Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
6th of November 2016
Sven Bulterijs

Longevity Reporter

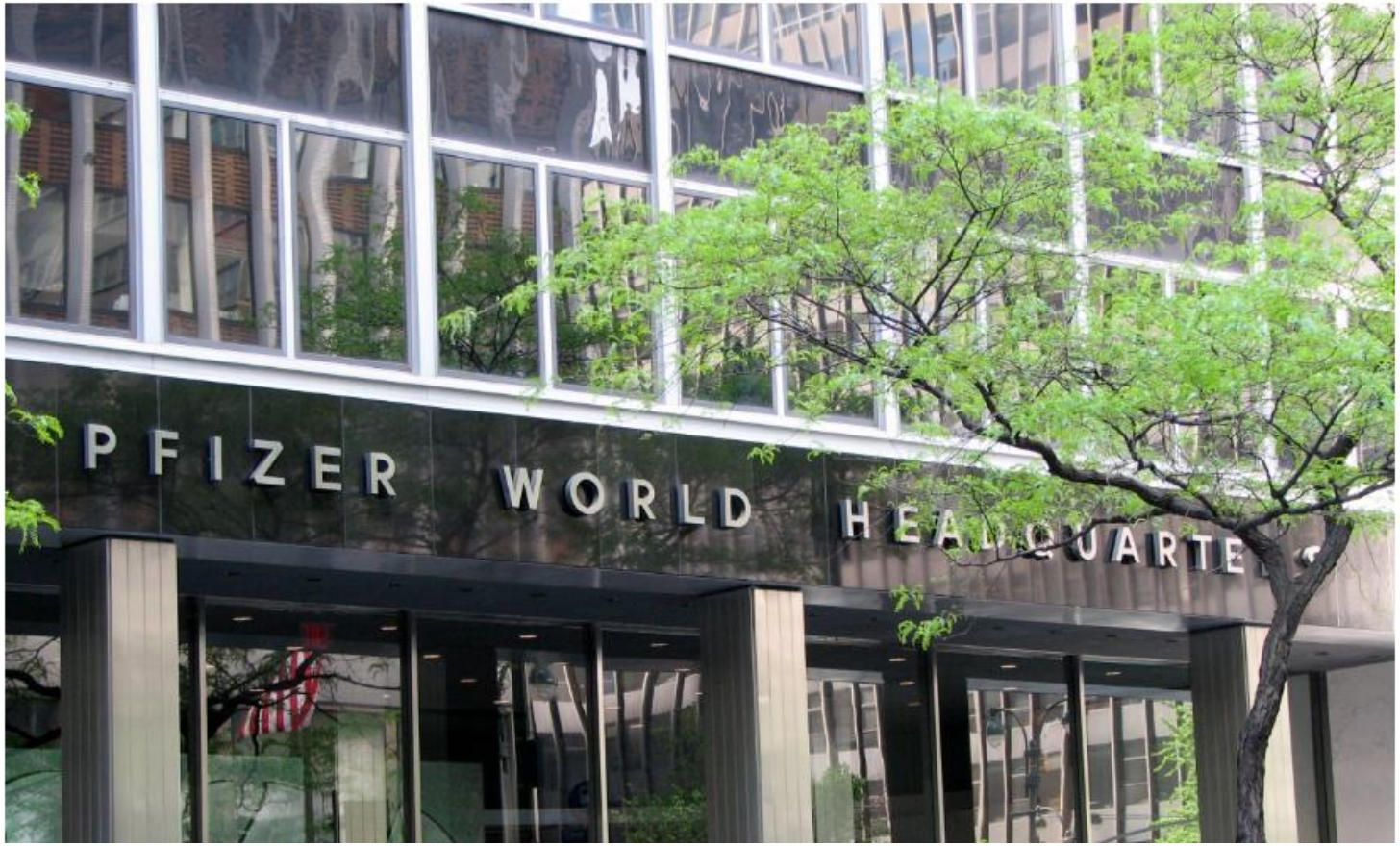
OCTOBER 11, 2016

This Years Nobel Prizes: A Link To Longevity

Heales
HEALTHY LIFE EXTENSION SOCIETY

Pfizer dumps PCSK9 inhibitor bococizumab after finding 'no value' in med

by *Ben Adams* | Nov 1, 2016 7:26am



Heales
HEALTHY LIFE EXTENSION SOCIETY

Evidence for a limit to human lifespan

Xiao Dong, Brandon Milholland & Jan Vijg

Driven by technological progress, human life expectancy has increased greatly since the nineteenth century. Demographic evidence has revealed an ongoing reduction in old-age mortality and a rise of the maximum age at death, which may gradually extend human longevity[1, 2]. Together with observations that lifespan in various animal species is flexible and can be increased by genetic or pharmaceutical intervention, these results have led to suggestions that longevity may not be subject to strict, species-specific genetic constraints. Here, by analysing global demographic data, we show that improvements in survival with age tend to decline after age 100, and that the age at death of the world's oldest person has not increased since the 1990s. Our results strongly suggest that the maximum lifespan of humans is fixed and subject to natural constraints.

"To further extend human lifespan beyond the limits set by these-longevity assurance systems would require interventions beyond improving health span, some of which are currently under investigation."

Heales
HEALTHY LIFE EXTENSION SOCIETY

Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015

Globally, life expectancy from birth increased from 61·7 years (95% uncertainty interval 61·4–61·9) in 1980 to 71·8 years (71·5–72·2) in 2015. Several countries in sub-Saharan Africa had very large gains in life expectancy from 2005 to 2015, rebounding from an era of exceedingly high loss of life due to HIV/AIDS. At the same time, many geographies saw life expectancy stagnate or decline, particularly for men and in countries with rising mortality from war or interpersonal violence. From 2005 to 2015, male life expectancy in Syria dropped by 11·3 years (3·7–17·4), to 62·6 years (56·5–70·2). Total deaths increased by 4·1% (2·6–5·6) from 2005 to 2015, rising to 55·8 million (54·9 million to 56·6 million) in 2015, but age-standardised death rates fell by 17·0% (15·8–18·1) during this time, underscoring changes in population growth and shifts in global age structures. The result was similar for non-communicable diseases (NCDs), with total deaths from these causes increasing by 14·1% (12·6–16·0) to 39·8 million (39·2 million to 40·5 million) in 2015, whereas age-standardised rates decreased by 13·1% (11·9–14·3). Globally, this mortality pattern emerged for several NCDs, including several types of cancer, ischaemic heart disease, cirrhosis, and Alzheimer's disease and other dementias. By contrast, both total deaths and age-standardised death rates due to communicable, maternal, neonatal, and nutritional conditions significantly declined from 2005 to 2015, gains largely attributable to decreases in mortality rates due to HIV/AIDS (42·1%, 39·1–44·6), malaria (43·1%, 34·7–51·8), neonatal preterm birth complications (29·8%, 24·8–34·9), and maternal disorders (29·1%, 19·3–37·1). Progress was slower for several causes, such as lower respiratory infections and nutritional deficiencies, whereas deaths increased for others, including dengue and drug use disorders. Age-standardised death rates due to injuries significantly declined from 2005 to 2015, yet interpersonal violence and war claimed increasingly more lives in some regions, particularly in the Middle East. In 2015, rotaviral enteritis (rotavirus) was the leading cause of under-5 deaths due to diarrhoea (146 000 deaths, 118 000–183 000) and pneumococcal pneumonia was the leading cause of under-5 deaths due to lower respiratory infections (393 000 deaths, 228 000–532 000), although pathogen-specific mortality varied by region. Globally, the effects of population growth, ageing, and changes in age-standardised death rates substantially differed by cause. Our analyses on the expected associations between cause-specific mortality and SDI show the regular shifts in cause of death composition and population age structure with rising SDI. Country patterns of premature mortality (measured as years of life lost [YLLs]) and how they differ from the level expected on the basis of SDI alone revealed distinct but highly heterogeneous patterns by region and country or territory. Ischaemic heart disease, stroke, and diabetes were among the leading causes of YLLs in most regions, but in many cases, intraregional results sharply diverged for ratios of observed and expected YLLs based on SDI. Communicable, maternal, neonatal, and nutritional diseases caused the most YLLs throughout sub-Saharan Africa, with observed YLLs far exceeding expected YLLs for countries in which malaria or HIV/AIDS remained the leading causes of early death.

Heales
HEALTHY LIFE EXTENSION SOCIETY

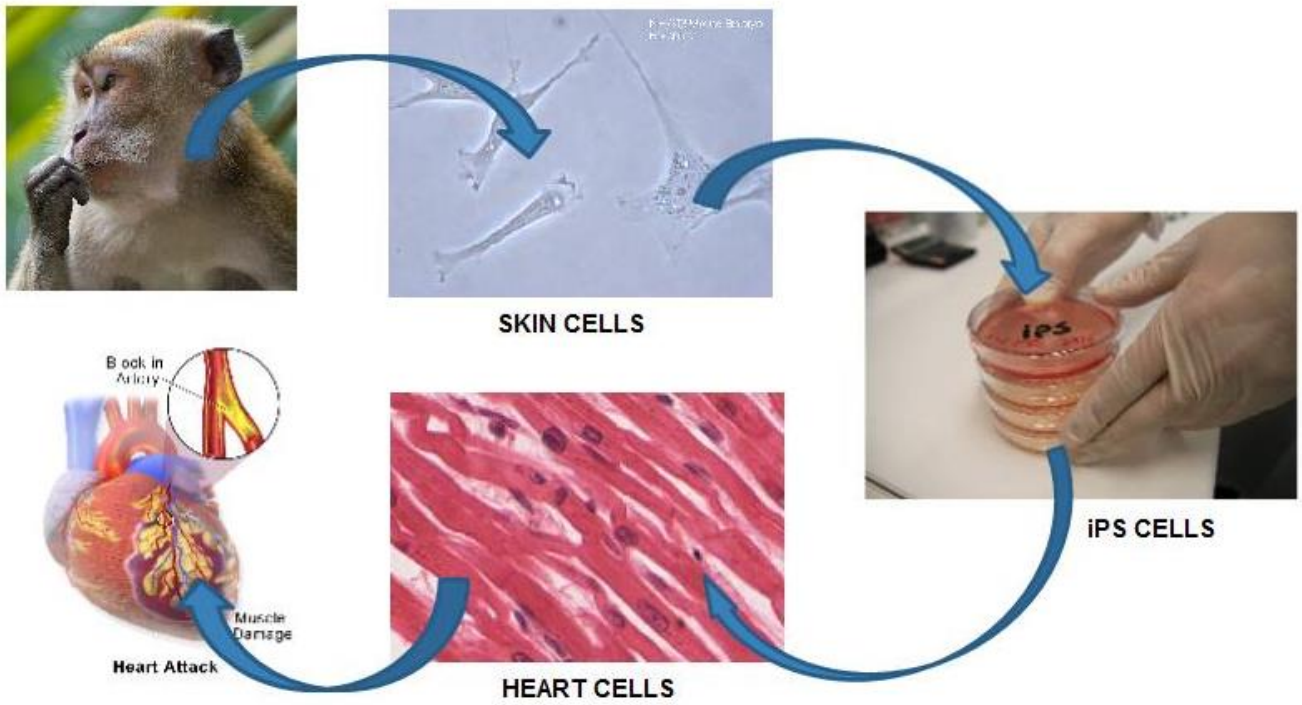
Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts

Induced pluripotent stem cells (iPSCs) constitute a potential source of autologous patient-specific cardiomyocytes for cardiac repair, providing a major benefit over other sources of cells in terms of immune rejection. However, autologous transplantation has substantial challenges related to manufacturing and regulation. Although major histocompatibility complex (MHC)-matched allogeneic transplantation is a promising alternative strategy[1], few immunological studies have been carried out with iPSCs. Here we describe an allogeneic transplantation model established using the cynomolgus monkey (*Macaca fascicularis*), the MHC structure of which is identical to that of humans. Fibroblast-derived iPSCs were generated from a MHC haplotype (HT4) homozygous animal and subsequently differentiated into cardiomyocytes (iPSC-CMs). Five HT4 heterozygous monkeys were subjected to myocardial infarction followed by direct intra-myocardial injection of iPSC-CMs. The grafted cardiomyocytes survived for 12 weeks with no evidence of immune rejection in monkeys treated with clinically relevant doses of methylprednisolone and tacrolimus, and showed electrical coupling with host cardiomyocytes as assessed by use of the fluorescent calcium indicator G-CaMP7.09. Additionally, transplantation of the iPSC-CMs improved cardiac contractile function at 4 and 12 weeks after transplantation; however, the incidence of ventricular tachycardia was transiently, but significantly, increased when compared to vehicle-treated controls. Collectively, our data demonstrate that allogeneic iPSC-CM transplantation is sufficient to regenerate the infarcted non-human primate heart; however, further research to control post-transplant arrhythmias is necessary.

Longevity Reporter

OCTOBER 16, 2016

Stem Cells Fix Heart Disease In Monkeys



Heales
HEALTHY LIFE EXTENSION SOCIETY

	Immune characteristic	Anti-rejection drugs	Rejection?
GROUP 1 →	Matched	3 drugs	No
GROUP 2 →	Mismatched	3 drugs	Yes
GROUP 3 →	Matched	1 drug	Yes
GROUP 4 →	Matched	No drug	Yes

Kawamura T et al. (2016). Stem Cell Reports 6: 312-320.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Senescent intimal foam cells are deleterious at all stages of atherosclerosis

Bennett G. Childs[1], Darren J. Baker[2], Tobias Wijshake[2,3], Cheryl A. Conover[4], Judith Campisi[5,6], Jan M. van Deursen[1,2,*]

Advanced atherosclerotic lesions contain senescent cells, but the role of these cells in atherogenesis remains unclear. Using transgenic and pharmacological approaches to eliminate senescent cells in atherosclerosis-prone low-density lipoprotein receptor–deficient (*Ldlr*$^{-/-}$) mice, we show that these cells are detrimental throughout disease pathogenesis. We find that foamy macrophages with senescence markers accumulate in the subendothelial space at the onset of atherosclerosis, where they drive pathology by increasing expression of key atherogenic and inflammatory cytokines and chemokines. In advanced lesions, senescent cells promote features of plaque instability, including elastic fiber degradation and fibrous cap thinning, by heightening metalloprotease production. Together, these results demonstrate that senescent cells are key drivers of atheroma formation and maturation and suggest that selective clearance of these cells by senolytic agents holds promise for the treatment of atherosclerosis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Break-induced telomere synthesis underlies alternative telomere maintenance

Robert L. Dilley, Priyanka Verma, Nam Woo Cho, Harrison D. Winters, Anne R. Wondisford & Roger A. Greenberg

Homology-directed DNA repair is essential for genome maintenance through templated DNA synthesis. Alternative lengthening of telomeres (ALT) necessitates homology-directed DNA repair to maintain telomeres in about 10–15% of human cancers. How DNA damage induces assembly and execution of a DNA replication complex (break-induced replisome) at telomeres or elsewhere in the mammalian genome is poorly understood. Here we define break-induced telomere synthesis and demonstrate that it utilizes a specialized replisome, which underlies ALT telomere maintenance. DNA double-strand breaks enact nascent telomere synthesis by long-tract unidirectional replication. Proliferating cell nuclear antigen (PCNA) loading by replication factor C (RFC) acts as the initial sensor of telomere damage to establish predominance of DNA polymerase δ (Pol δ) through its POLD3 subunit. Break-induced telomere synthesis requires the RFC–PCNA–Pol δ axis, but is independent of other canonical replisome components, ATM and ATR, or the homologous recombination protein Rad51. Thus, the inception of telomere damage recognition by the break-induced replisome orchestrates homology-directed telomere maintenance.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Nature. 2016 Oct 31. doi: 10.1038/nature20173. [Epub ahead of print]

Hypoxia induces heart regeneration in adult mice.

Nakada Y[1], Canseco DC[1], Thet S[1], Abdisalaam S[2], Asaithamby A[2], Santos CX[3], Shah A[3], Zhang H[4], Faber JE[4], Kinter MT[5], Szweda LI[5], Xing C[6], Deberardinis R[7], Oz O[8], Lu Z[9], Zhang CC[9], Kimura W[1,10], Sadek HA[1,11].

Author information

Abstract

The adult mammalian heart is incapable of regeneration following cardiomyocyte loss, which underpins the devastating impact of cardiomyopathy. Recently, it has become clear that the mammalian heart is not a post-mitotic organ. For example, the neonatal heart is capable of regenerating lost myocardium[1], and the adult heart is capable of modest self-renewal[2,3]. In both these scenarios, cardiomyocyte renewal occurs through proliferation of pre-existing cardiomyocytes, and is regulated by aerobic respiration-mediated oxidative DNA damage[4,5]. Therefore, we reasoned that systemic hypoxemia inhibits aerobic respiration and alleviates oxidative DNA damage, thereby inducing cardiomyocyte proliferation in adult mammals. Here we report that gradual exposure to severe systemic hypoxemia, where inspired oxygen is gradually decreased by 1% and maintained at 7% for two weeks, results in inhibition of oxidative metabolism, decreased reactive oxygen species (ROS) production and oxidative DNA damage, and reactivation of cardiomyocyte mitosis. Intriguingly, we found that exposure to hypoxemia 1 week after induction of myocardial infarction induces a robust regenerative response with decreased myocardial fibrosis and improvement of left ventricular systolic function. Finally, genetic fate mapping confirmed that the newly formed myocardium is derived from pre-existing cardiomyocytes. These results demonstrate that the endogenous regenerative properties of the adult mammalian heart can be reactivated by exposure to gradual systemic hypoxemia, and highlight the potential therapeutic role of hypoxia in regenerative medicine.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cell Metab. 2016 Oct 11;24(4):566-581. doi: 10.1016/j.cmet.2016.09.004.

NAD+ Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair.

Fang EF[1], Kassahun H[2], Croteau DL[1], Scheibye-Knudsen M[3], Marosi K[4], Lu H[1], Shamanna RA[1], Kalyanasundaram S[5], Bollineni RC[6], Wilson MA[4], Iser WB[4], Wollman BN[1], Morevati M[3], Li J[7], Kerr JS[1], Lu Q[1], Waltz TB[1], Tian J[1], Sinclair DA[8], Mattson MP[9], Nilsen H[2], Bohr VA[10].

⊕ Author information

Abstract

Ataxia telangiectasia (A-T) is a rare autosomal recessive disease characterized by progressive neurodegeneration and cerebellar ataxia. A-T is causally linked to defects in ATM, a master regulator of the response to and repair of DNA double-strand breaks. The molecular basis of cerebellar atrophy and neurodegeneration in A-T patients is unclear. Here we report and examine the significance of increased PARylation, low NAD^+, and mitochondrial dysfunction in ATM-deficient neurons, mice, and worms. Treatments that replenish intracellular NAD^+ reduce the severity of A-T neuropathology, normalize neuromuscular function, delay memory loss, and extend lifespan in both animal models. Mechanistically, treatments that increase intracellular NAD^+ also stimulate neuronal DNA repair and improve mitochondrial quality via mitophagy. This work links two major theories on aging, DNA damage accumulation, and mitochondrial dysfunction through nuclear DNA damage-induced nuclear-mitochondrial signaling, and demonstrates that they are important pathophysiological determinants in premature aging of A-T, pointing to therapeutic interventions.

Published by Elsevier Inc.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Age (Dordr). 2016 Sep 2. [Epub ahead of print]

Combined statin and angiotensin-converting enzyme (ACE) inhibitor treatment increases the lifespan of long-lived F1 male mice.

Spindler SR[1], Mote PL[2], Flegal JM[3].

⊕ Author information

Abstract

Statins, such as simvastatin, and ACE inhibitors (ACEis), such as ramipril, are standard therapies for the prevention and treatment of cardiovascular diseases. These types of drugs are commonly administered together. More recently, angiotensin II type 1 receptor (AT1R) antagonists, such as candesartan cilexetil (candesartan), have been used in the place of, or in combination with, ACEis. Here, we investigated the effects of simvastatin and ramipril single and combination therapy, and candesartan treatment on the lifespan of isocalorically fed, long-lived, B6C3F1 mice. Males were used for their relative endocrine simplicity and to minimize animal usage. The drugs were administered daily in food. The simvastatin and ramipril combination therapy significantly increased the mean and median lifespan by 9 %. In contrast, simvastatin, ramipril, or candesartan monotherapy was ineffective. All groups consumed the same number of calories. Simvastatin, alone or administered with ramipril, decreased body weight without changing caloric consumption, suggesting it may alter energy utilization in mice. Combination therapy elevated serum triglyceride and glucose levels, consistent with altered energy homeostasis. Few significant or consistent differences were found in mortality-associated pathologies among the groups. Simvastatin treatment did not reduce normal serum cholesterol or lipid levels in these mice, suggesting that the longevity effects may stem from the pleiotropic, non-cholesterol-related, effects of statins. Together, the results suggest that statins and ACEis together may enhance mouse longevity. Statins and ACE inhibitors are generally well-tolerated, and in combination, they have been shown to increase the lifespan of normotensive, normocholesterolemic humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging (Albany NY). 2016 Oct 28. doi: 10.18632/aging.101078. [Epub ahead of print]

Human exceptional longevity: transcriptome from centenarians is distinct from septuagenarians and reveals a role of Bcl-xL in successful aging.

Borras C[1], Abdelaziz KM[1], Gambini J[1], Serna E[1], Inglés M[2], de la Fuente M[3], Garcia I[4,5], Matheu A[4,5], Sanchís P[6], Belenguer A[6], Errigo A[7], Avellana JA[6], Barettino A[8], Lloret-Fernández C[8], Flames N[8], Pes G[7], Rodriguez-Mañas L, Viña J[1].

Author information

Abstract

Centenarians not only enjoy an extraordinary aging, but also show a compression of morbidity. Using functional transcriptomic analysis of peripheral blood mononuclear cells (PMBC) we identified 1721 mRNAs differentially expressed by centenarians when compared with septuagenarians and young people. Sub-network analysis led us to identify Bcl - xL as an important gene up-regulated in centenarians. It is involved in the control of apoptosis, cellular damage protection and also in modulation of immune response, all associated to healthy aging. Indeed, centenarians display lower plasma cytochrome C levels, higher mitochondrial membrane potential and also less cellular damage accumulation than septuagenarians. Leukocyte chemotaxis and NK cell activity are significantly impaired in septuagenarians compared with young people whereas centenarians maintain them. To further ascertain the functional role of Bcl- xL in cellular aging, we found thay lymphocytes from septuagenarians transduced with Bcl-xL display a reduction in senescent-related markers. Finally, to demonstrate the role of BcL-xL in longevity at the organism level, *C. elegans* bearing a gain of function mutation in the BcL-xL ortholog *ced-9*, showed a significant increase in mean and maximal life span. These results show that mRNA expression in centenarians is unique and reveals that BcL- xL plays an important role in exceptional aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

13

Lower circulating insulin-like growth factor-I is associated with better cognition in females with exceptional longevity without compromise to muscle mass and function

Leland Perice [1], Nir Barzilai [2, 3], Joe Verghese [2, 4], Erica F. Weiss [4], Roee Holtzer [4, 5], Pinchas Cohen [6], Sofiya Milman [2]

Mutations that reduce somatotropic signaling result in improved lifespan and health-span in model organisms and humans. However, whether reduced circulating insulin-like growth factor-I (IGF-I) level is detrimental to cognitive and muscle function in older adults remains understudied. A cross-sectional analysis was performed in Ashkenazi Jews with exceptional longevity (age ≥95 years). Cognition was assessed using the Mini-Mental State Examination and muscle function with the chair rise test, grip-strength, and gait speed. Muscle mass was estimated using the skeletal muscle index. Serum IGF-I was measured with liquid chromatography mass spectrometry. In gender stratified age-adjusted logistic regression analysis, females with IGF-I levels in the first tertile had lower odds of being cognitively impaired compared to females with IGF-I levels within the upper two tertiles, OR (95% CI) 0.39 (0.19-0.82). The result remained significant after adjustment for multiple parameters. No significant association was identified in males between IGF-I and cognition. No relationship was found between IGF-I tertiles and muscle function and muscle mass in females or males. Lower circulating IGF-I is associated with better cognitive function in females with exceptional longevity, with no detriment to skeletal muscle mass and function.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Extended Twilight among Isogenic *C. elegans* Causes a Disproportionate Scaling between Lifespan and Health

Although many genetic factors and lifestyle interventions are known to affect the mean lifespan of animal populations, the physiological variation displayed by individuals across their lifespans remains largely uncharacterized. Here, we use a custom culture apparatus to continuously monitor five aspects of aging physiology across hundreds of isolated *Caenorhabditis elegans* individuals kept in a constant environment from hatching until death. Aggregating these measurements into an overall estimate of senescence, we find two chief differences between longer- and shorter-lived individuals. First, though long- and short-lived individuals are physiologically equivalent in early adulthood, longer-lived individuals experience a lower rate of physiological decline throughout life. Second, and counter-intuitively, long-lived individuals have a disproportionately extended "twilight" period of low physiological function. While longer-lived individuals experience more overall days of good health, their proportion of good to bad health, and thus their average quality of life, is systematically lower than that of shorter-lived individuals. We conclude that, within a homogeneous population reared under constant conditions, the period of early-life good health is comparatively uniform, and the most plastic period in the aging process is end-of-life senescence.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Arterioscler Thromb Vasc Biol. 2016 Oct 20. pii: ATVBAHA.116.308271. [Epub ahead of print]

Estimating the Population Impact of Lp(a) Lowering on the Incidence of Myocardial Infarction and Aortic Stenosis.

Afshar M[1], Kamstrup PR[1], Williams K[1], Sniderman AD[1], Nordestgaard BG[1], Thanassoulis G[2].

Author information

Abstract

OBJECTIVE: High lipoprotein(a) (Lp[a]) is the most common genetic dyslipidemia and is a causal factor for myocardial infarction (MI) and aortic stenosis (AS). We sought to estimate the population impact of Lp(a) lowering that could be achieved in primary prevention using the therapies in development.

APPROACH AND RESULTS: We used published data from 2 prospective cohorts. High Lp(a) was defined as ≥50 mg/dL (≈20th percentile). Relative risk, attributable risk, the attributable risk percentage, population attributable risk, and the population attributable risk percentage were calculated as measures of the population impact. For MI, the event rate was 4.0% versus 2.8% for high versus low Lp(a) (relative risk, 1.46; 95% confidence interval [CI], 1.45-1.46). The attributable risk was 1.26% (95% CI, 1.24-1.27), corresponding to 31.3% (95% CI, 31.0-31.7) of the excess MI risk in those with high Lp(a). The population attributable risk was 0.21%, representing a population attributable risk percentage of 7.13%. For AS, the event rate was 1.51% versus 0.78% for high versus low Lp(a) (relative risk, 1.95; 95% CI, 1.94-1.97). The attributable risk was 0.74% (95% CI, 0.73-0.75), corresponding to 48.8% (95% CI, 48.3-49.3) of the excess AS risk in those with high Lp(a). The population attributable risk was 0.13%, representing a population attributable risk percentage of 13.9%. In sensitivity analyses targeting the top 10% of Lp(a), the population attributable risk percentage was 5.2% for MI and 7.8% for AS.

CONCLUSION: Lp(a) lowering among the top 20% of the population distribution for Lp(a) could prevent 1 in 14 cases of MI and 1 in 7 cases of AS, suggesting a major impact on reducing the burden of cardiovascular disease. Targeting the top 10% could prevent 1 in 20 MI cases and 1 in 12 AS cases.

Exp Gerontol. 2016 Sep 13;85:33-40. doi: 10.1016/j.exger.2016.09.010. [Epub ahead of print]

"What makes some rats live so long?" The mitochondrial contribution to longevity through balance of mitochondrial dynamics and mtDNA content.

Picca A[1], Pesce V[1], Sirago G[1], Fracasso F[1], Leeuwenburgh C[2], Lezza AM[3].

Author information

Abstract

Extremely interesting for aging research are those individuals able to reach older ages still with functions similar to those of younger counterparts. We examined liver samples from ad libitum-fed old (28-month-old, AL-28) and ad libitum-fed very old (32-month-old, AL-32) rats for a number of markers, relevant for mitochondrial functionality and mitochondrial DNA (mtDNA) content. As for the mtDNA content and the protein amounts of the citrate synthase and the antioxidant peroxiredoxin III there were no significant changes in the AL-32 animals. No significant longevity-related change was found for TFAM amount, but a 50% reduction in the amount of the Lon protease, responsible for turnover of TFAM inside mitochondria, characterized the AL-32 rats. No longevity-related change was observed also for the amounts of the mtDNA repair enzymes OGG1 and APE1, whereas the intra-mitochondrial amount of the cytochrome c protein showed a 50% increase in the AL-32 rats, indicating a likely reduced initiation of the intrinsic apoptotic pathway. Totally unexpected was the doubling of two proteins, very relevant for mitochondrial dynamics, namely MFN2 and DRP1, in the AL-32 rats. This prompted us to the calculation of all individual fusion indexes that grouped together in the AL-32 rats, while in the AL-28 animals were very different. We found a strong positive correlation between the fusion indexes and the respective mtDNA contents in two AL-28 and four AL-32 rats. This supports the idea that the limited prevalence of fusion above a still active fission should have ensured a functional mitochondrial network and should have led to a quite narrow range of high mtDNA contents, likely the best-suitable for extended longevity. Our findings strongly suggest that, among the multiple causes leading to the longevity of the AL-32 rats, the maintenance of an adult-like balance of mitochondrial dynamics seems to be very relevant for the regulation of mtDNA content and functionality.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Gut microbiota signatures of longevity

Fanli Kong[4], Yutong Hua[4], Bo Zeng, Ruihong Ning, Ying Li[5], Jiangchao Zhao[5,6]

[4] Co-first authors

[5] Co-senior author

[6] Lead Contact

DOI: http://dx.doi.org/10.1016/j.cub.2016.08.015 | CrossMark

Altmetric 16

Summary | Full Text | Images | References | Supp. Info. | Comments

Summary

An aging global population poses substantial challenges to society [1] . Centenarians are a model for healthy aging because they have reached the extreme limit of life by escaping, surviving, or delaying chronic diseases [2] . The genetics of centenarians have been extensively examined [3] , but less is known about their gut microbiotas. Recently, Biagi *et al.* [4] characterized the gut microbiota in Italian centenarians and semi-supercentenarians. Here, we compare the gut microbiota of Chinese long-living people with younger age groups, and with the results from the Italian population [4] , to identify gut-microbial signatures of healthy aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Age-related accrual of methylomic variability is linked to fundamental ageing mechanisms.

Slieker RC[1], van Iterson M[1], Luijk R[1], Beekman M[1], Zhernakova DV[2], Moed MH[1], Mei H[3], van Galen M[4], Deelen P[2], Bonder MJ[2], Zhernakova A[2], Uitterlinden AG[5], Tigchelaar EF[2], Stehouwer CD[6], Schalkwijk CG[6], van der Kallen CJ[6], Hofman A[7], van Heemst D[8], de Geus EJ[9], van Dongen J[9], Deelen J[1], van den Berg LH[10], van Meurs J[5], Jansen R[11], 't Hoen PA[4], Franke L[2], Wijmenga C[2], Veldink JH[10], Swertz MA[12], van Greevenbroek MM[6], van Duijn CM[13], Boomsma DI[9]; BIOS consortium, Slagboom PE[1], Heijmans BT[14].

⊕ Author information

Abstract

BACKGROUND: Epigenetic change is a hallmark of ageing but its link to ageing mechanisms in humans remains poorly understood. While DNA methylation at many CpG sites closely tracks chronological age, DNA methylation changes relevant to biological age are expected to gradually dissociate from chronological age, mirroring the increased heterogeneity in health status at older ages.

RESULTS: Here, we report on the large-scale identification of 6366 age-related variably methylated positions (aVMPs) identified in 3295 whole blood DNA methylation profiles, 2044 of which have a matching RNA-seq gene expression profile. aVMPs are enriched at polycomb repressed regions and, accordingly, methylation at those positions is associated with the expression of genes encoding components of polycomb repressive complex 2 (PRC2) in trans. Further analysis revealed trans-associations for 1816 aVMPs with an additional 854 genes. These trans-associated aVMPs are characterized by either an age-related gain of methylation at CpG islands marked by PRC2 or a loss of methylation at enhancers. This distinct pattern extends to other tissues and multiple cancer types. Finally, genes associated with aVMPs in trans whose expression is variably upregulated with age (733 genes) play a key role in DNA repair and apoptosis, whereas downregulated aVMP-associated genes (121 genes) are mapped to defined pathways in cellular metabolism.

CONCLUSIONS: Our results link age-related changes in DNA methylation to fundamental mechanisms that are thought to drive human ageing.

REVIEWS/COMMENTS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Curr Opin Lipidol. 2016 Dec;27(6):597-604.

Proprotein convertase subtilisin kexin type 9 inhibitors: update from clinical trials to real-world experience.

Farnier M[1].

Author information

Abstract

PURPOSE OF REVIEW: After the approval of alirocumab and evolocumab, the first two monoclonal antibodies (mAbs) targeting proprotein convertase subtilisin kexin type 9 (PCSK9), this review provides an update on recent PCSK9 inhibitors data and describes recommendations for the use before the results of the ongoing cardiovascular endpoint trials.

RECENT FINDINGS: New studies and complementary analysis of phase III trials have consistently shown that alirocumab and evolocumab are highly effective in reducing LDL-cholesterol and to some extent lipoprotein (a). Some preliminary findings coming from exploratory and post-hoc analyses of the longer-term safety phase III trials and meta-analyses suggest that these mAbs can decrease the incidence of cardiovascular events. Whether or not mAbs targeting PCSK9 definitively reduce the incidence of cardiovascular events without safety concerns shall be demonstrated with the ongoing cardiovascular outcome trials. Waiting these outcome trials and given the high cost of these mAbs, groups of experts have proposed as priorities groups of patients with familial hypercholesterolemia and with atherosclerotic cardiovascular disease who have substantially elevated LDL-cholesterol on maximally tolerated statin/ezetimibe therapy.

SUMMARY: Before the results of large cardiovascular outcome trials, PCSK9 inhibitors should be only used in some categories of patients with familial hypercholesterolemia and/or with atherosclerotic cardiovascular disease.

PMID: 27755114 DOI: 10.1097/MOL.0000000000000356

Drug Discov Today. 2016 Oct 26. pii: S1359-6446(16)30388-9. doi: 10.1016/j.drudis.2016.10.010. [Epub ahead of print]

Amyloid beta modulators and neuroprotection in Alzheimer's disease: a critical appraisal.

Kuruva CS[1], Reddy PH[2].

Author information

Abstract

Multiple cellular changes have been identified as being involved in Alzheimer's disease (AD) pathogenesis, including mitochondrial damage, synaptic loss, amyloid beta (Aβ) production and/or accumulation, inflammatory responses, and phosphorylated tau formation and/or accumulation. Studies have established that Aβ-induced synaptic dysfunction is dependent on abnormal amyloid precursor protein (APP) processing caused by β- and γ-secretases, resulting in the generation of Aβ. The Aβ formed as a result of abnormal APP processing induces phosphorylated tau and activates glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase-5 (CDK5). Here, we review the latest research on the development of Aβ modulators for neuroprotection in AD. We also review the use of molecular inhibitors as therapeutic targets in AD.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mitochondrial form, function and signalling in aging

Ignacio Amigo, Fernanda M. da Cunha, Maria Fernanda Forni, Wilson Garcia-Neto, Pâmela A. Kakimoto, Luis A. Luévano-Martínez, Felipe Macedo, Sergio L. Menezes-Filho, Julia Peloggia, Alicia J. Kowaltowski

Aging is often accompanied by a decline in mitochondrial mass and function in different tissues. Additionally, cell resistance to stress is frequently found to be prevented by higher mitochondrial respiratory capacity. These correlations strongly suggest mitochondria are key players in aging and senescence, acting by regulating energy homeostasis, redox balance and signalling pathways central in these processes. However, mitochondria display a wide array of functions and signalling properties, and the roles of these different characteristics are still widely unexplored. Furthermore, differences in mitochondrial properties and responses between tissues and cell types, and how these affect whole body metabolism are also still poorly understood. This review uncovers aspects of mitochondrial biology that have an impact upon aging in model organisms and selected mammalian cells and tissues.

OTHER RESEARCH