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# Scientific news - 5th of April 2015

Sven Bulterijs

# The Achilles' Heel of Senescent Cells: From Transcriptome to Senolytic Drugs

## Summary

The healthspan of mice is enhanced by killing senescent cells using a transgenic suicide gene. Achieving the same using small molecules would have a tremendous impact on quality of life and burden of age-related chronic diseases. Here, we describe the rationale for identification and validation of a new class of drugs termed senolytics, which selectively kill senescent cells. By transcript analysis, we discovered increased expression of pro-survival networks in senescent cells, consistent with their established resistance to apoptosis. Using siRNA to silence expression of key nodes of this network, including ephrins (EFNB1 or 3), PI3K $\delta$ , p21, BCL-xL, or plasminogen activated inhibitor-2, killed senescent cells, but not proliferating or quiescent, differentiated cells. Drugs targeting these factors selectively killed senescent cells. Dasatinib eliminated senescent human fat cell progenitors, while quercetin was more effective against senescent human endothelial cells and mouse BM-MSCs. The combination of dasatinib and quercetin was effective in eliminating senescent MEFs. *In vivo*, this combination reduced senescent cell burden in chronologically aged, radiation-exposed, and progeroid *Ercc1*<sup>- $\Delta$</sup>  mice. In old mice, cardiac function and carotid vascular reactivity were improved 5 days after a single dose. Following irradiation of one limb in mice, a single dose led to improved exercise capacity for at least 7 months following drug treatment. Periodic drug administration extended healthspan in *Ercc1*<sup>- $\Delta$</sup>  mice, delaying age-related symptoms and pathology, osteoporosis and loss of intervertebral disc proteoglycans. These results demonstrate the feasibility of selectively ablating senescent cells and the efficacy of senolytics for alleviating symptoms of frailty and extending healthspan.

# Regulation of Nrf2 signaling and longevity in naturally long-lived rodents

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The preternaturally long-lived naked mole-rat, like other long-lived species and experimental models of extended longevity, is resistant to both endogenous (e.g., reactive oxygen species) and environmental stressors and also resists age-related diseases such as cancer, cardiovascular disease, and neurodegeneration. The mechanisms behind the universal resilience of longer-lived organisms to stress, however, remain elusive. We hypothesize that this resilience is linked to the activity of a highly conserved transcription factor, nuclear factor erythroid 2-related factor (Nrf2). Nrf2 regulates the transcription of several hundred cytoprotective molecules, including antioxidants, detoxicants, and molecular chaperones (heat shock proteins). Nrf2 itself is tightly regulated by mechanisms that either promote its activity or increase its degradation. We used a comparative approach and examined Nrf2-signaling activity in naked mole-rats and nine other rodent species with varying maximum lifespan potential (MLSP). We found that constitutive Nrf2-signaling activity was positively correlated ( $P = 0.0285$ ) with MLSP and that this activity was also manifested in high levels of downstream gene expression and activity. Surprisingly, we found that species longevity was not linked to the protein levels of Nrf2 itself, but rather showed a significant ( $P < 0.01$ ) negative relationship with the regulators Kelch-like ECH-Associated Protein 1 (Keap1) and  $\beta$ -transducin repeat-containing protein ( $\beta$ TrCP), which target Nrf2 for degradation. These findings highlight the use of a comparative biology approach for the identification of evolved mechanisms that contribute to health span, aging, and longevity.

# Reduced fitness in progeny from old parents in a natural population

## Abstract

A nongenetic, transgenerational effect of parental age on offspring fitness has been described in many taxa in the laboratory. Such a transgenerational fitness effect will have important influences on population dynamics, population age structure, and the evolution of aging and lifespan. However, effects of parental age on offspring lifetime fitness have never been demonstrated in a natural population. We show that parental age has sex-specific negative effects on lifetime fitness, using data from a pedigreed insular population of wild house sparrows. Birds whose parents were older produced fewer recruits annually than birds with younger parents, and the reduced number of recruits translated into a lifetime fitness difference. Using a long-term cross-fostering experiment, we demonstrate that this parental age effect is unlikely to be the result of changes in the environment but that it potentially is epigenetically inherited. Our study reveals the hidden consequences of late-life reproduction that persist into the next generation.

## Macronutrient balance, reproductive function, and lifespan in aging mice

In invertebrates, reproductive output and lifespan are profoundly impacted by dietary macronutrient balance, with these traits achieving their maxima on different diet compositions, giving the appearance of a resource-based tradeoff between reproduction and longevity. For the first time in a mammal, to our knowledge, we evaluate the effects of dietary protein (P), carbohydrate (C), fat (F), and energy (E) on lifespan and reproductive function in aging male and female mice. We show that, as in invertebrates, the balance of macronutrients has marked and largely opposing effects on reproductive and longevity outcomes. Mice were provided ad libitum access to one of 25 diets differing in P, C, F, and E content, with reproductive outcomes assessed at 15 months. An optimal balance of macronutrients exists for reproductive function, which, for most measures, differs from the diets that optimize lifespan, and this response differs with sex. Maximal longevity was achieved on diets containing a P:C ratio of 1:13 in males and 1:11 for females. Diets that optimized testes mass and epididymal sperm counts (indicators of gamete production) contained a higher P:C ratio (1:1) than those that maximized lifespan. In females, uterine mass (an indicator of estrogenic activity) was also greatest on high P:C diets (1:1) whereas ovarian follicle number was greatest on P:C 3:1 associated with high-F intakes. By contrast, estrous cycling was more likely in mice on lower P:C (1:8), and the number of corpora lutea, indicative of recent ovulations, was greatest on P:C similar to those supporting greatest longevity (1:11).

# Sugar-based amphiphilic nanoparticles arrest atherosclerosis in vivo

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Atherosclerosis, the build-up of occlusive, lipid-rich plaques in arterial walls, is a focal trigger of chronic coronary, intracranial, and peripheral arterial diseases, which together account for the leading causes of death worldwide. Although the directed treatment of atherosclerotic plaques remains elusive, macrophages are a natural target for new interventions because they are recruited to lipid-rich lesions, actively internalize modified lipids, and convert to foam cells with diseased phenotypes. In this work, we present a nanomedicine platform to counteract plaque development based on two building blocks: first, at the single macrophage level, sugar-based amphiphilic macromolecules (AMs) were designed to competitively block oxidized lipid uptake via scavenger receptors on macrophages; second, for sustained lesion-level intervention, AMs were fabricated into serum-stable core/shell nanoparticles (NPs) to rapidly associate with plaques and inhibit disease progression in vivo. An AM library was designed and fabricated into NP compositions that showed high binding and down-regulation of both MSR1 and CD36 scavenger receptors, yielding minimal accumulation of oxidized lipids. When intravenously administered to a mouse model of cardiovascular disease, these AM NPs showed a pronounced increase in lesion association compared with the control nanoparticles, causing a significant reduction in neointimal hyperplasia, lipid burden, cholesterol clefts, and overall plaque occlusion. Thus, synthetic macromolecules configured as NPs are not only effectively mobilized to lipid-rich lesions but can also be deployed to counteract atheroinflammatory vascular diseases, highlighting the promise of nanomedicines for hyperlipidemic and metabolic syndromes.

# Integrity of the yeast mitochondrial genome, but not its distribution and inheritance, relies on mitochondrial fission and fusion

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Mitochondrial DNA (mtDNA) is essential for mitochondrial and cellular function. In *Saccharomyces cerevisiae*, mtDNA is organized in nucleoprotein structures termed nucleoids, which are distributed throughout the mitochondrial network and are faithfully inherited during the cell cycle. How the cell distributes and inherits mtDNA is incompletely understood although an involvement of mitochondrial fission and fusion has been suggested. We developed a LacO-LacI system to noninvasively image mtDNA dynamics in living cells. Using this system, we found that nucleoids are nonrandomly spaced within the mitochondrial network and observed the spatiotemporal events involved in mtDNA inheritance. Surprisingly, cells deficient in mitochondrial fusion and fission distributed and inherited mtDNA normally, pointing to alternative pathways involved in these processes. We identified such a mechanism, where we observed fission-independent, but F-actin-dependent, tip generation that was linked to the positioning of mtDNA to the newly generated tip. Although mitochondrial fusion and fission were dispensable for mtDNA distribution and inheritance, we show through a combination of genetics and next-generation sequencing that their absence leads to an accumulation of mitochondrial genomes harboring deleterious structural variations that cluster at the origins of mtDNA replication, thus revealing crucial roles for mitochondrial fusion and fission in maintaining the integrity of the mitochondrial genome.

# In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences

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NAD is an essential metabolite that exists in  $\text{NAD}^+$  or NADH form in all living cells. Despite its critical roles in regulating mitochondrial energy production through the  $\text{NAD}^+$ /NADH redox state and modulating cellular signaling processes through the activity of the  $\text{NAD}^+$ -dependent enzymes, the method for quantifying intracellular NAD contents and redox state is limited to a few in vitro or ex vivo assays, which are not suitable for studying a living brain or organ. Here, we present a magnetic resonance (MR)-based in vivo NAD assay that uses the high-field MR scanner and is capable of noninvasively assessing  $\text{NAD}^+$  and NADH contents and the  $\text{NAD}^+$ /NADH redox state in intact human brain. The results of this study provide the first insight, to our knowledge, into the cellular NAD concentrations and redox state in the brains of healthy volunteers. Furthermore, an age-dependent increase of intracellular NADH and age-dependent reductions in  $\text{NAD}^+$ , total NAD contents, and  $\text{NAD}^+$ /NADH redox potential of the healthy human brain were revealed in this study. The overall findings not only provide direct evidence of declined mitochondrial functions and altered NAD homeostasis that accompany the normal aging process but also, elucidate the merits and potentials of this new NAD assay for noninvasively studying the intracellular NAD metabolism and redox state in normal and diseased human brain or other organs in situ.





REPORT

## Time-restricted feeding attenuates age-related cardiac decline in *Drosophila*

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ABSTRACT

EDITOR'S SUMMARY

Circadian clocks orchestrate periods of rest or activity and feeding or fasting over the course of a 24-hour day and maintain homeostasis. To assess whether a consolidated 24-hour cycle of feeding and fasting can sustain health, we explored the effect of time-restricted feeding (TRF; food access limited to daytime 12 hours every day) on neural, peripheral, and cardiovascular physiology in *Drosophila melanogaster*. We detected improved sleep, prevention of body weight gain, and deceleration of cardiac aging under TRF, even when caloric intake and activity were unchanged. We used temporal gene expression profiling and validation through classical genetics to identify the TCP-1 ring complex (TRiC) chaperonin, the mitochondrial electron transport chain complexes, and the circadian clock as pathways mediating the benefits of TRF.

## RESEARCH ARTICLE

### ALZHEIMER'S DISEASE

## Scanning ultrasound removes amyloid- $\beta$ and restores memory in an Alzheimer's disease mouse model

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### Abstract

Amyloid- $\beta$  (A $\beta$ ) peptide has been implicated in the pathogenesis of Alzheimer's disease (AD). We present a nonpharmacological approach for removing A $\beta$  and restoring memory function in a mouse model of AD in which A $\beta$  is deposited in the brain. We used repeated scanning ultrasound (SUS) treatments of the mouse brain to remove A $\beta$ , without the need for any additional therapeutic agent such as anti-A $\beta$  antibody. Spinning disk confocal microscopy and high-resolution three-dimensional reconstruction revealed extensive internalization of A $\beta$  into the lysosomes of activated microglia in mouse brains subjected to SUS, with no concomitant increase observed in the number of microglia. Plaque burden was reduced in SUS-treated AD mice compared to sham-treated animals, and cleared plaques were observed in 75% of SUS-treated mice. Treated AD mice also displayed improved performance on three memory tasks: the Y-maze, the novel object recognition test, and the active place avoidance task. Our findings suggest that repeated SUS is useful for removing A $\beta$  in the mouse brain without causing overt damage, and should be explored further as a noninvasive method with therapeutic potential in AD.

REPORT

## A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging

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 <sup>\*</sup> These authors contributed equally to this work.

ABSTRACT

EDITOR'S SUMMARY

Deterioration of adult stem cells accounts for much of aging-associated compromised tissue maintenance. How stem cells maintain metabolic homeostasis remains elusive. Here, we identified a regulatory branch of the mitochondrial unfolded protein response (UPR<sup>mt</sup>), which is mediated by the interplay of SIRT7 and NRF1 and is coupled to cellular energy metabolism and proliferation. SIRT7 inactivation caused reduced quiescence, increased mitochondrial protein folding stress (PFS<sup>mt</sup>), and compromised regenerative capacity of hematopoietic stem cells (HSCs). SIRT7 expression was reduced in aged HSCs, and SIRT7 up-regulation improved the regenerative capacity of aged HSCs. These findings define the deregulation of a UPR<sup>mt</sup>-mediated metabolic checkpoint as a reversible contributing factor for HSC aging.

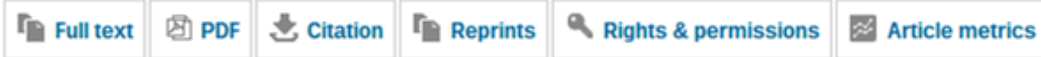
# A human tRNA synthetase is a potent PARP1-activating effector target for resveratrol

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Resveratrol is reported to extend lifespan<sup>1, 2</sup> and provide cardio-neuro-protective<sup>3</sup>, anti-diabetic<sup>4</sup>, and anti-cancer effects<sup>3, 5</sup> by initiating a stress response<sup>2</sup> that induces survival genes. Because human tyrosyl transfer-RNA (tRNA) synthetase (TyrRS) translocates to the nucleus under stress conditions<sup>6</sup>, we considered the possibility that the tyrosine-like phenolic ring of resveratrol might fit into the active site pocket to effect a nuclear role. Here we present a 2.1 Å co-crystal structure of resveratrol bound to the active site of TyrRS. Resveratrol nullifies the catalytic activity and redirects TyrRS to a nuclear function, stimulating NAD<sup>+</sup>-dependent auto-poly-ADP-ribosylation of poly(ADP-ribose) polymerase 1 (PARP1). Downstream activation of key stress signalling pathways are causally connected to TyrRS–PARP1–NAD<sup>+</sup> collaboration. This collaboration is also demonstrated in the mouse, and is specifically blocked *in vivo* by a resveratrol-displacing tyrosyl adenylate analogue. In contrast to functionally diverse tRNA synthetase catalytic nulls created by alternative splicing events that ablate active sites<sup>7</sup>, here a non-spliced TyrRS catalytic null reveals a new PARP1- and NAD<sup>+</sup>-dependent dimension to the physiological mechanism of resveratrol.

## Age, Sex, and APOE $\epsilon$ 4 Effects on Memory, Brain Structure, and $\beta$ -Amyloid Across the Adult Life Span.

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### ⊕ Author information

#### Abstract

**IMPORTANCE:** Typical cognitive aging may be defined as age-associated changes in cognitive performance in individuals who remain free of dementia. Ideally, the full adult age spectrum should be included to assess brain imaging findings associated with typical aging.

**OBJECTIVE:** To compare age, sex, and APOE  $\epsilon$ 4 effects on memory, brain structure (adjusted hippocampal volume [HVa]), and amyloid positron emission tomography (PET) in cognitively normal individuals aged 30 to 95 years old.

**DESIGN, SETTING, AND PARTICIPANTS:** Cross-sectional observational study (March 2006 to October 2014) at an academic medical center. We studied 1246 cognitively normal individuals, including 1209 participants aged 50 to 95 years old enrolled in a population-based study of cognitive aging and 37 self-selected volunteers aged 30 to 49 years old.

**MAIN OUTCOMES AND MEASURES:** Memory, HVa, and amyloid PET.

**RESULTS:** Overall, memory worsened from age 30 years through the 90s. The HVa worsened gradually from age 30 years to the mid-60s and more steeply beyond that age. The median amyloid PET was low until age 70 years and increased thereafter. Memory was worse in men than in women overall ( $P < .001$ ) and more specifically beyond age 40 years. The HVa was lower in men than in women overall ( $P < .001$ ) and more specifically beyond age 60 years. There was no sex difference in amyloid PET at any age. Within each sex, memory performance and HVa were not different by APOE  $\epsilon$ 4 status at any age. From age 70 years onward, APOE  $\epsilon$ 4 carriers had significantly greater median amyloid PET than noncarriers. However, the ages at which 10% of the population were amyloid PET positive were 57 years for APOE  $\epsilon$ 4 carriers and 64 years for noncarriers.

**CONCLUSIONS AND RELEVANCE:** Male sex is associated with worse memory and HVa among cognitively normal individuals, while APOE  $\epsilon$ 4 is not. In contrast, APOE  $\epsilon$ 4 is associated with greater amyloid PET (from age 70 years onward), while sex is not. Worsening memory and HVa occur at earlier ages than abnormal amyloid PET. Therefore, neuropathological processes other than  $\beta$ -amyloidosis must underlie declines in brain structure and memory function in middle age. Our findings are consistent with a model of late-onset Alzheimer disease in which  $\beta$ -amyloidosis arises in later life on a background of preexisting structural and cognitive decline that is associated with aging and not with  $\beta$ -amyloid deposits.

[Aging Cell](#). 2014 Jun;13(3):391-400. doi: 10.1111/acer.12207. Epub 2014 Mar 14.

## **Optimal body weight for health and longevity: bridging basic, clinical, and population research.**

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### **⊕ Author information**

#### **Abstract**

Excess body weight and adiposity cause insulin resistance, inflammation, and numerous other alterations in metabolic and hormonal factors that promote atherosclerosis, tumorigenesis, neurodegeneration, and aging. Studies in both animals and humans have demonstrated a beneficial role of dietary restriction and leanness in promoting health and longevity. Epidemiological studies have found strong direct associations between increasing body mass index (BMI) and risks of developing type 2 diabetes, cardiovascular disease, and several types of cancer, beginning from BMI of 20-21 kg m(-2). Although a recent meta-analysis suggests that overweight individuals have significantly lower overall mortality than normal-weight individuals, these data are likely to be an artifact produced by serious methodological problems, especially confounding by smoking, reverse causation due to existing chronic disease, and nonspecific loss of lean mass and function in the frail elderly. From a clinical and public health point of view, maintaining a healthy weight through diet and physical activity should remain the cornerstone in the prevention of chronic diseases and the promotion of healthy aging.

## Employing in vitro analysis to test the potency of methylglyoxal in inducing the formation of amyloid-like aggregates of caprine brain cystatin

Waseem Feroze Bhat, Sheraz Ahmad Bhat, Peerzada Shariq Shaheen Khaki, Bilqees Bano

Thiol protease inhibitors (cystatins) are implicated in various disease states from cancer to neurodegenerative conditions and immune responses. Cystatins have high amyloidogenic propensity and they are prone to form fibrillar aggregates leading to amyloidosis. Particularly challenging examples of such disorders occur in type 2 diabetes, Alzheimer's and Parkinson's diseases. The aim of the present study is to find an interaction between the compound methylglyoxal (MG) which is particularly elevated in type 2 diabetes with caprine brain cystatin (CBC). Results have shown that elevated concentration of MG forms amyloid aggregates of CBC. This was achieved by allowing slow growth in a solution containing moderate to high concentrations of MG. When analysed with microscopy, the protein aggregate present in the sample after incubation consisted of extended filaments with ordered structures. This fibrillar material possesses extensive  $\beta$ -sheet structure as revealed by far-UV CD and IR spectroscopy. Furthermore, the fibrils exhibit increased Thioflavin T fluorescence.

## Are Members of Long-Lived Families Healthier Than Their Equally Long-Lived Peers? Evidence From the Long Life Family Study.

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### ⊕ Author information

#### Abstract

**BACKGROUND:** The Long Life Family Study (LLFS) is a multicenter longitudinal study of exceptional survival among members of long-lived sibships (probands), their offspring, and spouses of either group. For these four "roles", we asked: Does membership in a long-lived family protect against disease?

**METHODS:** We used 2008-2010 Beneficiary Annual Summary Files from the Centers for Medicare & Medicaid Services (CMS) to compare prevalences of 17 conditions among 781 LLFS participants in Medicare with those of 3,227 non-LLFS matches from the general Medicare population. Analyses accounted for nesting within LLFS families.

**RESULTS:** Seven conditions were significantly less common among LLFS probands than their matches: Alzheimer's, hip fracture, diabetes, depression, prostate cancer, heart failure, and chronic kidney disease. Four diseases not strongly linked to mortality (arthritis, cataract, osteoporosis, glaucoma) were significantly more common for LLFS probands. Despite fewer people and less disease in those roles, LLFS offspring and LLFS spouses of either generation also had significantly lower risk for Alzheimer's, diabetes, and heart failure.

**CONCLUSIONS:** Common, severe mortality-associated diseases are less prevalent among LLFS probands and their offspring than in the general population of aging Americans. Quality-of-life-limiting diseases such as arthritis and cataract are more prevalent, potentially through more diagnosing of milder forms in otherwise healthy and active individuals. LLFS spouses are also relatively healthy. As the younger cohorts age into Medicare and develop more conditions, it will be important to see whether these tentative findings strengthen.



## Identification of age- and disease-related alterations in circulating miRNAs in a mouse model of Alzheimer's disease.

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#### Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized clinically by the progressive decline of memory and cognition. Histopathologically, two main hallmarks have been identified in AD: amyloid- $\beta$  peptide extracellular neuritic plaques and neurofibrillary tangles formed by posttranslational modified tau protein. A definitive diagnosis can only be achieved after the post mortem verification of the histological mentioned alterations. Therefore, the development of biomarkers that allow an early diagnosis and/or predict disease progression is imperative. The prospect of a blood-based biomarker is possible with the finding of circulating microRNAs (miRNAs), a class of small non-coding RNAs of 22-25 nucleotides length that regulate mRNA translation rate. miRNAs travel through blood and recent studies performed in potential AD cases suggest the possibility of finding pathology-associated differences in circulating miRNA levels that may serve to assist in early diagnosis of the disease. However, these studies analyzed samples at a single time-point, limiting the use of miRNAs as biomarkers in AD progression. In this study we evaluated miRNA levels in plasma samples at different time-points of the evolution of an AD-like pathology in a transgenic mouse model of the disease (3xTg-AD). We performed multiplex qRT-PCR and compared the plasmatic levels of 84 miRNAs previously associated to central nervous system development and disease. No significant differences were detected between WT and transgenic young mice. However, age-related significant changes in miRNA abundance were observed for both WT and transgenic mice, and some of these were specific for the 3xTg-AD. In agreement, variations in the levels of particular miRNAs were identified between WT and transgenic old mice thus suggesting that the age-dependent evolution of the AD-like pathology, rather than the presence and expression of the transgenes, modifies the circulating miRNA levels in the 3xTg-AD mice.

[Cell Cycle](#), 2015 Apr 3:0. [Epub ahead of print]

## **Inhibition of peroxisome fission, but not mitochondrial fission, increases yeast chronological lifespan.**

[Lefevre SD<sup>1</sup>](#), [Kumar S](#), [van der Kleij IJ](#).

### **⊕ Author information**

#### **Abstract**

Mitochondria are key players in ageing and cell death. It has been suggested that mitochondrial fragmentation, mediated by the Dnm1/Fis1 organelle fission machinery, stimulates ageing and cell death. This was based on the observation that *Saccharomyces cerevisiae*  $\Delta$ dnm1 and  $\Delta$ fis1 mutants show an enhanced lifespan and increased resistance to cell death inducers. However, the Dnm1/Fis1 fission machinery is also required for peroxisome division. Here we analyzed the significance of peroxisome fission in yeast chronological lifespan, using yeast strains in which fission of mitochondria was selectively blocked. Our data indicate that the lifespan extension caused by deletion of FIS1 is mainly due to a defect in peroxisome fission and not caused by a block in mitochondrial fragmentation. These observations are underlined by our observation that deletion of FIS1 does not lead to lifespan extension in yeast peroxisome deficient mutant cells.

[Protist](#). 2015 Mar 12;166(2):224-233. doi: 10.1016/j.protis.2015.03.002. [Epub ahead of print]

## **Amitotic Chromosome Loss Predicts Distinct Patterns of Senescence and Non-Senescence in Ciliates.**

[Morgens DW](#)<sup>1</sup>, [Cavalcanti AR](#)<sup>2</sup>.

### **⊕ Author information**

### **Abstract**

Over time and repeated asexual divisions, many ciliate species display the characteristics of senescence, reduced fecundity and increased mortality. Their only path to recovery is sexual conjugation or autogamy. While more traditional models of cellular aging have been proposed, one of the most accepted explanations relies on the faulty mechanism by which ciliates duplicate their somatic nucleus, a process referred to as amitosis. Amitosis involves the random segregation of chromosomes with no consideration for homology. Over subsequent divisions, chromosome copy numbers will fluctuate until an entire chromosome is lost, resulting in death. Via simulations of this process, we find that senescence and death via chromosome loss is not the only possible result of amitosis. Random chromosome loss is less damaging to populations than previously thought, and strict adherence to the model predicts that *Paramecium tetraurelia* would not senesce. A combination of the reciprocal nature of amitosis and lethal selection against low-copy number chromosomes is responsible for this startling prediction. Additionally, our results provide an alternate explanation to recent evidence for selection on chromosome copy number in *Tetrahymena thermophila* and peculiar patterns of senescence in *Tetrahymena pyriformis*.

## Subacute calorie restriction and rapamycin discordantly alter mouse liver proteome homeostasis and reverse aging effects.

Karunadharm PP<sup>1</sup>, Basisty N, Dai DF, Chiao YA, Quarles EK, Hsieh EJ, Crispin D, Bielas JH, Ericson NG, Beyer RP, MacKay VL, MacCoss MJ, Rabinovitch PS.

### ⊕ Author information

#### Abstract

Calorie restriction (CR) and rapamycin (RP) extend lifespan and improve health across model organisms. Both treatments inhibit mammalian target of rapamycin (mTOR) signaling, a conserved longevity pathway and a key regulator of protein homeostasis, yet their effects on proteome homeostasis are relatively unknown. To comprehensively study the effects of aging, CR, and RP on protein homeostasis, we performed the first simultaneous measurement of mRNA translation, protein turnover, and abundance in livers of young (3 month) and old (25 month) mice subjected to 10-week RP or 40% CR. Protein abundance and turnover were measured *in vivo* using <sup>2</sup>H<sub>3</sub>-leucine heavy isotope labeling followed by LC-MS/MS, and translation was assessed by polysome profiling. We observed 35-60% increased protein half-lives after CR and 15% increased half-lives after RP compared to age-matched controls. Surprisingly, the effects of RP and CR on protein turnover and abundance differed greatly between canonical pathways, with opposite effects in mitochondrial (mt) dysfunction and eIF2 signaling pathways. CR most closely recapitulated the young phenotype in the top pathways. Polysome profiles indicated that CR reduced polysome loading while RP increased polysome loading in young and old mice, suggesting distinct mechanisms of reduced protein synthesis. CR and RP both attenuated protein oxidative damage. Our findings collectively suggest that CR and RP extend lifespan in part through the reduction of protein synthetic burden and damage and a concomitant increase in protein quality. However, these results challenge the notion that RP is a faithful CR mimetic and highlight mechanistic differences between the two interventions.

## Assembly and interrogation of Alzheimer's disease genetic networks reveal novel regulators of progression.

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### ⊕ Author information

#### Abstract

Alzheimer's disease (AD) is a complex multifactorial disorder with poorly characterized pathogenesis. Our understanding of this disease would thus benefit from an approach that addresses this complexity by elucidating the regulatory networks that are dysregulated in the neural compartment of AD patients, across distinct brain regions. Here, we use a Systems Biology (SB) approach, which has been highly successful in the dissection of cancer related phenotypes, to reverse engineer the transcriptional regulation layer of human neuronal cells and interrogate it to infer candidate Master Regulators (MRs) responsible for disease progression. Analysis of gene expression profiles from laser-captured neurons from AD and controls subjects, using the Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe), yielded an interactome consisting of 488,353 transcription-factor/target interactions. Interrogation of this interactome, using the Master Regulator Inference algorithm (MARINa), identified an unbiased set of candidate MRs causally responsible for regulating the transcriptional signature of AD progression. Experimental assays in autopsy-derived human brain tissue showed that three of the top candidate MRs (YY1, p300 and ZMYM3) are indeed biochemically and histopathologically dysregulated in AD brains compared to controls. Our results additionally implicate p53 and loss of acetylation homeostasis in the neurodegenerative process. This study suggests that an integrative, SB approach can be applied to AD and other neurodegenerative diseases, and provide significant novel insight on the disease progression.

## A Remarkable Age-Related Increase in SIRT1 Protein Expression against Oxidative Stress in Elderly: SIRT1 Gene Variants and Longevity in Human.

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### ⊕ Author information

#### Abstract

Aging is defined as the accumulation of progressive organ dysfunction. Controlling the rate of aging by clarifying the complex pathways has a significant clinical importance. Nowadays, sirtuins have become famous molecules for slowing aging and decreasing age-related disorders. In the present study, we analyzed the SIRT1 gene polymorphisms (rs7895833 A>G, rs7069102 C>G and rs2273773 C>T) and its relation with levels of SIRT1, eNOS, PON-1, cholesterol, TAS, TOS, and OSI to demonstrate the association between genetic variation in SIRT1 and phenotype at different ages in humans. We observed a significant increase in the SIRT1 level in older people and found a significant positive correlation between SIRT1 level and age in the overall studied population. The oldest people carrying AG genotypes for rs7895833 have the highest SIRT1 level suggesting an association between rs7895833 SNP and lifespan longevity. Older people have lower PON-1 levels than those of adults and children which may explain the high levels of SIRT1 protein as a compensatory mechanism for oxidative stress in the elderly. The eNOS protein level was significantly decreased in older people as compared to adults. There was no significant difference in the eNOS level between older people and children. The current study is the first to demonstrate age-related changes in SIRT1 levels in humans and it is important for a much better molecular understanding of the role of the longevity gene SIRT1 and its protein product in aging. It is also the first study presenting the association between SIRT1 expression in older people and rs7895833 in SIRT1 gene.

## Drug synergy drives conserved pathways to increase fission yeast lifespan.

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### ⊕ Author information

#### Abstract

Aging occurs over time with gradual and progressive loss of physiological function. Strategies to reduce the rate of functional loss and mitigate the subsequent onset of deadly age-related diseases are being sought. We demonstrated previously that a combination of rapamycin and myriocin reduces age-related functional loss in the Baker's yeast *Saccharomyces cerevisiae* and produces a synergistic increase in lifespan. Here we show that the same drug combination also produces a synergistic increase in the lifespan of the fission yeast *Schizosaccharomyces pombe* and does so by controlling signal transduction pathways conserved across a wide evolutionary time span ranging from yeasts to mammals. Pathways include the target of rapamycin complex 1 (TORC1) protein kinase, the protein kinase A (PKA) and a stress response pathway, which in fission yeasts contains the Sty1 protein kinase, an ortholog of the mammalian p38 MAP kinase, a type of Stress Activated Protein Kinase (SAPK). These results along with previous studies in *S. cerevisiae* support the premise that the combination of rapamycin and myriocin enhances lifespan by regulating signaling pathways that couple nutrient and environmental conditions to cellular processes that fine-tune growth and stress protection in ways that foster long term survival. The molecular mechanisms for fine-tuning are probably species-specific, but since they are driven by conserved nutrient and stress sensing pathways, the drug combination may enhance survival in other organisms.

## Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials.

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### ⊕ Author information

#### Abstract

**BACKGROUND:** Obesity is associated with increased mortality, and weight loss trials show rapid improvement in many mortality risk factors. Yet, observational studies typically associate weight loss with higher mortality risk. The purpose of this meta-analysis of randomized controlled trials (RCTs) of weight loss was to clarify the effects of intentional weight loss on mortality.

**METHODS:** 2,484 abstracts were identified and reviewed in PUBMED, yielding 15 RCTs reporting (1) randomization to weight loss or non-weight loss arms, (2) duration of  $\geq 18$  months, and (3) deaths by intervention arm. Weight loss interventions were all lifestyle-based. Relative risks (RR) and 95% confidence intervals (95% CI) were estimated for each trial. For trials reporting at least one death ( $n = 12$ ), a summary estimate was calculated using the Mantel-Haenszel method. Sensitivity analysis using sparse data methods included remaining trials.

**RESULTS:** Trials enrolled 17,186 participants (53% female, mean age at randomization = 52 years). Mean body mass indices ranged from 30-46 kg/m<sup>2</sup>, follow-up times ranged from 18 months to 12.6 years (mean: 27 months), and average weight loss in reported trials was 5.5 $\pm$ 4.0 kg. A total of 264 deaths were reported in weight loss groups and 310 in non-weight loss groups. The weight loss groups experienced a 15% lower all-cause mortality risk (RR = 0.85; 95% CI: 0.73-1.00). There was no evidence for heterogeneity of effect (Cochran's Q = 5.59 (11 d.f.;  $p = 0.90$ );  $I^2 = 0$ ). Results were similar in trials with a mean age at randomization  $\geq 55$  years (RR = 0.84; 95% CI 0.71-0.99) and a follow-up time of  $\geq 4$  years (RR = 0.85; 95% CI 0.72-1.00).

**CONCLUSIONS:** In obese adults, intentional weight loss may be associated with approximately a 15% reduction in all-cause mortality.



## Clinicopathologic and $^{11}\text{C}$ -Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum

Thal amyloid phase, which describes the pattern of progressive amyloid- $\beta$  plaque deposition in Alzheimer's disease, was incorporated into the latest National Institute of Ageing – Alzheimer's Association neuropathologic assessment guidelines. Amyloid biomarkers (positron emission tomography and cerebrospinal fluid) were included in clinical diagnostic guidelines for Alzheimer's disease dementia published by the National Institute of Ageing – Alzheimer's Association and the International Work group. Our first goal was to evaluate the correspondence of Thal amyloid phase to Braak tangle stage and ante-mortem clinical characteristics in a large autopsy cohort. Second, we examined the relevance of Thal amyloid phase in a prospectively-followed autopsied cohort who underwent ante-mortem  $^{11}\text{C}$ -Pittsburgh compound B imaging; using the large autopsy cohort to broaden our perspective of  $^{11}\text{C}$ -Pittsburgh compound B results. The Mayo Clinic Jacksonville Brain Bank case series ( $n = 3618$ ) was selected regardless of ante-mortem clinical diagnosis and neuropathologic co-morbidities, and all assigned Thal amyloid phase and Braak tangle stage using thioflavin-S fluorescent microscopy.  $^{11}\text{C}$ -Pittsburgh compound B studies from Mayo Clinic Rochester were available for 35 participants scanned within 2 years of death. Cortical  $^{11}\text{C}$ -Pittsburgh compound B values were calculated as a standard uptake value ratio normalized to cerebellum grey/white matter. In the high likelihood Alzheimer's disease brain bank cohort ( $n = 1375$ ), cases with lower Thal amyloid phases were older at death, had a lower Braak tangle stage, and were less frequently *APOE- $\epsilon$ 4* positive. Regression modelling in these Alzheimer's disease cases, showed that Braak tangle stage, but not Thal amyloid phase predicted age at onset, disease duration, and final Mini-Mental State Examination score. In contrast, Thal amyloid phase, but not Braak tangle stage or cerebral amyloid angiopathy predicted  $^{11}\text{C}$ -Pittsburgh compound B standard uptake value ratio. In the 35 cases with ante-mortem amyloid imaging, a transition between Thal amyloid phases 1 to 2 seemed to correspond to  $^{11}\text{C}$ -Pittsburgh compound B standard uptake value ratio of 1.4, which when using our pipeline is the cut-off point for detection of clear amyloid-positivity regardless of clinical diagnosis. Alzheimer's disease cases who were older and were *APOE- $\epsilon$ 4* negative tended to have lower amyloid phases. Although Thal amyloid phase predicted clinical characteristics of Alzheimer's disease patients, the pre-mortem clinical status was driven by Braak tangle stage. Thal amyloid phase correlated best with  $^{11}\text{C}$ -Pittsburgh compound B values, but not Braak tangle stage or cerebral amyloid angiopathy. The  $^{11}\text{C}$ -Pittsburgh compound B cut-off point value of 1.4 was approximately equivalent to a Thal amyloid phase of 1–2.

# Direct visualization of alpha-synuclein oligomers reveals previously undetected pathology in Parkinson's disease brain

Oligomeric forms of alpha-synuclein are emerging as key mediators of pathogenesis in Parkinson's disease. Our understanding of the exact contribution of alpha-synuclein oligomers to disease is limited by the lack of a technique for their specific detection. We describe a novel method, the alpha-synuclein proximity ligation assay, which specifically recognizes alpha-synuclein oligomers. In a blinded study with post-mortem brain tissue from patients with Parkinson's disease ( $n = 8$ , age range 73–92 years, four males and four females) and age- and sex-matched controls ( $n = 8$ ), we show that the alpha-synuclein proximity ligation assay reveals previously unrecognized pathology in the form of extensive diffuse deposition of alpha-synuclein oligomers. These oligomers are often localized, in the absence of Lewy bodies, to neuroanatomical regions mildly affected in Parkinson's disease. Diffuse alpha-synuclein proximity ligation assay signal is significantly more abundant in patients compared to controls in regions including the cingulate cortex (1.6-fold increase) and the reticular formation of the medulla (6.5-fold increase). In addition, the alpha-synuclein proximity ligation assay labels very early perikaryal aggregates in morphologically intact neurons that may precede the development of classical Parkinson's disease lesions, such as pale bodies or Lewy bodies. Furthermore, the alpha-synuclein proximity ligation assay preferentially detects early-stage, loosely compacted lesions such as pale bodies in patient tissue, whereas Lewy bodies, considered heavily compacted late lesions are only very exceptionally stained. The alpha-synuclein proximity ligation assay preferentially labels alpha-synuclein oligomers produced *in vitro* compared to monomers and fibrils, while stained oligomers in human brain display a distinct intermediate proteinase K resistance, suggesting the detection of a conformer that is different from both physiological, presynaptic alpha-synuclein (proteinase K-sensitive) and highly aggregated alpha-synuclein within Lewy bodies (proteinase K-resistant). These disease-associated conformers represent previously undetected Parkinson's disease pathology uncovered by the alpha-synuclein proximity ligation assay.

# Reviews/Opinions/Editorials

Curr Opin Cardiol. 2015 May;30(3):235-239.

## Rejuvenating the senescent heart.

Nguyen N<sup>1</sup>, Sussman MA.

### ⊕ Author information

#### Abstract

**PURPOSE OF REVIEW:** The purpose of this review is to provide an update on the cardiac stem cell field with an emphasis on aging and to suggest some relevant strategies directed toward rejuvenation of the senescent heart.

**RECENT FINDINGS:** Stem cells were long considered as a fountain of youth and were assumed to be equipped against any form of aging effect. However, it is now clear that stem cells suffer the consequences of aging as well. With the discovery that cardiac stem cells reside in the heart comes the question whether these cells are also impaired upon aging. As cardiac stem cell properties are also altered with age, autologous stem cell-based therapy to treat heart failure will benefit from new improved strategies.

**SUMMARY:** With the goal to improve stem cell properties that are impaired upon aging, some strategies are highlighted. Genetic modification of adult human cardiac progenitor cells prior to autologous stem cell-based therapy, delivery of the next generation of stem cells such as CardioChimeras and CardioClusters, and improvement of the myocardial environment with rejuvenating factors constitute some of the possibilities and are discussed in more detail in this review.

[Metabolism](#). 2015 Mar 19. pii: S0026-0495(15)00086-4. doi: 10.1016/j.metabol.2015.03.008. [Epub ahead of print]

## **A review of potential metabolic etiologies of the observed association between red meat consumption and development of type 2 diabetes mellitus.**

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### **⊕ Author information**

#### **Abstract**

Epidemiological studies suggest that red and processed meat consumption is related to an increased risk of type 2 diabetes. However, it is not clearly understood which components of red and processed meat contribute to this increased risk. This review examines potential mechanisms addressing the role of saturated fatty acid, sodium, advanced glycation end products (AGEs), nitrates/nitrites, heme iron, trimethylamine N-oxide (TMAO), branched amino acids (BCAAs) and endocrine disruptor chemicals (EDCs) in the development of type 2 diabetes based on data from published clinical trials and animal models. TMAO which is derived from dietary carnitine and choline by the action of bacterial enzymes followed by oxidation in the liver may be a strong candidate molecule mediating the risk of type 2 diabetes. BCAAs may induce insulin resistance via the mammalian target of rapamycin complex 1 (mTORC1) and ribosomal protein S6 kinase  $\beta$  1 (S6k1)-associated pathways. The increased risk associated with processed meat compared with red meat suggests that there are interactions between the saturated fat, salt, and nitrates in processed meat and iron, AGEs and TMAO. Intervention studies are required to clarify potential mechanisms and explore interactions among components, in order to make firm recommendations on red and processed meat consumption.

## **Aberrant protein S-nitrosylation contributes to the pathophysiology of neurodegenerative diseases.**

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### **⊕ Author information**

#### **Abstract**

Nitric oxide (NO) is a gasotransmitter that impacts fundamental aspects of neuronal function in large measure through S-nitrosylation, a redox reaction that occurs on regulatory cysteine thiol groups. For instance, S-nitrosylation regulates enzymatic activity of target proteins via inhibition of active site cysteine residues or via allosteric regulation of protein structure. During normal brain function, protein S-nitrosylation serves as an important cellular mechanism that modulates a diverse array of physiological processes, including transcriptional activity, synaptic plasticity, and neuronal survival. In contrast, emerging evidence suggests that aging and disease-linked environmental risk factors exacerbate nitrosative stress via excessive production of NO. Consequently, aberrant S-nitrosylation occurs and represents a common pathological feature that contributes to the onset and progression of multiple neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. In the current review, we highlight recent key findings on aberrant protein S-nitrosylation showing that this reaction triggers protein misfolding, mitochondrial dysfunction, transcriptional dysregulation, synaptic damage, and neuronal injury. Specifically, we discuss the pathological consequences of S-nitrosylated parkin, myocyte enhancer factor 2 (MEF2), dynamin-related protein 1 (Drp1), protein disulfide isomerase (PDI), X-linked inhibitor of apoptosis protein (XIAP), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) under neurodegenerative conditions. We also speculate that intervention to prevent these aberrant S-nitrosylation events may produce novel therapeutic agents to combat neurodegenerative diseases.

## **mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy.**

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### **⊕ Author information**

#### **Abstract**

Compelling evidence indicates that the mammalian target of rapamycin (mTOR) signaling pathway is involved in cellular senescence, organismal aging and age-dependent diseases. mTOR is a conserved serine/threonine kinase that is known to be part of two different protein complexes: mTORC1 and mTORC2, which differ in some components and in upstream and downstream signalling. In multicellular organisms, mTOR regulates cell growth and metabolism in response to nutrients, growth factors and cellular energy conditions. Growing studies highlight that disturbance in mTOR signalling in the brain affects multiple pathways including glucose metabolism, energy production, mitochondrial function, cell growth and autophagy. All these events are key players in age-related cognitive decline such as development of Alzheimer disease (AD). The current review discusses the main regulatory roles of mTOR signalling in the brain, in particular focusing on autophagy, glucose metabolism and mitochondrial functions. Targeting mTOR in the CNS can offer new prospective for drug discovery; however further studies are needed for a comprehensive understanding of mTOR, which lies at the crossroads of multiple signals involved in AD etiology and pathogenesis.