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Scientific News
4th of February 2018
Sven Bulterijs

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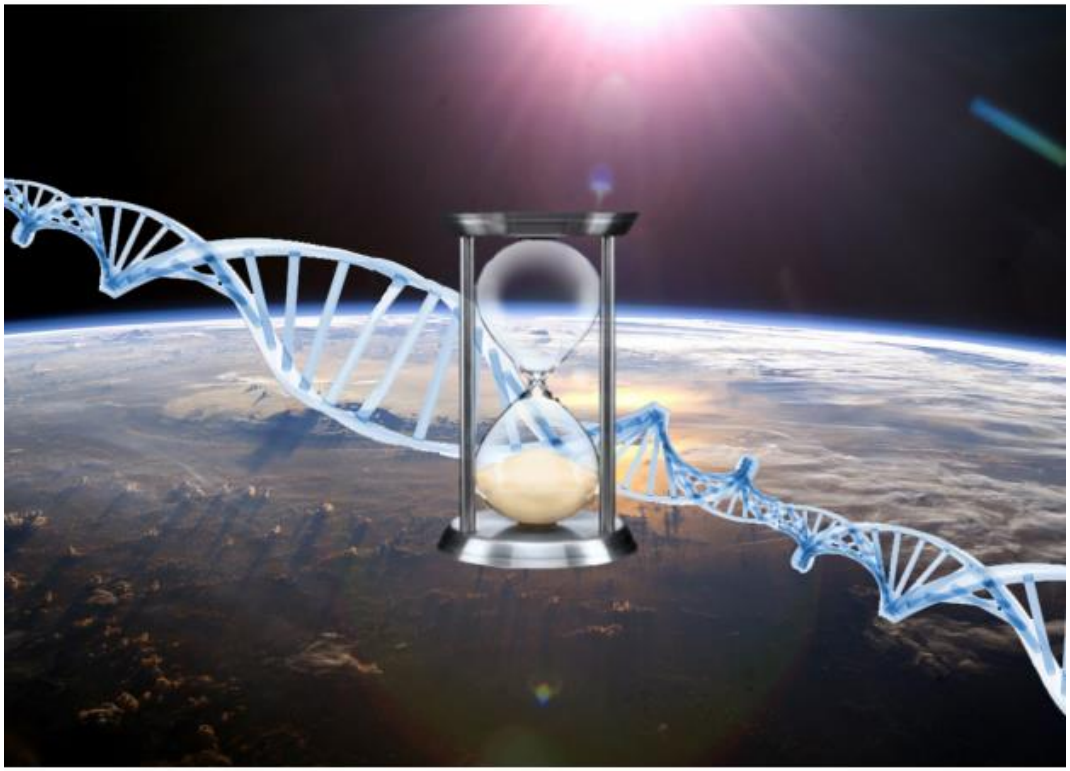
LONGEVITY INDUSTRY LANDSCAPE OVERVIEW 2017

Volume I: The Science of Longevity

Geroscience, Policy, and Economics
The Paradigm Shift: from Treatment to Prevention



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Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age

J Graham Ruby, Megan Smith, Rochelle Buffenstein
Calico Life Sciences LLC, United States

The longest-lived rodent, the naked mole-rat (*Heterocephalus glaber*), has a reported maximum lifespan of >30 years and exhibits delayed and/or attenuated age-associated physiological declines. We questioned whether these mouse-sized, eusocial rodents conform to Gompertzian mortality laws by experiencing an exponentially increasing risk of death as they get older. We compiled and analyzed a large compendium of historical naked mole-rat lifespan data with >3000 data points. Kaplan-Meier analyses revealed a substantial portion of the population to have survived at 30 years of age. Moreover, unlike all other mammals studied to date, and regardless of sex or breeding-status, the age-specific hazard of mortality did not increase with age, even at ages 25-fold past their time to reproductive maturity. This absence of hazard increase with age, in defiance of Gompertz's law, uniquely identifies the naked mole-rat as a non-aging mammal, confirming its status as an exceptional model for biogerontology.

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Int J Health Plann Manage. 2018 Jan 12. doi: 10.1002/hpm.2488. [Epub ahead of print]

Financing elderly people's long-term care needs: Evidence from China.

Li F[1], Otani J[2].

⊕ Author information

Abstract

Confronted by accelerated population aging, China is establishing a long-term care (LTC) system. This study discusses challenges and recommendations for financing China's LTC system. On the basis of the data on elderly people's self-care ability from the Chinese Longitudinal Healthy Longevity Survey, we calculate the size of the elderly population that need LTC for the period from 2015 to 2030 and analyse the increasing tendency of LTC expenses by considering the impact of price increase. We also analyse the local governments' financial capacity for LTC support by comparing the expense level to the fiscal revenue. The study found that aging will double the LTC expenses by 2030. Therefore, this study suggests the establishment of an LTC insurance system that allocates LTC expenses, which are currently borne by individuals and families, more fairly among the government, individuals, and families. Moreover, with the current LTC reforms, implemented primarily by local governments in China, we believe that the central government should bear some of the fiscal responsibility by conducting fiscal transfers to partially support undeveloped regions that are establishing an LTC system.

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Women live longer than men even during severe famines and epidemics

Women in almost all modern populations live longer than men. Research to date provides evidence for both biological and social factors influencing this gender gap. Conditions when both men and women experience extremely high levels of mortality risk are unexplored sources of information. We investigate the survival of both sexes in seven populations under extreme conditions from famines, epidemics, and slavery. Women survived better than men: In all populations, they had lower mortality across almost all ages, and, with the exception of one slave population, they lived longer on average than men. Gender differences in infant mortality contributed the most to the gender gap in life expectancy, indicating that newborn girls were able to survive extreme mortality hazards better than newborn boys. Our results confirm the ubiquity of a female survival advantage even when mortality is extraordinarily high. The hypothesis that the survival advantage of women has fundamental biological underpinnings is supported by the fact that under very harsh conditions females survive better than males even at infant ages when behavioral and social differences may be minimal or favor males. Our findings also indicate that the female advantage differs across environments and is modulated by social factors.

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Effects of rapamycin on growth hormone receptor knockout mice

Yimin Fang, Cristal M. Hill, Justin Darcy, Adriana Reyes-Ordoñez, Edwin Arauz, Samuel McFadden, Chi Zhang, Jared Osland, John Gao, Tian Zhang, Stuart J. Frank, Martin A. Javors, Rong Yuan, John J. Kopchick, Liou Y. Sun, Jie Chen, and Andrzej Bartke

It is well documented that inhibition of mTORC1 (defined by Raptor), a complex of mechanistic target of rapamycin (mTOR), extends life span, but less is known about the mechanisms by which mTORC2 (defined by Rictor) impacts longevity. Here, rapamycin (an inhibitor of mTOR) was used in GHR-KO (growth hormone receptor knockout) mice, which have suppressed mTORC1 and up-regulated mTORC2 signaling, to determine the effect of concurrently decreased mTORC1 and mTORC2 signaling on life span. We found that rapamycin extended life span in control normal (N) mice, whereas it had the opposite effect in GHR-KO mice. In the rapamycin-treated GHR-KO mice, mTORC2 signaling was reduced without further inhibition of mTORC1 in the liver, muscle, and s.c. fat. Glucose and lipid homeostasis were impaired, and old GHR-KO mice treated with rapamycin lost functional immune cells and had increased inflammation. In GHR-KO MEF cells, knockdown of Rictor, but not Raptor, decreased mTORC2 signaling. We conclude that drastic reduction of mTORC2 plays important roles in impaired longevity in GHR-KO mice via disruption of whole-body homeostasis.

N Engl J Med. 2018 Jan 25;378(4):321-330. doi: 10.1056/NEJMoa1705971.

Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease.

Honig LS[1], Vellas B[1], Woodward M[1], Boada M[1], Bullock R[1], Borrie M[1], Hager K[1], Andreasen N[1], Scarpini E[1], Liu-Seifert H[1], Case M[1], Dean RA[1], Hake A[1], Sundell K[1], Poole Hoffmann V[1], Carlson C[1], Khanna R[1], Mintun M[1], DeMattos R[1], Selzler KJ[1], Siemers E[1].

⊕ Author information

Abstract

BACKGROUND: Alzheimer's disease is characterized by amyloid-beta (Aβ) plaques and neurofibrillary tangles. The humanized monoclonal antibody solanezumab was designed to increase the clearance from the brain of soluble Aβ, peptides that may lead to toxic effects in the synapses and precede the deposition of fibrillary amyloid.

METHODS: We conducted a double-blind, placebo-controlled, phase 3 trial involving patients with mild dementia due to Alzheimer's disease, defined as a Mini-Mental State Examination (MMSE) score of 20 to 26 (on a scale from 0 to 30, with higher scores indicating better cognition) and with amyloid deposition shown by means of florbetapir positron-emission tomography or Aβ1-42 measurements in cerebrospinal fluid. Patients were randomly assigned to receive solanezumab at a dose of 400 mg or placebo intravenously every 4 weeks for 76 weeks. The primary outcome was the change from baseline to week 80 in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; scores range from 0 to 90, with higher scores indicating greater cognitive impairment).

RESULTS: A total of 2129 patients were enrolled, of whom 1057 were assigned to receive solanezumab and 1072 to receive placebo. The mean change from baseline in the ADAS-cog14 score was 6.65 in the solanezumab group and 7.44 in the placebo group, with no significant between-group difference at week 80 (difference, -0.80; 95% confidence interval, -1.73 to 0.14; P=0.10). As a result of the failure to reach significance with regard to the primary outcome in the prespecified hierarchical analysis, the secondary outcomes were considered to be descriptive and are reported without significance testing. The change from baseline in the MMSE score was -3.17 in the solanezumab group and -3.66 in the placebo group. Adverse cerebral edema or effusion lesions that were observed on magnetic resonance imaging after randomization occurred in 1 patient in the solanezumab group and in 2 in the placebo group.

CONCLUSIONS: Solanezumab at a dose of 400 mg administered every 4 weeks in patients with mild Alzheimer's disease did not significantly affect cognitive decline. (Funded by Eli Lilly; EXPEDITION3 ClinicalTrials.gov number, NCT01900665 .).

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Aging and neurodegeneration are associated with increased mutations in single human neurons

Abstract

It has long been hypothesized that aging and neurodegeneration are associated with somatic mutation in neurons; however, methodological hurdles have prevented testing this hypothesis directly. We used single-cell whole-genome sequencing to perform genome-wide somatic single-nucleotide variant (sSNV) identification on DNA from 161 single neurons from the prefrontal cortex and hippocampus of 15 normal individuals (aged 4 months to 82 years), as well as 9 individuals affected by early-onset neurodegeneration due to genetic disorders of DNA repair (Cockayne syndrome and xeroderma pigmentosum). sSNVs increased approximately linearly with age in both areas (with a higher rate in hippocampus) and were more abundant in neurodegenerative disease. The accumulation of somatic mutations with age—which we term genosenium—shows age-related, region-related, and disease-related molecular signatures and may be important in other human age-associated conditions.

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The mitochondrial ATP synthase is a shared drug target for aging and dementia

Summary

Aging is a major driving force underlying dementia, such as that caused by Alzheimer's disease (AD). While the idea of targeting aging as a therapeutic strategy is not new, it remains unclear how closely aging and age-associated diseases are coupled at the molecular level. Here, we discover a novel molecular link between aging and dementia through the identification of the molecular target for the AD drug candidate J147. J147 was developed using a series of phenotypic screening assays mimicking disease toxicities associated with the aging brain. We have previously demonstrated the therapeutic efficacy of J147 in several mouse models of AD. Here, we identify the mitochondrial α-F_1-ATP synthase (ATP5A) as a target for J147. By targeting ATP synthase, J147 causes an increase in intracellular calcium leading to sustained calcium/calmodulin-dependent protein kinase kinase β (CAMKK2)-dependent activation of the AMPK/mTOR pathway, a canonical longevity mechanism. Accordingly, modulation of mitochondrial processes by J147 prevents age-associated drift of the hippocampal transcriptome and plasma metabolome in mice and extends lifespan in drosophila. Our results link aging and age-associated dementia through ATP synthase, a molecular drug target that can potentially be exploited for the suppression of both. These findings demonstrate that novel screens for new AD drug candidates identify compounds that act on established aging pathways, suggesting an unexpectedly close molecular relationship between the two.

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Alzheimers Dement. 2018 Jan 6. pii: S1552-5260(17)33855-4. doi: 10.1016/j.jalz.2017.11.012. [Epub ahead of print]

Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies.

van der Lee SJ[1], Teunissen CE[2], Pool R[3], Shipley MJ[4], Teumer A[5], Chouraki V[6], Melo van Lent D[7], Tynkkynen J[8], Fischer K[9], Hernesniemi J[10], Metspalu A[9], Singh-Manoux A[11], Verhoeven A[12], Willemsen G[3], de Leeuw FA[13], Wagner H[14], van Dongen J[3], Hertel J[15], Budde K[16], Willems van Dijk K[17], Weinhold L[18], Ikram MA[19], Pietzner M[16], Perola M[20], Wagner M[21], Friedrich N[16], Slagboom PE[22], Scheltens P[23], Yang Q[24], Gertzen RE[25], Egert S[26], Li S[24], Hankemeier T[27], van Beijsterveldt CEM[3], Ramachandran V[28], Maier W[21], Peeters CFW[29], Jörgen Grabe H[30], Ramirez A[31], Seshadri S[32], Haller T[9], Kivimäki M[4], Salomaa V[33], Demirkan A[34], Boomsma D[3], van der Flier WM[35], Amin N[1], van Duijn CM[36].

⊕ Author information

Abstract

INTRODUCTION: Identifying circulating metabolites that are associated with cognition and dementia may improve our understanding of the pathogenesis of dementia and provide crucial readouts for preventive and therapeutic interventions.

METHODS: We studied 299 metabolites in relation to cognition (general cognitive ability) in two discovery cohorts (N total = 5658). Metabolites significantly associated with cognition after adjusting for multiple testing were replicated in four independent cohorts (N total = 6652), and the associations with dementia and Alzheimer's disease (N = 25,872) and lifestyle factors (N = 5168) were examined.

RESULTS: We discovered and replicated 15 metabolites associated with cognition including subfractions of high-density lipoprotein, docosahexaenoic acid, ornithine, glutamine, and glycoprotein acetyls. These associations were independent of classical risk factors including high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, and apolipoprotein E (APOE) genotypes. Six of the cognition-associated metabolites were related to the risk of dementia and lifestyle factors.

DISCUSSION: Circulating metabolites were consistently associated with cognition, dementia, and lifestyle factors, opening new avenues for prevention of cognitive decline and dementia.

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Neuronal complex I deficiency occurs throughout the Parkinson's disease brain, but is not associated with neurodegeneration or mitochondrial DNA damage.

Flønes IH[1,2], Fernandez-Vizarra E[3], Lykouri M[1,2], Brakedal B[1,2], Skeie GO[1,2], Miletic H[4,5], Lilleng PK[4,6], Alves G[7,8], Tysnes OB[1,2], Haugarvoll K[1,2], Dölle C[1,2], Zeviani M[3], Tzoulis C[9,10].

⊕ Author information

Abstract

Mitochondrial complex I deficiency occurs in the substantia nigra of individuals with Parkinson's disease. It is generally believed that this phenomenon is caused by accumulating mitochondrial DNA damage in neurons and that it contributes to the process of neurodegeneration. We hypothesized that if these theories are correct, complex I deficiency should extend beyond the substantia nigra to other affected brain regions in Parkinson's disease and correlate tightly with neuronal mitochondrial DNA damage. To test our hypothesis, we employed a combination of semiquantitative immunohistochemical analyses, Western blot and activity measurements, to assess complex I quantity and function in multiple brain regions from an extensively characterized population-based cohort of idiopathic Parkinson's disease (n = 18) and gender and age matched healthy controls (n = 11). Mitochondrial DNA was assessed in single neurons from the same areas by real-time PCR. Immunohistochemistry showed that neuronal complex I deficiency occurs throughout the Parkinson's disease brain, including areas spared by the neurodegenerative process such as the cerebellum. Activity measurements in brain homogenate confirmed a moderate decrease of complex I function, whereas Western blot was less sensitive, detecting only a mild reduction, which did not reach statistical significance at the group level. With the exception of the substantia nigra, neuronal complex I loss showed no correlation with the load of somatic mitochondrial DNA damage. Interestingly, α-synuclein aggregation was less common in complex I deficient neurons in the substantia nigra. We show that neuronal complex I deficiency is a widespread phenomenon in the Parkinson's disease brain which, contrary to mainstream theory, does not follow the anatomical distribution of neurodegeneration and is not associated with the neuronal load of mitochondrial DNA mutation. Our findings suggest that complex I deficiency in Parkinson's disease can occur independently of mitochondrial DNA damage and may not have a pathogenic role in the neurodegenerative process.

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The axolotl genome and the evolution of key tissue formation regulators

Salamanders serve as important tetrapod models for developmental, regeneration and evolutionary studies. An extensive molecular toolkit makes the Mexican axolotl (*Ambystoma mexicanum*) a key representative salamander for molecular investigations. Here we report the sequencing and assembly of the 32-gigabase-pair axolotl genome using an approach that combined long-read sequencing, optical mapping and development of a new genome assembler (MARVEL). We observed a size expansion of introns and intergenic regions, largely attributable to multiplication of long terminal repeat retroelements. We provide evidence that intron size in developmental genes is under constraint and that species-restricted genes may contribute to limb regeneration. The axolotl genome assembly does not contain the essential developmental gene *Pax3*. However, mutation of the axolotl *Pax3* paralogue *Pax7* resulted in an axolotl phenotype that was similar to those seen in $Pax3^{-/-}$ and $Pax7^{-/-}$ mutant mice. The axolotl genome provides a rich biological resource for developmental and evolutionary studies.

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Arterioscler Thromb Vasc Biol. 2018 Jan 11. pii: ATVBAHA.117.310587. doi: 10.1161/ATVBAHA.117.310587. [Epub ahead of print]

High-Density Lipoprotein Cholesterol and Mortality: Too Much of a Good Thing?

Hamer M[1], O'Donovan G[2], Stamatakis E[2].

⊕ Author information

Abstract

OBJECTIVE: The objective of this study was to examine the shape of the association between high-density lipoprotein cholesterol (HDL-C) and mortality in a large general population sample.

APPROACH AND RESULTS: Adult participants (n=37 059; age=57.7±11.9 years; 46.8% men) were recruited from general population household-based surveys (Health Survey for England and Scottish Health Survey). Individual participant data were linked with the British National Health Service Central Registry to record mortality. There were 2250 deaths from all causes during 326 016 person-years of follow-up. When compared with the reference category (HDL-C=1.5-1.99 mmol/L), a U-shaped association was apparent for all-cause mortality, with elevated risk in participants with the lowest (hazard ratio=1.23; 95% confidence interval, 1.06, 1.44) and highest (1.25; 0.97, 1.62) HDL-C concentration. Associations for cardiovascular disease were linear, and elevated risk was observed in those with the lowest HDL-C concentration (1.49; 1.15, 1.94).

CONCLUSIONS: A U-shaped association was observed between HDL-C and mortality in a large general population sample.

KEYWORDS: cardiovascular diseases; cholesterol, HDL; health surveys; lipoproteins, HDL; mortality

Large Cardiac-Muscle Patches Engineered from Human Induced-Pluripotent Stem-Cell-Derived Cardiac Cells Improve Recovery from Myocardial Infarction in Swine

Background—Here, we generated human cardiac muscle patches (hCMPs) of clinically relevant dimensions (4 cm × 2 cm × 1.25 mm) by suspending cardiomyocytes, smooth-muscle cells, and endothelial cells that had been differentiated from human induced-pluripotent stem cells (hiPSCs) in a fibrin scaffold and then culturing the construct on a dynamic (rocking) platform.

Methods—*In vitro* assessments of hCMPs suggest maturation in response to dynamic culture stimulation. *In vivo* assessments were conducted in a porcine model of myocardial infarction (MI). Animal groups included: MI hearts treated with two hCMPs (MI+hCMP, N=13), treated with two cell-free open fibrin patches (MI+OP, n=14), or with neither experimental patches (MI, n=15); a fourth group of animals underwent sham surgery (SHAM, n=8). Cardiac function and infarct size were evaluated by magnetic resonance imaging, arrhythmia incidence by implanted loop recorders, and the engraftment rate by calculation of quantitative PCR measurements of expression of the human Y chromosome. Additional studies examined the myocardial protein expression profile changes and potential mechanisms of action that related with exosomes from the cell patch.

Results—The hCMPs began to beat synchronously within 1 day of fabrication, and after 7 days of dynamic culture stimulation, *in vitro* assessments indicated the mechanisms related to the improvements in electronic mechanical coupling, calcium-handling, and force-generation suggesting a maturation process during the dynamic culture. The engraftment rate was 10.9±1.8% at 4 weeks after the transplantation. The hCMP transplantation was associated with significant improvements in left ventricular (LV) function, infarct size, myocardial wall stress, myocardial hypertrophy, and reduced apoptosis in the peri-scar boarder zone myocardium. hCMP transplantation also reversed some MI-associated changes in sarcomeric regulatory protein phosphorylation. The exosomes released from the hCMP appeared to have cytoprotective properties that improved cardiomyocyte survival.

Conclusions—We have fabricated a clinically relevant size of hCMP with trilineage cardiac cells derived from hiPSCs. The hCMP matures in vitro during 7 days of dynamic culture. Transplantation of this type of hCMP results in significantly reduced infarct size and improvements in cardiac function that are associated with reduction in LV wall stress. The hCMP treatment is not associated with significant changes in arrhythmogenicity.

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Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

Objective To conduct a meta-analysis of all large trials assessing the associations of omega-3 fatty acid supplements with the risk of fatal and nonfatal coronary heart disease and major vascular events in the full study population and prespecified subgroups.

Data Sources and Study Selection This meta-analysis included randomized trials that involved at least 500 participants and a treatment duration of at least 1 year and that assessed associations of omega-3 fatty acids with the risk of vascular events.

Data Extraction and Synthesis Aggregated study-level data were obtained from 10 large randomized clinical trials. Rate ratios for each trial were synthesized using observed minus expected statistics and variances. Summary rate ratios were estimated by a fixed-effects meta-analysis using 95% confidence intervals for major diseases and 99% confidence intervals for all subgroups.

Main Outcomes and Measures The main outcomes included fatal coronary heart disease, nonfatal myocardial infarction, stroke, major vascular events, and all-cause mortality, as well as major vascular events in study population subgroups.

Results Of the 77 917 high-risk individuals participating in the 10 trials, 47 803 (61.4%) were men, and the mean age at entry was 64.0 years; the trials lasted a mean of 4.4 years. The associations of treatment with outcomes were assessed on 6273 coronary heart disease events (2695 coronary heart disease deaths and 2276 nonfatal myocardial infarctions) and 12 001 major vascular events. Randomization to omega-3 fatty acid supplementation (eicosapentaenoic acid dose range, 226-1800 mg/d) had no significant associations with coronary heart disease death (rate ratio [RR], 0.93; 99% CI, 0.83-1.03; $P = .05$), nonfatal myocardial infarction (RR, 0.97; 99% CI, 0.87-1.08; $P = .43$) or any coronary heart disease events (RR, 0.96; 95% CI, 0.90-1.01; $P = .12$). Neither did randomization to omega-3 fatty acid supplementation have any significant associations with major vascular events (RR, 0.97; 95% CI, 0.93-1.01; $P = .10$), overall or in any subgroups, including subgroups composed of persons with prior coronary heart disease, diabetes, lipid levels greater than a given cutoff level, or statin use.

Conclusions and Relevance This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease.

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Gene pathways associated with mitochondrial function, oxidative stress and telomere length are differentially expressed in the liver of rats fed lifelong on virgin olive, sunflower or fish oils ☆

This study investigates the effect of lifelong intake of different fat sources rich in monounsaturated (virgin olive oil), n6 polyunsaturated (sunflower oil) or n3 polyunsaturated (fish oil) fatty acids in the aged liver. Male Wistar rats fed lifelong on diets differing in the fat source were killed at 6 and at 24 months of age. Liver histopathology, mitochondrial ultrastructure, biogenesis, oxidative stress, mitochondrial electron transport chain, relative telomere length and gene expression profiles were studied. Aging led to lipid accumulation in the liver. Virgin olive oil led to the lowest oxidation and ultrastructural alterations. Sunflower oil induced fibrosis, ultrastructural alterations and high oxidation. Fish oil intensified oxidation associated with age, lowered electron transport chain activity and enhanced the relative telomere length. Gene expression changes associated with age in animals fed virgin olive oil and fish oil were related mostly to mitochondrial function and oxidative stress pathways, followed by cell cycle and telomere length control. Sunflower oil avoided gene expression changes related to age. According to the results, virgin olive oil might be considered the dietary fat source that best preserves the liver during the aging process.

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J Gerontol A Biol Sci Med Sci. 2017 Dec 30. doi: 10.1093/gerona/glx247. [Epub ahead of print]

Analysis of Polymorphisms in 58 Potential Candidate Genes for Association with Human Longevity.

Donlon TA[1,2], Morris BJ[1,3,4], Chen R[1], Masaki KH[1,4], Allsopp RC[2], Willcox DC[5], Tiirikainen M[6], Willcox BJ[1,4].

Author information

Abstract

Longevity is a polygenic trait in which genetic predisposition is particularly important. We hypothesized that amongst genes differentially expressed in response to caloric restriction, several may be candidate longevity genes. We tested 459 single nucleotide polymorphisms (SNPs) in 46 genes differentially expressed in calorically-restricted mice and 12 other genes for association with longevity. Subjects were American men of Japanese ancestry, 440 aged ≥95 years and 374 with an average lifespan. Based on a dominant model of inheritance, an association with longevity at the $p < 0.05$ level was seen for SNPs in 13 of the genes. Testing by all possible models increased the number of genes to 18. After correction for multiple testing, 4 genes retained significance, namely, MAP3K5 (p=0.00004), SIRT7 (p=0.00004), SIRT5 (p=0.0007), and PIK3R1 (p=0.01). In a dominant model, association with longevity was seen for multiple adjacent SNPs within two of these genes (MAP3K5 and PIK3R1), as well as in FLT1, consistent with linkage disequilibrium with a causative variant in the vicinity of each respective SNP set. MAP3K5 and FLT1 haplotypes were associated with longevity. In conclusion, the present study implicates variation in MAP3K5, FLT1, PIK3R1, SIRT7 and SIRT5 in human longevity.

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Sirt4 is a mitochondrial regulator of metabolism and lifespan in *Drosophila melanogaster*

Sirtuins are a class of proteins known to regulate aspects of genomic stability, metabolism, and lifespan in many organisms. In this study, we show that the mitochondrial sirtuin Sirt4 plays an important role in regulating the organismal response to fasting as well as ensuring normal lifespan in *Drosophila*. Flies lacking Sirt4 are short-lived, while flies overexpressing Sirt4 are long-lived. Flies lacking Sirt4 display a number of metabolic defects, including sensitivity to starvation; decreased fertility and activity; and an inability to utilize energy stores, particularly long-chain fatty acids, suggesting Sirt4 is important for maintaining metabolic homeostasis. Our results suggest that boosting mitochondrial sirtuin activity may be an important avenue for treating age-related metabolic decline and preserving healthy lifespan.

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Global mapping of transcription factor motifs in human aging

David Alfego, Ulrich Rodeck, Andres Kriete

Biological aging is a complex process dependent on the interplay of cell autonomous and tissue contextual changes which occur in response to cumulative molecular stress and manifest through adaptive transcriptional reprogramming. Here we describe a transcription factor (TF) meta-analysis of gene expression datasets accrued from 18 tissue sites collected at different biological ages and from 7 different in-vitro aging models. In-vitro aging platforms included replicative senescence and an energy restriction model in quiescence (ERiQ), in which ATP was transiently reduced. TF motifs in promoter regions of trimmed sets of target genes were scanned using JASPAR and TRANSFAC. TF signatures established a global mapping of agglomerating motifs with distinct clusters when ranked hierarchically. Remarkably, the ERiQ profile was shared with the majority of in-vivo aged tissues. Fitting motifs in a minimalistic protein-protein network allowed to probe for connectivity to distinct stress sensors. The DNA damage sensors ATM and ATR linked to the subnetwork associated with senescence. By contrast, the energy sensors PTEN and AMPK connected to the nodes in the ERiQ subnetwork. These data suggest that metabolic dysfunction may be linked to transcriptional patterns characteristic of many aged tissues and distinct from cumulative DNA damage associated with senescence.

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Senescence chips for ultrahigh-throughput isolation and removal of senescent cells

Yuchao Chen, Pan Mao, Antoine M. Snijders, Daojing Wang

Cellular senescence plays an important role in organismal aging and age-related diseases. However, it is challenging to isolate low numbers of senescent cells from small volumes of biofluids for downstream analysis. Furthermore, there is no technology that could selectively remove senescent cells in a high-throughput manner. In this work, we developed a novel microfluidic chip platform, termed senescence chip, for ultrahigh-throughput isolation and removal of senescent cells. The core component of our senescence chip is a slanted and tunable 3D micropillar array with a variety of shutters in the vertical direction for rapid cell sieving, taking advantage of the characteristic cell size increase during cellular senescence. The 3D configuration achieves high throughput, high recovery rate, and device robustness with minimum clogging. We demonstrated proof-of-principle applications in isolation and enumeration of senescent mesenchymal stem cells (MSCs) from undiluted human whole blood, and senescent cells from mouse bone marrow after total body irradiation, with the single-cell resolution. After scale-up to a multilayer and multichannel structure, our senescence chip achieved ultrahigh-throughput removal of senescent cells from human whole blood with an efficiency of over 70% at a flow rate of 300 ml/hr. Sensitivity and specificity of our senescence chips could be augmented with implementation of multiscale size separation, and identification of background white blood cells using their cell surface markers such as CD45. With the advantages of high throughput, robustness, and simplicity, our senescence chips may find wide applications and contribute to diagnosis and therapeutic targeting of cellular senescence.

REVIEWS/COMMENTS/EDITORIALS

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Questioning the inevitability of aging

Josh Mitteldorf, and Gregory M. Fahy

Paul Nelson and Joanna Masel (1) are the most recent theorists to bypass evolution and seek an abstract answer to the question, “What is the cause of aging?” Their mathematics is not in question, but the process of somatic evolution that they model bears no obvious relation to aging as it has been characterized in humans. Regrettably, their result has been caricatured in the popular press to discredit medical research toward delayed aging.

Reply to Mitteldorf and Fahy: Aging is still inevitable

Paul Nelson, and Joanna Masel

We stand by our claim that aging is inevitable in multicellular organisms. However, our model of somatic evolution uses sign arguments and so does not inform the rate of aging nor the extent to which aging can be delayed. While we use the term “somatic mutation,” we explicitly define this to include any change in cell phenotype that can be inherited by daughter cells or …

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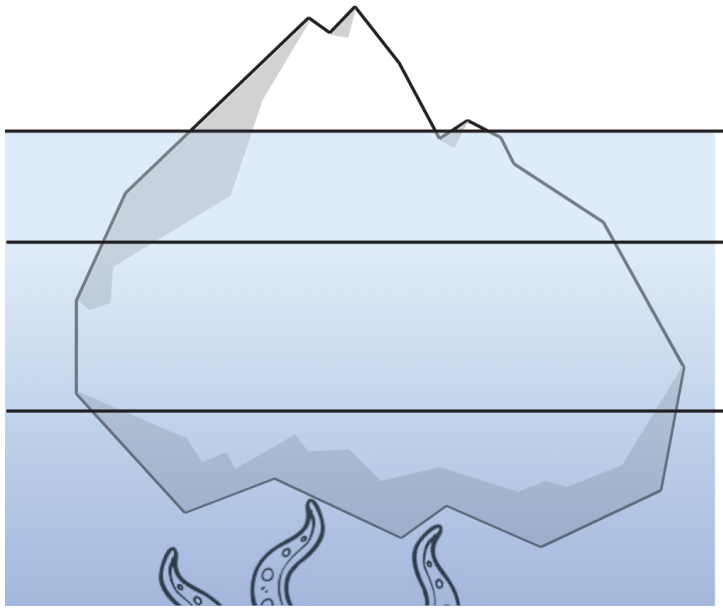
Aging and the rise of somatic cancer-associated mutations in normal tissues

Rosa Ana Risques, Scott R. Kennedy

DNA mutations are inevitable. Despite proficient DNA repair mechanisms, somatic cells accumulate mutations during development and aging, generating cells with different genotypes within the same individual, a phenomenon known as somatic mosaicism. While the existence of somatic mosaicism has long been recognized, in the last five years, advances in sequencing have provided unprecedented resolution to characterize the extent and nature of somatic genetic variation. Collectively, these new studies are revealing a previously uncharacterized aging phenotype: the accumulation of clones with cancer driver mutations. Here, we summarize the most recent findings, which converge in the novel notion that cancer-associated mutations are prevalent in normal tissue and accumulate with aging.



Mutation Type	Prevalence	Limit of Detection
Small CNVs and rearrangements	3% of older individuals	10% Sanger Seq.
SNV and small in/dels in selectable genes (large clones)	10% of older individuals	2-10% Standard NGS
SNV and small in/dels in selectable genes (small clones)	>95% of older individuals	0.001-0.1% Error-corrected NGS
SNV and small in/dels across genome (late arising or unselected event)	All cells in all people	Single genome Single-cell Seq. & Error-corrected NGS

OTHER RESEARCH

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CRISPR-Based Chromatin Remodeling of the Endogenous *Oct4* or *Sox2* Locus Enables Reprogramming to Pluripotency

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PlumX Metrics

DOI: https://doi.org/10.1016/j.stem.2017.12.001 | CrossMark

Article Info

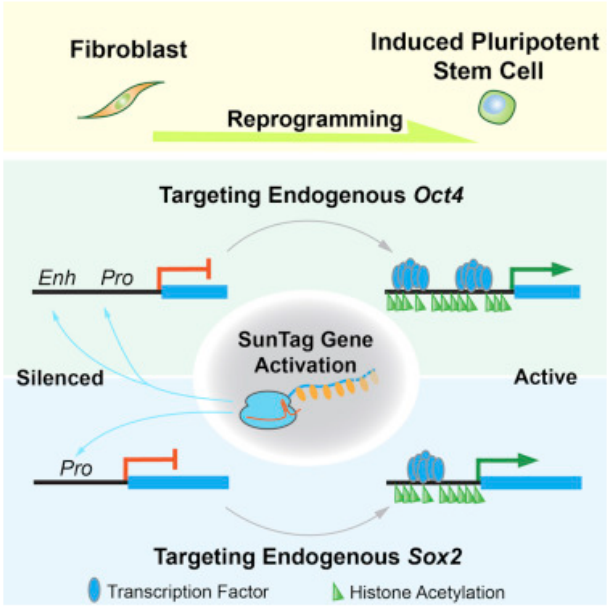
Highlights

- Endogenous *Oct4* and *Sox2* can be targeted and activated by CRISPR activation
- Activation of endogenous *Oct4* or *Sox2* triggers reprogramming to pluripotency
- *Oct4* promoter and enhancer are simultaneously remodeled by dCas9-SunTag-p300core
- Authentic induced pluripotent stem cells are generated with CRISPR activation

Summary

Generation of induced pluripotent stem cells typically requires the ectopic expression of transcription factors to reactivate the pluripotency network. However, it remains largely unclear what remodeling events on endogenous chromatin trigger reprogramming toward induced pluripotent stem cells (iPSCs). Toward this end, we employed CRISPR activation to precisely target and remodel endogenous gene loci of *Oct4* and *Sox2*. Interestingly, we found that single-locus targeting of *Sox2* was sufficient to remodel and activate *Sox2*, which was followed by the induction of other pluripotent genes and establishment of the pluripotency network. Simultaneous remodeling of the *Oct4* promoter and enhancer also triggered reprogramming. Authentic pluripotent cell lines were established in both cases. Finally, we showed that targeted manipulation of histone acetylation at the *Oct4* gene locus could also initiate reprogramming. Our study generated authentic iPSCs with CRISPR activation through precise epigenetic remodeling of endogenous loci and shed light on how targeted chromatin remodeling triggers pluripotency induction.

Graphical Abstract



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Cloning of Macaque Monkeys by Somatic Cell Nuclear Transfer

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Publication stage: In Press Corrected Proof

PlumX Metrics

DOI: https://doi.org/10.1016/j.cell.2018.01.020

Article Info

Highlights

- Somatic cell nuclear transfer (SCNT) using fetal fibroblasts yielded two live monkeys
- Epigenetic modulators promoted development and pregnancy rate of SCNT embryos
- SCNT using adult cumulus cells yielded live births of monkeys that were short-lived
- Genetic analysis confirmed the clonal origin of the SCNT monkey offspring

Summary

Generation of genetically uniform non-human primates may help to establish animal models for primate biology and biomedical research. In this study, we have successfully cloned cynomolgus monkeys (*Macaca fascicularis*) by somatic cell nuclear transfer (SCNT). We found that injection of H3K9me3 demethylase *Kdm4d* mRNA and treatment with histone deacetylase inhibitor trichostatin A at one-cell stage following SCNT greatly improved blastocyst development and pregnancy rate of transplanted SCNT embryos in surrogate monkeys. For SCNT using fetal monkey fibroblasts, 6 pregnancies were confirmed in 21 surrogates and yielded 2 healthy babies. For SCNT using adult monkey cumulus cells, 22 pregnancies were confirmed in 42 surrogates and yielded 2 babies that were short-lived. In both cases, genetic analyses confirmed that the nuclear DNA and mitochondria DNA of the monkey offspring originated from the nucleus donor cell and the oocyte donor monkey, respectively. Thus, cloning macaque monkeys by SCNT is feasible using fetal fibroblasts.

Graphical Abstract