformin therapies (HR=0.76, 95%CI 0.66-0.87) or insulin (HR=0.78, 95%CI 0.73-0.83). Differences in baseline characteristics were observed which had the potential to bias findings, although statistical adjustments were made. The apparent reductions in all-cause mortality and diseases of ageing associated with metformin use suggest that metformin could be extending life and healthspans by acting as a geroprotective agent.

Metformin extends *C. elegans* lifespan through lysosomal pathway

Jie Chen, Yuhui Ou, Yi Li, Shumei Hu, Li-Wa Shao, Ying Liu ✉
Institute of Molecular Medicine, Peking-Tsinghua Center for Life Sciences, Peking University, China; Peking University, China

Metformin, a widely used first-line drug for treatment of type 2 diabetes (T2D), has been shown to extend lifespan and delay the onset of age-related diseases. However, its primary locus of action remains unclear. Using a pure in vitro reconstitution system, we demonstrate that metformin acts through the v-ATPase-Ragulator lysosomal pathway to coordinate mTORC1 and AMPK, two hubs governing metabolic programs. We further show in *Caenorhabditis elegans* that both v-ATPase-mediated TORC1 inhibition and v-ATPase-AXIN/LKB1-mediated AMPK activation contribute to the lifespan extension effect of metformin. Elucidating the molecular mechanism of metformin regulated healthspan extension will boost its therapeutic application in the treatment of human aging and age-related diseases.

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Mitochondrial Stress Restores the Heat Shock Response and Prevents Proteostasis Collapse during Aging

Johnathan Labbadia [1, 3], Renee M. Brielmann [1], Mario F. Neto [1], Yi-Fan Lin [2], Cole M. Haynes [2], Richard I. Morimoto [1, 4]

In *Caenorhabditis elegans*, the programmed repression of the heat shock response (HSR) accompanies the transition to reproductive maturity, leaving cells vulnerable to environmental stress and protein aggregation with age. To identify the factors driving this event, we performed an unbiased genetic screen for suppressors of stress resistance and identified the mitochondrial electron transport chain (ETC) as a central regulator of the age-related decline of the HSR and cytosolic proteostasis. Mild downregulation of ETC activity, either by genetic modulation or exposure to mitochondria-targeted xenobiotics, maintained the HSR in adulthood by increasing HSF-1 binding and RNA polymerase II recruitment at HSF-1 target genes. This resulted in a robust restoration of cytoplasmic proteostasis and increased vitality later in life, without detrimental effects on fecundity. We propose that low levels of mitochondrial stress regulate cytoplasmic proteostasis and healthspan during aging by coordinating the long-term activity of HSF-1 with conditions preclusive to optimal fitness.

A lysosomal switch triggers proteostasis renewal in the immortal *C. elegans* germ lineage

K. Adam Bohnert & Cynthia Kenyon

Although individuals age and die with time, an animal species can continue indefinitely, because of its immortal germ-cell lineage[1]. How the germline avoids transmitting damage from one generation to the next remains a fundamental question in biology. Here we identify a lysosomal switch that enhances germline proteostasis before fertilization. We find that *Caenorhabditis elegans* oocytes whose maturation is arrested by the absence of sperm[2] exhibit hallmarks of proteostasis collapse, including protein aggregation. Remarkably, sperm-secreted hormones re-establish oocyte proteostasis once fertilization becomes imminent. Key to this restoration is activation of the vacuolar H^+-ATPase (V-ATPase), a proton pump that acidifies lysosomes[3]. Sperm stimulate V-ATPase activity in oocytes by signalling the degradation of GLD-1, a translational repressor[4] that blocks V-ATPase synthesis. Activated lysosomes, in turn, promote a metabolic shift that mobilizes protein aggregates for degradation, and reset proteostasis by enveloping and clearing the aggregates. Lysosome acidification also occurs during *Xenopus* oocyte maturation; thus, a lysosomal switch that enhances oocyte proteostasis in anticipation of fertilization may be conserved in other species.

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Neuronal inhibition of the autophagy nucleation complex extends life span in post-reproductive *C. elegans*

Thomas Wilhelm[1,2,4], Jonathan Byrne[1,2,4], Rebeca Medina[1], Ena Kolundžić[3], Johannes Geisinger[1,2], Martina Hajduskova[3], Baris Tursun[3] and Holger Richly[1]

Autophagy is a ubiquitous catabolic process that causes cellular bulk degradation of cytoplasmic components and is generally associated with positive effects on health and longevity. Inactivation of autophagy has been linked with detrimental effects on cells and organisms. The antagonistic pleiotropy theory postulates that some fitness-promoting genes during youth are harmful during aging. On this basis, we examined genes mediating post-reproductive longevity using an RNAi screen. From this screen, we identified 30 novel regulators of post-reproductive longevity, including *pha-4*. Through downstream analysis of *pha-4*, we identified that the inactivation of genes governing the early stages of autophagy up until the stage of vesicle nucleation, such as *bec-1*, strongly extend both life span and health span. Furthermore, our data demonstrate that the improvements in health and longevity are mediated through the neurons, resulting in reduced neurodegeneration and sarcopenia. We propose that autophagy switches from advantageous to harmful in the context of an age-associated dysfunction.

Autophagy is required for endothelial cell alignment and atheroprotection under physiological blood flow

It has been known for some time that atherosclerotic lesions preferentially develop in areas exposed to low SS and are characterized by a proinflammatory, apoptotic, and senescent endothelial phenotype. Conversely, areas exposed to high SS are protected from plaque development, but the mechanisms have remained elusive. Autophagy is a protective mechanism that allows recycling of defective organelles and proteins to maintain cellular homeostasis. We aimed to understand the role of endothelial autophagy in the atheroprotective effect of high SS. Atheroprotective high SS stimulated endothelial autophagic flux in human and murine arteries. On the contrary, endothelial cells exposed to atheroprone low SS were characterized by inefficient autophagy as a result of mammalian target of rapamycin (mTOR) activation, AMPKα inhibition, and blockade of the autophagic flux. In hypercholesterolemic mice, deficiency in endothelial autophagy increased plaque burden only in the atheroresistant areas exposed to high SS; plaque size was unchanged in atheroprone areas, in which endothelial autophagy flux is already blocked. In cultured cells and in transgenic mice, deficiency in endothelial autophagy was characterized by defects in endothelial alignment with flow direction, a hallmark of endothelial cell health. This effect was associated with an increase in endothelial apoptosis and senescence in high-SS regions. Deficiency in endothelial autophagy also increased TNF-α–induced inflammation under high-SS conditions and decreased expression of the antiinflammatory factor KLF-2. Altogether, these results show that adequate endothelial autophagic flux under high SS limits atherosclerotic plaque formation by preventing endothelial apoptosis, senescence, and inflammation.

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RNA polymerase III limits longevity downstream of TORC1

Danny Filer, Maximillian A. Thompson, Vakil Takhaveev, Adam J. Dobson, Ilektra Kotronaki, James W. M. Green, Matthias Heinemann, Jennifer M. A. Tullet ✉ & Nazif Alic ✉

Three distinct RNA polymerases transcribe different classes of genes in the eukaryotic nucleus[1]. RNA polymerase (Pol) III is the essential, evolutionarily conserved enzyme that generates short, non-coding RNAs, including tRNAs and 5S rRNA[2]. The historical focus on transcription of protein-coding genes has left the roles of Pol III in organismal physiology relatively unexplored. Target of rapamycin kinase complex 1 (TORC1) regulates Pol III activity, and is also an important determinant of longevity[3]. This raises the possibility that Pol III is involved in ageing. Here we show that Pol III limits lifespan downstream of TORC1. We find that a reduction in Pol III extends chronological lifespan in yeast and organismal lifespan in worms and flies. Inhibiting the activity of Pol III in the gut of adult worms or flies is sufficient to extend lifespan; in flies, longevity can be achieved by Pol III inhibition specifically in intestinal stem cells. The longevity phenotype is associated with amelioration of age-related gut pathology and functional decline, dampened protein synthesis and increased tolerance of proteostatic stress. Pol III acts on lifespan downstream of TORC1, and limiting Pol III activity in the adult gut achieves the full longevity benefit of systemic TORC1 inhibition. Hence, Pol III is a pivotal mediator of this key nutrient-signalling network for longevity; the growth-promoting anabolic activity of Pol III mediates the acceleration of ageing by TORC1. The evolutionary conservation of Pol III affirms its potential as a therapeutic target.

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Am J Epidemiol. 2017 Nov 15. doi: 10.1093/aje/kwx346. [Epub ahead of print]

Eleven Telomere, Epigenetic Clock, and Biomarker-Composite Quantifications of Biological Aging: Do They Measure the Same Thing?

Belsky DW, Moffitt TE, Cohen AA, Corcoran DL, Levine ME, Prinz JA, Schaefer J, Sugden K, Williams B, Poulton R, Caspi A.

Abstract

The geroscience hypothesis posits that therapies to slow biological processes of aging can prevent disease and extend healthy years of life. To test such "gero-protective" therapies in humans, outcome measures are needed that can assess extension of disease-free lifespan. This need has spurred development of different methods to quantify biological aging. But different methods have not been systematically compared in the same humans. We implemented seven methods to quantify biological aging using repeated-measures physiological and genomic data in 964 middle-aged humans in the Dunedin Study. We studied telomere-length and erosion, three epigenetic-clocks and their ticking rates, and three biomarker-composites, 11 measures in total. Contrary to expectation, we found low agreement between different measures of biological aging. We next compared associations between biological aging measures and outcomes gero-protective therapies seek to modify: physical functioning, cognitive decline, and subjective signs of aging, including aged facial appearance. The 71-CpG epigenetic clock and biomarker composites were consistently related to these aging-related outcomes. However, effect-sizes were modest. Results suggests that various proposed approaches to quantifying biological aging may not measure the same aspects of the aging process. Further systematic evaluation and refinement of measures of biological aging is needed to furnish outcomes for geroprotector trials.

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A High-Throughput Screen for Yeast Replicative Lifespan Identifies Lifespan-Extending Compounds

Ethan A. Sarnoski, Ping Liu, Murat Acar[5]

Progress in aging research is constrained by the time requirement of measuring lifespans. Even the most rapid model for eukaryotic aging, the replicative lifespan of *Saccharomyces cerevisiae*, is technically limited to only several lifespan measurements each day. Here we report a 384-well plate-based technique to measure replicative lifespan, termed High-Life. Using the High-Life technique, a single researcher can compare lifespan for more than 1,000 conditions per day. We validated the technique with long-lived mutant strains and the lifespan-extending compound ibuprofen. We also applied this technique to screen a small compound library for lifespan extension. Two hits, terreic acid and mycophenolic acid, were validated on our single-cell replicator device and found to extend mean replicative lifespan by 15% and 20%, respectively. Together, we report a technique for high-throughput lifespan measurement, and we identify two lifespan-extending compounds. Our technique could be used to efficiently drive early-stage discovery of pro-longevity therapeutics.

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Uncoupling of Metabolic Health from Longevity through Genetic Alteration of Adipose Tissue Lipid-Binding Proteins

Khanichi N. Charles[3,5], Min-Dian Li[5], Feyza Engin[4], Ana Paula Arruda, Karen Inouye, Gökhan S. Hotamisligil[6]

Deterioration of metabolic health is a hallmark of aging and generally assumed to be detrimental to longevity. Exposure to a high-calorie diet impairs metabolism and accelerates aging; conversely, calorie restriction (CR) prevents age-related metabolic diseases and extends lifespan. However, it is unclear whether preservation of metabolic health is sufficient to extend lifespan. We utilized a genetic mouse model lacking *Fabp4/5* that confers protection against metabolic diseases and shares molecular and lipidomic features with CR to address this question. *Fabp*-deficient mice exhibit extended metabolic healthspan, with protection against insulin resistance and glucose intolerance, inflammation, deterioration of adipose tissue integrity, and fatty liver disease. Surprisingly, however, *Fabp*-deficient mice did not exhibit any extension of lifespan. These data indicate that extension of metabolic healthspan in the absence of CR can be uncoupled from lifespan, indicating the potential for independent drivers of these pathways, at least in laboratory mice.

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Secreted αKlotho isoform protects against age-dependent memory deficits

A Massó, A Sánchez, A Bosch, L Giménez-Llort & M Chillón

αKlotho is a gene regulator of aging, increasing life expectancy when overexpressed and accelerating the development of aging phenotypes when inhibited. In mice, expression levels of the secreted isoform Klotho (s-KL) are very high in the brain, suggesting that s-KL activity may have an important role in the nervous system. Here we study the functional relevance at behavioural level of modifying s-KL levels in the aging brain. We used AAVrh10 vectors to deliver and sustained expression of s-KL in 6- and 12-month-old wild-type C57BL/6J males. This study demonstrates for we believe the first time *in vivo* that 6 months after a single injection of s-KL into the central nervous system, long-lasting and quantifiable enhancement of learning and memory capabilities are found. More importantly, cognitive improvement is also observable in 18-month-old mice treated once, at 12 months of age. These findings demonstrate the therapeutic potential of s-KL as a treatment for cognitive decline associated with aging.

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Early Alzheimer-type lesions in cognitively normal subjects.

Tsartsalis S[1], Xekardaki A[2], Hof PR[3], Kövari E[2], Bouras C[2].

Author information

Abstract

Amyloid deposits and tau-immunoreactive neurofibrillary tangles, together with neuronal and synaptic loss, are the neuropathological hallmarks of Alzheimer's disease (AD). Both proteins are present in the normal brain during aging. However, the temporal sequence of their involvement in the onset of AD pathology remains controversial. To define whether amyloid β protein deposits or tau protein lesions appear first during normal brain aging, we performed an immunohistological study on serial sections from 105 autopsy brains (age range: 40-104 years) from patients free of clinical signs of cognitive decline, using anti-tau (AT8) and anti-amyloid (4G8) antibodies in the hippocampus, entorhinal cortex, inferior temporal cortex (Brodmann area 20), prefrontal cortex (Brodmann area 9), occipital cortex (Brodmann areas 17 and 18), and in the brainstem. All cases older than 48 years displayed at least a few neurofibrillary tangles, which appeared more frequently in the entorhinal than in the transentorhinal cortex. Tau pathology in these areas preceded tau inclusions in the brainstem. Furthermore, the first site of the apparition of tau pathology is inconsistent, being the entorhinal cortex in most cases, and in fewer cases, the transentorhinal region. There was no case presenting with amyloid deposition in the absence of neurofibrillary tangles, lending evidence to the fact that neurofibrillary tangles appear earlier than amyloid plaques during normal brain aging. However, the role of amyloid in promoting tau deposition cannot be excluded in some cases but may not represent the sole mechanism of disease induction and progression.

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Neuropathological and transcriptomic characteristics of the aged brain

Jeremy A Miller, Angela Guillozet-Bongaarts, Laura E Gibbons, Nadia Postupna, Anne Renz, Allison E Beller, Susan M Sunkin, Lydia Ng, Shannon E Rose
see all »

As more people live longer, age-related neurodegenerative diseases are an increasingly important societal health issue. Treatments targeting specific pathologies such as amyloid beta in Alzheimer's disease (AD) have not led to effective treatments, and there is increasing evidence of a disconnect between traditional pathology and cognitive abilities with advancing age, indicative of individual variation in resilience to pathology. Here, we generated a comprehensive neuropathological, molecular, and transcriptomic characterization of hippocampus and two regions cortex in 107 aged donors (median = 90) from the Adult Changes in Thought (ACT) study as a freely-available resource (http://aging.brain-map.org/). We confirm established associations between AD pathology and dementia, albeit with increased, presumably aging-related variability, and identify sets of co-expressed genes correlated with pathological tau and inflammation markers. Finally, we demonstrate a relationship between dementia and RNA quality, and find common gene signatures, highlighting the importance of properly controlling for RNA quality when studying dementia.

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Naked Mole Rat Cells Have a Stable Epigenome that Resists iPSC Reprogramming

Li Tan[6], Zhonghe Ke[6], Gregory Tombline, Nicholas Macoretta, Kevin Hayes, Xiao Tian, Ruitu Lv, Julia Ablaeva, Michael Gilbert, Natarajan V. Bhanu, Zuo-Fei Yuan, Benjamin A. Garcia, Yujiang G. Shi, Yang Shi, Andrei Seluanov, Vera Gorbunova

Naked mole rat (NMR) is a valuable model for aging and cancer research due to its exceptional longevity and cancer resistance. We observed that the reprogramming efficiency of NMR fibroblasts in response to OSKM was drastically lower than that of mouse fibroblasts. Expression of SV40 LargeT antigen (LT) dramatically improved reprogramming of NMR fibroblasts. Inactivation of Rb alone, but not p53, was sufficient to improve reprogramming efficiency, suggesting that NMR chromatin may be refractory to reprogramming. Analysis of the global histone landscape revealed that NMR had higher levels of repressive H3K27 methylation marks and lower levels of activating H3K27 acetylation marks than mouse. ATAC-seq revealed that in NMR, promoters of reprogramming genes were more closed than mouse promoters, while expression of LT led to massive opening of the NMR promoters. These results suggest that NMR displays a more stable epigenome that resists de-differentiation, contributing to the cancer resistance and longevity of this species.

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Aged Gut Microbiota Contributes to Systemical Inflammaging after Transfer to Germ-Free Mice

 Floris Fransen[1,2]*, Adriaan A. van Beek[1,3], Theo Borghuis[1,2], Sahar El Aidy[4], Floor Hugenholtz[1,5], Christa van der Gaast – de Jongh[6], Huub F. J. Savelkoul[3], Marien I. De Jonge[6],  Mark V. Boekschoten[1,7], Hauke Smidt[1,5], Marijke M. Faas[2,8] and  Paul de Vos[1,2]

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Advanced age is associated with chronic low-grade inflammation, which is usually referred to as inflammaging. Elderly are also known to have an altered gut microbiota composition. However, whether inflammaging is a cause or consequence of an altered gut microbiota composition is not clear. In this study, gut microbiota from young or old conventional mice was transferred to young germ-free (GF) mice. Four weeks after gut microbiota transfer immune cell populations in spleen, Peyer's patches, and mesenteric lymph nodes from conventionalized GF mice were analyzed by flow cytometry. In addition, whole-genome gene expression in the ileum was analyzed by microarray. Gut microbiota composition of donor and recipient mice was analyzed with 16S rDNA sequencing. Here, we show by transferring aged microbiota to young GF mice that certain bacterial species within the aged microbiota promote inflammaging. This effect was associated with lower levels of *Akkermansia* and higher levels of TM7 bacteria and *Proteobacteria* in the aged microbiota after transfer. The aged microbiota promoted inflammation in the small intestine in the GF mice and enhanced leakage of inflammatory bacterial components into the circulation was observed. Moreover, the aged microbiota promoted increased T cell activation in the systemic compartment. In conclusion, these data indicate that the gut microbiota from old mice contributes to inflammaging after transfer to young GF mice.

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Whales, lifespan, phospholipids and cataracts

Douglas Borchman[1,*], Raphaela Stimmelmayr[2] and George Craig[3]

This study addresses the question: why do rats get cataracts at two years, dogs at eight years and whales do not develop cataracts for 200 years? Whale lens lipid phase transitions were compared to the phase transitions of other species that were recalculated. The major phospholipids of the whale lens were sphingolipids, mostly dihydrosphingomyelins with an average molar cholesterol/phospholipid ratio of 10. There was a linear correlation between the percentage of lens sphingolipid and lens lipid hydrocarbon chain order until about 60 % sphingolipid. The percentage of lens sphingolipid correlated with the lens lipid phase transition temperature. The lifespan of the bowhead whale was the longest of the species measured and the percentage of whale lens sphingolipid fit well in the correlation between the percentage of lens sphingolipid and lifespan for many species. In conclusion, bowhead whale lens membranes have a high sphingolipid content that confers resistance to oxidation, allowing these lenses to stay clear relatively longer than many other species. The strong correlation between sphingolipid and lifespan may form a basis for future studies which are needed since correlations do not infer cause. One could hope that if human lenses could be made to have a lipid composition similar to whales, like the bowhead, humans would not develop age-related cataracts for over 100 years.

REVIEWS/COMMENTS/EDITORIALS

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REVIEW ARTICLE

Monogenic Diseases of DNA Repair

Guido Keijzers, Ph.D., Daniela Bakula, Ph.D., and Morten Scheibye-Knudsen, M.D., Ph.D.
N Engl J Med 2017; 377:1868-1876 | November 9, 2017 | DOI: 10.1056/NEJMra1703366

Maintenance of genomic integrity involves cellular processes tailored to specific types of DNA damage. Monogenic disorders in DNA-repair pathways lead to a spectrum of clinical phenotypes that are not always correlated with our understanding of the affected repair pathway.

Review

Senescence and aging: Causes, consequences, and therapeutic avenues

Domhnall McHugh, Jesús Gil

Abstract

Aging is the major risk factor for cancer, cardiovascular disease, diabetes, and neurodegenerative disorders. Although we are far from understanding the biological basis of aging, research suggests that targeting the aging process itself could ameliorate many age-related pathologies. Senescence is a cellular response characterized by a stable growth arrest and other phenotypic alterations that include a proinflammatory secretome. Senescence plays roles in normal development, maintains tissue homeostasis, and limits tumor progression. However, senescence has also been implicated as a major cause of age-related disease. In this regard, recent experimental evidence has shown that the genetic or pharmacological ablation of senescent cells extends life span and improves health span. Here, we review the cellular and molecular links between cellular senescence and aging and discuss the novel therapeutic avenues that this connection opens.

OTHER RESEARCH

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Structure-guided chemical modification of guide RNA enables potent non-viral *in vivo* genome editing

Efficient genome editing with Cas9–sgRNA *in vivo* has required the use of viral delivery systems, which have limitations for clinical applications. Translational efforts to develop other RNA therapeutics have shown that judicious chemical modification of RNAs can improve therapeutic efficacy by reducing susceptibility to nuclease degradation. Guided by the structure of the Cas9–sgRNA complex, we identify regions of sgRNA that can be modified while maintaining or enhancing genome-editing activity, and we develop an optimal set of chemical modifications for *in vivo* applications. Using lipid nanoparticle formulations of these enhanced sgRNAs (e-sgRNA) and mRNA encoding Cas9, we show that a single intravenous injection into mice induces >80% editing of *Pcsk9* in the liver. Serum Pcsk9 is reduced to undetectable levels, and cholesterol levels are significantly lowered about 35% to 40% in animals. This strategy may enable non-viral, Cas9-based genome editing in the liver in clinical settings.