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17th of June 2018
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TECHNOLOGY

AstraZeneca, Lilly Join Others On Failed Alzheimer's Drug Heap



ALLISON GATLIN | 6/12/2018

AstraZeneca (AZN) and **Eli Lilly (LLY)** became the latest Tuesday in a series of pharmaceutical companies to scrap studies of a potential Alzheimer's disease treatment that appeared unlikely to work.

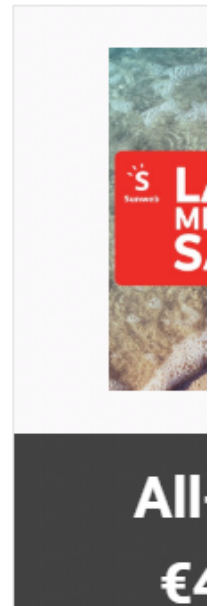


Illustration by Nicolás Ortega

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Longevity, the Greatest Investment Opportunity of All Time

Billionaire Jim Mellon bets that a “stock market mania” will be sparked by technologies that make people live past 100.

Jim Mellon became a billionaire by pouncing on a wide variety of opportunities, from the dawn of business privatization in Russia to uranium mining in Africa and real estate in Germany. But all of that might eventually look small, he says, compared to the money to be made in the next decade or so from biotechnologies that will increase human longevity well past 100.

UNITY files for \$85M IPO to Bring Anti-aging Drugs to Human Trials

Steve Hill April 11, 2018



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UNITY Biotechnology has now [filed](#) for an \$85 million initial public offering (IPO); if successful, it will bring the total raised funds to around \$300 million and pave the way for the company to move therapies to the clinic.

‘Reprogrammed’ stem cells approved to mend human hearts for the first time

The latest clinical use of induced pluripotent stem cells excites researchers, but some fear the therapy will be rushed to market.

David Cyranoski



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Disruption of the beclin 1–BCL2 autophagy regulatory complex promotes longevity in mice

Autophagy increases the lifespan of model organisms; however, its role in promoting mammalian longevity is less well-established^{1,2}. Here we report lifespan and healthspan extension in a mouse model with increased basal autophagy. To determine the effects of constitutively increased autophagy on mammalian health, we generated targeted mutant mice with a Phe121Ala mutation in beclin 1 (*Becn1*^{F121A/F121A}) that decreases its interaction with the negative regulator BCL2. We demonstrate that the interaction between beclin 1 and BCL2 is disrupted in several tissues in *Becn1*^{F121A/F121A} knock-in mice in association with higher levels of basal autophagic flux. Compared to wild-type littermates, the lifespan of both male and female knock-in mice is significantly increased. The healthspan of the knock-in mice also improves, as phenotypes such as age-related renal and cardiac pathological changes and spontaneous tumorigenesis are diminished. Moreover, mice deficient in the anti-ageing protein *klotho*³ have increased beclin 1 and BCL2 interaction and decreased autophagy. These phenotypes, along with premature lethality and infertility, are rescued by the beclin 1(F121A) mutation. Together, our data demonstrate that disruption of the beclin 1–BCL2 complex is an effective mechanism to increase autophagy, prevent premature ageing, improve healthspan and promote longevity in mammals.

Embryonic senescent cells re-enter cell cycle and contribute to tissues after birth

Yi Li, Huan Zhao, Xiuzhen Huang, Juan Tang, Shaohua Zhang, Yan Li, Xiuxiu Liu, Lingjuan He, Zhengyu Ju, Kathy O. Lui & Bin Zhou 

Cellular senescence (or senescence) has been regarded as a stable form of cell cycle arrest by *in vitro* cell culture experiments.¹ Recent studies indicate that senescence is associated with aging and diseases, including cancers.^{2,3} For instances, it suppresses tumor progression by halting the growth of premalignant cells,⁴ and promotes wound healing by preventing excessive tissue fibrosis or induction of cell dedifferentiation.^{5,6} Targeting senescent cells could restore tissue homeostasis in response to aging, chemotoxicity, or injury.⁷ In addition to these pathological conditions in adults, cellular senescence also occurs in physiological states such as mammalian mouse^{8,9} and human^{10,11} embryonic development. Embryonic senescent cells have been reported to be non-proliferative and subjected to clearance from tissues after apoptosis at late embryonic stage.^{8,9} However, the interpretation for clearance of senescent cells at late embryonic stage is based on the disappearance of Cdkn1a (P21) expression and senescence-associated beta-galactosidase (SA β -Gal) activity,^{8,9} two commonly used senescence markers in the field. Currently, there is no genetic fate mapping evidence for senescent cell fate *in vivo*. By lineage tracing of P21⁺ senescent cells, we found that embryonic senescent cells labeled at mid-embryonic stage gradually lost P21 expression and SA β -Gal activity at late embryonic stage. Unexpectedly, some of the previously labeled senescent cells re-entered the cell cycle and proliferated *in situ*. Moreover, these previously labeled senescent cells were not cleared at late embryonic stage and remained in the tissue after birth. This study unravels *in vivo* senescent cell fates during embryogenesis, indicating their potential plasticity.

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

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

Longevity and transposon defense, the case of termite reproductives

Social insects are promising new models in aging research. Within single colonies, longevity differences of several magnitudes exist that can be found elsewhere only between different species. Reproducing queens (and, in termites, also kings) can live for several decades, whereas sterile workers often have a lifespan of a few weeks only. We studied aging in the wild in a highly social insect, the termite *Macrotermes bellicosus*, which has one of the most pronounced longevity differences between reproductives and workers. We show that gene-expression patterns differed little between young and old reproductives, implying negligible aging. By contrast, old major workers had many genes up-regulated that are related to transposable elements (TEs), which can cause aging. Strikingly, genes from the PIWI-interacting RNA (piRNA) pathway, which are generally known to silence TEs in the germline of multicellular animals, were down-regulated only in old major workers but not in reproductives. Continued up-regulation of the piRNA defense commonly found in the germline of animals can explain the long life of termite reproductives, implying somatic cooption of germline defense during social evolution. This presents a striking germline/soma analogy as envisioned by the superorganism concept: the reproductives and workers of a colony reflect the germline and soma of multicellular animals, respectively. Our results provide support for the disposable soma theory of aging.

Overexpression of Nmnat3 efficiently increases NAD and NGD levels and ameliorates age-associated insulin resistance

Maryam Gulshan, Keisuke Yaku, Keisuke Okabe, Arshad Mahmood, Tsutomu Sasaki, Masashi Yamamoto, Keisuke Hikosaka, Isao Usui, Tadahiro Kitamura, ... [See all authors](#) ▾

Nicotinamide adenine dinucleotide (NAD) is an important cofactor that regulates various biological processes, including metabolism and gene expression. As a coenzyme, NAD controls mitochondrial respiration through enzymes of the tricarboxylic acid (TCA) cycle, β -oxidation, and oxidative phosphorylation and also serves as a substrate for posttranslational protein modifications, such as deacetylation and ADP-ribosylation by sirtuins and poly(ADP-ribose) polymerase (PARP), respectively. Many studies have demonstrated that NAD levels decrease with aging and that these declines cause various aging-associated diseases. In contrast, activation of NAD metabolism prevents declines in NAD levels during aging. In particular, dietary supplementation with NAD precursors has been associated with protection against age-associated insulin resistance. However, it remains unclear which NAD synthesis pathway is important and/or efficient at increasing NAD levels in vivo. In this study, Nmnat3 overexpression in mice efficiently increased NAD levels in various tissues and prevented aging-related declines in NAD levels. We also demonstrated that Nmnat3-overexpressing (Nmnat3 Tg) mice were protected against diet-induced and aging-associated insulin resistance. Moreover, in skeletal muscles of Nmnat3 Tg mice, TCA cycle activity was significantly enhanced, and the energy source for oxidative phosphorylation was shifted toward fatty acid oxidation. Furthermore, reactive oxygen species (ROS) generation was significantly suppressed in aged Nmnat3 Tg mice. Interestingly, we also found that concentrations of the NAD analog nicotinamide guanine dinucleotide (NGD) were dramatically increased in Nmnat3 Tg mice. These results suggest that Nmnat3 overexpression improves metabolic health and that Nmnat3 is an attractive therapeutic target for metabolic disorders that are caused by aging.

Mitochondria shape is controlled by membrane fusion and fission mediated by mitofusins, Opa1, and Drp1, whereas mitochondrial motility relies on microtubule motors. These processes govern mitochondria subcellular distribution, whose defects are emphasized in neurons because of their polarized structure. We have studied how perturbation of the fusion/fission balance affects mitochondria distribution in *Drosophila* axons. Knockdown of Marf or Opa1 resulted in progressive loss of distal mitochondria and in a distinct oxidative phosphorylation and membrane potential deficit. Downregulation of Drp1 rescued the lethality and bioenergetic defect caused by neuronal Marf RNAi, but induced only a modest restoration of axonal mitochondria distribution. Surprisingly, Drp1 knockdown rescued fragmentation and fully restored aberrant distribution of axonal mitochondria produced by Opa1 RNAi; however, Drp1 knockdown did not improve viability or mitochondria function. Our data show that proper morphology is critical for proper axonal mitochondria distribution independent of bioenergetic efficiency. The health of neurons largely depends on mitochondria function, but does not depend on shape or distribution.

Mitochondria are a major target for aging and are instrumental in the age-dependent deterioration of the human brain, but studying mitochondria in aging human neurons has been challenging. Direct fibroblast-to-induced neuron (iN) conversion yields functional neurons that retain important signs of aging, in contrast to iPSC differentiation. Here, we analyzed mitochondrial features in iNs from individuals of different ages. iNs from old donors display decreased oxidative phosphorylation (OXPHOS)-related gene expression, impaired axonal mitochondrial morphologies, lower mitochondrial membrane potentials, reduced energy production, and increased oxidized proteins levels. In contrast, the fibroblasts from which iNs were generated show only mild age-dependent changes, consistent with a metabolic shift from glycolysis-dependent fibroblasts to OXPHOS-dependent iNs. Indeed, OXPHOS-induced old fibroblasts show increased mitochondrial aging features similar to iNs. Our data indicate that iNs are a valuable tool for studying mitochondrial aging and support a bioenergetic explanation for the high susceptibility of the brain to aging.

Fast-Evolving Human-Specific Neural Enhancers Are Associated with Aging-Related Diseases

Han Chen ^{1, 4}, Chunyan Li ^{1, 2, 4}, Zhicheng Zhou ^{1, 3}, Han Liang ^{1, 3, 5}  

The antagonistic **pleiotropy** theory hypothesizes that **evolutionary adaptations** maximizing the fitness in early age increase disease burden after reproduction. This theory remains largely untested at the molecular level. Here, we analyzed enhancer evolution in primates to investigate the relationships between aging-related diseases and enhancers acquired after the human-chimpanzee divergence. We report a 5-fold increased evolutionary rate of enhancers that are activated in neural tissues, leading to fixation of ~100 human-specific enhancers potentially under adaptation. These enhancers show prognostic expression levels and correlations with driver genes in cancer, and their nearby genes are enriched in known loci associated with aging-related diseases. Using **CRISPR/Cas9**, we further functionally validated an enhancer on chr8p23.1 as activator counteracting REST, a master regulator known to be a **transcriptional suppressor** of Alzheimer disease. Our results suggest an evolutionary origin of aging-related diseases: the side effects of human-specific, neural-tissue expressed enhancers. Thus, adaptive molecular changes in human macroevolution may introduce vulnerabilities to disease development in modern populations.

Biological Processes Modulating Longevity across Primates: A Phylogenetic Genome-Phenome Analysis

Abstract

Aging is a complex process affecting different species and individuals in different ways. Comparing genetic variation across species with their aging phenotypes will help understanding the molecular basis of aging and longevity. Although most studies on aging have so far focused on short-lived model organisms, recent comparisons of genomic, transcriptomic, and metabolomic data across lineages with different lifespans are unveiling molecular signatures associated with longevity. Here, we examine the relationship between genomic variation and maximum lifespan across primate species. We used two different approaches. First, we searched for parallel amino-acid mutations that co-occur with increases in longevity across the primate lineage. Twenty-five such amino-acid variants were identified, several of which have been previously reported by studies with different experimental setups and in different model organisms. The genes harboring these mutations are mainly enriched in functional categories such as wound healing, blood coagulation, and cardiovascular disorders. We demonstrate that these pathways are highly enriched for pleiotropic effects, as predicted by the antagonistic pleiotropy theory of aging. A second approach was focused on changes in rates of protein evolution across the primate phylogeny. Using the phylogenetic generalized least squares, we show that some genes exhibit strong correlations between their evolutionary rates and longevity-associated traits. These include genes in the Sphingosine 1-phosphate pathway, PI3K signaling, and the Thrombin/protease-activated receptor pathway, among other cardiovascular processes. Together, these results shed light into human senescence patterns and underscore the power of comparative genomics to identify pathways related to aging and longevity.

Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome

Leslie B. Gordon, MD, PhD^{1,2,3}; Heather Shappell, PhD⁴; Joe Massaro, PhD⁴; et al

Objective To evaluate the association of monotherapy using the protein farnesyltransferase inhibitor lonafarnib with mortality rate in children with HGPS.

Design, Setting, and Participants Cohort study comparing contemporaneous (birth date ≥ 1991) untreated patients with HGPS matched with treated patients by age, sex, and continent of residency using conditional Cox proportional hazards regression. Treatment cohorts included patients from 2 single-group, single-site clinical trials (ProLon1 [n=27; completed] and ProLon2 [n=36; ongoing]). Untreated patients originated from a separate natural history study (n=103). The cutoff date for patient follow-up was January 1, 2018.




Exposure Treated patients received oral lonafarnib (150 mg/m²) twice daily. Untreated patients received no clinical trial medications.

Main Outcomes and Measures The primary outcome was mortality. The primary analysis compared treated patients from the first lonafarnib trial with matched untreated patients. A secondary analysis compared the combined cohorts from both lonafarnib trials with matched untreated patients.

Results Among untreated and treated patients (n=258) from 6 continents, 123 (47.7%) were female; 141 (54.7%) had a known genotype, of which 125 (88.7%) were classic (c.1824C>T in *LMNA*). When identified (n=73), the primary cause of death was heart failure (79.4%). The median treatment duration was 2.2 years. Median age at start of follow-up was 8.4 (interquartile range [IQR], 4.8-9.5) years in the first trial cohort and 6.5 (IQR, 3.7-9.0) years in the combined cohort. There was 1 death (3.7%) among 27 patients in the first trial group and there were 9 deaths (33.3%) among 27 patients in the matched untreated group. Treatment was associated with a lower mortality rate (hazard ratio, 0.12; 95% CI, 0.01-0.93; $P = .04$). In the combined cohort, there were 4 deaths (6.3%) among 63 patients in the treated group and 17 deaths (27.0%) among 63 patients in the matched untreated group (hazard ratio, 0.23; 95% CI, 0.06-0.90; $P = .04$).

Conclusions and Relevance Among patients with HGPS, lonafarnib monotherapy, compared with no treatment, was associated with a lower mortality rate after 2.2 years of follow-up. Study interpretation is limited by its observational design.

Upregulation of the aging related LMNA splice variant progerin in dilated cardiomyopathy

Moritz Messner , Santhosh Kumar Ghadge , Valentina Goetsch, Andreas Wimmer, Jakob Dörler, Gerhard Pözl, Marc-Michael Zaruba 

Background

Mutations in the LMNA gene are a common cause (6–8%) of dilated cardiomyopathy (DCM) leading to heart failure, a growing health care problem worldwide. The premature aging disease Hutchinson-Gilford syndrome (HGPS) is also caused by defined mutations in the LMNA gene resulting in activation of a cryptic splice donor site leading to a defective truncated prelamin A protein called progerin. Low levels of progerin are expressed in healthy individuals associated with ageing. Here, we aimed to address the role of progerin in dilated cardiomyopathy.

Methods and results

mRNA expression of progerin was analyzed in heart tissue of DCM ($n = 15$) and non-failing hearts ($n = 10$) as control and in blood samples from patients with DCM ($n = 56$) and healthy controls ($n = 10$). Sequencing confirmed the expression of progerin mRNA in the human heart. Progerin mRNA levels derived from DCM hearts were significantly upregulated compared to controls (1.27 ± 0.42 vs. 0.81 ± 0.24 ; $p = 0.005$). In contrast, progerin mRNA levels in whole blood cells were not significantly different in DCM patients compared to controls. Linear regression analyses revealed that progerin mRNA in the heart is significantly negatively correlated to ejection fraction ($r = -0.567$, $p = 0.003$) and positively correlated to left ventricular enddiastolic diameter ($r = 0.551$, $p = 0.004$) but not with age of the heart per se. Progerin mRNA levels were not influenced by inflammation in DCM hearts. Immunohistochemistry and Immunofluorescence analysis confirmed increased expression of progerin protein in cell nuclei of DCM hearts associated with increased TUNEL+ apoptotic cells.

Conclusion

Our data suggest that progerin is upregulated in human DCM hearts and strongly correlates with left ventricular remodeling. Progerin might be involved in progression of heart failure and myocardial aging.

Association of β -Amyloid and Apolipoprotein E ϵ 4 With Memory Decline in Preclinical Alzheimer Disease

Yen Ying Lim, PhD¹; Pawel Kalinowski, PhD²; Robert H. Pietrzak, PhD, MPH³; [et al](#)

Design, Setting, and Participants This longitudinal observational study included cognitively healthy older adults (age >60 years) enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study from March 31, 2006, through March 31, 2017; of 1583 individuals enrolled, 1136 refused or were excluded owing to other criteria (eg, having mild cognitive impairment or AD). Participants underwent $A\beta$ imaging in research clinics in Perth and Melbourne and more than 72 months of follow-up (at 18-month intervals). The association of age with memory was fitted to a quadratic model. Age was treated as a continuous, time-dependent variable.

Exposures β -Amyloid imaging using positron emission tomography, genotyping for *APOE* ϵ 4, and longitudinal neuropsychological assessments of episodic memory during the 72-month follow-up.

Main Outcomes and Measures Episodic memory composite score.

Results Of the 447 participants, 203 (45.4%) were men and 244 (54.6%) were women; mean (SD) age was 72.5 (6.6) years. Equal proportions of female participants were observed in each $A\beta$ - ϵ 4 group (24 of 51 $A\beta$ -positive ϵ 4 noncarriers [47.1%]; 35 of 64 $A\beta$ -negative ϵ 4 carriers [54.7%]; 40 of 72 $A\beta$ -positive ϵ 4 carriers [55.6%]; and 145 of 260 $A\beta$ -negative ϵ 4 noncarriers [55.8%]). Adults with $A\beta$ findings (mean [SD] age, 74.4 [6.8] years) were approximately 4 years older than those negative for $A\beta$ (mean [SD] age, 69.8 [6.1] years). Memory decline diverged significantly from $A\beta$ -negative ϵ 4 noncarriers at an earlier age in $A\beta$ -positive ϵ 4 carriers (64.5 years) than in $A\beta$ -positive ϵ 4 noncarriers (76.5 years), such that by 85 years of age, $A\beta$ -positive ϵ 4 carriers performed approximately 1.5 SD units worse on the episodic memory composite than $A\beta$ -negative ϵ 4 noncarriers and approximately 0.8 SD units worse than $A\beta$ -positive ϵ 4 noncarriers. Memory performance of $A\beta$ -negative ϵ 4 carriers did not differ from that of the $A\beta$ -negative ϵ 4 noncarriers (estimate [SE], 0.001 [0.001]; $t=0.526$; $P=.77$).

Conclusions and Relevance Prior work has shown that $A\beta$ and ϵ 4 combine to influence memory decline in nondemented older adults. Results of this study indicate that increasing age may further exacerbate these effects. The estimates provided may be used to determine the risk of memory decline associated with $A\beta$ and ϵ 4 at each age.

Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease

BACKGROUND Alzheimer's disease is characterized by the deposition of amyloid-beta ($A\beta$) plaques in the brain. $A\beta$ is produced from the sequential cleavage of amyloid precursor protein by β -site amyloid precursor protein–cleaving enzyme 1 (BACE-1) followed by γ -secretase. Verubecestat is an oral BACE-1 inhibitor that reduces the $A\beta$ level in the cerebrospinal fluid of patients with Alzheimer's disease.

METHODS We conducted a randomized, double-blind, placebo-controlled, 78-week trial to evaluate verubecestat at doses of 12 mg and 40 mg per day, as compared with placebo, in patients who had a clinical diagnosis of mild-to-moderate Alzheimer's disease. The coprimary outcomes were the change from baseline to week 78 in the score on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog; scores range from 0 to 70, with higher scores indicating worse dementia) and in the score on the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory scale (ADCS-ADL; scores range from 0 to 78, with lower scores indicating worse function).

RESULTS A total of 1958 patients underwent randomization; 653 were randomly assigned to receive verubecestat at a dose of 12 mg per day (the 12-mg group), 652 to receive verubecestat at a dose of 40 mg per day (the 40-mg group), and 653 to receive matching placebo. The trial was terminated early for futility 50 months after onset, which was within 5 months before its scheduled completion, and after enrollment of the planned 1958 patients was complete. The estimated mean change from baseline to week 78 in the ADAS-cog score was 7.9 in the 12-mg group, 8.0 in the 40-mg group, and 7.7 in the placebo group ($P=0.63$ for the comparison between the 12-mg group and the placebo group and $P=0.46$ for the comparison between the 40-mg group and the placebo group). The estimated mean change from baseline to week 78 in the ADCS-ADL score was -8.4 in the 12-mg group, -8.2 in the 40-mg group, and -8.9 in the placebo group ($P=0.49$ for the comparison between the 12-mg group and the placebo group and $P=0.32$ for the comparison between the 40-mg group and the placebo group). Adverse events, including rash, falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair-color change, were more common in the verubecestat groups than in the placebo group.

CONCLUSIONS Verubecestat did not reduce cognitive or functional decline in patients with mild-to-moderate Alzheimer's disease and was associated with treatment-related adverse events. (Funded by Merck; ClinicalTrials.gov number, NCT01739348.)

Abstract

Tau is a developmentally regulated axonal protein that stabilizes and bundles microtubules (MTs). Its hyperphosphorylation is thought to cause detachment from MTs and subsequent aggregation into fibrils implicated in Alzheimer's disease. It is unclear which tau residues are crucial for tau-MT interactions, where tau binds on MTs, and how it stabilizes them. We used cryo-electron microscopy to visualize different tau constructs on MTs and computational approaches to generate atomic models of tau-tubulin interactions. The conserved tubulin-binding repeats within tau adopt similar extended structures along the crest of the protofilament, stabilizing the interface between tubulin dimers. Our structures explain the effect of phosphorylation on MT affinity and lead to a model of tau repeats binding in tandem along protofilaments, tethering together tubulin dimers and stabilizing polymerization interfaces.

Cryo-EM structure of substrate-bound human telomerase holoenzyme

Thi Hoang Duong Nguyen, Jane Tam, Robert A. Wu, Basil J. Greber, Daniel Toso, Eva Nogales✉ & Kathleen Collins✉

Nature **557**, 190–195 (2018) | [Download Citation](#) ↓

Abstract

The enzyme telomerase adds telomeric repeats to chromosome ends to balance the loss of telomeres during genome replication. Telomerase regulation has been implicated in cancer, other human diseases, and ageing, but progress towards clinical manipulation of telomerase has been hampered by the lack of structural data. Here we present the cryo-electron microscopy structure of the substrate-bound human telomerase holoenzyme at subnanometre resolution, showing two flexibly RNA-tethered lobes: the catalytic core with telomerase reverse transcriptase (TERT) and conserved motifs of telomerase RNA (hTR), and an H/ACA ribonucleoprotein (RNP). In the catalytic core, RNA encircles TERT, adopting a well-ordered tertiary structure with surprisingly limited protein–RNA interactions. The H/ACA RNP lobe comprises two sets of heterotetrameric H/ACA proteins and one Cajal body protein, TCAB1, representing a pioneering structure of a large eukaryotic family of ribosome and spliceosome biogenesis factors. Our findings provide a structural framework for understanding human telomerase disease mutations and represent an important step towards telomerase-related clinical therapeutics.

Necroptosis increases with age and is reduced by dietary restriction

Sathyaseelan S. Deepa✉, Archana Unnikrishnan, Stephanie Matyi, Niran Hadad, Arlan Richardson

First published: 25 April 2018 | <https://doi.org/10.1111/ace.12770>

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Summary

Necroptosis is a newly identified programmed cell death pathway that is highly proinflammatory due to the release of cellular components that promote inflammation. To determine whether necroptosis might play a role in inflammaging, we studied the effect of age and dietary restriction (DR) on necroptosis in the epididymal white adipose tissue (eWAT), a major source of proinflammatory cytokines. Phosphorylated MLKL and RIPK3, markers of necroptosis, were increased 2.7- and 1.9-fold, respectively, in eWAT of old mice compared to adult mice, and DR reduced P-MLKL and P-RIPK3 to levels similar to adult mice. An increase in the expression of RIPK1 (1.6-fold) and MLKL (2.7-fold), not RIPK3, was also observed in eWAT of old mice, which was reduced by DR in old mice. The increase in necroptosis was paralleled by an increase in 14 inflammatory cytokines, including the pro-inflammatory cytokines IL-6 (3.9-fold), TNF- α (4.7-fold), and IL-1 β (5.1-fold), and 11 chemokines in old mice. DR attenuated the expression of IL-6, TNF- α , and IL-1 β as well as 85% of the other cytokines/chemokines induced with age. In contrast, inguinal WAT (iWAT), which is less inflammatory, did not show any significant increase with age in the levels of P-MLKL and MLKL or inflammatory cytokines/chemokines. Because the changes in biomarkers of necroptosis in eWAT with age and DR paralleled the changes in the expression of pro-inflammatory cytokines, our data support the possibility that necroptosis might play a role in increased chronic inflammation observed with age.

Short-Term, Intermittent Fasting Induces Long-Lasting Gut Health and TOR-Independent Lifespan Extension

James H. Catterson, Mobina Khericha, Miranda C. Dyson, Alec J. Vincent, Rebecca Callard, Steven M. Haveron, Arjunan Rajasingam, Mumtaz Ahmad, Linda Partridge³  

Intermittent fasting (IF) can improve function and health during aging in laboratory model organisms, but the mechanisms at work await elucidation. We subjected fruit flies (*Drosophila melanogaster*) to varying degrees of IF and found that just one month of a 2-day fed:5-day fasted IF regime at the beginning of adulthood was sufficient to extend lifespan. This long-lasting, beneficial effect of early IF was not due to reduced fecundity. Starvation resistance and resistance to oxidative and xenobiotic stress were increased after IF. Early-life IF also led to higher lipid content in 60-day-old flies, a potential explanation for increased longevity. Guts of flies 40 days post-IF showed a significant reduction in age-related pathologies and improved gut barrier function. Improved gut health was also associated with reduced relative bacterial abundance. Early IF thus induced profound long-term changes. Pharmacological and genetic epistasis analysis showed that IF acted independently of the TOR pathway because rapamycin and IF acted additively to extend lifespan, and global expression of a constitutively active S6K did not attenuate the IF-induced lifespan extension. We conclude that short-term IF during early life can induce long-lasting beneficial effects, with robust increase in lifespan in a TOR-independent manner, probably at least in part by preserving gut health.

Characteristic glycopeptides associated with extreme human longevity identified through plasma glycoproteomics

Background

Glycosylation is highly susceptible to changes of the physiological conditions, and accordingly, is a potential biomarker associated with several diseases and/or longevity. Semi-supercentenarians (SSCs; older than 105 years) are thought to be a model of human longevity. Thus, we performed **glycoproteomics** using plasma samples of SSCs, and identified proteins and conjugated *N*-glycans that are characteristic of extreme human longevity.

Methods

Plasma proteins from Japanese semi-supercentenarians (SSCs, 106–109 years), aged controls (70–88 years), and young controls (20–38 years) were analysed by using **lectin microarrays** and **liquid chromatography/mass spectrometry (LC/MS)**. Peak area ratios of **glycopeptides** to corresponding normalising **peptides** were subjected to orthogonal projections to latent structures discriminant analysis (OPLS-DA). Furthermore, plasma levels of clinical biomarkers were measured.

Results

We found two **lectins** such as *Phaseolus vulgaris*, and *Erythrina cristagalli* (ECA), of which **protein binding** were characteristically increased in SSCs. Peak area ratios of ECA-enriched glycopeptides were successfully discriminated between SSCs and controls using OPLS-DA, and indicated that tri-antennary and sialylated *N*-glycans of **haptoglobin** at Asn207 and Asn211 sites were characterized in SSCs. Sialylated **glycans** of haptoglobin are a potential biomarker of several diseases, such as hepatocellular carcinoma, liver cirrhosis, and IgA-nephritis. However, the SSCs analysed here did not suffer from these diseases.

Conclusions

Tri-antennary and sialylated *N*-glycans on haptoglobin at the Asn207 and Asn211 sites were abundant in SSCs and characteristic of extreme human longevity.

Restructuring of the Gut Microbiome by Intermittent Fasting Prevents Retinopathy and Prolongs Survival in db/db Mice

Intermittent fasting (IF) protects against the development of metabolic diseases and cancer, but whether it can prevent diabetic microvascular complications is not known. In db/db mice, we examined the impact of long-term IF on diabetic retinopathy (DR). Despite no change in glycated hemoglobin, db/db mice on the IF regimen displayed significantly longer survival and a reduction in DR endpoints, including acellular capillaries and leukocyte infiltration. We hypothesized that IF mediated changes in the gut microbiota would produce beneficial metabolites and prevent the development of DR. Microbiome analysis revealed increased levels of *Firmicutes* and decreased *Bacteroidetes* and *Verrucomicrobia*. Compared to db/db mice on ad-libitum (AL) feeding, changes in the microbiome of the db/db mice on IF were associated with increases in gut mucin, goblet cell number and villi length and reductions in plasma peptidoglycan. Consistent with the known modulatory effects of *Firmicutes* on bile acid (BA) metabolism, measurement of BAs demonstrated a significant increase of tauroursodeoxycholate (TUDCA), a neuroprotective BA, in db/db on IF but not in db/db on AL feeding. TGR-5, the TUDCA receptor, was found in neural cells of the retina primary ganglion cells. Expression of TGR5 did not change with IF or diabetes. However, IF reduced retinal TNF- α mRNA, which is a key downstream target of TGR-5 activation. Pharmacological activation of TGR5 using INT-767 prevented DR in a second diabetic mouse model. These findings support the concept that IF prevents DR by restructuring the microbiota towards species producing TUDCA and subsequent retinal protection by TGR5 activation.

REVIEWS/COMMENTS/ED
ITORIALS

Diverse mechanisms for endogenous regeneration and repair in mammalian organs

James M. Wells [✉](#) & Fiona M. Watt [✉](#)

Nature **557**, 322–328 (2018) | [Download Citation](#) ↓

Abstract

Mammalian organs comprise an extraordinary diversity of cell and tissue types. Regenerative organs, such as the skin and gastrointestinal tract, use resident stem cells to maintain tissue function. Organs with a lower cellular turnover, such as the liver and lungs, mostly rely on proliferation of committed progenitor cells. In many organs, injury reveals the plasticity of both resident stem cells and differentiated cells. The ability of resident cells to maintain and repair organs diminishes with age, whereas, paradoxically, the risk of cancer increases. New therapeutic approaches aim to harness cell plasticity for tissue repair and regeneration while avoiding the risk of malignant transformation of cells.

CircRNA accumulation: A new hallmark of aging?

David Knupp, Pedro Miura  

Circular RNAs (circRNAs) are a newly appreciated class of RNAs found across phyla that are generated most commonly from back-splicing of protein-coding exons. Recent profiling of circRNAs genome-wide has shown that hundreds of circRNAs dramatically increase in expression during aging in the brains of multiple organisms. No other class of transcripts has been found to show such a strong correlation with aging as circRNAs—could they be playing a role in the aging process? Here, we discuss the different methods used to profile circRNAs and discuss current limitations of these approaches. We argue that age-related increases in global circRNA levels likely result from their high stability. The functions of circRNAs are only beginning to emerge, and it is an open question whether circRNA accumulation impacts the aging brain. We discuss experimental approaches that could illuminate whether age-accumulation of circRNAs are detrimental or protective to the aging brain.

Interventions to promote cardiometabolic health and slow cardiovascular ageing

Luigi Fontana [✉](#)

Nature Reviews Cardiology (2018) | [Download Citation](#) ↓

Abstract

Cardiovascular ageing and the atherosclerotic process begin very early in life, most likely in utero. They progress over decades of exposure to suboptimal or abnormal metabolic and hormonal risk factors, eventually culminating in very common, costly, and mostly preventable target-organ pathologies, including coronary heart disease, stroke, heart failure, aortic aneurysm, peripheral artery disease, and vascular dementia. In this Review, we discuss findings from preclinical and clinical studies showing that calorie restriction (CR), intermittent fasting, and adjusted diurnal rhythm of feeding, with adequate intake of specific macronutrients and micronutrients, are powerful interventions not only for the prevention of cardiovascular disease but also for slowing the accumulation of molecular damage leading to cardiometabolic dysfunction. Furthermore, we discuss the mechanisms through which a number of other nondietary interventions, such as regular physical activity, mindfulness-based stress-reduction exercises, and some CR-mimetic drugs that target pro-ageing pathways, can potentiate the beneficial effects of a healthy diet in promoting cardiometabolic health.

Mitochondria and aging: A role for the mitochondrial transition pore?

Mathieu Panel, Bijan Ghaleh, Didier Morin 

The cellular mechanisms responsible for aging are poorly understood. Aging is considered as a degenerative process induced by the accumulation of cellular lesions leading progressively to organ dysfunction and death. The free radical theory of aging has long been considered the most relevant to explain the mechanisms of aging. As the mitochondrion is an important source of reactive oxygen species (ROS), this organelle is regarded as a key intracellular player in this process and a large amount of data supports the role of mitochondrial ROS production during aging. Thus, mitochondrial ROS, oxidative damage, aging, and aging-dependent diseases are strongly connected. However, other features of mitochondrial physiology and dysfunction have been recently implicated in the development of the aging process. Here, we examine the potential role of the mitochondrial permeability transition pore (mPTP) in normal aging and in aging-associated diseases.

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

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

OTHER RESEARCH

p53 inhibits CRISPR–Cas9 engineering in human pluripotent stem cells

CRISPR/Cas9 has revolutionized our ability to engineer genomes and conduct genome-wide screens in human cells^{1,2,3}. Whereas some cell types are amenable to genome engineering, genomes of human pluripotent stem cells (hPSCs) have been difficult to engineer, with reduced efficiencies relative to tumour cell lines or mouse embryonic stem cells^{3,4,5,6,7,8,9,10,11,12,13}. Here, using hPSC lines with stable integration of Cas9 or transient delivery of Cas9-ribonucleoproteins (RNPs), we achieved an average insertion or deletion (indel) efficiency greater than 80%. This high efficiency of indel generation revealed that double-strand breaks (DSBs) induced by Cas9 are toxic and kill most hPSCs. In previous studies, the toxicity of Cas9 in hPSCs was less apparent because of low transfection efficiency and subsequently low DSB induction³. The toxic response to DSBs was P53/TP53-dependent, such that the efficiency of precise genome engineering in hPSCs with a wild-type P53 gene was severely reduced. Our results indicate that Cas9 toxicity creates an obstacle to the high-throughput use of CRISPR/Cas9 for genome engineering and screening in hPSCs. Moreover, as hPSCs can acquire P53 mutations¹⁴, cell replacement therapies using CRISPR/Cas9-engineered hPSCs should proceed with caution, and such engineered hPSCs should be monitored for P53 function.

Universal Chimeric Antigen Receptors for Multiplexed and Logical Control of T Cell Responses

T cells expressing chimeric antigen receptors (CARs) are promising cancer therapeutic agents, with the prospect of becoming the ultimate smart cancer therapeutics. To expand the capability of CAR T cells, here, we present a split, universal, and programmable (SUPRA) CAR system that simultaneously encompasses multiple critical "upgrades," such as the ability to switch targets without re-engineering the T cells, finely tune T cell activation strength, and sense and logically respond to multiple antigens. These features are useful to combat relapse, mitigate over-activation, and enhance specificity. We test our SUPRA system against two different tumor models to demonstrate its broad utility and humanize its components to minimize potential immunogenicity concerns. Furthermore, we extend the orthogonal SUPRA CAR system to regulate different T cell subsets independently, demonstrating a dually inducible CAR system. Together, these SUPRA CARs illustrate that multiple advanced logic and control features can be implemented into a single, integrated system.

Two-Step Senescence-Focused Cancer Therapies









Cynthia J. Sieben, Ines Sturmlechner, Bart van de Sluis, Jan M. van Deursen  

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Highlights

Senescent cells are a cell cycle-arrested but highly bioactive cell type. Although the proportion of senescent cells in tissues is relatively low, these cells are causally implicated in aging and in an ever-expanding list of diseases including cancer.

Cancer-associated senescent cells can modulate all stages of tumor development, with their contributions being either detrimental or beneficial towards tumor initiation, growth, metastasis, or cancer relapse.

Although highly context-dependent, the senescence-associated secretory phenotype (SASP) serves many functions in the tumor microenvironment, including mitogenic induction, immune surveillance, or immune deterrence.

A two-step anticancer therapeutic concept, senescence-inducing chemotherapy followed by senotherapy, may represent a viable option to maximize therapeutic efficiency and patient outcome.

Damaged cells at risk of neoplastic transformation can be neutralized by apoptosis or engagement of the senescence program, which induces permanent cell-cycle arrest and a bioactive secretome that is implicated in tumor immunosurveillance. While from an evolutionary perspective senescence is beneficial in that it protects against malignancies, the accumulation of senescent cells in tissues and organs with aging and at sites of various pathologies is largely detrimental. Because induction of senescence in cancer cells is emerging as a therapeutic concept, it will be important to consider these detrimental effects, including tumor-promoting properties that may drive the formation of secondary tumors or cancer relapse. In this review we discuss the complex relationship between senescence and cancer, and highlight important

Machine learning, a collection of data-analytical techniques aimed at building predictive models from multi-dimensional datasets, is becoming integral to modern biological research. By enabling one to generate models that learn from large datasets and make predictions on likely outcomes, machine learning can be used to study complex cellular systems such as biological networks. Here, we provide a **primer** on machine learning for life scientists, including an introduction to deep learning. We discuss opportunities and challenges at the intersection of machine learning and network biology, which could impact disease biology, drug discovery, **microbiome** research, and synthetic biology.