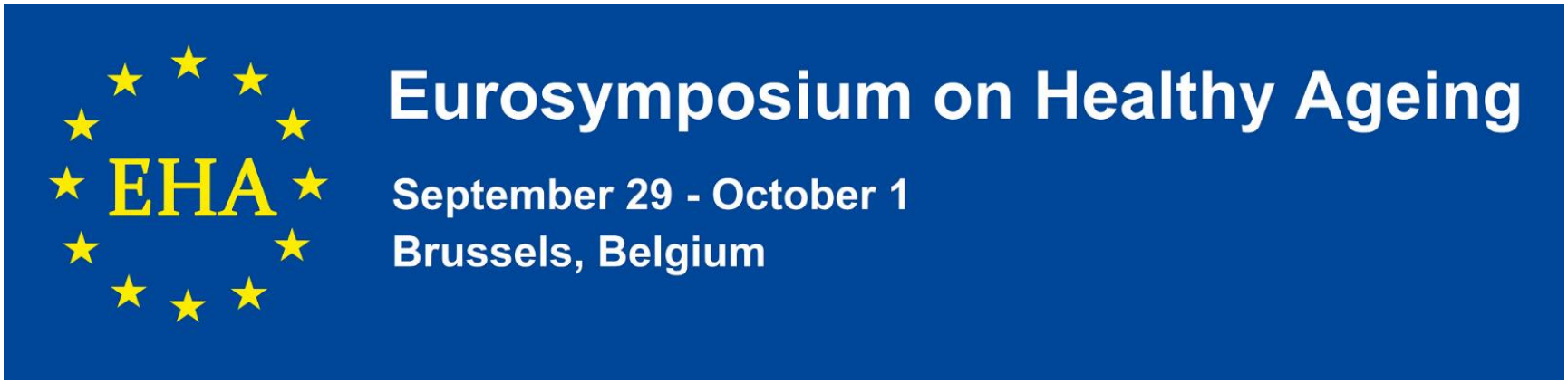
Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
7th of August 2016
Sven Bulterijs

Early registration ends on the 15th of August!



http://www.eha-heales.org/

Heales
HEALTHY LIFE EXTENSION SOCIETY

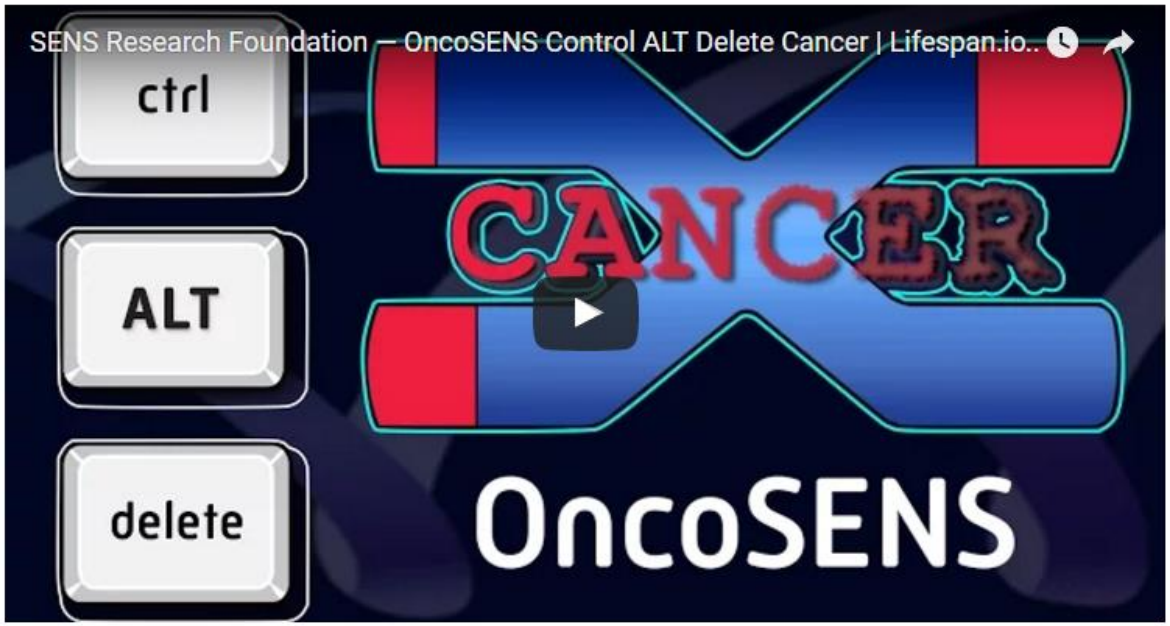
ONCOSENS CONTROL ALT DELETE CANCER

High-throughput screening of a library of diverse drugs to find treatments for 'ALT' cancers, those which rely on Alternative Lengthening of Telomeres.

BY DR. HAROLDO SILVA

OVERVIEW | UPDATES | COMMENTS | BACKERS

SEARCH



$25,235
PLEDGED OF $60,000 GOAL

283 BACKERS

12 DAYS TO GO

CONTRIBUTE NOW

Flexible Funding: All funds this campaign raises will be collected.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Michael Greve Commits $10 Million

INTERNET ENTREPRENEUR MICHAEL GREVE COMMITS $10 MILLION TO SENS RELATED RESEARCH AND STARTUPS INCLUDING A $5 MILLION DONATION OVER 5 YEARS TO SENS RESEARCH FOUNDATION

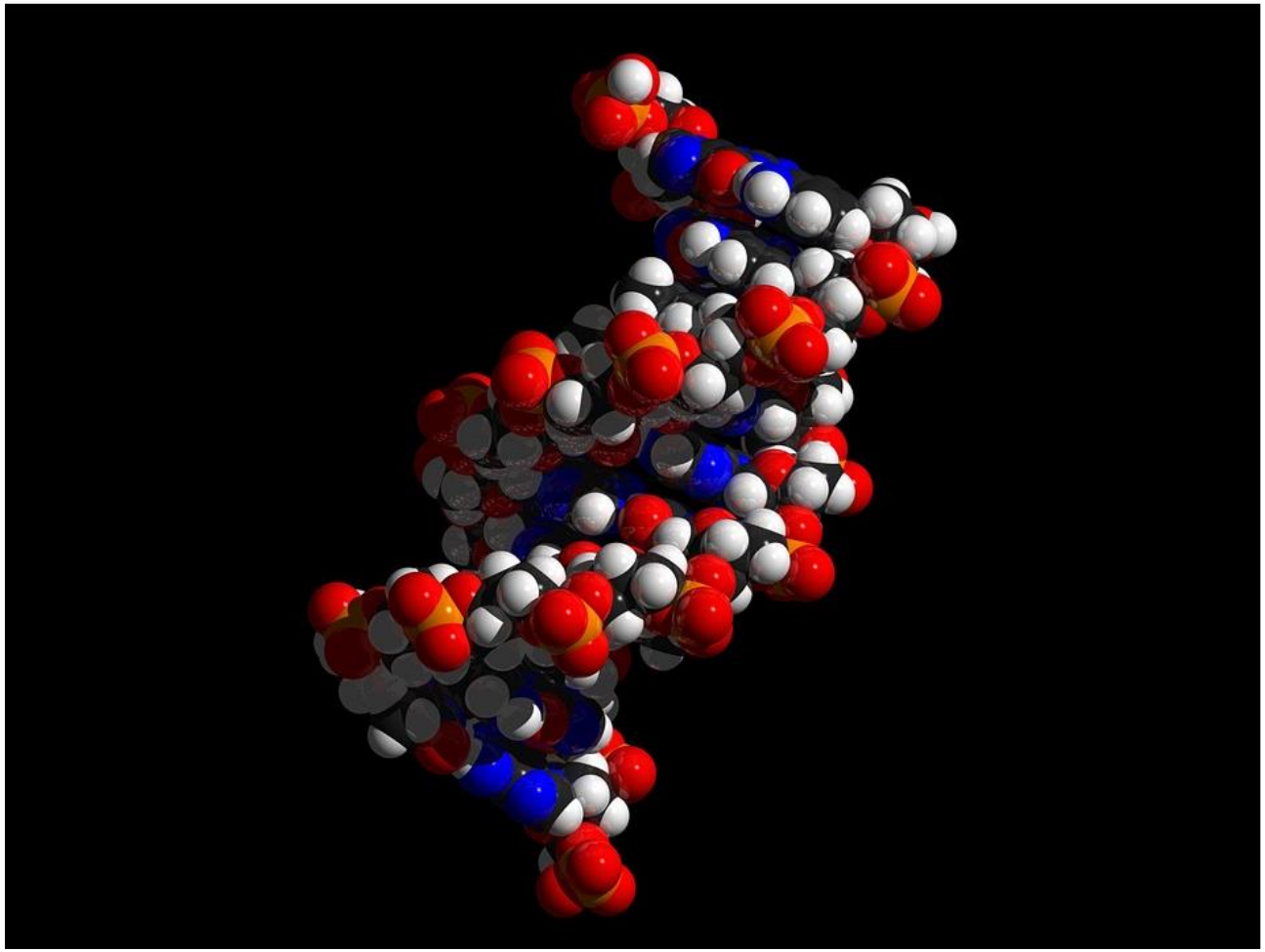
$5 Million To Be Invested in Rejuvenation Biotechnology Related Startups

MOUNTAIN VIEW, Calif. — July 12, 2016 — German Internet Entrepreneur Michael Greve today announced that his Forever Healthy Foundation will be committing $5 million in philanthropic support over the next five years to the SENS Research Foundation (SRF), a non-profit organization focused on transforming the way the world researches and treats age-related disease. In addition Michael Greve's company KIZOO Technology Ventures will be committing seed investments of $5 million in startups focused on bringing rejuvenation biotechnology treatments to market.

"My goal is to provide support for the critical research of the SENS Research Foundation and to facilitate the development of the rejuvenation biotech industry and ecosystem. I think we should have more people contribute to the step-by-step creation of cures for the root causes of all age-related diseases. And we should have a whole rejuvenation industry based on the SENS treatment model including the self-accelerating feedback-loop of success stories and amazing opportunities for scientist, entrepreneurs and VC investors. This will truly accelerate both research and therapies. I have decided to lead by example and make this $10 million commitment," said Michael Greve.

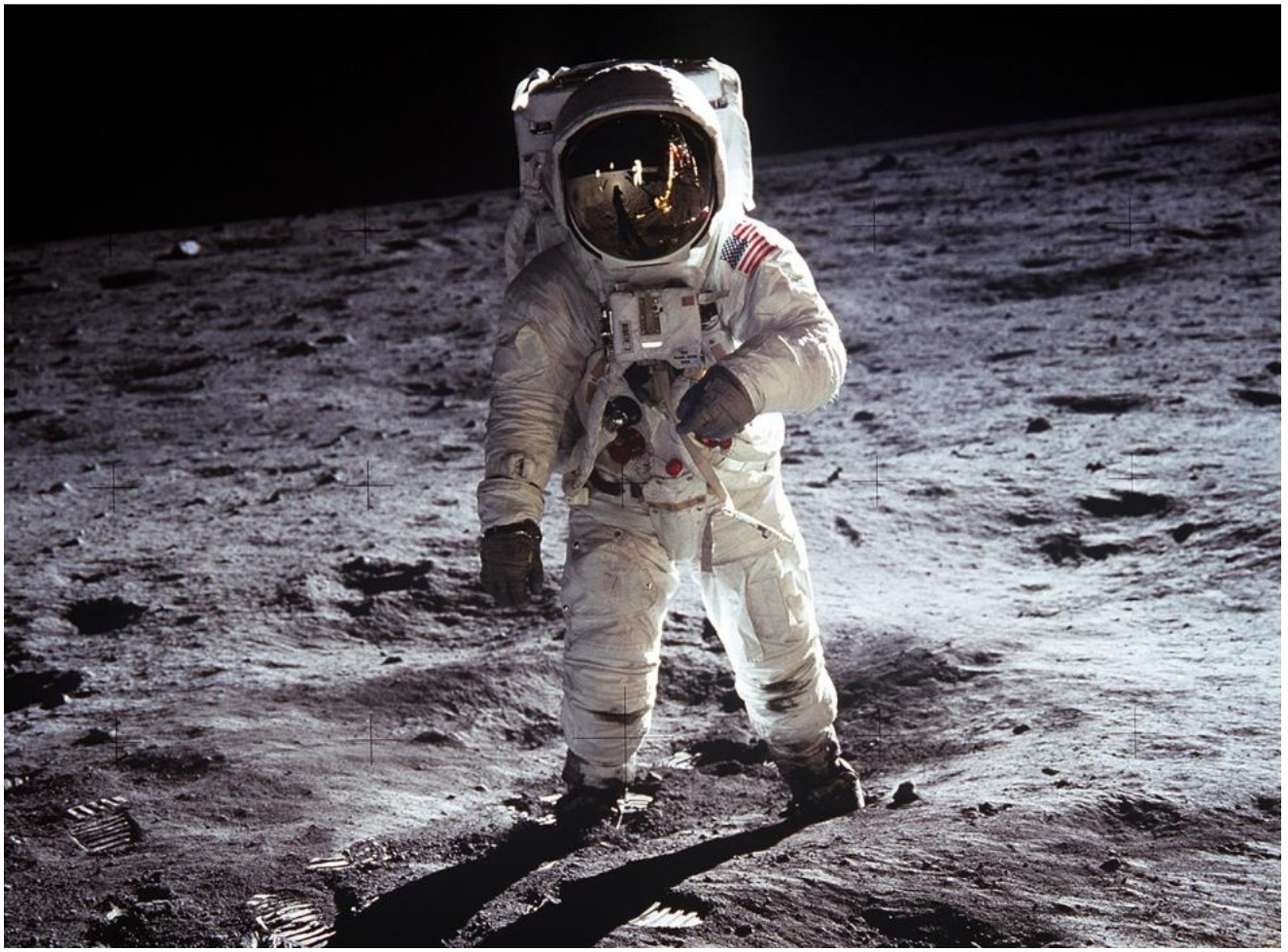
Heales
HEALTHY LIFE EXTENSION SOCIETY

NIH Announces $55 Million Towards Precision Medicine Initiative



Heales
HEALTHY LIFE EXTENSION SOCIETY

Anti-Aging Treatments: A Giant Leap For Mankind?



Heales
HEALTHY LIFE EXTENSION SOCIETY

What We Learned At The DNA Conference

Heales
HEALTHY LIFE EXTENSION SOCIETY

Population aging and comparative advantage *

Jie Cai[a], Andrey Stovanov[b]

In this paper we show that demographic differences between countries are a source of comparative advantage in international trade. Since many skills are age-dependent, population aging decreases the relative supply and increases the relative price of skills which depreciate with age. Thus, industries relying on skills in which younger workers are relatively more efficient will be more productive in countries with a younger labor force and less productive in countries with an older population. Building upon the neuroscience and economics literature, we construct industry-level measures of intensities in various age-dependent skills and show that population aging leads to specialization in industries which use age-appreciating skills intensively and erodes comparative advantage in industries for which age-depreciating skills are more important.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Care Received by Elderly US Stroke Survivors May Be Underestimated

Background and Purpose—Previous studies exploring stroke-related caregiving focused solely on informal caregiving and a relatively limited set of activities. We sought to determine whether, and at what cost, stroke survivors receive more care than matched controls using an expanded definition of caregiving and inclusion of paid caregivers.

Methods—Data were drawn from the National Health and Aging Trends Study (NHATS), a nationally representative survey of Medicare beneficiaries. NHATS personnel conducted in-person interviews with respondents or proxies to determine the weekly hours of care received. We compared hours of assistance received between self-reported stroke survivors (n=892) and demography- and comorbidity-matched nonstroke controls (n=892). The annual cost of stroke caregiving was estimated using reported paid caregiving data and estimates of unpaid caregiving costs.

Results—Of community-dwelling elderly stroke survivors, 51.4% received help from a caregiver. Stroke survivors received an average of 10 hours of additional care per week compared with demography- and comorbidity-matched controls (22.3 hours versus 11.8 hours; $P<0.01$). We estimate that the average annual cost for caregiving for an elderly stroke survivor is ≈$11 300 or ≈$40 billion annually, for all elderly stroke survivors, of which $5000 per person, or $18.2 billion annually, is specific to stroke.

Conclusions—Although stroke survivors are known to require considerable caregiving resources, our findings suggest that previous assessments may underestimate hours of care received and hence costs.

Atomic-resolution structure of a disease-relevant Aβ(1–42) amyloid fibril

Amyloid-β (Aβ) is present in humans as a 39- to 42-amino acid residue metabolic product of the amyloid precursor protein. Although the two predominant forms, Aβ(1–40) and Aβ(1–42), differ in only two residues, they display different biophysical, biological, and clinical behavior. Aβ(1–42) is the more neurotoxic species, aggregates much faster, and dominates in senile plaque of Alzheimer's disease (AD) patients. Although small Aβ oligomers are believed to be the neurotoxic species, Aβ amyloid fibrils are, because of their presence in plaques, a pathological hallmark of AD and appear to play an important role in disease progression through cell-to-cell transmissibility. Here, we solved the 3D structure of a disease-relevant Aβ(1–42) fibril polymorph, combining data from solid-state NMR spectroscopy and mass-per-length measurements from EM. The 3D structure is composed of two molecules per fibril layer, with residues 15–42 forming a double-horseshoe–like cross–β-sheet entity with maximally buried hydrophobic side chains. Residues 1–14 are partially ordered and in a β-strand conformation, but do not display unambiguous distance restraints to the remainder of the core structure.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Atomic Resolution Structure of Monomorphic $A\beta_{42}$ Amyloid Fibrils

Amyloid-β (Aβ) is a 39–42 residue protein produced by the cleavage of the amyloid precursor protein (APP), which subsequently aggregates to form cross-β amyloid fibrils that are a hallmark of Alzheimer's disease (AD). The most prominent forms of Aβ are $A\beta_{1-40}$ and $A\beta_{1-42}$, which differ by two amino acids (I and A) at the C-terminus. However, $A\beta_{42}$ is more neurotoxic and essential to the etiology of AD. Here, we present an atomic resolution structure of a monomorphic form of $A\beta_{M01-42}$ amyloid fibrils derived from over 500 ^{13}C–^{13}C, ^{13}C–^{15}N distance and backbone angle structural constraints obtained from high field magic angle spinning NMR spectra. The structure (PDB ID: 5KK3) shows that the fibril core consists of a dimer of $A\beta_{42}$ molecules, each containing four β-strands in a S-shaped amyloid fold, and arranged in a manner that generates two hydrophobic cores that are capped at the end of the chain by a salt bridge. The outer surface of the monomers presents hydrophilic side chains to the solvent. The interface between the monomers of the dimer shows clear contacts between M35 of one molecule and L17 and Q15 of the second. Intermolecular ^{13}C–^{15}N constraints demonstrate that the amyloid fibrils are parallel in register. The RMSD of the backbone structure (Q15–A42) is 0.71 ± 0.12 Å and of all heavy atoms is 1.07 ± 0.08 Å. The structure provides a point of departure for the design of drugs that bind to the fibril surface and therefore interfere with secondary nucleation and for other therapeutic approaches to mitigate $A\beta_{42}$ aggregation.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The aged lymphoid tissue environment fails to support naïve T cell homeostasis

Aging is associated with a gradual loss of naïve T cells and a reciprocal increase in the proportion of memory T cells. While reduced thymic output is important, age-dependent changes in factors supporting naïve T cells homeostasis may also be involved. Indeed, we noted a dramatic decrease in the ability of aged mice to support survival and homeostatic proliferation of naïve T cells. The defect was not due to a reduction in IL-7 expression, but from a combination of changes in the secondary lymphoid environment that impaired naïve T cell entry and access to key survival factors. We observed an age-related shift in the expression of homing chemokines and structural deterioration of the stromal network in T cell zones. Treatment with IL-7/mAb complexes can restore naïve T cell homeostatic proliferation in aged mice. Our data suggests that homeostatic mechanisms that support the naïve T cell pool deteriorate with age.

Compression of Morbidity Is Observed Across Cohorts with Exceptional Longevity

Khadija Ismail MS, Lisa Nussbaum MPH, Paola Sebastiani PhD, Stacy Andersen PhD, Thomas Perls MD, MPH, Nir Barzilai MD, Sofiya Milman MD, MS

Results

Long-lived individuals from LGP and NECS had later age of onset of cancer, cardiovascular disease, diabetes mellitus, hypertension, and osteoporosis than their respective younger reference groups. The risk of overall morbidity was lower in participants with exceptional longevity than in younger participants (NECS men: relative risk (RR) = 0.12, women: RR = 0.20; LGP men: RR = 0.18, women: RR = 0.24). The age at which 20% of each of the groups with exceptional longevity experienced specific diseases was between 18 and 24 years later than in the reference groups, stratified according to sex.

Conclusion

The similar extension of health span and compression of morbidity seen in NECS and LGP participants with exceptional longevity further validates the utility of these rare individuals for the study of factors that delay or prevent a broad spectrum of diseases otherwise associated with mortality and disability.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Phase 3 Trial of the Tau Aggregation Inhibitor Leuco-Methylthioninium-Bis(hydromethanesulfonate) (LMTM) in Mild to Moderate Alzheimer's Disease

Background: Leuco-methylthioninium-bis(hydromethanesulfonate) (LMTM; TRx-0237) is a novel stabilized reduced form of the methylthioninium (MT) moiety (Harrington et al. J Biol Chem 2015;290:10862) with potential for efficacy in treatment of Alzheimer's disease (AD). A previous trial using the oxidized form of MT identified dose dependent absorption limitations (Wischik et al. J Alzheimers Dis 2015;44:705). LMTM is better absorbed and tolerated (Baddeley et al. J Pharmacol Exptl Therapeutics 2015;352:110) permitting higher doses to be tested. It acts as a selective tau aggregation inhibitor in vitro (Harrington et al. J Biol Chem 2015;290:10862) and in transgenic mouse models (Melis et al. Behav Pharmacol 2015;26:353). Methods: The present 15-month double-blind, placebo-controlled trial (NCT01689246) was performed in patients with probable AD, Mini-Mental State Examination (MMSE) score in the range 14-26, Clinical Dementia Rating (CDR) 1-2 and age < 90 years. Patients were randomized 3:3:4 to receive oral LMTM at doses of 150 or 250 mg/day or placebo (containing 8 mg/day, to maintain blinding) respectively. Primary efficacy outcomes were change from baseline on cognitive (Alzheimer's Disease Assessment Scale cognitive subscale; ADAS-Cog) and functional (Alzheimer's Disease Cooperative Study Activities of Daily Living; ADCS-ADL) scores. Three-monthly assessment included magnetic resonance imaging (MRI) as a disease modifying outcome. Other secondary outcomes included ADCS-CGIC and MMSE. Results: A total of 891 patients were randomized, of whom 62% were female. Approved AD treatments were being taken in 85%. The mean age was 70.6 (SD 9.0) years and baseline MMSE score was 18.7 (SD 3.4). Dementia was of moderate severity (MMSE score 14-19) in 61%. The study efficacy and safety outcomes will be reported. Conclusions: The outcomes of this phase 3 trial will highlight the potential therapeutic value of tau aggregation inhibitor therapy in AD. A second phase 3 trial of LMTM for AD will be completed and reported later in 2016.

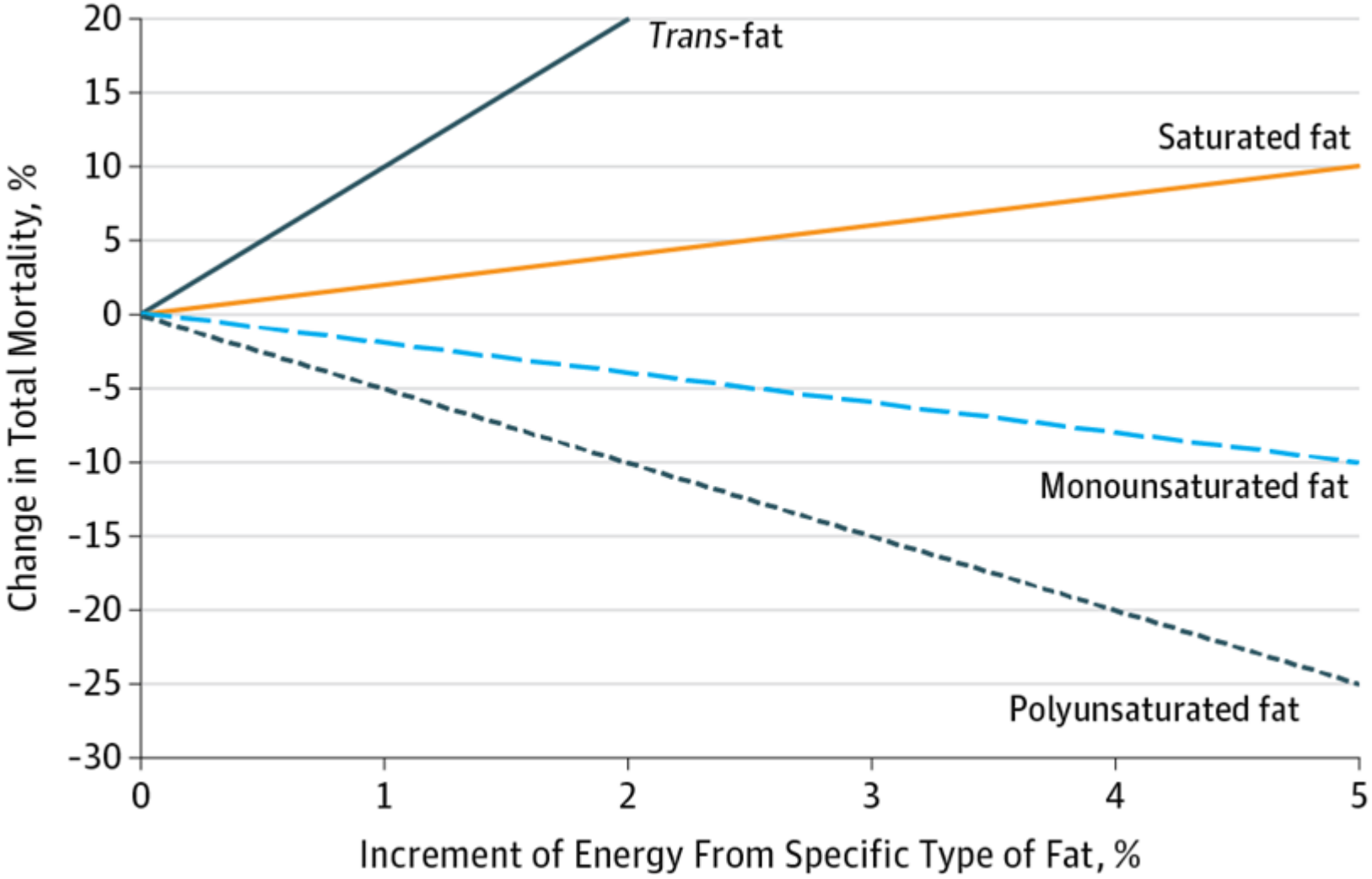
Heales
HEALTHY LIFE EXTENSION SOCIETY

Association of Specific Dietary Fats With Total and Cause-Specific Mortality

Results During 3439 954 person-years of follow-up, 33304 deaths were documented. After adjustment for known and suspected risk factors, dietary total fat compared with total carbohydrates was inversely associated with total mortality (hazard ratio [HR] comparing extreme quintiles, 0.84; 95% CI, 0.81-0.88; P < .001 for trend). The HRs of total mortality comparing extreme quintiles of specific dietary fats were 1.08 (95% CI, 1.03-1.14) for saturated fat, 0.81 (95% CI, 0.78-0.84) for polyunsaturated fatty acid (PUFA), 0.89 (95% CI, 0.84-0.94) for monounsaturated fatty acid (MUFA), and 1.13 (95% CI, 1.07-1.18) for *trans*-fat (P < .001 for trend for all). Replacing 5% of energy from saturated fats with equivalent energy from PUFA and MUFA was associated with estimated reductions in total mortality of 27% (HR, 0.73; 95% CI, 0.70-0.77) and 13% (HR, 0.87; 95% CI, 0.82-0.93), respectively. The HR for total mortality comparing extreme quintiles of ω-6 PUFA intake was 0.85 (95% CI, 0.81-0.89; P < .001 for trend). Intake of ω-6 PUFA, especially linoleic acid, was inversely associated with mortality owing to most major causes, whereas marine ω-3 PUFA intake was associated with a modestly lower total mortality (HR comparing extreme quintiles, 0.96; 95% CI, 0.93-1.00; P = .002 for trend).

Conclusions and Relevance Different types of dietary fats have divergent associations with total and cause-specific mortality. These findings support current dietary recommendations to replace saturated fat and *trans*-fat with unsaturated fats.

Heales
HEALTHY LIFE EXTENSION SOCIETY



Heales
HEALTHY LIFE EXTENSION SOCIETY

Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality

FREE

ONLINE FIRST

Importance Defining what represents a macronutritionally balanced diet remains an open question and a high priority in nutrition research. Although the amount of protein may have specific effects, from a broader dietary perspective, the choice of protein sources will inevitably influence other components of diet and may be a critical determinant for the health outcome.

Objective To examine the associations of animal and plant protein intake with the risk for mortality.

Design, Setting, and Participants This prospective cohort study of US health care professionals included 131342 participants from the Nurses' Health Study (1980 to end of follow-up on June 1, 2012) and Health Professionals Follow-up Study (1986 to end of follow-up on January 31, 2012). Animal and plant protein intake was assessed by regularly updated validated food frequency questionnaires. Data were analyzed from June 20, 2014, to January 18, 2016.

Main Outcomes and Measures Hazard ratios (HRs) for all-cause and cause-specific mortality.

Results Of the 131342 participants, 85 013 were women (64.7%) and 46329 were men (35.3%) (mean [SD] age, 49 [9] years). The median protein intake, as assessed by percentage of energy, was 14% for animal protein (5th-95th percentile, 9%-22%) and 4% for plant protein (5th-95th percentile, 2%-6%). After adjusting for major lifestyle and dietary risk factors, animal protein intake was weakly associated with higher mortality, particularly cardiovascular mortality (HR, 1.08 per 10% energy increment; 95% CI, 1.01-1.16; *P* for trend = .04), whereas plant protein was associated with lower mortality (HR, 0.90 per 3% energy increment; 95% CI, 0.86-0.95; *P* for trend < .001). These associations were confined to participants with at least 1 unhealthy lifestyle factor based on smoking, heavy alcohol intake, overweight or obesity, and physical inactivity, but not evident among those without any of these risk factors. Replacing animal protein of various origins with plant protein was associated with lower mortality. In particular, the HRs for all-cause mortality were 0.66 (95% CI, 0.59-0.75) when 3% of energy from plant protein was substituted for an equivalent amount of protein from processed red meat, 0.88 (95% CI, 0.84-0.92) from unprocessed red meat, and 0.81 (95% CI, 0.75-0.88) from egg.

Conclusions and Relevance High animal protein intake was positively associated with mortality and high plant protein intake was inversely associated with mortality, especially among individuals with at least 1 lifestyle risk factor. Substitution of plant protein for animal protein, especially that from processed red meat, was associated with lower mortality, suggesting the importance of protein source.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents

Findings

All-cause mortality was minimal at 20·0–25·0 kg/m^2 (HR 1·00, 95% CI 0·98–1·02 for BMI 20·0–<22·5 kg/m^2; 1·00, 0·99–1·01 for BMI 22·5–<25·0 kg/m^2), and increased significantly both just below this range (1·13, 1·09–1·17 for BMI 18·5–<20·0 kg/m^2; 1·51, 1·43–1·59 for BMI 15·0–<18·5) and throughout the overweight range (1·07, 1·07–1·08 for BMI 25·0–<27·5 kg/m^2; 1·20, 1·18–1·22 for BMI 27·5–<30·0 kg/m^2). The HR for obesity grade 1 (BMI 30·0–<35·0 kg/m^2) was 1·45, 95% CI 1·41–1·48; the HR for obesity grade 2 (35·0–<40·0 kg/m^2) was 1·94, 1·87–2·01; and the HR for obesity grade 3 (40·0–<60·0 kg/m^2) was 2·76, 2·60–2·92. For BMI over 25·0 kg/m^2, mortality increased approximately log-linearly with BMI; the HR per 5 kg/m^2 units higher BMI was 1·39 (1·34–1·43) in Europe, 1·29 (1·26–1·32) in North America, 1·39 (1·34–1·44) in east Asia, and 1·31 (1·27–1·35) in Australia and New Zealand. This HR per 5 kg/m^2 units higher BMI (for BMI over 25 kg/m^2) was greater in younger than older people (1·52, 95% CI 1·47–1·56, for BMI measured at 35–49 years *vs* 1·21, 1·17–1·25, for BMI measured at 70–89 years; $p_{heterogeneity}$<0·0001), greater in men than women (1·51, 1·46–1·56, *vs* 1·30, 1·26–1·33; $p_{heterogeneity}$<0·0001), but similar in studies with self-reported and measured BMI.

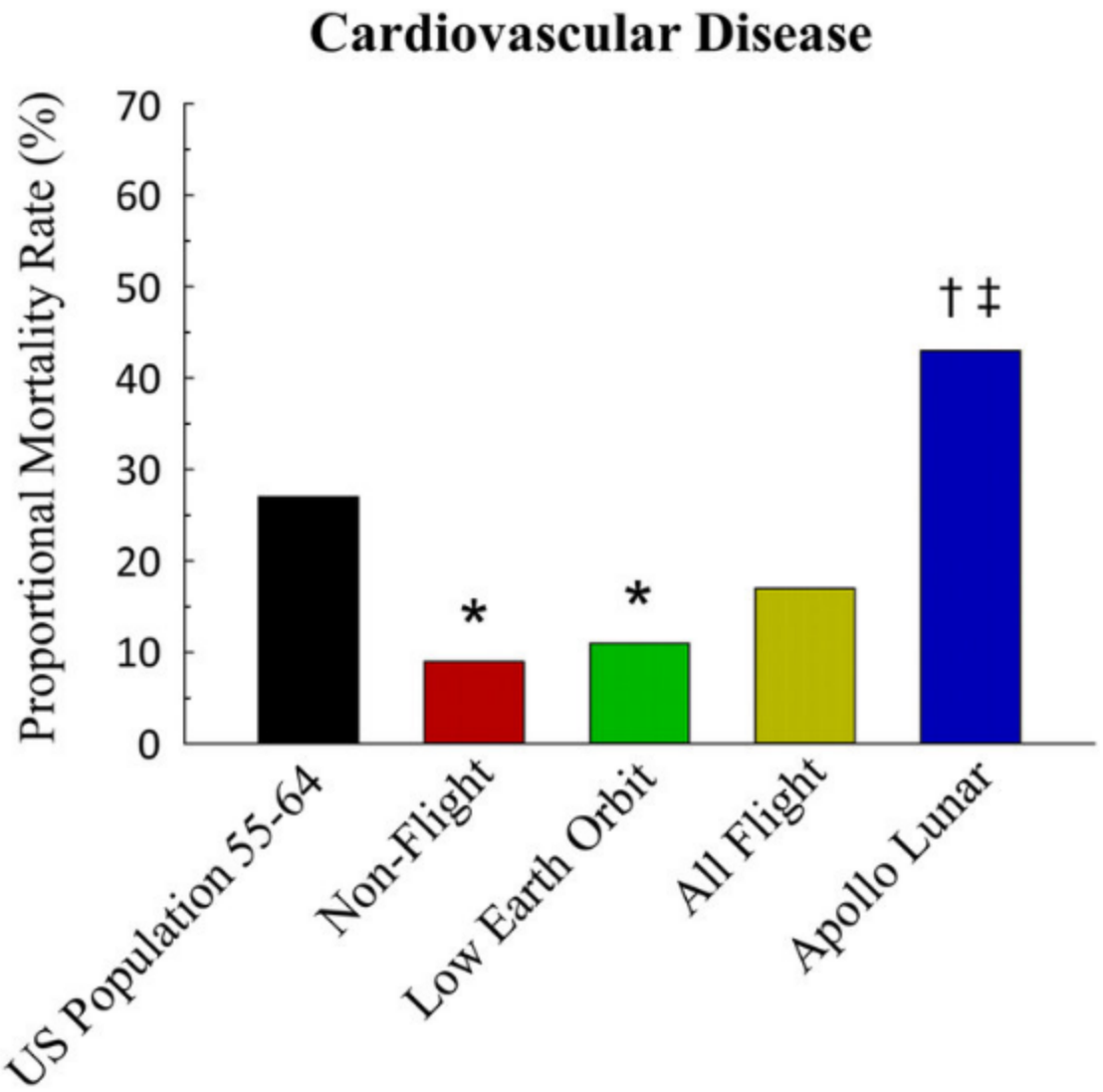
Interpretation

The associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents. This finding supports strategies to combat the entire spectrum of excess adiposity in many populations.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Apollo Lunar Astronauts Show Higher Cardiovascular Disease Mortality: Possible Deep Space Radiation Effects on the Vascular Endothelium

As multiple spacefaring nations contemplate extended manned missions to Mars and the Moon, health risks could be elevated as travel goes beyond the Earth's protective magnetosphere into the more intense deep space radiation environment. The primary purpose of this study was to determine whether mortality rates due to cardiovascular disease (CVD), cancer, accidents and all other causes of death differ in (1) astronauts who never flew orbital missions in space, (2) astronauts who flew only in low Earth orbit (LEO), and (3) Apollo lunar astronauts, the only humans to have traveled beyond Earth's magnetosphere. Results show there were no differences in CVD mortality rate between non-flight (9%) and LEO (11%) astronauts. However, the CVD mortality rate among Apollo lunar astronauts (43%) was 4–5 times higher than in non-flight and LEO astronauts. To test a possible mechanistic basis for these findings, a secondary purpose was to determine the long-term effects of simulated weightlessness and space-relevant total-body irradiation on vascular responsiveness in mice. The results demonstrate that space-relevant irradiation induces a sustained vascular endothelial cell dysfunction. Such impairment is known to lead to occlusive artery disease, and may be an important risk factor for CVD among astronauts exposed to deep space radiation.


Cardiovascular Disease
Proportional Mortality Rate (%)
70
60
50
40
30
20
10
0
*
*
† ‡
US Population 55-64
Non-Flight
Low Earth Orbit
All Flight
Apollo Lunar

Healthy ageing of cloned sheep

K. D. Sinclair, S. A. Corr, C. G. Gutierrez, P. A. Fisher, J.-H. Lee, A. J. Rathbone, I. Choi, K. H. S. Campbell & D. S. Gardner

Affiliations | Contributions | Corresponding author

Nature Communications **7**, Article number: 12359 | doi:10.1038/ncomms12359
Received 06 April 2016 | Accepted 27 June 2016 | Published 26 July 2016

Abstract

The health of cloned animals generated by somatic-cell nuclear transfer (SCNT) has been of concern since its inception; however, there are no detailed assessments of late-onset, non-communicable diseases. Here we report that SCNT has no obvious detrimental long-term health effects in a cohort of 13 cloned sheep. We perform musculoskeletal assessments, metabolic tests and blood pressure measurements in 13 aged (7–9 years old) cloned sheep, including four derived from the cell line that gave rise to Dolly. We also perform radiological examinations of all main joints, including the knees, the joint most affected by osteoarthritis in Dolly, and compare all health parameters to groups of 5-and 6-year-old sheep, and published reference ranges. Despite their advanced age, these clones are euglycaemic, insulin sensitive and normotensive. Importantly, we observe no clinical signs of degenerative joint disease apart from mild, or in one case moderate, osteoarthritis in some animals. Our study is the first to assess the long-term health outcomes of SCNT in large animals.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Single-cell genome-wide bisulfite sequencing uncovers extensive heterogeneity in the mouse liver methylome.

Gravina S, et al. Genome Biol. 2016.
Show full citation

Abstract

BACKGROUND: Transmission fidelity of CpG DNA methylation patterns is not foolproof, with error rates from less than 1 to well over 10 % per CpG site, dependent on preservation of the methylated or unmethylated state and the type of sequence. This suggests a fairly high chance of errors. However, the consequences of such errors in terms of cell-to-cell variation have never been demonstrated by experimentally measuring intra-tissue heterogeneity in an adult organism.

RESULTS: We employ single-cell DNA methylomics to analyze heterogeneity of genome-wide 5-methylcytosine (5mC) patterns within mouse liver. Our results indicate a surprisingly high level of heterogeneity, corresponding to an average epivariation frequency of approximately 3.3 %, with regions containing H3K4me1 being the most variable and promoters and CpG islands the most stable. Our data also indicate that the level of 5mC heterogeneity is dependent on genomic features. We find that non-functional sites such as repeat elements and introns are mostly unstable and potentially functional sites such as gene promoters are mostly stable.

CONCLUSIONS: By employing a protocol for whole-genome bisulfite sequencing of single cells, we show that the liver epigenome is highly unstable with an epivariation frequency in DNA methylation patterns of at least two orders of magnitude higher than somatic mutation frequencies.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Resveratrol Activates the CNS Sirtuin1/Matrix Mettaloproteinase-9 Pathway and Regulates Neuroinflammation in Alzheimer's Disease

Abstract ID: a11567

View Session Detail to Add to Schedule

Abstract:

Charbel E-H Moussa, M.D., Ph.D.[1];Michaeline Hebron, M.S.[1];Xu Huang, M.S.[1];Hannah J Brown[1];Robert A Rissman, PhD[2];Paul S Aisen, MD[3] and **Raymond Scott Turner, MD, PhD**[1], (1)Georgetown University, Washington, DC, USA, (2)University of California, San Diego, La Jolla, CA, USA, (3)University of Southern California, San Diego, CA, USA

Background: Activation of sirtuin 1 (SIRT1) decreases matrix metalloproteinase-9 (MMP-9) expression and activity, thus regulating macrophage and neutrophil activity. The SIRT1 pathway may be involved in Alzheimer's disease (AD) pathogenesis since caloric restriction attenuates CNS amyloid accumulation with aging in animal models. Resveratrol pharmacologically activates SIRT1 and suggests a novel therapeutic target for MCI and AD. Methods: We recently completed a Phase 2 trial of resveratrol versus placebo (up to 2 g by mouth daily, with 12 months treatment) in AD subjects with mild to moderate dementia (Turner et al., Neurology 2015;85(16):1383-91). We analyzed CSF samples from a subset of enrolled individuals with < 600 ng/ml CSF Aβ42 at baseline (biomarker supported AD) by Milliplex© ELISA. Results: Resveratrol treatment significantly reduced CSF MMP9 levels and attenuated the decline in CSF Aβ40 and Aβ42 found over 12 months. In contrast, there was no treatment effect on CSF MMP2, MMP10, total tau, or pTau181. Resveratrol increased the level of CSF macrophage-derived chemokine (MDC/CCl22) produced by macrophages and dendritic cells and up-regulated by TH2-type cytokines, such as IL-4, which was also increased. Resveratrol increased monocyte-specific chemokine-3 (MCP-3/CCL7) that regulates macrophage function and interacts with MMPs. Conclusions: Collectively these data suggest that resveratrol activates the SIRT1/MMP9 pathway leading to regulation of neuroinflammation in subjects with AD.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing

Human mitochondrial DNA (mtDNA) shows extensive within-population sequence variability[1]. Many studies suggest that mtDNA variants may be associated with ageing or diseases[2, 3, 4], although mechanistic evidence at the molecular level is lacking[5, 6]. Mitochondrial replacement has the potential to prevent transmission of disease-causing oocyte mtDNA. However, extension of this technology requires a comprehensive understanding of the physiological relevance of mtDNA sequence variability and its match with the nuclear-encoded mitochondrial genes. Studies in conplastic animals[7, 8, 9] allow comparison of individuals with the same nuclear genome but different mtDNA variants, and have provided both supporting and refuting evidence that mtDNA variation influences organismal physiology. However, most of these studies did not confirm the conplastic status, focused on younger animals, and did not investigate the full range of physiological and phenotypic variability likely to be influenced by mitochondria. Here we systematically characterized conplastic mice throughout their lifespan using transcriptomic, proteomic, metabolomic, biochemical, physiological and phenotyping studies. We show that mtDNA haplotype profoundly influences mitochondrial proteostasis and reactive oxygen species generation, insulin signalling, obesity, and ageing parameters including telomere shortening and mitochondrial dysfunction, resulting in profound differences in health longevity between conplastic strains.

Mol Nutr Food Res. 2016 Jul 9. doi: 10.1002/mnfr.201600140. [Epub ahead of print]

Quantitative assessment of organ distribution of dietary protein-bound 13 C-labeled Nε -carboxymethyllysine after a chronic oral exposure in mice.

Tessier FJ[1,2], Niquet-Léridon C[2], Jacolot P[2], Jouquand C[2], Genin M[3], Schmidt AM[4], Grossin N[1], Boulanger E[1].

Author information

Abstract

SCOPE: N^{ε} -Carboxymethyl-lysine (CML) is a prominent advanced glycation end-product which is not only found in vivo but also in food. It is known that a percentage of the dietary CML (dCML) is absorbed into the circulation and only partly excreted in the urine. Several studies have tried to measure how much dCML remains in tissues. However obstacles to interpreting the data have been found.

METHODS AND RESULTS: A new protocol which discriminates dCML from native CML (nCML) has been developed. Three CML isotopes with different mass-to-charge ratios were used: nCML N^{ε} -carboxymethyl-L-lysine, dCML N^{ε} -[^{13} C]carboxy[^{13} C]methyl-L-lysine and internal standard N^{ε} -carboxymethyl-L-[4,4,5,5-^{2} H_4]lysine. Wild-type(n = 7) and $RAGE^{-/-}$ (n = 8) mice were fed for 30 days with either a control, or a BSA-bound dCML-enriched diet. Organs were analysed for nCML and dCML using liquid chromatography-tandem mass spectrometry. Mice exposed to dCML showed an accumulation in all tissues tested except fat. The rate of deposition was high (81 to 320 μg_{dCML} /g dry matter) in kidneys, intestine and lungs and low (<5 µg/g) in heart, muscle and liver. This accumulation was not RAGE-dependent.

CONCLUSION: The kidney is not the only organ affected by the accumulation of dCML. Its high accumulation in other tissues and organs may also, however, have important physiological consequences. This article is protected by copyright. All rights reserved.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Assessment of the genetic variance of late-onset Alzheimer's disease

Alzheimer's disease (AD) is a complex genetic disorder with no effective treatments. More than 20 common markers have been identified, which are associated with AD. Recently, several rare variants have been identified in Amyloid Precursor Protein (*APP*), Triggering Receptor Expressed On Myeloid Cells 2 (*TREM2*) and Unc-5 Netrin Receptor C (*UNC5C*) that affect risk for AD. Despite the many successes, the genetic architecture of AD remains unsolved. We used Genome-wide Complex Trait Analysis to (1) estimate phenotypic variance explained by genetics; (2) calculate genetic variance explained by known AD single nucleotide polymorphisms (SNPs); and (3) identify the genomic locations of variation that explain the remaining unexplained genetic variance. In total, 53.24% of phenotypic variance is explained by genetics, but known AD SNPs only explain 30.62% of the genetic variance. Of the unexplained genetic variance, approximately 41% is explained by unknown SNPs in regions adjacent to known AD SNPs, and the remaining unexplained genetic variance outside these regions.

Int J Cardiol. 2016 Jun 23;220:718-725. doi: 10.1016/j.ijcard.2016.06.069. [Epub ahead of print]

Lipoprotein(a) and risk of sudden cardiac death in middle-aged Finnish men: A new prospective cohort study.

Kunutsor SK[1], Khan H[2], Nyyssönen K[3], Laukkanen JA[4].

Author information

Abstract

BACKGROUND: Lipoprotein(a) [Lp(a)] is an established and independent risk factor for cardiovascular outcomes. However, the relationship of Lp(a) with risk of sudden cardiac death (SCD) is unknown. We aimed to assess the association of Lp(a) with risk of SCD in the Kuopio Ischemic Heart Disease prospective cohort study of 1881 men aged 42-61years at recruitment.

METHODS AND RESULTS: Plasma Lp(a) concentration was assessed at baseline and repeat measurements made several years apart. After a median follow-up of 24.7years, 141 SCDs were recorded. Hazard ratios (HRs) (95% confidence intervals [CI]) were assessed and were corrected for within-person variability in Lp(a) levels. The regression dilution ratio of $\log_e$ Lp(a) adjusted for age was 0.84 (95% CI: 0.81-0.88). Lipoprotein(a) levels were log-linearly associated with risk of SCD. In analyses adjusted for established risk factors, the HR (95% CI) for SCD per 1 standard deviation (3.56-fold) higher baseline $\log_e$ Lp(a) was 1.24 (1.05-1.47; P=0.013). This remained consistent on further adjustment for alcohol consumption, resting heart rate, lipids, and C-reactive protein 1.23 (1.04-1.46; P=0.018). HRs remained unchanged after accounting for incident coronary events and did not vary importantly in several relevant clinical subgroups. Adding Lp(a) to a SCD risk prediction model did not significantly improve risk discrimination beyond established risk factors, but improved the continuous net reclassification 30.2% (1.1 to 59.2%, P=0.042).

CONCLUSIONS: Available evidence shows a continuous and independent association between Lp(a) levels and risk of SCD. Further research is needed to replicate these findings.

Heales
HEALTHY LIFE EXTENSION SOCIETY

N- and *O*-glycan cell surface protein modifications associated with cellular senescence and human aging

Yoko Itakura, Norihiko Sasaki, Daisuke Kami, Satoshi Gojo, Akihiro Umezawa and Masashi Toyoda

Background

Glycans play essential roles in biological functions such as differentiation and cancer. Recently, glycans have been considered as biomarkers for physiological aging. However, details regarding the specific glycans involved are limited. Here, we investigated cellular senescence- and human aging-dependent glycan changes in human diploid fibroblasts derived from differently aged skin donors using a lectin microarray.

Results

We found that α2-6sialylated glycans in particular differed between elderly- and fetus-derived cells at early passage. However, both cell types exhibited sequentially decreasing α2-3sialylated *O*-glycan structures during the cellular senescence process and showed similar overall glycan profiles.

Conclusions

We observed a senescence-associated decrease in sialylation and increase in galactose exposure. Therefore, glycan profiling using lectin microarrays might be useful for the characterization of biomarkers of aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

J Am Chem Soc. 2016 Aug 4. [Epub ahead of print]

Spontaneous Binding of Molecular Oxygen at the Qo-Site of the bc1 Complex Could Stimulate Superoxide Formation.

Husen P[1], Solov'yov IA[1].

Author information

Abstract

A key part of the respiratory and photosynthetic pathways is the bc_1 protein complex embedded in the inner membrane of mitochondria and the plasma membrane of photosynthetic bacteria. The protein complex pumps protons across the membrane to maintain an electrostatic potential, which is in turn used to drive ATP synthesis. This molecular machinery, however, is suspected to be a source of superoxide, which is toxic to the cell, even in minuscular quantities, and believed to be a factor in aging. Through molecular dynamics simulations, we investigate here the migration of molecular oxygen in the bc_1 complex in order to identify possible reaction sites that could lead to superoxide formation. It is found, in particular, that oxygen penetrates spontaneously the Q_o binding site of the bc_1 complex in the presence of an intermediate semiquinone radical, thus making the Q_o-site a strong candidate for being a center of superoxide production.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis

Multifactorial mechanisms underlying late-onset Alzheimer's disease (LOAD) are poorly characterized from an integrative perspective. Here spatiotemporal alterations in brain amyloid-β deposition, metabolism, vascular, functional activity at rest, structural properties, cognitive integrity and peripheral proteins levels are characterized in relation to LOAD progression. We analyse over 7,700 brain images and tens of plasma and cerebrospinal fluid biomarkers from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Through a multifactorial data-driven analysis, we obtain dynamic LOAD–abnormality indices for all biomarkers, and a tentative temporal ordering of disease progression. Imaging results suggest that intra-brain vascular dysregulation is an early pathological event during disease development. Cognitive decline is noticeable from initial LOAD stages, suggesting early memory deficit associated with the primary disease factors. High abnormality levels are also observed for specific proteins associated with the vascular system's integrity. Although still subjected to the sensitivity of the algorithms and biomarkers employed, our results might contribute to the development of preventive therapeutic interventions.

CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis

Atherosclerosis is the disease process that underlies heart attack and stroke[1]. Advanced lesions at risk of rupture are characterized by the pathological accumulation of diseased vascular cells and apoptotic cellular debris[2]. Why these cells are not cleared remains unknown[3]. Here we show that atherogenesis is associated with upregulation of CD47, a key anti-phagocytic molecule that is known to render malignant cells resistant to programmed cell removal, or 'efferocytosis'[4, 5, 6, 7]. We find that administration of CD47-blocking antibodies reverses this defect in efferocytosis, normalizes the clearance of diseased vascular tissue, and ameliorates atherosclerosis in multiple mouse models. Mechanistic studies implicate the pro-atherosclerotic factor TNF-α as a fundamental driver of impaired programmed cell removal, explaining why this process is compromised in vascular disease. Similar to recent observations in cancer[5], impaired efferocytosis appears to play a pathogenic role in cardiovascular disease, but is not a fixed defect and may represent a novel therapeutic target.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Human gut microbes impact host serum metabolome and insulin sensitivity

Insulin resistance is a forerunner state of ischaemic cardiovascular disease and type 2 diabetes. Here we show how the human gut microbiome impacts the serum metabolome and associates with insulin resistance in 277 non-diabetic Danish individuals. The serum metabolome of insulin-resistant individuals is characterized by increased levels of branched-chain amino acids (BCAAs), which correlate with a gut microbiome that has an enriched biosynthetic potential for BCAAs and is deprived of genes encoding bacterial inward transporters for these amino acids. *Prevotella copri* and *Bacteroides vulgatus* are identified as the main species driving the association between biosynthesis of BCAAs and insulin resistance, and in mice we demonstrate that *P. copri* can induce insulin resistance, aggravate glucose intolerance and augment circulating levels of BCAAs. Our findings suggest that microbial targets may have the potential to diminish insulin resistance and reduce the incidence of common metabolic and cardiovascular disorders.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Small molecule proteostasis regulators that reprogram the ER to reduce extracellular protein aggregation

Imbalances in endoplasmic reticulum (ER) proteostasis are associated with etiologically-diverse degenerative diseases linked to excessive extracellular protein misfolding and aggregation. Reprogramming of the ER proteostasis environment through genetic activation of the Unfolded Protein Response (UPR)-associated transcription factor ATF6 attenuates secretion and extracellular aggregation of amyloidogenic proteins. Here, we employed a screening approach that included complementary arm-specific UPR reporters and medium-throughput transcriptional profiling to identify non-toxic small molecules that phenocopy the ATF6-mediated reprogramming of the ER proteostasis environment. The ER reprogramming afforded by our molecules requires activation of endogenous ATF6 and occurs independent of global ER stress. Furthermore, our molecules phenocopy the ability of genetic ATF6 activation to selectively reduce secretion and extracellular aggregation of amyloidogenic proteins. These results show that small molecule-dependent ER reprogramming, achieved through preferential activation of the ATF6 transcriptional program, is a promising strategy to ameliorate imbalances in ER function associated with degenerative protein aggregation diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Eating increases oxidative damage in a reptile

Michael W. Butler, Thomas J. Lutz, H. Bobby Fokidis, Zachary R. Stahlschmidt

While eating has substantial benefits in terms of both nutrient and energy acquisition, there are physiological costs associated with digesting and metabolizing a meal. Frequently, these costs have been documented in the context of energy expenditure while other physiological costs have been relatively unexplored. Here, we tested whether the seemingly innocuous act of eating affects either systemic pro-oxidant (reactive oxygen metabolite, ROM) levels or antioxidant capacity of corn snakes (*Pantherophis guttatus*) by collecting plasma during absorptive (peak increase in metabolic rate due to digestion of a meal) and non-absorptive (baseline) states. When individuals were digesting a meal, there was a minimal increase in antioxidant capacity relative to baseline (4%), but a substantial increase in ROMs (nearly 155%), even when controlling for circulating nutrient levels. We report an oxidative cost of eating that is much greater than that due to long distance flight or mounting an immune response in other taxa. This result demonstrates the importance of investigating non-energetic costs associated with meal processing, and it begs future work to identify the mechanism(s) driving this increase in ROM levels. Because energetic costs associated with eating are taxonomically widespread, identifying the taxonomic breadth of eating-induced ROM increases may provide insights into the interplay between oxidative damage and life history theory.

Lamin Mutations Accelerate Aging via Defective Export of Mitochondrial mRNAs through Nuclear Envelope Budding

Highlights

- Mitochondrial RNAs, such as mitofusin, localize to nuclear envelope budding sites
- A fly model of progeroid syndrome caused by A-type lamin mutation ages prematurely
- Aging phenotypes include mitochondrial degeneration and mitofusin RNA depletion
- Accelerated aging phenotypes are preceded by a block of nuclear envelope budding

Summary

Defective RNA metabolism and transport are implicated in aging and degeneration [1, 2], but the underlying mechanisms remain poorly understood. A prevalent feature of aging is mitochondrial deterioration [3]. Here, we link a novel mechanism for RNA export through nuclear envelope (NE) budding [4, 5] that requires A-type lamin, an inner nuclear membrane-associated protein, to accelerated aging observed in *Drosophila* LaminC (LamC) mutations. These LamC mutations were modeled after A-lamin (LMNA) mutations causing progeroid syndromes (PSs) in humans. We identified mitochondrial assembly regulatory factor (Marf), a mitochondrial fusion factor (mitofusin), as well as other transcripts required for mitochondrial integrity and function, in a screen for RNAs that exit the nucleus through NE budding. PS-modeled LamC mutations induced premature aging in adult flight muscles, including decreased levels of specific mitochondrial protein transcripts (RNA) and progressive mitochondrial degradation. PS-modeled LamC mutations also induced the accelerated appearance of other phenotypes associated with aging, including a progressive accumulation of polyubiquitin aggregates [6, 7] and myofibril disorganization [8, 9]. Consistent with these observations, the mutants had progressive jumping and flight defects. Downregulating *marf* alone induced the above aging defects. Nevertheless, restoring *marf* was insufficient for rescuing the aging phenotypes in PS-modeled LamC mutations, as other mitochondrial RNAs are affected by inhibition of NE budding. Analysis of NE budding in dominant and recessive PS-modeled LamC mutations suggests a mechanism by which abnormal lamina organization prevents the egress of these RNAs via NE budding. These studies connect defects in RNA export through NE budding to progressive loss of mitochondrial integrity and premature aging.

Lifespan Control by Redox-Dependent Recruitment of Chaperones to Misfolded Proteins

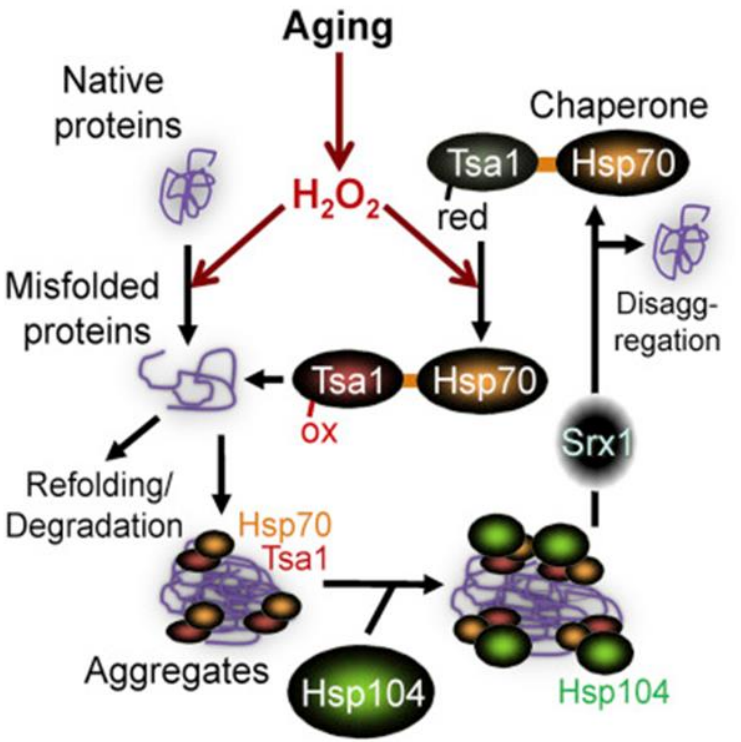
Highlights

- Increased peroxiredoxin Tsa1 levels extend lifespan in a chaperone-dependent manner
- A redox switch in Tsa1 recruits Hsp70 and Hsp104 to misfolded proteins during aging
- Disaggregation of misfolded proteins requires enzyme-dependent reduction of Tsa1
- Distinct chaperone pathways recognize protein aggregates on H_2O_2 stress and heat shock

Summary

Caloric restriction (CR) extends the lifespan of flies, worms, and yeast by counteracting age-related oxidation of H_2O_2-scavenging peroxiredoxins (Prxs). Here, we show that increased dosage of the major cytosolic Prx in yeast, Tsa1, extends lifespan in an Hsp70 chaperone-dependent and CR-independent manner without increasing H_2O_2 scavenging or genome stability. We found that Tsa1 and Hsp70 physically interact and that hyperoxidation of Tsa1 by H_2O_2 is required for the recruitment of the Hsp70 chaperones and the Hsp104 disaggregase to misfolded and aggregated proteins during aging, but not heat stress. Tsa1 counteracted the accumulation of ubiquitinated aggregates during aging and the reduction of hyperoxidized Tsa1 by sulfiredoxin facilitated clearance of H_2O_2-generated aggregates. The data reveal a conceptually new role for H_2O_2 signaling in proteostasis and lifespan control and shed new light on the selective benefits endowed to eukaryotic peroxiredoxins by their reversible hyperoxidation.

Graphical Abstract



Heales
HEALTHY LIFE EXTENSION SOCIETY

Stem Cells. 2016 Jul 18. doi: 10.1002/stem.2460. [Epub ahead of print]

Restoration of Mitochondrial NAD+ Levels Delays Stem Cell Senescence and Facilitates Reprogramming of Aged Somatic Cells.

Son MJ[1,2], Kwon Y[1,2], Son T[3], Cho YS[2,4].

Author information

Abstract

The fundamental tenet that aging is irreversible has been challenged by the development of reprogramming technology that can restore molecular and cellular age by reversing the progression of aging. The use of cells from aged individuals as sources for reprogramming or transplantation creates a major barrier in stem cell therapy with respect to cell quality and quantity. Here, we investigated the molecular features underlying senescence and rejuvenation during aged cell reprogramming and identified novel factors that can overcome age-associated barriers. Enzymes, such as nicotinamide nucleotide transhydrogenase (NNT) and nicotinamide mononucleotide adenylyltransferase 3 (NMNAT3), that control mitochondrial NAD^+ levels appear to be susceptible to aging. In aged cells, mitochondrial NAD^+ levels decrease, accompanied by reduced SIRT3 activity; these changes severely impede cell fate transition. However, in cells collected from aged p16 knockout mice, which exhibit delayed cellular senescence, no changes in NNT or NMNAT3 expression were found. Importantly, restoring mitochondrial NAD^+ levels by overexpressing NNT and NMNAT3 enhanced reprogramming efficiency of aged somatic cells and extended the lifespan of human mesenchymal stem cells by delaying replicative senescence. These results demonstrate that maintenance of mitochondrial NAD^+ levels is critical for reversing the mechanisms of aging and ensuring that cells collected from aged individuals are of high quality. Stem Cells 2016.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Honey bee (*Apis mellifera*) drones survive oxidative stress due to increased tolerance instead of avoidance or repair of oxidative damage

Oxidative stress can lead to premature aging symptoms and cause acute mortality at higher doses in a range of organisms. Oxidative stress resistance and longevity are mechanistically and phenotypically linked; considerable variation in oxidative stress resistance exists among and within species and typically covaries with life expectancy. However, it is unclear whether stress-resistant, long-lived individuals avoid, repair, or tolerate molecular damage to survive longer than others. The honey bee (*Apis mellifera* L.) is an emerging model system that is well-suited to address this question. Furthermore, this species is the most economically important pollinator, whose health may be compromised by pesticide exposure, including oxidative stressors. Here, we develop a protocol for inducing oxidative stress in honey bee males (drones) via Paraquat injection. After injection, individuals from different colony sources were kept in common social conditions to monitor their survival compared to saline-injected controls. Oxidative stress was measured in susceptible and resistant individuals. Paraquat drastically reduced survival but individuals varied in their resistance to treatment within and among colony sources. Longer-lived individuals exhibited higher levels of lipid peroxidation than individuals dying early. In contrast, the level of protein carbonylation was not significantly different between the two groups. This first study of oxidative stress in male honey bees suggests that survival of an acute oxidative stressor is due to tolerance, not prevention or repair, of oxidative damage to lipids. It also demonstrates colony differences in oxidative stress resistance that might be useful for breeding stress-resistant honey bees.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Rapamycin Increases Mortality in *db/db* Mice, a Mouse Model of Type 2 Diabetes

We examined the effect of rapamycin on the life span of a mouse model of type 2 diabetes, *db/db* mice. At 4 months of age, male and female C57BLKSJ-*lepr* $^{db/db}$ mice (*db/db*) were placed on either a control diet, lacking rapamycin or a diet containing rapamycin and maintained on these diets over their life span. Rapamycin was found to reduce the life span of the *db/db* mice. The median survival of male db/db mice fed the control and rapamycin diets was 349 and 302 days, respectively, and the median survival of female *db/db* mice fed the control and rapamycin diets was 487 and 411 days, respectively. Adjusting for gender differences, rapamycin increased the mortality risk 1.7-fold in both male and female *db/db* mice. End-of-life pathological data showed that suppurative inflammation was the main cause of death in the *db/db* mice, which is enhanced slightly by rapamycin treatment.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Estimating the Upper Limit of Lifetime Probability Distribution, Based on Data of Japanese Centenarians

Nobutane Hanayama[1] and Masaaki Sibuya[2]

In modern biology, theories of aging fall mainly into two groups: damage theories and programed theories. If programed theories are true, the probability that human beings live beyond a specific age will be zero. In contrast, if damage theories are true, such an age does not exist, and a longevity record will be eventually destroyed. In this article, for examining real state, a special type of binomial model based on the generalized Pareto distribution has been applied to data of Japanese centenarians. From the results, it is concluded that the upper limit of lifetime probability distribution in the Japanese population has been estimated 123 years.

REVIEWS/COMMENTS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

MouseAge: Leading the way in the development of geroprotectors in Europe

Ilaria Bellantuono · Stathis Gonos

AGE Mouse

COST Action BM1402

Search

Home | About | News | Events | Working Groups | STSMs | Network Participants | Resources | Contact Us

COST Action BM1402:MouseAGE is formed to develop a European network for preclinical testing of interventions in mouse models of age and age-related diseases.

The number of people over 65 is predicted to double in the next 50 years. Age is the most important risk factor for stroke, heart attacks, cancers, diabetes, and many other chronic diseases.

Tackling the effects of the ageing population in Europe has stimulated funding of research initiatives at both national and European levels. A key requisite to develop new interventions for age-related conditions and promote healthier ageing is the availability and use of preclinical murine models. COST Action BM1402 - MouseAGE - aims to bring together European scientitists to promote best practice and train a new generation of scientists.

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

COST Action BM1402

This website is based upon work from COST Action BM1402 (MouseAge), supported by COST (European

Heales
HEALTHY LIFE EXTENSION SOCIETY

A synopsis on aging—Theories, mechanisms and future prospects

Answering the question as to why we age is tantamount to answering the question of what is life itself. There are countless theories as to why and how we age, but, until recently, the very definition of aging – senescence – was still uncertain. Here, we summarize the main views of the different models of senescence, with a special emphasis on the biochemical processes that accompany aging.

Though inherently complex, aging is characterized by numerous changes that take place at different levels of the biological hierarchy. We therefore explore some of the most relevant changes that take place during aging and, finally, we overview the current status of emergent aging therapies and what the future holds for this field of research.

From this multi-dimensional approach, it becomes clear that an integrative approach that couples aging research with systems biology, capable of providing novel insights into how and why we age, is necessary.

The Metabolic Impact on Histone Acetylation and Transcription in Ageing

Loss of cellular homeostasis during aging results in altered tissue functions and leads to a general decline in fitness and, ultimately, death. As animals age, the control of gene expression, which is orchestrated by multiple epigenetic factors, degenerates. In parallel, metabolic activity and mitochondrial protein acetylation levels also change. These two hallmarks of aging are effectively linked through the accumulating evidence that histone acetylation patterns are susceptible to alterations in key metabolites such as acetyl-CoA and NAD^+, allowing chromatin to function as a sensor of cellular metabolism. In this review we discuss experimental data supporting these connections and provide a context for the possible medical and physiological relevance.

Trends

Aging animals show global, often nonspecific changes in gene expression.

Epigenetic marks such as the acetylation of histones change substantially when animals age. These changes can already be observed when animals reach midlife.

Changes in key metabolites during early aging result in changes in post-translational modifications of metabolic enzymes. This potentially leads to a transient increase in metabolic activity when animals reach midlife.

Age-dependent changes of histone acetylation are coupled to altered metabolic activity in aging animals, which could potentially influence global gene expression.

Mutations in genes that link metabolism and chromatin, such as lysine acetyl transferases (KATs), lysine deacetylases (KDACs) (sirtuins), and ATP citrate lyase (ACLY/ATPCL), have been shown to influence lifespan and the development of age-associated diseases.

Mamm Genome. 2016 Aug;27(7-8):259-78. doi: 10.1007/s00335-016-9648-5. Epub 2016 Jun 30.

Unraveling the message: insights into comparative genomics of the naked mole-rat.

Lewis KN[1], Soifer I[1], Melamud E[1], Roy M[1], McIsaac RS[1], Hibbs M[2], Buffenstein R[3].

Author information

Abstract

Animals have evolved to survive, and even thrive, in different environments. Genetic adaptations may have indirectly created phenotypes that also resulted in a longer lifespan. One example of this phenomenon is the preternaturally long-lived naked mole-rat. This strictly subterranean rodent tolerates hypoxia, hypercapnia, and soil-based toxins. Naked mole-rats also exhibit pronounced resistance to cancer and an attenuated decline of many physiological characteristics that often decline as mammals age. Elucidating mechanisms that give rise to their unique phenotypes will lead to better understanding of subterranean ecophysiology and biology of aging. Comparative genomics could be a useful tool in this regard. Since the publication of a naked mole-rat genome assembly in 2011, analyses of genomic and transcriptomic data have enabled a clearer understanding of mole-rat evolutionary history and suggested molecular pathways (e.g., NRF2-signaling activation and DNA damage repair mechanisms) that may explain the extraordinarily longevity and unique health traits of this species. However, careful scrutiny and re-analysis suggest that some identified features result from incorrect or imprecise annotation and assembly of the naked mole-rat genome: in addition, some of these conclusions (e.g., genes involved in cancer resistance and hairlessness) are rejected when the analysis includes additional, more closely related species. We describe how the combination of better study design, improved genomic sequencing techniques, and new bioinformatic and data analytical tools will improve comparative genomics and ultimately bridge the gap between traditional model and nonmodel organisms.

Maturitas. 2016 Jun 9. pii: S0378-5122(16)30140-2. doi: 10.1016/j.maturitas.2016.06.008. [Epub ahead of print]

Animal and human models to understand ageing.

Lees H[1], Walters H[1], Cox LS[2].

Author information

Abstract

Human ageing is the gradual decline in organ and tissue function with increasing chronological time, leading eventually to loss of function and death. To study the processes involved over research-relevant timescales requires the use of accessible model systems that share significant similarities with humans. In this review, we assess the usefulness of various models, including unicellular yeasts, invertebrate worms and flies, mice and primates including humans, and highlight the benefits and possible drawbacks of each model system in its ability to illuminate human ageing mechanisms. We describe the strong evolutionary conservation of molecular pathways that govern cell responses to extracellular and intracellular signals and which are strongly implicated in ageing. Such pathways centre around insulin-like growth factor signalling and integration of stress and nutritional signals through mTOR kinase. The process of cellular senescence is evaluated as a possible underlying cause for many of the frailties and diseases of human ageing. Also considered is ageing arising from systemic changes that cannot be modelled in lower organisms and instead require studies either in small mammals or in primates. We also touch briefly on novel therapeutic options arising from a better understanding of the biology of ageing.

Deciphering hallmark processes of aging from interaction networks

Scope of review

The majority of aging-related studies are based on reductionist approaches, focusing on single genes/proteins or on individual pathways without considering possible interactions between them. Over the last few decades, several such genes/proteins were independently analysed and linked to a role that is affecting the longevity of an organism. However, an isolated analysis on genes and proteins largely fails to explain the mechanistic insight of a complex phenotype due to the involvement and integration of multiple factors.

Major conclusions

Technological advance makes it possible to generate high-throughput temporal and spatial data that provide an opportunity to use computer-based methods. These techniques allow us to go beyond reductionist approaches to analyse large-scale networks that provide deeper understanding of the processes that drive aging.

General significance

In this review, we focus on systems biology approaches, based on network inference methods to understand the dynamics of hallmark processes leading to aging phenotypes. We also describe computational methods for the interpretation and identification of important molecular hubs involved in the mechanistic linkage between aging related processes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Methods Enzymol. 2016;574:183-211. doi: 10.1016/bs.mie.2016.03.011. Epub 2016 Mar 28.

Biology, Chemistry, and Pharmacology of Sirtuins.

Bedalov A[1], Chowdhury S[1], Simon JA[2].

⊕ Author information

Abstract

Sirtuins are a family of protein deacylases related by amino acid sequence and cellular function to the yeast Saccharomyces cerevisiae protein Sir2 (Silent Information Regulator-2), the first of this class of enzymes to be identified and studied in detail. Based on its initially discovered activity, Sir2 was classified as a histone deacetylase that removes acetyl groups from histones H3 and H4. The acetylation/deacetylation of these particular substrates leads to changes in transcriptional silencing at specific loci in the yeast genome, hence its name. Sirtuins, however, have been shown to regulate a wide variety of cellular processes beyond transcriptional repression in varied subcellular compartments and in different cell types. Mechanistically distinct from Zn(2+)-dependent deacylases, sirtuins use nicotinamide adenine dinucleotide as a cofactor in the removal of acetyl and other acyl groups linking metabolic status and posttranslational modification. Sirtuins' unique position has made them attractive targets for small-molecule drug development. In this chapter, we describe the biological roles, therapeutic areas in which sirtuins may play a role and development of small-molecule inhibitors of sirtuins employing phenotypic screening technologies ranging from assays in yeast, as well as biochemical screens to yield lead drug development candidates targeting a broad spectrum of human diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The Expensive Germline and the Evolution of Ageing

Alexei A. Maklakov, Simone Immler

The trade-off between survival and reproduction is the bedrock of the evolutionary theory of ageing. The reproductive system regulates ageing of the soma, and removal of germ cells extends somatic lifespan and increases resistance to a broad variety of abiotic and biotic stresses. The general explanation for this somatic response is that reduced reproduction frees up resources for survival. Remarkably, however, the disruption of molecular signaling pathways that regulate ageing increases lifespan without the obligatory reduction in fecundity, thus challenging the key role of the survival–reproduction trade-off. Here, we review the diverse literature on the costs of lifespan extension and suggest that the current paradigm is overly centered on the trade-off between lifespan and fecundity, often neglecting key aspects of fitness, such as development time, defense against parasites and, in particular, the high costs of germline maintenance. Compromised germline maintenance increases germline mutation rate, which reduces offspring fitness and ultimately can terminate germline proliferation across generations. We propose that future work should incorporate the costs of germline maintenance in the study of ageing evolution, as well as in applied biomedical research, by assessing offspring fitness.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cellular lifespan and senescence: a complex balance between multiple cellular pathways

The study of cellular senescence and proliferative lifespan is becoming increasingly important because of the promises of autologous cell therapy, the need for model systems for tissue disease and the implication of senescent cell phenotypes in organismal disease states such as sarcopenia, diabetes and various cancers, among others. Here, we explain the concepts of proliferative cellular lifespan and cellular senescence, and we present factors that have been shown to mediate cellular lifespan positively or negatively. We review much recent literature and present potential molecular mechanisms by which lifespan mediation occurs, drawing from the fields of telomere biology, metabolism, NAD^+ and sirtuin biology, growth factor signaling and oxygen and antioxidants. We conclude that cellular lifespan and senescence are complex concepts that are governed by multiple independent and interdependent pathways, and that greater understanding of these pathways, their interactions and their convergence upon specific cellular phenotypes may lead to viable therapies for tissue regeneration and treatment of age-related pathologies, which are caused by or exacerbated by senescent cells in vivo.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging Cell. 2016 Jul 4. doi: 10.1111/acel.12503. [Epub ahead of print]

Has gene duplication impacted the evolution of Eutherian longevity?

Doherty A[1], de Magalhães JP[1].

Author information

Abstract

One of the greatest unresolved questions in aging biology is determining the genetic basis of interspecies longevity variation. Gene duplication is often the key to understanding the origin and evolution of important Eutherian phenotypes. We systematically identified longevity-associated genes in model organisms that duplicated throughout Eutherian evolution. Longevity-associated gene families have a marginally significantly higher rate of duplication compared to non-longevity-associated gene families. Anti-longevity-associated gene families have significantly increased rate of duplication compared to pro-longevity gene families and are enriched in neurodegenerative disease categories. Conversely, duplicated pro-longevity-associated gene families are enriched in cell cycle genes. There is a cluster of longevity-associated gene families that expanded solely in long-lived species that is significantly enriched in pathways relating to 3-UTR-mediated translational regulation, metabolism of proteins and gene expression, pathways that have the potential to affect longevity. The identification of a gene cluster that duplicated solely in long-lived species involved in such fundamental processes provides a promising avenue for further exploration of Eutherian longevity evolution.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Telomeres in aging and disease: lessons from zebrafish

Madalena C. Carneiro, Inês Pimenta de Castro, Miguel Godinho Ferreira

Age is the highest risk factor for some of the most prevalent human diseases, including cancer. Telomere shortening is thought to play a central role in the aging process in humans. The link between telomeres and aging is highlighted by the fact that genetic diseases causing telomerase deficiency are associated with premature aging and increased risk of cancer. For the last two decades, this link has been mostly investigated using mice that have long telomeres. However, zebrafish has recently emerged as a powerful and complementary model system to study telomere biology. Zebrafish possess human-like short telomeres that progressively decline with age, reaching lengths in old age that are observed when telomerase is mutated. The extensive characterization of its well-conserved molecular and cellular physiology makes this vertebrate an excellent model to unravel the underlying relationship between telomere shortening, tissue regeneration, aging and disease. In this Review, we explore the advantages of using zebrafish in telomere research and discuss the primary discoveries made in this model that have contributed to expanding our knowledge of how telomere attrition contributes to cellular senescence, organ dysfunction and disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Hallmarks of progeroid syndromes: lessons from mice and reprogrammed cells

Dido Carrero, Clara Soria-Valles, Carlos López-Otín

Ageing is a process that inevitably affects most living organisms and involves the accumulation of macromolecular damage, genomic instability and loss of heterochromatin. Together, these alterations lead to a decline in stem cell function and to a reduced capability to regenerate tissue. In recent years, several genetic pathways and biochemical mechanisms that contribute to physiological ageing have been described, but further research is needed to better characterize this complex biological process. Because premature ageing (progeroid) syndromes, including progeria, mimic many of the characteristics of human ageing, research into these conditions has proven to be very useful not only to identify the underlying causal mechanisms and identify treatments for these pathologies, but also for the study of physiological ageing. In this Review, we summarize the main cellular and animal models used in progeria research, with an emphasis on patient-derived induced pluripotent stem cell models, and define a series of molecular and cellular hallmarks that characterize progeroid syndromes and parallel physiological ageing. Finally, we describe the therapeutic strategies being investigated for the treatment of progeroid syndromes, and their main limitations.

Glycoconj J. 2016 Jul 9. [Epub ahead of print]

Targeting advanced glycation with pharmaceutical agents: where are we now?

Borg DJ[1], Forbes JM[2,3,4,5].

Author information

Abstract

Advanced glycation end products (AGEs) are the final products of the Maillard reaction, a complex process that has been studied by food chemists for a century. Over the past 30 years, the biological significance of advanced glycation has also been discovered. There is mounting evidence that advanced glycation plays a homeostatic role within the body and that food-related Maillard products, intermediates such as reactive α-dicarbonyl compounds and AGEs, may influence this process. It remains to be understood, at what point AGEs and their intermediates become pathogenic and contribute to the pathogenesis of chronic diseases that inflict current society. Diabetes and its complications have been a major focus of AGE biology due to the abundance of excess sugar and α-dicarbonyls in this family of diseases. While further temporal information is required, a number of pharmacological agents that inhibit components of the advanced glycation pathway have already showed promising results in preclinical models. These therapies appear to have a wide range of mechanistic actions to reduce AGE load. Some of these agents including Alagebrium, have translated successfully to clinical trials, while others such as aminoguanidine, have had undesirable side-effect profiles. This review will discuss different pharmacological agents that have been used to reduce AGE burden in preclinical models of disease with a focus on diabetes and its complications, compare outcomes of those therapies that have reached clinical trials, and provide further rationale for the use of inhibitors of the glycation pathway in chronic diseases.

OTHER RESEARCH

Heales
HEALTHY LIFE EXTENSION SOCIETY

Global initiative seeks 1,000 new cancer models

The effort will use next-generation cell-culture methods and fresh patient samples.

Heidi Ledford

11 July 2016

An international collaboration of cancer-research heavy-weights aims to grow 1,000 new cell lines for scientists to study — and that could be just the beginning.

The Human Cancer Models Initiative announced its pilot project on 11 July, and intends to complete the initial 1,000 models within 3 years. Members of the initiative include the US National Cancer Institute (NCI) in Bethesda, Maryland; Cancer Research UK in London; the Wellcome Trust Sanger Institute in Hinxton, UK; and Hubrecht Organoid Technology of Utrecht in the Netherlands.

The initial goal of 1,000 cell lines would roughly double the world's collection of accessible cancer cell models, says Louis Staudt, head of the NCI's Center for Cancer Genomics. But if all goes well during the pilot, the project will generate thousands more. Staudt estimates that researchers need about 10,000 models to fully capture the diversity of relatively common genetic subtypes of cancer. "Whether we actually will push into that depends a lot upon how easy and valuable the cell lines are from the pilot," he says.