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Scientific News
5th of November 2017
Sven Bulterijs

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ALKAHEST

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Alkahest to Present Clinical Results from PLASMA Study in Patients with Mild to Moderate Alzheimer's Disease at the 10th Clinical Trials on Alzheimer's Disease (CTAD) Conference

November 1, 2017

SAN CARLOS, Calif. — Alkahest, Inc. ("Alkahest"), a clinical-stage biotechnology company focused on developing innovative therapies to treat age-related diseases, today announced an upcoming oral presentation at the 10th Clinical Trials on Alzheimer's Disease (CTAD) conference. The Principal Investigator, Sharon Sha, M.D., will present clinical results from the PLasma for Alzheimer SymptoM Amelioration (PLASMA) Study in patients with mild to moderate Alzheimer's Disease (AD). Alkahest sponsored the study which was conducted at the Stanford University School of Medicine.

"We are pleased to present these results from the PLASMA study, which demonstrate the safety of plasma-derived products and suggest their potential efficacy in Alzheimer's disease," said Karoly Nikolich, Ph.D., Chief Executive Officer of Alkahest. "These data add to the growing body of evidence supporting the ability of plasma compositions to counteract the biological processes underlying neurodegeneration, and reaffirm our confidence in our pipeline of first-in-class products targeting the pathways implicated in age-related disease. We look forward to advancing our lead clinical candidate, a proprietary plasma fraction, as a potential treatment for mild to moderate Alzheimer's disease."

The PLasma for Alzheimer SymptoM Amelioration (PLASMA) Study

Albert Einstein College of Medicine

Einstein Researchers Share $9 Million Grant to Find Anti-Aging Therapies

Newswise — October 16, 2017—BRONX, NY—Scientists now believe that the Fountain of Youth flows from our genes, or at least from the genes of people who live healthy lives to age 100 or later. To discover what's special about the genes of these centenarians—and apply that knowledge to extend the healthy lives of the rest of us —the National Institutes of Health has awarded researchers at Albert Einstein College of Medicine, part of Montefiore Medicine, and the Florida campus of The Scripps Research Institute (TSRI) a five-year, $9 million grant.

"Aging is arguably the key risk factor for the most common diseases that afflict us, including type 2 diabetes, cardiovascular disease, most types of cancer and Alzheimer's and other neurodegenerative diseases," says Jan Vijg, Ph.D., professor and chair of genetics and the Lola and Saul Kramer Chair in Molecular Genetics at Einstein and the study's principal investigator.

Rather than study age-related diseases, says Dr. Vijg, "We're focusing on the genetic differences between healthy centenarians and people with no family history of extreme longevity, looking for rare genetic variants that account for the centenarians' longevity. Once we pinpoint the beneficial effects that these novel gene variants are causing, we'll be in a position to develop drugs that mimic those effects and, ideally, help people attain longer, healthier lifespans."

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Using AI and Computer Vision Techniques to Determine Age and Assess the Effect of Therapies Against Aging in Mice, Increasing the Pace of Research.

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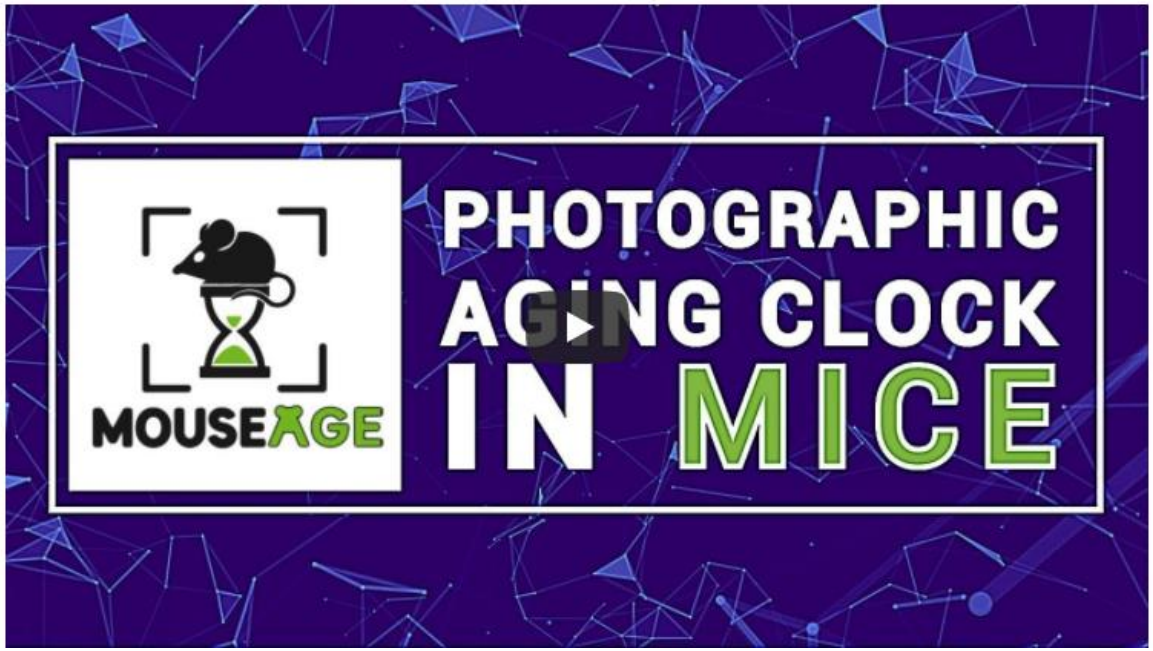

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Intercellular competition and the inevitability of multicellular aging

Paul Nelson[a,1] and Joanna Masel[a]

Current theories attribute aging to a failure of selection, due to either pleiotropic constraints or declining strength of selection after the onset of reproduction. These theories implicitly leave open the possibility that if senescence-causing alleles could be identified, or if antagonistic pleiotropy could be broken, the effects of aging might be ameliorated or delayed indefinitely. These theories are built on models of selection between multicellular organisms, but a full understanding of aging also requires examining the role of somatic selection within an organism. Selection between somatic cells (i.e., intercellular competition) can delay aging by purging nonfunctioning cells. However, the fitness of a multicellular organism depends not just on how functional its individual cells are but also on how well cells work together. While intercellular competition weeds out nonfunctional cells, it may also select for cells that do not cooperate. Thus, intercellular competition creates an inescapable double bind that makes aging inevitable in multicellular organisms.

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Endothelial transplantation rejuvenates aged hematopoietic stem cell function

Michael G. Poulos,[1,2,3] Pradeep Ramalingam,[1,2,3] Michael C. Gutkin,[1,2,3] Pierre Llanos,[4] Katherine Gilleran,[4] Sina Y. Rabbany,[4] and Jason M. Butler[1,2,3]

First published October 16, 2017 - More info

See the related Commentary at Young endothelial cells revive aging blood.

Abstract

Age-related changes in the hematopoietic compartment are primarily attributed to cell-intrinsic alterations in hematopoietic stem cells (HSCs); however, the contribution of the aged microenvironment has not been adequately evaluated. Understanding the role of the bone marrow (BM) microenvironment in supporting HSC function may prove to be beneficial in treating age-related functional hematopoietic decline. Here, we determined that aging of endothelial cells (ECs), a critical component of the BM microenvironment, was sufficient to drive hematopoietic aging phenotypes in young HSCs. We used an ex vivo hematopoietic stem and progenitor cell/EC (HSPC/EC) coculture system as well as in vivo EC infusions following myelosuppressive injury in mice to demonstrate that aged ECs impair the repopulating activity of young HSCs and impart a myeloid bias. Conversely, young ECs restored the repopulating capacity of aged HSCs but were unable to reverse the intrinsic myeloid bias. Infusion of young, HSC-supportive BM ECs enhanced hematopoietic recovery following myelosuppressive injury and restored endogenous HSC function in aged mice. Coinfusion of young ECs augmented aged HSC engraftment and enhanced overall survival in lethally irradiated mice by mitigating damage to the BM vascular microenvironment. These data lay the groundwork for the exploration of EC therapies that can serve as adjuvant modalities to enhance HSC engraftment and accelerate hematopoietic recovery in the elderly population following myelosuppressive regimens.

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Dysfunction of the MDM2/p53 axis is linked to premature aging

Davor Lessel,[1] Danyi Wu,[2] Carlos Trujillo,[3] Thomas Ramezani,[4] Ivana Lessel,[1] Mohammad K. Alwasiyah,[5] Bidisha Saha,[6] Fuki M. Hisama,[7] Katrin Rading,[1] Ingrid Goebel,[1] Petra Schütz,[8] Günter Speit,[8] Josef Högel,[8] Holger Thiele,[9] Gudrun Nürnberg,[9] Peter Nürnberg,[9,10,11] Matthias Hammerschmidt,[4,10,11] Yan Zhu,[2] David R. Tong,[2] Chen Katz,[2] George M. Martin,[6,12] Junko Oshima,[6,13] Carol Prives,[2] and Christian Kubisch[1,8]

First published August 28, 2017 - More info

Abstract

The tumor suppressor p53, a master regulator of the cellular response to stress, is tightly regulated by the E3 ubiquitin ligase MDM2 via an autoregulatory feedback loop. In addition to its well-established role in tumorigenesis, p53 has also been associated with aging in mice. Several mouse models with aberrantly increased p53 activity display signs of premature aging. However, the relationship between dysfunction of the MDM2/p53 axis and human aging remains elusive. Here, we have identified an antiterminating homozygous germline mutation in *MDM2* in a patient affected by a segmental progeroid syndrome. We show that this mutation abrogates MDM2 activity, thereby resulting in enhanced levels and stability of p53. Analysis of the patient's primary cells, genome-edited cells, and in vitro and in vivo analyses confirmed the MDM2 mutation's aberrant regulation of p53 activity. Functional data from a zebrafish model further demonstrated that mutant Mdm2 was unable to rescue a p53-induced apoptotic phenotype. Altogether, our findings indicate that mutant MDM2 is a likely driver of the observed segmental form of progeria.

Dietary Restriction and AMPK Increase Lifespan via Mitochondrial Network and Peroxisome Remodeling

Heather J. Weir, Pallas Yao, Frank K. Huynh, Caroline C. Escoubas, Renata L. Goncalves, Kristopher Burkewitz, Raymond Laboy[3], Matthew D. Hirschey, William B. Mair[4]

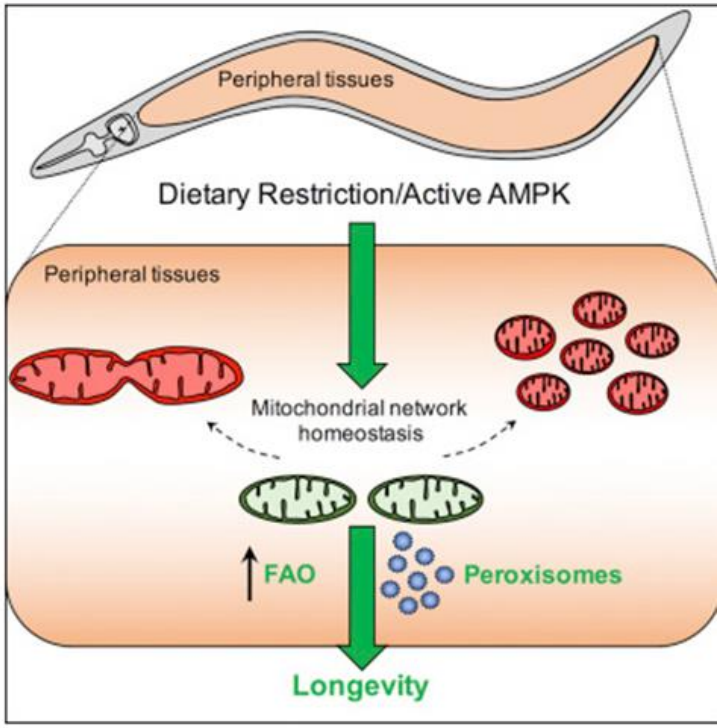
Highlights

- AMPK and DR maintain mitochondrial network homeostasis with age
- Mitochondrial fusion and fission are required for DR- and AMPK-mediated longevity
- Preserving mitochondrial homeostasis increases lifespan via fatty acid oxidation
- These longevity pathways require coordination between mitochondria and peroxisomes

Summary

Mitochondrial network remodeling between fused and fragmented states facilitates mitophagy, interaction with other organelles, and metabolic flexibility. Aging is associated with a loss of mitochondrial network homeostasis, but cellular processes causally linking these changes to organismal senescence remain unclear. Here, we show that AMP-activated protein kinase (AMPK) and dietary restriction (DR) promote longevity in *C. elegans* via maintaining mitochondrial network homeostasis and functional coordination with peroxisomes to increase fatty acid oxidation (FAO). Inhibiting fusion or fission specifically blocks AMPK- and DR-mediated longevity. Strikingly, however, preserving mitochondrial network homeostasis during aging by co-inhibition of fusion and fission is sufficient itself to increase lifespan, while dynamic network remodeling is required for intermittent fasting-mediated longevity. Finally, we show that increasing lifespan via maintaining mitochondrial network homeostasis requires FAO and peroxisomal function. Together, these data demonstrate that mechanisms that promote mitochondrial homeostasis and plasticity can be targeted to promote healthy aging.

Graphical Abstract



Redox Biol. 2017 Oct 7;14:386-390. doi: 10.1016/j.redox.2017.10.003. [Epub ahead of print]

Do developmental temperatures affect redox level and lifespan in C. elegans through upregulation of peroxiredoxin?

Henderson D[1], Huebner C[1], Markowitz M[1], Taube N[1], Harvanek ZM[1], Jakob U[2], Knoefler D[3].

Author information

Abstract

Lifespan in poikilothermic organisms, such as Caenorhabditis elegans, can be substantially increased simply by decreasing growth temperature. To gain insights into the mechanistic underpinnings of this effect, we investigated the effects of temperature in development and adulthood on C. elegans lifespan. We found that worms exposed to 25°C during development and shifted to 15°C in adulthood exhibited an even longer lifespan than animals constantly kept at 15°C. Analysis of the in vivo redox status demonstrated that at 25°C, C. elegans larvae have a more reduced redox state and higher Prdx-2 expression levels than animals raised at 15°C. Worms lacking prdx-2 fail to show the additional lifespan extension upon shift from 25°C to 15°C and reveal a lifespan similar to prdx-2 worms always kept at 15°C. These results suggest that transiently altering the in vivo redox state during development can have highly beneficial long-term consequences for organisms.

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Biol Open. 2017 Oct 20. pii: bio.027433. doi: 10.1242/bio.027433. [Epub ahead of print]

The addition of a developmental factor, unc-62, to already long-lived worms increases lifespan and healthspan.

Saqi D[1].

Author information

Abstract

Aging is a complex trait that is affected by multiple genetic pathways. A relatively unexplored approach is to manipulate multiple independent aging pathways simultaneously in order to observe their cumulative effect on lifespan. Here, we report the phenotypic characterization of a strain with changes in five aging pathways: 1) mitochondrial ROS production, 2) innate immunity, 3) stress response, 4) metabolic control and 5) developmental regulation in old age. The quintuply-modified strain has a lifespan that is 160% longer than the transgenic control strain. Additionally, the quintuply-modified strain maintains several physiological markers of aging for a longer time than the transgenic control. Our results support a modular approach as a general scheme to study how multiple pathways interact to achieve extreme longevity.

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A conserved KLF-autophagy pathway modulates nematode lifespan and mammalian age-associated vascular dysfunction

Loss of protein and organelle quality control secondary to reduced autophagy is a hallmark of aging. However, the physiologic and molecular regulation of autophagy in long-lived organisms remains incompletely understood. Here we show that the Kruppel-like family of transcription factors are important regulators of autophagy and healthspan in *C. elegans*, and also modulate mammalian vascular age-associated phenotypes. Kruppel-like family of transcription factor deficiency attenuates autophagy and lifespan extension across mechanistically distinct longevity nematode models. Conversely, Kruppel-like family of transcription factor overexpression extends nematode lifespan in an autophagy-dependent manner. Furthermore, we show the mammalian vascular factor Kruppel-like family of transcription factor 4 has a conserved role in augmenting autophagy and improving vessel function in aged mice. Kruppel-like family of transcription factor 4 expression also decreases with age in human vascular endothelium. Thus, Kruppel-like family of transcription factors constitute a transcriptional regulatory point for the modulation of autophagy and longevity in *C. elegans* with conserved effects in the murine vasculature and potential implications for mammalian vascular aging.

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J Neurosci. 2017 Oct 20. pii: 1230-17. doi: 10.1523/JNEUROSCI.1230-17.2017. [Epub ahead of print]

Pathological tau strains from human brains recapitulate the diversity of tauopathies in non-transgenic mouse brain.

Narasimhan S[1], Guo JL[1], Changolkar L[1], Stieber A[1], McBride JD[1], Silva LV[1], He Z[1], Zhang B[1], Gathagan RJ[1], Trojanowski JQ[1], Lee VMY[2].

Author information

Abstract

Pathological tau aggregates occur in Alzheimer's disease (AD) and other neurodegenerative tauopathies. It is not clearly understood why tauopathies vary greatly in the neuroanatomical and histopathological patterns of tau aggregation, which contribute to clinical heterogeneity in these disorders. Recent studies have shown that tau aggregates may form distinct structural conformations, known as tau strains. Here, we developed a novel model to test the hypothesis that cell-to-cell transmission of different tau strains occurs in non-transgenic (non-Tg) mice, and to investigate whether there are strain-specific differences in the pattern of tau transmission. By injecting pathological tau extracted from postmortem brains of AD (AD-tau), progressive supranuclear palsy (PSP-tau) and corticobasal degeneration (CBD-tau) patients into different brain regions of female non-Tg mice, we demonstrated the induction and propagation of endogenous mouse tau aggregates. Specifically, we identified differences in tau strain potency between AD-tau, CBD-tau, and PSP-tau in non-Tg mice. Moreover, differences in cell-type specificity of tau aggregate transmission were observed between tau strains such that only PSP-tau and CBD-tau strains induce astroglial and oligodendroglial tau inclusions, recapitulating the diversity of neuropathology in human tauopathies. Furthermore, we demonstrated the neuronal connectome, but not the tau strain, determines which brain regions develop tau pathology. Finally, CBD-tau and PSP-tau-injected mice showed spatiotemporal transmission of glial tau pathology, suggesting glial tau transmission contributes to the progression of tauopathies. Taken together, our data suggest that different tau strains determine seeding potency and cell-type specificity of tau aggregation that underlie the diversity of human tauopathies. **Significance Statement:** Tauopathies show great clinical and neuropathological heterogeneity, despite the fact that tau aggregates in each disease. This heterogeneity could be due to tau aggregates forming distinct structural conformations, or strains. We now report the development of a sporadic tauopathy model to study human tau strains by intracerebrally injecting non-Tg mice with pathological tau enriched from human tauopathy brains. We show human tau strains seed different types and cellular distributions of tau neuropathology in our model that recapitulate the heterogeneity seen in these human diseases.

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Evolution. 2017 Oct 20. doi: 10.1111/evo.13379. [Epub ahead of print]

The Williams' legacy: A critical reappraisal of his nine predictions about the evolution of senescence.

Gaillard JM[1], Lemaître JF[1].

⊕ Author information

Abstract

Williams' evolutionary theory of senescence based on antagonistic pleiotropy has become a landmark in evolutionary biology, and more recently in biogerontology and evolutionary medicine. In his original article, Williams launched a set of nine 'testable deductions' from his theory. Although some of these predictions have been repeatedly discussed, most have been overlooked and no systematic evaluation of the whole set of Williams' original predictions has been performed. For the sixtieth anniversary of the publication of the Williams' paper, we provide an updated evaluation of all these predictions. We present the pros and cons of each prediction based on recent accumulation of both theoretical and empirical studies performed in the laboratory and in the wild. From our viewpoint, six predictions are mostly supported by our current knowledge at least under some conditions (although Williams' theory cannot thoroughly explain why for some of them). Three predictions, all involving the timing of senescence, are not supported. Our critical review of Williams' predictions highlights the importance of William's contribution and clearly demonstrates that, 60 years after its publication, his paper does not show any sign of senescence.

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Cancer Biol Ther. 2017 Oct 20:0. doi: 10.1080/15384047.2017.1385675. [Epub ahead of print]

Some chemotherapeutics-treated colon cancer cells display a specific phenotype being a combination of stem-like and senescent cell features.

Was H[1,2], Czarnecka J[1], Kowalczyk A[3], Barszcz K[1], Bernas T[4], Piwocka K[3], Kaminska B[1].

Author information

Abstract

Colorectal cancer (CRC) is the second leading cause of death among cancer patients in the Northern countries. CRC can reappear a long time after treatment. Recent clinical studies demonstrated that, in response to chemotherapy, cancer cells may undergo stress-induced premature senescence (SIPS), which typically results in growth arrest. Nonetheless, these senescent cells were reported to divide in an atypical manner and thus contribute to cancer re-growth. Therefore, we examined if SIPS escape may follow treatment with chemotherapeutics used clinically: 5-fluorouracil (5-FU), oxaliplatin (OXA) and irinotecan (IRINO). To mimic the therapeutic regimes we exposed human colon cancer HCT116 and SW480 cells to repeated cycles of drug treatment. The cells treated with 5-FU or IRINO exhibited several hallmarks of SIPS: growth arrest, increased size and granularity, polyploidization, augmented activity of the SA-β-galactosidase, accumulation of P21 and CYCLIN D1 proteins, and the senescence-associated secretory phenotype. Moreover, re-population of the cancer cell cultures was delayed upon treatment with the senescence-inducing agents. At the same time, we detected a subpopulation of senescent colon cancer cells with features of stemness: elevated NANOG expression, exclusion of Hoechst 33342 (typical for side population) and increased CD24 expression. Additionally, rare, polyploid cells exhibited blastocyst-like morphology and produced progeny. In parallel, majority of chemotherapeutics-treated cells underwent mesenchymal to epithelial transition, as the percentage of CD44-positve cells was reduced, and levels of E-cadherin (epithelial marker) were elevated. Our study demonstrates that a subpopulation of chemotherapeutics-treated colon cancer cells display a specific phenotype being a combination of stem-like and senescent cell features. This may contribute to their resistance to chemotherapy and their ability to re-grow cancer after completion of therapeutic intervention.

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The Gut Microbiota of Healthy Aged Chinese Is Similar to That of the Healthy Young

The microbiota of the aged is variously described as being more or less diverse than that of younger cohorts, but the comparison groups used and the definitions of the aged population differ between experiments. The differences are often described by null hypothesis statistical tests, which are notoriously irreproducible when dealing with large multivariate samples. We collected and examined the gut microbiota of a cross-sectional cohort of more than 1,000 very healthy Chinese individuals who spanned ages from 3 to over 100 years. The analysis of 16S rRNA gene sequencing results used a compositional data analysis paradigm coupled with measures of effect size, where ordination, differential abundance, and correlation can be explored and analyzed in a unified and reproducible framework. Our analysis showed several surprising results compared to other cohorts. First, the overall microbiota composition of the healthy aged group was similar to that of people decades younger. Second, the major differences between groups in the gut microbiota profiles were found before age 20. Third, the gut microbiota differed little between individuals from the ages of 30 to >100. Fourth, the gut microbiota of males appeared to be more variable than that of females. Taken together, the present findings suggest that the microbiota of the healthy aged in this cross-sectional study differ little from that of the healthy young in the same population, although the minor variations that do exist depend upon the comparison cohort.

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Nat Commun. 2017 Oct 10;8(1):845. doi: 10.1038/s41467-017-00900-1.

The gut microbiome in atherosclerotic cardiovascular disease.

Jie Z[1,2,3], Xia H[1,2], Zhong SL[4,5], Feng Q[1,2,6,7,8], Li S[1], Liang S[1,2], Zhong H[1,2,3,7], Liu Z[1,9], Gao Y[1,2], Zhao H[1], Zhang D[1], Su Z[1], Fang Z[1], Lan Z[1], Li J[1,2,3,10], Xiao L[1,2,6], Li J[1], Li R[11], Li X[1,2], Li F[1,2,9], Ren H[1], Huang Y[1], Peng Y[1,12], Li G[1], Wen B[1,2], Dong B[1], Chen JY[4], Geng QS[4], Zhang ZW[4], Yang H[1,2,13], Wang J[1,2,13], Wang J[1,14,15], Zhang X[16], Madsen L[1,2,7,17], Brix S[18], Ning G[19], Xu X[1,2], Liu X[1,2], Hou Y[1,2], Jia H[20,21,22,23], He K[24], Kristiansen K[25,26,27].

⊕ Author information

Abstract

The gut microbiota has been linked to cardiovascular diseases. However, the composition and functional capacity of the gut microbiome in relation to cardiovascular diseases have not been systematically examined. Here, we perform a metagenome-wide association study on stools from 218 individuals with atherosclerotic cardiovascular disease (ACVD) and 187 healthy controls. The ACVD gut microbiome deviates from the healthy status by increased abundance of Enterobacteriaceae and Streptococcus spp. and, functionally, in the potential for metabolism or transport of several molecules important for cardiovascular health. Although drug treatment represents a confounding factor, ACVD status, and not current drug use, is the major distinguishing feature in this cohort. We identify common themes by comparison with gut microbiome data associated with other cardiometabolic diseases (obesity and type 2 diabetes), with liver cirrhosis, and rheumatoid arthritis. Our data represent a comprehensive resource for further investigations on the role of the gut microbiome in promoting or preventing ACVD as well as other related diseases.The gut microbiota may play a role in cardiovascular diseases. Here, the authors perform a metagenome-wide association study on stools from individuals with atherosclerotic cardiovascular disease and healthy controls, identifying microbial strains and functions associated with the disease.

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Deposition and hydrolysis of serine dipeptide lipids of Bacteroidetes bacteria in human arteries: relationship to atherosclerosis

Reza Nemati[1,*], Christopher Dietz[1,*], Emily J. Anstadt[†], Jorge Cervantes[§], Yaling Liu[**], Floyd E. Dewhirst[††], Robert B. Clark[†], Sydney Finegold[§§], James J. Gallagher[***], Michael B. Smith[*], Xudong Yao[*,†††] and Frank C. Nichols[2,**]

Multiple reaction monitoring–MS analysis of lipid extracts from human carotid endarterectomy and carotid artery samples from young individuals consistently demonstrated the presence of bacterial serine dipeptide lipid classes, including Lipid 654, an agonist for human and mouse Toll-like receptor (TLR)2, and Lipid 430, the deacylated product of Lipid 654. The relative levels of Lipid 654 and Lipid 430 were also determined in common oral and intestinal bacteria from the phylum Bacteroidetes and human serum and brain samples from healthy adults. The median Lipid 430/Lipid 654 ratio observed in carotid endarterectomy samples was significantly higher than the median ratio in lipid extracts of common oral and intestinal Bacteroidetes bacteria, and serum and brain samples from healthy subjects. More importantly, the median Lipid 430/Lipid 654 ratio was significantly elevated in carotid endarterectomies when compared with control artery samples. Our results indicate that deacylation of Lipid 654 to Lipid 430 likely occurs in diseased artery walls due to phospholipase A2 enzyme activity. These results suggest that commensal Bacteriodetes bacteria of the gut and the oral cavity may contribute to the pathogenesis of TLR2-dependent atherosclerosis through serine dipeptide lipid deposition and metabolism in artery walls.

Monitoring inflammation injuries in the progression of atherosclerosis with contrast enhanced ultrasound molecular imaging

Purpose

The upregulation of vascular cell adhesion molecule-1(VCAM-1) on vascular endothelium plays a great role in the progression of atherosclerosis (AS). In this study, ultrasound molecular imaging was performed to monitor the inflammation injuries in the onset and progression of atherosclerosis with microbubbles targeted to VCAM-1.

Methods

Mice deficient for the apolipoprotein E ($ApoE^{-/-}$mice) with high-cholesterol diet were studied as an age-dependent model of atherosclerosis. At 8, 16, 24, and 32 weeks of age, contrast enhanced ultrasound (CEU) molecular imaging of proximal ascending aorta was performed with microbubbles targeted to VCAM-1. Plaque size, monocytes infiltration and the expression of VCAM-1 in the proximal ascending aorta were assessed by histology and western blot analysis, separately.

Results

In $ApoE^{-/-}$ mice, molecular imaging for VCAM-1 detected selective signal enhancement ($P<0.01$ versus non-targeted microbubbles) at all ages of $ApoE^{-/-}$ mice. Moreover, signals from targeted microbubbles increased from 8wks to 32wks age ($P<0.05$ for trend) in $ApoE^{-/-}$ mice, indicating the upregulation of VCAM-1 with the progression of atherosclerosis. Consistent with CEU imaging results, both western blot analysis and immunohistochemistry revealed the expression of VCAM-1 and monocytes infiltration were age-dependent in $ApoE^{-/-}$ mice.

Conclusions

CEU molecular imaging can be used to noninvasively detect the VCAM-1 expression on the endothelium in the progression of atherosclerosis. By investigating specific molecular biomarkers, it could help to monitor the inflammation and the progression of AS, which may in some extent contribute to the prediction of vulnerable plaque.

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MicroRNAs miR-203-3p, miR-664-3p and miR-708-5p are associated with median strain lifespan in mice

MicroRNAs (miRNAs) are small non-coding RNA species that have been shown to have roles in multiple processes that occur in higher eukaryotes. They act by binding to specific sequences in the 3' untranslated region of their target genes and causing the transcripts to be degraded by the RNA-induced silencing complex (RISC). MicroRNAs have previously been reported to demonstrate altered expression in several aging phenotypes such as cellular senescence and age itself. Here, we have measured the expression levels of 521 small regulatory microRNAs (miRNAs) in spleen tissue from young and old animals of 6 mouse strains with different median strain lifespans by quantitative real-time PCR. Expression levels of 3 microRNAs were robustly associated with strain lifespan, after correction for multiple statistical testing (miR-203-3p [β-coefficient = –0.6447, $p = 4.8 \times 10^{-11}$], miR-664-3p [β-coefficient = 0.5552, $p = 5.1 \times 10^{-8}$] and miR-708-5p [β-coefficient = 0.4986, $p = 1.6 \times 10^{-6}$]). Pathway analysis of binding sites for these three microRNAs revealed enrichment of target genes involved in key aging and longevity pathways including mTOR, FOXO and MAPK, most of which also demonstrated associations with longevity. Our results suggests that miR-203-3p, miR-664-3p and miR-708-5p may be implicated in pathways determining lifespan in mammals.

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Age-associated microRNA expression in human peripheral blood is associated with all-cause mortality and age-related traits

Recent studies provide evidence of correlations of DNA methylation and expression of protein-coding genes with human aging. The relations of microRNA expression with age and age-related clinical outcomes have not been characterized thoroughly. We explored associations of age with whole-blood microRNA expression in 5221 adults and identified 127 microRNAs that were differentially expressed by age at $P < 3.3 \times 10^{-4}$ (Bonferroni-corrected). Most microRNAs were underexpressed in older individuals. Integrative analysis of microRNA and mRNA expression revealed changes in age-associated mRNA expression possibly driven by age-associated microRNAs in pathways that involve RNA processing, translation, and immune function. We fitted a linear model to predict 'microRNA age' that incorporated expression levels of 80 microRNAs. MicroRNA age correlated modestly with predicted age from DNA methylation ($r = 0.3$) and mRNA expression ($r = 0.2$), suggesting that microRNA age may complement mRNA and epigenetic age prediction models. We used the difference between microRNA age and chronological age as a biomarker of accelerated aging (Δage) and found that Δage was associated with all-cause mortality (hazards ratio 1.1 per year difference, $P = 4.2 \times 10^{-5}$ adjusted for sex and chronological age). Additionally, Δage was associated with coronary heart disease, hypertension, blood pressure, and glucose levels. In conclusion, we constructed a microRNA age prediction model based on whole-blood microRNA expression profiling. Age-associated microRNAs and their targets have potential utility to detect accelerated aging and to predict risks for age-related diseases.

Small molecule modulation of splicing factor expression is associated with rescue from cellular senescence

Eva Latorre, Vishal C. Birar, Angela N. Sheerin, J. Charles C. Jeynes, Amy Hooper, Helen R. Dawe, David Melzer, Lynne S. Cox, Richard G. A. Faragher, Elizabeth L. Ostler ✉ and Lorna W. Harries ✉

Background

Altered expression of mRNA splicing factors occurs with ageing in vivo and is thought to be an ageing mechanism. The accumulation of senescent cells also occurs in vivo with advancing age and causes much degenerative age-related pathology. However, the relationship between these two processes is opaque. Accordingly we developed a novel panel of small molecules based on resveratrol, previously suggested to alter mRNA splicing, to determine whether altered splicing factor expression had potential to influence features of replicative senescence.

Results

Treatment with resveralogues was associated with altered splicing factor expression and rescue of multiple features of senescence. This rescue was independent of cell cycle traverse and also independent of SIRT1, SASP modulation or senolysis. Under growth permissive conditions, cells demonstrating restored splicing factor expression also demonstrated increased telomere length, re-entered cell cycle and resumed proliferation. These phenomena were also influenced by ERK antagonists and agonists.

Conclusions

This is the first demonstration that moderation of splicing factor levels is associated with reversal of cellular senescence in human primary fibroblasts. Small molecule modulators of such targets may therefore represent promising novel anti-degenerative therapies.

A Young Blood Environment Decreases Aging of Senile Mice Kidneys

Qi Huang, MD, Yichun Ning, MD, Dong Liu, MD, Ying Zhang, MD, Diangeng Li, MD, Yinping Zhang, MD, Zhong Yin, MD, Bo Fu, MD, Guangyan Cai, MD, Xuefeng Sun, PhD ✉ ..
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The Journals of Gerontology: Series A, glx183, https://doi.org/10.1093/gerona/glx183
Published: 13 October 2017 **Article history ▾**

Abstract

Whether changes in internal body environment affect kidney aging remains unclear. Specifically, it is unknown whether transplanted kidneys from older donors recover from tissue damage after placement in younger recipients. In this study, a parabiosis animal model was established to investigate the effects of a young internal body environment on aged kidneys. The animals were divided into six groups: young (Ycon) and old control (Ocon) groups, isochronic youth–youth group (Y-IP), elderly–elderly group (O-IP), and heterochronic youth (Y-HP) and elderly (O-HP) groups. After parabiosis, tubule and interstitial tissue scores in the O-HP group were significantly lower than in the Ocon and O-IP groups. The expression of aging-related protein p16 and SA-β-gal in the O-HP group was significantly reduced compared with the Ocon and O-IP groups. Autophagy factors Atg5 and LC3BII were significantly upregulated, whereas the expression of the autophagic degradation marker (P62) was significantly downregulated in the O-HP group compared with the Ocon and O-IP groups. With the same comparison, the positive cells of TUNEL staining and the expression of IL-6 and IL-1β were significantly reduced, whereas the total/cleaved caspase-3 and total/pNF-κB were significantly increased in the O-HP group. The results demonstrated that a young blood environment significantly reduces kidney aging. These findings provide new evidence supporting an increase in the upper age limit for human kidney transplantation donors.

Hum Mol Genet. 2017 Sep 1. doi: 10.1093/hmg/ddx341. [Epub ahead of print]

Low-dose rapamycin extends lifespan in a mouse model of mtDNA depletion syndrome.

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Author information

Abstract

Mitochondrial disorders affecting oxidative phosphorylation (OxPhos) are caused by mutations in both the nuclear and mitochondrial genomes. One promising candidate for treatment is the drug rapamycin, which has been shown to extend lifespan in multiple animal models, and which was previously shown to ameliorate mitochondrial disease in a knock-out mouse model lacking a nuclear-encoded gene specifying an OxPhos structural subunit (Ndufs4). In that model, relatively high-dose intraperitoneal rapamycin extended lifespan and improved markers of neurological disease, via an unknown mechanism. Here, we administered low-dose oral rapamycin to a knock-in (KI) mouse model of authentic mtDNA disease, specifically, progressive mtDNA depletion syndrome, resulting from a mutation in the mitochondrial nucleotide salvage enzyme thymidine kinase 2 (TK2). Importantly, low-dose oral rapamycin was sufficient to extend Tk2KI/KI mouse lifespan significantly, and did so in the absence of detectable improvements in mitochondrial dysfunction. We found no evidence that rapamycin increased survival by acting through canonical pathways, including mitochondrial autophagy. However, transcriptomics and metabolomics analyses uncovered systemic metabolic changes pointing to a potential "rapamycin metabolic signature." These changes also implied that rapamycin may have enabled the Tk2KI/KI mice to utilize alternative energy reserves, and possibly triggered indirect signaling events that modified mortality through developmental reprogramming. From a therapeutic standpoint, our results support the possibility that low-dose rapamycin, while not targeting the underlying mtDNA defect, could represent a crucial therapy for the treatment of mtDNA-driven, and some nuclear DNA-driven, mitochondrial diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

TORC1 organized in inhibited domains (TOROIDs) regulate TORC1 activity

Manoël Prouteau, Ambroise Desfosses, Christian Sieben, Clélia Bourgoint, Nour Lydia Mozaffari, Davide Demurtas, Alok K. Mitra, Paul Guichard, Suliana Manley & Robbie Loewith

The target of rapamycin (TOR) is a eukaryotic serine/threonine protein kinase that functions in two distinct complexes, TORC1 and TORC2, to regulate growth and metabolism[1, 2]. GTPases, responding to signals generated by abiotic stressors, nutrients, and, in metazoans, growth factors, play an important[3] but poorly understood role in TORC1 regulation. Here we report that, in budding yeast, glucose withdrawal (which leads to an acute loss of TORC1 kinase activity[4]) triggers a similarly rapid Rag GTPase-dependent redistribution of TORC1 from being semi-uniform around the vacuolar membrane to a single, vacuole-associated cylindrical structure visible by super-resolution optical microscopy. Three-dimensional reconstructions of cryo-electron micrograph images of these purified cylinders demonstrate that TORC1 oligomerizes into a higher-level hollow helical assembly, which we name a TOROID (TORC1 organized in inhibited domain). Fitting of the recently described mammalian TORC1 structure into our helical map reveals that oligomerization leads to steric occlusion of the active site. Guided by the implications from our reconstruction, we present a *TOR1* allele that prevents both TOROID formation and TORC1 inactivation in response to glucose withdrawal, demonstrating that oligomerization is necessary for TORC1 inactivation. Our results reveal a novel mechanism by which Rag GTPases regulate TORC1 activity and suggest that the reversible assembly and/or disassembly of higher-level structures may be an underappreciated mechanism for the regulation of protein kinases.

Less than 5% had side effects after a one year rapamycin treatment.

Lung function response and side effects to rapamycin for lymphangioleiomyomatosis: a prospective national cohort study

Janet Bee[1], Sharon Fuller[1], Suzanne Miller[2], Simon R Johnson[1, 2]

Author affiliations +

Abstract

Rationale Mechanistic target of rapamycin inhibitors reduce loss of lung function in lymphangioleiomyomatosis (LAM), although their benefit varies between individuals. We examined lung function response and side effects to rapamycin in a national cohort.

Methods Subjects were receiving rapamycin for progressive lung disease. Clinical evaluation, detailed phenotyping, serial lung function, rapamycin and safety monitoring were performed according to a clinical protocol. Lung function change, measured as FEV_1 slope (ΔFEV_1), was reported for those treated for 1 year or longer.

Results Rapamycin was associated with improved ΔFEV_1 in 21 individuals where pretreatment data were available ($p<0.0001$). In 47 treated for a mean duration of 35.8 months, mean ΔFEV_1 was +11 (SD 75) mL/year, although it varied from +254 to −148 mL/year. The quartile with the highest positive ΔFEV_1 had greater pretreatment FEV_1 ($p=0.02$) and shorter disease durations ($p=0.02$) than the lowest quartile. Serum rapamycin level was positively associated with side effects ($p=0.02$) but not ΔFEV_1 over 1 year. Within the first month of therapy, apthous ulcers, nausea and diarrhoea were associated with higher rapamycin levels. Acne, oedema and menstrual irregularities tended to increase over the first year of therapy. At the end of observation, the prevalence of side effects was 5% or less.

Conclusions Rapamycin reduces lung function loss in LAM, although in some, ΔFEV_1 continues to fall at an accelerated rate. Poor response to rapamycin was associated with lower pretreatment lung function and longer disease duration but not serum level. Early intervention with low-dose rapamycin may preserve lung function and reduce side effects.

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HEALTHY LIFE EXTENSION SOCIETY

Genome-wide meta-analysis associates *HLA-DQA1/DRB1* and *LPA* and lifestyle factors with human longevity

Genomic analysis of longevity offers the potential to illuminate the biology of human aging. Here, using genome-wide association meta-analysis of 606,059 parents' survival, we discover two regions associated with longevity (*HLA-DQA1/DRB1* and *LPA*). We also validate previous suggestions that APOE, *CHRNA3/5*, *CDKN2A/B*, *SH2B3* and *FOXO3A* influence longevity. Next we show that giving up smoking, educational attainment, openness to new experience and high-density lipoprotein (HDL) cholesterol levels are most positively genetically correlated with lifespan while susceptibility to coronary artery disease (CAD), cigarettes smoked per day, lung cancer, insulin resistance and body fat are most negatively correlated. We suggest that the effect of education on lifespan is principally mediated through smoking while the effect of obesity appears to act via CAD. Using instrumental variables, we suggest that an increase of one body mass index unit reduces lifespan by 7 months while 1 year of education adds 11 months to expected lifespan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Do "big guys" really die younger? An examination of height and lifespan in former professional basketball players

While factors such as genetics may mediate the relationship between height and mortality, evidence suggests that larger body size may be an important risk indicator of reduced lifespan longevity in particular. This study critically examined this relationship in professional basketball players. We examined living and deceased players who have played in the National Basketball Association (debut between 1946–2010) and/or the American Basketball Association (1967–1976) using descriptive and Kaplan-Meier and Cox regression analyses. The cut-off date for death data collection was December 11, 2015. Overall, 3,901 living and deceased players were identified and had a mean height of 197.78 cm (± 9.29, Range: 160.02–231.14), and of those, 787 former players were identified as deceased with a mean height of 193.88 cm (± 8.83, Range: 167.6–228.6). Descriptive findings indicated that the tallest players (top 5%) died younger than the shortest players (bottom 5%) in all but one birth decade (1941–1950). Similarly, survival analyses showed a significant relationship between height and lifespan longevity when both dichotomizing [χ^2 (1) = 13.04, $p < .05$] and trichotomizing [χ^2 (2) = 18.05, $p < .05$] the predictor variable height per birth decade, where taller players had a significantly higher mortality risk compared to shorter players through median (HR: 1.30, 95% CI: 1.13–1.50, $p < .05$) and trichotomized tertile split (HR: 1.40, 95% CI: 1.18–1.68, $p < .05$; tallest 33.3% compared to shortest 33.3%) analyses. The uniqueness of examining the height-longevity hypothesis in this relatively homogeneous sub-population should be considered when interpreting these results. Further understanding of the potential risks of early mortality can help generate discourse regarding potential at-risk cohorts of the athlete population.

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Angew Chem Int Ed Engl. 2017 Oct 9;56(42):12873-12877. doi: 10.1002/anie.201705873. Epub 2017 Sep 13.

HKOH-1: A Highly Sensitive and Selective Fluorescent Probe for Detecting Endogenous Hydroxyl Radicals in Living Cells.

Bai X[1], Huang Y[1], Lu M[1], Yang D[1].

Author information

Abstract

The hydroxyl radical (· OH), one of the most reactive and deleterious reactive oxygen species (ROS), has been suggested to play an essential role in many physiological and pathological scenarios. However, a reliable and robust method to detect endogenous · OH is currently lacking owing to its extremely high reactivity and short lifetime. Herein we report a fluorescent probe HKOH-1 with superior in vitro selectivity and sensitivity towards · OH. With this probe, we have calibrated and quantified the scavenging capacities of a wide range of reported · OH scavengers. Furthermore, HKOH-1r, which was designed for better cellular uptake and retention, has performed robustly in detection of endogenous · OH generation by both confocal imaging and flow cytometry. Furthermore, this probe has been applied to monitor · OH generation in HeLa cells in response to UV light irradiation. Therefore, HKOH-1 could be used for elucidating · OH related biological functions.

Hippo pathway deficiency reverses systolic heart failure after infarction

John P. Leach, Todd Heallen, Min Zhang, Mahdis Rahmani, Yuka Morikawa, Matthew C. Hill, Ana Segura, James T. Willerson & James F. Martin

Mammalian organs vary widely in regenerative capacity. Poorly regenerative organs, such as the heart are particularly vulnerable to organ failure. Once established, heart failure commonly results in mortality[1]. The Hippo pathway, a kinase cascade that prevents adult cardiomyocyte proliferation and regeneration[2], is upregulated in human heart failure. Here we show that deletion of the Hippo pathway component Salvador (Salv) in mouse hearts with established ischaemic heart failure after myocardial infarction induces a reparative genetic program with increased scar border vascularity, reduced fibrosis, and recovery of pumping function compared with controls. Using translating ribosomal affinity purification, we isolate cardiomyocyte-specific translating messenger RNA. Hippo-deficient cardiomyocytes have increased expression of proliferative genes and stress response genes, such as the mitochondrial quality control gene, *Park2*. Genetic studies indicate that *Park2* is essential for heart repair, suggesting a requirement for mitochondrial quality control in regenerating myocardium. Gene therapy with a virus encoding *Salv* short hairpin RNA improves heart function when delivered at the time of infarct or after ischaemic heart failure following myocardial infarction was established. Our findings indicate that the failing heart has a previously unrecognized reparative capacity involving more than cardiomyocyte renewal.

REVIEWS/COMMENTS/EDITORIALS

Biochemistry. 2017 Oct 24. doi: 10.1021/acs.biochem.7b00862. [Epub ahead of print]

Noncanonical Roles of Lipids in Different Cellular Fates.

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Author information

Abstract

Lipids are a diverse class of biomolecules. The biosynthesis and transport of these molecules are controlled by a considerable number of proteins, which facilitate spatiotemporal regulation of lipids during different fundamental cellular processes. Although lipids are traditionally considered as molecules for energy storage and as structural components of membranes, they are being increasingly recognized for their signaling roles. There is a growing appreciation of lipids' chemical diversity, which approaches that of proteins. In this Perspective, we discuss recent studies that suggest novel functions for distinct lipid species during different cellular processes. In particular, we discuss findings from our laboratory that illuminate the involvement of ceramides, polyunsaturated triacylglycerols, and very long chain fatty acids in different cellular fates. We also highlight recent innovative methods that have enabled the recognition of previously unknown lipid classes and/or roles of these molecules in different biological processes. We envision that advances in lipid identification, visualization, and perturbation will pave the way for broader investigations into this fascinating and influential class of biomolecules.

Exp Gerontol. 2017 Oct 17. pii: S0531-5565(17)30464-3. doi: 10.1016/j.exger.2017.10.015. [Epub ahead of print]

Mechanisms driving the ageing heart.

Anderson R[1], Richardson GD[2], Passos JF[3].

Author information

Abstract

Cardiovascular disease (CVD) is the leading cause of death globally. Although the number one risk factor for CVD is age, the detrimental biological processes that occur in the heart during ageing remain elusive. It is therefore vitality important to understand the fundamental mechanisms driving heart ageing to enable the development of preventions and treatments targeting these processes. Cellular senescence has been described more than fifty years ago as the irreversible cell-cycle arrest which occurs in somatic cells. Emerging evidence suggests that cellular senescence plays a key role in heart ageing, however the cell-types involved and the underlying mechanisms are not yet elucidated. In this review we discuss the current understanding of how mechanisms known to contribute to senescence impact on heart ageing and CVD. Finally, we will review recent data suggesting that targeting senescent cells may be a viable therapy to counteract the ageing of the heart.

Exp Gerontol. 2017 Oct 17. pii: S0531-5565(17)30714-3. doi: 10.1016/j.exger.2017.10.014. [Epub ahead of print]

Adipose tissue inflammation in aging.

Mau T, Yung R.

Abstract

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

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging, Metabolism, and Cancer Development: from Peto's Paradox to the Warburg Effect

Tia R. Tidwell,[1,2] Kjetil Søreide,[2,3,4] and Hanne R. Hagland[1,2,*]

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Abstract

Go to:

Medical advances made over the last century have increased our lifespan, but age-related diseases are a fundamental health burden worldwide. Aging is therefore a major risk factor for cardiovascular disease, cancer, diabetes, obesity, and neurodegenerative diseases, all increasing in prevalence. However, huge inter-individual variations in aging and disease risk exist, which cannot be explained by chronological age, but rather physiological age decline initiated even at young age due to lifestyle. At the heart of this lies the metabolic system and how this is regulated in each individual. Metabolic turnover of food to energy leads to accumulation of co-factors, byproducts, and certain proteins, which all influence gene expression through epigenetic regulation. How these epigenetic markers accumulate over time is now being investigated as the possible link between aging and many diseases, such as cancer. The relationship between metabolism and cancer was described as early as the late 1950s by Dr. Otto Warburg, before the identification of DNA and much earlier than our knowledge of epigenetics. However, when the stepwise gene mutation theory of cancer was presented, Warburg's theories garnered little attention. Only in the last decade, with epigenetic discoveries, have Warburg's data on the metabolic shift in cancers been brought back to life. The stepwise gene mutation theory fails to explain why large animals with more cells, do not have a greater cancer incidence than humans, known as Peto's paradox. The resurgence of research into the Warburg effect has given us insight to what may explain Peto's paradox. In this review, we discuss these connections and how age-related changes in metabolism are tightly linked to cancer development, which is further affected by lifestyle choices modulating the risk of aging and cancer through epigenetic control.

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ILAR J. 2017 Aug 28:1-16. doi: 10.1093/ilar/ilx025. [Epub ahead of print]

Nonhuman Primates and Translational Research-Cardiovascular Disease.

Cox LA[1], Olivier M[1], Spradling-Reeves K[1], Karere GM[1], Comuzzie AG[1], VandeBerg JL[1].

⊕ Author information

Abstract

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States. Human epidemiological studies provide challenges for understanding mechanisms that regulate initiation and progression of CVD due to variation in lifestyle, diet, and other environmental factors. Studies describing metabolic and physiologic aspects of CVD, and those investigating genetic and epigenetic mechanisms influencing CVD initiation and progression, have been conducted in multiple Old World nonhuman primate (NHP) species. Major advantages of NHPs as models for understanding CVD are their genetic, metabolic, and physiologic similarities with humans, and the ability to control diet, environment, and breeding. These NHP species are also genetically and phenotypically heterogeneous, providing opportunities to study gene by environment interactions that are not feasible in inbred animal models. Each Old World NHP species included in this review brings unique strengths as models to better understand human CVD. All develop CVD without genetic manipulation providing multiple models to discover genetic variants that influence CVD risk. In addition, as each of these NHP species age, their age-related comorbidities such as dyslipidemia and diabetes are accelerated proportionally 3 to 4 times faster than in humans.In this review, we discuss current CVD-related research in NHPs focusing on selected aspects of CVD for which nonprimate model organism studies have left gaps in our understanding of human disease. We include studies on current knowledge of genetics, epigenetics, calorie restriction, maternal calorie restriction and offspring health, maternal obesity and offspring health, nonalcoholic steatohepatitis and steatosis, Chagas disease, microbiome, stem cells, and prevention of CVD.

OTHER RESEARCH

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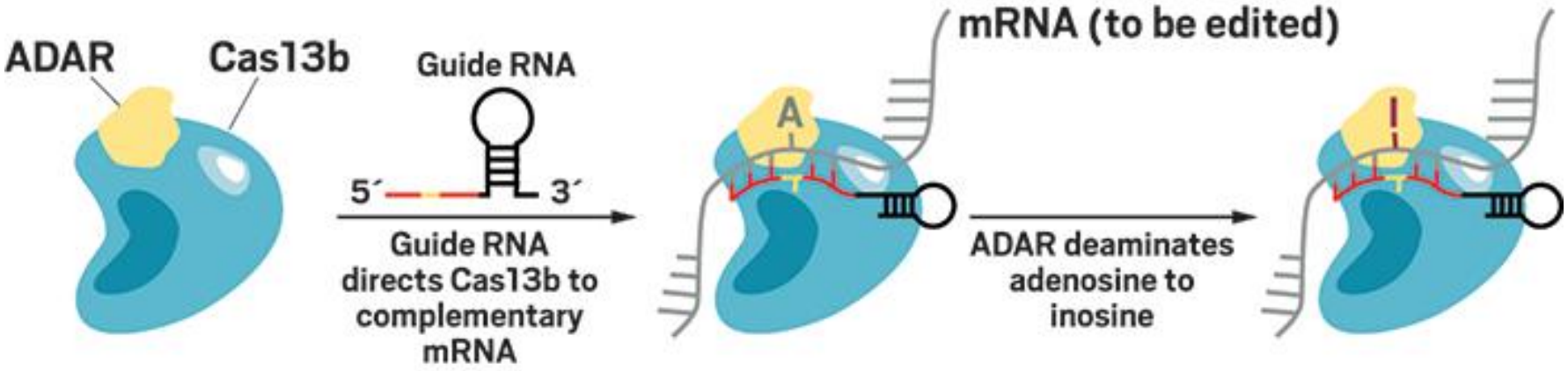
Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage

Nicole M. Gaudelli, Alexis C. Komor, Holly A. Rees, Michael S. Packer, Ahmed H. Badran, David I. Bryson & David R. Liu

The spontaneous deamination of cytosine is a major source of C•G to T•A transitions, which account for half of known human pathogenic point mutations. The ability to efficiently convert target A•T base pairs to G•C could therefore advance the study and treatment of genetic diseases. While the deamination of adenine yields inosine, which is treated as guanine by polymerases, no enzymes are known to deaminate adenine in DNA. Here we report adenine base editors (ABEs) that mediate conversion of A•T to G•C in genomic DNA. We evolved a tRNA adenosine deaminase to operate on DNA when fused to a catalytically impaired CRISPR-Cas9. Extensive directed evolution and protein engineering resulted in seventh-generation ABEs (*e.g.*, ABE7.10), that convert target A•T to G•C base pairs efficiently (~50% in human cells) with very high product purity (typically ≥ 99.9%) and very low rates of indels (typically ≤ 0.1%). ABEs introduce point mutations more efficiently and cleanly than a current Cas9 nuclease-based method, induce less off-target genome modification than Cas9, and can install disease-correcting or disease-suppressing mutations in human cells. Together with our previous base editors, ABEs advance genome editing by enabling the direct, programmable introduction of all four transition mutations without double-stranded DNA cleavage.


ADAR
Cas13b
Guide RNA
5´
3´
Guide RNA directs Cas13b to complementary mRNA
mRNA (to be edited)
A
ADAR deaminates adenosine to inosine

Heales
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Fresh human brains yield delicious data

By Roni Dengler | Oct. 25, 2017 , 3:01 AM

One man's neuron is another man's knowledge. That's the stance of the Allen Institute for Brain Science, which this week released **the first open-access database of live human brain cells**. It contains data on the electrical properties of about 300 cortical neurons taken from 36 patients and 3D reconstructions of 100 of those cells, plus gene expression data from 16,000 neurons from three other patients. Working with Seattle, Washington–area neurosurgeons, the Allen Institute acquired healthy cells from the cortex—the outermost layer of the brain that coordinates perception, memory, thoughts, and consciousness—from patients undergoing surgery for epilepsy or brain tumors. Normally considered medical waste, these tissues can now provide scientists with a unique resource for understanding the human brain. That's because most studies on single human brain cells use dead rather than living tissue, and many others rely on cells from common laboratory animals, especially mice. The new data should help researchers pin down what makes human brains unique from other species—and what makes for a healthy versus diseased brain.

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