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Sven Bulterijs

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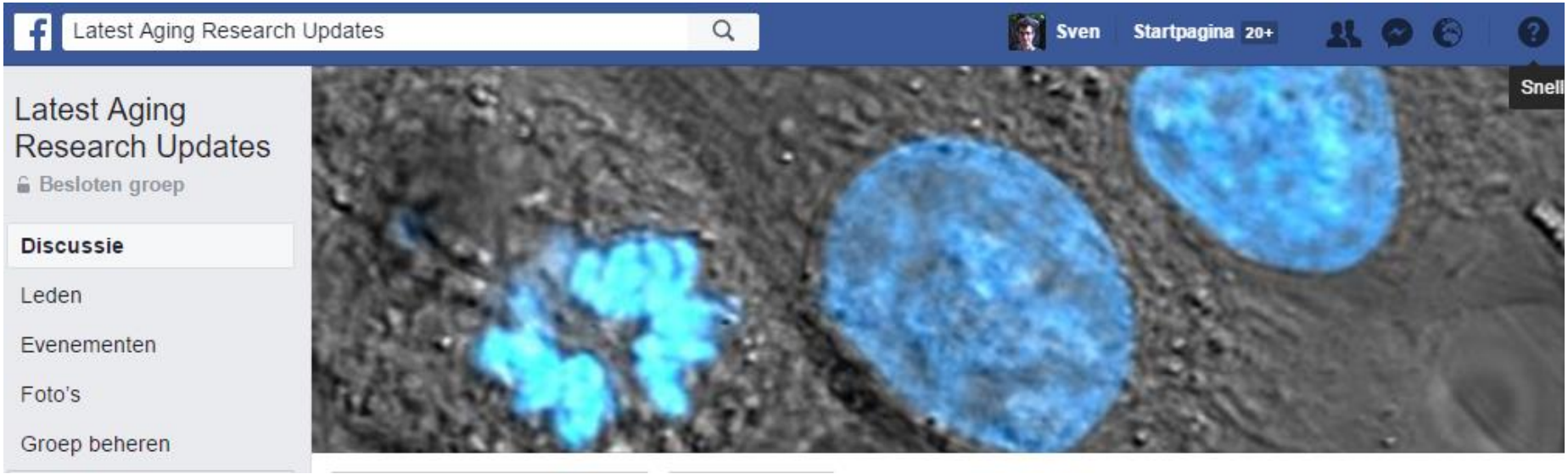

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Geroscience: Addressing the mismatch between its exciting research opportunities, its economic imperative and its current funding crisis

George M. Martin

There is at present a huge disconnect between levels of funding for basic research on fundamental mechanisms of biological aging and, given demographic projections, the anticipated enormous social and economic impacts of a litany of chronic diseases for which aging is by far the major risk factor: One valuable approach, recently instigated by Felipe Sierra & colleagues at the US National Institute on Aging, is the development of a Geroscience Interest Group among virtually all of the NIH institutes. A complementary approach would be to seek major escalations of private funding. The American Federation for Aging Research, the Paul Glenn Foundation and the Ellison Medical Foundation pioneered efforts by the private sector to provide substantial supplements to public sources of funding. It is time for our community to organize efforts towards the enhancements of such crucial contributions, especially in support of the emerging generation of young investigators, many of whom are leaving our ranks to seek alternative employment. To do so, we must provide potential donors with strong economic, humanitarian and scientific rationales. An initial approach to such efforts is briefly outlined in this manuscript as a basis for wider discussions within our community.

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2017 Alzheimer's disease facts and figures

This article describes the public health impact of Alzheimer's disease (AD), including incidence and prevalence, mortality rates, costs of care, and the overall impact on caregivers and society. The Special Report examines how the use of biomarkers may influence the AD diagnostic process and estimates of prevalence and incidence of the disease. An estimated 5.5 million Americans have Alzheimer's dementia. By mid-century, the number of people living with Alzheimer's dementia in the United States is projected to grow to 13.8 million, fueled in large part by the aging baby boom generation. Today, someone in the country develops Alzheimer's dementia every 66 seconds. By 2050, one new case of Alzheimer's dementia is expected to develop every 33 seconds, resulting in nearly 1 million new cases per year. In 2014, official death certificates recorded 93,541 deaths from AD, making AD the sixth leading cause of death in the United States and the fifth leading cause of death in Americans age ≥65 years. Between 2000 and 2014, deaths resulting from stroke, heart disease, and prostate cancer decreased 21%, 14%, and 9%, respectively, whereas deaths from AD increased 89%. The actual number of deaths to which AD contributes is likely much larger than the number of deaths from AD recorded on death certificates. In 2017, an estimated 700,000 Americans age ≥65 years will have AD when they die, and many of them will die because of the complications caused by AD. In 2016, more than 15 million family members and other unpaid caregivers provided an estimated 18.2 billion hours of care to people with Alzheimer's or other dementias. This care is valued at more than $230 billion. Average per-person Medicare payments for services to beneficiaries age ≥65 years with Alzheimer's or other dementias are more than three times as great as payments for beneficiaries without these conditions, and Medicaid payments are more than 23 times as great. Total payments in 2017 for health care, long-term care, and hospice services for people age ≥65 years with dementia are estimated to be $259 billion. In recent years, efforts to develop and validate AD biomarkers, including those detectable with brain imaging and in the blood and cerebrospinal fluid, have intensified. Such efforts could transform the practice of diagnosing AD from one that focuses on cognitive and functional symptoms to one that incorporates biomarkers. This new approach could promote diagnosis at an earlier stage of disease and lead to a more accurate understanding of AD prevalence and incidence.

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Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging

The accumulation of irreparable cellular damage restricts healthspan after acute stress or natural aging. Senescent cells are thought to impair tissue function, and their genetic clearance can delay features of aging. Identifying how senescent cells avoid apoptosis allows for the prospective design of anti-senescence compounds to address whether homeostasis can also be restored. Here, we identify FOXO4 as a pivot in senescent cell viability. We designed a FOXO4 peptide that perturbs the FOXO4 interaction with p53. In senescent cells, this selectively causes p53 nuclear exclusion and cell-intrinsic apoptosis. Under conditions where it was well tolerated in vivo, this FOXO4 peptide neutralized doxorubicin-induced chemotoxicity. Moreover, it restored fitness, fur density, and renal function in both fast aging $Xpd^{TTD/TTD}$ and naturally aged mice. Thus, therapeutic targeting of senescent cells is feasible under conditions where loss of health has already occurred, and in doing so tissue homeostasis can effectively be restored.

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Quantitative identification of senescent cells in aging and disease.

Biran A[1], Zada L[1], Abou Karam P[1], Vadai E[1], Roitman L[1], Ovadya Y[1], Porat Z[2], Krizhanovsky V[1].

Author information

Abstract

Senescent cells are present in premalignant lesions and sites of tissue damage and accumulate in tissues with age. In vivo identification, quantification and characterization of senescent cells are challenging tasks that limit our understanding of the role of senescent cells in diseases and aging. Here, we present a new way to precisely quantify and identify senescent cells in tissues on a single-cell basis. The method combines a senescence-associated beta-galactosidase assay with staining of molecular markers for cellular senescence and of cellular identity. By utilizing technology that combines flow cytometry with high-content image analysis, we were able to quantify senescent cells in tumors, fibrotic tissues, and tissues of aged mice. Our approach also yielded the finding that senescent cells in tissues of aged mice are larger than nonsenescent cells. Thus, this method provides a basis for quantitative assessment of senescent cells and it offers proof of principle for combination of different markers of senescence. It paves the way for screening of senescent cells for identification of new senescence biomarkers, genes that bypass senescence or senolytic compounds that eliminate senescent cells, thus enabling a deeper understanding of the senescent state in vivo.

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KEYWORDS: ImageStreamX; aging; cancer; cellular senescence; flow cytometry; senescence-associated beta-galactosidase

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Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment

Senescent cells (SnCs) accumulate in many vertebrate tissues with age and contribute to age-related pathologies[1, 2, 3], presumably through their secretion of factors contributing to the senescence-associated secretory phenotype (SASP)[4, 5, 6]. Removal of SnCs delays several pathologies[7, 8, 9] and increases healthy lifespan[8]. Aging and trauma are risk factors for the development of osteoarthritis (OA)[10], a chronic disease characterized by degeneration of articular cartilage leading to pain and physical disability. Senescent chondrocytes are found in cartilage tissue isolated from patients undergoing joint replacement surgery[11, 12, 13, 14], yet their role in disease pathogenesis is unknown. To test the idea that SnCs might play a causative role in OA, we used the p16-3MR transgenic mouse, which harbors a $p16^{INK4a}$ (*Cdkn2a*) promoter driving the expression of a fusion protein containing synthetic *Renilla* luciferase and monomeric red fluorescent protein domains, as well as a truncated form of herpes simplex virus 1 thymidine kinase (HSV-TK)[15, 16]. This mouse strain allowed us to selectively follow and remove SnCs after anterior cruciate ligament transection (ACLT). We found that SnCs accumulated in the articular cartilage and synovium after ACLT, and selective elimination of these cells attenuated the development of post-traumatic OA, reduced pain and increased cartilage development. Intra-articular injection of a senolytic molecule that selectively killed SnCs validated these results in transgenic, non-transgenic and aged mice. Selective removal of the SnCs from *in vitro* cultures of chondrocytes isolated from patients with OA undergoing total knee replacement decreased expression of senescent and inflammatory markers while also increasing expression of cartilage tissue extracellular matrix proteins. Collectively, these findings support the use of SnCs as a therapeutic target for treating degenerative joint disease.

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DNA damage and senescence in osteoprogenitors expressing Osx1 may cause their decrease with age

Age-related bone loss in mice results from a decrease in bone formation and an increase in cortical bone resorption. The former is accounted by a decrease in the number of postmitotic osteoblasts which synthesize the bone matrix and is thought to be the consequence of age-dependent changes in mesenchymal osteoblast progenitors. However, there are no specific markers for these progenitors, and conclusions rely on results from *in vitro* cultures of mixed cell populations. Moreover, the culprits of such changes remain unknown. Here, we have used Osx1-Cre;TdRFP mice in which osteoprogenitors express the TdRFP fluorescent protein. We report that the number of TdRFP-Osx1 cells, freshly isolated from the bone marrow, declines by more than 50% between 6 and 24 months of age in both female and male mice. Moreover, TdRFP-Osx1 cells from old mice exhibited markers of DNA damage and senescence, such as γH2AX foci, G1 cell cycle arrest, phosphorylation of p53, increased $p21^{CIP1}$ levels, as well as increased levels of GATA4 and activation of NF-κB – two major stimulators of the senescence-associated secretory phenotype (SASP). Bone marrow stromal cells from old mice also exhibited elevated expression of SASP genes, including several pro-osteoclastogenic cytokines, and increased capacity to support osteoclast formation. These changes were greatly attenuated by the senolytic drug ABT263. Together, these findings suggest that the decline in bone mass with age is the result of intrinsic defects in osteoprogenitor cells, leading to decreased osteoblast numbers and increased support of osteoclast formation.

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Adipocyte. 2017 Jan 2;6(1):62-67. doi: 10.1080/21623945.2016.1274470. Epub 2016 Dec 21.

Functionally enhanced brown adipose tissue in Ames dwarf mice.

Darcy J[1,2], Bartke A[1,2].

⊕ Author information

Abstract

Reduced insulin-like growth factor 1/insulin signaling (IIS) has been linked to extended longevity in species ranging from yeast to mammals. In mammals, this is exemplified in Ames dwarf ($Prop1^{df/df}$) mice, which have a 40%-60% increase in longevity (males and females, respectively) due to their recessive Prop1 loss-of-function mutation that results in lack of growth hormone (GH), thyroid-stimulating hormone and prolactin. Our laboratory has previously shown that Ames dwarf mice have functionally unique white adipose tissue (WAT) that improves, rather than impairs, insulin sensitivity. Because GH and thyroid hormone are integral to adipose tissue development and function, we hypothesized that brown adipose tissue (BAT) in Ames dwarf mice may also be functionally unique and/or enhanced. Here, we elaborate on our recent findings, which demonstrate that BAT is functionally enhanced in Ames dwarf mice, and suggest that BAT removal in these mice results in utilization of WAT depots as an energy source. We also discuss how our findings compare to those in other long-lived dwarf mice with altered IIS, which unlike Ames dwarf mice, are essentially euthyroid. Lastly, we provide some insights into the implications of these findings and discuss some of the necessary future work in this area.

KEYWORDS: Ames dwarf; GHRKO; brown adipose tissue; energy metabolism; growth hormone; thermogenesis; thyroid hormone

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The role of transplanted visceral fat from the long-lived growth hormone receptor knockout mice on insulin signaling

Growth hormone receptor knockout mice (GHRKO) are characterized by high insulin sensitivity and extended lifespan. Interestingly, the secretory activity of visceral fat in GHRKO mice is altered, stimulating whole body insulin sensitivity. In this study, we transplanted normal (N) mice with visceral fat pads from GHRKO or N mice to determine the role of visceral fat on the insulin signaling. We found that the transplant of visceral fat from GHRKO mice to N mice (N-GHRKO) improved whole body insulin sensitivity when comparing with sham-operated mice (N-S) and with mice that received visceral fat from N mice (N-N). This was associated with increased hepatic insulin sensitivity as observed by the increased phosphorylated insulin receptor and increased hepatic expression of *Ppara* and *Pparγ*. In conclusion, we demonstrated that visceral fat transplant from GHRKO mice into normal mice enhanced insulin sensitivity and glucose tolerance. These results further confirm the differential physiological role played by visceral adipose tissue from GH receptor deficient mice, indicating that the increase of this fat depot can be associated with beneficial effects on insulin signaling and longevity.

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Characterization of physiological defects in adult SIRT6-/- mice.

Peshti V[1], Obolensky A[2], Nahum L[1], Kanfi Y[1], Rathaus M[1], Avraham M[1], Tinman S[1], Alt FW[3], Banin E[2], Cohen HY[1].

Author information

Abstract

The NAD+-dependent SIRT6 deacetylase was shown to be a major regulator of lifespan and healthspan. Mice deficient for SIRT6 develop a premature aging phenotype and metabolic defects, and die before four weeks of age. Thus, the effect of SIRT6 deficiency in adult mice is unknown. Here we show that SIRT6-/- mice in mixed 129/SvJ/BALB/c background reach adulthood, allowing examination of SIRT6-related metabolic and developmental phenotypes in adult mice. In this mixed background, at 200 days of age, more than 80% of the female knock-out mice were alive whereas only 10% of male knock-out mice survived. In comparison to their wild-type littermates, SIRT6 deficient mice have reduced body weight, increased glucose uptake and exhibit an age-dependent progressive impairment of retinal function accompanied by thinning of retinal layers. Together, these results demonstrate a role for SIRT6 in metabolism and age-related ocular changes in adult mice and suggest a gender specific regulation of lifespan by SIRT6.

PMID: 28448551 DOI: 10.1371/journal.pone.0176371

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SIRT6 Overexpression Improves Various Aspects of Mouse Healthspan

The extension in human lifespan in the last century results in a significant increase in incidence of age related diseases. It is therefore crucial to identify key factors that control elderly healthspan. Similar to dietary restriction, mice overexpressing the NAD^+ dependent protein deacylase SIRT6 (MOSES) live longer and have reduced IGF-1 levels. However, it is as yet unknown whether SIRT6 also affects various healthspan parameters. Here, a range of age related phenotypes was evaluated in MOSES mice. In comparison to their wild-type (WT) littermates, old MOSES mice showed amelioration of a variety of age-related disorders, including: improved glucose tolerance, younger hormonal profile, reduced age-related adipose inflammation and increased physical activity. The increased activity was accompanied with increased muscle AMP-activated protein kinase (AMPK) activity. Altogether, these results indicate that overexpression of SIRT6 in mice retards important aspects of the aging process and suggest SIRT6 to be a potential therapeutic target for the treatment of a set of age-related disorders.

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Caenorhabditis elegans orthologs of human genes differentially expressed with age are enriched for determinants of longevity

We report a systematic RNAi longevity screen of 82 *Caenorhabditis elegans* genes selected based on orthology to human genes differentially expressed with age. We find substantial enrichment in genes for which knockdown increased lifespan. This enrichment is markedly higher than published genomewide longevity screens in *C. elegans* and similar to screens that preselected candidates based on longevity-correlated metrics (e.g., stress resistance). Of the 50 genes that affected lifespan, 46 were previously unreported. The five genes with the greatest impact on lifespan (>20% extension) encode the enzyme kynureninase (*kynu-1*), a neuronal leucine-rich repeat protein (*iglr-1*), a tetraspanin (*tsp-3*), a regulator of calcineurin (*rcan-1*), and a voltage-gated calcium channel subunit (*unc-36*). Knockdown of each gene extended healthspan without impairing reproduction. *kynu-1*(*RNAi*) alone delayed pathology in *C. elegans* models of Alzheimer's disease and Huntington's disease. Each gene displayed a distinct pattern of interaction with known aging pathways. In the context of published work, *kynu-1*, *tsp-3*, and *rcan-1* are of particular interest for immediate follow-up. *kynu-1* is an understudied member of the kynurenine metabolic pathway with a mechanistically distinct impact on lifespan. Our data suggest that *tsp-3* is a novel modulator of hypoxic signaling and *rcan-1* is a context-specific calcineurin regulator. Our results validate *C. elegans* as a comparative tool for prioritizing human candidate aging genes, confirm age-associated gene expression data as valuable source of novel longevity determinants, and prioritize select genes for mechanistic follow-up.

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Four Genome-Wide Association Studies Identify New Extreme Longevity Variants

Paola Sebastiani; Anastasia Gurinovich; Harold Bae; Stacy Andersen; Alberto Malovini; Gil Atzmon; Francesco Villa; Aldi T. Kraja; Danny Ben-Avraham; Nir Barzilai; ... Show more

Abstract

The search for the genetic determinants of extreme human longevity has been challenged by the phenotype's rarity and its nonspecific definition by investigators. To address these issues, we established a consortium of four studies of extreme longevity that contributed 2,070 individuals who survived to the oldest one percentile of survival for the 1900 U.S. birth year cohort. We conducted various analyses to discover longevity-associated variants (LAV) and characterized those LAVs that differentiate survival to extreme age at death (eSAVs) from those LAVs that become more frequent in centenarians because of mortality selection (eg, survival to younger years). The analyses identified new rare variants in chromosomes 4 and 7 associated with extreme survival and with reduced risk for cardiovascular disease and Alzheimer's disease. The results confirm the importance of studying truly rare survival to discover those combinations of common and rare variants associated with extreme longevity and longer health span.

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Genetic interplay between human longevity and metabolic pathways — a large-scale eQTL study

Human longevity is a complex phenotype influenced by genetic and environmental components. Unraveling the contribution of genetic vs. nongenetic factors to longevity is a challenging task. Here, we conducted a large-scale RNA-sequencing-based expression quantitative trait loci study (eQTL) with subsequent heritability analysis. The investigation was performed on blood samples from 244 individuals from Germany and Denmark, representing various age groups including long-lived subjects up to the age of 104 years. Our eQTL-based approach revealed for the first time that human longevity is associated with a depletion of metabolic pathways in a genotype-dependent and independent manner. Further analyses indicated that 20% of the differentially expressed genes are influenced by genetic variants in *cis*. The subsequent study of twins showed that the transcriptional activity of a third of the differentially regulated genes is heritable. These findings suggest that longevity-associated biological processes such as altered metabolism are, to a certain extent, also the driving force of longevity rather than just a consequence of old age.

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Am J Epidemiol. 2017 Apr 28:1-10. doi: 10.1093/aje/kww210. [Epub ahead of print]

Leukocyte Telomere Length and All-Cause, Cardiovascular Disease, and Cancer Mortality: Results From Individual-Participant-Data Meta-Analysis of 2 Large Prospective Cohort Studies.

Mons U, Müezzinler A, Schöttker B, Dieffenbach AK, Butterbach K, Schick M, Peasey A, De Vivo I, Trichopoulou A, Boffetta P, Brenner H.

Abstract

We studied the associations of leukocyte telomere length (LTL) with all-cause, cardiovascular disease, and cancer mortality in 12,199 adults participating in 2 population-based prospective cohort studies from Europe (ESTHER) and the United States (Nurses' Health Study). Blood samples were collected in 1989-1990 (Nurses' Health Study) and 2000-2002 (ESTHER). LTL was measured by quantitative polymerase chain reaction. We calculated z scores for LTL to standardize LTL measurements across the cohorts. Cox proportional hazards regression models were used to calculate relative mortality according to continuous levels and quintiles of LTL z scores. The hazard ratios obtained from each cohort were subsequently pooled by meta-analysis. Overall, 2,882 deaths were recorded during follow-up (Nurses' Health Study, 1989-2010; ESTHER, 2000-2015). LTL was inversely associated with age in both cohorts. After adjustment for age, a significant inverse trend of LTL with all-cause mortality was observed in both cohorts. In random-effects meta-analysis, age-adjusted hazard ratios for the shortest LTL quintile compared with the longest were 1.23 (95% confidence interval (CI): 1.04, 1.46) for all-cause mortality, 1.29 (95% CI: 0.83, 2.00) for cardiovascular mortality, and 1.10 (95% CI: 0.88, 1.37) for cancer mortality. In this study population with an age range of 43-75 years, we corroborated previous evidence suggesting that LTL predicts all-cause mortality beyond its association with age.

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KEYWORDS: aging; all-cause mortality; cancer mortality; cardiovascular disease mortality; cohort studies; leukocytes; telomere length

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Telomeres and the natural lifespan limit in humans

Abstract

An ongoing debate in demography has focused on whether the human lifespan has a maximal natural limit. Taking a mechanistic perspective, and knowing that short telomeres are associated with diminished longevity, we examined whether telomere length dynamics during adult life could set a maximal natural lifespan limit. We define leukocyte telomere length of 5 kb as the 'telomeric brink', which denotes a high risk of imminent death. We show that a subset of adults may reach the telomeric brink within the current life expectancy and more so for a 100-year life expectancy. Thus, secular trends in life expectancy should confront a biological limit due to crossing the telomeric brink.

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Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction

Netusha Thevaranjan[1, 2, 3, 8], Alicja Puchta[1, 2, 3, 8], Christian Schulz[1, 2, 3], Avee Naidoo[1, 2, 3], J.C. Szamosi[4], Chris P. Verschoor[1, 2, 3], Dessi Loukov[1, 2, 3], Louis P. Schenck[3, 4, 5], Jennifer Jury[4, 6],

Summary

Levels of inflammatory mediators in circulation are known to increase with age, but the underlying cause of this age-associated inflammation is debated. We find that, when maintained under germ-free conditions, mice do not display an age-related increase in circulating pro-inflammatory cytokine levels. A higher proportion of germ-free mice live to 600 days than their conventional counterparts, and macrophages derived from aged germ-free mice maintain anti-microbial activity. Co-housing germ-free mice with old, but not young, conventionally raised mice increases pro-inflammatory cytokines in the blood. In tumor necrosis factor (TNF)-deficient mice, which are protected from age-associated inflammation, age-related microbiota changes are not observed. Furthermore, age-associated microbiota changes can be reversed by reducing TNF using anti-TNF therapy. These data suggest that aging-associated microbiota promote inflammation and that reversing these age-related microbiota changes represents a potential strategy for reducing age-associated inflammation and the accompanying morbidity.

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Prevalence and incidence of sarcopenia in the very old: findings from the Newcastle 85+ Study

Introduction Recognition that an older person has sarcopenia is important because this condition is linked to a range of adverse outcomes. Sarcopenia becomes increasingly common with age, and yet there are few data concerning its descriptive epidemiology in the very old (aged 85 years and above). Our aims were to describe risk factors for sarcopenia and estimate its prevalence and incidence in a British sample of the very old.

Methods We used data from two waves (2006/07 and 2009/10) of the Newcastle 85+ Study, a cohort born in 1921 and registered with a Newcastle/North Tyneside general practice. We assessed sarcopenia status using the European Working Group on Sarcopenia in Older People (EWGSOP) definition. Grip strength was measured using a Takei digital dynamometer (Takei Scientific Instruments Ltd., Niigata, Japan), gait speed was calculated from the Timed Up and Go test, and lean mass was estimated using a Tanita-305 body fat analyzer. We used logistic regression to examine associations between risk factors for prevalent sarcopenia at baseline and incident sarcopenia at follow-up.

Results European Working Group on Sarcopenia in Older People sarcopenia was present in 21% of participants at baseline [149/719 participants, mean age 85.5 (0.4) years]. Many participants had either slow gait speed or weak grip strength (74.3%), and hence measurement of muscle mass was frequently indicated by the EWGSOP definition. Incidence data were available for 302 participants, and the incident rate was 3.7 cases per 100 person years at risk. Low Standardized Mini-Mental State Examination, lower occupational social class, and shorter duration of education were associated with sarcopenia at baseline, while low muscle mass was associated with incident sarcopenia. Low body mass index (BMI) was a risk factor for both in a graded fashion, with each unit decrease associated with increased odds of prevalent [odds ratio (OR) 1.29, 95% confidence interval (CI): 1.21, 1.37] and incident (OR 1.20, 95% CI: 1.08, 1.33) sarcopenia.

Conclusions To our knowledge, this is the first study to describe prevalence and incidence of EWGSOP sarcopenia in the very old. Low BMI was a risk factor for both current and future sarcopenia; indeed, there was some evidence that low BMI may be a reasonable proxy for low lean mass. Overall, the high prevalence of sarcopenia among the very old suggests that this group should be a focus for future research.

Keywords Sarcopenia; Very old; Risk factors; Prevalence; Incidence

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Allogeneic Human Mesenchymal Stem Cell Infusions for Aging Frailty

Background:

Impaired endogenous stem cell repair capacity is hypothesized to be a biologic basis of frailty. Therapies that restore regenerative capacity may therefore be beneficial. This Phase 1 study evaluated the safety and potential efficacy of intravenous, allogeneic, human mesenchymal stem cell (allo-hMSC)-based therapy in patients with aging frailty.

Methods:

In this nonrandomized, dose-escalation study, patients received a single intravenous infusion of allo-hMSCs: 20-million (n = 5), 100-million (n = 5), or 200-million cells (n = 5). The primary endpoint was incidence of any treatment-emergent serious adverse events measured at 1 month postinfusion. The secondary endpoints were functional efficacy domains and inflammatory biomarkers, measured at 3 and 6 months, respectively.

Results:

There were no treatment-emergent serious adverse events at 1-month postinfusion or significant donor-specific immune reactions during the first 6 months. There was one death at 258 days postinfusion in the 200-million group. In all treatment groups, 6-minute walk distance increased at 3 months (p = .02) and 6 months (p = .001) and TNF-α levels decreased at 6 months (p < .0001). Overall, the 100-million dose showed the best improvement in all parameters, with the exception of TNF-α, which showed an improvement in both the 100- and 200-million groups (p = .0001 and p = .0001, respectively). The 100-million cell-dose group also showed significant improvements in the physical component of the SF-36 quality of life assessment at all time points relative to baseline.

Conclusions:

Allo-hMSCs are safe and immunologically tolerated in aging frailty patients. Improvements in functional and immunologic status suggest that ongoing clinical development of cell-based therapy is warranted for frailty.

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Ketone bodies mimic the life span extending properties of caloric restriction.

Veech RL[1], Bradshaw PC[2], Clarke K[3], Curtis W[1], Pawlosky R[1], King MT[1].

Author information

Abstract

The extension of life span by caloric restriction has been studied across species from yeast and Caenorhabditis elegans to primates. No generally accepted theory has been proposed to explain these observations. Here, we propose that the life span extension produced by caloric restriction can be duplicated by the metabolic changes induced by ketosis. From nematodes to mice, extension of life span results from decreased signaling through the insulin/insulin-like growth factor receptor signaling (IIS) pathway. Decreased IIS diminishes phosphatidylinositol (3,4,5) triphosphate (PIP_3) production, leading to reduced PI3K and AKT kinase activity and decreased forkhead box O transcription factor (FOXO) phosphorylation, allowing FOXO proteins to remain in the nucleus. In the nucleus, FOXO proteins increase the transcription of genes encoding antioxidant enzymes, including superoxide dismutase 2, catalase, glutathione peroxidase, and hundreds of other genes. An effective method for combating free radical damage occurs through the metabolism of ketone bodies, ketosis being the characteristic physiological change brought about by caloric restriction from fruit flies to primates. A dietary ketone ester also decreases circulating glucose and insulin leading to decreased IIS. The ketone body, d-β-hydroxybutyrate (d-βHB), is a natural inhibitor of class I and IIa histone deacetylases that repress transcription of the FOXO3a gene. Therefore, ketosis results in transcription of the enzymes of the antioxidant pathways. In addition, the metabolism of ketone bodies results in a more negative redox potential of the NADP antioxidant system, which is a terminal destructor of oxygen free radicals. Addition of d-βHB to cultures of C. elegans extends life span. We hypothesize that increasing the levels of ketone bodies will also extend the life span of humans and that calorie restriction extends life span at least in part through increasing the levels of ketone bodies. An exogenous ketone ester provides a new tool for mimicking the effects of caloric restriction that can be used in future research. The ability to power mitochondria in aged individuals that have limited ability to oxidize glucose metabolites due to pyruvate dehydrogenase inhibition suggests new lines of research for preventative measures and treatments for aging and aging-related disorders. © 2017 The Authors IUBMB Life published by Wiley Periodicals, Inc. on behalf of International Union of Biochemistry and Molecular Biology, 69(5):305-314, 2017.

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Genome-Wide Mechanisms of Lifespan Extension by Dietary Restriction in Yeast

Dietary restriction is arguably the most promising non-pharmacological intervention to extend human life and health span. Yet, only few genetic regulators mediating the cellular response to dietary restriction are known, and the question remains which other transcription factors and regulatory pathways are involved. To gain a comprehensive view of how lifespan extension under dietary restriction is elicited, we compared the chronological lifespan of most gene deletions of the budding yeast Saccharomyces cerevisiae between restricted and non-restricted conditions. We identified 472 mutants with enhanced or diminished extension of lifespan relative to the WT. Functional analyses of such DR-genes revealed novel processes underlying lifespan extension specifically by dietary restriction. Importantly, our set of DR-genes allowed us to generate a prioritized catalogue of transcription factors, underscoring the relevance of cell-cycle control as a mechanism of chronological-lifespan extension in yeast. In particular, we show that the transcription factor Ste12 is needed for full lifespan extension and cell-cycle arrest in response to nutrient limitation, linking the pheromone-response pathway with cell survivorship. Our global picture of the genetic players of lifespan extension by dietary restriction highlights intricate regulatory cross-talks in aging cells.

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Nutr Healthy Aging. 2017 Mar 31;4(2):147-156. doi: 10.3233/NHA-160017.

Long-term calorie restriction in humans is not associated with indices of delayed immunologic aging: A descriptive study.

Tomiyama AJ[1], Milush JM[2], Lin J[3], Flynn JM[4], Kapahi P[4], Verdin E[5], Sinclair E[2], Melov S[4], Epel ES[6].

Author information

Abstract

BACKGROUND: Delayed immunologic aging is purported to be a major mechanism through which calorie restriction (CR) exerts its anti-aging effects in non-human species. However, in non-obese humans, the effect of CR on the immune system has been understudied relative to its effects on the cardiometabolic system. **OBJECTIVE:** To examine whether CR is associated with delayed immunologic aging in non-obese humans. **METHODS:** We tested whether long-term CR practitioners (average 10.03 years of CR) evidenced decreased expression of T cell immunosenescence markers and longer immune cell telomeres compared to gender-, race/ethnicity-, age-, and education-matched "healthy" Body Mass Index (BMI) and "overweight"/"obese" BMI groups. **RESULTS:** Long-term human CR practitioners had lower BMI ($p < 0.001$) and fasting glucose ($p < 0.001$), as expected. They showed similar frequencies of pre-senescent cells ($CD8^+CD28^-$ T cells and CD57 and PD-1 expressing T cells) to the comparison groups. Even after adjusting for covariates, including cytomegalovirus status, we observed shorter peripheral blood mononuclear cell telomeres in the CR group ($p=0.012$) and no difference in granulocyte telomeres between groups ($p=0.42$). **CONCLUSIONS:** We observed no clear evidence that CR as it is currently practiced in humans delays immune aging related to telomere length or T cell immunosenescent markers.

KEYWORDS: Caloric restriction; T-cells; cellular aging; eating behavior; immunosenescence; telomeres

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Intermittent food restriction initiated late in life prolongs lifespan and retards the onset of age-related markers in the annual fish *Nothobranchius guentheri*

Two of the most studied and widely accepted conjectures on possible aging mechanisms are the oxidative stress hypothesis and the insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway. Intermittent fasting (IF) is known to modulate aging and to prolong lifespan in a variety of organisms, but the mechanisms are still under debate. In this study, we first demonstrated that late-onset two consecutive days a week fasting, a form of IF, termed intermittent food restriction (IFR), exhibited a time-dependent effect, and long-term late-onset IFR extended the mean lifespan and maximum lifespan by approximately 3.5 and 3 weeks, respectively, in the annual fish *Nothobranchius guentheri*. We also showed that IFR reduced the accumulation of lipofuscin in the gills and the protein oxidation and lipid peroxidation levels in the muscles. Moreover, IFR was able to enhance the activities of antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase in the fish. Finally, IFR was also able to decelerate the decrease of SirT1 and Foxo3A, but accelerate the decrease of IGF-1. Collectively, our findings suggest that late-onset IFR can retard the onset of age-related markers, and prolong the lifespan of the aging fish, via a synergistic action of an anti-oxidant system and the IIS pathway. It also proposes that the combined assessment of anti-oxidant system and IIS pathway will contribute to providing a more comprehensive view of anti-aging process.

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Caloric Restriction and Healthy Life Span: Frail Phenotype of Nonhuman Primates in the Wisconsin National Primate Research Center Caloric Restriction Study

Abstract

Calorie restriction without malnutrition increases longevity and delays the onset of age-associated disorders in multiple species. Recently, greater emphasis has been placed on healthy life span and preventing frailty than on longevity. Here, we show the beneficial effect of long-term calorie restriction on frailty in later life in a nonhuman primate. Frail phenotypes were evaluated using metabolic and physical activity data and defined using the Fried index. Shrinking was defined as unintentional weight loss of greater than 5% of body weight. Weakness was indicated by decline in high intensity spontaneous physical activity. Poor endurance or exhaustion was indicated by a reduction in energy efficiency of movements. Slowness was indicated by physical activity counts in the morning. Low physical activity level was measured by total energy expenditure using doubly labeled water divided by sleeping metabolic rate. Weakness, poor endurance, slowness, and low physical activity level were significantly higher in control compared with calorie restriction ($p < .05$) as was total incidence of frailty ($p < .001$). In conclusion, we established a novel set of measurable criteria of frailty in nonhuman primates, and using these criteria, showed that calorie restriction reduces the incidence of frailty and increases healthy life span in nonhuman primates.

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Caloric Restriction and Rapamycin Differentially Alter Energy Metabolism in Yeast

Abstract

Rapamycin (RM), a drug that inhibits the mechanistic target of rapamycin (mTOR) pathway and responds to nutrient availability, seemingly mimics the effects of caloric restriction (CR) on healthy life span. However, the extent of the mechanistic overlap between RM and CR remains incompletely understood. Here, we compared the impact of CR and RM on cellular metabolic status. Both regimens maintained intracellular ATP through the chronological aging process and showed enhanced mitochondrial capacity. Comparative transcriptome analysis showed that CR had a stronger impact on global gene expression than RM. We observed a like impact on the metabolome and identified distinct metabolites affected by CR and RM. CR severely reduced the level of energy storage molecules including glycogen and lipid droplets, whereas RM did not. RM boosted the production of enzymes responsible for the breakdown of glycogen and lipid droplets. Collectively, these results provide insights into the distinct energy metabolism mechanisms induced by CR and RM, suggesting that these two anti-aging regimens might extend life span through distinctive pathways.

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Rapamycin inhibits the secretory phenotype of senescent cells by a Nrf2-independent mechanism

Senescent cells contribute to age-related pathology and loss of function, and their selective removal improves physiological function and extends longevity. Rapamycin, an inhibitor of mTOR, inhibits cell senescence *in vitro* and increases longevity in several species. Nrf2 levels have been shown to decrease with aging and silencing Nrf2 gene induces premature senescence. Therefore, we explored whether Nrf2 is involved in the mechanism by which rapamycin delays cell senescence. In wild-type (WT) mouse fibroblasts, rapamycin increased the levels of Nrf2, and this correlates with the activation of autophagy and a reduction in the induction of cell senescence, as measured by SA-β-galactosidase (β-gal) staining, senescence-associated secretory phenotype (SASP), and p16 and p21 molecular markers. In Nrf2KO fibroblasts, however, rapamycin still decreased β-gal staining and the SASP, but rapamycin did not activate the autophagy pathway or decrease p16 and p21 levels. These observations were further confirmed *in vivo* using Nrf2KO mice, where rapamycin treatment led to a decrease in β-gal staining and pro-inflammatory cytokines in serum and fat tissue; however, p16 levels were not significantly decreased in fat tissue. Consistent with literature demonstrating that the Stat3 pathway is linked to the production of SASP, we found that rapamycin decreased activation of the Stat3 pathway in cells or tissue samples from both WT and Nrf2KO mice. Our data thus suggest that cell senescence is a complex process that involves at least two arms, and rapamycin uses Nrf2 to regulate cell cycle arrest, but not the production of SASP.

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A randomized controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs

Age is the single greatest risk factor for most causes of morbidity and mortality in humans and their companion animals. As opposed to other model organisms used to study aging, dogs share the human environment, are subject to similar risk factors, receive comparable medical care, and develop many of the same age-related diseases humans do. In this study, 24 middle-aged healthy dogs received either placebo or a non-immunosuppressive dose of rapamycin for 10 weeks. All dogs received clinical and hematological exams before, during, and after the trial and echocardiography before and after the trial. Our results showed no clinical side effects in the rapamycin-treated group compared to dogs receiving the placebo. Echocardiography suggested improvement in both diastolic and systolic age-related measures of heart function (E/A ratio, fractional shortening, and ejection fraction) in the rapamycin-treated dogs. Hematological values remained within the normal range for all parameters studied; however, the mean corpuscular volume (MCV) was decreased in rapamycin-treated dogs. Based on these results, we will test rapamycin on a larger dog cohort for a longer period of time in order to validate its effects on cardiac function and to determine whether it can significantly improve healthspan and reduce mortality in companion dogs.

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Caloric Restriction Mimetics Slow Aging of Neuromuscular Synapses and Muscle Fibers

Jessica Stockinger; Nicholas Maxwell; Dillon Shapiro; Rafael deCabo; Gregorio Valdez

Abstract

Resveratrol and metformin have been shown to mimic some aspects of caloric restriction and exercise. However, it remains unknown if these molecules also slow age-related synaptic degeneration, as previously shown for caloric restriction and exercise. In this study, we examined the structural integrity of neuromuscular junctions (NMJs) in 2-year-old mice treated with resveratrol and metformin starting at 1 year of age. We found that resveratrol significantly slows aging of NMJs in the extensor digitorum longus muscle of 2-year-old mice. Resveratrol also preserved the morphology of muscle fibers in old mice. Although metformin slowed the rate of muscle fiber aging, it did not significantly affect aging of NMJs. Based on these findings, we sought to determine if resveratrol directly affects NMJs. For this, we examined postsynaptic sites, the NMJ region located on the muscle peripheral membrane, on cultured myotubes derived from C2C12 cells. We discovered that resveratrol increases the number of postsynaptic sites on myotubes exhibiting a youthful architecture, suggesting that resveratrol directly affects the NMJ. Altogether, we provide compelling evidence indicating that resveratrol slows aging of NMJs and muscle fibers.

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Metabolome analysis of effect of aspirin on *Drosophila* lifespan extension

Effective approaches for drug development involve the repurposing of existing drugs which are already approved by the FDA. Aspirin has been shown to have many health benefits since its discovery as a nonsteroidal anti-inflammatory drug (NSAID) to treat pain and inflammation. Recent experiments demonstrated the longevity effects of aspirin in *Drosophila*, but its mechanism remains to be explored. In order to elucidate the effects of drug on metabolism, we carried out the metabolic analysis of aspirin-treated flies. The results identified 404 active metabolites in addition to the extended lifespan and improved healthspan in fly. There were 28 metabolites having significant changes between aspirin-treated group and the control group, out of which 22 compounds were found to have detailed information. These compounds are reported to have important functions in energy metabolism, amino sugar metabolism, and urea metabolism, indicating that aspirin might be playing positive roles in the fly's lifespan and healthspan improvement. Because of the conservation of major longevity pathways and mechanisms in different species, the health benefits of aspirin administration could be extended to other animals and humans as well.

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Lifespan differences between queens and workers are not explained by rates of molecular damage

The biological processes that underlie senescence are of universal biological importance, yet they remain poorly understood. A popular theory proposes that senescence is the result of limited investment into mechanisms involved in the prevention and repair of molecular damage, leading to an accumulation of molecular damage with age. In ants, queen and worker lifespans differ by an order of magnitude, and this remarkable difference in lifespan has been shown to be associated with differences in the expression of genes involved in DNA and protein repair. Here we use the comet assay and Western Blotting for poly-ubiquitinated proteins to explore whether these differences in expression lead to differences in the accumulation of DNA damage (comet assay) or protein damage (protein ubiquitination) with age. Surprisingly, there was no difference between queens and workers in the rate of accumulation of DNA damage. We also found that levels of ubiquitinated proteins decreased with age, as previously reported in honeybees. This is in contrast to what has been found in model organisms such as worms and flies. Overall, these results reveal that the link between investment into macromolecular repair, age-related damage accumulation and lifespan is more complex than usually recognised.

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Moderate lifelong overexpression of tuberous sclerosis complex 1 (TSC1) improves health and survival in mice

The tuberous sclerosis complex 1/2 (TSC1/2) is an endogenous regulator of the mechanistic target of rapamycin (mTOR). While mTOR has been shown to play an important role in health and aging, the role of TSC1/2 in aging has not been fully investigated. In the current study, a constitutive TSC1 transgenic ($Tsc1^{tg}$) mouse model was generated and characterized. mTORC1 signaling was reduced in majority of the tissues, except the brain. In contrast, mTORC2 signaling was enhanced in $Tsc1^{tg}$ mice. $Tsc1^{tg}$ mice are more tolerant to exhaustive exercises and less susceptible to isoproterenol-induced cardiac hypertrophy at both young and advanced ages. $Tsc1^{tg}$ mice have less fibrosis and inflammation in aged as well as isoproterenol-challenged heart than age-matched wild type mice. The female $Tsc1^{tg}$ mice exhibit a higher fat to lean mass ratio at advanced ages than age-matched wild type mice. More importantly, the lifespan increased significantly in female $Tsc1^{tg}$ mice, but not in male $Tsc1^{tg}$ mice. Collectively, our data demonstrated that moderate increase of TSC1 expression can enhance overall health, particularly cardiovascular health, and improve survival in a gender-specific manner.

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NF-κB Immunity in the Brain Determines Fly Lifespan in Healthy Aging and Age-Related Neurodegeneration

During aging, innate immunity progresses to a chronically active state. However, what distinguishes those that "age well" from those developing age-related neurological conditions is unclear. We used *Drosophila* to explore the cost of immunity in the aging brain. We show that mutations in intracellular negative regulators of the IMD/NF-κB pathway predisposed flies to toxic levels of antimicrobial peptides, resulting in early locomotor defects, extensive neurodegeneration, and reduced lifespan. These phenotypes were rescued when immunity was suppressed in glia. In healthy flies, suppressing immunity in glial cells resulted in increased adipokinetic hormonal signaling with high nutrient levels in later life and an extension of active lifespan. Thus, when levels of IMD/NF-κB deviate from normal, two mechanisms are at play: lower levels derepress an immune-endocrine axis, which mobilizes nutrients, leading to lifespan extension, whereas higher levels increase antimicrobial peptides, causing neurodegeneration. Immunity in the fly brain is therefore a key lifespan determinant.

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How a Mutation that Slows Aging Can Also Disproportionately Extend End-of-Life Decrepitude.

Podshivalova K[1], Kerr RA[1], Kenyon C[2].

⊕ Author information

Abstract

The goal of aging research is to extend healthy, active life. For decades, C. elegans daf-2 insulin/insulin-like growth factor 1 (IGF-1) receptor mutants have served as a model for extended lifespan and youthfulness. However, a recent report suggested that their longevity is associated with an undesirable phenotype: a disproportionately long period of decrepitude at the end of life. In the human population, such an outcome would be a burden to society, bringing into question the relevance of daf-2 mutants as a model for life extension. However, here we report that, following an extended period of movement, daf-2 mutants survive longer in a decrepit state because of a beneficial trait: they are resistant to colonization of the digestive tract by dietary bacteria, a condition that leads to premature death in the wild-type and prevents their manifestation of decrepitude. If bacterial colonization is prevented, then daf-2 mutants lead both chronologically and proportionately healthier lives relative to the wild-type.

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Thyroid hormones in extreme longevity

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Abstract

The aim of the present review was to summarize knowledge about thyroid hormones (THs) and longevity. Longevity is a complex multifactorial phenomenon on which specific biological pathways, including hormonal networks involved in the regulation of homeostasis and survival, exert a strong impact. THs are the key responsible for growth, metabolism rate and energy expenditure, and help in maintaining cognition, bone and cardiovascular health. THs production and metabolism are fine tuned, and may help the organism to cope with a variety of environmental challenges. Experimental evidence suggests that hypothyroid state may favor longevity by reducing metabolism rate, oxidative stress and cell senescence. Data from human studies involving healthy subjects and centenarians seem to confirm this view, but THs changes observed in older patients affected by chronic diseases cannot be always interpreted as a protective adaptive mechanism aimed at reducing catabolism and prolonging survival. Medications, selected chronic diseases and multi-morbidity can interfere with thyroid function, and their impact is still to be elucidated.

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IGF-1 has sexually dimorphic, pleiotropic, and time-dependent effects on healthspan, pathology, and lifespan

Reduced circulating levels of IGF-1 have been proposed as a conserved anti-aging mechanism that contributes to increased lifespan in diverse experimental models. However, IGF-1 has also been shown to be essential for normal development and the maintenance of tissue function late into the lifespan. These disparate findings suggest that IGF-1 may be a pleiotropic modulator of health and aging, as reductions in IGF-1 may be beneficial for one aspect of aging, but detrimental for another. We postulated that the effects of IGF-1 on tissue health and function in advanced age are dependent on the tissue, the sex of the animal, and the age at which IGF-1 is manipulated. In this study, we examined how alterations in IGF-1 levels at multiple stages of development and aging influence overall lifespan, healthspan, and pathology. Specifically, we investigated the effects of perinatal, post-pubertal, and late-adult onset IGF-1 deficiency using genetic and viral approaches in both male and female $igf^{f/f}$ C57Bl/6 mice. Our results support the concept that IGF-1 levels early during lifespan establish the conditions necessary for subsequent healthspan and pathological changes that contribute to aging. Nevertheless, these changes are specific for each sex and tissue. Importantly, late-life IGF-1 deficiency (a time point relevant for human studies) reduces cancer risk but does not increase lifespan. Overall, our results indicate that the levels of IGF-1 during development influence late-life pathology, suggesting that IGF-1 is a developmental driver of healthspan, pathology, and lifespan.

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The influence of different calorie restriction protocols on serum pro-inflammatory cytokines, adipokines and IGF-I levels in female C57BL6 mice: short term and long term diet effects.

Dogan S[1], Ray A[2], Cleary MP[2].

Author information

Abstract

Calorie restriction (CR) is an effective intervention to prevent chronic diseases including cancer. Although many factors, i.e., sex hormones, IGF-I and mTOR have been studied in response to CR, the molecular mechanisms of CR remain to be identified. Our objective was to determine the short and long-term effects of different CR protocols on pro-inflammatory cytokines. Our hypothesis was that Intermittent CR (ICR) would result in greater inhibition of pro-inflammatory serum cytokines compared to Chronic CR (CCR) as we previously found ICR to be more protective in the prevention of mammary tumor development. From ten weeks of age female C57BL6 mice were maintained on either ad libitum (AL) fed, ICR or CCR protocols (overall CR of ~75% of AL) for up to 74 weeks of age. Blood samples were collected for measurements of serum interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), adiponectin, leptin, IGF-I and insulin at specified ages. For ICR mice samples were collected following 3 weeks of restriction (ICR-R) and after one week of refeeding (ICR-RF). In general, both modes of CR significantly reduced serum IL-6, TNF-α, IGF-I and leptin levels compared to AL with IL-6 levels 24 and 3.5 fold and TNF-α levels t 11 and 1.5 fold lower in ICR and CCR groups, respectively at study termination. There was a trend for adiponectin and insulin to be highest in ICR-RF mice. Body weights were positively correlated with IL-6, TNF-α, insulin and leptin but negatively correlated with adiponectin-to-leptin ratio. Moreover, there was a positive correlation between IL-6 and TNF-α. Beneficial effects of ICR may function through pro-inflammatory cytokine pathways.

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The Ubiquitin Ligase CHIP Integrates Proteostasis and Aging by Regulation of Insulin Receptor Turnover

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Summary

Aging is attended by a progressive decline in protein homeostasis (proteostasis), aggravating the risk for protein aggregation diseases. To understand the coordination between proteome imbalance and longevity, we addressed the mechanistic role of the quality-control ubiquitin ligase CHIP, which is a key regulator of proteostasis. We observed that CHIP deficiency leads to increased levels of the insulin receptor (INSR) and reduced lifespan of worms and flies. The membrane-bound INSR regulates the insulin and IGF1 signaling (IIS) pathway and thereby defines metabolism and aging. INSR is a direct target of CHIP, which triggers receptor monoubiquitylation and endocytic-lysosomal turnover to promote longevity. However, upon proteotoxic stress conditions and during aging, CHIP is recruited toward disposal of misfolded proteins, reducing its capacity to degrade the INSR. Our study indicates a competitive relationship between proteostasis and longevity regulation through CHIP-assisted proteolysis, providing a mechanistic concept for understanding the impact of proteome imbalance on aging.

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CD34+ cell count predicts long lasting life in the oldest old

Giuseppe Mandraffino[a], Caterina Oriana Aragona[a], Giorgio Basile[b], Valentina Cairo[a], Federica Mamone[a], Carmela Morace[a], Angela D'Ascola[c], Angela Alibrandi[d], Alberto Lo Gullo[a], Saverio Loddo[c],

Circulating progenitor cells (CPCs) represent a pool of cells capable of differentiating into mature cells of different organs and systems, promoting tissue maintenance and repair. Among CPCs, CD34 + cells (CD34 + CPCs) seem to predict outcome in CV disease, also in elderly people. A decline in CD34 + CPCs was reported with advancing age. Moreover, aging is associated with a state of chronic inflammation, influencing life expectancy. Our purpose was to investigate a 10-year predictive ability of CD34 + CPCs, inflammatory marker levels, classic CV risk factors (CVRFs), and Framingham Risk Score (FRS) in a population of healthy, self-sufficient octogenarians. We found that baseline CD34 + CPCs was strongly associated with mortality, showing a significant difference in CD34 + CPC numbers between deceased and living patients. Moreover, by dividing our patients into tertiles based on age reached, this difference was more remarkable the higher the age reached. Regressive analyses suggested that the chances of reaching an older age depend on higher CD34 + CPCs at baseline and are not significantly affected by inflammatory markers levels, FRS, CVFRs, or HDL-C levels. We found that higher CD34 + CPCs predict longer life also in the oldest old, providing additional insights on the predictive role of CD34 + CPCs in subjects aged 80 years or more.

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Using DNA Methylation Profiling to Evaluate Biological Age and Longevity Interventions

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The DNA methylation levels of certain CpG sites are thought to reflect the pace of human aging. Here, we developed a robust predictor of mouse biological age based on 90 CpG sites derived from partial blood DNA methylation profiles. The resulting clock correctly determines the age of mouse cohorts, detects the longevity effects of calorie restriction and gene knockouts, and reports rejuvenation of fibroblast-derived iPSCs. The data show that mammalian DNA methylomes are characterized by CpG sites that may represent the organism's biological age. They are scattered across the genome, they are distinct in human and mouse, and their methylation gradually changes with age. The clock derived from these sites represents a biomarker of aging and can be used to determine the biological age of organisms and evaluate interventions that alter the rate of aging.

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Epigenetic aging signatures in mice livers are slowed by dwarfism, calorie restriction and rapamycin treatment

Background

Global but predictable changes impact the DNA methylome as we age, acting as a type of molecular clock. This clock can be hastened by conditions that decrease lifespan, raising the question of whether it can also be slowed, for example, by conditions that increase lifespan. Mice are particularly appealing organisms for studies of mammalian aging; however, epigenetic clocks have thus far been formulated only in humans.

Results

We first examined whether mice and humans experience similar patterns of change in the methylome with age. We found moderate conservation of CpG sites for which methylation is altered with age, with both species showing an increase in methylome disorder during aging. Based on this analysis, we formulated an epigenetic-aging model in mice using the liver methylomes of 107 mice from 0.2 to 26.0 months old. To examine whether epigenetic aging signatures are slowed by longevity-promoting interventions, we analyzed 28 additional methylomes from mice subjected to lifespan-extending conditions, including $Prop1^{df/df}$ dwarfism, calorie restriction or dietary rapamycin. We found that mice treated with these lifespan-extending interventions were significantly younger in epigenetic age than their untreated, wild-type age-matched controls.

Conclusions

This study shows that lifespan-extending conditions can slow molecular changes associated with an epigenetic clock in mice livers.

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Multi-tissue DNA methylation age predictor in mouse

Thomas M. Stubbs, Marc Jan Bonder, Anne-Katrien Stark, Felix Krueger, BI Ageing Clock Team, Ferdinand von Meyenn ✉, Oliver Stegle ✉ and Wolf Reik ✉

Background

DNA methylation changes at a discrete set of sites in the human genome are predictive of chronological and biological age. However, it is not known whether these changes are causative or a consequence of an underlying ageing process. It has also not been shown whether this epigenetic clock is unique to humans or conserved in the more experimentally tractable mouse.

Results

We have generated a comprehensive set of genome-scale base-resolution methylation maps from multiple mouse tissues spanning a wide range of ages. Many CpG sites show significant tissue-independent correlations with age which allowed us to develop a multi-tissue predictor of age in the mouse. Our model, which estimates age based on DNA methylation at 329 unique CpG sites, has a median absolute error of 3.33 weeks and has similar properties to the recently described human epigenetic clock. Using publicly available datasets, we find that the mouse clock is accurate enough to measure effects on biological age, including in the context of interventions. While females and males show no significant differences in predicted DNA methylation age, ovariectomy results in significant age acceleration in females. Furthermore, we identify significant differences in age-acceleration dependent on the lipid content of the diet.

Conclusions

Here we identify and characterise an epigenetic predictor of age in mice, the mouse epigenetic clock. This clock will be instrumental for understanding the biology of ageing and will allow modulation of its ticking rate and resetting the clock in vivo to study the impact on biological age.

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β Cell Aging Markers Have Heterogeneous Distribution and Are Induced by Insulin Resistance

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We hypothesized that the known heterogeneity of pancreatic β cells was due to subpopulations of β cells at different stages of their life cycle with different functional capacities and that further changes occur with metabolic stress and aging. We identified new markers of aging in β cells, including IGF1R. In β cells IGF1R expression correlated with age, dysfunction, and expression of known age markers $p16^{ink4a}$, p53BP1, and senescence-associated β-galactosidase. The new markers showed striking heterogeneity both within and between islets in both mouse and human pancreas. Acute induction of insulin resistance with an insulin receptor antagonist or chronic ER stress resulted in increased expression of aging markers, providing insight into how metabolic stress might accelerate dysfunction and decline of β cells. These novel findings about β cell and islet heterogeneity, and how they change with age, open up an entirely new set of questions about the pathogenesis of type 2 diabetes.

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Human umbilical cord plasma proteins revitalize hippocampal function in aged mice

Ageing drives changes in neuronal and cognitive function, the decline of which is a major feature of many neurological disorders. The hippocampus, a brain region subserving roles of spatial and episodic memory and learning, is sensitive to the detrimental effects of ageing at morphological and molecular levels. With advancing age, synapses in various hippocampal subfields exhibit impaired long-term potentiation[1], an electrophysiological correlate of learning and memory. At the molecular level, immediate early genes are among the synaptic plasticity genes that are both induced by long-term potentiation[2, 3, 4] and downregulated in the aged brain[5, 6, 7, 8]. In addition to revitalizing other aged tissues[9, 10, 11, 12, 13], exposure to factors in young blood counteracts age-related changes in these central nervous system parameters[14, 15, 16], although the identities of specific cognition-promoting factors or whether such activity exists in human plasma remains unknown[17]. We hypothesized that plasma of an early developmental stage, namely umbilical cord plasma, provides a reservoir of such plasticity-promoting proteins. Here we show that human cord plasma treatment revitalizes the hippocampus and improves cognitive function in aged mice. Tissue inhibitor of metalloproteinases 2 (TIMP2), a blood-borne factor enriched in human cord plasma, young mouse plasma, and young mouse hippocampi, appears in the brain after systemic administration and increases synaptic plasticity and hippocampal-dependent cognition in aged mice. Depletion experiments in aged mice revealed TIMP2 to be necessary for the cognitive benefits conferred by cord plasma. We find that systemic pools of TIMP2 are necessary for spatial memory in young mice, while treatment of brain slices with TIMP2 antibody prevents long-term potentiation, arguing for previously unknown roles for TIMP2 in normal hippocampal function. Our findings reveal that human cord plasma contains plasticity-enhancing proteins of high translational value for targeting ageing- or disease-associated hippocampal dysfunction.

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REVIEWS/COMMENTS/EDITORIALS

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The NAD World 2.0: the importance of the inter-tissue communication mediated by NAMPT/NAD^+/SIRT1 in mammalian aging and longevity control

The original concept of the NAD World was proposed in 2009, providing a comprehensive framework to investigate critical issues of biological robustness and trade-offs in mammalian aging and longevity control. Significant progress has been made over the past 7 years, advancing our understanding of the mechanisms by which biological robustness is maintained, and providing extensive support to the concept of the NAD World. Three key organs and tissues have been identified as basic elements in this control system for mammalian aging and longevity: the hypothalamus as the control center of aging, skeletal muscle as an effector, and adipose tissue as a modulator. While the hypothalamus sends a signal to skeletal muscle through the sympathetic nervous system, adipose tissue remotely regulates hypothalamic function by coordinating NAD^+ biosynthesis at a systemic level. Skeletal muscle might also communicate with other organs and tissues by secreting various myokines. The mammalian NAD^+-dependent protein deacetylase SIRT1 and the key NAD^+ biosynthetic enzyme NAMPT mediate these inter-tissue communications. In this review, the function of each organ or tissue and their inter-tissue communications will be discussed in terms of understanding mammalian aging and longevity control. With such an emphasis on the system architecture, the concept is now reformulated as the NAD World 2.0, providing several important predictions. The concept of the NAD World 2.0 will provide a new foundation to understand a control system for mammalian aging and longevity and accelerate the development of an effective anti-aging intervention for humans.

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Anorexia of ageing: a key component in the pathogenesis of both sarcopenia and cachexia.

Morley JE[1].

Author information

Abstract

The anorexia of aging was first recognized as a physiological syndrome 30 years ago. Its major causes are an alteration in fundal compliance with an increase in antral stretch and enhanced cholecystokinin activity leading to increased satiation.This anorexia leads to weight loss in aging persons and is one of the component causes of the aging related sarcopenia. This physiological anorexia also increases the risk of more severe anorexia when an older person has an increase in inflammatory cytokines such as occurs when they have an illness. This results in an increase in the anorexia due to cachexia in older persons.

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Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue

Age is the most important risk factor for most diseases. Mitochondria play a central role in bioenergetics and metabolism. In addition, several lines of evidence indicate the impact of mitochondria in lifespan determination and ageing. The best-known hypothesis to explain ageing is the free radical theory, which proposes that cells, organs, and organisms age because they accumulate reactive oxygen species (ROS) damage over time. Mitochondria play a central role as the principle source of intracellular ROS, which are mainly formed at the level of complex I and III of the respiratory chain. Dysfunctional mitochondria generating less ATP have been observed in various aged organs. Mitochondrial dysfunction comprises different features including reduced mitochondrial content, altered mitochondrial morphology, reduced activity of the complexes of the electron transport chain, opening of the mitochondrial permeability transition pore, and increased ROS formation. Furthermore, abnormalities in mitochondrial quality control or defects in mitochondrial dynamics have also been linked to senescence. Among the tissues affected by mitochondrial dysfunction are those with a high-energy demand and thus high mitochondrial content. Therefore, the present review focuses on the impact of mitochondria in the ageing process of heart and skeletal muscle. In this article, we review different aspects of mitochondrial dysfunction and discuss potential therapeutic strategies to improve mitochondrial function. Finally, novel aspects of adipose tissue biology and their involvement in the ageing process are discussed.

Keywords Mitochondria; Ageing; Heart; Skeletal muscle; Reactive oxygen species; Caloric restriction

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REVIEW

Sleep and Human Aging

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Older adults do not sleep as well as younger adults. Why? What alterations in sleep quantity and quality occur as we age, and are there functional consequences? What are the underlying neural mechanisms that explain age-related sleep disruption? This review tackles these questions. First, we describe canonical changes in human sleep quantity and quality in cognitively normal older adults. Second, we explore the underlying neurobiological mechanisms that may account for these human sleep alterations. Third, we consider the functional consequences of age-related sleep disruption, focusing on memory impairment as an exemplar. We conclude with a discussion of a still-debated question: do older adults simply need less sleep, or rather, are they unable to generate the sleep that they still need?

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Mutation and catastrophe in the aging genome

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In the 1960s, Leslie Orgel proposed what is now known as the error catastrophe theory of aging, arguing that errors in protein translation that reduce the fidelity of the protein-translating enzymes would lead to a feedback loop of increasingly inaccurate protein synthesis, terminating in the death of the organism. This mechanism of aging would be consistent with the exponential increase of mortality observed in humans, but the error catastrophe theory of aging has been generally disregarded by researchers due to a lack of evidence for an age-related increase in protein errors. Another theory of aging, proposed at roughly the same time, is Leo Szilard's two-hit model of somatic mutation accumulation, which assumed a linear increase in mutations over time but explained the nonlinear pattern of human mortality through a mechanism of genetic and cellular redundancy which kept mortality low until the redundancy was exhausted, at which point mortality rapidly rose. Here, we synthesize the two theories, along with the latest advances in genomics research. We propose a new catastrophe theory of aging, this time with somatic mutations as the primary agent of the feedback loop. Similar to protein errors affecting translation itself, somatic mutations in genes involved in DNA replication and repair would lead to a feedback loop of exponentially increasing mutation load. The difference from protein errors is that somatic mutations would mainly affect gene regulatory regions rather than the much smaller part of the genome encoding protein-coding information. Although the self-stimulating accumulation of somatic mutations is not mutually exclusive with the Szilard-based loss of redundancy, we present evidence that suggests that the accumulated mutations themselves could be numerous enough to cause mortality. Finally, we acknowledge the limits of our current knowledge and propose a course of research practices that will help to confirm or refute our model and advance the field of aging research as a whole.

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The genetics of human longevity: an intricacy of genes, environment, culture and microbiome

Approximately one-quarter of the variation in lifespan in developed countries can be attributed to genetic factors. However, even large population based studies investigating genetic influence on human lifespan have been disappointing, identifying only a few genes accounting for genetic susceptibility to longevity. Some environmental and lifestyle determinants associated with longevity have been identified, which interplay with genetic factors in an intricate way. The study of gene-environment and gene–gene interactions can significantly improve our chance to disentangle this complex scenario. In this review, we first describe the most recent approaches for genetic studies of longevity, from those enriched with health parameters and frailty measures to pathway-based and SNP–SNP interaction analyses. Then, we go deeper into the concept of "environmental influences" in human aging and longevity, focusing on the contribution of life style changes, social and cultural influences, as important determinants of survival differences among individuals in a population. Finally, we discuss the contribution of the microbiome in human longevity, as an example of complex interaction between organism and environment. In conclusion, evidences collected from the latest studies on human longevity provide a support for the collection of life-long genetic and environmental/lifestyle variables with beneficial or detrimental effects on health, to improve our understanding of the determinants of human lifespan.

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OTHER RESEARCH

2014 in review: FDA approval of new drugs

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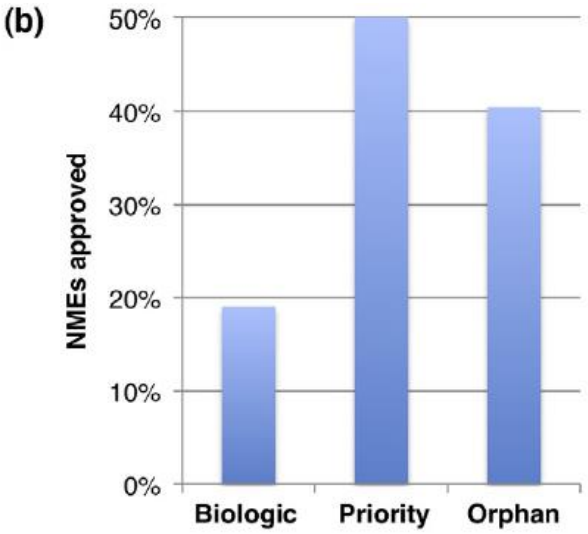
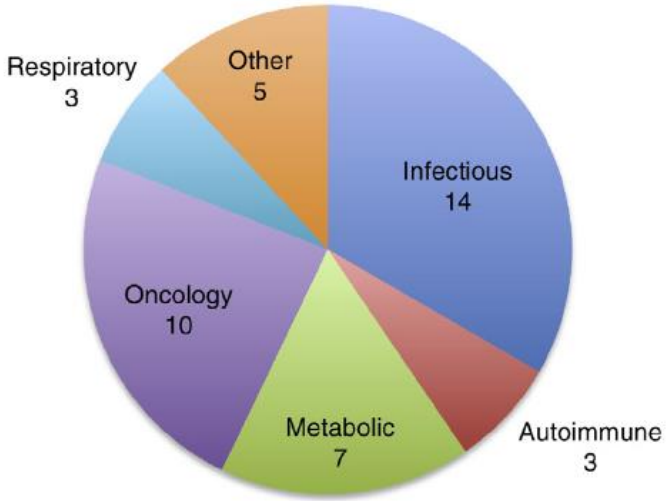
The year 2014 witnessed the approval by the US Food and Drug Administration (FDA) of 42 new molecular entities (NMEs), which is well above recent averages. These molecules targeted a range of molecular pathways and clinical indications, although the latter was skewed toward hepatitis C virus (HCV) infection and diabetes. By contrast, a single drug was approved for cardiovascular diseases and none for neurological indications (excepting sleeping disorders). Of note is a continued trend toward consolidation because the net number of biotechnology companies has reached its lowest point in over 25 years, raising questions about sustainability.





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Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat.

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Abstract

The African naked mole-rat's (*Heterocephalus glaber*) social and subterranean lifestyle generates a hypoxic niche. Under experimental conditions, naked mole-rats tolerate hours of extreme hypoxia and survive 18 minutes of total oxygen deprivation (anoxia) without apparent injury. During anoxia, the naked mole-rat switches to anaerobic metabolism fueled by fructose, which is actively accumulated and metabolized to lactate in the brain. Global expression of the GLUT5 fructose transporter and high levels of ketohexokinase were identified as molecular signatures of fructose metabolism. Fructose-driven glycolytic respiration in naked mole-rat tissues avoids feedback inhibition of glycolysis via phosphofructokinase, supporting viability. The metabolic rewiring of glycolysis can circumvent the normally lethal effects of oxygen deprivation, a mechanism that could be harnessed to minimize hypoxic damage in human disease.

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