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Scientific News
9th of December 2018
Sven Bulterijs

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Fundraiser for Sens Foundation Inc by Sven Bulterijs ·

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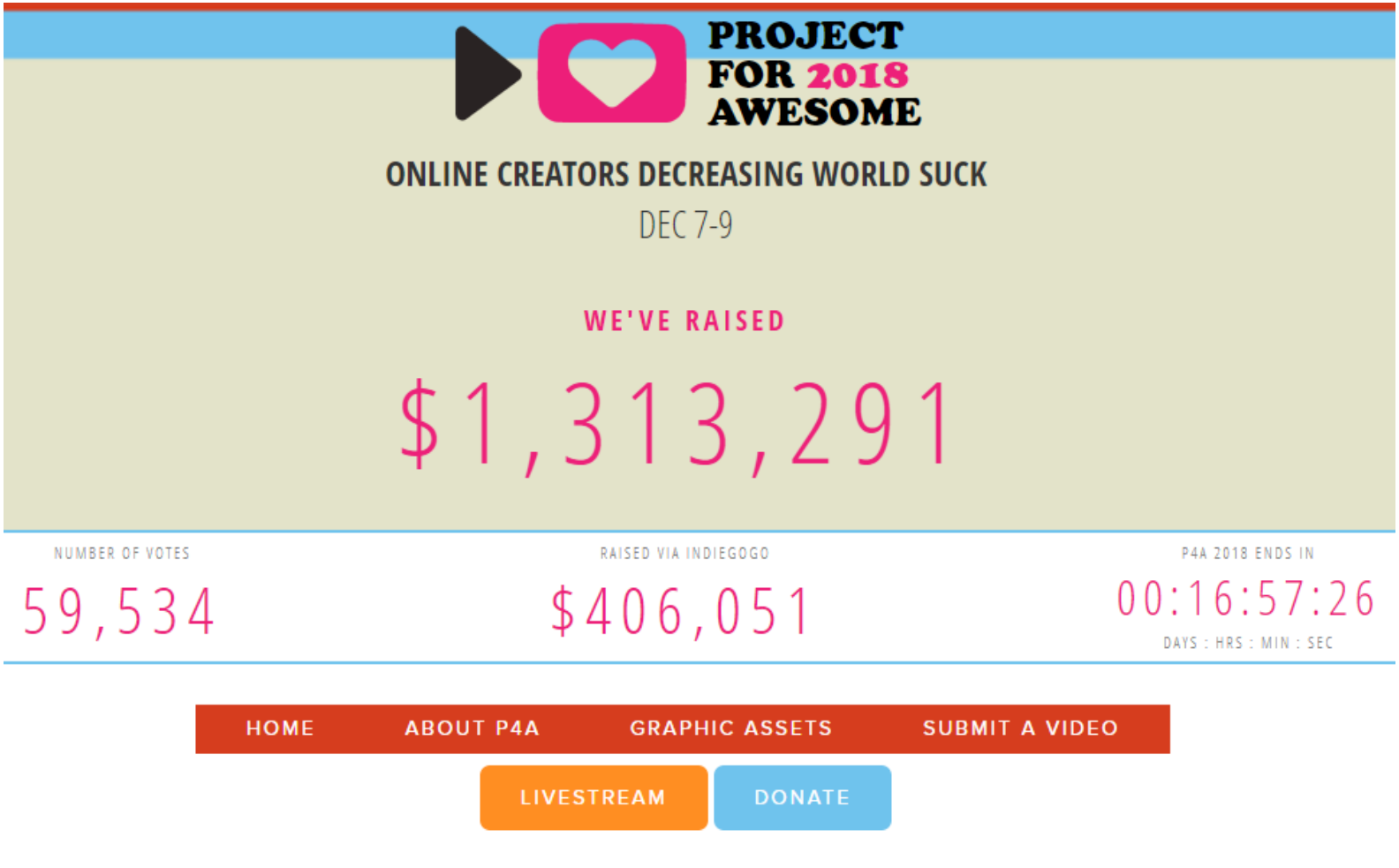

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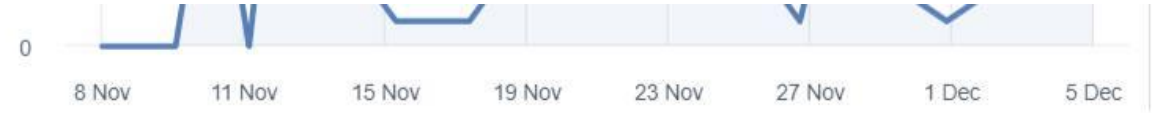

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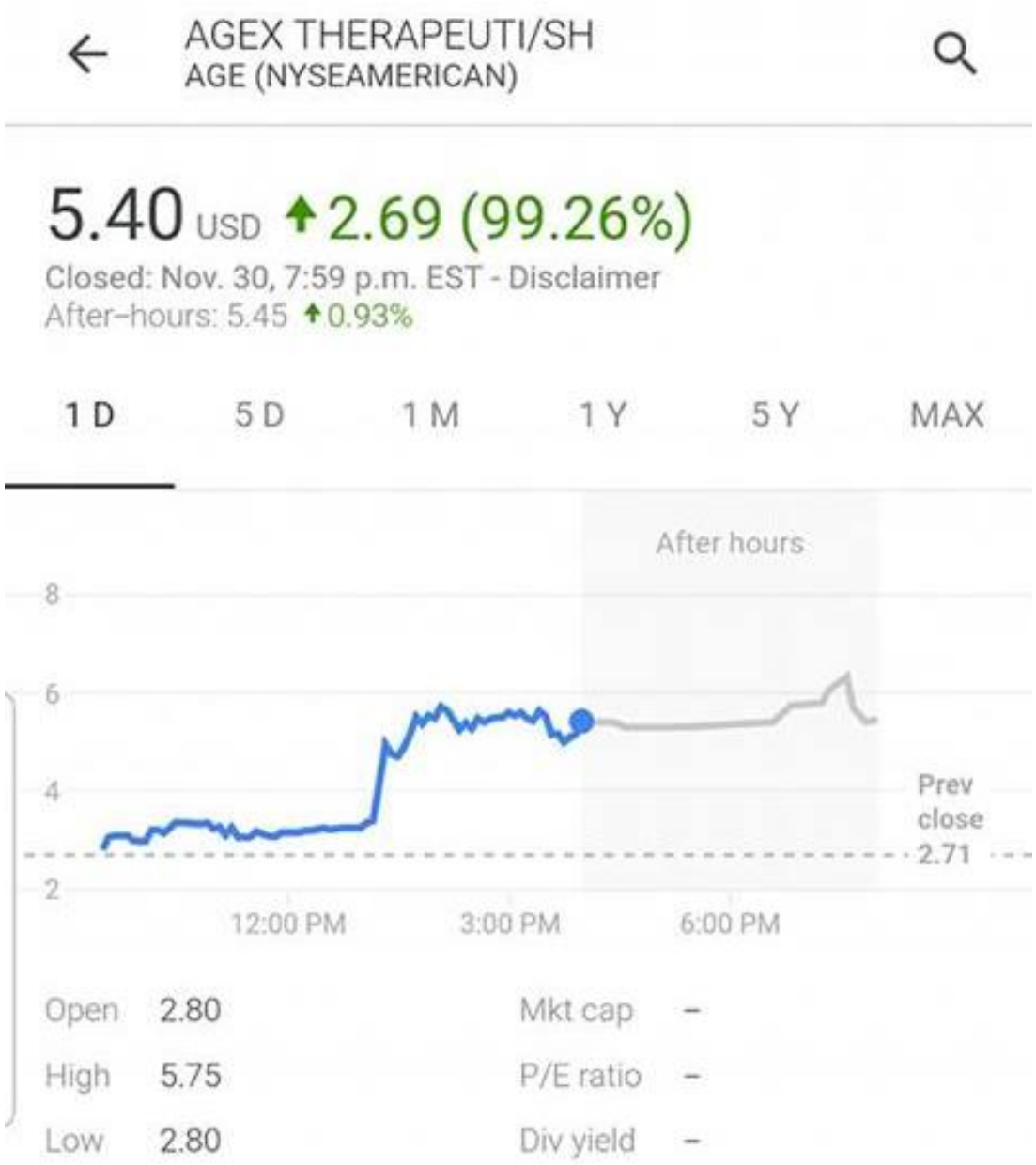

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1,105 views | Nov 1, 2018, 01:31pm

Longevity Innovators – Investing In The Growing Longevity Market

Paul Irving Contributor ⓘ
Retirement
I write about the future of aging in America and the world.

Jim Mellon is an entrepreneur, investor, and frequent speaker on topics ranging from longevity investment to future trends in technology. In an interview with my staff at the Milken Institute Center for the Future of Aging (CFA), Mellon talks about his book *Juvenescence* and shares his ideas and advice for future investors in longevity science. This is the first of three interviews celebrating "Longevity Innovators," a project celebrating insights about enhancing quality of life for people around the world. Click here for the full collection.

CFA: Can you assess the current climate of longevity science? Is the market ready for this opportunity?

Mellon: The market is now ripe for

Investors have bet $850 million on aging and longevity startups so far this year, compared with $324 million from last year.

Investors are pouring money into startups that are trying to find a cure for aging

Charlotte Hu
Oct. 26, 2018, 5:05 PM 597

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- A recent report published by CB Insights shows that funding for aging-related companies has far surpassed previous years.
- It comes at a time where scientists are understanding more about how humans age and how

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Genome-edited baby claim provokes international outcry

The startling announcement by a Chinese scientist represents a controversial leap in the use of genome editing.

David Cyranoski & Heidi Ledford

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George Church takes a more nuanced view than many scientists on the recently revealed gene editing of human babies. © KEN RICHARDSON

‘I feel an obligation to be balanced.’ Noted biologist comes to defense of gene editing babies

By Jon Cohen | Nov. 28, 2018 , 2:50 PM

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Biogerontology
19 November at 11:02

BIOGERONTOLOGY is saddened to inform that one of the pioneers of modern biogerontology - ZHORES MEDVEDEV - has died - one day after reaching the age of 93 (14 November 1925 to 15 November 2018). From about mid-1970s, Zhores worked at the National Institute for Medical Research (NIMR) Mill Hill, London, when invited by Robin Holliday.
In this picture from 2012, Zhores Medvedev and his wife Rita Medvedeva, with Suresh Rattan for whom Zhores was one of his mentors during his PhD studies at NIMR (1979-1982)

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Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories

Globally, most independent drivers of health were forecast to improve by 2040, but 36 were forecast to worsen. As shown by the better health scenarios, greater progress might be possible, yet for some drivers such as high body-mass index (BMI), their toll will rise in the absence of intervention. We forecasted global life expectancy to increase by 4·4 years (95% UI 2·2 to 6·4) for men and 4·4 years (2·1 to 6·4) for women by 2040, but based on better and worse health scenarios, trajectories could range from a gain of 7·8 years (5·9 to 9·8) to a non-significant loss of 0·4 years (–2·8 to 2·2) for men, and an increase of 7·2 years (5·3 to 9·1) to essentially no change (0·1 years [–2·7 to 2·5]) for women. In 2040, Japan, Singapore, Spain, and Switzerland had a forecasted life expectancy exceeding 85 years for both sexes, and 59 countries including China were projected to surpass a life expectancy of 80 years by 2040. At the same time, Central African Republic, Lesotho, Somalia, and Zimbabwe had projected life expectancies below 65 years in 2040, indicating global disparities in survival are likely to persist if current trends hold. Forecasted YLLs showed a rising toll from several non-communicable diseases (NCDs), partly driven by population growth and ageing. Differences between the reference forecast and alternative scenarios were most striking for HIV/AIDS, for which a potential increase of 120·2% (95% UI 67·2–190·3) in YLLs (nearly 118 million) was projected globally from 2016–40 under the worse health scenario. Compared with 2016, NCDs were forecast to account for a greater proportion of YLLs in all GBD regions by 2040 (67·3% of YLLs [95% UI 61·9–72·3] globally); nonetheless, in many lower-income countries, communicable, maternal, neonatal, and nutritional (CMNN) diseases still accounted for a large share of YLLs in 2040 (eg, 53·5% of YLLs [95% UI 48·3–58·5] in Sub-Saharan Africa). There were large gaps for many health risks between the reference forecast and better health scenario for attributable YLLs. In most countries, metabolic risks amenable to health care (eg, high blood pressure and high plasma fasting glucose) and risks best targeted by population-level or intersectoral interventions (eg, tobacco, high BMI, and ambient particulate matter pollution) had some of the largest differences between reference and better health scenarios. The main exception was sub-Saharan Africa, where many risks associated with poverty and lower levels of development (eg, unsafe water and sanitation, household air pollution, and child malnutrition) were projected to still account for substantive disparities between reference and better health scenarios in 2040.

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Parrot Genomes and the Evolution of Heightened Longevity and Cognition

Parrots are one of the most distinct and intriguing groups of birds, with highly expanded brains [1], highly developed cognitive [2] and vocal communication [3] skills, and a long lifespan compared to other similar-sized birds [4]. Yet the genetic basis of these traits remains largely unidentified. To address this question, we have generated a high-coverage, annotated assembly of the genome of the blue-fronted Amazon (*Amazona aestiva*) and carried out extensive comparative analyses with 30 other avian species, including 4 additional parrots. We identified several genomic features unique to parrots, including parrot-specific novel genes and parrot-specific modifications to coding and regulatory sequences of existing genes. We also discovered genomic features under strong selection in parrots and other long-lived birds, including genes previously associated with lifespan determination as well as several hundred new candidate genes. These genes support a range of cellular functions, including telomerase activity; DNA damage repair; control of cell proliferation, cancer, and immunity; and anti-oxidative mechanisms. We also identified brain-expressed, parrot-specific paralogs with known functions in neural development or vocal-learning brain circuits. Intriguingly, parrot-specific changes in conserved regulatory sequences were overwhelmingly associated with genes that are linked to cognitive abilities and have undergone similar selection in the human lineage, suggesting convergent evolution. These findings bring novel insights into the genetics and evolution of longevity and cognition, as well as provide novel targets for exploring the mechanistic basis of these traits.

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Giant tortoise genomes provide insights into longevity and age-related disease

Víctor Quesada, Sandra Freitas-Rodríguez, [...] Carlos López-Otín ✉

Giant tortoises are among the longest-lived vertebrate animals and, as such, provide an excellent model to study traits like longevity and age-related diseases. However, genomic and molecular evolutionary information on giant tortoises is scarce. Here, we describe a global analysis of the genomes of Lonesome George—the iconic last member of *Chelonoidis abingdonii*—and the Aldabra giant tortoise (*Aldabrachelys gigantea*). Comparison of these genomes with those of related species, using both unsupervised and supervised analyses, led us to detect lineage-specific variants affecting DNA repair genes, inflammatory mediators and genes related to cancer development. Our study also hints at specific evolutionary strategies linked to increased lifespan, and expands our understanding of the genomic determinants of ageing. These new genome sequences also provide important resources to help the efforts for restoration of giant tortoise populations.

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Lymph nodes as barriers to T-cell rejuvenation in aging mice and nonhuman primates

Heather L. Thompson, Megan J. Smithey, Jennifer L. Uhrlaub, Ilija Jeftić, Mladen Jergović, Sarah E. White, Noreen Currier, Anna M. Lang, Afam Okoye, Byung Park, ... See all authors

First published: 14 November 2018 | https://doi.org/10.1111/acel.12865

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Abstract

In youth, thymic involution curtails production of new naïve T cells, placing the onus of T-cell maintenance upon secondary lymphoid organs (SLO). This peripheral maintenance preserves the size of the T-cell pool for much of the lifespan, but wanes in the last third of life, leading to a dearth of naïve T cells in blood and SLO, and contributing to suboptimal immune defense. Both keratinocyte growth factor (KGF) and sex steroid ablation (SSA) have been shown to transiently increase the size and cellularity of the old thymus. It is less clear whether this increase can improve protection of old animals from infectious challenge. Here, we directly measured the extent to which thymic rejuvenation benefits the peripheral T-cell compartment of old mice and nonhuman primates. Following treatment of old animals with either KGF or SSA, we observed robust rejuvenation of thymic size and cellularity, and, in a reporter mouse model, an increase in recent thymic emigrants (RTE) in the blood. However, few RTE were found in the spleen and even fewer in the lymph nodes, and SSA-treated mice showed no improvement in immune defense against West Nile virus. In parallel, we found increased disorganization and fibrosis in old LN of both mice and nonhuman primates. These results suggest that SLO defects with aging can negate the effects of successful thymic rejuvenation in immune defense.

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Stem Cells. 2018 Nov 9. doi: 10.1002/stem.2934. [Epub ahead of print]

Single-Cell Transcriptomics of Human Mesenchymal Stem Cells Reveal Age-Related Cellular Subpopulation Depletion and Impaired Regenerative Function.

Khong SML[1], Lee M[1,2], Kosaric N[1], Khong DM[3], Dong Y[1], Hopfner U[4], Aitzetmüller MM[4], Duscher D[1,4], Schäfer R[5], Gurtner GC[1].

Author information

Abstract

Although bone marrow-derived mesenchymal stem cells (BM-MSCs) are widely recognized as promising therapeutic agents, the age-related impacts on cellular function remain largely uncharacterized. In this study, we found that BM-MSCs from young donors healed wounds in a xenograft model faster compared with their aged counterparts ($p < .001$). Given this significant healing advantage, we then used single-cell transcriptomic analysis to provide potential molecular insights into these observations. We found that the young cells contained a higher proportion of cells characterized by a higher expression of genes involved in tissue regeneration. In addition, we identified a unique, quiescent subpopulation that was exclusively present in young donor cells. Together, these findings may explain a novel mechanism for the enhanced healing capacity of young stem cells and may have implications for autologous cell therapy in the extremes of age. Stem Cells 2018.

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Macrophage cells secrete factors including LRP1 that orchestrate the rejuvenation of bone repair in mice

The pace of repair declines with age and, while exposure to a young circulation can rejuvenate fracture repair, the cell types and factors responsible for rejuvenation are unknown. Here we report that young macrophage cells produce factors that promote osteoblast differentiation of old bone marrow stromal cells. Heterochronic parabiosis exploiting young mice in which macrophages can be depleted and fractionated bone marrow transplantation experiments show that young macrophages rejuvenate fracture repair, and old macrophage cells slow healing in young mice. Proteomic analysis of the secretomes identify differential proteins secreted between old and young macrophages, such as low-density lipoprotein receptor-related protein 1 (Lrp1). Lrp1 is produced by young cells, and depleting *Lrp1* abrogates the ability to rejuvenate fracture repair, while treating old mice with recombinant Lrp1 improves fracture healing. Macrophages and proteins they secrete orchestrate the fracture repair process, and young cells produce proteins that rejuvenate fracture repair in mice.

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Age-related declines in α-Klotho drive progenitor cell mitochondrial dysfunction and impaired muscle regeneration

A. Sahu, H. Mamiya, S. N. Shinde, A. Cheikhi, L. L. Winter, N. V. Vo, D. Stolz, V. Roginskaya, W. Y. Tang, C. St. Croix, L. H. Sanders, M. Franti, B. Van Houten, T. A. Rando, A. Barchowsky & F. Ambrosio

Nature Communications **9**, Article number: 4859 (2018) | Download Citation

Abstract

While young muscle is capable of restoring the original architecture of damaged myofibers, aged muscle displays a markedly reduced regeneration. We show that expression of the "anti-aging" protein, α-Klotho, is up-regulated within young injured muscle as a result of transient *Klotho* promoter demethylation. However, epigenetic control of the *Klotho* promoter is lost with aging. Genetic inhibition of α-Klotho in vivo disrupted muscle progenitor cell (MPC) lineage progression and impaired myofiber regeneration, revealing a critical role for α-Klotho in the regenerative cascade. Genetic silencing of *Klotho* in young MPCs drove mitochondrial DNA (mtDNA) damage and decreased cellular bioenergetics. Conversely, supplementation with α-Klotho restored mtDNA integrity and bioenergetics of aged MPCs to youthful levels in vitro and enhanced functional regeneration of aged muscle in vivo in a temporally-dependent manner. These studies identify a role for α-Klotho in the regulation of MPC mitochondrial function and implicate α-Klotho declines as a driver of impaired muscle regeneration with age.

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Expanded genetic screening in *Caenorhabditis elegans* identifies new regulators and an inhibitory role for NAD^+ in axon regeneration

The mechanisms underlying axon regeneration in mature neurons are relevant to the understanding of normal nervous system maintenance and for developing therapeutic strategies for injury. Here, we report novel pathways in axon regeneration, identified by extending our previous function-based screen using the *C. elegans* mechanosensory neuron axotomy model. We identify an unexpected role of the nicotinamide adenine dinucleotide (NAD^+) synthesizing enzyme, NMAT-2/NMNAT, in axon regeneration. NMAT-2 inhibits axon regrowth via cell-autonomous and non-autonomous mechanisms. NMAT-2 enzymatic activity is required to repress regrowth. Further, we find differential requirements for proteins in membrane contact site, components and regulators of the extracellular matrix, membrane trafficking, microtubule and actin cytoskeleton, the conserved Kelch-domain protein IVNS-1, and the orphan transporter MFSD-6 in axon regrowth. Identification of these new pathways expands our understanding of the molecular basis of axonal injury response and regeneration.

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Estimates of the Heritability of Human Longevity Are Substantially Inflated due to Assortative Mating

J. Graham Ruby, Kevin M. Wright, Kristin A. Rand, Amir Kermany, Keith Noto, Don Curtis, Neal Varner, Daniel Garrigan, Dmitri Slinkov, Ilya Dorfman, Julie M. Granka, Jake Byrnes, Natalie Myres and Catherine Ball

Human life span is a phenotype that integrates many aspects of health and environment into a single ultimate quantity: the elapsed time between birth and death. Though it is widely believed that long life runs in families for genetic reasons, estimates of life span "heritability" are consistently low (~15–30%). Here, we used pedigree data from *Ancestry* public trees, including hundreds of millions of historical persons, to estimate the heritability of human longevity. Although "nominal heritability" estimates based on correlations among genetic relatives agreed with prior literature, the majority of that correlation was also captured by correlations among nongenetic (in-law) relatives, suggestive of highly assortative mating around life span-influencing factors (genetic and/or environmental). We used structural equation modeling to account for assortative mating, and concluded that the true heritability of human longevity for birth cohorts across the 1800s and early 1900s was well below 10%, and that it has been generally overestimated due to the effect of assortative mating.

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Translation attenuation by minocycline enhances longevity and proteostasis in old post-stress-responsive organisms

Aging impairs the activation of stress signaling pathways (SSPs), preventing the induction of longevity mechanisms late in life. Here, we show that the antibiotic minocycline increases lifespan and reduces protein aggregation even in old, SSP-deficient *Caenorhabditis elegans* by targeting cytoplasmic ribosomes, preferentially attenuating translation of highly translated mRNAs. In contrast to most other longevity paradigms, minocycline inhibits rather than activates all major SSPs and extends lifespan in mutants deficient in the activation of SSPs, lysosomal or autophagic pathways. We propose that minocycline lowers the concentration of newly synthesized aggregation-prone proteins, resulting in a relative increase in protein-folding capacity without the necessity to induce protein-folding pathways. Our study suggests that in old individuals with incapacitated SSPs or autophagic pathways, pharmacological attenuation of cytoplasmic translation is a promising strategy to reduce protein aggregation. Altogether, it provides a geroprotecive mechanism for the many beneficial effects of tetracyclines in models of neurodegenerative disease.

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Aging Cell. 2018 Oct;17(5):e12814. doi: 10.1111/acel.12814. Epub 2018 Jul 24.

Clonal expansion of mitochondrial DNA deletions is a private mechanism of aging in long-lived animals.

Lakshmanan LN[1,2], Yee Z[3], Ng LF[4], Gunawan R[1,2], Halliwell B[3], Gruber J[3,4].

⊕ Author information

Abstract

Disruption of mitochondrial metabolism and loss of mitochondrial DNA (mtDNA) integrity are widely considered as evolutionarily conserved (public) mechanisms of aging (López-Otín et al., Cell, 153, 2013 and 1194). Human aging is associated with loss in skeletal muscle mass and function (Sarcopenia), contributing significantly to morbidity and mortality. Muscle aging is associated with loss of mtDNA integrity. In humans, clonally expanded mtDNA deletions colocalize with sites of fiber breakage and atrophy in skeletal muscle. mtDNA deletions may therefore play an important, possibly causal role in sarcopenia. The nematode Caenorhabditis elegans also exhibits age-dependent decline in mitochondrial function and a form of sarcopenia. However, it is unclear if mtDNA deletions play a role in C. elegans aging. Here, we report identification of 266 novel mtDNA deletions in aging nematodes. Analysis of the mtDNA mutation spectrum and quantification of mutation burden indicates that (a) mtDNA deletions in nematode are extremely rare, (b) there is no significant age-dependent increase in mtDNA deletions, and (c) there is little evidence for clonal expansion driving mtDNA deletion dynamics. Thus, mtDNA deletions are unlikely to drive the age-dependent functional decline commonly observed in C. elegans. Computational modeling of mtDNA dynamics in C. elegans indicates that the lifespan of short-lived animals such as C. elegans is likely too short to allow for significant clonal expansion of mtDNA deletions. Together, these findings suggest that clonal expansion of mtDNA deletions is likely a private mechanism of aging predominantly relevant in long-lived animals such as humans and rhesus monkey and possibly in rodents.

KEYWORDS: Caenorhabditis elegans ; aging; clonal expansion; deletions; mitochondrial DNA; sarcopenia

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High prevalence of focal and multi-focal somatic genetic variants in the human brain

Michael J. Keogh, Wei Wei, Juvid Aryaman, Lauren Walker, Jelle van den Ameele, Jon Coxhead, Ian Wilson, Matthew Bashton, Jon Beck, John West, Richard Chen, Christian Haudenschild, Gabor Bartha, Shujun Luo, Chris M. Morris, Nick S. Jones, Johannes Attems & Patrick F. Chinnery

Nature Communications **9**, Article number: 4257 (2018) | Download Citation

Abstract

Somatic mutations during stem cell division are responsible for several cancers. In principle, a similar process could occur during the intense cell proliferation accompanying human brain development, leading to the accumulation of regionally distributed foci of mutations. Using dual platform >5000-fold depth sequencing of 102 genes in 173 adult human brain samples, we detect and validate somatic mutations in 27 of 54 brains. Using a mathematical model of neurodevelopment and approximate Bayesian inference, we predict that macroscopic islands of pathologically mutated neurons are likely to be common in the general population. The detected mutation spectrum also includes *DNMT3A* and *TET2* which are likely to have originated from blood cell lineages. Together, these findings establish developmental mutagenesis as a potential mechanism for neurodegenerative disorders, and provide a novel mechanism for the regional onset and focal pathology in sporadic cases.

The bystander effect contributes to the accumulation of senescent cells in vivo

Paulo F. L. da Silva[1*] | Mikolaj Ogrodnik[1*] | Olena Kucheryavenko[1*] | Julien Glibert[1] | Satomi Miwa[1] | Kerry Cameron[1] | Abbas Ishaq[1] | Gabriele Saretzki[1] | Sushma Nagaraja-Grellscheid[2] | Glyn Nelson[1†] | Thomas von Zglinicki[1,3†]

Abstract

Senescent cells accumulate with age in multiple tissues and may cause age-associated disease and functional decline. In vitro, senescent cells induce senescence in bystander cells. To see how important this bystander effect may be for accumulation of senescent cells in vivo, we xenotransplanted senescent cells into skeletal muscle and skin of immunocompromised NSG mice. 3 weeks after the last transplantation, mouse dermal fibroblasts and myofibres displayed multiple senescence markers in the vicinity of transplanted senescent cells, but not where non-senescent or no cells were injected. Adjacent to injected senescent cells, the magnitude of the bystander effect was similar to the increase in senescence markers in myofibres between 8 and 32 months of age. The age-associated increase of senescence markers in muscle correlated with fibre thinning, a widely used marker of muscle aging and sarcopenia. Senescent cell transplantation resulted in borderline induction of centrally nucleated fibres and no significant thinning, suggesting that myofibre aging might be a delayed consequence of senescence-like signalling. To assess the relative importance of the bystander effect versus cell-autonomous senescence, we compared senescent hepatocyte frequencies in livers of wild-type and NSG mice under ad libitum and dietary restricted feeding. This enabled us to approximate cell-autonomous and bystander-driven senescent cell accumulation as well as the impact of immunosurveillance separately. The results suggest a significant impact of the bystander effect for accumulation of senescent hepatocytes in liver and indicate that senostatic interventions like dietary restriction may act as senolytics in immunocompetent animals.

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Aging (Albany NY). 2018 Nov 14;10(11):3294-3307. doi: 10.18632/aging.101633.

Azithromycin and Roxithromycin define a new family of "senolytic" drugs that target senescent human fibroblasts.

Ozsvari B[#1], Nuttall JR[#1], Sotgia F[1], Lisanti MP[1].

Author information

Abstract

Here, we employed a "senolytic" assay system as a screening tool, with the goal of identifying and repurposing FDA-approved antibiotics, for the targeting of the senescent cell population. Briefly, we used two established human fibroblast cell lines (MRC-5 and/or BJ) as model systems to induce senescence, via chronic treatment with a DNA-damaging agent, namely BrdU (at a concentration of 100 μM for 8 days). Cell viability was then monitored by using the SRB assay, to measure protein content. As a consequence of this streamlined screening strategy, we identified Azithromycin and Roxithromycin as two novel clinically-approved senolytic drugs. However, Erythromycin - the very closely-related parent compound - did not show any senolytic activity, highlighting the dramatic specificity of these interactions. Interestingly, we also show that Azithromycin treatment of human fibroblasts was indeed sufficient to strongly induce both aerobic glycolysis and autophagy. However, the effects of Azithromycin on mitochondrial oxygen consumption rates (OCR) were bi-phasic, showing inhibitory activity at 50 μM and stimulatory activity at 100 μM. These autophagic/metabolic changes induced by Azithromycin could mechanistically explain its senolytic activity. We also independently validated our findings using the xCELLigence real-time assay system, which measures electrical impedance. Using this approach, we see that Azithromycin preferentially targets senescent cells, removing approximately 97% of them with great efficiency. This represents a near 25-fold reduction in senescent cells. Finally, we also discuss our current results in the context of previous clinical findings that specifically document the anti-inflammatory activity of Azithromycin in patients with cystic fibrosis - a genetic lung disorder that results in protein mis-folding mutations that cause protein aggregation.

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Glycolytic inhibitor 2-deoxy-D-glucose at chronic low dose mimics calorie restriction in rats through mitohormetic induction of ROS

Ms. Komal SaraswatMr. Raushan KumarDr. Syed Ibrahim Rizvi

Published Online: 18 Nov 2018 | https://doi.org/10.1089/rej.2018.2125

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Abstract

Caloric restriction mimetics (CRMs) provide an exciting anti-aging intervention strategy. 2-deoxy-D-glucose (2-DG), a glycolytic inhibitor is known to works as a CRM at high doses, however chronic high dose has been linked to increased mortality in rats. We have investigated chronic low dose dietary administration of 2-DG on age-related stress protection in young and old age male wistar rats by evaluating age-dependent biomarkers in plasma and erythrocytes. Significant increase was observed in ROS generation in 2-DG treated rats (both young and old), concomitant with increase in erythrocyte plasma membrane redox system (PMRS), catalase (CAT) and superoxide dismutase (SOD). 2-DG treatment also decreased plasma sialic acid and advanced glycation end products (AGEs). We propose that 2-DG induces a mitohormetic response resulting in augmentation of defence mechanism(s) manifested by higher activity of PMRS, CAT and SOD. Our findings provide evidence that at chronic low dose 2-DG could be a potential CRM.

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Cell Rep. 2018 Nov 20;25(8):2234-2243.e6. doi: 10.1016/j.celrep.2018.10.070.

Comparing the Effects of Low-Protein and High-Carbohydrate Diets and Caloric Restriction on Brain Aging in Mice.

Wahl D[1], Solon-Biet SM[2], Wang QP[3], Wali JA[2], Pulpitel T[2], Clark X[2], Raubenheimer D[2], Senior AM[4], Sinclair DA[5], Cooney GJ[2], de Cabo R[6], Cogger VC[1], Simpson SJ[7], Le Couteur DG[8].

⊕ Author information

Abstract

Calorie restriction (CR) increases lifespan and improves brain health in mice. Ad libitum low-protein, high-carbohydrate (LPHC) diets also extend lifespan, but it is not known whether they are beneficial for brain health. We compared hippocampus biology and memory in mice subjected to 20% CR or provided ad libitum access to one of three LPHC diets or to a control diet. Patterns of RNA expression in the hippocampus of 15-month-old mice were similar between mice fed CR and LPHC diets when we looked at genes associated with longevity, cytokines, and dendrite morphogenesis. Nutrient-sensing proteins, including SIRT1, mTOR, and PGC1α, were also influenced by diet; however, the effects varied by sex. CR and LPHC diets were associated with increased dendritic spines in dentate gyrus neurons. Mice fed CR and LPHC diets had modest improvements in the Barnes maze and novel object recognition. LPHC diets recapitulate some of the benefits of CR on brain aging.

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Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes

Ole Snorgaard[1], Grith M Poulsen[2], Henning K Andersen[3], Arne Astrup[2]

Author affiliations +

Abstract

Objective Nutrition therapy is an integral part of self-management education in patients with type 2 diabetes. Carbohydrates with a low glycemic index are recommended, but the ideal amount of carbohydrate in the diet is unclear. We performed a meta-analysis comparing diets containing low to moderate amounts of carbohydrate (LCD) (energy percentage below 45%) to diets containing high amounts of carbohydrate (HCD) in subjects with type 2 diabetes.

Research design and methods We systematically reviewed Cochrane library databases, EMBASE, and MEDLINE in the period 2004–2014 for guidelines, meta-analyses, and randomized trials assessing the outcomes HbA1c, BMI, weight, LDL cholesterol, quality of life (QoL), and attrition.

Results We identified 10 randomized trials comprising 1376 participants in total. In the first year of intervention, LCD was followed by a 0.34% lower HbA1c (3.7 mmol/mol) compared with HCD (95% CI 0.06 (0.7 mmol/mol), 0.63 (6.9 mmol/mol)). The greater the carbohydrate restriction, the greater the glucose-lowering effect ($R=-0.85$, $p<0.01$). At 1 year or later, however, HbA1c was similar in the 2 diet groups. The effect of the 2 types of diet on BMI/body weight, LDL cholesterol, QoL, and attrition rate was similar throughout interventions.

Limitations Glucose-lowering medication, the nutrition therapy, the amount of carbohydrate in the diet, glycemic index, fat and protein intake, baseline HbA1c, and adherence to the prescribed diets could all have affected the outcomes.

Conclusions Low to moderate carbohydrate diets have greater effect on glycemic control in type 2 diabetes compared with high-carbohydrate diets in the first year of intervention. The greater the carbohydrate restriction, the greater glucose lowering, a relationship that has not been demonstrated earlier. Apart from this lowering of HbA1c over the short term, there is no superiority of low-carbohydrate diets in terms of glycemic control, weight, or LDL cholesterol.

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Aging (Albany NY). 2018 Nov 9;10(11):3249-3259. doi: 10.18632/aging.101629.

PhotoAgeClock: deep learning algorithms for development of non-invasive visual biomarkers of aging.

Bobrov E[#1,2], Georgievskaya A[#1,3], Kiselev K[#1], Sevastopolsky A[1,4], Zhavoronkov A[5,6,7], Gurov S[2], Rudakov K[3], Del Pilar Bonilla Tobar M[8], Jaspers S[8], Clemann S[8].

⊕ Author information

Abstract

Aging biomarkers are the qualitative and quantitative indicators of the aging processes of the human body. Estimation of biological age is important for assessing the physiological state of an organism. The advent of machine learning lead to the development of the many age predictors commonly referred to as the "aging clocks" varying in biological relevance, ease of use, cost, actionability, interpretability, and applications. Here we present and investigate a novel non-invasive class of visual photographic biomarkers of aging. We developed a simple and accurate predictor of chronological age using just the anonymized images of eye corners called the PhotoAgeClock. Deep neural networks were trained on 8414 anonymized high-resolution images of eye corners labeled with the correct chronological age. For people within the age range of 20 to 80 in a specific population, the model was able to achieve a mean absolute error of 2.3 years and 95% Pearson and Spearman correlation.

KEYWORDS: age prediction; biomedical imaging; computer vision; deep learning; photographic aging biomarker; photographic aging clock

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Machine learning based classification of cells into chronological stages using single-cell transcriptomics

Sumeet Pal Singh ✉, Sharan Janjuha, Samata Chaudhuri, Susanne Reinhardt, Annekathrin Kränkel, Sevina Dietz, Anne Eugster, Halil Bilgin, Selçuk Korkmaz, Gökmen Zararsız, Nikolay Ninov & John E. Reid

Age-associated deterioration of cellular physiology leads to pathological conditions. The ability to detect premature aging could provide a window for preventive therapies against age-related diseases. However, the techniques for determining cellular age are limited, as they rely on a limited set of histological markers and lack predictive power. Here, we implement GERAS (GEnetic Reference for Age of Single-cell), a machine learning based framework capable of assigning individual cells to chronological stages based on their transcriptomes. GERAS displays greater than 90% accuracy in classifying the chronological stage of zebrafish and human pancreatic cells. The framework demonstrates robustness against biological and technical noise, as evaluated by its performance on independent samplings of single-cells. Additionally, GERAS determines the impact of differences in calorie intake and BMI on the aging of zebrafish and human pancreatic cells, respectively. We further harness the classification ability of GERAS to identify molecular factors that are potentially associated with the aging of beta-cells. We show that one of these factors, *junba*, is necessary to maintain the proliferative state of juvenile beta-cells. Our results showcase the applicability of a machine learning framework to classify the chronological stage of heterogeneous cell populations, while enabling detection of candidate genes associated with aging.

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Front Biosci (Landmark Ed). 2019 Jan 1;24:555-563.

Generation of sRAGE^{high} transgenic mice to study inflammaging.

Peng Y[1], Park HS[1], Tang LA[1], Horwitz N[1], Lin L[2].

Author information

Abstract

The receptor for advanced glycation end products (RAGE) interacts with multiple ligands and transmits inflammatory signals from damage- and pathogen-associated molecular patterns (DAMPs and PAMPs) to cellular programs. RAGE shares ligands with another group of PRRs, *i.e.*, Toll-like receptors. Such ligand-receptor promiscuity generates coordinated and complex signaling patterns that provide a basis for the development of multiple inflammaging diseases. Soluble RAGE (sRAGE) functions as a RAGE decoy that scavenges DAMP/PAMP ligands and dampens inflammatory signals. Epidemiological studies have shown that a lower level of circulating sRAGE is associated with metabolic syndromes including obesity, diabetes, hypertension, and subclinical brain disease. We hypothesize that an elevated level of circulating sRAGE serves to modulate systemic and low-grade chronical inflammation that often occurs in old age, and therefore minimizes the risk of inflammaing diseases. Consequently, a higher level of circulating sRAGE may improve the health-span of the organism. A newly generated transgenic mouse that has a higher level of circulating sRAGE and maintains normal expression levels of RAGE serves as a model to test this hypothesis.

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Rapamycin improves healthspan but not inflammaging in *nfκb1*$^{-/-}$ mice

Clara Correia-Melo, Jodie Birch, Edward Fielder, Dina Rahmatika, Jennifer Taylor, James Chapman, Anthony Lagnado, Bernadette M. Carroll, Satomi Miwa, Gavin Richardson, ... See all authors

Increased activation of the major pro-inflammatory NF-κB pathway leads to numerous age-related diseases, including chronic liver disease (CLD). Rapamycin, an inhibitor of mTOR, extends lifespan and healthspan, potentially via suppression of inflammaging, a process which is partially dependent on NF-κB signalling. However, it is unknown if rapamycin has beneficial effects in the context of compromised NF-κB signalling, such as that which occurs in several age-related chronic diseases. In this study, we investigated whether rapamycin could ameliorate age-associated phenotypes in a mouse model of genetically enhanced NF-κB activity (*nfκb1*$^{-/-}$) characterized by low-grade chronic inflammation, accelerated aging and CLD. We found that, despite showing no beneficial effects in lifespan and inflammaging, rapamycin reduced frailty and improved long-term memory, neuromuscular coordination and tissue architecture. Importantly, markers of cellular senescence, a known driver of age-related pathology, were alleviated in rapamycin-fed animals. Our results indicate that, in conditions of genetically enhanced NF-κB, rapamycin delays aging phenotypes and improves healthspan uncoupled from its role as a suppressor of inflammation.

mTOR inhibitors may benefit kidney transplant recipients with mitochondrial diseases

Simon C. Johnson [1, 2], Frank Martinez [3, 11], Alessandro Bitto [4, 11], Brenda Gonzalez [1, 11], Cagdas Tazaerslan [1], Camille Cohen [3], Laure Delaval [3], José Timsit [5, 6], Bertrand Knebelmann [3, 6, 7], Fabiola Terzi [7], Tarika Mahal [1], Yizhou Zhu [1], Philip G. Morgan [2, 8], Margaret M. Sedensky [2, 8], Matt Kaeberlein [4], Christophe Legendre [3, 6, 7], Yousin Suh [1, 9, 10], Guillaume Canaud [3, 6, 7]

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https://doi.org/10.1016/j.kint.2018.08.038

Mitochondrial diseases represent a significant clinical challenge. Substantial efforts have been devoted to identifying therapeutic strategies for mitochondrial disorders, but effective interventions have remained elusive. Recently, we reported attenuation of disease in a mouse model of the human mitochondrial disease Leigh syndrome through pharmacological inhibition of the mechanistic target of rapamycin (mTOR). The human mitochondrial disorder MELAS/MIDD (Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episodes/Maternally Inherited Diabetes and Deafness) shares many phenotypic characteristics with Leigh syndrome. MELAS/MIDD often leads to organ failure and transplantation and there are currently no effective treatments. To examine the therapeutic potential of mTOR inhibition in human mitochondrial disease, four kidney transplant recipients with MELAS/MIDD were switched from calcineurin inhibitors to mTOR inhibitors for immunosuppression. Primary fibroblast lines were generated from patient dermal biopsies and the impact of rapamycin was studied using cell-based end points. Metabolomic profiles of the four patients were obtained before and after the switch. pS6, a measure of mTOR signaling, was significantly increased in MELAS/MIDD cells compared to controls in the absence of treatment, demonstrating mTOR overactivation. Rapamycin rescued multiple deficits in cultured cells including mitochondrial morphology, mitochondrial membrane potential, and replicative capacity. Clinical measures of health and mitochondrial disease progression were improved in all four patients following the switch to an mTOR inhibitor. Metabolomic analysis was consistent with mitochondrial function improvement in all patients.

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Identity Noise and Adipogenic Traits Characterize Dermal Fibroblast Aging

During aging, stromal functions are thought to be impaired, but little is known whether this stems from changes of fibroblasts. Using population- and single-cell transcriptomics, as well as long-term lineage tracing, we studied whether murine dermal fibroblasts are altered during physiological aging under different dietary regimes that affect longevity. We show that the identity of old fibroblasts becomes undefined, with the fibroblast states present in young skin no longer clearly demarcated. In addition, old fibroblasts not only reduce the expression of genes involved in the formation of the extracellular matrix, but also gain adipogenic traits, paradoxically becoming more similar to neonatal pro-adipogenic fibroblasts. These alterations are sensitive to systemic metabolic changes: long-term caloric restriction reversibly prevents them, whereas a high-fat diet potentiates them. Our results therefore highlight loss of cell identity and the acquisition of adipogenic traits as a mechanism underlying cellular aging, which is influenced by systemic metabolism.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Aging (Albany NY). 2018 Nov 17. doi: 10.18632/aging.101647. [Epub ahead of print]

Disease or not, aging is easily treatable.

Blagosklonny MV[1].

Author information

Abstract

Is aging a disease? It does not matter because aging is already treated using a combination of several clinically-available drugs, including rapamycin. Whether aging is a disease depends on arbitrary definitions of both disease and aging. For treatment purposes, aging is a deadly disease (or more generally, pre-disease), despite being a normal continuation of normal organismal growth. It must and, importantly, can be successfully treated, thereby delaying classic age-related diseases such as cancer, cardiovascular and metabolic diseases, and neurodegeneration.

KEYWORDS: gerossuppresants; lifespan; longevity; senolytics

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Ageing Res Rev. 2018 Dec 1. pii: S1568-1637(18)30254-X. doi: 10.1016/j.arr.2018.11.008. [Epub ahead of print]

Reversibility of irreversible aging.

Galkin F[1], Zhang B[2], Dmitriev SE[1], Gladyshev VN[3].

Author information

Abstract

Most multicellular organisms are known to age, due to accumulation of damage and other deleterious changes over time. These changes are often irreversible as organisms, humans included, evolved fully differentiated, irreplaceable cells (e.g. neurons) and structures (e.g. skeleton). Hence, deterioration or loss of at least some cells and structures should lead to inevitable aging of these organisms. Yet, some cells may escape this fate: adult somatic cells may be converted to partially reprogrammed cells or induced pluripotent stem cells (iPSCs). By their nature, iPSCs are the cells representing the early stages of life, indicating a possibility of reversing the age of cells within the organism. Reprogramming strategies may be accomplished both in vitro and in vivo, offering opportunities for rejuvenation in the context of whole organisms. Similarly, older organs may be replaced with the younger ones prepared ex vivo, or grown within other organisms or even other species. How could the irreversibility of aging of some parts of the organism be reconciled with the putative reversal of aging in the other parts of the same organism? Resolution of this question holds promise for dramatically extending lifespan, which is currently not possible with traditional genetic, dietary and pharmacological approaches. Critical issues in this challenge are the nature of aging, relationship between aging of an organism and aging of its parts, relationship between cell dedifferentiation and rejuvenation, and increased risk of cancer that goes hand in hand with rejuvenation approaches.

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Rejuvenation Research, Ahead of Print |

"Aging, Geroscience, and Freedom"

Colin Farrelly

Published Online: 18 Oct 2018 | https://doi.org/10.1089/rej.2018.2106

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Abstract

In this article, I argue that senescence (biological aging) is one of the greatest threats to human freedom in the 21st century. The two most prominent conceptions of freedom are "negative" and "positive" liberty. The negative conception of liberty equates freedom with the *absence of interference*, whereas the positive conception equates freedom with having the capacity to be *self-determining*. By critically examining both the negative and positive conceptions of liberty, I make the case that senescence does violate our liberty, on both accounts of freedom. Also, if this is correct, then the development of an applied gerontological intervention ought to be considered an integral commitment of a society dedicated to freedom. An aging intervention holds great emancipatory potential for the world's aging populations.

Artificial intelligence for aging and longevity research: Recent advances and perspectives

Alex Zhavoronkov [a, b, c], Polina Mamoshina [a, d], Quentin Vanhaelen [a], Morten Scheibye-Knudsen [e], Alexey Moskalev [f], Alex Aliper [a]

The applications of modern artificial intelligence (AI) algorithms within the field of aging research offer tremendous opportunities. Aging is an almost universal unifying feature possessed by all living organisms, tissues, and cells. Modern deep learning techniques used to develop age predictors offer new possibilities for formerly incompatible dynamic and static data types. AI biomarkers of aging enable a holistic view of biological processes and allow for novel methods for building causal models—extracting the most important features and identifying biological targets and mechanisms. Recent developments in generative adversarial networks (GANs) and reinforcement learning (RL) permit the generation of diverse synthetic molecular and patient data, identification of novel biological targets, and generation of novel molecular compounds with desired properties and geroprotectors. These novel techniques can be combined into a unified, seamless end-to-end biomarker development, target identification, drug discovery and real world evidence pipeline that may help accelerate and improve pharmaceutical research and development practices. Modern AI is therefore expected to contribute to the credibility and prominence of longevity biotechnology in the healthcare and pharmaceutical industry, and to the convergence of countless areas of research.

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Biogerontology
December 2018, Volume 19, Issue 6, pp 547–566 | Cite as

Gene expression hallmarks of cellular ageing

Authors | Authors and affiliations

Stephen Frenk, Jonathan Houseley

Ageing leads to dramatic changes in the physiology of many different tissues resulting in a spectrum of pathology. Nonetheless, many lines of evidence suggest that ageing is driven by highly conserved cell intrinsic processes, and a set of unifying hallmarks of ageing has been defined. Here, we survey reports of age-linked changes in basal gene expression across eukaryotes from yeast to human and identify six gene expression hallmarks of cellular ageing: downregulation of genes encoding mitochondrial proteins; downregulation of the protein synthesis machinery; dysregulation of immune system genes; reduced growth factor signalling; constitutive responses to stress and DNA damage; dysregulation of gene expression and mRNA processing. These encompass widely reported features of ageing such as increased senescence and inflammation, reduced electron transport chain activity and reduced ribosome synthesis, but also reveal a surprising lack of gene expression responses to known age-linked cellular stresses. We discuss how the existence of conserved transcriptomic hallmarks relates to genome-wide epigenetic differences underlying ageing clocks, and how the changing transcriptome results in proteomic alterations where data is available and to variations in cell physiology characteristic of ageing. Identification of gene expression events that occur during ageing across distant organisms should be informative as to conserved underlying mechanisms of ageing, and provide additional biomarkers to assess the effects of diet and other environmental factors on the rate of ageing.

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Geroneuroprotectors: Effective Geroprotectors for the Brain

David Schubert • Antonio Currais • Joshua Goldberg • ... Kim Finley • Michael Petrascheck • Pamela Maher • Show all authors

Geroprotectors are compounds that slow the rate of biological aging and therefore may reduce the incidence of age-associated diseases such as Alzheimer's disease (AD). However, few have therapeutic efficacy in mammalian AD models. Here we describe the identification of geroneuroprotectors (GNPs), novel AD drug candidates that meet the criteria for geroprotectors.

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Impact of Growth Hormone-Related Mutations on Mammalian Aging

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Mutations of a single gene can lead to a major increase in longevity in organisms ranging from yeast and worms to insects and mammals. Discovering these mutations (sometimes referred to as "longevity genes") led to identification of evolutionarily conserved molecular, cellular, and organismal mechanisms of aging. Studies in mice provided evidence for the important role of growth hormone (GH) signaling in mammalian aging. Mice with mutations or gene deletions leading to GH deficiency or GH resistance have reduced body size and delayed maturation, but are healthier and more resistant to stress, age slower, and live longer than their normal (wild type) siblings. Mutations of the same genes in people can provide remarkable protection from age-related disease, but have no consistent impact on lifespan. Ongoing research indicates that genetic defects in GH signaling are linked to extension of healthspan and lifespan via a variety of interlocking mechanism, including improvements in genome and stem cell maintenance, stress resistance, glucose homeostasis, and thermogenesis, along with reductions in the mechanistic target of rapamycin (mTOR) C1 complex signaling and in chronic low grade inflammation.

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Senescent cells: A new Achilles' heel to exploit for cancer medicine?

Boyi Zhang, Eric W.-F. Lam, Yu Sun

Cellular senescence is a typical tumor-suppressive mechanism that restricts the proliferation of premalignant cells. However, mounting evidence suggests that senescent cells, which also persist *in vivo*, can promote the incidence of aging-related disorders principally via the senescence-associated secretory phenotype (SASP), among which cancer is particularly devastating. Despite the beneficial effects of the SASP on certain physiological events such as wound healing and tissue repair, more studies have demonstrated that senescent cells can substantially contribute to pathological conditions and accelerate disease exacerbation, particularly cancer resistance, relapse and metastasis. To limit the detrimental properties while retaining the beneficial aspects of senescent cells, research advancements that support screening, design and optimization of anti-aging therapeutic agents are in rapid progress in the setting of prospective development of clinical strategies, which together represent a new wave of efforts to control human malignancies or mitigate degenerative complications.

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The senescent cell epigenome

Na Yang [1] , Payel Sen [2]

A critical hallmark of aging is cellular senescence, a state of growth arrest and inflammatory cytokine release in cells, caused by a variety of stresses. Recent work has convincingly linked the accumulation of senescent cells in aged tissues to a decline in health and a limit of lifespan, primarily through "inflammaging". Importantly, interventions that clear senescent cells have achieved marked improvements in healthspan and lifespan in mice. A growing list of studies show that environmental stimuli can affect aging and longevity through conserved pathways which, in turn, modulate chromatin states. This review consolidates key findings of chromatin state changes in senescence including histone modifications, histone variants, DNA methylation and changes in three-dimensional genome organization. This information will facilitate the identification of mechanisms and discovery of potential epigenetic targets for therapeutic interventions in aging and age-related disease.

Cause or casualty: The role of mitochondrial DNA in aging and age-associated disease

E. Sandra Chocron [a, 1], Erin Munkácsy [a, 1], Andrew M. Pickering [a, b]

The mitochondrial genome (mtDNA) represents a tiny fraction of the whole genome, comprising just 16.6 kilobases encoding 37 genes involved in oxidative phosphorylation and the mitochondrial translation machinery. Despite its small size, much interest has developed in recent years regarding the role of mtDNA as a determinant of both aging and age-associated diseases. A number of studies have presented compelling evidence for key roles of mtDNA in age-related pathology, although many are correlative rather than demonstrating cause. In this review we will evaluate the evidence supporting and opposing a role for mtDNA in age-associated functional declines and diseases. We provide an overview of mtDNA biology, damage and repair as well as the influence of mitochondrial haplogroups, epigenetics and maternal inheritance in aging and longevity.

Nutrients. 2018 Nov 22;10(12). pii: E1821. doi: 10.3390/nu10121821.

Calorie Restriction Mimetics: Upstream-Type Compounds for Modulating Glucose Metabolism.

Shintani H[1], Shintani T[2], Ashida H[3], Sato M[4].

Author information

Abstract

Calorie restriction (CR) can prolong the human lifespan, but enforcing long-term CR is difficult. Therefore, a compound that reproduces the effect of CR without CR is needed. In this review, we summarize the current knowledge on compounds with CR mimetic (CRM) effects. More than 10 compounds have been listed as CRMs, some of which are conventionally categorized as upstream-type CRMs showing glycolytic inhibition, while the others are categorized as downstream-type CRMs that regulate or genetically modulate intracellular signaling proteins. Among these, we focus on upstream-type CRMs and propose their classification as compounds with energy metabolism inhibition effects, particularly glucose metabolism modulation effects. The upstream-type CRMs reviewed include chitosan, acarbose, sodium-glucose cotransporter 2 inhibitors, and hexose analogs such as 2-deoxy-d-glucose, d-glucosamine, and d-allulose, which show antiaging and longevity effects. Finally, we discuss the molecular definition of upstream-type CRMs.

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Biochim Biophys Acta Mol Basis Dis. 2018 Nov 24. pii: S0925-4439(18)30477-0. doi: 10.1016/j.bbadis.2018.11.016. [Epub ahead of print]

Genetic regulation of longevity and age-associated diseases through the methionine sulfoxide reductase system.

Oien DB[1], Moskovitz J[2].

Author information

Abstract

Methionine sulfoxide reductase enzymes are a protective system against biological oxidative stress in aerobic organisms. Modifications to this antioxidant system have been shown to impact the lifespan of several model system organisms. In humans, methionine oxidation of critical proteins and deficiencies in the methionine sulfoxide reductase system have been linked to age-related diseases, including cancer and neurodegenerative disease. Substrates for methionine sulfoxide reductases have been reviewed multiple times, and are still an active area of discovery. In contrast, less is known about the genetic regulation of methionine sulfoxide reductases. In this review, we discuss studies on the genetic regulation of the methionine sulfoxide reductase system with relevance to longevity and age-related diseases. A better understanding of genetic regulation for methionine sulfoxide reductases may lead to new therapeutic approaches for age-related diseases in the future.

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Sarcopenia: Aging-Related Loss of Muscle Mass and Function

Lars Larsson , Hans Degens, Meishan Li, Leonardo Salviati, Young il Lee, ... Show all Authors

14 NOV 2018 // https://doi.org/10.1152/physrev.00061.2017

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Abstract

Sarcopenia is a loss of muscle mass and function in the elderly that reduces mobility, diminishes quality of life, and can lead to fall-related injuries, which require costly hospitalization and extended rehabilitation. This review focuses on the aging-related structural changes and mechanisms at cellular and subcellular levels underlying changes in the individual motor unit: specifically, the perikaryon of the α-motoneuron, its neuromuscular junction(s), and the muscle fibers that it innervates. Loss of muscle mass with aging, which is largely due to the progressive loss of motoneurons, is associated with reduced muscle fiber number and size. Muscle function progressively declines because motoneuron loss is not adequately compensated by reinnervation of muscle fibers by the remaining motoneurons. At the intracellular level, key factors are qualitative changes in posttranslational modifications of muscle proteins and the loss of coordinated control between contractile, mitochondrial, and sarcoplasmic reticulum protein expression. Quantitative and qualitative changes in skeletal muscle during the process of aging also have been implicated in the pathogenesis of acquired and hereditary neuromuscular disorders. In experimental models, specific intervention strategies have shown encouraging results on limiting deterioration of motor unit structure and function under conditions of impaired innervation. Translated to the clinic, if these or similar interventions, by saving muscle and improving mobility, could help alleviate sarcopenia in the elderly, there would be both great humanitarian benefits and large cost savings for health care systems.

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Insulin Resistance in Alzheimer's Disease

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The epidemiological connection between diabetes, obesity, and dementia represents an important public health challenge but also an opportunity to further understand these conditions. The key intersection among the three diseases is insulin resistance, which has been classically described to occur in peripheral tissues in diabetes and obesity and has recently been shown to develop in Alzheimer's disease (AD) brains. Here we review encouraging preclinical and clinical data indicating the potential of targeting impaired insulin signaling with antidiabetic drugs to treat dementia. We further discuss biological mechanisms through which peripheral metabolic dysregulation may lead to brain malfunction, providing possible explanations for the connection between diabetes, obesity, and AD. Finally, we briefly discuss how lifelong allostatic load may interact with aging to increase the risk of dementia in late life.

Biomed Pharmacother. 2018 Nov 2;109:304-313. doi: 10.1016/j.biopha.2018.10.065. [Epub ahead of print]

Stem cells as therapy for heart disease: iPSCs, ESCs, CSCs, and skeletal myoblasts.

Rikhtegar R[1], Pezeshkian M[2], Dolati S[1], Safaie N[2], Afrasiabi Rad A[2], Mahdipour M[3], Nouri M[3], Jodati AR[2], Yousefi M[4].

⊕ Author information

Abstract

Heart Diseases are serious and global public health concern. In spite of remarkable therapeutic developments, the prediction of patients with Heart Failure (HF) is weak, and present therapeutic attitudes do not report the fundamental problem of the cardiac tissue loss. Innovative therapies are required to reduce mortality and limit or abolish the necessity for cardiac transplantation. Stem cell-based therapies applied to the treatment of heart disease is according to the understanding that natural self-renewing procedures are inherent to the myocardium, nonetheless may not be adequate to recover the infarcted heart muscle. Following the first account of cell therapy in heart diseases, examination has kept up to rapidity; besides, several animals and human clinical trials have been conducted to preserve the capacity of numerous stem cell population in advance cardiac function and decrease infarct size. The purpose of this study was to censoriously evaluate the works performed regarding the usage of four major subgroups of stem cells, including induced Pluripotent Stem Cells (iPSC), Embryonic Stem Cells (ESCs), Cardiac Stem Cells (CDC), and Skeletal Myoblasts, in heart diseases, at the preclinical and clinical studies. Moreover, it is aimed to argue the existing disagreements, unsolved problems, and prospect directions.

KEYWORDS: Heart disease; Myocardial regeneration; Stem cells; Tissue repair

OTHER RESEARCH

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Predictable and precise template-free CRISPR editing of pathogenic variants

Max W. Shen, Mandana Arbab, Jonathan Y. Hsu, Daniel Worstell, Sannie J. Culbertson, Olga Krabbe, Christopher A. Cassa, David R. Liu ✉, David K. Gifford ✉ & Richard I. Sherwood ✉

Following Cas9 cleavage, DNA repair without a donor template is generally considered stochastic, heterogeneous and impractical beyond gene disruption. Here, we show that template-free Cas9 editing is predictable and capable of precise repair to a predicted genotype, enabling correction of disease-associated mutations in humans. We constructed a library of 2,000 Cas9 guide RNAs paired with DNA target sites and trained inDelphi, a machine learning model that predicts genotypes and frequencies of 1- to 60-base-pair deletions and 1-base-pair insertions with high accuracy ($r = 0.87$) in five human and mouse cell lines. inDelphi predicts that 5–11% of Cas9 guide RNAs targeting the human genome are 'precise-50', yielding a single genotype comprising greater than or equal to 50% of all major editing products. We experimentally confirmed precise-50 insertions and deletions in 195 human disease-relevant alleles, including correction in primary patient-derived fibroblasts of pathogenic alleles to wild-type genotype for Hermansky–Pudlak syndrome and Menkes disease. This study establishes an approach for precise, template-free genome editing.

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Predicting the mutations generated by repair of Cas9-induced double-strand breaks

Felicity Allen ✉, Luca Crepaldi, Clara Alsinet, Alexander J. Strong, Vitalii Kleshchevnikov, Pietro De Angeli, Petra Páleníková, Anton Khodak, Vladimir Kiselev, Michael Kosicki, Andrew R. Bassett, Heather Harding, Yaron Galanty, Francisco Muñoz-Martínez, Emmanouil Metzakopian, Stephen P. Jackson & Leopold Parts ✉

The DNA mutation produced by cellular repair of a CRISPR–Cas9-generated double-strand break determines its phenotypic effect. It is known that the mutational outcomes are not random, but depend on DNA sequence at the targeted location. Here we systematically study the influence of flanking DNA sequence on repair outcome by measuring the edits generated by >40,000 guide RNAs (gRNAs) in synthetic constructs. We performed the experiments in a range of genetic backgrounds and using alternative CRISPR–Cas9 reagents. In total, we gathered data for $>10^9$ mutational outcomes. The majority of reproducible mutations are insertions of a single base, short deletions or longer microhomology-mediated deletions. Each gRNA has an individual cell-line-dependent bias toward particular outcomes. We uncover sequence determinants of the mutations produced and use these to derive a predictor of Cas9 editing outcomes. Improved understanding of sequence repair will allow better design of gene editing experiments.

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Bright multicolor labeling of neuronal circuits with fluorescent proteins and chemical tags

Richi Sakaguchi, Marcus N Leiwe, Takeshi Imai
Kyushu University, Japan; Kyoto University, Japan; RIKEN Center for Developmental Biology, Japan

The stochastic multicolor labeling method 'Brainbow' is a powerful strategy to label multiple neurons differentially with fluorescent proteins; however, the fluorescence levels provided by the original attempts to use this strategy were inadequate. In the present study, we developed a stochastic multicolor labeling method with enhanced expression levels that uses a tetracycline-operator system (Tetbow). We optimized Tetbow for either plasmid or virus vector-mediated multicolor labeling. When combined with tissue clearing, Tetbow was powerful enough to visualize the three-dimensional architecture of individual neurons. Using Tetbow, we were able to visualize the axonal projection patterns of individual mitral/tufted cells along several millimeters in the mouse olfactory system. We also developed a Tetbow system with chemical tags, in which genetically encoded chemical tags were labeled with synthetic fluorophores. This was useful in expanding the repertoire of the fluorescence labels and the applications of the Tetbow system. Together, these new tools facilitate light-microscopy-based neuronal tracing at both a large scale and a high resolution.

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An integrative tissue-network approach to identify and test human disease genes

Victoria Yao, Rachel Kaletsky, William Keyes, Danielle E Mor, Aaron K Wong, Salman Sohrabi, Coleen T Murphy & Olga G Troyanskaya

Effective discovery of causal disease genes must overcome the statistical challenges of quantitative genetics studies and the practical limitations of human biology experiments. Here we developed *disease*QUEST, an integrative approach that combines data from human genome-wide disease studies with *in silico* network models of tissue- and cell-type-specific function in model organisms to prioritize candidates within functionally conserved processes and pathways. We used *disease*QUEST to predict candidate genes for 25 different diseases and traits, including cancer, longevity, and neurodegenerative diseases. Focusing on Parkinson's disease (PD), a *disease*QUEST-directed *Caenhorhabditis elegans* behavioral screen identified several candidate genes, which we experimentally verified and found to be associated with age-dependent motility defects mirroring PD clinical symptoms. Furthermore, knockdown of the top candidate gene, *bcat-1*, encoding a branched chain amino acid transferase, caused spasm-like 'curling' and neurodegeneration in *C. elegans*, paralleling decreased BCAT1 expression in PD patient brains. *disease*QUEST is modular and generalizable to other model organisms and human diseases of interest.

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Highly parallel single-molecule identification of proteins in zeptomole-scale mixtures

Jagannath Swaminathan, Alexander A Boulgakov, Erik T Hernandez, Angela M Bardo, James L Bachman, Joseph Marotta, Amber M Johnson, Eric V Anslyn ✉ & Edward M Marcotte ✉

The identification and quantification of proteins lags behind DNA-sequencing methods in scale, sensitivity, and dynamic range. Here, we show that sparse amino acid–sequence information can be obtained for individual protein molecules for thousands to millions of molecules in parallel. We demonstrate selective fluorescence labeling of cysteine and lysine residues in peptide samples, immobilization of labeled peptides on a glass surface, and imaging by total internal reflection microscopy to monitor decreases in each molecule's fluorescence after consecutive rounds of Edman degradation. The obtained sparse fluorescent sequence of each molecule was then assigned to its parent protein in a reference database. We tested the method on synthetic and naturally derived peptide molecules in zeptomole-scale quantities. We also fluorescently labeled phosphoserines and achieved single-molecule positional readout of the phosphorylated sites. We measured >93% efficiencies for dye labeling, survival, and cleavage; further improvements should enable studies of increasingly complex proteomic mixtures, with the high sensitivity and digital quantification offered by single-molecule sequencing.