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Scientific News
1st of October 2017
Sven Bulterijs

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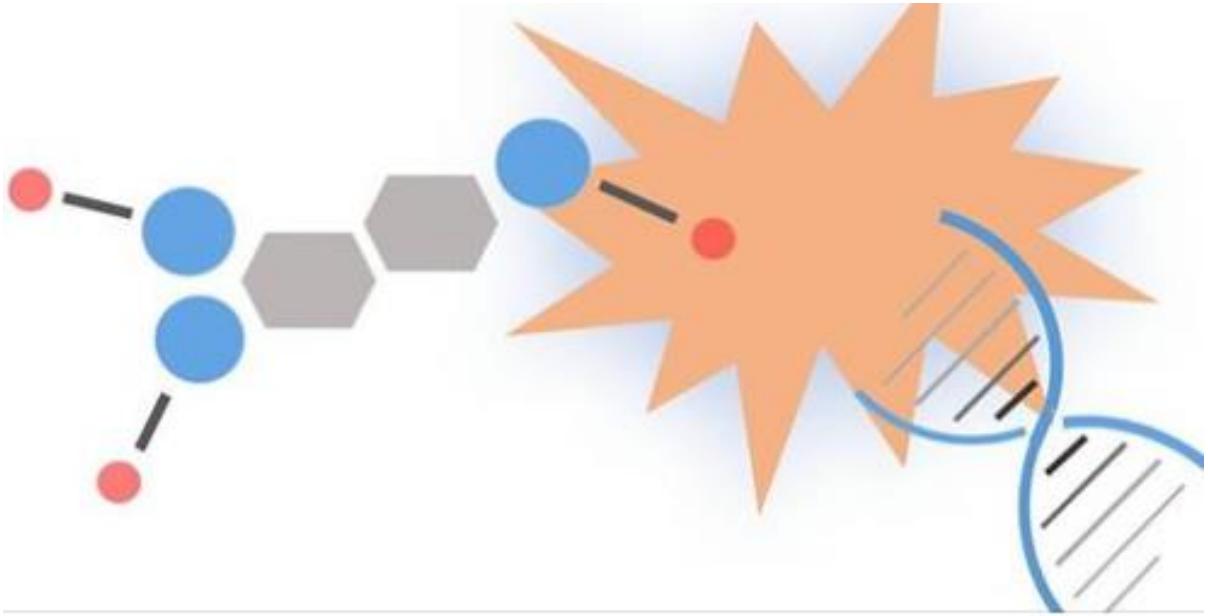

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26

Ageing Genomics and Bioinformatics Workshop

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French government proposes big science-spending boost

President Emmanuel Macron's 2018 draft budget would raise research funds by 6%.

Barbara Casassus

29 September 2017

Ludovic Marin/AFP/Getty Images

Frédérique Vidal, France's higher education, research and innovation minister, said the budget would give 'fresh oxygen' to the country's research.

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Cell Metab. 2017 Sep 5;26(3):539-546.e5. doi: 10.1016/j.cmet.2017.08.005.

A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice.

Roberts MN[1], Wallace MA[2], Tomilov AA[1], Zhou Z[1], Marcotte GR[2], Tran D[1], Perez G[1], Gutierrez-Casado E[3], Koike S[4], Knotts TA[1], Imai DM[5], Griffey SM[5], Kim K[6], Hagopian K[1], Haj FG[4], Baar K[7], Cortopassi GA[1], Ramsey JJ[8], Lopez-Dominguez JA[9].

Author information

Abstract

Calorie restriction, without malnutrition, has been shown to increase lifespan and is associated with a shift away from glycolysis toward beta-oxidation. The objective of this study was to mimic this metabolic shift using low-carbohydrate diets and to determine the influence of these diets on longevity and healthspan in mice. C57BL/6 mice were assigned to a ketogenic, low-carbohydrate, or control diet at 12 months of age and were either allowed to live their natural lifespan or tested for physiological function after 1 or 14 months of dietary intervention. The ketogenic diet (KD) significantly increased median lifespan and survival compared to controls. In aged mice, only those consuming a KD displayed preservation of physiological function. The KD increased protein acetylation levels and regulated mTORC1 signaling in a tissue-dependent manner. This study demonstrates that a KD extends longevity and healthspan in mice.

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Cell Metab. 2017 Sep 5;26(3):547-557.e8. doi: 10.1016/j.cmet.2017.08.004.

Ketogenic Diet Reduces Midlife Mortality and Improves Memory in Aging Mice.

Newman JC[1], Covarrubias AJ[2], Zhao M[3], Yu X[4], Gut P[5], Ng CP[2], Huang Y[6], Haldar S[6], Verdin E[7].

Author information

Abstract

Ketogenic diets recapitulate certain metabolic aspects of dietary restriction such as reliance on fatty acid metabolism and production of ketone bodies. We investigated whether an isoprotein ketogenic diet (KD) might, like dietary restriction, affect longevity and healthspan in C57BL/6 male mice. We find that Cyclic KD, KD alternated weekly with the Control diet to prevent obesity, reduces midlife mortality but does not affect maximum lifespan. A non-ketogenic high-fat diet (HF) fed similarly may have an intermediate effect on mortality. Cyclic KD improves memory performance in old age, while modestly improving composite healthspan measures. Gene expression analysis identifies downregulation of insulin, protein synthesis, and fatty acid synthesis pathways as mechanisms common to KD and HF. However, upregulation of PPARα target genes is unique to KD, consistent across tissues, and preserved in old age. In all, we show that a non-obesogenic ketogenic diet improves survival, memory, and healthspan in aging mice.

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Caloric restriction delays age-related methylation drift

In mammals, caloric restriction consistently results in extended lifespan. Epigenetic information encoded by DNA methylation is tightly regulated, but shows a striking drift associated with age that includes both gains and losses of DNA methylation at various sites. Here, we report that epigenetic drift is conserved across species and the rate of drift correlates with lifespan when comparing mice, rhesus monkeys, and humans. Twenty-two to 30-year-old rhesus monkeys exposed to 30% caloric restriction since 7–14 years of age showed attenuation of age-related methylation drift compared to ad libitum-fed controls such that their blood methylation age appeared 7 years younger than their chronologic age. Even more pronounced effects were seen in 2.7–3.2-year-old mice exposed to 40% caloric restriction starting at 0.3 years of age. The effects of caloric restriction on DNA methylation were detectable across different tissues and correlated with gene expression. We propose that epigenetic drift is a determinant of lifespan in mammals.

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Caloric Restriction Promotes Structural and Metabolic Changes in the Skin

Maria Fernanda Forni, Julia Peloggia, Tárcio T. Braga, Jesús Eduardo Ortega Chinchilla, Jorge Shinohara, Carlos Arturo Navas, Niels Olsen Saraiva Camara, Alicia J. Kowaltowski[5]

Caloric restriction (CR) is the most effective intervention known to enhance lifespan, but its effect on the skin is poorly understood. Here, we show that CR mice display fur coat remodeling associated with an expansion of the hair follicle stem cell (HFSC) pool. We also find that the dermal adipocyte depot (dWAT) is underdeveloped in CR animals. The dermal/vennule annulus vasculature is enlarged, and a vascular endothelial growth factor (VEGF) switch and metabolic reprogramming in both the dermis and the epidermis are observed. When the fur coat is removed, CR mice display increased energy expenditure associated with lean weight loss and locomotion impairment. Our findings indicate that CR promotes extensive skin and fur remodeling. These changes are necessary for thermal homeostasis and metabolic fitness under conditions of limited energy intake, suggesting a potential adaptive mechanism.

Identification of HSP90 inhibitors as a novel class of senolytics

Aging is the main risk factor for many chronic degenerative diseases and cancer. Increased senescent cell burden in various tissues is a major contributor to aging and age-related diseases. Recently, a new class of drugs termed senolytics were demonstrated to extending healthspan, reducing frailty and improving stem cell function in multiple murine models of aging. To identify novel and more optimal senotherapeutic drugs and combinations, we established a senescence associated β-galactosidase assay as a screening platform to rapidly identify drugs that specifically affect senescent cells. We used primary *Ercc1*$^{-/-}$ murine embryonic fibroblasts with reduced DNA repair capacity, which senesce rapidly if grown at atmospheric oxygen. This platform was used to screen a small library of compounds that regulate autophagy, identifying two inhibitors of the HSP90 chaperone family as having significant senolytic activity in mouse and human cells. Treatment of *Ercc1*$^{-/\Delta}$ mice, a mouse model of a human progeroid syndrome, with the HSP90 inhibitor 17-DMAG extended healthspan, delayed the onset of several age-related symptoms and reduced p16^{INK4a} expression. These results demonstrate the utility of our screening platform to identify senotherapeutic agents as well as identified HSP90 inhibitors as a promising new class of senolytic drugs.

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Nature. 2017 Sep 27. doi: 10.1038/nature24022. [Epub ahead of print]

Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing.

Camell CD[1,2], Sander J[3], Spadaro O[1,2], Lee A[1,2], Nguyen KY[1,2], Wing A[4], Goldberg EL[1,2], Youm YH[1,2], Brown CW[5], Elsworth J[6], Rodeheffer MS[1], Schultze JL[3,7], Deep Dixit V[1,2,8].

⊕ Author information

Abstract

Catecholamine-induced lipolysis, the first step in the generation of energy substrates by the hydrolysis of triglycerides, declines with age. The defect in the mobilization of free fatty acids in the elderly is accompanied by increased visceral adiposity, lower exercise capacity, failure to maintain core body temperature during cold stress, and reduced ability to survive starvation. Although catecholamine signalling in adipocytes is normal in the elderly, how lipolysis is impaired in ageing remains unknown. Here we show that adipose tissue macrophages regulate the age-related reduction in adipocyte lipolysis in mice by lowering the bioavailability of noradrenaline. Unexpectedly, unbiased whole-transcriptome analyses of adipose macrophages revealed that ageing upregulates genes that control catecholamine degradation in an NLRP3 inflammasome-dependent manner. Deletion of NLRP3 in ageing restored catecholamine-induced lipolysis by downregulating growth differentiation factor-3 (GDF3) and monoamine oxidase A (MAOA) that is known to degrade noradrenaline. Consistent with this, deletion of GDF3 in inflammasome-activated macrophages improved lipolysis by decreasing levels of MAOA and caspase-1. Furthermore, inhibition of MAOA reversed the age-related reduction in noradrenaline concentration in adipose tissue, and restored lipolysis with increased levels of the key lipolytic enzymes adipose triglyceride lipase (ATGL) and hormone sensitive lipase (HSL). Our study reveals that targeting neuro-immunometabolic signalling between the sympathetic nervous system and macrophages may offer new approaches to mitigate chronic inflammation-induced metabolic impairment and functional decline.

PMID: 28953873 DOI: 10.1038/nature24022

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Mutations in the promoter of the telomerase gene *TERT* contribute to tumorigenesis by a two-step mechanism

Abstract

TERT promoter mutations (TPMs) are the most common noncoding mutations in cancer. The timing and consequences of TPMs have not been fully established. Here, we show that TPMs acquired at the transition from benign nevus to malignant melanoma do not support telomere maintenance. In vitro experiments revealed that TPMs do not prevent telomere attrition, resulting in cells with critically short and unprotected telomeres. Immortalization by TPMs requires a gradual up-regulation of telomerase, coinciding with telomere fusions. These data suggest that TPMs contribute to tumorigenesis by promoting immortalization and genomic instability in two phases. In an initial phase, TPMs do not prevent bulk telomere shortening but extend cellular life span by healing the shortest telomeres. In the second phase, the critically short telomeres lead to genome instability and telomerase is further up-regulated to sustain cell proliferation.

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J Gerontol A Biol Sci Med Sci. 2017 Aug 18. doi: 10.1093/gerona/glx047. [Epub ahead of print]

Stable Isotope Labeling Reveals Novel Insights Into Ubiquitin-Mediated Protein Aggregation With Age, Calorie Restriction, and Rapamycin Treatment.

Basisty NB[1,2], Liu Y[3], Reynolds J[4], Karunadharma PP[5], Dai DF[1,6], Fredrickson J[1], Beyer RP[7], MacCoss MJ[8], Rabinovitch PS[1].

Author information

Abstract

Accumulation of protein aggregates with age was first described in aged human tissue over 150 years ago and has since been described in virtually every human tissue. Ubiquitin modifications are a canonical marker of insoluble protein aggregates; however, the composition of most age-related inclusions remains relatively unknown. To examine the landscape of age-related protein aggregation in vivo, we performed an antibody-based pulldown of ubiquitinated proteins coupled with metabolic labeling and mass spectrometry on young and old mice on calorie restriction (CR), rapamycin (RP)-supplemented, and control diets. We show increased abundance of many ubiquitinated proteins in old mice and greater retention of preexisting (unlabeled) ubiquitinated proteins relative to their unmodified counterparts-fitting the expected profile of age-increased accumulation of long-lived aggregating proteins. Both CR and RP profoundly affected ubiquitinome composition, half-live, and the insolubility of proteins, consistent with their ability to mobilize these age-associated accumulations. Finally, confocal microscopy confirmed the aggregation of two of the top predicted aggregating proteins, keratins 8/18 and catalase, as well as their attenuation by CR and RP. Stable-isotope labeling is a powerful tool to gain novel insights into proteostasis mechanisms, including protein aggregation, and could be used to identify novel therapeutic targets in aging and protein aggregation diseases.

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Meta-Analysis of 29 Experiments Evaluating the Effects of Rapamycin on Life Span in the Laboratory Mouse

William R. Swindell

Rapamycin has favorable effects on aging in mice and may eventually be applied to encourage "healthy aging" in humans. This study analyzed raw data from 29 survival studies of rapamycin- and control-treated mice, with the goals of estimating summary statistics and identifying factors associated with effect size heterogeneity. Meta-analysis demonstrated significant heterogeneity across studies, with hazard ratio (HR) estimates ranging from 0.22 (95% confidence interval [CI]: 0.06–0.82) to 0.92 (95% CI: 0.65–1.28). Sex was the major factor accounting for effect size variation, and mortality was decreased more in females (HR = 0.41; 95% CI: 0.35–0.48) as compared with males (HR = 0.63; 95% CI: 0.55–0.71). Rapamycin effects were also genotype dependent, however, with stronger survivorship increases in hybrid mice (14.4%; 95% CI: 12.5–16.3%) relative to pure inbred strains (8.8%; 95% CI: 6.2–11.6%). Number needed to treat was applied as an effect size metric, which consistently identified early senescence as the age of peak treatment benefit. These results provide synthesis of existing data to support the potential translation of findings from mouse to primate species. Because rapamycin's effect on survival depends on sex and genotype, further work is justified to understand how these factors shape treatment response.

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Eur J Radiol. 2017 Sep;94:16-24. doi: 10.1016/j.ejrad.2017.07.014. Epub 2017 Jul 20.

The diagnostic value of FDG and amyloid PET in Alzheimer's disease-A systematic review.

Rice L[1], Bisdas S[2].

Author information

Abstract

PURPOSE: By 2050 it is projected that 115 million people worldwide will have Alzheimer's Disease (AD) [1]. Recent attempts have been made to redefine the diagnostic criteria of AD to include markers of neurodegeneration - measurable by FDG-PET - and markers of amyloid accumulation - measurable by amyloid-PET.

MATERIALS AND METHODS: A systematic review of the literature was performed to examine the current diagnostic use of amyloid and FDG PET. MEDLINE and EMBASE databases and the Cochrane Database were searched for relevant papers RESULTS AND DISCUSSION: This search resulted in twenty-nine papers on amyloid imaging, twenty-three papers on FDG-PET and eight papers which utilized both techniques. Both modalities are considered in turn with regards to their diagnostic accuracy, their role in mild cognitive impairment (MCI) and prognostication, their use in the differential diagnosis of AD and their clinical application. As evidenced from the current literature, both amyloid and FDG-PET meet criteria for suitable biomarkers for the diagnosis of AD. They both indicate pathophysiological processes, albeit at different stages of the Alzheimer's process, and are distinct from normal patterns of aging.

CONCLUSION: Both techniques have been shown to detect AD with high sensitivity and specificity compared to other neurodegenerative processes and cognitively normal age-matched individuals. However, future studies with standardised, uniform thresholds and a lengthier longitudinal follow-up need to be conducted to allow us to make surer conclusions about the future role of PET in clinical practice. In addition, comparison with post-mortem diagnosis, rather than clinical diagnosis with its acknowledged flaws, would result in more powerful statistical outcomes - which is becoming increasingly important given that several disease-modifying AD drugs are now in phase 3 trials.

KEYWORDS: Alzheimer's; Amyloid; Dementia; FDG; PET

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Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease

Lena F. Burbulla[1,2], Pingping Song[1], Joseph R. Mazzulli[1,2], Enrico Zampese[3], Yvette C. Wong[1], Sohee Jeon[1], David P. Santos...

Mitochondrial and lysosomal dysfunction have been implicated in substantia nigra dopaminergic neurodegeneration in Parkinson's disease (PD), but how these pathways are linked in human neurons remains unclear. Here we studied dopaminergic neurons derived from patients with idiopathic and familial PD. We identified a time-dependent pathological cascade beginning with mitochondrial oxidant stress leading to oxidized dopamine accumulation, ultimately resulting in reduced glucocerebrosidase enzymatic activity, lysosomal dysfunction and α-synuclein accumulation. This toxic cascade was observed only in human, but not in mouse PD neurons, at least in part due to species-specific differences in dopamine metabolism. Increasing dopamine synthesis or α-synuclein levels in mouse midbrain neurons recapitulated pathological phenotypes observed in human neurons. Thus, dopamine oxidation represents an important link between mitochondrial and lysosomal dysfunction in PD pathogenesis.

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Nat Genet. 2017 Oct;49(10):1511-1516. doi: 10.1038/ng.3955. Epub 2017 Sep 11.

A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci.

Chang D[1], Nalls MA[2,3], Hallgrímsdóttir IB[4], Hunkapiller J[1], van der Brug M[1], Cai F[1]; International Parkinson's Disease Genomics Consortium; 23andMe Research Team, Kerchner GA[1], Ayalon G[1], Bingol B[1], Sheng M[1], Hinds D[4], Behrens TW[1], Singleton AB[2], Bhangale TR[1], Graham RR[1].

Author information

Abstract

Common variant genome-wide association studies (GWASs) have, to date, identified >24 risk loci for Parkinson's disease (PD). To discover additional loci, we carried out a GWAS comparing 6,476 PD cases with 302,042 controls, followed by a meta-analysis with a recent study of over 13,000 PD cases and 95,000 controls at 9,830 overlapping variants. We then tested 35 loci ($P < 1 \times 10^{-6}$) in a replication cohort of 5,851 cases and 5,866 controls. We identified 17 novel risk loci ($P < 5 \times 10^{-8}$) in a joint analysis of 26,035 cases and 403,190 controls. We used a neurocentric strategy to assign candidate risk genes to the loci. We identified protein-altering or cis-expression quantitative trait locus (cis-eQTL) variants in linkage disequilibrium with the index variant in 29 of the 41 PD loci. These results indicate a key role for autophagy and lysosomal biology in PD risk, and suggest potential new drug targets for PD.

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Metformin reverses TRAP1 mutation-associated alterations in mitochondrial function in Parkinson's disease FREE

The mitochondrial proteins TRAP1 and HTRA2 have previously been shown to be phosphorylated in the presence of the Parkinson's disease kinase PINK1 but the downstream signalling is unknown. HTRA2 and PINK1 loss of function causes parkinsonism in humans and animals. Here, we identified TRAP1 as an interactor of HTRA2 using an unbiased mass spectrometry approach. In our human cell models, TRAP1 overexpression is protective, rescuing HTRA2 and PINK1-associated mitochondrial dysfunction and suggesting that TRAP1 acts downstream of HTRA2 and PINK1. HTRA2 regulates TRAP1 protein levels, but TRAP1 is not a direct target of HTRA2 protease activity. Following genetic screening of Parkinson's disease patients and healthy controls, we also report the first *TRAP1* mutation leading to complete loss of functional protein in a patient with late onset Parkinson's disease. Analysis of fibroblasts derived from the patient reveal that oxygen consumption, ATP output and reactive oxygen species are increased compared to healthy individuals. This is coupled with an increased pool of free NADH, increased mitochondrial biogenesis, triggering of the mitochondrial unfolded protein response, loss of mitochondrial membrane potential and sensitivity to mitochondrial removal and apoptosis. These data highlight the role of TRAP1 in the regulation of energy metabolism and mitochondrial quality control. Interestingly, the diabetes drug metformin reverses mutation-associated alterations on energy metabolism, mitochondrial biogenesis and restores mitochondrial membrane potential. In summary, our data show that TRAP1 acts downstream of PINK1 and HTRA2 for mitochondrial fine tuning, whereas TRAP1 loss of function leads to reduced control of energy metabolism, ultimately impacting mitochondrial membrane potential. These findings offer new insight into mitochondrial pathologies in Parkinson's disease and provide new prospects for targeted therapies.

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Aging Cell. 2017 Sep 21. doi: 10.1111/acel.12658. [Epub ahead of print]

Genetic interaction with temperature is an important determinant of nematode longevity.

Miller H[1], Fletcher M[2], Primitivo M[2], Leonard A[2], Sutphin GL[2], Rintala N[2], Kaeberlein M[2], Leiser SF[1,3,4].

⊕ Author information

Abstract

As in other poikilotherms, longevity in C. elegans varies inversely with temperature; worms are longer-lived at lower temperatures. While this observation may seem intuitive based on thermodynamics, the molecular and genetic basis for this phenomenon is not well understood. Several recent reports have argued that lifespan changes across temperatures are genetically controlled by temperature-specific gene regulation. Here, we provide data that both corroborate those studies and suggest that temperature-specific longevity is more the rule than the exception. By measuring the lifespans of worms with single modifications reported to be important for longevity at 15, 20, or 25 °C, we find that the effect of each modification on lifespan is highly dependent on temperature. Our results suggest that genetics play a major role in temperature-associated longevity and are consistent with the hypothesis that while aging in C. elegans is slowed by decreasing temperature, the major cause(s) of death may also be modified, leading to different genes and pathways becoming more or less important at different temperatures. These differential mechanisms of age-related death are not unlike what is observed in humans, where environmental conditions lead to development of different diseases of aging.

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Responsive monitoring of mitochondrial redox states in heart muscle predicts impending cardiac arrest

Dorothy A. Perry[1,2,*], Joshua W. Salvin[1,2,*], Padraic Romfh[3], Peili Chen[3], Kalyani Krishnamurthy[3], Lindsay M. Thomson[1], Bri…
+ See all authors and affiliations

Abstract

Assessing the adequacy of oxygen delivery to tissues is vital, particularly in the fields of intensive care medicine and surgery. As oxygen delivery to a cell becomes deficient, changes in mitochondrial redox state precede changes in cellular function. We describe a technique for the continuous monitoring of the mitochondrial redox state on the epicardial surface using resonance Raman spectroscopy. We quantify the reduced fraction of specific electron transport chain cytochromes, a metric we name the resonance Raman reduced mitochondrial ratio (3RMR). As oxygen deficiency worsens, heme moieties within the electron transport chain become progressively more reduced, leading to an increase in 3RMR. Myocardial 3RMR increased from baseline values of 18.1 ± 5.9 to 44.0 ± 16.9% (P = 0.0039) after inferior vena cava occlusion in rodents (n = 8). To demonstrate the diagnostic power of this measurement, 3RMR was continuously measured in rodents (n = 31) ventilated with 5 to 8% inspired oxygen for 30 min. A 3RMR value exceeding 40% at 10 min predicted subsequent cardiac arrest with 95% sensitivity and 100% specificity [area under the curve (AUC), 0.98], outperforming all current measures, including contractility (AUC, 0.51) and ejection fraction (AUC, 0.39). 3RMR correlated with indices of intracellular redox state and energy production. This technique may permit the real-time identification of critical defects in organ-specific oxygen delivery.

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

RESULTS

At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P=0.30); in the 150-mg group, 0.85 (95% CI, 0.74 to 0.98; P=0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P=0.031). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P=0.005). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

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Mol Syst Biol. 2017 Sep 15;13(9):939. doi: 10.15252/msb.20177663.

A proteomic atlas of insulin signalling reveals tissue-specific mechanisms of longevity assurance.

Tain LS[1], Sehlke R[1,2], Jain C[1], Chokkalingam M[2], Nagaraj N[3], Essers P[1], Rassner M[1], Grönke S[1], Froelich J[1], Dieterich C[4,5], Mann M[3], Alic N[6], Beyer A[7,8], Partridge L[9,6].

Author information

Abstract

Lowered activity of the insulin/IGF signalling (IIS) network can ameliorate the effects of ageing in laboratory animals and, possibly, humans. Although transcriptome remodelling in long-lived IIS mutants has been extensively documented, the causal mechanisms contributing to extended lifespan, particularly in specific tissues, remain unclear. We have characterized the proteomes of four key insulin-sensitive tissues in a long-lived *Drosophila* IIS mutant and control, and detected 44% of the predicted proteome (6,085 proteins). Expression of ribosome-associated proteins in the fat body was reduced in the mutant, with a corresponding, tissue-specific reduction in translation. Expression of mitochondrial electron transport chain proteins in fat body was increased, leading to increased respiration, which was necessary for IIS-mediated lifespan extension, and alone sufficient to mediate it. Proteasomal subunits showed altered expression in IIS mutant gut, and gut-specific over-expression of the RPN6 proteasomal subunit, was sufficient to increase proteasomal activity and extend lifespan, whilst inhibition of proteasome activity abolished IIS-mediated longevity. Our study thus uncovered strikingly tissue-specific responses of cellular processes to lowered IIS acting in concert to ameliorate ageing.

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A Long-lived Mouse Lacking Both Growth Hormone and Growth Hormone Receptor: A New Animal Model for Aging Studies

Disruption of the growth hormone (GH) signaling pathway promotes insulin sensitivity and is associated with both delayed aging and extended longevity. Two kinds of long-lived mice—Ames dwarfs (df/df) and GH receptor gene–disrupted knockouts (GHRKO) are characterized by a suppressed GH axis with a significant reduction of body size and decreased plasma insulin-like growth factor-1 (IGF-1) and insulin levels. Ames dwarf mice are deficient in GH, prolactin, and thyrotropin, whereas GHRKOs are GH resistant and are dwarf with decreased circulating IGF-1 and increased GH. Crossing Ames dwarfs and GHRKOs produced a new mouse line (df/KO), lacking both GH and GH receptor. These mice are characterized by improved glucose tolerance and increased adiponectin level, which could imply that these mice should be also characterized by additional life-span extension when comparing with GHRKOs and Ames dwarfs. Importantly, our longevity experiments showed that df/KO mice maintain extended longevity when comparing with N control mice; however, they do not live longer than GHRKO and Ames df/df mice. These important findings indicate that silencing GH signal is important to extend the life span; however, further decrease of body size in mice with already inhibited GH signal does not extend the life span regardless of improved some health-span markers.

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Cell Rep. 2017 Sep 12;20(11):2527-2537. doi: 10.1016/j.celrep.2017.08.059.

Piwi Is Required to Limit Exhaustion of Aging Somatic Stem Cells.

Sousa-Victor P[1], Ayyaz A[1], Hayashi R[2], Qi Y[1], Madden DT[3], Lunyak VV[4], Jasper H[5].

Author information

Abstract

Sophisticated mechanisms that preserve genome integrity are critical to ensure the maintenance of regenerative capacity while preventing transformation of somatic stem cells (SCs), yet little is known about mechanisms regulating genome maintenance in these cells. Here, we show that intestinal stem cells (ISCs) induce the Argonaute family protein Piwi in response to JAK/STAT signaling during acute proliferative episodes. Piwi function is critical to ensure heterochromatin maintenance, suppress retrotransposon activation, and prevent DNA damage in homeostasis and under regenerative pressure. Accordingly, loss of Piwi results in the loss of actively dividing ISCs and their progenies by apoptosis. We further show that Piwi expression is sufficient to allay age-related retrotransposon expression, DNA damage, apoptosis, and mis-differentiation phenotypes in the ISC lineage, improving epithelial homeostasis. Our data identify a role for Piwi in the regulation of somatic SC function, and they highlight the importance of retrotransposon control in somatic SC maintenance.

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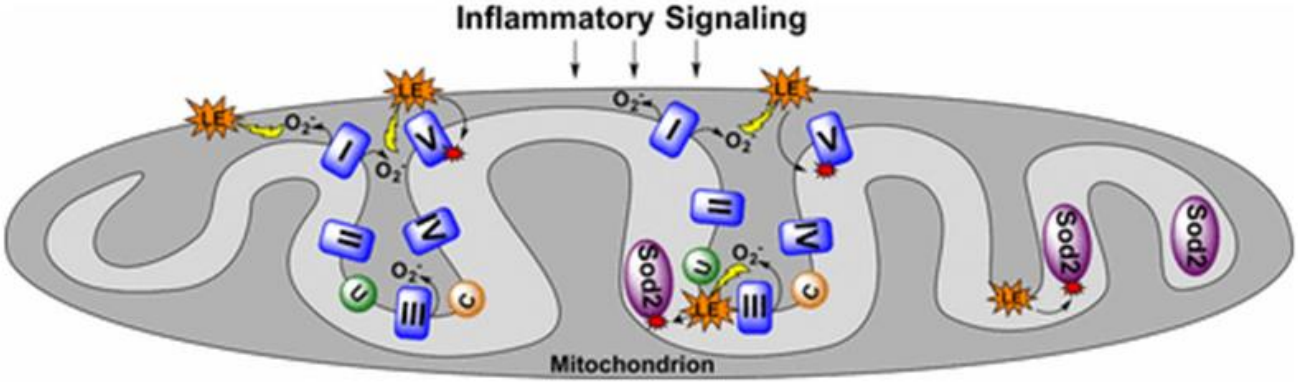
Protein Modification by Endogenously Generated Lipid Electrophiles: Mitochondria as the Source and Target

William N. Beavers†, Kristie L. Rose‡⊥, James J. Galligan‡, Michelle M. Mitchener†, Carol A. Rouzer‡, Keri A. Tallman†, Connor R. Lamberson†, Xiaojing Wang∥, Salisha Hill⊥, Pavlina T. Ivanova§, H. Alex Brown‡§, Bing Zhang∥, Ned A. Porter†, and Lawrence J. Marnett*†‡§



Determining the impact of lipid electrophile-mediated protein damage that occurs during oxidative stress requires a comprehensive analysis of electrophile targets adducted under pathophysiological conditions. Incorporation of ω-alkynyl linoleic acid into the phospholipids of macrophages prior to activation by Kdo_2-lipid A, followed by protein extraction, click chemistry, and streptavidin affinity capture, enabled a systems-level survey of proteins adducted by lipid electrophiles generated endogenously during the inflammatory response. Results revealed a dramatic enrichment for membrane and mitochondrial proteins as targets for adduction. A marked decrease in adduction in the presence of MitoTEMPO demonstrated a primary role for mitochondrial superoxide in electrophile generation and indicated an important role for mitochondria as both a source and target of lipid electrophiles, a finding that has not been revealed by prior studies using exogenously provided electrophiles.

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Promoting Drp1-mediated mitochondrial fission in midlife prolongs healthy lifespan of *Drosophila melanogaster*

The accumulation of dysfunctional mitochondria has been implicated in aging, but a deeper understanding of mitochondrial dynamics and mitophagy during aging is missing. Here, we show that upregulating Drp1—a Dynamin-related protein that promotes mitochondrial fission—in midlife, prolongs *Drosophila* lifespan and healthspan. We find that short-term induction of Drp1, in midlife, is sufficient to improve organismal health and prolong lifespan, and observe a midlife shift toward a more elongated mitochondrial morphology, which is linked to the accumulation of dysfunctional mitochondria in aged flight muscle. Promoting Drp1-mediated mitochondrial fission, in midlife, facilitates mitophagy and improves both mitochondrial respiratory function and proteostasis in aged flies. Finally, we show that autophagy is required for the anti-aging effects of midlife Drp1-mediated mitochondrial fission. Our findings indicate that interventions that promote mitochondrial fission could delay the onset of pathology and mortality in mammals when applied in midlife.

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Indoles from commensal bacteria extend healthspan

Multiple studies have identified conserved genetic pathways and small molecules associated with extension of lifespan in diverse organisms. However, extending lifespan does not result in concomitant extension in healthspan, defined as the proportion of time that an animal remains healthy and free of age-related infirmities. Rather, mutations that extend lifespan often reduce healthspan and increase frailty. The question arises as to whether factors or mechanisms exist that uncouple these processes and extend healthspan and reduce frailty independent of lifespan. We show that indoles from commensal microbiota extend healthspan of diverse organisms, including *Caenorhabditis elegans*, *Drosophila melanogaster*, and mice, but have a negligible effect on maximal lifespan. Effects of indoles on healthspan in worms and flies depend upon the aryl hydrocarbon receptor (AHR), a conserved detector of xenobiotic small molecules. In *C. elegans*, indole induces a gene expression profile in aged animals reminiscent of that seen in the young, but which is distinct from that associated with normal aging. Moreover, in older animals, indole induces genes associated with oogenesis and, accordingly, extends fecundity and reproductive span. Together, these data suggest that small molecules related to indole and derived from commensal microbiota act in diverse phyla via conserved molecular pathways to promote healthy aging. These data raise the possibility of developing therapeutics based on microbiota-derived indole or its derivatives to extend healthspan and reduce frailty in humans.

REVIEWS/COMMENTS/EDITORIALS

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Mitochondrial proteostasis as a shared characteristic of slowed aging: the importance of considering cell proliferation

Karyn L. Hamilton ✉, Benjamin F. Miller

Proteostasis is one of the seven "pillars of aging research" identified by the Trans-NIH Geroscience Initiative and loss of proteostasis is associated with aging and age-related chronic disease. Accumulated protein damage and resultant cellular dysfunction are consequences of limited protein repair systems and slowed protein turnover. When relatively high rates of protein turnover are maintained despite advancing age, damaged proteins are more quickly degraded and replaced, maintaining proteome fidelity. Therefore, maintenance of protein turnover represents an important proteostatic mechanism. However, measurement of protein synthesis without consideration for cell proliferation can result in an incomplete picture, devoid of information about how new proteins are being allocated. Simultaneous measurement of protein and DNA synthesis provides necessary mechanistic insight about proteins apportioned for newly proliferating cells versus for somatic maintenance. Using this approach with a number of murine models of slowed aging shows that, compared to controls, energetic resources are directed more toward somatic maintenance and proteostasis, and away from cell growth and proliferation. In particular, slowed aging models are associated with heightened mechanisms of mitochondrial proteostatic maintenance. Taking cell proliferation into account may explain the paradoxical findings that aging itself and slowed aging interventions can both be characterized by slower rates of protein synthesis.

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Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases

Nard Kubben & Tom Misteli

Ageing is the predominant risk factor for many common diseases. Human premature ageing diseases are powerful model systems to identify and characterize cellular mechanisms that underpin physiological ageing. Their study also leads to a better understanding of the causes, drivers and potential therapeutic strategies of common diseases associated with ageing, including neurological disorders, diabetes, cardiovascular diseases and cancer. Using the rare premature ageing disorder Hutchinson–Gilford progeria syndrome as a paradigm, we discuss here the shared mechanisms between premature ageing and ageing-associated diseases, including defects in genetic, epigenetic and metabolic pathways; mitochondrial and protein homeostasis; cell cycle; and stem cell-regenerative capacity.

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Molecular Mechanisms Determining Lifespan in Short- and Long-Lived Species

Xiao Tian, Andrei Seluanov, Vera Gorbunova

Aging is a global decline of physiological functions, leading to an increased susceptibility to diseases and ultimately death. Maximum lifespans differ up to 200-fold between mammalian species. Although considerable progress has been achieved in identifying conserved pathways that regulate individual lifespan within model organisms, whether the same pathways are responsible for the interspecies differences in longevity remains to be determined. Recent cross-species studies have begun to identify pathways responsible for interspecies differences in lifespan. Here, we review the evidence supporting the role of anticancer mechanisms, DNA repair machinery, insulin/insulin-like growth factor 1 signaling, and proteostasis in defining species lifespans. Understanding the mechanisms responsible for the dramatic differences in lifespan between species will have a transformative effect on developing interventions to improve human health and longevity.

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CELL REPROGRAMMING: THERAPEUTIC POTENTIAL AND THE PROMISE OF REJUVENATION FOR THE AGING BRAIN.

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Author information

Abstract

Aging is associated with a progressive increase in the incidence of neurodegenerative diseases, with Alzheimer's (AD) and Parkinson's (PD) disease being the most conspicuous examples. Within this context, the absence of efficacious therapies for most age-related brain pathologies has increased the interest in regenerative medicine. In particular, cell reprogramming technologies have ushered in the era of personalized therapies that not only show a significant potential for the treatment of neurodegenerative diseases but also promise to make biological rejuvenation feasible. We will first review recent evidence supporting the emerging view that aging is a reversible epigenetic phenomenon. Next, we will describe novel reprogramming approaches that overcome some of the intrinsic limitations of conventional induced-pluripotent-stem-cell technology. One of the alternative approaches, lineage reprogramming, consists of the direct conversion of one adult cell type into another by transgenic expression of multiple lineage-specific transcription factors (TF). Another strategy, termed pluripotency factor-mediated direct reprogramming, uses universal TF to generate epigenetically unstable intermediates able to differentiate into somatic cell types in response to specific differentiation factors. In the third part we will review studies showing the potential relevance of the above approaches for the treatment of AD and PD.

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Molecular signatures of longevity: Insights from cross-species comparative studies.

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Abstract

Much of the current research on longevity focuses on the aging process within a single species. Several molecular players (e.g. IGF1 and MTOR), pharmacological compounds (e.g. rapamycin and metformin), and dietary approaches (e.g. calorie restriction and methionine restriction) have been shown to be important in regulating and modestly extending lifespan in model organisms. On the other hand, natural lifespan varies much more significantly across species. Within mammals alone, maximum lifespan differs more than 100 fold, but the underlying regulatory mechanisms remain poorly understood. Recent comparative studies are beginning to shed light on the molecular signatures associated with exceptional longevity. These include genome sequencing of microbats, naked mole rat, blind mole rat, bowhead whale and African turquoise killifish, and comparative analyses of gene expression, metabolites, lipids and ions across multiple mammalian species. Together, they point towards several putative strategies for lifespan regulation and cancer resistance, as well as the pathways and metabolites associated with longevity variation. In particular, longevity may be achieved by both lineage-specific adaptations and common mechanisms that apply across the species. Comparing the resulting cross-species molecular signatures with the within-species lifespan extension strategies will improve our understanding of mechanisms of longevity control and provide a starting point for novel and effective interventions.

OTHER RESEARCH

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Correction of β-thalassemia mutant by base editor in human embryos

β-Thalassemia is a global health issue, caused by mutations in the *HBB* gene. Among these mutations, *HBB* −28 (A>G) mutations is one of the three most common mutations in China and Southeast Asia patients with β-thalassemia. Correcting this mutation in human embryos may prevent the disease being passed onto future generations and cure anemia. Here we report the first study using base editor (BE) system to correct disease mutant in human embryos. Firstly, we produced a 293T cell line with an exogenous *HBB* −28 (A>G) mutant fragment for gRNAs and targeting efficiency evaluation. Then we collected primary skin fibroblast cells from a β-thalassemia patient with HBB −28 (A>G) homozygous mutation. Data showed that base editor could precisely correct *HBB* −28 (A>G) mutation in the patient's primary cells. To model homozygous mutation disease embryos, we constructed nuclear transfer embryos by fusing the lymphocyte or skin fibroblast cells with enucleated *in vitro* matured (IVM) oocytes. Notably, the gene correction efficiency was over 23.0% in these embryos by base editor. Although these embryos were still mosaic, the percentage of repaired blastomeres was over 20.0%. In addition, we found that base editor variants, with narrowed deamination window, could promote G-to-A conversion at *HBB* −28 site precisely in human embryos. Collectively, this study demonstrated the feasibility of curing genetic disease in human somatic cells and embryos by base editor system.