Heales

HEALTHY LIFE EXTENSION SOCIETY

Scientific News
6th of May 2018
Sven Bulterijs

Heales
HEALTHY LIFE EXTENSION SOCIETY

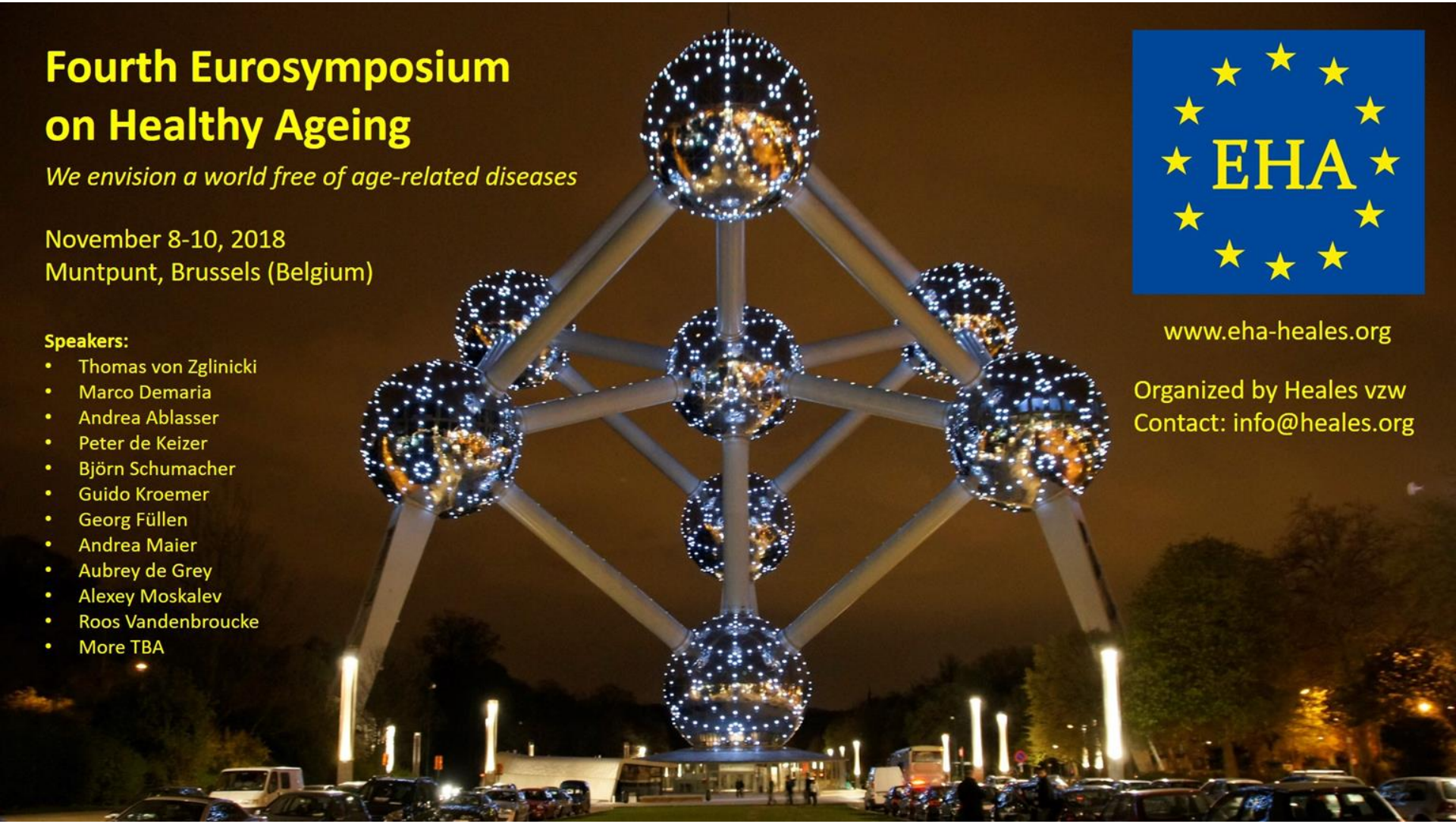
Fourth Eurosymposium on Healthy Ageing

We envision a world free of age-related diseases

November 8-10, 2018
Muntpunt, Brussels (Belgium)

Speakers:

- Thomas von Zglinicki
- Marco Demaria
- Andrea Ablasser
- Peter de Keizer
- Björn Schumacher
- Guido Kroemer
- Georg Füllen
- Andrea Maier
- Aubrey de Grey
- Alexey Moskalev
- Roos Vandenbroucke
- More TBA



EHA

www.eha-heales.org

Organized by Heales vzw
Contact: info@heales.org

Heales
HEALTHY LIFE EXTENSION SOCIETY

Neurodegenerative diseases have genetic hallmarks of autoinflammatory disease

Robert I Richards ✉, Sarah A Robertson, Daniel L Kastner

Human Molecular Genetics, ddy139, https://doi.org/10.1093/hmg/ddy139
Published: 19 April 2018 **Article history** ▾

Abstract

The notion that one common pathogenic pathway could account for the various clinically distinguishable, typically late-onset neurodegenerative diseases might appear unlikely given the plethora of diverse primary causes of neurodegeneration. On the contrary, an autoinflammatory pathogenic mechanism allows diverse genetic and environmental factors to converge into a common chain of causality. Inflammation has long been known to correlate with neurodegeneration. Until recently this relationship was seen as one of consequence rather than cause – with inflammatory cells and events acting to "clean up the mess" after neurological injury. This explanation is demonstrably inadequate and it is now clear that inflammation is at the very least, rate-limiting for neurodegeneration (and more likely, a principal underlying cause in most if not all neurodegenerative diseases), protective in its initial acute phase, but pernicious in its latter chronic phase.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Gain of toxic apolipoprotein E4 effects in human iPSC-derived neurons is ameliorated by a small-molecule structure corrector

Efforts to develop drugs for Alzheimer's disease (AD) have shown promise in animal studies, only to fail in human trials, suggesting a pressing need to study AD in human model systems. Using human neurons derived from induced pluripotent stem cells that expressed apolipoprotein E4 (ApoE4), a variant of the APOE gene product and the major genetic risk factor for AD, we demonstrated that ApoE4-expressing neurons had higher levels of tau phosphorylation, unrelated to their increased production of amyloid-β (Aβ) peptides, and that they displayed GABAergic neuron degeneration. ApoE4 increased Aβ production in human, but not in mouse, neurons. Converting ApoE4 to ApoE3 by gene editing rescued these phenotypes, indicating the specific effects of ApoE4. Neurons that lacked APOE behaved similarly to those expressing ApoE3, and the introduction of ApoE4 expression recapitulated the pathological phenotypes, suggesting a gain of toxic effects from ApoE4. Treatment of ApoE4-expressing neurons with a small-molecule structure corrector ameliorated the detrimental effects, thus showing that correcting the pathogenic conformation of ApoE4 is a viable therapeutic approach for ApoE4-related AD.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A Reassessment of Genes Modulating Aging in Mice Using Demographic Measurements of the Rate of Aging

João Pedro de Magalhães, Louise Thompson, Izabella de Lima, Dale Gaskill, Xiaoyu Li, Daniel Thornton, Chenhao Yang and Daniel Palmer

Many studies have reported genetic interventions that have an effect on mouse life span; however, it is crucial to discriminate between manipulations of aging and aging-independent causes of life extension. Here, we used the Gompertz equation to determine whether previously reported aging-related mouse genes statistically affect the demographic rate of aging. Of 30 genetic manipulations previously reported to extend life span, for only two we found evidence of retarding demographic aging: *Cisd2* and *hMTH1*. Of 24 genetic manipulations reported to shorten life span and induce premature aging features, we found evidence of five accelerating demographic aging: *Casp2*, *Fn1*, *IKK*-β, *JunD*, and *Stub1*. Overall, our reassessment found that only 15% of the genetic manipulations analyzed significantly affected the demographic rate of aging as predicted, suggesting that a relatively small proportion of interventions affecting longevity do so by regulating the rate of aging. By contrast, genetic manipulations affecting longevity tend to impact on aging-independent mortality. Our meta-analysis of multiple mouse longevity studies also reveals substantial variation in the controls used across experiments, suggesting that a short life span of controls is a potential source of bias. Overall, the present work leads to a reassessment of genes affecting the aging process in mice, with broad implications for our understanding of the genetics of mammalian aging and which genes may be more promising targets for drug discovery.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Comparative metabolomics of aging in a long-lived bat: Insights into the physiology of extreme longevity

Hope C. Ball, Shiva Ievari-Shariati, Lisa Noelle Cooper, Michel Aliani

Vespertilionid bats (Mammalia: Order Chiroptera) live 3–10 times longer than other mammals of an equivalent body size. At present, nothing is known of how bat fecal metabolic profiles shift with age in any taxa. This study established the feasibility of using a non-invasive, fecal metabolomics approach to examine age-related differences in the fecal metabolome of young and elderly adult big brown bats (*Eptesicus fuscus*) as an initial investigation into using metabolomics for age determination. Samples were collected from captive, known-aged big brown bats (*Eptesicus fuscus*) from 1 to over 14 years of age: these two ages represent age groups separated by approximately 75% of the known natural lifespan of this taxon. Results showed 41 metabolites differentiated young (n = 22) and elderly (n = 6) *Eptesicus*. Significant differences in metabolites between young and elderly bats were associated with tryptophan metabolism and incomplete protein digestion. Results support further exploration of the physiological mechanisms bats employ to achieve exceptional longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Comparative transcriptomics across 14 *Drosophila* species reveals signatures of longevity

Siming Ma, Andrei S. Avanesov, Emily Porter, Byung Cheon Lee, Marco Mariotti, Nadezhda Zemskaya, Roderic Guigo, Alexey A. Moskalev, Vadim N. Gladyshev

Lifespan varies dramatically among species, but the biological basis is not well understood. Previous studies in model organisms revealed the importance of nutrient sensing, mTOR, NAD/sirtuins, and insulin/IGF1 signaling in lifespan control. By studying life-history traits and transcriptomes of 14 *Drosophila* species differing more than sixfold in lifespan, we explored expression divergence and identified genes and processes that correlate with longevity. These longevity signatures suggested that longer-lived flies upregulate fatty acid metabolism, downregulate neuronal system development and activin signaling, and alter dynamics of RNA splicing. Interestingly, these gene expression patterns resembled those of flies under dietary restriction and several other lifespan-extending interventions, although on the individual gene level, there was no significant overlap with genes previously reported to have lifespan-extension effects. We experimentally tested the lifespan regulation potential of several candidate genes and found no consistent effects, suggesting that individual genes generally do not explain the observed longevity patterns. Instead, it appears that lifespan regulation across species is modulated by complex relationships at the system level represented by global gene expression.

An epigenetic biomarker of aging for lifespan and healthspan

Morgan E. Levine [1], Ake T. Lu [1], Austin Quach [1], Brian H. Chen [2], Themistocles L. Assimes [3], Stefania Bandinelli [4], Lifang Hou [5], Andrea A. Baccarelli [6], James D. Stewart [7], Yun Li [8], Eric A. Whitsel [7, 9], James G Wilson [10], Alex P Reiner [11], Abraham Aviv [12], Kurt Lohman [12], Yongmei Liu [14], Luigi Ferrucci [2, *], Steve Horvath [1, 15, *]

Identifying reliable biomarkers of aging is a major goal in geroscience. While the first generation of epigenetic biomarkers of aging were developed using chronological age as a surrogate for biological age, we hypothesized that incorporation of composite clinical measures of phenotypic age that capture differences in lifespan and healthspan may identify novel CpGs and facilitate the development of a more powerful epigenetic biomarker of aging. Using an innovative two-step process, we develop a new epigenetic biomarker of aging, DNAm PhenoAge, that strongly outperforms previous measures in regards to predictions for a variety of aging outcomes, including all-cause mortality, cancers, healthspan, physical functioning, and Alzheimer's disease. While this biomarker was developed using data from whole blood, it correlates strongly with age in every tissue and cell tested. Based on an in-depth transcriptional analysis in sorted cells, we find that increased epigenetic, relative to chronological age, is associated with increased activation of pro-inflammatory and interferon pathways, and decreased activation of transcriptional/translational machinery, DNA damage response, and mitochondrial signatures. Overall, this single epigenetic biomarker of aging is able to capture risks for an array of diverse outcomes across multiple tissues and cells, and provide insight into important pathways in aging.

Int J Endocrinol Metab. 2017 Dec 30;16(1):e12089. doi: 10.5812/ijem.12089. eCollection 2018 Jan.

Comparison of Two Calorie-Reduced Diets of Different Carbohydrate and Fiber Contents and a Simple Dietary Advice Aimed to Modify Carbohydrate Intake on Glycemic Control and Inflammatory Markers in Type 2 Diabetes: A Randomized Trial.

Ghalandari H[1], Kamalpour M[1], Alimadadi A[2], Nasrollahzadeh J[1].

Author information

Abstract

OBJECTIVES: The aim of this study was to compare the effect of a simple dietary advice with two energy-restricted diets with different carbohydrate and fiber contents on anthropometric, biochemical, and inflammatory markers over an 8-wk intervention period in individuals with diabetes.

METHODS: Forty-seven patients with type 2 diabetes (31 women and 16 men; age: 52.9 ± 8.0 years, body mass index: 29.5 ± 4.9 $kg.m^{-2}$) completed an 8-wk randomized intervention trial that compared a simple dietary advice aimed to modulate carbohydrate intake (n = 13) with the two calorie-restricted (CR) diets (25% caloric restriction from total energy requirements) differing with regard to carbohydrate and fiber content, one with higher fiber (CRHF) containing 55% energy from carbohydrate plus a tablespoon of psyllium powder (n = 18) and the other with lower carbohydrate (CRLC) containing 40% energy from carbohydrate plus placebo powder (n = 16). Weight, plasma concentrations of glucose, insulin, lipids, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) were determined at baseline and after 8 weeks.

RESULTS: The mean change of body weight and plasma lipids were not different between the groups. Fasting plasma insulin and the homeostasis model assessment of insulin resistance (HOMA-IR) were significantly lower in the CRHF group (changes from baseline values in simple advice, CRHF, and CRLC were 1.3 ± 1.9, -1.0 ± 1.2, and 0.3 ± 3.1 μIL/mL for insulin and 0.5 ± 0.7, -0.3 ± 0.6, and 0.2 ± 0.9 for HOMA-IR, respectively). The levels of IL-6 significantly decreased in the CRHF and CRLC groups (changes from baseline values in simple advice, CRHF, and CRLC were 7.5 ± 6.8, -1.2 ± 4.7, and -4.2 ± 5.6 pg/mL, respectively). TNF-α levels were significantly lower only in the CRHF compared to the advice group ($P < 0.05$).

CONCLUSIONS: Our results suggest that in comparison with simple advice to modify carbohydrate intake, a calorie-restricted, moderate carbohydrate diet supplemented with psyllium has better effects on plasma insulin and pro-inflammatory cytokines in patients with type 2 diabetes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Caloric restriction increases lifespan but affects brain integrity in grey mouse lemur primates

The health benefits of chronic caloric restriction resulting in lifespan extension are well established in many short-lived species, but the effects in humans and other primates remain controversial. Here we report the most advanced survival data and the associated follow-up to our knowledge of age-related alterations in a cohort of grey mouse lemurs (*Microcebus murinus*, lemurid primate) exposed to a chronic moderate (30%) caloric restriction. Compared to control animals, caloric restriction extended lifespan by 50% (from 6.4 to 9.6 years, median survival), reduced aging-associated diseases and preserved loss of brain white matter in several brain regions. However, caloric restriction accelerated loss of grey matter throughout much of the cerebrum. Cognitive and behavioural performances were, however, not modulated by caloric restriction. Thus chronic moderate caloric restriction can extend lifespan and enhance health of a primate, but it affects brain grey matter integrity without affecting cognitive performances.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Chronic Supplementation With a Mitochondrial Antioxidant (MitoQ) Improves Vascular Function in Healthy Older Adults

Matthew J. Rossman, Jessica R. Santos-Parker, Chelsea A.C. Steward, Nina Z. Bispham, Lauren M. Cuevas, Hannah L. Rosenberg, Kayla A. Woodward, Michel Chonchol, Rachel A. Gioscia-Ryan, Michael P. Murphy, Douglas R. Seals

Excess reactive oxygen species production by mitochondria is a key mechanism of age-related vascular dysfunction. Our laboratory has shown that supplementation with the mitochondrial-targeted antioxidant MitoQ improves vascular endothelial function by reducing mitochondrial reactive oxygen species and ameliorates arterial stiffening in old mice, but the effects in humans are unknown. Here, we sought to translate our preclinical findings to humans and determine the safety and efficacy of MitoQ. Twenty healthy older adults (60–79 years) with impaired endothelial function (brachial artery flow–mediated dilation <6%) underwent 6 weeks of oral supplementation with MitoQ (20 mg/d) or placebo in a randomized, placebo-controlled, double-blind, crossover design study. MitoQ was well tolerated, and plasma MitoQ was higher after the treatment versus placebo period ($P<0.05$). Brachial artery flow–mediated dilation was 42% higher after MitoQ versus placebo ($P<0.05$); the improvement was associated with amelioration of mitochondrial reactive oxygen species–related suppression of endothelial function (assessed as the increase in flow-mediated dilation with acute, supratherapeutic MitoQ [160 mg] administration; n=9; $P<0.05$). Aortic stiffness (carotid–femoral pulse wave velocity) was lower after MitoQ versus placebo ($P<0.05$) in participants with elevated baseline levels (carotid–femoral pulse wave velocity >7.60 m/s; n=11). Plasma oxidized LDL (low-density lipoprotein), a marker of oxidative stress, also was lower after MitoQ versus placebo ($P<0.05$). Participant characteristics, endothelium-independent dilation (sublingual nitroglycerin), and circulating markers of inflammation were not different (all $P>0.1$). These findings in humans extend earlier preclinical observations and suggest that MitoQ and other therapeutic strategies targeting mitochondrial reactive oxygen species may hold promise for treating age-related vascular dysfunction.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Long term rapamycin treatment improves mitochondrial DNA quality in aging mice

Jason Bielas [a], Allen Herbst [b], Kevin Widjaja [c], Jessica Hui [c], Judd M. Aiken [b], Debbie McKenzie [d], Richard A. Miller [e], Susan V. Brooks [f], Jonathan Wanagat [c]

Age-induced mitochondrial DNA deletion mutations may underlie cell loss and tissue aging. Rapamycin extends mouse lifespan and modulates mitochondrial quality control. We hypothesized that reduced deletion mutation abundance may contribute to rapamycin's life extension effects. To test this hypothesis, genetically heterogeneous male and female mice were treated with rapamycin, compounded in chow at 14 or 42 ppm, from 9 months to 22 months of age. Mice under a 40% dietary restriction were included as a control known to protect mtDNA quality. To determine if chronic rapamycin treatment affects mitochondrial DNA quality, we assayed mtDNA deletion frequency and electron transport chain deficient fiber abundances in mouse quadriceps muscle.

At 42 ppm rapamycin, we observed a 57% decrease in deletion frequency, a 2.8-fold decrease in ETC deficient fibers, and a 3.4-fold increase in the number of mice without electron transport chain deficient fibers. We observed a similar trend with the 14 ppm dose. DR significantly decreased ETC deficient fiber abundances with a trend toward lower mtDNA deletion frequency. The effects of rapamycin treatment on mitochondrial DNA quality were greatest in females at the highest dose. Rapamycin treatment at 14 ppm did not affect muscle mass or function. Dietary restriction also reduced deletion frequency and ETC deficient fibers. These data support the concept that the lifespan extending effects of rapamycin treatment result from enhanced mitochondrial DNA quality.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Blocking negative effects of senescence in human skin fibroblasts with a plant extract

There is increasing evidence that senescent cells are a driving force behind many age-related pathologies and that their selective elimination increases the life- and healthspan of mice. Senescent cells negatively affect their surrounding tissue by losing their cell specific functionality and by secreting a pro-tumorigenic and pro-inflammatory mixture of growth hormones, chemokines, cytokines and proteases, termed the senescence-associated secretory phenotype (SASP). Here we identified an extract from the plant *Solidago virgaurea* subsp. *alpestris*, which exhibited weak senolytic activity, delayed the acquisition of a senescent phenotype and induced a papillary phenotype with improved functionality in human dermal fibroblasts. When administered to stress-induced premature senescent fibroblasts, this extract changed their global mRNA expression profile and particularly reduced the expression of various SASP components, thereby ameliorating the negative influence on nearby cells. Thus, the investigated plant extract represents a promising possibility to block age-related loss of tissue functionality.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Spontaneous DNA damage to the nuclear genome promotes senescence, redox imbalance and aging

Accumulation of senescent cells over time contribute to aging and age-related diseases. However, what drives senescence *in vivo* is not clear. Here we used a genetic approach to determine if spontaneous nuclear DNA damage is sufficient to initiate senescence in mammals. *Ercc1*$^{-/\Delta}$ mice with reduced expression of ERCC1-XPF endonuclease have impaired capacity to repair the nuclear genome. *Ercc1*$^{-/\Delta}$ mice accumulated spontaneous, oxidative DNA damage more rapidly than wild-type (WT) mice. As a consequence, senescent cells accumulated more rapidly in *Ercc1*$^{-/\Delta}$ mice compared to repair-competent animals. However, the levels of DNA damage and senescent cells in *Ercc1*$^{-/\Delta}$ mice never exceeded that in old WT mice. Surprisingly, reactive oxygen species (ROS) levels were increased in tissues of *Ercc1*$^{-/\Delta}$ mice to an extent identical to naturally-aged WT mice. Increased enzymatic production of ROS and decreased antioxidants contributed to the elevation in oxidative stress in both *Ercc1*$^{-/\Delta}$ and aged WT mice. Chronic treatment of *Ercc1*$^{-/\Delta}$ mice with the mitochondrial-targeted radical scavenger XJB-5-131 attenuated oxidative DNA damage, senescence and age-related pathology. Our findings indicate that nuclear genotoxic stress arises, at least in part, due to mitochondrial-derived ROS, and this spontaneous DNA damage is sufficient to drive increased levels of ROS, cellular senescence, and the consequent age-related physiological decline.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Advanced maturation of human cardiac tissue grown from pluripotent stem cells

Kacey Ronaldson-Bouchard, Stephen P. Ma, Keith Yeager, Timothy Chen, LouJin Song, Dario Sirabella, Kumi Morikawa, Diogo Teles, Masayuki Yazawa & Gordana Vunjak-Novakovic

Cardiac tissues generated from human induced pluripotent stem cells (iPSCs) can serve as platforms for patient-specific studies of physiology and disease[1,2,3,4,5,6]. However, the predictive power of these models is presently limited by the immature state of the cells[1, 2, 5, 6]. Here we show that this fundamental limitation can be overcome if cardiac tissues are formed from early-stage iPSC-derived cardiomyocytes soon after the initiation of spontaneous contractions and are subjected to physical conditioning with increasing intensity over time. After only four weeks of culture, for all iPSC lines studied, such tissues displayed adult-like gene expression profiles, remarkably organized ultrastructure, physiological sarcomere length (2.2 μm) and density of mitochondria (30%), the presence of transverse tubules, oxidative metabolism, a positive force–frequency relationship and functional calcium handling. Electromechanical properties developed more slowly and did not achieve the stage of maturity seen in adult human myocardium. Tissue maturity was necessary for achieving physiological responses to isoproterenol and recapitulating pathological hypertrophy, supporting the utility of this tissue model for studies of cardiac development and disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mice lacking the mitochondrial exonuclease MGME1 accumulate mtDNA deletions without developing progeria

Replication of mammalian mitochondrial DNA (mtDNA) is an essential process that requires high fidelity and control at multiple levels to ensure proper mitochondrial function. Mutations in the mitochondrial genome maintenance exonuclease 1 (*MGME1*) gene were recently reported in mitochondrial disease patients. Here, to study disease pathophysiology, we generated *Mgme1* knockout mice and report that homozygous knockouts develop depletion and multiple deletions of mtDNA. The mtDNA replication stalling phenotypes vary dramatically in different tissues of *Mgme1* knockout mice. Mice with MGME1 deficiency accumulate a long linear subgenomic mtDNA species, similar to the one found in mtDNA mutator mice, but do not develop progeria. This finding resolves a long-standing debate by showing that point mutations of mtDNA are the main cause of progeria in mtDNA mutator mice. We also propose a role for MGME1 in the regulation of replication and transcription termination at the end of the control region of mtDNA.

REVIEWS/COMMENTS/ EDITORIALS

Special issue on tissue engineering

Trends in Biotechnology

SUPPORTS OPEN ACCESS

Articles in press | Latest issue | Special issues | All issues | About the journal ↗ | Follow journal

Volume 36, Issue 4

Pages 337-472 (April 2018)

< Previous vol/issue | Next vol/issue >

Special issue on cell senescence

Senescent cells: a therapeutic target for cardiovascular disease

Bennett G. Childs, ... , Hu Li, Jan M. van Deursen

Published April 2, 2018

Citation Information: *J Clin Invest*. 2018;128(4):1217-1228. https://doi.org/10.1172/JCI95146.

View: Text | PDF

Senescent cells and osteoarthritis: a painful connection

Ok Hee Jeon, ... , Judith Campisi, Jennifer H. Elisseeff

Published April 2, 2018

Citation Information: *J Clin Invest*. 2018;128(4):1229-1237. https://doi.org/10.1172/JCI95147.

View: Text | PDF

Mechanisms and functions of cellular senescence

Nicolás Herranz, Jesús Gil

Published April 2, 2018

Citation Information: *J Clin Invest*. 2018;128(4):1238-1246. https://doi.org/10.1172/JCI95148.

View: Text | PDF

Strategies targeting cellular senescence

Yossi Ovadya, Valery Krizhanovsky

Published April 2, 2018

Citation Information: *J Clin Invest*. 2018;128(4):1247-1254. https://doi.org/10.1172/JCI95149.

View: Text | PDF

Heales
HEALTHY LIFE EXTENSION SOCIETY

Front Med (Lausanne). 2018 Apr 17;5:104. doi: 10.3389/fmed.2018.00104. eCollection 2018.

Genomic Instabilities, Cellular Senescence, and Aging: *In Vitro, In Vivo* and Aging-Like Human Syndromes.

Lidzbarsky G[1], Gutman D[1], Shekhidem HA[1], Sharvit L[1], Atzmon G[1].

Author information

Abstract

As average life span and elderly people prevalence in the western world population is gradually increasing, the incidence of age-related diseases such as cancer, heart diseases, diabetes, and dementia is increasing, bearing social and economic consequences worldwide. Understanding the molecular basis of aging-related processes can help extend the organism's health span, i.e., the life period in which the organism is free of chronic diseases or decrease in basic body functions. During the last few decades, immense progress was made in the understanding of major components of aging and healthy aging biology, including genomic instability, telomere attrition, epigenetic changes, proteostasis, nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and intracellular communications. This progress has been made by three spear-headed strategies: *in vitro* (cell and tissue culture from various sources), *in vivo* (includes diverse model and non-model organisms), both can be manipulated and translated to human biology, and the study of aging-like human syndromes and human populations. Herein, we will focus on current repository of genomic "senescence" stage of aging, which includes health decline, structural changes of the genome, faulty DNA damage response and DNA damage, telomere shortening, and epigenetic alterations. Although aging is a complex process, many of the "hallmarks" of aging are directly related to DNA structure and function. This review will illustrate the variety of these studies, done in *in vitro, in vivo* and human levels, and highlight the unique potential and contribution of each research level and eventually the link between them.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Recent insights into the cellular and molecular determinants of aging

Linhao Ruan, Xi Zhang, Rong Li

J Cell Sci 2018 131: jcs210831 doi: 10.1242/jcs.210831 Published 2 February 2018

Article | Figures & tables | Info & metrics | PDF

ABSTRACT

Aging is the gradual decline of physiological functions and organismal fitness, which leads to age-dependent fitness loss, diseases and eventually mortality. Understanding the cause of aging constitutes one of most intriguing areas of research in biology. On both the cellular and molecular levels, it has been hypothesized that there are aging determinants to control the onset and progression of aging, including the loss of beneficial components and accumulation of detrimental factors. This Review highlights the recent advance in identifying various factors that affect the aging process, focusing on how these determinants affect the lifespan and fitness of a cell or organism. With more and more aging determinants revealed, further understanding about their functions and interconnections could enable the development of specific intervention to extend healthy lifespan and reduce the risk of age-related diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Physiological basis for sex-specific differences in longevity

Catherine J Cheng, James F Nelson
Show more

https://doi.org/10.1016/j.cophys.2018.04.003

Highlights

- Sex differences in longevity are striking.
- Sex differences in response to lifespan extending interventions are common.
- Behavior and social factors only partly account for the sex differences in mortality.
- Intrinsic biological factors also underlie sex differences in mortality.
- New methods enable disentanglement of chromosomal from gonadal effects.

The female survival advantage is incredibly robust, spanning almost all ages and societies in the past two centuries. While sociobehavioral factors account for part of the mortality differential, the female survival advantage extends beyond sex differences in risk-taking and aggression. Several physiological explanations have been proposed for broad protection against various chronic diseases and mortality in females, but much work remains to be done before we can fully understand how sex influences aging and longevity. Recent methods enable the disentanglement of classical gonadal steroid effects from those of sex chromosomes. Understanding the basis for sex differences in aging will ultimately lead to improved sex-specific therapies for increasing healthy longevity in both women and men.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mitochondrial Proteostasis in the Context of Cellular and Organismal Health and Aging

Erica A Moehle[1], Koning Shen[1] and Andrew Dillin[2*]

+ Author Affiliations

* Corresponding author; email: dillin@berkeley.edu

Author contributions: E.A.M., K.S., and A.D. writing-original draft; E.A.M., K.S., and A.D. writing-review and editing; A.D. supervision; A.D. funding acquisition.

Abstract

As a central hub of cellular metabolism and signaling, the mitochondrion is a crucial organelle whose dysfunction can cause disease and whose activity is intimately connected to aging. We review how the mitochondrial network maintains proteomic integrity, how mitochondrial proteotoxic stress is communicated and resolved in the context of the entire cell, and how mitochondrial systems function in the context of organismal health and aging. A deeper understanding of how mitochondrial protein quality control mechanisms are coordinated across these distinct biological levels should help explain why these mechanisms fail with age and, ultimately, how routes to intervention might be attained.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Adipose tissue inflammation in aging

Theresa Mau [a], Raymond Yung [b]

Show more

https://doi.org/10.1016/j.exger.2017.10.014

Abstract

Adipose tissue has traditionally been viewed as an organ of interest within studies of obesity and diet-associated metabolic disorders. However, as studies reveal the role white adipose tissue plays as an energy storage, a lipid metabolism site, and an adipokine secretor, it has become recognized as an organ of importance for metabolic health in both the young obese and the old obese. Within the realms of aging research, the pursuit of senolytics has taken the field's spotlight, where the clearance of senescent cells has shown to attenuate aspects of age-related disorders. More interestingly, these senolytics have also revealed that these senescent cells, specifically $p16^{Ink4a}$ cells, accumulate within adipose tissue, skeletal muscles, and eye (Baker et al., 2011). These results implicate the importance of adipose tissue inflammation in aging and widen the discussion on how senescent cells among other immune and non-immune cells cross paths to influence an organism's lifespan and healthspan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging, inflammation and the environment

Arsun Bektas [a, 1], Shepherd H. Schurman [b, 1], Ranjan Sen [c], Luigi Ferrucci [a]

The aging process is driven by interrelated mechanisms that lead to the emergence of characteristic phenotypes that include changes in body composition, energy production and utilization imbalance, homeostatic dysregulation, and neurodegeneration and loss of neuroplasticity. Mainstream theories of aging all recognize that the aging phenotypes result from an imbalance between stressors and stress buffering mechanisms and a resultant loss of compensatory reserve leading to accumulation of unrepaired damage. This in turn results in increased disease susceptibility, reduced functional reserve, reduced healing capacity and stress resistance, unstable health and finally failure to thrive. The resultant physical and cognitive decline that culminates with the frailty syndrome is a tipping point of healthspan and implies a high risk of system decompensation and death. Preserving physical and cognitive function is the main focus of geriatric and gerontological research, but it is important to recognize that accomplishing this goal requires a profound understanding of the molecular, cellular and physiological mechanisms that ultimately determine functional changes. In this context, the proinflammatory state of aging plays a major role. Longitudinal studies have shown that with aging most individuals tend to develop a chronic low-grade proinflammatory state, and that such a state is a strong risk factor for multimorbidity, physical and cognitive disability, frailty and death. A number of environmental factors may play an important role in modifying the proinflammatory state. We explore processes and mechanisms of aging that affect human biology and the possible links of inflammation and the environment to aging, especially those related to metabolism. We point out that longitudinal studies with a life course approach are needed to gain further mechanistic insight on the processes that lead to functional decline with aging, and the role played in this process by inflammation and environmental challenges.

Age and immunity: What is “immunosenescence”?

Graham Pawelec

Show more

https://doi.org/10.1016/j.exger.2017.10.024

Get rights and content

Highlights

- Opinion on the nature of immunosenescence
- Opinion on inflammageing
- Importance of longitudinal studies in humans

Abstract

As is apparent from the many contributions to this Special Issue of the Journal, the impact of age on immunity is nefarious, with all manner of dysregulated responses attributed to “immunosenescence”. These range from poorer responses to vaccination, lower capacity to mediate anti-cancer responses, more inflammation and tissue damage, along with autoimmunity and loss of control of persistent infections. Given the grave clinical implications of altered immune status in aged people, it is of paramount importance to understand the nature of and mechanisms responsible for “immunosenescence”. As in any rapidly developing research area, certain paradigms establish themselves early on, by necessity based on earlier and fewer data, and have a disproportionate influence on how investigators think about the subject, especially investigators from other disciplines. It may therefore be appropriate to reconsider our basic knowledge at this juncture, asking exactly what do we mean by the term “immunosenescence”? This is attempted in this contribution to the Special Issue.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?

Tamas Fulop,[1,*] Anis Larbi,[2] Gilles Dupuis,[3] Aurélie Le Page,[1] Eric H. Frost,[4] Alan A. Cohen,[5] Jacek M. Witkowski,[6] and Claudio Franceschi[7]

Author information ► Article notes ► Copyright and License information ► Disclaimer

Abstract

Go to:

The immune system is the most important protective physiological system of the organism. It has many connections with other systems and is, in fact, often considered as part of the larger neuro–endocrine–immune axis. Most experimental data on immune changes with aging show a decline in many immune parameters when compared to young healthy subjects. The bulk of these changes is termed immunosenescence. Immunosenescence has been considered for some time as detrimental because it often leads to subclinical accumulation of pro-inflammatory factors and inflamm-aging. Together, immunosenescence and inflamm-aging are suggested to stand at the origin of most of the diseases of the elderly, such as infections, cancer, autoimmune disorders, and chronic inflammatory diseases. However, an increasing number of immune-gerontologists have challenged this negative interpretation of immunosenescence with respect to its significance in aging-related alterations of the immune system. If one considers these changes from an evolutionary perspective, they can be viewed preferably as adaptive or remodeling rather than solely detrimental. Whereas it is conceivable that global immune changes may lead to various diseases, it is also obvious that these changes may be needed for extended survival/longevity. Recent cumulative data suggest that, without the existence of the immunosenescence/inflamm-aging duo (representing two sides of the same phenomenon), human longevity would be greatly shortened. This review summarizes recent data on the dynamic reassessment of immune changes with aging. Accordingly, attempts to intervene on the aging immune system by targeting its rejuvenation, it may be more suitable to aim to maintain general homeostasis and function by appropriately improving immune-inflammatory-functions.

OTHER RESEARCH

Heales
HEALTHY LIFE EXTENSION SOCIETY

"In this issue of *Cell* and in papers appearing in *Cell Reports*, *Cancer Cell*, *Cell Systems*, and *Immunity*, we are proud to present the Pan-Cancer Atlas. The Pan-Cancer Atlas is the culmination of more than a decade of work from The Cancer Genome Atlas (TCGA) consortium. By analyzing over 11,000 tumors from 33 of the most prevalent forms of cancer (see SnapShot, page 530), the atlas provides a uniquely comprehensive, in-depth, and cohesive understanding of how, where, and why tumors arise in humans."