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Scientific News
12th of February 2017
Sven Bulterijs

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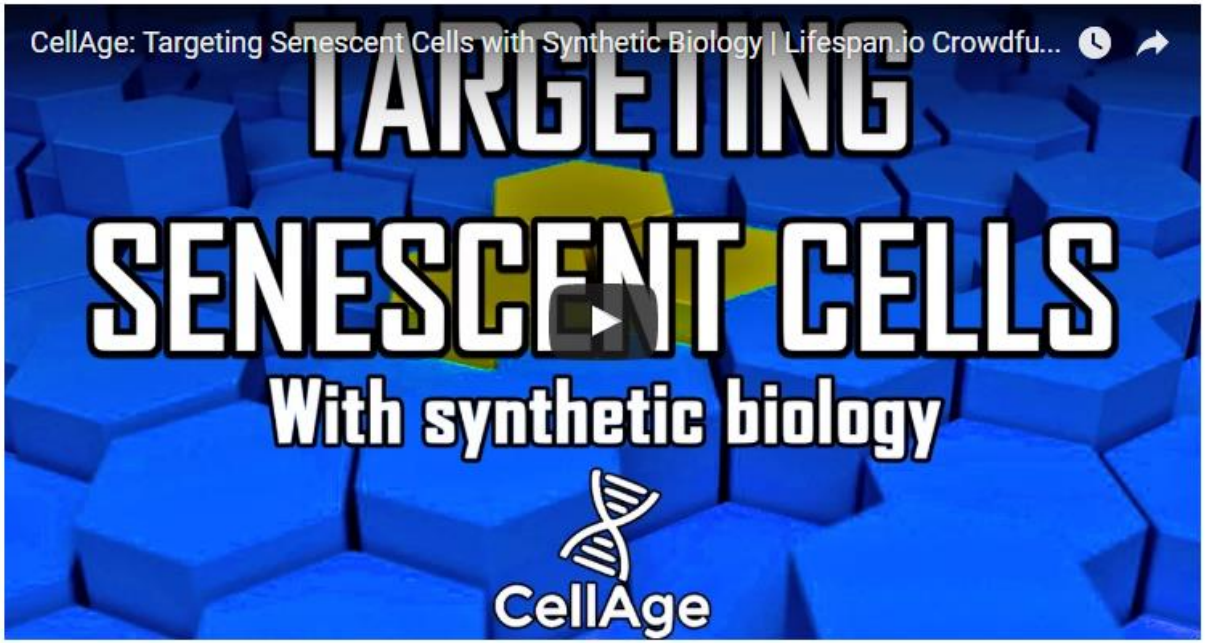
CELLAGE: TARGETING SENESCENT CELLS WITH SYNTHETIC BIOLOGY

Designing better systems for detection and safe removal of dysfunctional "senescent" cells to improve health and treat age-related diseases.

OVERVIEW | UPDATES | COMMENTS | BACKERS

SEARCH



$16,623
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Flexible Funding: All funds this campaign raises will be collected.

$3,000 matching grant for the CellAge fundraiser

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CellAge fundraiser support

Posted by caliban, in News 28 January 2017 · 610 views

fundraiser cellage

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FEATURED Options

UPDATE Feb.9th 2017: success!

LongeCity.Org has decided to support the current CellAge Fundraiser initiative beyond its standard support for certified 'star-rated' community fundraiser through an extension of its affiliate lab programme. To this end we have identified a specific small 'sub goal' within the first work project of the CellAge programme to get behind:

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Caloric restriction improves health and survival of rhesus monkeys

Caloric restriction (CR) without malnutrition extends lifespan and delays the onset of age-related disorders in most species but its impact in nonhuman primates has been controversial. In the late 1980s two parallel studies were initiated to determine the effect of CR in rhesus monkeys. The University of Wisconsin study reported a significant positive impact of CR on survival, but the National Institute on Aging study detected no significant survival effect. Here we present a direct comparison of longitudinal data from both studies including survival, bodyweight, food intake, fasting glucose levels and age-related morbidity. We describe differences in study design that could contribute to differences in outcomes, and we report species specificity in the impact of CR in terms of optimal onset and diet. Taken together these data confirm that health benefits of CR are conserved in monkeys and suggest that CR mechanisms are likely translatable to human health.

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A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012

Results The study cohorts had an average age of 75.0 years (95% CI, 74.8-75.2 years) in 2000 and 74.8 years (95% CI, 74.5-75.1 years) in 2012 ($P = .24$); 58.4% (95% CI, 57.3%-59.4%) of the 2000 cohort was female compared with 56.3% (95% CI, 55.5%-57.0%) of the 2012 cohort ($P < .001$). Dementia prevalence among those 65 years or older decreased from 11.6% (95% CI, 10.7%-12.7%) in 2000 to 8.8% (95% CI, 8.2%-9.4%) (8.6% with age- and sex-standardization) in 2012 ($P < .001$). More years of education was associated with a lower risk for dementia, and average years of education increased significantly (from 11.8 years [95% CI, 11.6-11.9 years] to 12.7 years [95% CI, 12.6-12.9 years]; $P < .001$) between 2000 and 2012. The decline in dementia prevalence occurred even though there was a significant age- and sex-adjusted increase between years in the cardiovascular risk profile (eg, prevalence of hypertension, diabetes, and obesity) among older US adults.

Conclusions and Relevance The prevalence of dementia in the United States declined significantly between 2000 and 2012. An increase in educational attainment was associated with some of the decline in dementia prevalence, but the full set of social, behavioral, and medical factors contributing to the decline is still uncertain. Continued monitoring of trends in dementia incidence and prevalence will be important for better gauging the full future societal impact of dementia as the number of older adults increases in the decades ahead.

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Sci Rep. 2017 Dec;7(1):5. doi: 10.1038/s41598-017-00037-7. Epub 2017 Jan 31.

Lipidome determinants of maximal lifespan in mammals.

Bozek K[1,2], Khrameeva EE[3,4], Reznick J[5], Omerbašić D[6], Bennett NC[7], Lewin GR[6], Azpurua J[8], Gorbunova V[8], Seluanov A[8], Regnard P[9], Wanert F[9], Marchal J[10], Pifferi F[10], Aujard F[10], Liu Z[11], Shi P[11], Pääbo S[12], Schroeder F[13], Willmitzer L[13], Giavalisco P[14], Khaitovich P[15,16,17].

Author information

Abstract

Maximal lifespan of mammalian species, even if closely related, may differ more than 10-fold, however the nature of the mechanisms that determine this variability is unresolved. Here, we assess the relationship between maximal lifespan duration and concentrations of more than 20,000 lipid compounds, measured in 669 tissue samples from 6 tissues of 35 species representing three mammalian clades: primates, rodents and bats. We identify lipids associated with species' longevity across the three clades, uncoupled from other parameters, such as basal metabolic rate, body size, or body temperature. These lipids clustered in specific lipid classes and pathways, and enzymes linked to them display signatures of greater stabilizing selection in long-living species, and cluster in functional groups related to signaling and protein-modification processes. These findings point towards the existence of defined molecular mechanisms underlying variation in maximal lifespan among mammals.

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Polyhedral 3D structure of human plasma very low density lipoproteins by individual particle cryo-electron tomography[1][S]

Human VLDLs assembled in the liver and secreted into the circulation supply energy to peripheral tissues. VLDL lipolysis yields atherogenic LDLs and VLDL remnants that strongly correlate with CVD. Although the composition of VLDL particles has been well-characterized, their 3D structure is elusive because of their variations in size, heterogeneity in composition, structural flexibility, and mobility in solution. Here, we employed cryo-electron microscopy and individual-particle electron tomography to study the 3D structure of individual VLDL particles (without averaging) at both below and above their lipid phase transition temperatures. The 3D reconstructions of VLDL and VLDL bound to antibodies revealed an unexpected polyhedral shape, in contrast to the generally accepted model of a spherical emulsion-like particle. The smaller curvature of surface lipids compared with HDL may also reduce surface hydrophobicity, resulting in lower binding affinity to the hydrophobic distal end of the N-terminal β-barrel domain of cholesteryl ester transfer protein (CETP) compared with HDL. The directional binding of CETP to HDL and VLDL may explain the function of CETP in transferring TGs and cholesteryl esters between these particles. This first visualization of the 3D structure of VLDL could improve our understanding of the role of VLDL in atherogenesis.

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Ectopic fat deposition contributes to age-associated pathology in *Caenorhabditis elegans*[S]

Age-dependent collapse of lipid homeostasis results in spillover of lipids and excessive fat deposition in nonadipose tissues. Ectopic fat contributes to lipotoxicity and has been implicated in the development of a metabolic syndrome that increases risk of age-associated diseases. However, the molecular mechanisms coupling ectopic fat accumulation with aging remain obscure. Here, we use nonlinear imaging modalities to visualize and quantify age-dependent ectopic lipid accumulation in *Caenorhabditis elegans*. We find that aging is accompanied by pronounced deposition of lipids in nonadipose tissues, including the nervous system. Importantly, interventions that promote longevity such as low insulin signaling, germ-line loss, and dietary restriction, which effectively delay aging in evolutionary divergent organisms, diminish the rate of ectopic fat accumulation and the size of lipid droplets. Suppression of lipotoxic accumulation of fat in heterologous tissues is dependent on helix-loop-helix (HLH)-30/transcription factor EB (TFEB) and autophagy. Our findings in their totality highlight the pivotal role of HLH-30/TFEB and autophagic processes in the maintenance of lipid homeostasis during aging, in addition to establishing nonlinear imaging as a powerful tool for monitoring ectopic lipid droplet deposition in vivo.

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Strehler-Mildvan correlation is a degenerate manifold of Gompertz fit

Highlights

- Strehler-Mildvan correlation is a degenerate manifold of Gompertz fit, coinciding with a narrow stripe of iso-average lifespan curves.
- As far as Gompertz law adequately describes mortality, the linear Strehler-Mildvan correlation is observed only in experiments with a modest change in lifespan and breaks down for dramatic lifespan changes.
- Gompertz fit applied to high-dimensional mortality changes might lead to abnormal behavior of Strehler-Mildvan correlation, such as its breakdowns.
- The average lifespan is the only stable feature in experiments with low-quality survival curves.
- An analytical derivation of the degeneracy manifold of Gompertz fit (i.e. Strehler-Mildvan correlation) is presented.

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Structural Basis of Sirtuin 6 Activation by Synthetic Small Molecules

Sirtuins are protein deacylases regulating metabolism and stress responses, and are implicated in aging-related diseases. Small molecule activators for the human sirtuins Sirt1-7 are sought as chemical tools and potential therapeutics, such as for cancer. Activators are available for Sirt1 and exploit its unique N-terminus, whereas drug-like activators for Sirt2–7 are lacking. We synthesized and screened pyrrolo[1,2-a]quinoxaline derivatives, yielding the first synthetic Sirt6 activators. Biochemical assays show direct, substrate-independent compound binding to the Sirt6 catalytic core and potent activation of Sirt6-dependent deacetylation of peptide substrates and complete nucleosomes. Crystal structures of Sirt6/activator complexes reveal that the compounds bind to a Sirt6-specific acyl channel pocket and identify key interactions. Our results establish potent Sirt6 activation with small molecules and provide a structural basis for further development of Sirt6 activators as tools and therapeutics.

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BMC Syst Biol. 2016 Dec 23;10(Suppl 4):131. doi: 10.1186/s12918-016-0362-4.

Screening lifespan-extending drugs in Caenorhabditis elegans via label propagation on drug-protein networks.

Liu H[1,2], Guo M[1], Xue T[1], Guan J[3], Luo L[4], Zhuang Z[5,6].

Author information

Abstract

BACKGROUND: One of the most challenging tasks in the exploration of anti-aging is to discover drugs that can promote longevity and delay the incidence of age-associated diseases of human. Up to date, a number of drugs, including some antioxidants, metabolites and synthetic compounds, have been found to effectively delay the aging of nematodes and insects.

RESULTS: We proposed a label propagation algorithm on drug-protein network to infer drugs that can extend the lifespan of C. elegans. We collected a set of drugs of which functions on lifespan extension of C. elegans have been reliably determined, and then built a large-scale drug-protein network by collecting a set of high-confidence drugprotein interactions. A label propagation algorithm was run on the drug-protein bipartite network to predict new drugs with lifespan-extending effect on C. elegans. We calibrated the performance of the proposed method by conducting performance comparison with two classical models, kNN and SVM. We also showed that the screened drugs significantly mediate in the aging-related pathways, and have higher chemical similarities to the effective drugs than ineffective drugs in promoting longevity of C. elegans. Moreover, we carried out wet-lab experiments to verify a screened drugs, 2- Bromo-4'-nitroacetophenone, and found that it can effectively extend the lifespan of C. elegans. These results showed that our method is effective in screening lifespanextending drugs in C. elegans.

CONCLUSIONS: In this paper, we proposed a semi-supervised algorithm to predict drugs with lifespan-extending effects on C. elegans. In silico empirical evaluations and in vivo experiments in C. elegans have demonstrated that our method can effectively narrow down the scope of candidate drugs needed to be verified by wet lab experiments.

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Drug repurposing for ageing research using model organisms

Summary

Many increasingly prevalent diseases share a common risk factor: age. However, little is known about pharmaceutical interventions against ageing, despite many genes and pathways shown to be important in the ageing process and numerous studies demonstrating that genetic interventions can lead to a healthier ageing phenotype. An important challenge is to assess the potential to repurpose existing drugs for initial testing on model organisms, where such experiments are possible. To this end, we present a new approach to rank drug-like compounds with known mammalian targets according to their likelihood to modulate ageing in the invertebrates *C. elegans* and *Drosophila*. Our approach combines information on genetic effects on ageing, orthology relationships and sequence conservation, 3D protein structures, drug binding and bioavailability. Overall, we rank 743 different drug-like compounds for their likelihood to modulate ageing. We provide various lines of evidence for the successful enrichment of our ranking for compounds modulating ageing, despite sparse public data suitable for validation. The top ranked compounds are thus prime candidates for *in vivo* testing of their effects on lifespan in *C. elegans* or *Drosophila*. As such, these compounds are promising as research tools and ultimately a step towards identifying drugs for a healthier human ageing.

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Recognizing Degenerative Aging as a Treatable Medical Condition: Methodology and Policy

Ilia Stambler

It is becoming increasingly clear that in order to accomplish healthy longevity for the population, there is an urgent need for the research and development of effective therapies against degenerative aging processes underlying major aging-related diseases, including heart disease, neurodegenerative diseases, type 2 diabetes, cancer, pulmonary obstructive diseases, as well as aging-related complications and susceptibilities of infectious communicable diseases. Yet, an important incentive for the research and development of such therapies appears to be the development of clinically applicable and scientifically grounded definitions and criteria for the multifactorial degenerative aging process (or "senility" using the existing ICD category), underlying those diseases, as well as for the safety and effectiveness of interventions against it. Such generally agreed definitions and criteria are currently absent. The devising of such criteria is important not only for the sake of their scientific value and their utility for the development of therapeutic solutions for the aging population, but also to comply with and implement major existing national and international programmatic and regulatory requirements. Some methodological suggestions and potential pitfalls for the development of such criteria are examined.

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Glycation inhibitors extend yeast chronological lifespan by reducing advanced glycation end products and by back regulation of proteins involved in mitochondrial respiration

Advanced Glycation End products (AGEs) are implicated in aging process. Thus, reducing AGEs by using glycation inhibitors may help in attenuating the aging process. In this study using *Saccharomyces cerevisiae* yeast system, we show that Aminoguanidine (AMG), a well-known glycation inhibitor, decreases the AGE modification of proteins in non-calorie restriction (NR) (2% glucose) and extends chronological lifespan (CLS) similar to that of calorie restriction (CR) condition (0.5% glucose). Proteomic analysis revealed that AMG back regulates the expression of differentially expressed proteins especially those involved in mitochondrial respiration in NR condition, suggesting that it switches metabolism from fermentation to respiration, mimicking CR. AMG induced back regulation of differentially expressed proteins could be possibly due to its chemical effect or indirectly by glycation inhibition. To delineate this, Metformin (MET), a structural analog of AMG and a mild glycation inhibitor and Hydralazine (HYD), another potent glycation inhibitor but not structural analog of AMG were used. HYD was more effective than MET in mimicking AMG suggesting that glycation inhibition was responsible for restoration of differentially expressed proteins. Thus glycation inhibitors particularly AMG, HYD and MET extend yeast CLS by reducing AGEs, modulating the expression of proteins involved in mitochondrial respiration and possibly by scavenging glucose.

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Limitations and risks of meta-analyses of longevity studies

Abstract

Searching for genetic determinants of human longevity has been challenged by the rarity of data sets with large numbers of individuals who have reached extreme old age, inconsistent definitions of the phenotype, and the difficulty of defining appropriate controls. Meta-analysis – a statistical method to summarize results from different studies – has become a common tool in genetic epidemiology to accrue large sample sizes for powerful genetic association studies. In conducting a meta-analysis of studies of human longevity however, particular attention must be made to the definition of cases and controls (including their health status) and on the effect of possible confounders such as sex and ethnicity upon the genetic effect to be estimated. We will show examples of how a meta-analysis can inflate the false negative rates of genetic association studies or it can bias estimates of the association between a genetic variant and extreme longevity.

Influence of donor age on induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are being pursued as a source of cells for autologous therapies, many of which will be aimed at aged patients. To explore the impact of age on iPSC quality, we produced iPSCs from blood cells of 16 donors aged 21–100. We find that iPSCs from older donors retain an epigenetic signature of age, which can be reduced through passaging. Clonal expansion via reprogramming also enables the discovery of somatic mutations present in individual donor cells, which are missed by bulk sequencing methods. We show that exomic mutations in iPSCs increase linearly with age, and all iPSC lines analyzed carry at least one gene-disrupting mutation, several of which have been associated with cancer or dysfunction. Unexpectedly, elderly donors (>90 yrs) harbor fewer mutations than predicted, likely due to a contracted blood progenitor pool. These studies establish that donor age is associated with an increased risk of abnormalities in iPSCs and will inform clinical development of reprogramming technology.

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Phylogenetic analysis of the human antibody repertoire reveals quantitative signatures of immune senescence and aging

The elderly have reduced humoral immunity, as manifested by increased susceptibility to infections and impaired vaccine responses. To investigate the effects of aging on B-cell receptor (BCR) repertoire evolution during an immunological challenge, we used a phylogenetic distance metric to analyze Ig heavy-chain transcript sequences in both young and elderly individuals before and after influenza vaccination. We determined that BCR repertoires become increasingly specialized over a span of decades, but less plastic. In 50% of the elderly individuals, a large space in the repertoire was occupied by a small number of recall lineages that did not decline during vaccine response and contained hypermutated IgD^{+} B cells. Relative to their younger counterparts, older subjects demonstrated a contracted naive repertoire and diminished intralineage diversification, signifying a reduced substrate for mounting novel responses and decreased fine-tuning of BCR specificities by somatic hypermutation. Furthermore, a larger proportion of the repertoire exhibited premature stop codons in some elderly subjects, indicating that aging may negatively affect the ability of B cells to discriminate between functional and nonfunctional receptors. Finally, we observed a decreased incidence of radical mutations compared with conservative mutations in elderly subjects' vaccine responses, which suggests that accumulating original antigenic sin may be limiting the accessible space for paratope evolution. Our findings shed light on the complex interplay of environmental and gerontological factors affecting immune senescence, and provide direct molecular characterization of the effects of senescence on the immune repertoire.

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Peptidylarginine deiminase 4 promotes age-related organ fibrosis

Aging promotes inflammation, a process contributing to fibrosis and decline in organ function. The release of neutrophil extracellular traps (NETs [NETosis]), orchestrated by peptidylarginine deiminase 4 (PAD4), damages organs in acute inflammatory models. We determined that NETosis is more prevalent in aged mice and investigated the role of PAD4/NETs in age-related organ fibrosis. Reduction in fibrosis was seen in the hearts and lungs of aged $PAD4^{-/-}$ mice compared with wild-type (WT) mice. An increase in left ventricular interstitial collagen deposition and a decline in systolic and diastolic function were present only in WT mice, and not in $PAD4^{-/-}$ mice. In an experimental model of cardiac fibrosis, cardiac pressure overload induced NETosis and significant platelet recruitment in WT but not $PAD4^{-/-}$ myocardium. DNase 1 was given to assess the effects of extracellular chromatin. PAD4 deficiency or DNase 1 similarly protected hearts from fibrosis. We propose a role for NETs in cardiac fibrosis and conclude that PAD4 regulates age-related organ fibrosis and dysfunction.

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Antagonistic pleiotropy and mutation accumulation influence human senescence and disease

Senescence has long been a public health challenge as well as a fascinating evolutionary problem. There is neither a universally accepted theory for its ultimate causes, nor a consensus about what may be its impact on human health. Here we test the predictions of two evolutionary explanations of senescence—mutation accumulation and antagonistic pleiotropy—which postulate that genetic variants with harmful effects in old ages can be tolerated, or even favoured, by natural selection at early ages. Using data from genome-wide association studies (GWAS), we study the effects of genetic variants associated with diseases appearing at different periods in life, when they are expected to have different impacts on fitness. Data fit theoretical expectations. Namely, we observe higher risk allele frequencies combined with large effect sizes for late-onset diseases, and detect a significant excess of early–late antagonistically pleiotropic variants that, strikingly, tend to be harboured by genes related to ageing. Beyond providing systematic, genome-wide evidence for evolutionary theories of senescence in our species and contributing to the long-standing question of whether senescence is the result of adaptation, our approach reveals relationships between previously unrelated pathologies, potentially contributing to tackling the problem of an ageing population.

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Theor Popul Biol. 2017 Jan 18;114:107-116. doi: 10.1016/j.tpb.2017.01.001. [Epub ahead of print]

Stochasticity, heterogeneity, and variance in longevity in human populations.

Hartemink N[1], Missov TI[2], Caswell H[3].

Author information

Abstract

Inter-individual variance in longevity (or any other demographic outcome) may arise from heterogeneity or from individual stochasticity. Heterogeneity refers to differences among individuals in the demographic rates experienced at a given age or stage. Stochasticity refers to variation due to the random outcome of demographic rates applied to individuals with the same properties. The variance due to individual stochasticity can be calculated from a Markov chain description of the life cycle. The variance due to heterogeneity can be calculated from a multistate model that incorporates the heterogeneity. We show how to use this approach to decompose the variance in longevity into contributions from stochasticity and heterogeneous frailty for male and female cohorts from Sweden (1751-1899), France (1816-1903), and Italy (1872-1899), and also for a selection of period data for the same countries. Heterogeneity in mortality is described by the gamma-Gompertz-Makeham model, in which a gamma distributed "frailty" modifies a baseline Gompertz-Makeham mortality schedule. Model parameters were estimated by maximum likelihood for a range of starting ages. The estimates were used to construct an age×frailty-classified matrix model, from which we compute the variance of longevity and its components due to heterogeneous frailty and to individual stochasticity. The estimated fraction of the variance in longevity due to heterogeneous frailty (averaged over time) is less than 10% for all countries and for both sexes. These results suggest that most of the variance in human longevity arises from stochasticity, rather than from heterogeneous frailty.

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Neurobiol Aging. 2016 Dec 27;52:23-31. doi: 10.1016/j.neurobiolaging.2016.12.016. [Epub ahead of print]

Transcriptional profiling reveals protective mechanisms in brains of long-lived mice.

Frahm C[1], Srivastava A[2], Schmidt S[2], Mueller J[2], Groth M[3], Guenther M[2], Ji Y[2], Priebe S[4], Platzer M[3], Witte OW[2].

Author information

Abstract

The brain plays a central role in organismal aging but is itself most sensitive to aging-related functional impairments and pathologies. Insights into processes underlying brain aging are the basis to positively impact brain health. Using high-throughput RNA sequencing and quantitative polymerase chain reaction (PCR), we monitored cerebral gene expression in mice throughout their whole lifespan (2, 9, 15, 24, and 30 months). Differentially expressed genes were clustered in 6 characteristic temporal expression profiles, 3 of which revealed a distinct change between 24 and 30 months, the period when most mice die. Functional annotation of these genes indicated a participation in protection against cancer and oxidative stress. Specifically, the most enriched pathways for the differentially expressed genes with higher expression at 30 versus 24 months were found to be glutathione metabolism and chemokine signaling pathway, whereas those lower expressed were enriched in focal adhesion and pathways in cancer. We therefore conclude that brains of very old mice are protected from certain aspects of aging, in particular cancer, which might have an impact on organismal health and lifespan.

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Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states

Low-grade, chronic inflammation has been associated with many diseases of aging, but the mechanisms responsible for producing this inflammation remain unclear. Inflammasomes can drive chronic inflammation in the context of an infectious disease or cellular stress, and they trigger the maturation of interleukin-1β (IL-1β). Here we find that the expression of specific inflammasome gene modules stratifies older individuals into two extremes: those with constitutive expression of IL-1β, nucleotide metabolism dysfunction, elevated oxidative stress, high rates of hypertension and arterial stiffness; and those without constitutive expression of IL-1β, who lack these characteristics. Adenine and N^4-acetylcytidine, nucleotide-derived metabolites that are detectable in the blood of the former group, prime and activate the NLRC4 inflammasome, induce the production of IL-1β, activate platelets and neutrophils and elevate blood pressure in mice. In individuals over 85 years of age, the elevated expression of inflammasome gene modules was associated with all-cause mortality. Thus, targeting inflammasome components may ameliorate chronic inflammation and various other age-associated conditions.

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J Intern Med. 2017 Jan;281(1):86-95. doi: 10.1111/joim.12545. Epub 2016 Sep 7.

Fish consumption and all-cause mortality in a cohort of Swedish men and women.

Bellavia A[1], Larsson SC[1], Wolk A[1].

Author information

Abstract

BACKGROUND: Epidemiological studies of fish consumption and all-cause mortality have provided inconsistent results.

OBJECTIVE: We examined the dose-response association between fish consumption and mortality from all causes in a large population-based cohort of Swedish men and women.

METHODS: The study included 72 522 participants (33 973 women and 38 549 men), aged 45-83 years, from the Swedish Mammography Cohort and the Cohort of Swedish Men. Information on fish consumption was obtained through a self-administered questionnaire in 1997. Participants were followed for 17 years (1 January 1998 to 31 December 2014), and data on death and causes of death were ascertained through linkage to the Swedish Cause of Death Register. We used Cox proportional hazard regression to estimate hazard ratios (HRs) of death. Fish consumption was evaluated as a continuous predictor, flexibly modelled with restricted cubic splines to assess potential nonlinear associations.

RESULTS: During follow-up, 16 730 deaths (7168 women and 9562 men) were recorded. The dose-response association between fish consumption and all-cause mortality was U-shaped. Compared with the median fish consumption (women: 25.0; men: 30.5 g day^{-1}), lower levels of consumption were progressively associated with higher mortality risk up to 25% for women [HR 1.25; 95% confidence interval (CI): 1.11, 1.40] and 19% for men (HR 1.19; 95% CI: 1.07, 1.32) with no reported consumption. Increasingly higher levels of fish consumption were associated with higher mortality risk only amongst women, with a 39% higher mortality risk amongst women reporting the highest level of fish consumption (80 g day^{-1} ; HR 1.39; 95% CI: 1.15, 1.68).

CONCLUSION: These results indicate a U-shaped association between fish consumption and all-cause mortality, particularly amongst women.

REVIEWS/COMMENTS/EDITORIALS

Rejuvenation Res. 2016 Dec;19(6):445-446.

Don't Call Aging a Risk Factor for Age-Related Disease.

de Grey AD[1].

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Geroscience and the trans-NIH Geroscience Interest Group, GSIG

Age is by far the major risk factor for most chronic diseases. This has been common knowledge since time immemorial. Aging encompasses the biological changes most often seen as declines of function and increasing burden of disease. The close linkage of these two has led people to believe that aging, like age, is immutable. It is only recently that research into the basic molecular and cellular mechanisms of aging has led to potential interventions that increase lifespan and appear to increase healthspan, as well. Geroscience is an interdisciplinary field that aims to understand the relationship between the biology of aging and the biology of age-related diseases. The "geroscience hypothesis" posits that manipulation of aging will delay (in parallel) the appearance or severity of many chronic diseases because these diseases share the same underlying major risk factor (age). The hope is that this will lead to health improvements in the older population with perhaps greater efficiency than can be achieved through the successful cure and management of diseases of aging as they arise individually or as comorbidities.

With those concepts in mind, the Geroscience Interest Group (GSIG) was launched as a trans-institute interest group within the NIH in November 2012. Here, we discuss the genesis of the trans-NIH group and the most salient activities that have occurred in the last 5 years.

Osteoarthritis year in review 2016

- Osteoarthritis year in review 2016: biology Review Article
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- Osteoarthritis Year in Review 2016: biomarkers (biochemical markers) Review Article
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- Osteoarthritis year in review 2016: clinical Review Article
  Pages 209-215
  N.E. Lane, K. Shidara, B.L. Wise
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- Osteoarthritis year in review 2016: imaging Review Article
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Alzheimer disease in 2016: Putting AD treatments and biomarkers to the test

Eric M. Reiman

Nature Reviews Neurology **13**, 74–76 (2017) | doi:10.1038/nrneurol.2017.1
Published online 13 January 2017

Investigational treatments to impede the progression of Alzheimer disease (AD) are being evaluated in clinical trials, and biomarkers to detect and track the disease are being developed and deployed. Recent findings underscore the importance of ongoing clinical trials and biomarker developments in the understanding, treatment and prevention of AD.

Review

Peroxisomal Dysfunction in Age-Related Diseases

Peroxisomes carry out many key functions related to lipid and reactive oxygen species (ROS) metabolism. The fundamental importance of peroxisomes for health in humans is underscored by the existence of devastating genetic disorders caused by impaired peroxisomal function or lack of peroxisomes. Emerging studies suggest that peroxisomal function may also be altered with aging and contribute to the pathogenesis of a variety of diseases, including diabetes and its related complications, neurodegenerative disorders, and cancer. With increasing evidence connecting peroxisomal dysfunction to the pathogenesis of these acquired diseases, the possibility of targeting peroxisomal function in disease prevention or treatment becomes intriguing. Here, we review recent developments in understanding the pathophysiological implications of peroxisomal dysfunctions outside the context of inherited peroxisomal disorders.

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Life in the cold: links between mammalian hibernation and longevity

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Abstract: The biological process of aging is the primary determinant of lifespan, but the factors that influence the rate of aging are not yet clearly understood and remain a challenging question. Mammals are characterized by >100-fold differences in maximal lifespan, influenced by relative variances in body mass and metabolic rate. Recent discoveries have identified long-lived mammalian species that deviate from the expected longevity quotient. A commonality among many long-lived species is the capacity to undergo metabolic rate depression, effectively re-programming normal metabolism in response to extreme environmental stress and enter states of torpor or hibernation. This stress tolerant phenotype often involves a reduction in overall metabolic rate to just 1–5% of the normal basal rate as well as activation of cytoprotective responses. At the cellular level, major energy savings are achieved via coordinated suppression of many ATP-expensive cell functions; e.g. global rates of protein synthesis are strongly reduced via inhibition of the insulin signaling axis. At the same time, various studies have shown activation of stress survival signaling during hibernation including up-regulation of protein chaperones, increased antioxidant defenses, and transcriptional activation of pro-survival signaling such as the FOXO and p53 pathways. Many similarities and parallels exist between hibernation phenotypes and different long-lived models, e.g. signal transduction pathways found to be commonly regulated during hibernation are also known to induce lifespan extension in animals such as *Drosophila melanogaster* and *Caenorhabditis elegans*. In this review, we highlight some of the molecular mechanisms that promote longevity in classic aging models *C. elegans*, *Drosophila*, and mice, while providing a comparative analysis to how they are regulated during mammalian hibernation.

A review of the biomedical innovations for healthy longevity

The field of biogerontology and regenerative medicine is rapidly evolving with many new advances in aging research promising to transform healthcare and extend healthy productive longevity. Recent breakthroughs in epigenetic, transcriptomic and multimodal biomarkers of aging, discovery of new and validation of old geroprotectors and advances in gene therapy provide an optimistic outlook. However, the propagation of laboratory advances into clinical practice has been comparatively slow with few focused investment and technology integration programs worldwide.

To evaluate the technological readiness of the biomedical advances in biogerontology and accelerate the translation from laboratory to clinical and commercial setting, a community of scientists with support from the innovative investment companies organized the third bi-annual international conference titled "Biomedical Innovation for healthy longevity" in Saint-Petersburg, Russia in 25-27 of April 2016. The conference was organized by **Alexey Moskalev**, **Alex Zhavoronkov**, **Vladimir Anisimov**, **Olga Tkacheva** with support from the Fomenko family including **Andrei Fomenko**, **Lada Fomenko** and **Isabel Fomenko** acknowledged in this paper and attended by over 400 scientists from over 20 countries, representing the largest biomedical centers and presenting their work.

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Gut microbiota: A player in aging and a target for anti-aging intervention

Aging-associated alterations in composition, diversity and functional features of intestinal microbiota are well-described in the modern literature. They are suggested to be caused by an age-related decline in immune system functioning (immunosenescence) and a low-grade chronic inflammation (inflammaging), which accompany many aging-associated pathologies. The microbiota-targeted dietary and probiotic interventions have been shown to favorably affect the host health and aging by an enhancement of antioxidant activity, improving immune homeostasis, suppression of chronic inflammation, regulation of fat deposition and metabolism and prevention of insulin resistance. Recently, a high effectiveness and safety of novel therapeutic application such as fecal microbiota transplantation in the prevention and treatment of age-related pathological conditions including atherosclerosis, type 2 diabetes and Parkinson's disease has been demonstrated. In this review, recent research findings are summarized on the role of gut micribiota in aging processes with emphasis on therapeutic potential of microbiome-targeted interventions in anti-aging medicine,

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