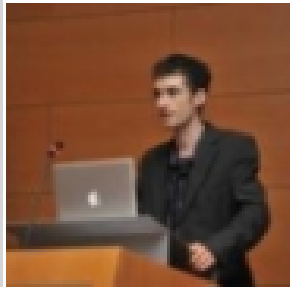




Heales
**HEALTHY LIFE EXTENSION
SOCIETY**

Scientific News
30th of July 2017
Sven Bulterijs

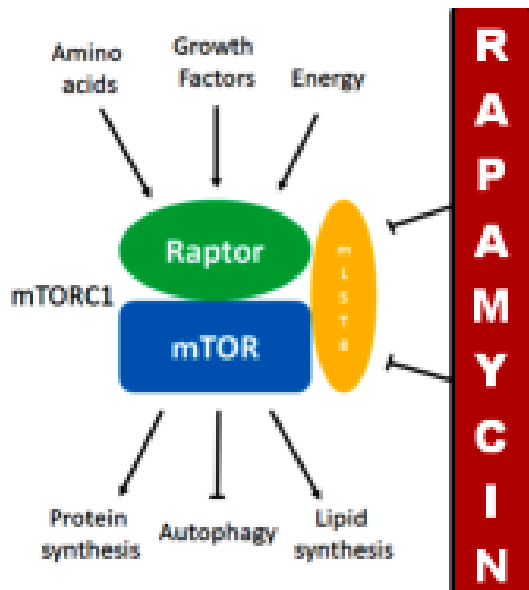


★★★★★ 1 votes

Geroprotector review: Rapamycin

Posted by [s123](#), 18 July 2017 · 452 views

rapamycin



Rapamycin and other mTOR inhibitors as geroprotectors

This article is solely for information purposes, not a substitute for

Wanted: biotech for an aging population

Nature Biotechnology **35**, 597 (2017) | doi:10.1038/nbt.3925

Published online 12 July 2017

Digital medicine's extraordinary ability to communicate with patients, especially in underserved communities, could help reorient the biotech industry to better address aging and its associated diseases.

Hypothalamic stem cells control ageing speed partly through exosomal miRNAs

Yalin Zhang, Min Soo Kim, Baosen Jia, Jingqi Yan, Juan Pablo Zuniga-Hertz, Cheng Han & Dongsheng Cai

It has been proposed that the hypothalamus helps to control ageing, but the mechanisms responsible remain unclear. Here we develop several mouse models in which hypothalamic stem/progenitor cells that co-express Sox2 and Bmi1 are ablated, as we observed that ageing in mice started with a substantial loss of these hypothalamic cells. Each mouse model consistently displayed acceleration of ageing-like physiological changes or a shortened lifespan. Conversely, ageing retardation and lifespan extension were achieved in mid-aged mice that were locally implanted with healthy hypothalamic stem/progenitor cells that had been genetically engineered to survive in the ageing-related hypothalamic inflammatory microenvironment. Mechanistically, hypothalamic stem/progenitor cells contributed greatly to exosomal microRNAs (miRNAs) in the cerebrospinal fluid, and these exosomal miRNAs declined during ageing, whereas central treatment with healthy hypothalamic stem/progenitor cell-secreted exosomes led to the slowing of ageing. In conclusion, ageing speed is substantially controlled by hypothalamic stem cells, partially through the release of exosomal miRNAs.

Aging Cell, 2017 Jul 5. doi: 10.1111/acer.12635. [Epub ahead of print]

Anti-aging pharmacology in cutaneous wound healing: effects of metformin, resveratrol, and rapamycin by local application.

Zhao P^{1,2}, Sui BD^{1,3}, Liu N^{1,3,4}, Lv YJ^{1,5}, Zheng CX^{1,3}, Lu YB², Huang WT², Zhou CH^{1,2}, Chen J¹, Pang DL^{1,3}, Fei DD¹, Xuan K^{1,3}, Hu CH^{1,2}, Jin Y^{1,3}.

⊕ Author information

Abstract

Cutaneous wounds are among the most common soft tissue injuries and are particularly hard to heal in aging. Caloric restriction (CR) is well documented to extend longevity; pharmacologically, profound rejuvenative effects of CR mimetics have been uncovered, especially metformin (MET), resveratrol (RSV), and rapamycin (RAPA). However, locally applied impacts and functional differences of these agents on wound healing remain to be established. Here, we discovered that chronic topical administration of MET and RSV, but not RAPA, accelerated wound healing with improved epidermis, hair follicles, and collagen deposition in young rodents, and MET exerted more profound effects. Furthermore, locally applied MET and RSV improved vascularization of the wound beds, which were attributed to stimulation of adenosine monophosphate-activated protein kinase (AMPK) pathway, the key mediator of wound healing. Notably, in aged skin, AMPK pathway was inhibited, correlated with impaired vasculature and reduced healing ability. As therapeutic approaches, local treatments of MET and RSV prevented age-related AMPK suppression and angiogenic inhibition in wound beds. Moreover, in aged rats, rejuvenative effects of topically applied MET and RSV on cell viability of wound beds were confirmed, of which MET showed more prominent anti-aging effects. We further verified that only MET promoted wound healing and cutaneous integrity in aged skin. These findings clarified differential effects of CR-based anti-aging pharmacology in wound healing, identified critical angiogenic and rejuvenative mechanisms through AMPK pathway in both young and aged skin, and unraveled chronic local application of MET as the optimal and promising regenerative agent in treating cutaneous wound defects.

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Elovanoids are novel cell-specific lipid mediators necessary for neuroprotective signaling for photoreceptor cell integrity

Docosahexaenoic acid (DHA, 22:6 n-3) is abundant in the retina and is enzymatically converted into pro-homeostatic docosanoids. The DHA- or eicosapentaenoic acid (EPA)-derived 26 carbon fatty acid is a substrate of elongase ELOVL4, which is expressed in photoreceptor cells and generates very long chain ($\geq C28$) polyunsaturated fatty acids including n-3 (VLC-PUFAs, n-3). While ELOVL4 mutations are linked to vision loss and neuronal dysfunctions, the roles of VLC-PUFAs remain unknown. Here we report a novel class of lipid mediators biosynthesized in human retinal pigment epithelial (RPE) cells that are oxygenated derivatives of VLC-PUFAs, n-3; we termed these mediators elovanoids (ELV). ELVs have structures reminiscent of docosanoids but with different physicochemical properties and alternatively-regulated biosynthetic pathways. The structures, stereochemistry, and bioactivity of ELVs were determined using synthetic materials produced by stereo-controlled chemical synthesis. ELVs enhance expression of pro-survival proteins in cells undergoing uncompensated oxidative stress. Our findings unveil a novel autocrine/paracrine pro-homeostatic RPE cell signaling that aims to sustain photoreceptor cell integrity and reveal potential therapeutic targets for retinal degenerations.

Cholesterol crystallization in human atherosclerosis is triggered in smooth muscle cells during the transition from fatty streak to fibroatheroma

Recent studies have shown that in addition to being major constituents of the atheromatous core, solid cholesterol crystals (CCs) promote atherosclerotic lesion development and rupture by causing mechanical damage and exerting cytotoxic and pro-inflammatory effects. These findings suggest that targeting CCs might represent a therapeutic strategy for plaque stabilization. However, little is known about how cholesterol crystallization is initiated in human atherothrombotic disease. Here, we investigated these mechanisms. We performed a thorough immunohistological analysis of non-embedded, minimally processed human aortic tissues, combining polarized light and fluorescence microscopy. We found that CC formation was initiated during the fatty streak to fibroatheroma transition in tight association with the death of intralésional smooth muscle cells (SMCs). Cholesterol-loaded human SMCs were capable of producing CCs *in vitro*, a process that was enhanced by type I collagen and by inhibition of autophagy and cholesterol esterification. The fibrous transition, which was characterized by increased type I collagen expression, was associated with changes in the expression of autophagy and cholesterol flux-related genes, including a decrease in the autophagic adapter p62 and an increase in the cholesterol intracellular transporter Niemann-Pick C1. Collagen was identified as a potent inducer of these changes in SMCs. Collagen-induced changes in cholesterol metabolism and autophagy flux in smooth muscle foam cells at the fibrolipid transition likely contribute to initiate cholesterol crystallization in human atherosclerosis. Also, our data are in support of a protective role of autophagy against CC formation. Copyright © 2016 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

PLoS One. 2017 Jun 23;12(6):e0174469. doi: 10.1371/journal.pone.0174469. eCollection 2017.

Fragmentation of the mitochondrial network in skin in vivo.

[Mellem D](#)^{1,2}, [Sattler M](#)², [Pagel-Wolff S](#)², [Jaspers S](#)², [Wenck H](#)², [Rübhausen MA](#)¹, [Fischer F](#)².

Author information

Abstract

Mitochondria form dynamic networks which adapt to the environmental requirements of the cell. We investigated the aging process of these networks in human skin cells in vivo by multiphoton microscopy. A study on the age-dependency of the mitochondrial network in young and old volunteers revealed that keratinocytes in old skin establish a significantly more fragmented network with smaller and more compact mitochondrial clusters than keratinocytes in young skin. Furthermore, we investigated the mitochondrial network during differentiation processes of keratinocytes within the epidermis of volunteers. We observe a fragmentation similar to the age-dependent study in almost all parameters. These parallels raise questions about the dynamics of biophysical network structures during aging processes.

PMID: 28644888 PMCID: [PMC5482427](#) DOI: [10.1371/journal.pone.0174469](#)

Free PMC Article



Analysis of individual cells identifies cell-to-cell variability following induction of cellular senescence

Christopher D. Wiley, James M. Flynn, Christopher Morrissey, Ronald Lebofsky, Joe Shuga, Xiao Dong, Marc A. Unger, Jan Vijg, Simon Melov, Judith Campisi ✉

Senescent cells play important roles in both physiological and pathological processes, including cancer and aging. In all cases, however, senescent cells comprise only a small fraction of tissues. Senescent phenotypes have been studied largely in relatively homogeneous populations of cultured cells. *In vivo*, senescent cells are generally identified by a small number of markers, but whether and how these markers vary among individual cells is unknown. We therefore utilized a combination of single-cell isolation and a nanofluidic PCR platform to determine the contributions of individual cells to the overall gene expression profile of senescent human fibroblast populations. Individual senescent cells were surprisingly heterogeneous in their gene expression signatures. This cell-to-cell variability resulted in a loss of correlation among the expression of several senescence-associated genes. Many genes encoding senescence-associated secretory phenotype (SASP) factors, a major contributor to the effects of senescent cells *in vivo*, showed marked variability with a subset of highly induced genes accounting for the increases observed at the population level. Inflammatory genes in clustered genomic loci showed a greater correlation with senescence compared to nonclustered loci, suggesting that these genes are coregulated by genomic location. Together, these data offer new insights into how genes are regulated in senescent cells and suggest that single markers are inadequate to identify senescent cells *in vivo*.

[Cell Rep.](#) 2017 Jul 11;20(2):451-463. doi: 10.1016/j.celrep.2017.06.048.

Reduced Circulating Insulin Enhances Insulin Sensitivity in Old Mice and Extends Lifespan.

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Abstract

The causal relationships between insulin levels, insulin resistance, and longevity are not fully elucidated. Genetic downregulation of insulin/insulin-like growth factor 1 (Igf1) signaling components can extend invertebrate and mammalian lifespan, but insulin resistance, a natural form of decreased insulin signaling, is associated with greater risk of age-related disease in mammals. We compared *Ins2*^{+/-} mice to *Ins2*^{+/+} littermate controls, on a genetically stable *Ins1* null background. Proteomic and transcriptomic analyses of livers from 25-week-old mice suggested potential for healthier aging and altered insulin sensitivity in *Ins2*^{+/-} mice. Halving *Ins2* lowered circulating insulin by 25%-34% in aged female mice, without altering Igf1 or circulating Igf1. Remarkably, decreased insulin led to lower fasting glucose and improved insulin sensitivity in aged mice. Moreover, lowered insulin caused significant lifespan extension, observed across two diverse diets. Our study indicates that elevated insulin contributes to age-dependent insulin resistance and that limiting basal insulin levels can extend lifespan.

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Longevity is impacted by growth hormone action during early postnatal period

Life-long lack of growth hormone (GH) action can produce remarkable extension of longevity in mice. Here we report that GH treatment limited to a few weeks during development influences the lifespan of long-lived Ames dwarf and normal littermate control mice in a genotype and sex-specific manner. Studies in a separate cohort of Ames dwarf mice show that this short period of the GH exposure during early development produces persistent phenotypic, metabolic and molecular changes that are evident in late adult life. These effects may represent mechanisms responsible for reduced longevity of dwarf mice exposed to GH treatment early in life. Our data suggest that developmental programming of aging importantly contributes to (and perhaps explains) the well documented developmental origins of adult disease.

Association of Plasma Total Tau Level With Cognitive Decline and Risk of Mild Cognitive Impairment or Dementia in the Mayo Clinic Study on Aging

Exposures Concentration of plasma total tau.

Main Outcomes and Measures Risk of MCI and dementia; global and domain-specific cognitive decline.

Results Of the 458 participants, 287 (62.7%) were men; mean (SD) age was 80.6 (5.6) years. Among cognitively normal (CN) participants oversampled for elevated brain A β , both the middle (hazard ratio [HR], 2.43; 95% CI, 1.25-4.72) and highest (HR, 2.02; 95% CI, 1.01-4.06) tertiles of plasma total tau level, compared with the lowest, were associated with an increased risk of MCI. Among participants with MCI, higher plasma total tau levels were not significantly associated with risk of dementia (all-cause dementia or Alzheimer disease). Among all participants, higher levels of plasma total tau, examined as a continuous variable, were associated with significant ($P < .05$) declines in global cognition, memory, attention, and visuospatial ability over a median follow-up of 3.0 years (range, 1.1-4.9 years). In additional analyses restricting the follow-up to 15 months, plasma total tau did not predict decline among CN participants. However, among participants with MCI, higher plasma total tau levels were associated with greater decline in both visuospatial ability (regression coefficient [b] = -0.50 [0.15], $P < .001$) and global cognition (b = -0.27 [0.10], $P = .009$) at 15 months. Adjusting for elevated brain A β did not attenuate any association. There was no interaction between plasma total tau level and brain A β for prognosis with any outcome.

Conclusions and Relevance These results suggest that elevated plasma total tau levels are associated with cognitive decline, but the results differ based on cognitive status and the duration of follow-up. The association between plasma total tau levels and cognition is independent of elevated brain A β .

Metformin, Lifestyle Intervention, and Cognition in the Diabetes Prevention Program Outcomes Study

OBJECTIVE We examined the association of the Diabetes Prevention Program (DPP) intervention arms (lifestyle intervention, metformin, and placebo) with cognition in the Diabetes Prevention Program Outcomes Study (DPPOS). We also examined metformin use, incident type 2 diabetes, and glycemia as exposures.

RESEARCH DESIGN AND METHODS The DPP lasted 2.8 years, followed by a 13-month bridge to DPPOS. Cognition was assessed in DPPOS years 8 and 10 (12 and 14 years after randomization) with the Spanish English Verbal Learning Test (SEVLT), letter fluency and animal fluency tests, Digit Symbol Substitution Test (DSST), and a composite cognitive score.

RESULTS A total of 2,280 participants (749 lifestyle, 776 metformin, and 755 placebo) aged 63.1 ± 10.7 years underwent cognitive assessments; 67.7% women, 54.6% non-Hispanic white, 20.7% non-Hispanic black, 14.6% Hispanic, 5.5% American Indian, and 4.6% Asian; 26.6% were homozygous or heterozygous for APOE- $\epsilon 4$. At the time of cognitive assessment, type 2 diabetes was higher in the placebo group (57.9%; $P < 0.001$) compared with lifestyle (47.0%) and metformin (50.4%). Metformin exposure was higher in the metformin group (8.72 years; $P < 0.001$) compared with placebo (1.43 years) and lifestyle (0.96 years). There were no differences in cognition across intervention arms. Type 2 diabetes was not related to cognition, but higher glycated hemoglobin at year 8 was related to worse cognition after confounder adjustment. Cumulative metformin exposure was not related to cognition.

CONCLUSIONS Exposure to intensive lifestyle intervention or metformin was not related to cognition among DPPOS participants. Higher glycemia was related to worse cognitive performance. Metformin seemed cognitively safe among DPPOS participants.

Rare progerin-expressing preadipocytes and adipocytes contribute to tissue depletion over time

Accumulation of progerin is believed to underlie the pathophysiology of Hutchinson-Gilford progeria syndrome, a disease characterized by clinical features suggestive of premature aging, including loss of subcutaneous white adipose tissue (sWAT). Although progerin has been found in cells and tissues from apparently healthy individuals, its significance has been debated given its low expression levels and rare occurrence. Here we demonstrate that sustained progerin expression in a small fraction of preadipocytes and adipocytes of mouse sWAT (between 4.4% and 6.7% of the sWAT cells) results in significant tissue pathology over time, including fibrosis and lipoatrophy. Analysis of sWAT from mice of various ages showed senescence, persistent DNA damage and cell death that preceded macrophage infiltration, and systemic inflammation. Our findings suggest that continuous progerin expression in a small cell fraction of a tissue contributes to aging-associated diseases, the adipose tissue being particularly sensitive.

REVIEWS/COMMENTS/EDITORIALS

Opinion

Biphasic Modeling of Mitochondrial Metabolism Dysregulation during Aging

Darren J. Baker ^{1, 2}, Shahaf Peleg ³  

Organismal aging is classically viewed as a gradual decline of cellular functions and a systemic deterioration of tissues that leads to an increased mortality rate in older individuals. According to the prevailing theory, aging is accompanied by a continuous and progressive decline in mitochondrial metabolic activity in cells. However, the most robust approaches to extending healthy lifespan are frequently linked with reduced energy intake or with lowering of mitochondrial activity. While these observations appear contradictory, recent work and technological advances demonstrate that metabolic deregulation during aging is potentially biphasic. In this Opinion we propose a novel framework where middle-age is accompanied by increased mitochondrial activity that subsequently declines at advanced ages.

More comments on the 2016 Nature paper “Evidence for a limit to human lifespan”

Nature. 2017 Jun 28;546(7660):E13-E14. doi: 10.1038/nature22790.

Questionable evidence for a limit to human lifespan.

Lenart A^{1,2}, Vaupel JW^{1,2}.

Nature. 2017 Jun 28;546(7660):E11-E12. doi: 10.1038/nature22788.

Is there evidence for a limit to human lifespan?

Roziq MP^{1,2}, Kirkwood TBL^{1,3}, Westendorp RGJ^{1,2}.

Hum Vaccin Immunother. 2017 Jul 14;0. doi: [10.1080/21645515.2017.1343226](https://doi.org/10.1080/21645515.2017.1343226). [Epub ahead of print]

Influenza vaccination in the elderly.

[Jan S¹](#), [Roman C¹](#), [Jana S^{2,3}](#), [Miroslav S¹](#), [Roman P^{2,4}](#).

⊕ Author information

Abstract

Seasonal influenza is a prevalent and serious annual illness resulting in widespread morbidity and economic disruption throughout the population; the elderly and immunocompromised are particularly vulnerable to serious sequelae and mortality. The changing demographics worldwide to an aging society have important implications for public health policy and pharmaceutical innovations. For instance, primary prevention via immunization is effective in reducing the burden of influenza illness among the elderly. However, the elderly may be insufficiently protected by vaccination due to the immunosenescence which accompanies aging. In addition, vaccine hesitancy among the younger populations increases the likelihood of circulating infectious diseases, and thus concomitant exposure. While it is clear that the development of more immunogenic vaccines is an imperative and worthy endeavor, clinical trials continue to demonstrate that the current influenza vaccine formulation remains highly effective in reducing morbidity and mortality when well matched to circulating strains.

KEYWORDS: Influenza vaccination; burden of flu; efficacy; elderly; immunization strategies

PMID: 28708957 DOI: [10.1080/21645515.2017.1343226](https://doi.org/10.1080/21645515.2017.1343226)

Humans and other mammals are limited in their natural abilities to regenerate lost body parts. By contrast, many salamanders are highly regenerative and can spontaneously replace lost limbs even as adults. Because salamander limbs are anatomically similar to human limbs, knowing how they regenerate should provide important clues for regenerative medicine. Although interest in understanding the mechanics of this process has never wavered, until recently researchers have been vexed by seemingly impenetrable logistics of working with these creatures at a molecular level. Chief among the problems has been the very large size of salamander genomes, and not a single salamander genome has been fully sequenced to date. Recently the enormous gap in sequence information has been bridged by approaches that leverage mRNA as the starting point. Together with functional experimentation, these data are rapidly enabling researchers to finally uncover the molecular mechanisms underpinning the astonishing biological process of limb regeneration.

Trends

The salamander experimental toolset has now largely caught up with the interest in understanding limb regeneration, finally allowing precise experimentation at a cellular and molecular level.

A huge amount of transcript data has emerged from which to gather clues about how limb regeneration occurs.

Differential gene expression analysis has enabled the identification of transcripts that are highly enriched, as well as highly repressed, in key tissues required for limb regeneration. These are prime starting points for hypothesis generation and functional experimentation.

Several genes whose involvement would not have been predicted by candidate gene approaches have now been implicated in limb regeneration, underscoring the need to take unbiased approaches to gene discovery.

De novo transcriptomes and reference-tissue sequence data are important new resources for the field.

Genome-wide studies of aging have identified subsets of genes that show age-related changes in expression. Although the types of genes that are age regulated vary among different tissues and organisms, some patterns emerge from these large data sets. First, aging is associated with a broad induction of stress response pathways, although the specific genes and pathways involved differ depending on cell type and species. In contrast, a wide variety of functional classes of genes are downregulated with age, often including tissue-specific genes. Although the upregulation of age-regulated genes is likely to be governed by stress-responsive transcription factors, questions remain as to why particular genes are susceptible to age-related transcriptional decline. Here, we discuss recent findings showing that splicing is misregulated with age. While defects in splicing could lead to changes in protein isoform levels, they could also impact gene expression through nonsense-mediated decay of intron-retained transcripts. The discovery that splicing is misregulated with age suggests that other aspects of gene expression, such as transcription elongation, termination, and polyadenylation, must also be considered as potential mechanisms for age-related changes in transcript levels. Moreover, the considerable variation between genome-wide aging expression studies indicates that there is a critical need to analyze the transcriptional signatures of aging in single-cell types rather than whole tissues. Since age-associated decreases in gene expression could contribute to a progressive decline in cellular function, understanding the mechanisms that determine the aging transcriptome provides a potential target to extend healthy cellular lifespan.

Aging across the tree of life: The importance of a comparative perspective for the use of animal models in aging ☆

Alan A. Cohen ✉

Use of model organisms in aging research is problematic because our ability to extrapolate across the tree of life is not clear. On one hand, there are conserved pathways that regulate lifespan in organisms including yeast, nematodes, fruit flies, and mice. On the other, many intermediate taxa across the tree of life appear not to age at all, and there is substantial variation in aging mechanisms and patterns, sometimes even between closely related species. There are good evolutionary and mechanistic reasons to expect this complexity, but it means that model organisms must be used with caution and that results must always be interpreted through a broader comparative framework. Additionally, it is essential to include research on non-traditional and unusual species, and to integrate mechanistic and demographic research. There will be no simple answers regarding the biology of aging, and research approaches should reflect this. This article is part of a Special Issue entitled: Animal models of aging - edited by Houtkooper Riekelt.

The emerging role of alternative splicing in senescence and aging

Mathieu Deschênes, Benoit Chabot ✉

Deregulation of precursor mRNA splicing is associated with many illnesses and has been linked to age-related chronic diseases. Here we review recent progress documenting how defects in the machinery that performs intron removal and controls splice site selection contribute to cellular senescence and organismal aging. We discuss the functional association linking *p53*, *IGF-1*, *SIRT1*, and *ING-1* splice variants with senescence and aging, and review a selection of splicing defects occurring in accelerated aging (progeria), vascular aging, and Alzheimer's disease. Overall, it is becoming increasingly clear that changes in the activity of splicing factors and in the production of key splice variants can impact cellular senescence and the aging phenotype.

Cellular senescence was first described by Hayflick and Moorhead in the 1960s as the irreversible arrest of cells following prolonged cultivation. Telomere shortening is the key mechanism driving replicative senescence in human fibroblasts. Later, pioneering work by Olivier Toussaint and others showed that stress plays a major role in the induction of senescence *in vitro*, a phenomenon known as stress-induced premature senescence or SIPS. It is also now widely accepted that senescence plays a role *in vivo*. An emerging body of evidence from animal models, and particularly mice, has demonstrated an important role for senescence in several processes such as embryonic development, wound healing, tumour suppression and ageing. However, mostly due to a lack of availability of tissues and specific markers, less is known about the importance of cell senescence in humans. In this review, we summarize some of the key findings in the field of senescence, stress-induced senescence and telomeres. We focus particularly on the role of telomere dysfunction and senescence during the ageing process as well as potential interventions, including pharmacological approaches like telomerase activators and senolytics, to counteract their detrimental effects in ageing and disease.

OTHER RESEARCH



Disease model discovery from 3,328 gene knockouts by The International Mouse Phenotyping Consortium

Although next-generation sequencing has revolutionized the ability to associate variants with human diseases, diagnostic rates and development of new therapies are still limited by a lack of knowledge of the functions and pathobiological mechanisms of most genes. To address this challenge, the International Mouse Phenotyping Consortium is creating a genome- and phenome-wide catalog of gene function by characterizing new knockout-mouse strains across diverse biological systems through a broad set of standardized phenotyping tests. All mice will be readily available to the biomedical community. Analyzing the first 3,328 genes identified models for 360 diseases, including the first models, to our knowledge, for type C Bernard–Soulier, Bardet–Biedl-5 and Gordon Holmes syndromes. 90% of our phenotype annotations were novel, providing functional evidence for 1,092 genes and candidates in genetically uncharacterized diseases including arrhythmogenic right ventricular dysplasia 3. Finally, we describe our role in variant functional validation with The 100,000 Genomes Project and others.

Verily chases a perfectly healthy human

Nature Biotechnology **35**, 490 (2017) | doi:10.1038/nbt0617-490

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Google startup Verily Life Sciences is expecting 10,000 people to sign up for a four-year study to find out why healthy people transition from health to illness. Verily, located in Mountain View, California, is partnering with Duke University and Stanford Medicine to enroll participants from different backgrounds in the next...

CRISPR/Cas9-mediated gene editing ameliorates neurotoxicity in mouse model of Huntington's disease

Su Yang,¹ Renbao Chang,^{1,2,3} Huiming Yang,¹ Ting Zhao,¹ Yan Hong,¹ Ha Eun Kong,¹ Xiaobo Sun,⁴ Zhaohui Qin,⁵ Peng Jin,¹ Shihua Li,¹ and Xiao-Jiang Li^{1,6}

First published June 19, 2017 - [More info](#)

Huntington's disease is a neurodegenerative disorder caused by a polyglutamine repeat in the Huntingtin gene (*HTT*). Although suppressing the expression of mutant HTT (mHTT) has been explored as a therapeutic strategy to treat Huntington's disease, considerable efforts have gone into developing allele-specific suppression of mHTT expression, given that loss of *Htt* in mice can lead to embryonic lethality. It remains unknown whether depletion of HTT in the adult brain, regardless of its allele, could be a safe therapy. Here, we report that permanent suppression of endogenous mHTT expression in the striatum of mHTT-expressing mice (HD140Q-knockin mice) using CRISPR/Cas9-mediated inactivation effectively depleted HTT aggregates and attenuated early neuropathology. The reduction of mHTT expression in striatal neuronal cells in adult HD140Q-knockin mice did not affect viability, but alleviated motor deficits. Our studies suggest that non-allele-specific CRISPR/Cas9-mediated gene editing could be used to efficiently and permanently eliminate polyglutamine expansion-mediated neuronal toxicity in the adult brain.