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Scientific News
6th of December 2015
Sven Bulterijs

Heales meets Ms. Morano (116 years)

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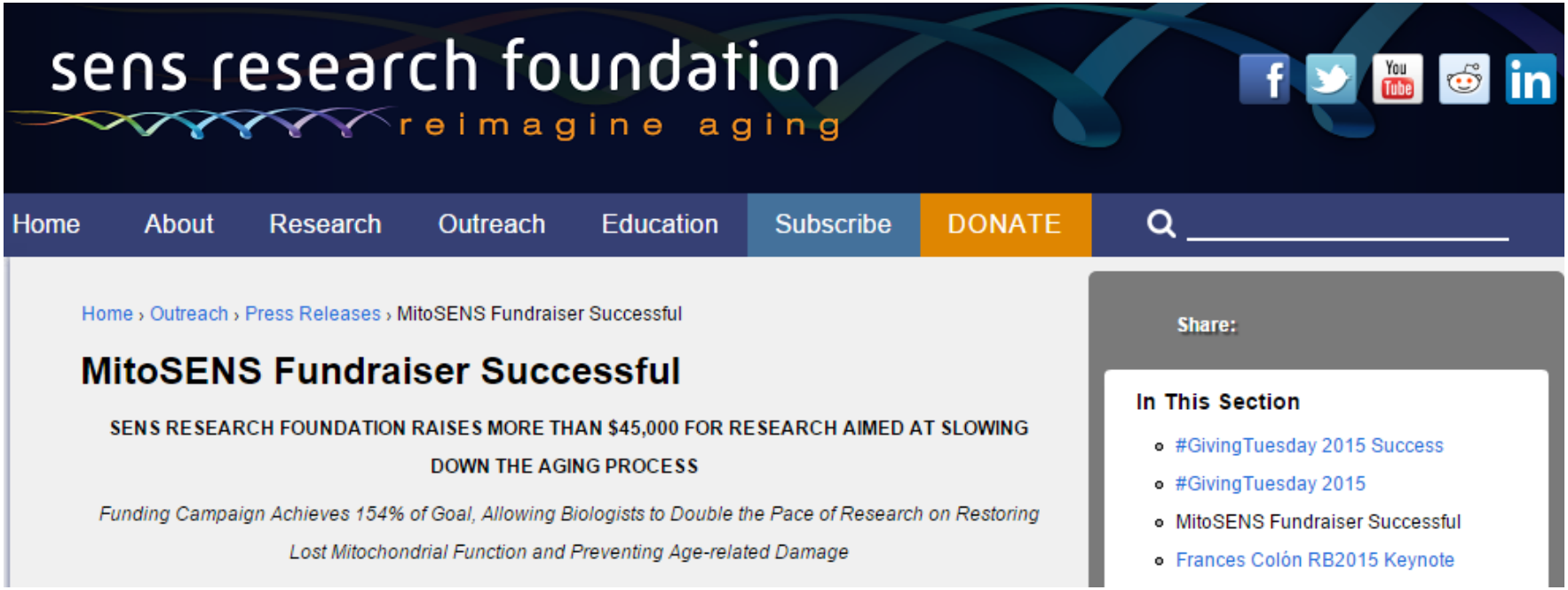
Success!!!



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OVERZICHT. Dit zijn de belangrijkste doodsoorzaken in Vlaanderen

01/12/2015 om 14:29 door Joram Nijs | Bron: BELGA

Print Corrigeer

In 2013 stierven 61.063 mensen in Vlaanderen. In meer dan de helft van de gevallen lag de oorzaak bij hartziekten of kanker.
Foto: SS

In 2013 stierven 61.063 mensen in Vlaanderen, 678 meer dan in 2012, en het hoogste aantal in 15 jaar. "De koude maanden maart en april vorig jaar, volgend op een uitzonderlijk lange griepepidemie, zitten daar voor veel tussen", klinkt het bij het Agentschap Zorg en Gezondheid. Vanaf de leeftijd van 50 jaar zijn hartaandoeningen en kanker de belangrijkste doodsoorzaken, bij jongere mensen is dat zelfdoding

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No designer babies, but summit calls for cautious research

December 3, 2015 by By Lauran Neergaard

The summit's organizers endorsed treatment-related gene editing research, and said lab research on germline issues "is clearly needed and should proceed" with appropriate oversight as international debate continues.

Geneticists Are Concerned Transhumanists Will Use CRISPR on Themselves

WRITTEN BY ALEX PEARLMAN

3 December 2015 // 05:53 PM CET

“Enhancement will creep in the door,” Church said. “The point is that [human enhancements] will come after very serious diseases and they will be spread by somatic gene therapies.”

More conservative voices from the bioethics community are advocating for a full ban on the technology, regardless of how it’s used. But just because some people want to use the technology in ways that so-called “bioconservatives” may not like, Daley says it’d be wrong for regulators dismiss CRISPR’s human potential.

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Gene-editing summit supports some research in human embryos

Three-day meeting calls for further discussions on modifications to the gene pool.

“It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved … and (ii) there is broad societal consensus about the appropriateness of the proposed application,” the statement said.

The work now continues: over the next year, scientists and ethicists from the three hosting countries will convene to examine issues raised at the meeting. Their consensus report is scheduled to be released in late 2016.

Inside the summit on human gene editing: A reporter’s notebook

The conference ended with the organizing committee, a mix of 12 biologists, physicians, and bioethicists, strongly endorsing the use of CRISPR and similar methods for basic research that involves altering the DNA sequences of human eggs, sperm, or embryos—work that is at the moment ineligible for federal funding in the United States and that in Germany could even get a scientist imprisoned. But the summit’s organizers concluded that actually trying to produce a human pregnancy from such modified germ cells or embryos, either through in vitro fertilization (IVF) with the sperm or eggs or the implantation of an embryo, is currently “irresponsible” because of ongoing safety concerns and a lack of societal consensus.

FDA approval for TAME trial!

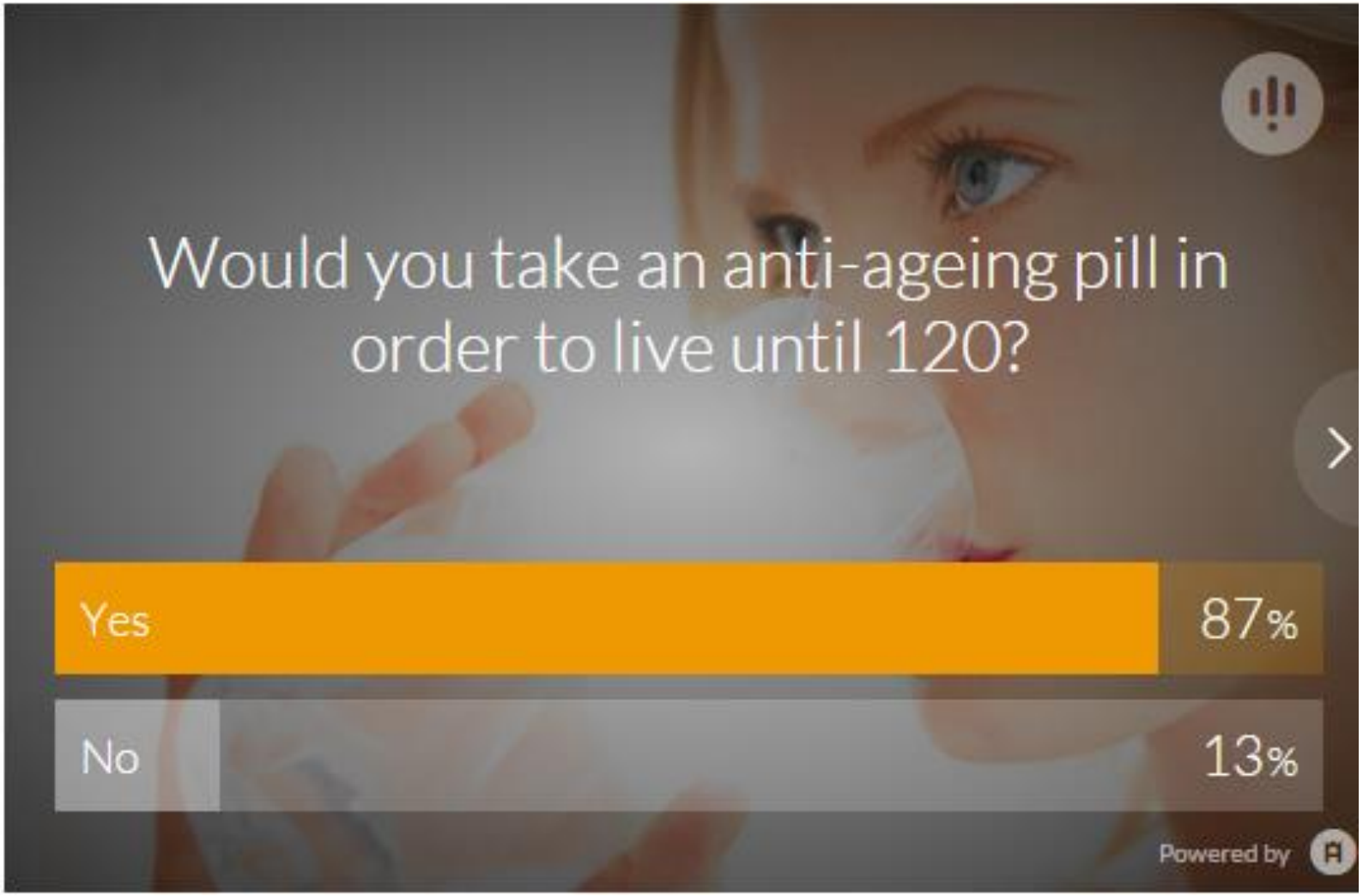
A common diabetes drug will be trialled as an anti-ageing elixir from next year

Research suggests it could help people live to 120.

FIONA MACDONALD 1 DEC 2015

The trial will be known as the Targeting Ageing with Metformin (TAME) study, and it'll involve giving either the drug or a placebo to around 3,000 elderly people who suffer from or have a high risk of developing conditions such as cancer, heart disease, and Alzheimer's.

Poll in the newspaper Telegraph



The NIA Interventions Testing Program Announces the 2016 Solicitation of Proposals

The National Institute on Aging (NIA) Interventions Testing Program (ITP) investigates dietary supplements purported to extend lifespan and/or delay the onset of disease and disability. The NIA ITP tests such compounds in mice, using a variety of measured endpoints to assess the efficacy of interventions. The NIA ITP is not a mechanism for funding sponsors' laboratories to perform the work, but rather it is a collaborative effort between the three NIA-funded testing sites and the sponsors who propose interventions for study. The sponsor's role is to provide the rationale for investigating the intervention, make recommendations on the dose, route and timing for administration of the intervention, and propose assays and measurements to document the efficacy of the intervention. The sponsors have access to all data developed from the treated mice, assist in analysis of the data and co-author on resulting publications.

The ITP provides a venue for early exploratory studies on compounds with potential to impact aging and lifespan and also an opportunity to follow up on significant findings. One of the first exciting findings from the ITP was the report that treatment with rapamycin, an inhibitor of the mTOR kinase, produced robust lifespan in both male and female mice, albeit skewed in favor of females (Harrison *et al*., 2009). The ITP followed up with a more in depth study, including a dose–response curve for the lifespan analysis and further characterization of the cellular effects of rapamycin treatment. At the two lowest doses, 4.7 and 14 ppm in the food, female mice again responded with a greater extension of lifespan than did male mice, while at the highest dose, 42 ppm, males and females showed similar increases in median lifespan, 23% and 26%, respectively (Miller *et al*., 2014). There was a sex difference in the blood levels of rapamycin, but that did not explain the difference in lifespan, as the greatest difference in the blood levels was at the highest dose, where the effect on lifespan was very similar for males and females. And while rapamycin and dietary restriction both impact the mTOR pathway, this study demonstrated distinct difference in some metabolic parameters between rapamycin and dietary restriction, such as in the effect on leptin and FGF-21 levels (Miller *et al*., 2014).

The NIA ITP is soliciting proposals for compounds to enter the study in 2017. The deadline for receipt of proposals is February 24, 2016. Information on the NIA ITP and guidelines for proposal development are posted at: http://www.nia.nih.gov/research/dab/interventions-testing-program-itp. Questions should be directed to Dr. Nancy Nadon (nadonn@nia.nih.gov).

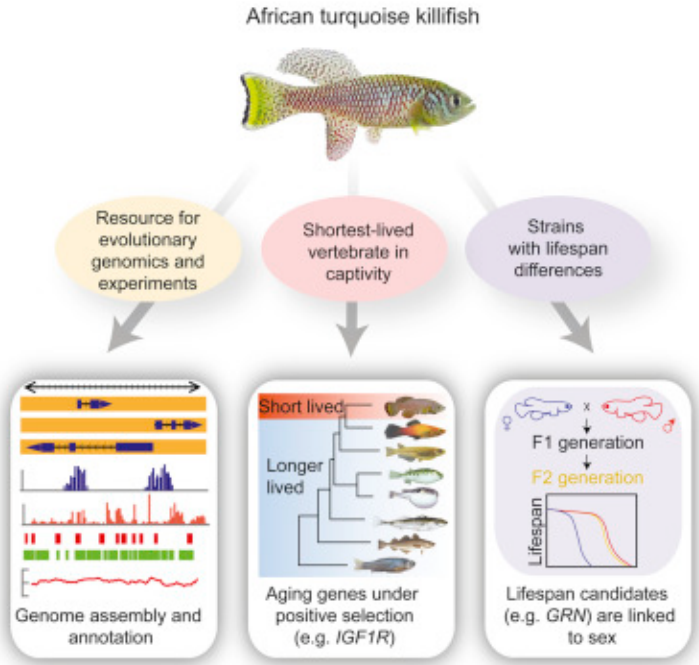
The African Turquoise Killifish Genome Provides Insights into Evolution and Genetic Architecture of Lifespan

Dario Riccardo Valenzano[7,8], Bérénice A. Benayoun[7], Param Priya Singh[7], Elisa Zhang, Paul D. Etter, Chi-Kuo Hu, Mathieu Clément-Ziza, David Willemsen, Rongfeng Cui, Itamar Harel, Ben E. Machado, Muh-Ching Yee[9], Sabrina C. Sharp, Carlos D. Bustamante, Andreas Beyer, Eric A. Johnson, Anne Brunet

Highlights

- De novo genome assembly and annotation of the African turquoise killifish
- Key aging genes are under positive selection in the turquoise killifish
- Differences in lifespan between killifish strains are genetically linked to sex
- A resource for comparative genomics and experimental aging studies

Graphical Abstract



Summary

Lifespan is a remarkably diverse trait ranging from a few days to several hundred years in nature, but the mechanisms underlying the evolution of lifespan differences remain elusive. Here we de novo assemble a reference genome for the naturally short-lived African turquoise killifish, providing a unique resource for comparative and experimental genomics. The identification of genes under positive selection in this fish reveals potential candidates to explain its compressed lifespan. Several aging genes are under positive selection in this short-lived fish and long-lived species, raising the intriguing possibility that the same gene could underlie evolution of both compressed and extended lifespans. Comparative genomics and linkage analysis identify candidate genes associated with lifespan differences between various turquoise killifish strains. Remarkably, these genes are clustered on the sex chromosome, suggesting that short lifespan might have co-evolved with sex determination. Our study provides insights into the evolutionary forces that shape lifespan in nature.

Personalized Nutrition by Prediction of Glycemic Responses

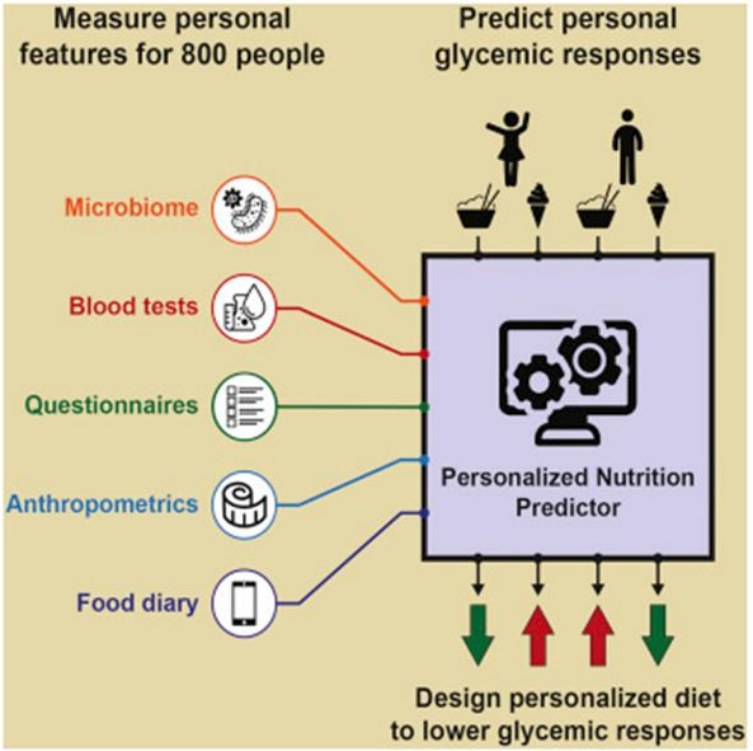
David Zeevi[8], Tal Korem[8], Niv Zmora[8], David Israeli[8], Daphna Rothschild, Adina Weinberger, Orly Ben-Yacov, Dar Lador, Tali Avnit-Sagi, Maya Lotan-Pompan, Jotham Suez, Jemal Ali Mahdi, Elad Matot, Gal Malka, Noa Kosower, Michal Rein, Gili Zilberman-Schapira, Lenka Dohnalová, Meirav Pevsner-Fischer, Rony Bikovsky, Zamir Halpern, Eran Elinav[9], Eran Segal[9]

[8] Co-first author

Highlights

- High interpersonal variability in post-meal glucose observed in an 800-person cohort
- Using personal and microbiome features enables accurate glucose response prediction
- Prediction is accurate and superior to common practice in an independent cohort
- Short-term personalized dietary interventions successfully lower post-meal glucose

Graphical Abstract | Video Abstract



Summary

Elevated postprandial blood glucose levels constitute a global epidemic and a major risk factor for prediabetes and type II diabetes, but existing dietary methods for controlling them have limited efficacy. Here, we continuously monitored week-long glucose levels in an 800-person cohort, measured responses to 46,898 meals, and found high variability in the response to identical meals, suggesting that universal dietary recommendations may have limited utility. We devised a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measured in this cohort and showed that it accurately predicts personalized postprandial glycemic response to real-life meals. We validated these predictions in an independent 100-person cohort. Finally, a blinded randomized controlled dietary intervention based on this algorithm resulted in significantly lower postprandial responses and consistent alterations to gut microbiota configuration. Together, our results suggest that personalized diets may successfully modify elevated postprandial blood glucose and its metabolic consequences.

Frequent Somatic Mutation in Adult Intestinal Stem Cells Drives Neoplasia and Genetic Mosaicism during Aging

Katarzyna Siudeja, Sonya Nassari, Louis Gervais, Patricia Skorski, Sonia Lameiras, Donato Stolfa, Maria Zande, Virginie Bernard, Thomas Rio Frio, Allison J. Bardin

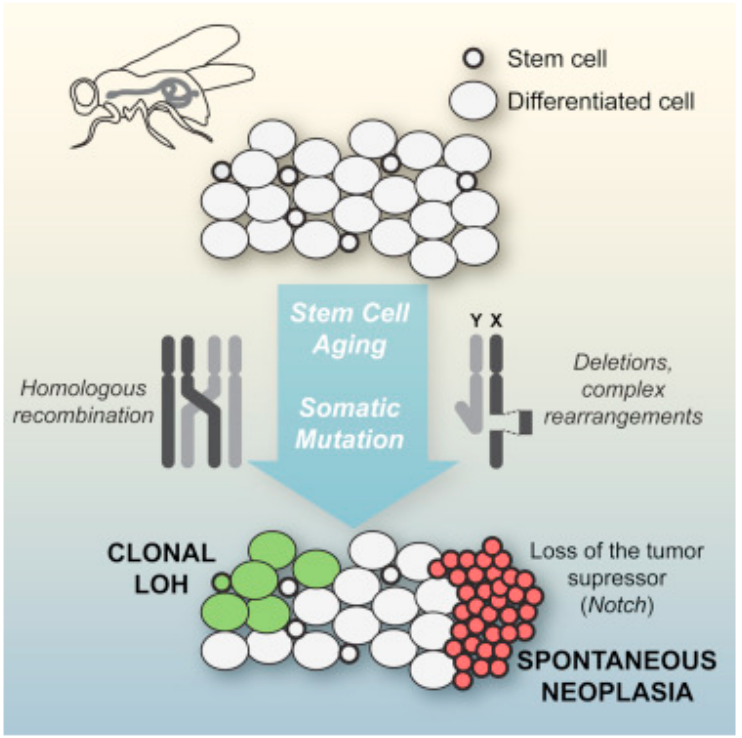
Highlights

- The aging *Drosophila* intestine is genetically mosaic
- Somatic recombination, genomic deletions, and rearrangements occur in aging ISCs
- Somatic inactivation of the tumor-suppressor *Notch* causes male-specific neoplasia

Summary

Adult stem cells may acquire mutations that modify cellular behavior, leading to functional declines in homeostasis or providing a competitive advantage resulting in premalignancy. However, the frequency, phenotypic impact, and mechanisms underlying spontaneous mutagenesis during aging are unclear. Here, we report two mechanisms of genome instability in adult *Drosophila* intestinal stem cells (ISCs) that cause phenotypic alterations in the aging intestine. First, we found frequent loss of heterozygosity arising from mitotic homologous recombination in ISCs that results in genetic mosaicism. Second, somatic deletion of DNA sequences and large structural rearrangements, resembling those described in cancers and congenital diseases, frequently result in gene inactivation. Such modifications induced somatic inactivation of the X-linked tumor suppressor *Notch* in ISCs, leading to spontaneous neoplasias in wild-type males. Together, our findings reveal frequent genomic modification in adult stem cells and show that somatic genetic mosaicism has important functional consequences on aging tissues.

Graphical Abstract



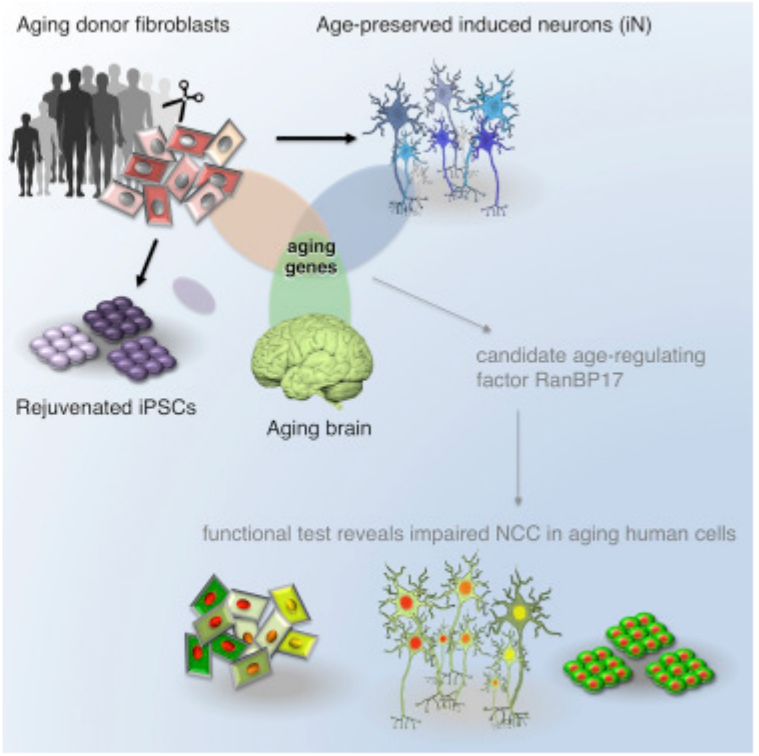
Directly Reprogrammed Human Neurons Retain Aging-Associated Transcriptomic Signatures and Reveal Age-Related Nucleocytoplasmic Defects

Jerome Mertens, Apuã C.M. Paquola, Manching Ku, Emily Hatch, Lena Böhnke, Shauheen Ladjevardi, Sean McGrath, Benjamin Campbell, Hyungjun Lee, Joseph R. Herdy, J. Tiago Gonçalves, Tomohisa Toda, Yongsung Kim, Jürgen Winkler, Jun Yao, Martin W. Hetzer, Fred H. Gage

Highlights

- Human iPSCs erase aging signatures and hiPSC-derived neurons remain rejuvenated
- Directly converted iNs preserve donor age-dependent transcriptomic signatures
- Nuclear transport receptor RanBP17 is decreased in aged human cells and iNs
- Aged and RanBP17-depleted cells show nucleocytoplasmic compartmentalization defects

Graphical Abstract



Summary

Aging is a major risk factor for many human diseases, and in vitro generation of human neurons is an attractive approach for modeling aging-related brain disorders. However, modeling aging in differentiated human neurons has proved challenging. We generated neurons from human donors across a broad range of ages, either by iPSC-based reprogramming and differentiation or by direct conversion into induced neurons (iNs). While iPSCs and derived neurons did not retain aging-associated gene signatures, iNs displayed age-specific transcriptional profiles and revealed age-associated decreases in the nuclear transport receptor RanBP17. We detected an age-dependent loss of nucleocytoplasmic compartmentalization (NCC) in donor fibroblasts and corresponding iNs and found that reduced RanBP17 impaired NCC in young cells, while iPSC rejuvenation restored NCC in aged cells. These results show that iNs retain important aging-related signatures, thus allowing modeling of the aging process in vitro, and they identify impaired NCC as an important factor in human aging.

Protein biogenesis machinery is a driver of replicative aging in yeast

Georges E Janssens, Anne C Meinema, Javier González, Justina C Wolters, Alexander Schmidt, Victor Guryev, Rainer Bischoff, Ernst C Wit, Liesbeth M Veenhoff ✉, Matthias Heinemann ✉

An integrated account of the molecular changes occurring during the process of cellular aging is crucial towards understanding the underlying mechanisms. Here, using novel culturing and computational methods as well as latest analytical techniques, we mapped the proteome and transcriptome during the replicative lifespan of budding yeast. With age, we found primarily proteins involved in protein biogenesis to increase relative to their transcript levels. Exploiting the dynamic nature of our data, we reconstructed high-level directional networks, where we found the same protein biogenesis-related genes to have the strongest ability to predict the behavior of other genes in the system. We identified metabolic shifts and the loss of stoichiometry in protein complexes as being consequences of aging. We propose a model whereby the uncoupling of protein levels of biogenesis-related genes from their transcript levels is causal for the changes occurring in aging yeast. Our model explains why targeting protein synthesis, or repairing the downstream consequences, can serve as interventions in aging.

DOI: http://dx.doi.org/10.7554/eLife.08527.001

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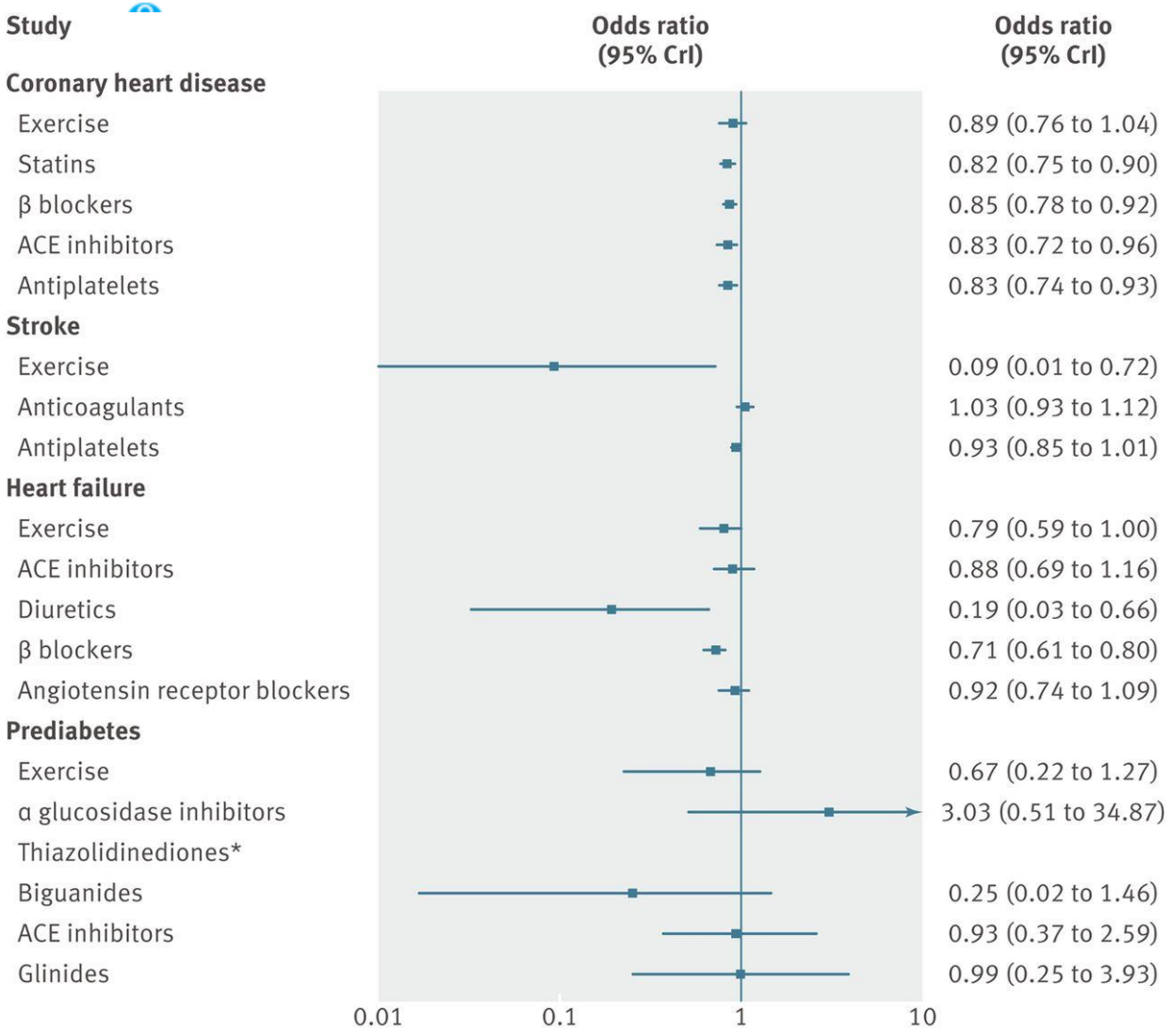
Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study



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O-GlcNAc modification blocks the aggregation and toxicity of the protein α-synuclein associated with Parkinson's disease

Nicholas P. Marotta, Yu Hsuan Lin, Yuka E. Lewis, Mark R. Ambroso, Balyn W. Zaro, Maxwell T. Roth, Don B. Arnold, Ralf Langen & Matthew R. Pratt

Affiliations | **Contributions** | **Corresponding author**

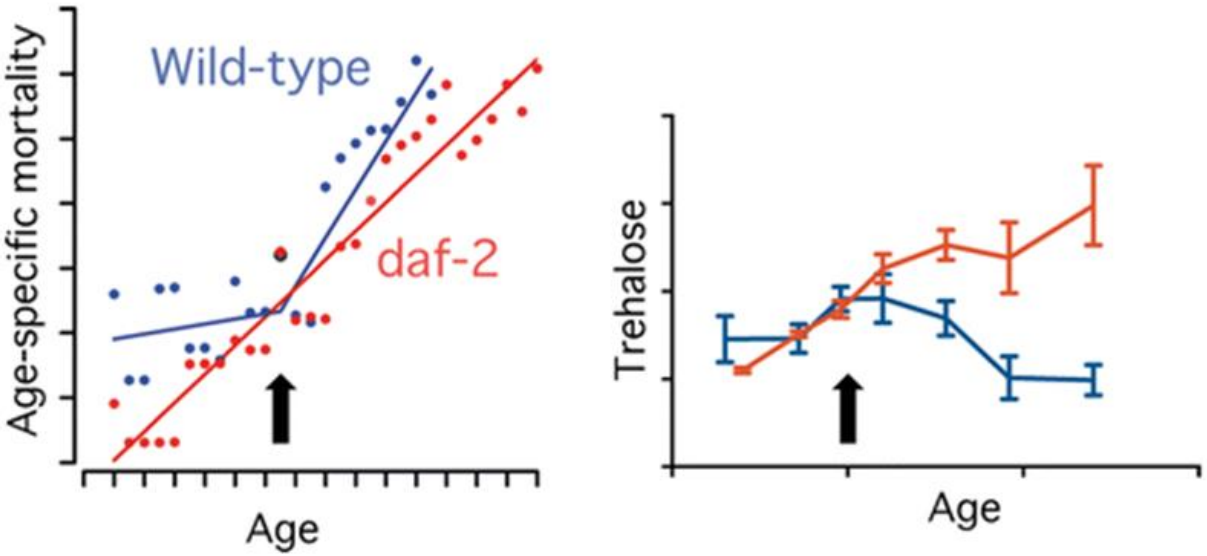
Nature Chemistry **7**, 913–920 (2015) | doi:10.1038/nchem.2361
Received 09 January 2015 | Accepted 28 August 2015 | Published online 12 October 2015

Abstract

Abstract • **References** • **Author information** • **Supplementary information**

Several aggregation-prone proteins associated with neurodegenerative diseases can be modified by O-linked *N*-acetyl-glucosamine (O-GlcNAc) *in vivo*. One of these proteins, α-synuclein, is a toxic aggregating protein associated with synucleinopathies, including Parkinson's disease. However, the effect of O-GlcNAcylation on α-synuclein is not clear. Here, we use synthetic protein chemistry to generate both unmodified α-synuclein and α-synuclein bearing a site-specific O-GlcNAc modification at the physiologically relevant threonine residue 72. We show that this single modification has a notable and substoichiometric inhibitory effect on α-synuclein aggregation, while not affecting the membrane binding or bending properties of α-synuclein. O-GlcNAcylation is also shown to affect the phosphorylation of α-synuclein *in vitro* and block the toxicity of α-synuclein that was exogenously added to cells in culture. These results suggest that increasing O-GlcNAcylation may slow the progression of synucleinopathies and further support a general function for O-GlcNAc in preventing protein aggregation.

Metabolic Youth in Middle Age: Predicting Aging in *Caenorhabditis elegans* Using Metabolomics



Many mutations and allelic variants are known that influence the rate at which animals age, but when in life do such variants diverge from normal patterns of aging? Is this divergence visible in their physiologies? To investigate these questions, we have used ^{1}H NMR spectroscopy to study how the metabolome of the nematode *Caenorhabditis elegans* changes as it grows older. We identify a series of metabolic changes that, collectively, predict the age of wild-type worms. We then show that long-lived mutant *daf-2(m41)* worms are metabolically youthful compared to wild-type worms, but that this relative youth only appears in middle age. Finally, we show that metabolic age predicts the timing and magnitude of differences in age-specific mortality between these strains. Thus, the future mortality of these two genotypes can be predicted long before most of the worms die.

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Protein profiling reveals consequences of lifestyle choices on predicted biological aging

Ageing is linked to a number of changes in how the body and its organs function. On a molecular level, ageing is associated with a reduction of telomere length, changes in metabolic and gene-transcription profiles and an altered DNA-methylation pattern. Lifestyle factors such as smoking or stress can impact some of these molecular processes and thereby affect the ageing of an individual. Here we demonstrate by analysis of 77 plasma proteins in 976 individuals, that the abundance of circulating proteins accurately predicts chronological age, as well as anthropometrical measurements such as weight, height and hip circumference. The plasma protein profile can also be used to identify lifestyle factors that accelerate and decelerate ageing. We found smoking, high BMI and consumption of sugar-sweetened beverages to increase the predicted chronological age by 2–6 years, while consumption of fatty fish, drinking moderate amounts of coffee and exercising reduced the predicted age by approximately the same amount. This method can be applied to dried blood spots and may thus be useful in forensic medicine to provide basic anthropometrical measures for an individual based on a biological evidence sample.

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Aβ-dependent reduction of NCAM2-mediated synaptic adhesion contributes to synapse loss in Alzheimer's disease

Iryna Leshchyns'ka, Heng Tai Liew, Claire Shepherd, Glenda M. Halliday, Claire H. Stevens, Yazi D. Ke, Lars M. Ittner & Vladimir Sytnyk

Abstract

Alzheimer's disease (AD) is characterized by synapse loss due to mechanisms that remain poorly understood. We show that the neural cell adhesion molecule 2 (NCAM2) is enriched in synapses in the human hippocampus. This enrichment is abolished in the hippocampus of AD patients and in brains of mice overexpressing the human amyloid-β (Aβ) precursor protein carrying the pathogenic Swedish mutation. Aβ binds to NCAM2 at the cell surface of cultured hippocampal neurons and induces removal of NCAM2 from synapses. In AD hippocampus, cleavage of the membrane proximal external region of NCAM2 is increased and soluble extracellular fragments of NCAM2 (NCAM2-ED) accumulate. Knockdown of NCAM2 expression or incubation with NCAM2-ED induces disassembly of GluR1-containing glutamatergic synapses in cultured hippocampal neurons. Aβ-dependent disassembly of GluR1-containing synapses is inhibited in neurons overexpressing a cleavage-resistant mutant of NCAM2. Our data indicate that Aβ-dependent disruption of NCAM2 functions in AD hippocampus contributes to synapse loss.

Special issue on aging

Special issue: mitochondrial dysfunction in aging

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Biochimica et Biophysica Acta (BBA) - Bioenergetics
Volume 1847, Issue 11, Pages 1345-1478 (November 2015)

SI: Mitochondrial dysfunction in aging
Edited by Aleksandra Trifunovic and Elena Rugarli

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PDF version

A comprehensive multiomics approach toward understanding the relationship between aging and dementia

Antonio Currais[1], Joshua Goldberg[1], Catherine Farrokhi[1], Max Chang[1], Marguerite Prior[1], Richard Dargusch[1], Daniel Daugherty[1], Aaron Armando[2], Oswald Quehenberger[2], Pamela Maher[1], and David Schubert[1]

[1] The Salk Institute for Biological Studies, La Jolla, CA 92037, USA;

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Key words: *aging, Alzheimer's disease, multiomics, SAMP8 mice, inflammation, J147*

Received: *09/15/15; Accepted: 10/30/15; Published: 11/11/15*

Correspondence: David Schuber , PhD; E-mail: schubert@salk.edu

Abstract

Because age is the greatest risk factor for sporadic Alzheimer's disease (AD), phenotypic screens based upon old age-associated brain toxicities were used to develop the potent neurotrophic drug J147. Since certain aspects of aging may be primary cause of AD, we hypothesized that J147 would be effective against AD-associated pathology in rapidly aging SAMP8 mice and could be used to identify some of the molecular contributions of aging to AD. An inclusive and integrative multiomics approach was used to investigate protein and gene expression, metabolite levels, and cognition in old and young SAMP8 mice. J147 reduced cognitive deficits in old SAMP8 mice, while restoring multiple molecular markers associated with human AD, vascular pathology, impaired synaptic function, and inflammation to those approaching the young phenotype. The extensive assays used in this study identified a subset of molecular changes associated with aging that may be necessary for the development of AD.

J Am Geriatr Soc. 2015 Nov 14. doi: 10.1111/jgs.13830. [Epub ahead of print]

Methylomic Aging as a Window onto the Influence of Lifestyle: Tobacco and Alcohol Use Alter the Rate of Biological Aging.

Beach SR[1,2], Dogan MV[3,4], Lei MK[2], Cutrona CE[5], Gerrard M[6], Gibbons FX[6], Simons RL[2,7], Brody GH[2], Philibert RA[3,4].

Author information

Abstract

OBJECTIVES: To examine the effect of the relationship between alcohol and cigarette consumption on biological aging using deoxyribonucleic acid methylation-based indices.

DESIGN: Hierarchical linear regression modeling followed by fitting of higher-order effects.

SETTING: Longitudinal studies of aging and the effect of psychosocial stress.

PARTICIPANTS: Participants in two ethnically informative cohorts (n = 656 white, n = 180 black).

MEASUREMENTS: Deviation of biological age from chronological age as a result of smoking and alcohol consumption.

RESULTS: Greater cigarette consumption was associated with accelerated biological aging, with strong effects evident at even low levels of exposure. In contrast, alcohol consumption was associated with a mixed effect on biological aging and pronounced nonlinear effects. At low and heavy levels of alcohol consumption, there was accelerated biological aging, whereas at intermediate levels of consumption there was a relative decelerating effect. The decelerating effects of alcohol were particularly notable at loci for which methylation increased with age.

CONCLUSION: These data support prior epidemiological studies indicating that moderate alcohol use is associated with healthy aging, but we urge caution in interpreting these results. Conversely, smoking has strong negative effects at all levels of consumption. These results also support the use of methylomic indices as a tool for assessing the impact of lifestyle on aging.

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Sex- and tissue-specific changes in mTOR signaling with age in C57BL/6J mice

Summary

Inhibition of the mTOR (mechanistic Target Of Rapamycin) signaling pathway robustly extends the lifespan of model organisms including mice. The precise molecular mechanisms and physiological effects that underlie the beneficial effects of rapamycin are an exciting area of research. Surprisingly, while some data suggest that mTOR signaling normally increases with age in mice, the effect of age on mTOR signaling has never been comprehensively assessed. Here, we determine the age-associated changes in mTORC1 (mTOR complex 1) and mTORC2 (mTOR complex 2) signaling in the liver, muscle, adipose, and heart of C57BL/6J.Nia mice, the lifespan of which can be extended by rapamycin treatment. We find that the effect of age on several different readouts of mTORC1 and mTORC2 activity varies by tissue and sex in C57BL/6J.Nia mice. Intriguingly, we observed increased mTORC1 activity in the liver and heart tissue of young female mice compared to male mice of the same age. Tissue and substrate-specific results were observed in the livers of HET3 and DBA/2 mouse strains, and in liver, muscle and adipose tissue of F344 rats. Our results demonstrate that aging does not result in increased mTOR signaling in most tissues and suggest that rapamycin does not promote lifespan by reversing or blunting such an effect.

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Chronic mTOR inhibition in mice with rapamycin alters T, B, myeloid, and innate lymphoid cells and gut flora and prolongs life of immune-deficient mice

Summary

The mammalian (mechanistic) target of rapamycin (mTOR) regulates critical immune processes that remain incompletely defined. Interest in mTOR inhibitor drugs is heightened by recent demonstrations that the mTOR inhibitor rapamycin extends lifespan and healthspan in mice. Rapamycin or related analogues (rapalogues) also mitigate age-related debilities including increasing antigen-specific immunity, improving vaccine responses in elderly humans, and treating cancers and autoimmunity, suggesting important new clinical applications. Nonetheless, immune toxicity concerns for long-term mTOR inhibition, particularly immunosuppression, persist. Although mTOR is pivotal to fundamental, important immune pathways, little is reported on immune effects of mTOR inhibition in lifespan or healthspan extension, or with chronic mTOR inhibitor use. We comprehensively analyzed immune effects of rapamycin as used in lifespan extension studies. Gene expression profiling found many and novel changes in genes affecting differentiation, function, homeostasis, exhaustion, cell death, and inflammation in distinct T- and B-lymphocyte and myeloid cell subpopulations. Immune functions relevant to aging and inflammation, and to cancer and infections, and innate lymphoid cell effects were validated *in vitro* and *in vivo*. Rapamycin markedly prolonged lifespan and healthspan in cancer- and infection-prone mice supporting disease mitigation as a mechanism for mTOR suppression-mediated longevity extension. It modestly altered gut metagenomes, and some metagenomic effects were linked to immune outcomes. Our data show novel mTOR inhibitor immune effects meriting further studies in relation to longevity and healthspan extension.

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Genetic evidence for common pathways in human age-related diseases

Summary

Aging is the single largest risk factor for chronic disease. Studies in model organisms have identified conserved pathways that modulate aging rate and the onset and progression of multiple age-related diseases, suggesting that common pathways of aging may influence age-related diseases in humans as well. To determine whether there is genetic evidence supporting the notion of common pathways underlying age-related diseases, we analyzed the genes and pathways found to be associated with five major categories of age-related disease using a total of 410 genomewide association studies (GWAS). While only a small number of genes are shared among all five disease categories, those found in at least three of the five major age-related disease categories are highly enriched for apoliprotein metabolism genes. We found that a more substantial number of gene ontology (GO) terms are shared among the 5 age-related disease categories and shared GO terms include canonical aging pathways identified in model organisms, such as nutrient-sensing signaling, translation, proteostasis, stress responses, and genome maintenance. Taking advantage of the vast amount of genetic data from the GWAS, our findings provide the first direct evidence that conserved pathways of aging simultaneously influence multiple age-related diseases in humans as has been demonstrated in model organisms.

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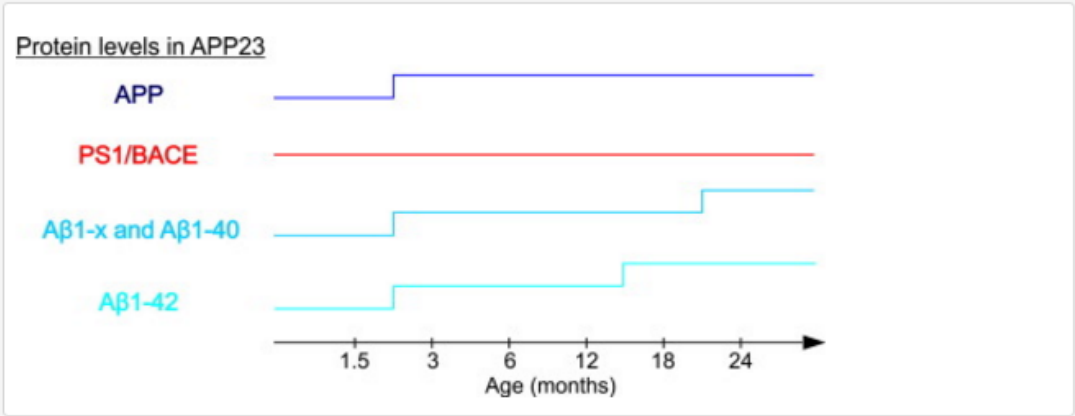
Late age increase in soluble amyloid-beta levels in the APP23 mouse model despite steady-state levels of amyloid-beta-producing proteins

Abstract

Age is considered the most important risk factor for Alzheimer's disease. Soluble amyloid-beta (Aβ) has been implicated as the primary neurotoxic agent in Alzheimer's disease pathology. The link between aging and Aβ, however, remains unclear. In this study, we aimed to investigate the evolution of soluble Aβ over various age groups in the APP23 amyloidosis mouse model and correlate these changes to alterations in the levels of proteins involved in Aβ production. We found a distinct pattern with an initial buildup of Aβ which could be linked to an increase in amyloid precursor protein (APP). Following this increase, Aβ concentrations remained stable until a surge in $Aβ_{1–42}$ at 18 months. This rise was followed by an increase in $Aβ_{1–40}$ and overall Aβ levels. The rise in Aβ at later age did not correlate to changes in the levels of APP, presenilin, and β-secretase and is suggested to result from a decrease in clearance. The APP23 model could provide an interesting tool for future research regarding aging and Aβ clearance.

Graphical abstract



REVIEWS/COMMENTS/EDITORIALS

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Cold Spring Harb Perspect Med. 2015 Nov 2;5(11). pii: a025114. doi: 10.1101/cshperspect.a025114.

Biochemical Genetic Pathways that Modulate Aging in Multiple Species.

Bitto A[1], Wang AM[1], Bennett CF[1], Kaeberlein M[1].

⊕ Author information

Abstract

The mechanisms underlying biological aging have been extensively studied in the past 20 years with the avail of mainly four model organisms: the budding yeast Saccharomyces cerevisiae, the nematode Caenorhabditis elegans, the fruitfly Drosophila melanogaster, and the domestic mouse Mus musculus. Extensive research in these four model organisms has identified a few conserved genetic pathways that affect longevity as well as metabolism and development. Here, we review how the mechanistic target of rapamycin (mTOR), sirtuins, adenosine monophosphate-activated protein kinase (AMPK), growth hormone/insulin-like growth factor 1 (IGF-1), and mitochondrial stress-signaling pathways influence aging and life span in the aforementioned models and their possible implications for delaying aging in humans. We also draw some connections between these biochemical pathways and comment on what new developments aging research will likely bring in the near future.

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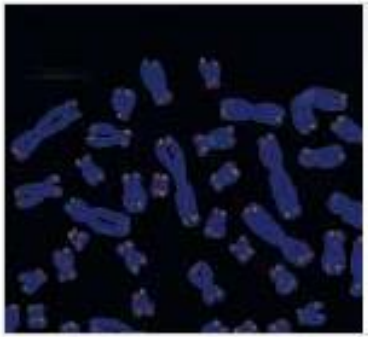
Focus on Telomeres



Focus issue: November 2015 Volume **22**, No 11

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A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome

Abstract

Abstract • References • Author information • Supplementary information

Down syndrome, which arises in individuals carrying an extra copy of chromosome 21, is associated with a greatly increased risk of early-onset Alzheimer disease. It is thought that this risk is conferred by the presence of three copies of the gene encoding amyloid precursor protein (APP) — an Alzheimer disease risk factor — although the possession of extra copies of other chromosome 21 genes may also play a part. Further study of the mechanisms underlying the development of Alzheimer disease in people with Down syndrome could provide insights into the mechanisms that cause dementia in the general population.

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Genomic integrity and the ageing brain

Hei-man Chow & Karl Herrup

Affiliations | **Corresponding author**

Nature Reviews Neuroscience **16**, 672–684 (2015) | doi:10.1038/nrn4020
Published online 14 October 2015

Abstract

Abstract • **References** • **Author information**

DNA damage is correlated with and may drive the ageing process. Neurons in the brain are postmitotic and are excluded from many forms of DNA repair; therefore, neurons are vulnerable to various neurodegenerative diseases. The challenges facing the field are to understand how and when neuronal DNA damage accumulates, how this loss of genomic integrity might serve as a 'time keeper' of nerve cell ageing and why this process manifests itself as different diseases in different individuals.

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Hippocampal insulin resistance and cognitive dysfunction

Geert Jan Biessels & Lawrence P. Reagan

Affiliations | **Corresponding author**

Nature Reviews Neuroscience **16**, 660–671 (2015) | doi:10.1038/nrn4019
Published online 14 October 2015

Abstract

Abstract • References • Author information

Clinical studies suggest a link between type 2 diabetes mellitus (T2DM) and insulin resistance (IR) and cognitive dysfunction, but there are significant gaps in our knowledge of the mechanisms underlying this relationship. Animal models of IR help to bridge these gaps and point to hippocampal IR as a potential mediator of cognitive dysfunction in T2DM, as well as in Alzheimer disease (AD). This Review highlights these observations and discusses intervention studies which suggest that the restoration of insulin activity in the hippocampus may be an effective strategy to alleviate the cognitive decline associated with T2DM and AD.

J Physiol. 2015 Nov 26. doi: 10.1113/JP270543. [Epub ahead of print]

Calorie restriction as an intervention in ageing.

López-Lluch G[1], Navas P[1].

Author information

Abstract

Ageing causes loss of functions in tissues and organs, is accompanied by a chronic inflammatory process and affects life and health span. Calorie restriction (CR) is a non-genetic intervention that prevents age-associated diseases and extends longevity in most of the animal models studied so far. CR produces a pleiotropic effect and improves multiple metabolic pathways leading generating benefits to the whole organism. Among the effects of CR, modulation of the mitochondrial activity and decrease of oxidative damage are two of the hallmarks. Oxidative damage is reduced by the induction of endogenous antioxidant systems and modulation of the peroxidability index in cell membranes. Mitochondrial activity changes are regulated by inhibition of IGF-1 and TOR-dependent activities and activation of AMPK and the sirtuin family of proteins Activity of PGC-1α and FoxO is regulated by these systems and involved in mitochondria biogenesis, oxidative metabolism activity and mitochondrial turnover. The use of mimetics and the regulation of common factors have demonstrated that these molecular pathways are essential to explain the effect of CR in the organism. Finally, the anti-inflammatory effect of CR is an interesting emerging factor to be taken into consideration. In the present revision we focus on the general effect of CR and other mimetics in longevity focusing especially on cardiovascular system and skeletal muscle. This article is protected by copyright. All rights reserved.

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DNA methylation and healthy human aging

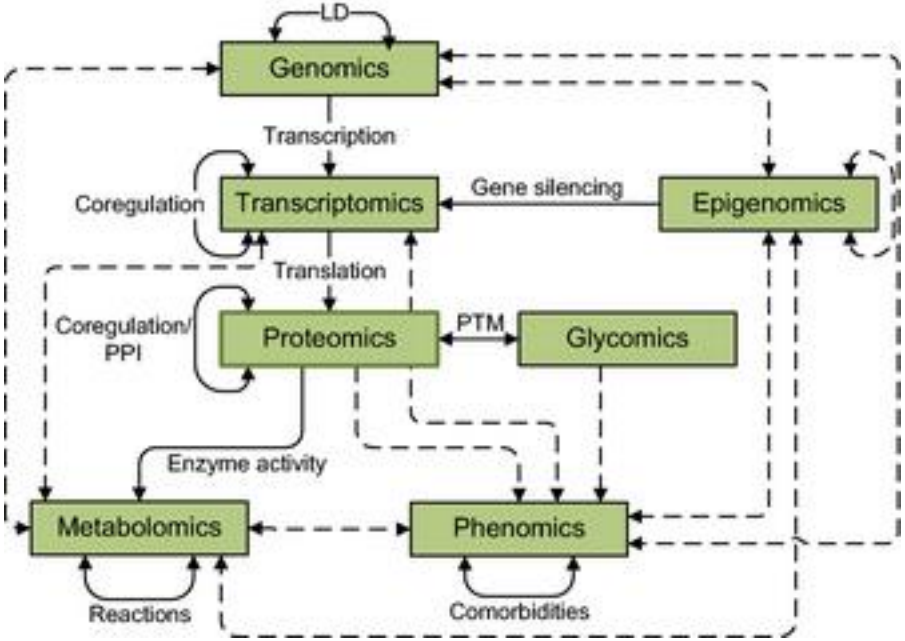
Summary

The process of aging results in a host of changes at the cellular and molecular levels, which include senescence, telomere shortening, and changes in gene expression. Epigenetic patterns also change over the lifespan, suggesting that epigenetic changes may constitute an important component of the aging process. The epigenetic mark that has been most highly studied is DNA methylation, the presence of methyl groups at CpG dinucleotides. These dinucleotides are often located near gene promoters and associate with gene expression levels. Early studies indicated that global levels of DNA methylation increase over the first few years of life and then decrease beginning in late adulthood. Recently, with the advent of microarray and next-generation sequencing technologies, increases in variability of DNA methylation with age have been observed, and a number of site-specific patterns have been identified. It has also been shown that certain CpG sites are highly associated with age, to the extent that prediction models using a small number of these sites can accurately predict the chronological age of the donor. Together, these observations point to the existence of two phenomena that both contribute to age-related DNA methylation changes: epigenetic drift and the epigenetic clock. In this review, we focus on healthy human aging throughout the lifetime and discuss the dynamics of DNA methylation as well as how interactions between the genome, environment, and the epigenome influence aging rates. We also discuss the impact of determining 'epigenetic age' for human health and outline some important caveats to existing and future studies.

Integration of 'omics' data in aging research: from biomarkers to systems biology

Summary

Age is the strongest risk factor for many diseases including neurodegenerative disorders, coronary heart disease, type 2 diabetes and cancer. Due to increasing life expectancy and low birth rates, the incidence of age-related diseases is increasing in industrialized countries. Therefore, understanding the relationship between diseases and aging and facilitating healthy aging are major goals in medical research. In the last decades, the dimension of biological data has drastically increased with high-throughput technologies now measuring thousands of (epi) genetic, expression and metabolic variables. The most common and so far successful approach to the analysis of these data is the so-called reductionist approach. It consists of separately testing each variable for association with the phenotype of interest such as age or age-related disease. However, a large portion of the observed phenotypic variance remains unexplained and a comprehensive understanding of most complex phenotypes is lacking. Systems biology aims to integrate data from different experiments to gain an understanding of the system as a whole rather than focusing on individual factors. It thus allows deeper insights into the mechanisms of complex traits, which are caused by the joint influence of several, interacting changes in the biological system. In this review, we look at the current progress of applying omics technologies to identify biomarkers of aging. We then survey existing systems biology approaches that allow for an integration of different types of data and highlight the need for further developments in this area to improve epidemiologic investigations.



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The etiology of human age-related cataract. Proteins don't last forever ☆

Background

It is probable that the great majority of human cataract results from the spontaneous decomposition of long-lived macromolecules in the human lens. Breakdown/reaction of long-lived proteins is of primary importance and recent proteomic analysis has enabled the identification of the particular crystallins, and their exact sites of amino acid modification.

Scope of review

Analysis of proteins from cataractous lenses revealed that there are sites on some structural proteins that show a consistently greater degree of deterioration than age-matched normal lenses.

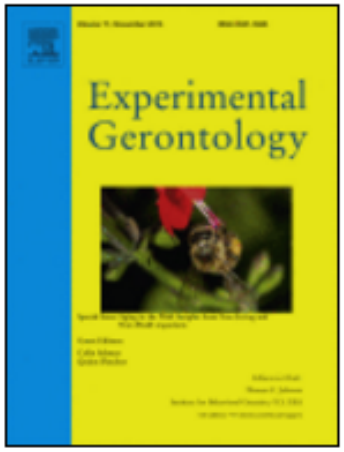
Major conclusions

The most abundant posttranslational modification of aged lens proteins is racemization. Deamidation, truncation and crosslinking, each arising from the spontaneous breakdown of susceptible amino acids within proteins, are also present. Fundamental to an understanding of nuclear cataract etiology, it is proposed that once a certain degree of modification at key sites occurs, that protein–protein interactions are disrupted and lens opacification ensues.

General Significance

Since long-lived proteins are now recognized to be present in many other sites of the body, such as the brain, the information gleaned from detailed analyses of degraded proteins from aged lenses will apply more widely to other age-related human diseases. This article is part of a Special Issue entitled Crystallin Biochemistry in Health and Disease.

Special issue: Aging in the Wild: Insights from Free-Living and Non-Model organisms



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Experimental Gerontology
Volume 71, Pages 1-146 (November 2015)

Aging in the Wild: Insights from Free-Living and Non-Model organisms
Edited by Colin Selman and Quinn Fletcher

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Telomeres shorten more slowly in slow-aging wild animals than in fast-aging ones

Research on the physiological causes of senescence aim to identify common physiological mechanisms that explain age-related declines in fitness across taxonomic groups. Telomeres are repetitive nucleotide sequences found on the ends of eukaryotic chromosomes. Past research indicates that telomere attrition is strongly correlated with inter-specific rates of aging, though these studies cannot distinguish whether telomere attrition is a cause or consequence of the aging process. We extend previous research on this topic by incorporating recent studies to test the hypothesis that telomeres shorten more slowly with age in slow-aging animals than in fast-aging ones. We assembled all studies that have quantified cross-sectional (i.e. between-individual) telomere rates of change (TROC) over the lifespans of wild animals. This included 22 estimates reflecting absolute TROC (TROCabs, bp/yr, primarily measured using the terminal restriction fragment length method), and 10 estimates reflecting relative TROC (TROCrel, relative telomere length/yr, measured using qPCR), from five classes (Aves, Mammalia, Bivalvia, Reptilia, and Actinopterygii). In 14 bird species, we correlated between-individual (i.e. cross-sectional) TROCabs estimates with both maximum lifespan and a phylogenetically-corrected principle component axis (pcPC1) that reflected the slow-fast axis of life-history variation. Bird species characterized by faster life-histories and shorter maximum lifespans had faster TROCabs. In nine studies, both between-individual and within-individual TROC estimates were available (n = 8 for TROCabs, n = 1 for TROCrel). Within-individual TROC estimates were generally greater than between-individual TROC estimates, which is indicative of selective disappearance of individuals with shorter telomeres. However, the difference between within- and between-individual TROC estimates was only significant in two out of nine studies. The relationship between within-individual TROCabs and maximum lifespan did not differ from the relationship of between-individual TROCabs and maximum lifespan. Overall, our results provide additional support for the hypothesis that TROC is correlated with inter-specific rates of aging and complement the intra-specific research that also find relationships between telomere attrition and components of fitness.

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Why is the dog an ideal model for aging research?

Abstract

With many caveats to the traditional vertebrate species pertaining to biogerontology investigations, it has been suggested that a most informative model is the one which: 1) examines closely related species, or various members of the same species with naturally occurring lifespan variation, 2) already has adequate medical procedures developed, 3) has a well annotated genome, 4) does not require artificial housing, and can live in its natural environment while being investigated, and 5) allows considerable information to be gathered within a relatively short period of time. The domestic dog unsurprisingly fits each criterion mentioned. The dog has already become a key model system in which to evaluate surgical techniques and novel medications because of the remarkable similarity between human and canine conditions, treatments, and response to therapy. The dog naturally serves as a disease model for study, obviating the need to construct artificial genetically modified examples of disease. Just as the dog offers a natural model for human conditions and diseases, simple observation leads to the conclusion that the canine aging phenotype also mimics that of the human. Genotype information, biochemical information pertaining to the GH/IGF-1 pathway, and some limited longitudinal investigations have begun the establishment of the domestic dog as a model of aging. Although we find that dogs indeed are a model to study aging and there are many independent pieces of canine aging data, there are many more “open” areas, ripe for investigation.

Review

What can long-lived mutants tell us about mechanisms causing aging and lifespan variation in natural environments?

Long-lived mutants of model organisms have brought remarkable progress in our understanding of aging mechanisms. However, long-lived mutants are usually maintained in optimal standardized laboratory environments (SLEs), and it is not obvious to what extent insights from long-lived mutants in SLEs can be generalized to more natural environments. To address this question, we reviewed experiments that compared the fitness and lifespan advantage of long-lived mutants relative to wild type controls in SLEs and more challenging environments in various model organisms such as yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruitfly *Drosophila melanogaster* and the mouse *Mus musculus*. In competition experiments over multiple generations, the long-lived mutants had a lower fitness relative to wild type controls, and this disadvantage was the clearest when the environment included natural challenges such as limited food (N = 6 studies). It is well known that most long-lived mutants have impaired reproduction, which provides one reason for the fitness disadvantage. However, based on 12 experiments, we found that the lifespan advantage of long-lived mutants is diminished in more challenging environments, often to the extent that the wild type controls outlive the long-lived mutants. Thus, it appears that information on aging mechanisms obtained from long-lived mutants in SLEs may be specific to such environments, because those same mechanisms do not extend lifespan in more natural environments. This suggests that different mechanisms cause variation in aging and lifespan in SLEs compared to natural populations.